

头孢他啶/阿维巴坦

指南共识手册

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头孢他啶/阿维巴坦在指南共识中的推荐

医院获得性肺炎与呼吸机相关性肺炎（HAP/VAP）

- 各地区国家的 HAP/VAP 相关指南对于头孢他啶/阿维巴坦的推荐侧重有所不同：2018 ERS 等指南总结中推荐头孢他啶/阿维巴坦用于治疗产 ESBL 菌感染的高危患者，而 2018 中国成人 HAP/VAP 诊疗指南中推荐头孢他啶/阿维巴坦用于治疗 CRE 感染。最新的 2019 英国 HAP：抗菌药物处方推荐头孢他啶/阿维巴坦是 HAP 严重感染或较高耐药菌感染情况下的首选用药

复杂性腹腔内感染（cIAI）

- 2017 WSES 指南推荐头孢他啶/阿维巴坦用于经验性或目标性治疗感染产 KPC 的医疗保健相关性 IAI 重症患者，另外，为了减少碳青霉类的使用，头孢他啶/阿维巴坦联合甲硝唑和万古霉素/替考拉宁可作为碳青霉烯类一般方案的替代方案
- 2017 SISA IAI 管理指南除推荐产 KPC 肠杆菌科细菌应用头孢他啶/阿维巴坦，也推荐 MDR 铜绿假单胞菌，另外，该指南推荐人群不仅包含医疗保健相关性 IAI 患者，也包含医院获得性 IAI 患者
- 2016 XDR-GNB 感染中国专家共识：表述了阿维巴坦对 ESBL、AmpC、部分 D 类 β 内酰胺酶（如 OXA-48）及 KPC 均具有抑制作用，认可头孢他啶/阿维巴坦联合甲硝唑治疗复杂性 cIAI 的疗效及不良反应与美罗培南相仿

目标性治疗 XDR/PDR/MDR-GNB 的各指南推荐

- 2018 英国感染协会等联合工作组报告：推荐头孢他啶/阿维巴坦用于治疗 MDR-GNB，可以使用头孢他啶阿维巴坦作为碳青霉烯类替代药，治疗产 ESBL 和 AmpC 肠杆菌科细菌、产 OXA-48 的革兰阴性菌感染，以及联合美罗培南治疗产 KPC 革兰阴性菌
- 2019 美国桑福德抗微生物治疗指南：推荐头孢他啶/阿维巴坦用于治疗产 KPC 的肠杆菌科，联合氨曲南治疗产金属碳青霉烯酶的革兰阴性杆菌
- 2019 中国器官移植耐药菌感染指南：MDR 肠杆菌属及铜绿假单胞菌感染初始治疗失败后，推荐换用头孢他啶/阿维巴坦

- 2018 西班牙实体器官移植 MDR-GNB 感染管理指南：推荐头孢他啶/阿维巴坦用于治疗 CPE 感染
- 2019 西班牙血液恶性肿瘤患者发热性粒缺的管理共识文件：推荐头孢他啶/阿维巴坦可用于治疗产 KPC 或产 OXA-48 的肠杆菌科感，或对于广泛耐药或 PDR 铜绿假单胞菌感染



Summary of the international clinical guidelines for the management of hospital-acquired and ventilator-acquired pneumonia

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A summary of the evidence and recommendations made in the ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia <http://ow.ly/S3zA30iZfLa>

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The most recent European guidelines and task force reports on hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) were published almost 10 years ago. Since then, further randomised clinical trials of HAP and VAP have been conducted and new information has become available. Studies of epidemiology, diagnosis, empirical treatment, response to treatment, new antibiotics or new forms of antibiotic administration, and disease prevention have changed old paradigms. In addition, important differences between approaches in Europe and the USA have become apparent. The European Respiratory Society (ERS) launched a project to develop new international guidelines for HAP and VAP.

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Other European societies, including the European Society of Intensive Care Medicine (ESICM) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), were invited to participate and appointed their representatives. The Latin American Society of Thoracic Diseases (ALAT) was also invited to participate. This manuscript summarises the evidence and recommendations of these international guidelines on HAP and VAP.

Background

Nosocomial pneumonia is a frequent infection that is classified into two groups [1]: HAP, which develops in hospitalised patients after 48 h of admission, and does not require (but may include) artificial ventilation at the time of diagnosis [2, 3]; and VAP, which occurs in intensive care unit (ICU) patients who have received mechanical ventilation for at least 48 h [2, 3].

HAP is the second most common hospital infection and has the highest crude mortality, while VAP is the most frequent cause of nosocomial infection in the ICU [2, 3]. Both types of pneumonia lengthen hospital stay and consume considerable health resources [2, 3].

Recently, the ERS, ESICM, ESCMID and ALAT published clinical guidelines on the therapeutic and management strategies for adult patients with HAP and VAP, designed to guide clinical decisions made not only by pulmonologists and intensivists but by all health professionals who treat these patients [2]. These clinical guidelines are evidence-based (Grading of Recommendations Assessment, Development and Evaluation) and follow the PICO (population-intervention-comparison-outcome) model.

Each section in this article refers to a specific PICO question addressed in the guidelines.

Obtaining samples in intubated patients

To identify the causative agent of nosocomial pneumonia, the recommendation is to perform a qualitative or quantitative (preferred) analysis of the respiratory secretions. In both cases, the quality of the respiratory samples should be assessed [3].

Both invasive techniques (fibre-optic bronchoscopy or mini-bronchoalveolar lavage) and noninvasive techniques can be used to obtain samples of respiratory secretions for quantitative or qualitative analysis. Examples of both types of technique listed in table 1.

Quantitative analyses use the bacteriological growth count to assist differentiation between infection (when there are high concentrations of a certain organism) and colonisation (when the concentrations are low); qualitative analyses focus on the presence or absence of pathogens [4].

Qualitative cultures of tracheal aspirates are simple and noninvasive, but the main methodological limitation is that samples are often contaminated by the flora colonising the upper tracts and are therefore less specific [5].

Invasive techniques also present several disadvantages: the need for qualified personnel to perform these procedures, potential risks for the patient, and the associated costs [2, 3]. Techniques such as bronchoalveolar lavage and the application of quantitative cultures achieve reliable identification of the causative agents of the infection, especially in patients at high risk, such as those undergoing mechanical ventilation [5], and can thus guide antibiotic treatment [2].

No randomised controlled clinical studies have compared quantitative and qualitative cultures of the same sample [2]. However, a Cochrane review from 2014 included five studies that compared invasive methods

TABLE 1 Examples of invasive and noninvasive techniques for obtaining samples of respiratory secretions

Technique	Example
Invasive	Fibre-optic bronchoscopy with protected specimen brush [#] Fibre-optic bronchoscopy with alveolar lavage [#] Lung biopsy and tissue culture
Noninvasive	Simple culture of endotracheal aspirate (qualitative) Quantitative culture of endotracheal aspirate [#] Blind culture with protected/plugged telescopic catheter [#] Blind protected specimen brush [#] Blind alveolar lavage [#]
[#] : samples obtained by these methods require quantitative cultures.	

using quantitative cultures with noninvasive ones using qualitative cultures [4]. The authors concluded that there was no clear advantage between quantitative and qualitative cultures, or invasive and noninvasive techniques [4].

Noninvasive methods may overestimate the presence of bacteria in the initial examination of the samples, which can lead to excessive antibiotic use [2]. If the sample is obtained before changing the antibiotic treatment and yields a negative result, the antibiotic can be withdrawn since the possibility of no infection is high [6, 7]. However, a negative result may also indicate that the infection has been controlled [2].

Key points

- The European guidelines indicate that it is preferable to obtain the distal quantitative samples before antibiotic treatment [2], since it is known that if samples are obtained within 48 h of the start of antibiotic treatment the result may be altered or emerge as negative [2, 5].
- In view of the general overuse of antibiotics, the reduction in their prescription through use of distal quantitative cultures may have a positive impact on the appearance of resistance and consequently on health expenditure, although no studies of cost effectiveness have been carried out to date [2].

Treatment of early nosocomial pneumonia (before 5 days) and late nosocomial pneumonia (after 5 days)

A distinction should be made between patients with risk factors for antibiotic resistance and patients without these risk factors, and also between early and late episodes.

In early VAP without risk factors, the most frequent causative pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae* and methicillin-sensitive *Staphylococcus aureus*. By contrast, in late VAP the causative agents are at high risk for antibiotic resistance: for example, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, methicillin-resistant *S. aureus* (MRSA) and other Gram-negative bacilli, depending on the predominant microorganism in each hospital and ICU [5]. Gram-negative bacilli are considered multidrug resistant (MDR) if they are resistant to three or more families of antibiotics to which they are normally sensitive, including β -lactams (penicillins and cephalosporins), carbapenems, aminoglycosides and quinolones [8]. The rate of resistant pathogens in local microbiological data is considered high when it exceeds 25% (figure 1) [2].

Patients with early nosocomial pneumonia who do not have risk factors for multidrug resistance, have a low mortality risk, and are treated in an ICU with a low rate of MDR pathogens, should be treated with antibiotics that cover community pathogens, while in patients with late nosocomial pneumonia or who present risk factors for multidrug resistance or a high risk of mortality, initial broad spectrum empirical treatment should be performed [3]. In the latter case, a combination of antibiotics should be prescribed in order to expand the spectrum and avoid resistance [3].

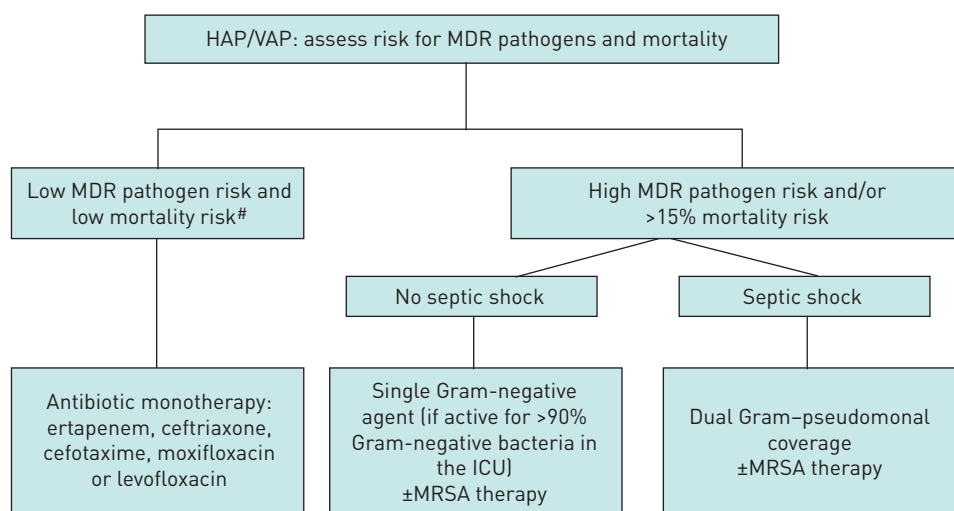


FIGURE 1 Empirical antibiotic treatment algorithm for hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP). MDR: multidrug-resistant; ICU: intensive care unit; MRSA: methicillin-resistant *Staphylococcus aureus*. #: low risk for mortality is defined as a $\leq 15\%$ chance of dying, a mortality rate that has been associated with better outcomes using monotherapy than combination therapy when treating serious infection [18]. Reproduced from [2].

It is necessary to define the nosocomial pneumonia patients who can receive narrow-spectrum empirical treatment and those who should receive broad-spectrum empirical treatment, in order to prevent the appearance of resistance and secondary effects related to antibiotics [2]. Patients susceptible to colonisation by MDR microorganisms usually present with more severe condition, are often immunocompromised and present risk factors, as is the case with many patients requiring mechanical ventilation [8].

The European guidelines defined low-risk patients as those who do not present with septic shock, do not have other risk factors for MDR pathogens and are not admitted to ICUs with a high rate of resistant pathogens (25%) [2].

An important variable for identifying MDR pathogens is the time of pneumonia onset. Early HAP and VAP are defined by an occurrence within 4 days of hospital admission and are associated with a better prognosis, since they are more likely to be caused by microorganisms that are generally sensitive to antibiotics. Late-onset pneumonias develop after 5 days of hospitalisation and are more likely to be caused by MDR microorganisms, with higher morbidity and mortality [2, 9]. Prior antimicrobial therapy or hospitalisation for longer than 2 days during the 3 months prior to the episode have also been identified as risk factors [2].

Previous studies found advanced age and previous use of antibiotics to be risk factors for MDR pathogens in ICU-acquired pneumonia [2, 10]. Also, patients over 65 years of age are at a greater risk of infection with methicillin-resistant *S. aureus* [11], and acute renal failure is associated with an increased risk of community-acquired pneumonia due to *P. aeruginosa*, Enterobacteria producing extended spectrum β -lactamase (ESBL) and multidrug-resistance [2, 12].

Despite the lack of cost-effectiveness studies, the European guidelines consider that narrow-spectrum antibiotic treatment is associated with fewer direct costs, since the costs incurred by drug-related toxicity are lower and the emergence of multidrug resistance may also be reduced [2]. By contrast, administration of an inadequate narrow-spectrum antibiotic may entail higher costs due to the prolongation of mechanical ventilation and hospital stay and a greater final use of antibiotics [9].

Key points

- The selection of patients with early-onset nosocomial pneumonia to receive empirical treatment with narrow-spectrum antibiotics should be based on the individual risks, the severity of the clinical situation (shock), and the frequency and type of MDR pathogens detected in the ICU [2].
- Narrow-spectrum antibiotics can be used in patients with early onset of HAP or VAP, whenever the risk of resistance and mortality is considered to be low [2].
- In patients with early-onset HAP/VAP who develop septic shock, a broad-spectrum empirical treatment against *P. aeruginosa* and ESBL producing organisms is recommended [2]. In addition, MRSA should be covered if prevalent in the unit (>25% *S. aureus* in the unit).
- Multiple broad-spectrum antibiotics should not be used routinely, in order to prevent drug-related toxicities, such as renal failure due to the use of the nephrotoxic drugs aminoglycosides and vancomycin, but may be necessary in selected patients [2].

One or two antibiotics for initial broad-spectrum empirical treatment

The aims of combined antibiotic treatment are to obtain synergies between different groups of antibiotics, extending the spectrum of action against Gram-negative bacilli and avoiding the emergence of resistance [3, 8]. However, combined treatments may also have disadvantages (at least potentially) such as the increased risk of toxicity, the higher cost of treatment and problems of superinfection [8].

European guidelines (and also those provided by ALAT) define high-risk patients as those who present with HAP/VAP and septic shock and/or the following risk factors for MDR pathogens: 1) admitted into units with high rates of MDR pathogens (*i.e.* above 25%, including Gram-negative bacteria and MRSA); 2) prior use of antibiotics; 3) recent prolonged hospitalisation (>5 days); and 4) previous colonisation by MDR pathogens [2].

The 2016 American guidelines indicate that when HAP is suspected, coverage for *S. aureus*, *P. aeruginosa* and other Gram-negative bacilli should be included in the empirical treatment [13]. The European guidelines indicate that, in certain patients, if a single antibiotic is effective against more than 90% of Gram-negative bacteria, the initial empirical therapy can be monotherapy if the patient is not in septic shock (table 2) [2].

Some studies suggest that survival in patients admitted to the ICU depends on the early initiation of effective antibiotic treatment [2, 14], while others indicate that combined treatments in critical patients

早期（5 天前）医院获得性肺炎和晚期（5 天后）医院获得性肺炎的治疗

应当区分具有抗生素耐药危险因素和不具有此危险因素的患者，以及区分早期和晚期发病的患者。

在无耐药危险因素的早期 VAP 患者中，最常见的致病菌是肺炎链球菌、流感嗜血杆菌和甲氧西林敏感金黄色葡萄球菌。相比之下，在晚期 VAP 患者中，致病菌具有较高的抗生素耐药性风险：例如，铜绿假单胞菌、鲍曼不动杆菌、耐甲氧西林金黄色葡萄球菌（MRSA）和其他革兰氏阴性杆菌，这取决于各医院和 ICU 的主要微生物种类⁵。如果革兰氏阴性杆菌对三个或三个以上通常敏感的抗生素家族（包括 β -内酰胺类「青霉素类和头孢菌素类」、碳青霉烯类、氨基糖苷类和喹诺酮类）具有耐药性，则视为多药耐药（MDR）⁸。当地微生物数据中的耐药率超过 25% 时被认为是具有很高的耐药率（图 1）²。

重点

- 应当基于患者个体风险、临床情况（休克）的严重程度、ICU 中检测到的 MDR 病原体的频率和类型，来选择窄谱抗生素的经验性治疗应用于早期发病的院内获得性肺炎患者。
- 当耐药性和死亡率较低时，可以将窄谱抗生素应用于早期发生 HAP 或 VAP 的患者中。
- 对于发生脓毒性休克的早发性 HAP/VAP 患者，建议对铜绿假单胞菌和产 ESBL 的病原体进行广谱经验性治疗。此外，如果医疗单元普遍存在 MRSA，则应予以覆盖（单元中金黄色葡萄球菌 > 25%）。
- 除了在特定的患者，不应常规使用多种广谱抗生素，以防止与药物有关的毒性，例如因使用肾毒性氨基糖苷类和万古霉素引起的肾功能衰竭。

TABLE 2 Empirical antibiotic treatments for high-risk patients

High risk of multidrug resistance and/or >15% risk of mortality in ICU	No septic shock	Monotherapy against Gram-negative (if active against >90% of the probable ICU pathogens) ± MRSA treatment
	Septic shock	Dual treatment with <i>Pseudomonas</i> Gram-negative coverage ± MRSA treatment

ICU: intensive care unit; MRSA: methicillin-resistant *Staphylococcus aureus*.

may be associated with increased toxicity and an increased risk of late-onset multidrug resistance and superinfection [2, 15–17].

When HAP/VAP is associated with septic shock or is produced by Gram-negative bacteria, the combination of two Gram-negative specific antibiotics may be beneficial [18, 19]. Some studies even indicate that dual therapy (β -lactams in combination with aminoglycosides, fluoroquinolones or macrolides/clindamycin) presents a significantly lower risk of death compared with monotherapy [2, 19].

In patients with a low risk of MDR and low mortality risk, the recommended therapy consists of a narrow-spectrum drug with activity against non-antibiotic-resistant Gram-negatives and MRSA. The appropriate drugs are ertapenem, ceftriaxone, cefotaxime, moxifloxacin or levofloxacin [2, 13].

The percentage of MDR microorganisms isolated in each ICU should also be taken into account. According to European guidelines, in high-risk patients in an ICU in which >25% of *S. aureus* respiratory isolates are methicillin-resistant (between 10% and 20% according to American guidelines) an agent with coverage for this pathogen should be added to the empirical treatment [2, 13].

Initially, a dual regimen should be used for *P. aeruginosa* in high-risk patients who are critically ill or with septic shock [2, 13]. If the pathogen in the ICU may be *Actinobacter* spp., colistin should be used as the second agent. The agents for high-risk patients are displayed in table 3.

Key points

- It is important to start combined empirical treatment if there is a high risk of HAP/VAP due to MDR Gram-negative bacilli, and the patient has septic shock. If there is a high risk of MRSA in the unit, a specific antibiotic directed at this pathogen should be added [2].
- If combined therapy is started, it should be continued in the presence of pan-resistant or MDR non-fermenting Gram-negative bacteria or carbapenem-resistant Enterobacteria isolates [2].
- Combined therapy may be changed to monotherapy depending on the results of the cultures [2].

Duration of treatment

The duration of antibiotic treatment in HAP is a controversial point that has triggered spirited debate [5].

Several studies have compared different durations of antibiotic treatments. One study compared 8-day versus 15-day treatment regimens, and found no differences in mortality (18.8% in the group treated for 8 days and 17.2% in the group treated for 15 days). However, differences were observed in relapse of pneumonia. In particular, patients who had pneumonia due to non-fermenting Gram-negative bacilli, including *Pseudomonas* spp., in the 8-day regimen group presented more recurrences (40.6%) than those

TABLE 3 Agents for high-risk patients

Anti-Pseudomonal β -lactams	Aminoglycosides	Anti-ESBL producers
Imipenem Meropenem Cefepime Piperacillin/Tazobactam Ceftazidime Ceftolozane-Tazobactam [#]	Amikacin (first line) Gentamicin Tobramycin	Carbapenem (first line) Cefepime Piperacillin/Tazobactam Ceftazidime-Avibactam [#]

ESBL: extended spectrum β -lactamase. [#]: these two antibiotics were not commercialised during the guideline revision period and were not mentioned in the guidelines.

用于初始广谱经验治疗的一种或两种抗生素

表 2，针对高危患者的经验性抗生素治疗		
ICU 患多药耐药的风险高， 和/或死亡风险> 15%	无脓毒性休克	针对革兰氏阴性的单药治疗（如果对可能的 ICU 病原体有> 90%有效） ±MRSA 治疗
	脓毒性休克	覆盖革兰氏阴性铜绿假单胞菌的双 药联合治疗±MRSA 治疗

ICU：重症监护病房；MRSA：耐甲氧西林金黄色葡萄球菌。

最初，对于危重症或感染性休克的高危患者，针对铜绿假单胞菌应采用双药联合治疗方案。如果 ICU 中的病原体可能是鲍曼不动杆菌，则应使用粘菌素作为二线治疗药物。高风险患者的药物列于表 3。

表 3，高危人群的药物		
抗铜绿假单胞菌 β-内酰胺类	氨基糖苷类	抗产 ESBL 病原体
亚胺培南	阿米卡星（一线）	碳青霉烯（一线）
美罗培南	庆大霉素	头孢吡肟
头孢吡肟	妥布霉素	哌拉西林/他唑巴坦
哌拉西林/他唑巴坦		头孢他啶-阿维巴坦 [#]
头孢他啶		
头孢洛扎-他唑巴坦 [#]		

重点

- 如果由于 MDR 革兰氏阴性杆菌引起的高风险 HAP/VAP 并且患者患有脓毒性休克，则开始联合经验治疗是重要的。如果该医疗单元存在高风险的 MRSA，则应添加针对 MRSA 的抗生素。
- 如果开始联合治疗，应在泛耐药性或 MDR 非发酵革兰氏阴性细菌或耐碳青霉烯的肠杆菌分离株的存在下继续治疗。
- 根据培养结果，联合治疗可以改为单药治疗。

ESBL：超广谱 β-内酰胺酶。[#]：这两种抗生素在此期间未上市 指南修订期并未在指南中提及。

treated with the 15-day regimen (25.4%), although they presented less MDR pathogens [20]. Similarly, a Cochrane review assessing the efficacy of short *versus* long regimens (7–8 days *versus* 10–15 days) in patients with VAP concluded short-course antibiotic therapy does not increase the risk of adverse outcomes by non-fermenting Gram-negative bacilli; in addition, compared with longer treatments they may reduce MDR [21].

No differences were observed between the short and long treatments regarding the duration of mechanical ventilation or ICU stay [2].

Currently, both European and American guidelines recommend 7–8 day regimens in patients with VAP who do not have immunodeficiency, cystic fibrosis or other pulmonary problems such as pulmonary empyema, lung abscess, cavitation or necrotising pneumonia, and in those who respond well to antibiotic treatments [2].

A study using a 3-day course of antibiotics in patients with suspected HAP, but with low scores on the Clinical Pulmonary Infection Scale (CPIS) observed that this short course was associated with a reduced risk of superinfection or resistance compared with the standard duration of antibiotic treatment [21].

Rates of treatment discontinuation, due to adverse effects, appear to be similar in the two therapeutic options, although shorter treatments are likely to be associated with better tolerability [2].

Key points

- The current recommendation is to use 7–8 day treatments in patients with VAP without other respiratory comorbidities such as pulmonary empyema, lung abscess, cavitation or necrotising pneumonia, and who present a good response to treatment [2], in order to avoid the appearance of multidrug resistance. There are specific instances where longer durations of therapy may have benefit, as discussed later in this article (table 4).
- The European guidelines argue against routine antibiotic therapy for more than 3 days in patients with a low probability of HAP and no clinical deterioration within 72 h of symptom onset [2].

Clinical assessment or detection of biomarkers as a predictor of response

The ideal biomarker for appraising response to treatment is yet to be found. Theoretically, such a biomarker should be inexpensive, easily acquired and should provide results in a timely manner. This potential biomarker could help reduce antibiotic consumption and promote clinical research [1].

Several biomarkers for nosocomial pneumonia have been determined, including C-reactive protein, procalcitonin (PCT), copeptin and the mid-regional pro-atrial natriuretic peptide [1, 2]. However, there are no clinical studies comparing treatment outcomes in HAP/VAP patients managed according to the patient's bedside clinical assessment or biomarker determinations [2].

In addition to the clinical signs of respiratory infection, the clinical assessment of the patient includes radiological tests, cultures of respiratory samples, analytical determinations and the scores from various rating scales such as the CPIS [2]. It is also known that the clinical criteria for the diagnosis of VAP have high sensitivity but low specificity; other complications in critically ill ventilated patients such as atelectasis, pulmonary oedema, pulmonary embolism and pulmonary trauma may closely resemble VAP [1].

The CPIS is a semi-objective evaluation of several clinical factors of pneumonia. A study assessing its ability to identify patients with VAP who might respond to treatment concluded that serial CPIS measurements might define the clinical course of VAP, identifying patients with a good response after 3 days from the diagnosis [22]. Another score used for the assessment of these patients is the Sequential Organ Failure Assessment (SOFA) score. A direct relationship has been observed between a decrease in the SOFA score and survival [23]. The same study concluded that the measurement of PCT and C-reactive protein at the beginning of VAP infection and on day 4 could predict mortality, and that a decrease in

TABLE 4 Patients in whom short antibiotic treatment is not possible and in whom treatment should be individualised, and in whom procalcitonin may be useful to assess the efficacy and duration of antibiotic treatment

Inadequate initial antibiotic treatment
Severely immunocompromised patients (neutropenia or stem cell transplant)
Highly antibiotic-resistant pathogens
<i>Pseudomonas aeruginosa</i>
Carbapenem-resistant <i>Acinetobacter</i> spp.
Carbapenem-resistant <i>Enterobacteriaceae</i>
Second-line antibiotic treatment (e.g. colistin, tigecycline)

either one of these markers was a predictor of survival [23]. Similar results were observed in other studies which measured these markers on days 1, 3 and 7, confirming that PCT levels on day 3 were a strong predictor of mortality [2]. However, it should be emphasised that PCT has limited value in cases of renal failure, haemodialysis and resuscitated cardiac arrest [24].

For copeptin, studies indicate that its levels at the onset of the VAP episode were lower in eventual survivors than in eventual non-survivors [2].

Key points

- There are no studies comparing management of HAP/VAP patients through sequential evaluation of biomarkers. The current recommendation is to use clinical criteria to decide whether or not to initiate antibiotic treatment or follow-up [2, 13].
- PCT alone is the greatest predictor of mortality risks [25].
- Biomarkers such as copeptin and the SOFA score can predict mortality in patients with VAP [25].

PCT as a marker of treatment duration in patients with nosocomial pneumonia with severe sepsis or VAP

Although PCT may be limited as a marker of treatment response, it has been abundantly studied and it is the most common biomarker evaluated in daily clinical practice [1]. Among the studies evaluating its usefulness for predicting VAP, one systematic review of seven studies found that high plasma PCT levels were associated with an increased risk of pneumonia [26]. Another study found that high baseline PCT levels were associated with lower survival [1].

A meta-analysis and a Cochrane review also indicated that the use of clinical algorithms based on PCT levels produce a significant reduction in antibiotic consumption without increasing mortality rates or treatment failure [27, 28].

A later study conducted in China with 115 critically ill patients with VAP found that high PCT levels were associated with an increased risk of mortality within 2 months of diagnosis [29]. An open prospective study conducted with more than 1500 patients randomised to be treated following PCT results or with standard management, found that the average duration of antibiotic treatment in the PCT group was 5 days (range 3–9 days), compared with 4 days (range 4–11 days) in the standard antibiotic treatment group; 28-day mortality rates were 20% and 25%, respectively [30]. Other studies have shown that routine determination of serum PCT shortens the duration of antibiotic treatment by ~3 days and significantly lowers 28-day mortality [2].

It should be highlighted that inappropriate initial antibiotic treatment may delay the clinical response. Serial PCT measurement may help to plan the duration of antibiotic treatment, although this practice has not yet been validated for decision making upon initiation of treatment [2]. Similarly, it has not been possible to determine the shortest duration of appropriate antibiotic treatment in severely immunocompromised patients [2].

The European guidelines indicate that serial measurement of PCT serum levels can be performed together with clinical assessment in specific clinical circumstances (table 4) in order to shorten the duration of antibiotic treatment [2].

Key points

- Since the expected duration of antibiotic treatment in patients with HAP/VAP is 7–8 days, performing serial determinations of PCT levels has marginal effects on shortening antibiotic treatment in patients with a good response to initial treatment [2].
- Neither the initiation nor the duration of antibiotic treatment should depend solely on biomarkers [31].

Topical application of non-absorbable antimicrobials in patients undergoing mechanical ventilation for more than 48 h

The oral flora of patients admitted to the hospital rapidly shifts to a predominance of aerobic Gram-negative pathogens that can be aspirated into the lower respiratory tract, ultimately resulting in the development of pneumonia. Therefore, appropriate hygiene of the oral cavity of hospitalised patients is mandatory. However, whether the use of oral antiseptics can reduce the incidence of VAP is still elusive [32].

Several systematic reviews have compared the use of oral chlorhexidine to prevent VAP in patients admitted to the ICU [2]. A meta-analysis of clinical trials including more than 3500 patients reported fewer respiratory infections in patients undergoing cardiac surgery (three studies) treated with oral chlorhexidine, although no differences in VAP were detected in studies of patients admitted to other ICUs [33]. Of note, oral chlorhexidine did not improve survival, duration of mechanical ventilation, or

ICU length of stay in any ICU population (13 studies) [33]. In a later retrospective study of more than 5500 patients undergoing mechanical ventilation, the same authors reported that the daily use of chlorhexidine was associated with a lower risk of VAP, but higher mortality risk, possibly due to the aspiration of chlorhexidine and the development of acute respiratory distress syndrome [34].

Given these contradictory results, and the absence of a clear clinical benefit to offset the possible increase in mortality associated with chlorhexidine, the European guidelines did not issue a recommendation regarding its use [2].

To reduce the incidence of infectious complications in patients undergoing mechanical ventilation, selective oral or digestive decontamination (SOD and SDD, respectively) can be applied [2]. SDD involves the prevention of colonisation by both Gram-negative and Gram-positive bacteria and yeasts, through topical use of non-absorbable antibiotics in the oropharynx and the gastrointestinal tract, with or without parenteral antibiotic [3]. Oral decontamination with chlorhexidine is an alternative antiseptic in ecological niches with high levels of antibiotic resistance [3].

Studies comparing SOD with non-absorbable topical antibiotics indicate a reduction in the incidence of VAP, with no differences in the duration of mechanical ventilation or ICU stay. However, some studies found differences in mortality and others did not, sustaining controversy [2]. The effectiveness of SDD with non-absorbable topical antibiotics in the oropharynx and in the digestive tract has been evaluated in different clinical studies with a consistent reduction in mortality [35, 36].

Another meta-analysis evaluating resistance with the use of SOD and SDD or usual care indicated that there were no differences in the prevalence of colonisation or infection with resistant Gram-positives, including MRSA and vancomycin-resistant Enterococci, although a reduction of Gram-negative bacilli resistant to polymyxin and resistant to third-generation cephalosporins was found in patients who received selective decontamination [37].

In settings with low levels of antibiotic resistance, SOD (with non-absorbable topical antibiotics) and SDD (with administration of non-absorbable topical antibiotics in the oropharynx and gastrointestinal tract, and intravenous antibiotics) may be associated with reductions in nosocomial pneumonia and death. The potential effects of these antibiotics on antimicrobial resistance are uncertain [2].

Key points

- Because of the contradictory results reported, the European guidelines do not make any recommendations on the use of chlorhexidine for performing SOD in patients requiring mechanical ventilation [2].
- There are no major differences between benefits associated with SOD and SDD. Therefore, the European guidelines recommend the use of SOD rather than SDD, especially in environments with low resistance rates and low antibiotic consumption, in order to avoid the use of supplementary intravenous antibiotics [2].

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· 诊疗方案 ·

中国成人医院获得性肺炎与呼吸机相关性肺炎诊断和治疗指南(2018 年版)



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中华医学会呼吸病学分会感染学组

医院获得性肺炎(hospital-acquired pneumonia, HAP)与呼吸机相关性肺炎(ventilator-associated pneumonia, VAP)是我国最常见的医院获得性感染, 诊断和治疗较为困难, 病死率高。我国于 1999 年发表了“医院获得性肺炎诊断和治疗指南(草案)”^[1], 迄今已近 20 年, 在此期间国内外发表了许多 HAP/VAP 相关指南并历经更新^[2-10]。随着相关研究的日益深入, HAP/VAP 的定义在发生变化, 流行病学、病原学、临床诊断和治疗等方面也积累了大量新的研究成果, 特别是我国自己的研究证据日渐增多, 结果显示我国 HAP/VAP 在病原学分布和耐药率方面与国外有较大差异。因此, 需要对原有的指南进行修订, 以更好地指导临床实践。

本指南由中华医学会呼吸病学分会感染学组组织修订。经过多次现场工作会议, 确定了 HAP/VAP 的整体框架和主要更新内容; 在遵循循证医学证据的基础上, 经全体学组委员反复讨论, 形成统一意见, 并广泛征求国内外相关领域专家的意见后, 经过多次修改, 最终定稿。证据等级和推荐等级参照“中国成人社区获得性肺炎(community-acquired pneumonia, CAP)诊断和治疗指南(2016 年版)”^[11]。证据等级是对研究证据质量的评价, 推荐等级是对一项干预措施利大于弊的确定程度的评价(表 1)。一般来讲, 证据等级越高, 推荐等级也越高, 但有时证据等级和推荐等级并不完全对应, 还需要权衡证据的来源、患者的意愿、价值观和资源消耗等做出判断。我们强调, 在同等循证医学证据等级的前提下, 优先采纳我国的证据和研究成果。

本指南的适用范围为年龄 ≥ 18 周岁的非免疫缺陷的 HAP/VAP 患者, 主体分为 8 个部分及 1 个附件。期望通过本次修订和推广, 进一步规范我国 HAP/VAP 的诊断和治疗。

表 1 证据等级和推荐等级

证据等级与推荐等级	说明
证据等级	
等级 I (高等级)	高质量的随机对照临床研究(RCT)、权威指南以及高质量的系统综述和荟萃分析
等级 II (中等级)	有一定研究局限性的 RCT 研究(如无隐藏分组、未设盲、未报告失访)、队列研究、病例系列研究及病例对照研究
等级 III (低等级)	病例报道、专家意见及无临床资料的抗菌药物体外药敏试验结果
推荐等级	
A(强推荐)	该方案绝大多数患者、医师和政策制定者均会采纳
B(中度推荐)	该方案多数人会采纳, 但仍有部分人不采纳, 要结合患者具体情况作出体现其价值观和意愿的决定
C(弱推荐)	证据不足, 需要患者、医师和政策制定者共同讨论决定

一、定义

HAP 是指患者住院期间没有接受有创机械通气、未处于病原感染的潜伏期, 而于入院 48 h 后新发生的肺炎。VAP 是指气管插管或气管切开患者接受机械通气 48 h 后发生的肺炎, 机械通气撤机、拔管后 48 h 内出现的肺炎也属于 VAP 范畴^[2-3]。

HAP 的早期定义为任何发生在医院内的、由医院环境中存在的病原菌引起的肺实质感染。1999 年我国“医院获得性肺炎诊断和治疗指南(草案)”^[1]中 HAP 的定义包括了建立人工气道和机械通气后发生的肺炎。以往国内外众多关于 HAP 的临床研究混杂因素较多, 包括了一部分机械通气的患者, 但均认为 VAP 是 HAP 的特殊类型。由于 HAP 和 VAP 在临床特征、经验性治疗和预防策略上存在较大的差异, 2005 年版美国感染性疾病协会(IDSA)/美国胸科协会(ATS)制定的 HAP/VAP 指南中将原有的广义 HAP 区分为狭义的 HAP 与 VAP 两大类型^[2]。近年来的证据进一步证实 HAP 和 VAP 在经验性治疗和临床预后方面均有明显不同, 2016 年版美国 HAP/VAP 指南更新时特别强调 HAP 仅指住院后发生的没有气管插管的、与机械通

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气无关的肺炎,而 VAP 则为气管插管及机械通气后发生的肺炎,两者为完全不同的群体^[7]。由于地域与认识之间的差别,目前欧美国家对于 HAP/VAP 的定义仍然存在争议,我们仍然认为 VAP 是 HAP 的特殊类型,正是因其特殊性,本指南在病原学、治疗和预防中将 HAP 与 VAP 分别进行阐述。因病情加重而接受气管插管和机械通气治疗的 HAP 患者仍然属于 HAP,但其处理方式与 VAP 相似。接受无创通气治疗的住院患者发生的肺炎仍归于狭义的 HAP 范围。

二、流行病学

HAP/VAP 属于医院获得性感染,我国大规模的医院感染横断面调查结果显示,住院患者中医院获得性感染的发生率为 3.22% ~ 5.22%,其中医院获得性下呼吸道感染为 1.76% ~ 1.94%^[12-13]。美国的住院患者中医院获得性感染的发生率为 4.0%,其中肺炎占医院获得性感染的 21.8%^[14]。国内外研究结果均显示,包括 HAP/VAP 在内的下呼吸道感染居医院获得性感染构成比之首。

国外的研究结果表明,HAP 的发病率为(5 ~ 10)/1 000 例住院患者,占重症监护病房(intensive care unit,ICU)内感染总数的 25.0%。发生 HAP 后平均住院时间延长 7 ~ 10 d^[15],住院医疗费用大幅度增加;HAP 也是最终导致危重患者死亡的直接原因,由其引起的相关病死率高达 15.5% ~ 38.2%^[16-17]。

中国 13 家大型教学医院的 HAP 临床调查结果显示,在呼吸科病房与呼吸重症监护病房(RICU)中 HAP 的平均发生率为 1.4%,其中 RICU 为 15.3%,普通病房为 0.9%。HAP 平均全因病死率为 22.3%,其中 VAP 为 34.5%。发生 HAP 后平均住院时间达(23.8 ± 20.5) d,较非 HAP 患者延长 10 d,抗感染治疗的疗程平均达(19 ± 17) d,人均住院诊疗费用与非 HAP 住院患者比较增加了 9.0 万余元,其中 6.6 万余元医疗费用发生在 HAP 之后,治疗 HAP 的抗菌药物费用人均达 2.7 万余元^[18]。

国外大规模的研究结果显示,ICU 中 VAP 的发病率为 2.5% ~ 40.0%,或为(1.3 ~ 20.2)/1 000 机械通气日,病死率为 13.0% ~ 25.2%^[19-21]。我国一项调查结果显示,46 所医院的 17 358 例 ICU 住院患者,插管总天数为 91 448 d,VAP 的发病率为 8.9/1 000 机械通气日^[22]。机械通气患者中 VAP 的发病率为 9.7% ~ 48.4%,或为(1.3 ~ 28.9)/1 000 机械通气日,病死率为 21.2% ~ 43.2%^[18, 23-27]。

国内外的研究结果均表明,若病原菌为多重耐药(multi-drug resistance,MDR)或全耐药(pan-drug resistant,PDR)病原菌,归因病死率可高达 38.9% ~ 60.0%。VAP 的病死率与高龄、合并糖尿病或慢性阻塞性肺疾病(慢阻肺)、感染性休克(septic shock,脓毒症休克)及高耐药病原菌感染等相关^[27-31]。VAP 导致机械通气时间延长 5.4 ~ 21.8 d,ICU 滞留时间延长 6.1 ~ 20.5 d,住院时间延长 11.0 ~ 32.6 d,在美国因发生 VAP 而导致每例患者的平均住院费用增加 4 万美元^[20,32-34]。由于各项研究采用的诊断标准、研究方案、观察对象和统计学方法等不同,国内外有关 HAP/VAP 发病率和病死率的众多报道差异很大,上述临床数据仅供参考^[15-36]。

三、危险因素和发病机制

(一)危险因素

发生 HAP/VAP 的危险因素涉及各个方面,可分为宿主自身和医疗环境两大类因素,主要危险因素见表 2^[18,25,37-39]。患者往往因多种因素同时存在或混杂,导致 HAP/VAP 的发生、发展。因此,改善基础疾病,加强预防与控制感染发生的相关措施十分重要。

表 2 医院获得性肺炎/呼吸机相关性肺炎发生的危险因素

分类	危险因素
宿主自身因素	高龄
	误吸
	基础疾病(慢性肺部疾病、糖尿病、恶性肿瘤、心功能不全等)
	免疫功能受损
医疗环境因素	意识障碍、精神状态失常
	颅脑等严重创伤
	电解质紊乱、贫血、营养不良或低蛋白血症
	长期卧床、肥胖、吸烟、酗酒等
	ICU 滞留时间、有创机械通气时间
	侵袭性操作,特别是呼吸道侵袭性操作
	应用提高胃液 pH 值的药物(H ₂ -受体阻断剂、质子泵抑制剂)
	应用镇静剂、麻醉药物
	头颈部、胸部或上腹部手术
	留置胃管
	平卧位
	交叉感染(呼吸器械及手污染)

(二)发病机制

HAP 和 VAP 的共同发病机制是病原体到达支气管远端和肺泡,突破宿主的防御机制,从而在肺部繁殖并引起侵袭性损害。致病微生物主要通过两种途径进入下呼吸道:(1)误吸(aspiration),住院患者

在抗菌药物暴露、使用制酸剂或留置胃管等危险因素作用下,口腔正常菌群改变,含定植菌的口咽分泌物通过会厌或气管插管进入下呼吸道,为内源性致病微生物导致感染的主要途径^[38-39];(2)致病微生物以气溶胶或凝胶微粒等形式通过吸入(inhalation)进入下呼吸道,也是导致院内感染暴发的重要原因,其致病微生物多为外源性,如结核分枝杆菌、曲霉和病毒等。此外,HAP/VAP 也有其他感染途径,如感染病原体经血行播散至肺部、邻近组织直接播散或污染器械操作直接感染等。

VAP 的发生机制与 HAP 稍有不同:气管插管使得原来相对无菌的下呼吸道直接暴露于外界,同时增加口腔清洁的困难,口咽部定植菌大量繁殖,含有大量定植菌的口腔分泌物在各种因素(气囊放气或压力不足、体位变动等)作用下通过气囊与气管壁之间的缝隙进入下呼吸道^[40];气管插管的存在使得患者无法进行有效咳嗽,干扰了纤毛的清除功能,降低了气道保护能力,使得 VAP 发生风险明显增高;气管插管内外表面容易形成生物被膜,各种原因(如吸痰等)导致形成的生物被膜脱落,引起小气道阻塞,导致 VAP^[41]。此外,为缓解患者气管插管的不耐受,需使用镇痛镇静药物,使咳嗽能力受到抑制,从而增加 VAP 的发生风险^[42]。

HAP/VAP 可自局部感染逐步发展到脓毒症(sepsis),甚至感染性休克。其主要机制是致病微生物进入血液引起机体失控的炎症反应,导致多个器官功能障碍,除呼吸系统外,尚可累及循环、泌尿、神经和凝血系统,导致代谢异常等^[43-44]。

四、病原学

非免疫缺陷患者的 HAP/VAP 通常由细菌感染引起,由病毒或真菌引起者较少,常见病原菌的分布及其耐药性特点随地区、医院等级、患者人群及暴露于抗菌药物的情况不同而异,并且随时间而改变。我国 HAP/VAP 常见的病原菌包括鲍曼不动杆菌、铜绿假单胞菌、肺炎克雷伯菌、金黄色葡萄球菌及大肠埃希菌等。但需要强调的是,了解当地医院的病原学监测数据更为重要,在经验性治疗时应根据及时更新的本地区、本医院甚至特定科室的细菌耐药特点针对性选择抗菌药物。

(一)病原谱

相对欧美国家而言,我国大规模的 HAP 流行病学数据较少。3 项对大型综合医院 HAP 病原学的调查结果显示,我国 HAP 病原谱的构成与欧美国家有很大差异,主要体现在鲍曼不动杆菌最多,占

16.2% ~ 35.8%;铜绿假单胞菌占 16.9% ~ 22.0%,金黄色葡萄球菌占 8.9% ~ 16.0%,肺炎克雷伯菌占 8.3% ~ 15.4%^[28]。二级医院铜绿假单胞菌和鲍曼不动杆菌的比例略低于三级医院,而肺炎克雷伯菌比例高于三级医院^[18,45-46]。≥65 岁的患者是 HAP 的主要群体,约占 70%;铜绿假单胞菌比例高,鲍曼不动杆菌比例稍低^[18,45,47-48](表 3)。

我国 VAP 患者主要见于 ICU。VAP 病原谱与 HAP 略有不同,其中鲍曼不动杆菌分离率高达 35.7% ~ 50.0%,其次为铜绿假单胞菌和金黄色葡萄球菌,两者比例相当(表 4)。≥65 岁的患者中铜绿假单胞菌的分离率高于其他人群^[18,49-54]。

由于我国二级及以下医院高质量前瞻性的 HAP/VAP 流行病学研究尚不足,目前查到的文献绝大部分为回顾性研究,以上数据仅供参考。

表 3 我国医院获得性肺炎患者常见细菌的分离率(%)

菌种	三级医院 ^a		二级医院 ^[46]
	≥18 岁 ^b [18,28]	≥65 岁 ^c [45,47-48]	
鲍曼不动杆菌	20.6 ~ 25.7	7.9 ~ 14.6	18.0
铜绿假单胞菌	18.7 ~ 20.0	23.8 ~ 28.3	11.0
肺炎克雷伯菌	8.9 ~ 14.9	5.3 ~ 17.1	21.0
金黄色葡萄球菌	9.8 ~ 12.0	8.6 ~ 15.0	11.0
大肠埃希菌	3.8 ~ 7.4	9.2 ~ 11.8	8.0
阴沟肠杆菌	2.1 ~ 4.3	2.5	无数据
嗜麦芽窄食单胞菌	4.3 ~ 6.0	1.2 ~ 2.6	无数据

注:除文献[18]和[28]为全国多中心前瞻性研究外,其余文献均为单中心或局部地区回顾性研究;^a数据主要来自三级医院,且多为回顾性研究,标本类型大部分为痰标本,因此数据存在一定的局限性;^b≥18 岁人群中包含 65 岁以上人群,文献未对年龄进行分组;^c二级医院数据很少,只查到 1 篇质量较高的文献,此文献中细菌分离率进位到整数

表 4 我国呼吸机相关性肺炎患者常见细菌的分离率(%)

菌种	≥18 岁 ^[28,49-50,53-54]	≥65 岁 ^[51-52]
鲍曼不动杆菌	12.1 ~ 50.5	10.3 ~ 18.5
铜绿假单胞菌	12.5 ~ 27.5	27.7 ~ 34.6
肺炎克雷伯菌	9.0 ~ 16.1	5.1 ~ 13.9
金黄色葡萄球菌	6.9 ~ 21.4	5.8 ~ 15.4
大肠埃希菌	4.0 ~ 11.5	1.3 ~ 6.2
阴沟肠杆菌	2.0 ~ 3.4	3.1
嗜麦芽窄食单胞菌	1.8 ~ 8.6	4.6 ~ 9.6

注:除文献[28]为全国多中心前瞻性研究外,其余文献均为单中心或局部地区回顾性研究;文献中的数据主要来自三级医院,多为回顾性研究,标本类型大部分为痰标本,因此数据存在一定的局限性

(二)常见病原菌的耐药性

细菌耐药给 HAP/VAP 的治疗带来了严峻挑战。临床上 MDR 的定义是指对 3 类或 3 类以上抗

菌药物(除天然耐药的抗菌药物)耐药,广泛耐药(extensive drug resistance, XDR)为仅对 1~2 类抗菌药物敏感而对其他抗菌药物耐药, PDR 为对能得到的、在常规抗菌谱范围内的药物均耐药。

HAP/VAP 常见的耐药细菌包括碳青霉烯类耐药的鲍曼不动杆菌(carbapenem-resistant *Acinetobacter baumannii*, CRAB)、碳青霉烯类耐药的铜绿假单胞菌(carbapenem-resistant *Pseudomonas aeruginosa*, CRPA)、产超广谱 β -内酰胺酶(extended-spectrum β -lactamases, ESBLs)的肠杆菌科细菌、甲氧西林耐药的金黄色葡萄球菌(methicillin-resistant *Staphylococcus aureus*, MRSA)及碳青霉烯类耐药的肠杆菌科细菌(carbapenem resistant enterobacteriaceae, CRE)等。我国多中心细菌耐药监测网中的中国细菌耐药监测网(China surveillance network for bacterial resistance, CHINET)和中国院内感染的抗菌药物耐药监测(Chinese antimicrobial resistance surveillance of nosocomial infection, CARES)数据均显示,在各种标本中(血、尿、痰等)CRAB 的分离率高达 60%~70%, CRPA 的分离率为 20%~40%, 产 ESBLs 的肺炎克雷伯菌和大肠埃希菌的分离率分别为 25%~35% 和 45%~60%, MRSA 的分离率为 35%~40%, CRE 的分离率为 5%~18%^[55-56]。而来自痰标本中的某些耐药菌,如 MRSA 的发生率往往更高。

2007—2013 年 CARES 有关 HAP/VAP 的耐药性数据显示,MDR 鲍曼不动杆菌的分离率呈逐年上升的趋势,而 MDR 铜绿假单胞菌的分离率呈逐年下降的趋势,由 2007 年的 23.0% 下降至 2013 年的 10.3%。除了 CRE(VAP 为 0.7%, HAP 为 1.9%)外,VAP 患者其他 MDR 细菌的分离率高于 HAP,如 CRAB(63.9%, 59.8%)、CRPA(41.0%, 33.4%)、产 ESBLs 的大肠埃希菌(64.7%, 57.3%)、产 ESBLs 的肺炎克雷伯菌(47.4%, 32.4%)及 MRSA(85.7%, 74.3%)。CRE 呈上升趋势,尤其是肺炎克雷伯菌。2015 年 CARES 的数据显示,来源于我国呼吸科下呼吸道标本中分离的碳青霉烯类耐药的肺炎克雷伯菌(carbapenem-resistant *Klebsiella pneumoniae*, CRKP)占 4.9%, CRAB 占 52.1%。上述耐药菌的分离率三级医院高于二级医院,分别为 5.2% 和 2.5%、53.5% 和 33.9%。RICU 高于普通病房;产 ESBLs 肠杆菌科细菌的分离率二级医院与三级医院类似甚至更高,以产 ESBLs 的大肠埃希菌最为明显,为 63.9% 和 53.5%^[57]。

CHINET 和 CARES 的数据显示,对鲍曼不动杆菌而言,敏感率较高的抗菌药物为多黏菌素 B(97%~100%)和替加环素(85%~100%)。铜绿假单胞菌对多黏菌素、阿米卡星、哌拉西林/他唑巴坦、头孢吡肟、环丙沙星、头孢他啶、美罗培南及亚胺培南的敏感率仍在 70% 以上。大肠埃希菌和肺炎克雷伯菌对碳青霉烯类(82%~98%)、酶抑制剂复合制剂(80%~96%)及阿米卡星(90%~97%)的敏感率较高。嗜麦芽窄食单胞菌对米诺环素(81%~94%)、左氧氟沙星(76%~90%)及磺胺甲噁唑/甲氧苄啶(67%~92%)的敏感率较高。万古霉素、替考拉宁及利奈唑胺等对 MRSA 仍保持极高的抗菌活性(100% 敏感)。

应当指出,我国城市大医院(三级医院)与基层医院(二级及以下医院),无论是 HAP/VAP 的致病菌分布还是耐药性均有很大差别,而基层医院相关高质量的研究数据仍十分缺乏。因此,基层医院在确定经验性治疗方案时不能完全参照城市大医院的数据,而应尽量参考当地医院微生物学的资料。

五、诊断与鉴别诊断

(一)临床诊断标准

HAP/VAP 的临床表现及病情严重程度不同,从单一的典型肺炎到快速进展的重症肺炎伴脓毒症、感染性休克均可发生,目前尚无临床诊断的“金标准”。肺炎相关的临床表现满足的条件越多,临床诊断的准确性越高。

胸部 X 线或 CT 显示新出现或进展性的浸润影、实变影或磨玻璃影^[58-59],加上下列 3 种临床症候中的 2 种或以上,可建立临床诊断:(1)发热,体温 $>38^{\circ}\text{C}$;(2)脓性气道分泌物;(3)外周血白细胞计数 $>10 \times 10^9/\text{L}$ 或 $<4 \times 10^9/\text{L}$ ^[7]。

影像学是诊断 HAP/VAP 的重要基本手段,应常规行 X 线胸片,尽可能行胸部 CT 检查。对于危重症或无法行胸部 CT 的患者,有条件的单位可考虑床旁肺超声检查^[60-61]。技术熟练的医师操作肺超声有助于判别肺组织通气改变情况,与肺栓塞及肺不张等疾病进行鉴别^[62](I B)。在临床决策中,需根据患者情况选取一种或多种影像学检查技术,以提高早期诊断率。

(二)病原学诊断

在临床诊断的基础上,若同时满足以下任一项,可作为确定致病菌的依据。

1. 合格的下呼吸道分泌物(中性粒细胞数 >25 个/低倍镜视野,上皮细胞数 <10 个/低倍镜视野,或二

者比值 $>2.5:1$)、经支气管镜防污染毛刷(protected specimen brush, PSB)、支气管肺泡灌洗液(bronchoalveolar lavage fluid, BALF)、肺组织或无菌体液培养出病原菌,且与临床表现相符^[5]。

2. 肺组织标本病理学、细胞病理学或直接镜检见到真菌并有组织损害的相关证据^[63-64]。

3. 非典型病原体或病毒的血清 IgM 抗体由阴转阳或急性期和恢复期双份血清特异性 IgG 抗体滴度呈 4 倍或 4 倍以上变化。呼吸道病毒流行期间且有流行病学接触史,呼吸道分泌物相应病毒抗原、核酸检测或病毒培养阳性^[5]。

(三) 鉴别诊断

HAP/VAP 的临床表现和影像学缺乏特异性,需要与住院后发生的其他发热伴肺部阴影疾病相鉴别,包括感染性和非感染性疾病^[65]。

1. 其他感染性疾病累及肺部:(1) 系统性感染累及肺:如导管相关性血流感染、感染性心内膜炎,可继发多个肺脓肿;(2) 局灶性感染累及肺:如膈下脓肿、肝脓肿。鉴别要点是注重病史询问和体检,寻找肺外感染病灶及针对性进行病原学检查。

2. 易与 HAP 相混淆的常见非感染性疾病:(1) 急性肺血栓栓塞症伴肺梗死^[66];(2) 肺不张;(3) 急性呼吸窘迫综合征(acute respiratory distress syndrome, ARDS)^[67];(4) 肺水肿^[68];(5) 其他疾病:如肿瘤、支气管扩张、药源性肺病、结缔组织病及神经源性发热等。鉴别要点是评估基础疾病的控制情况,同时排除感染性发热的可能。

(四) 实验室技术在诊疗中的应用价值

临床诊断 HAP/VAP 后,应积极留取标本行微生物学检查。

1. 标本的采集:包括呼吸道、血液及胸腔积液。

呼吸道标本:主要包括痰(气道吸引物)、BALF 和肺组织。标本应尽可能先进行涂片镜检(如革兰染色、抗酸染色,必要时行氢氧化钾浮载剂镜检、六胺银染色等),再做培养、抗原及核酸定量等检测(ⅢC)。呼吸道标本可通过非侵入性或侵入性方法获得。非侵入性方法指经咳痰、鼻咽拭子、鼻咽吸引物或气管导管内吸引(endotracheal aspiration, ETA)收集标本;侵入性方法指经支气管镜留取下呼吸道标本(如 BALF)、经支气管镜或经皮肺穿刺活检留取组织标本等。与非侵入性标本半定量培养相比,侵入性标本定量对判断预后并没有优势^[69-70]。气道分泌物定量培养技术要求高,不一定能改变预后,仅限在必要时、有条件的单位开展。对于 HAP 患

者,建议先通过非侵入性方法留取呼吸道分泌物涂片及半定量培养;经验性治疗无效、疑似特殊病原菌感染或采用常规方法获得的呼吸道标本无法明确致病菌时,再通过侵入性方法采集标本行微生物学检查(ⅢB)。对于 VAP 患者,由于人工气道提供了有利条件,除了常规经气管导管吸取呼吸道分泌物涂片和半定量培养外,可通过侵入性方法采集标本,以明确病原菌;每周 2 次的气道分泌物培养有助于预测 VAP 的病原学^[71];若定量培养结果已转为阴性,有助于判断是否需要及时停用抗菌药物^[72-73](ⅡB)。

血液:血培养是诊断菌血症的重要方法。成人每次应采集 2~3 套,每套从不同穿刺点进行采集。从同一穿刺点采集的血液标本通常分别注入需氧和厌氧培养瓶,每瓶采血量为 8~10 ml,以提高阳性率^[58]。采血应在寒战或发热初起时进行,抗菌药物应用之前采集最佳^[74]。

胸腔积液:HAP/VAP 合并胸腔积液时,可行胸腔穿刺抽液送常规、生化、涂片(革兰染色、抗酸染色等)、培养等检测。

2. 病原学结果的判断方法:包括涂片镜检、微生物培养、病原体抗原检测及高通量测序等分子生物学技术。

涂片镜检:对于 VAP 患者,经气管导管吸引分泌物涂片革兰染色,每个高倍镜视野检出 $\geq 2\%$ 的白细胞有微生物吞噬现象^[75],对病原学诊断有一定的参考价值,可作为初始经验性抗感染治疗的依据^[76-81]。

微生物培养:传统观点认为,痰定量培养的细菌浓度 $\geq 10^7$ cfu/ml、经 ETA 细菌培养浓度 $\geq 10^5$ cfu/ml、经 BALF 培养细菌浓度 $\geq 10^4$ cfu/ml 或经 PSB 所取样本培养的细菌浓度 $\geq 10^3$ cfu/ml 为致病菌的可能性较大^[82-84]。机械通气患者的气道和(或)人工气道易有不动杆菌属、假单胞菌属或念珠菌属定植,培养到这些微生物时需鉴别是否为致病菌。建议综合评估以下三方面来判定:(1) 宿主情况:免疫状态、基础疾病及目前临床表现等;(2) 细菌因素:气道分泌物涂片镜检是否存在白细胞吞噬现象及与培养结果是否一致,分离到的细菌菌落计数;(3) 抗菌药物因素:近期抗菌药物的使用情况,针对该病原菌治疗后临床症状是否改善。如果患者无与肺炎相关的临床表现及实验室依据,气道分泌物检出的细菌很可能为定植或污染。虽然血培养对早期明确诊断、针对性选择抗菌药物有重要意义,但即使血培养

阳性,亦不能判定细菌来自于肺内,因仅 10% ~ 37% 的菌血症源自肺部^[83,85-89]。胸腔积液培养阳性有助于明确病原学诊断,标本来源于胸腔穿刺术或首次置管时结果更可靠;而由已留置的胸管直接抽取时则需谨慎解读其结果,注意污染的可能(ⅢC)。呼吸道病毒培养阳性可作为确诊病毒感染的依据。

病原体抗原检测:肺炎链球菌和嗜肺军团菌尿抗原检测及血清隐球菌荚膜多糖抗原检测的敏感度和特异度均很高。血清 1,3-β-D 葡聚糖检测(G 试验)、血清或 BALF 半乳甘露聚糖抗原检测(GM 试验)连续 2 次(BALF 仅需 1 次)阳性,具有辅助诊断价值。

高通量测序等分子生物学技术:基于测序技术的临床宏基因组学,通过分析临床标本中微生物的 DNA 或 RNA 含量与丰度判断致病菌,显著提高了病原检测的敏感度,缩短了检测时间,对罕见病原菌感染的诊断具有优势,可审慎地用于现有成熟检测技术不能确定的病原体,或经恰当与规范抗感染治疗无效的患者,但检测结果需结合流行病学和临床特征综合评估是否为致病菌。但该技术应用于临床尚需解决许多问题,包括标本中人类基因组的干扰、生物信息学分析、结果判断和解释等,特别是呼吸道本身为非无菌状态,大量定植菌核酸的存在给临床结果的判读带来了挑战^[90-92]。

3. 感染相关生物标志物:C 反应蛋白(c-reactive protein,CRP)和降钙素原(procalcitonin,PCT)是临床上最常用的鉴别感染与否的生物标志物^[93-94]。机体感染时 CRP 明显升高,但特异度较低^[95-96],可作辅助诊断的参考(ⅡC)。PCT 对细菌感染和脓毒症反应迅速^[97-98],是较 CRP 更特异的细菌性感染指标^[93,99]。PCT 数值越高,提示细菌感染越严重,存在细菌性 VAP 及脓毒症的可能性越大^[97,100]。其诊断效率虽受先前抗菌药物暴露的影响,但不受疾病类型及 VAP 发生时间的影响,且是 VAP 患者死亡的重要预测因素^[100]。在病程中动态监测 PCT 水平,有助于指导抗菌药物的疗程^[101-104](ⅡB)。应强调的是:CRP 和 PCT 不能代替微生物学检查;任何与感染相关的生物标志物均需要与临床表现结合,综合判断,其动态变化往往比绝对值参考价值更大^[94]。为了提高治疗的成功率,不要因等待检测结果而延误早期经验性抗菌治疗的时机。

(五)病情严重程度评估

HAP/VAP 病情严重程度的评估对于经验性选择抗菌药物和判断预后有重要意义,但目前尚无统

一的标准。常用的病情严重程度评分系统有序贯器官衰竭(sequential organ failure assessment,SOFA,表 5)评分及急性生理与慢性健康(acute physiology and chronic health evaluation,APACHE)Ⅱ评分等。各评分系统预测死亡的效力相当,病死率随着分值的升高而升高^[105]。SOFA 评分侧重于器官功能不全或衰竭的评估,与 VAP 的复发相关^[106-107]。APACHEⅡ>16 分是 VAP 患者死亡的独立预测因素^[106-109]。有学者建议可使用 SOFA 评分作为判断病情危重程度的标准之一。对于非 ICU 患者,快速 SOFA(qSOFA)评分简单方便,预测住院病死率的效能优于 SOFA 评分^[110]。qSOFA 评分由意识改变、收缩压≤100 mmHg(1 mmHg=0.133 kPa)和呼吸频率≥22 次/min 构成,当 qSOFA 评分≥2 时,应警惕危重症的发生。

本指南认为,HAP 患者若符合下列任一项标准,可考虑存在高死亡风险,视为危重症患者:(1)需要气管插管机械通气治疗;(2)感染性休克经积极液体复苏后仍需要血管活性药物治疗。相对于狭义 HAP,一般 VAP 应视为危重症患者,但有些患者因原发疾病不能有效控制,需要长期有创机械通气,若发生 VAP(有时是反复发生)并非均为危重症,可依据 qSOFA 评分或 APACHE Ⅱ评分辅助判断。

六、临床诊疗思路

第 1 步:依据症状、体征和影像学征象确定 HAP/VAP 的临床诊断是否成立,与其他发热伴肺部阴影的疾病进行初步鉴别,并评估病情的严重程度(是否合并脓毒症)、可能的病原菌及其耐药危险因素。

第 2 步:尽快采集呼吸道分泌物和血液标本送病原微生物及感染相关生物标志物检测,并立即开始经验性抗感染治疗,根据抗菌药物的理化特性和药代动力学/药效学(pharmacokinetic/pharmacodynamics,PK/PD)参数确定药物的种类、单药还是联合、负荷剂量和维持剂量。

第 3 步:48~72 h 后对实验室检测结果和初始抗菌治疗反应进行再评估,按不同情况分别处理:(1)临床显示早发性治疗反应,病原菌培养获得有意义的阳性结果时,改为目标治疗(降阶梯);(2)临床病情稳定、无脓毒症或病原菌培养阴性时,试停抗菌药物进行观察;(3)临床病情无改善、病原菌培养阳性时,应仔细评估阳性结果的临床意义(是否为致病菌,有无复数菌感染)、是否有并发症或其他部位感染,从而调整抗菌药物治疗方案(根据抗

表 5 序贯器官衰竭评分的预测指标与评分标准

病变部位	预测指标	评分标准(分)				
		0	1	2	3	4
呼吸系统	氧合指数 (mmHg)	≥400	300 ~ 399	200 ~ 299	100 ~ 199, 呼吸支持	<100, 呼吸支持
凝血系统	血小板计数(×10 ⁹ /L)	>150	101 ~ 150	51 ~ 100	21 ~ 50	<21
肝脏系统	胆红素(μmol/L)	<20	20 ~ 32	33 ~ 101	102 ~ 204	>204
心血管系统	平均动脉压(mmHg)	≥70	<70			
	儿茶酚胺类药物剂量(μg·kg ⁻¹ ·min ⁻¹)			多巴胺≤5 或多巴酚丁胺(任何剂量)	多巴胺>5 或肾上腺素≤0.1 或去甲肾上腺素≤0.1	多巴胺>15 或肾上腺素>0.1 或去甲肾上腺素>0.1
中枢神经系统	Glasgow 评分	15	13 ~ 14	10 ~ 12	6 ~ 9	<6
肾脏	肌酐(μmol/L)	<110	110 ~ 170	171 ~ 299	300 ~ 440	>440
	24 h 尿量(ml)				201 ~ 500	<200

注:取 6 项评分指标的总和,每日评估时应取每日最差值;1 mmHg=0.133 kPa

菌谱是否覆盖、有无耐药、体内疗效与体外敏感性是否一致、抗菌药物的 PK/PD 等因素);(4)临床病情无改善、病原菌培养阴性时,需要拓宽诊断思路,进一步完善病原学检测和非感染性病因的检查。

第 4 步:继续动态监测病情,观察感染相关生物标志物水平的变化,评估第 3 步中不同情况的处理结果,并确定抗菌治疗的疗程和其他后续处理。

七、治疗

HAP/VAP 的治疗包括抗感染治疗、呼吸支持技术、器官功能支持治疗、非抗菌药物治疗等综合治疗措施,其中抗感染是最主要的治疗方式,包括经验性抗感染治疗和病原(目标)治疗。

(一)经验性抗感染治疗

1. 经验性抗感染治疗原则:(1)抗感染治疗时机的选择:在确立 HAP/VAP 临床诊断并安排病原学检查后,应尽早进行经验性抗感染治疗;如果延迟治疗,即使药物选择恰当,仍可导致病死率增加及住院时间延长^[111-112],因此,HAP 和 VAP 患者应尽早进行抗菌药物的经验性治疗(ⅢA)。(2)正确评估 MDR 菌感染的危险因素:HAP 和 VAP 致病菌的常见耐药菌感染危险因素见表 6。此外,表 7 中列举了几种常见 MDR 菌感染相对特定的危险因素。

2. 初始经验性治疗抗菌药物的选择:HAP/VAP 初始经验性抗菌治疗的策略见图 1 和图 2。应根据患者的病情严重程度、所在医疗机构常见的病原菌、耐药情况及患者耐药危险因素等选择恰当的药物,同时也应兼顾患者的临床特征、基础疾病、器官功能状态、药物的 PK/PD 特性、既往用药情况和药物过敏史等相关因素选择抗菌药物(表 8,9)^[113]。我国不同地区和不同等级医院的病原学及其耐药性差别较大,所以治疗推荐仅仅是原则性的,需要结合患者的具体情况进行选择:(1)有条件的医院应定期制

表 6 HAP 和 VAP 中 MDR 菌感染的危险因素

分类	MDR 菌感染危险因素 ^[114-121]
证据充分的耐药危险因素	
HAP	前 90 d 内曾静脉使用过抗菌药物
VAP	前 90 d 内曾静脉使用过抗菌药物 住院 5 d 以上发生的 VAP 病情危重、合并感染性休克 发生 VAP 前有 ARDS 接受持续肾脏替代治疗等
可能的耐药危险因素	
HAP/VAP	有 MDR 菌感染或定植史 反复或长期住院病史 入住 ICU 存在结构性肺病 重度肺功能减退 接受糖皮质激素,或免疫抑制剂治疗,或存在免疫功能障碍 在耐药菌高发的医疗机构住院 皮肤黏膜屏障破坏(如气管插管、留置胃管或深静脉导管等)

注:MDR:多重耐药;HAP:医院获得性肺炎;VAP:呼吸机相关性肺炎

表 7 常见 MDR 菌感染相对特定的危险因素

耐药菌类别	耐药菌感染相对特定危险因素
产 ESBLs 肠杆菌科细菌	有产 ESBLs 菌感染或定植史,近 90 d 内曾经使用三代头孢菌素 ^[122-125]
MRSA	呼吸道存在 MRSA 定植 ^[126] ,所在医疗单元内 MRSA 分离率高
铜绿假单胞菌	皮肤黏膜屏障破坏,免疫功能低下,慢性结构性肺病,重度肺功能减退等 ^[116-117]
鲍曼不动杆菌	严重基础疾病,鲍曼不动杆菌定植
CRE	CRE 定植,近 90 d 内使用过碳青霉烯类药物、高龄、病情危重、外科手术等 ^[122]

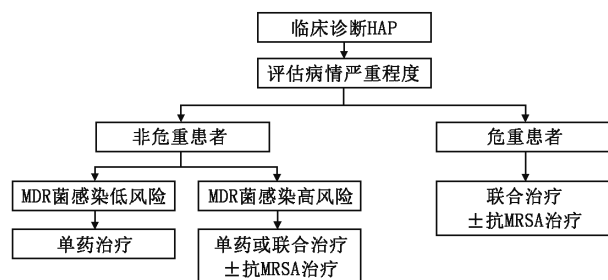
注:ESBLs:超广谱 β-内酰胺酶;MRSA:耐甲氧西林金黄色葡萄球菌;CRE:碳青霉烯类耐药肠杆菌科细菌

定并发布 HAP/VAP 致病菌组成及其药敏谱^[127-129];经验性治疗方案应依据所在医院的 HAP/VAP 病原

表 8 HAP(非 VAP)的初始经验性抗感染治疗建议

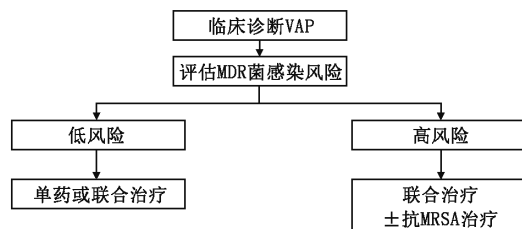
非危重患者		危重患者 ^a
MDR 菌感染低风险	MDR 菌感染高风险	
单药治疗	单药或联合治疗 ^{b,c}	联合治疗 ^{b,c}
抗铜绿假单胞菌青霉素类(哌拉西林等) 或 β-内酰胺酶抑制剂合剂(阿莫西林/克拉维酸、哌拉西林/他唑巴坦、头孢哌酮/舒巴坦等) 或 第三代头孢菌素(头孢噻肟、头孢曲松、头孢他啶等) 或 第四代头孢菌素(头孢吡肟、头孢噻利等) 或 氧头孢烯类(拉氧头孢、氟氧头孢等) 或 喹诺酮类(环丙沙星、左氧氟沙星、莫西沙星等)	抗铜绿假单胞菌 β-内酰胺酶抑制剂合剂(哌拉西林/他唑巴坦、头孢哌酮/舒巴坦等) 或 抗铜绿假单胞菌头孢菌素类(头孢他啶、头孢吡肟、头孢噻利等) 或 抗铜绿假单胞菌碳青霉烯类(亚胺培南、美罗培南、比阿培南等) 以上药物单药或联合下列中的一种 抗铜绿假单胞菌喹诺酮类(环丙沙星、左氧氟沙星等) 或 氨基糖苷类(阿米卡星、异帕米星等) 有MRSA 感染风险时可联合 糖肽类(万古霉素、去甲万古霉素、替考拉宁等) 或 利奈唑胺	抗铜绿假单胞菌 β-内酰胺酶抑制剂合剂(哌拉西林/他唑巴坦、头孢哌酮/舒巴坦等) 或 抗铜绿假单胞菌碳青霉烯类(亚胺培南、美罗培南、比阿培南等) 以上药物联合下列中的一种 抗铜绿假单胞菌喹诺酮类(环丙沙星、左氧氟沙星) 或 氨基糖苷类(阿米卡星、异帕米星等) 有XDR 阴性菌感染风险时可联合下列药物 多黏菌素(多黏菌素 B、多黏菌素 E) 或 替加环素 有 MRSA 感染风险时可联合 糖肽类(如万古霉素、去甲万古霉素、替考拉宁等) 或 利奈唑胺

注:MDR:多重耐药,XDR:广泛耐药;^a 危重患者包括需要机械通气和感染性休克患者;^b 通常不采用 2 种 β-内酰胺类药物联合治疗;^c 氨基糖苷类药物仅用于联合治疗



注:HAP:医院获得性肺炎;MDR:多重耐药;MRSA:耐甲氧西林金黄色葡萄球菌

图 1 HAP 经验性抗菌治疗推荐



注:VAP:呼吸机相关性肺炎;MDR:多重耐药;MRSA:耐甲氧西林金黄色葡萄球菌

图 2 VAP 经验性抗菌治疗推荐

单元内的患者,建议经验性覆盖 MRSA(ⅢC)。(3)对于具有 MDR 铜绿假单胞菌和其他 MDR 革兰阴性杆菌感染的危险因素或死亡风险较高的 HAP/VAP 患者,建议联合使用两种不同类别的抗菌药物;对于非危重、无 MDR 感染危险因素的 HAP/VAP 患者,经验性治疗时可只使用一种抗菌药物(ⅢA)。(4)建议多黏菌素和替加环素仅用于具有 XDR 革兰阴性菌感染风险的患者。(5)在伴有脓毒症的 HAP/VAP 患者,需要根据抗菌药物的理化特性、PK/PD 特点和器官(特别是肾脏和肝脏)功能障碍程度调整药物的负荷剂量与维持剂量。

(二)HAP/VAP 的病原治疗

病原治疗即目标性(针对性)抗感染治疗,是指针对已经明确的感染病原菌,参照体外药敏试验结果制定相应的抗菌药物治疗方案(窄谱或广谱、单药或联合用药)。HAP/VAP 的病原治疗需注意以下几点。

1. 抗感染治疗前或调整方案前尽可能送检合格的病原学标本,并评估检查结果,排除污染或定植的干扰。
2. 根据检测出的病原菌及其药敏试验结果,在初始经验性治疗疗效评估的基础上酌情调整治疗方案。

谱及药敏试验结果制定^[116,130-131](ⅢA)。(2)呼吸道存在 MRSA 定植或住在 MRSA 分离率高的医疗

表 9 VAP 患者的初始经验性抗感染治疗建议

MDR 菌感染低风险	MDR 菌感染高风险
单药或联合治疗 ^a 抗铜绿假单胞菌青霉素类(哌拉西林等) 或 抗铜绿假单胞菌的第三四代头孢菌素(头孢他啶、头孢吡肟、头孢噻利等) 或 β-内酰胺酶抑制剂合剂(哌拉西林/他唑巴坦、头孢哌酮/舒巴坦等) 或 抗铜绿假单胞菌碳青霉烯类(亚胺培南、美罗培南、比阿培南等) 或 喹诺酮类(环丙沙星、左氧氟沙星等) 或 氨基糖苷类(阿米卡星、异帕米星等) ^b	联合治疗 ^a 抗铜绿假单胞菌 β-内酰胺酶抑制剂合剂(哌拉西林/他唑巴坦、头孢哌酮/舒巴坦等) 或 抗铜绿假单胞菌第三四代头孢菌素(头孢他啶、头孢吡肟、头孢噻利等) 或 氨基曲南 或 抗铜绿假单胞菌碳青霉烯类(亚胺培南、美罗培南、比阿培南等) 或 抗假单胞菌喹诺酮类(环丙沙星、左氧氟沙星等) 或 氨基糖苷类(阿米卡星、异帕米星等) 有 XDR 阴性菌感染风险时可联合下列药物 多黏菌素类(多黏菌素 B、多黏菌素 E) 或 替加环素 有 MRSA 感染风险时可联合 糖肽类(万古霉素、去甲万古霉素、替考拉宁) 或 利奈唑胺

注:^a 特殊情况下才使用 2 种 β-内酰胺类药物联合治疗;^b 氨基糖苷类药物仅用于联合治疗

表 10 HAP/VAP 常见耐药菌抗感染治疗方案

病原菌类别	病原菌	推荐药物	备注
革兰阳性球菌	MRSA	糖肽类(万古霉素、去甲万古霉素、替考拉宁)或利奈唑胺	万古霉素等糖肽类和利奈唑胺大致等效 ^[7] 万古霉素谷浓度应维持在 10 ~ 15 mg/L ^[132] ;重症患者应给予 25 ~ 30 mg/kg 的负荷剂量 ^[133] ,谷浓度维持在 10 ~ 20 mg/L ^[132,134] 替考拉宁应给予 6 ~ 12 mg/kg (或 400 ~ 800 mg), 1 次/12 h 的负荷剂量,连续 3 次,再以 400 mg, 1 次/d 维持 ^[135-138]
	VRE	利奈唑胺或替考拉宁	VRE 较少引起肺部感染,需排除定植和污染 ^[139] ; VRE 对头孢菌素类等多种抗菌药物天然耐药,应结合药敏试验结果选择 ^[139-141] ;替考拉宁仅用于 VanB 型 VRE 感染 ^[139,142]
肠杆菌科细菌	产 ESBLs 肠杆菌科细菌	轻中度感染:头霉素类(头孢西丁、头孢美唑、头孢米诺)、氧头孢烯类(拉氧头孢、氟氧头孢)、β-内酰胺酶抑制剂合剂(哌拉西林/他唑巴坦、头孢哌酮/舒巴坦) 中重度感染:碳青霉烯类(亚胺培南、美罗培南、比阿培南),或联合治疗方案 联合治疗方案:碳青霉烯类 + 喹诺酮类或氨基糖苷类, β-内酰胺酶抑制剂合剂 + 喹诺酮类或氨基糖苷类	方案应结合药敏试验结果及个体因素选择 ^[7] 大部分仅需单药治疗,仅少数严重感染需要联合用药 ^[143]
	CRE	主要治疗药物:多黏菌素类(多黏菌素 B、多黏菌素 E)、替加环素、头孢他啶/阿维巴坦 联合治疗药物:磷霉素、氨基糖苷类(阿米卡星、异帕米星)、碳青霉烯类(亚胺培南、美罗培南、比阿培南) 当碳青霉烯类 MIC 为 4 ~ 16 μg/ml 时,需与其他药物联合使用 ^[122,144-145] ;增加给药次数或剂量,延长滴注时间 ^[146] 当碳青霉烯类 MIC > 16 μg/ml 时,应避免使用 ^[122] 当多黏菌素 B 或 E 的 MIC ≤ 2 μg/ml 时可使用,XDR 或 PDR 菌感染时可同时辅助吸入多黏菌素 E ^[147-148] 当多黏菌素 B 或 E MIC > 2 μg/ml,联合使用敏感药物(如磷霉素、替加环素) ^[149-150] 。因缺乏证据,当 MIC > 8 μg/ml 时需慎用 联合治疗方案 含碳青霉烯类方案:碳青霉烯类 + 多黏菌素或替加环素;碳青霉烯类 + 多黏菌素 + 替加环素 不含碳青霉烯类方案:替加环素 + 氨基糖苷类或磷霉素;多黏菌素 + 替加环素或磷霉素;氨基糖苷类 + 磷霉素或氨基曲南	应以早期、足量、联合为原则 ^[151-155] 针对我国流行的碳青霉烯酶(主要是 KPC);头孢他啶/阿维巴坦 ^[156-158] 多黏菌素 B 剂量可增加至 300 mg/d ^[159-160] ,美罗培南可用至 2 g,1 次/8 h,比阿培南可用至 0.3 ~ 0.6 g, 1 次/6 ~ 8 h,均持续静脉滴注 3 h 以上 ^[161-163] 2 种碳青霉烯类联用:厄他培南 + 多利培南,或亚胺培南,或美罗培南 ^[164-167] ;由于体内研究证据较少,需谨慎使用 ^[164,168-169]

续表

病原菌类别	病原菌	推荐药物	备注
非发酵菌	铜绿假单胞菌	具有抗铜绿假单胞菌活性药物: 头孢菌素类(头孢他啶、头孢吡肟、头孢噻利)、碳青霉烯类(亚胺培南、美罗培南、比阿培南)、β-内酰胺酶抑制剂合剂(哌拉西林/他唑巴坦、头孢哌酮/舒巴坦)、喹诺酮类(环丙沙星、左氧氟沙星)、氨基糖苷类(阿米卡星、妥布霉素、异帕米星)、氨基糖苷类(多黏菌素 B、多黏菌素 E) 单药治疗: 非 MDR 轻症患者且无明显基础疾病时, 可单独应用除氨基糖苷类外的具有抗铜绿假单胞菌活性的抗菌药物 联合方案 MDR 菌 抗铜绿假单胞菌 β-内酰胺类 + 氨基糖苷类、喹诺酮类、磷霉素 多黏菌素 + β-内酰胺类、环丙沙星、磷霉素 氨基糖苷类 + 环丙沙星、左氧氟沙星 XDR 菌 多黏菌素 + β-内酰胺类 + 环丙沙星、磷霉素 XDR 或 PDR 菌引起的肺炎: 可在静脉用药的基础上, 雾化吸入氨基糖苷类(如妥布霉素、阿米卡星)^[170-171]、多黏菌素 E^[172] 双 β-内酰胺类联用: 头孢他啶或氨基糖苷类 + 哌拉西林/他唑巴坦、头孢他啶 + 头孢哌酮/舒巴坦; 头孢他啶或头孢吡肟 + 氨基糖苷类^[173-174] 对碳青霉烯类耐药的铜绿假单胞菌 多黏菌素; 多黏菌素 + β-内酰胺类, 或环丙沙星, 或磷霉素, 或碳青霉烯类; β-内酰胺类 + 氨基糖苷类, 或磷霉素; 氨基糖苷类 + 环丙沙星, 或左氧氟沙星	给予充足的剂量: 如哌拉西林/他唑巴坦可用至 4.5 g, 1 次/6 h, 持续滴注 3 h^[175] 严重感染时, 可增加剂量、延长滴注时间或持续滴注^[176] 双 β-内酰胺类联用可能有效, 但需谨慎
	鲍曼不动杆菌	可供选择的药物: 舒巴坦及其合剂(头孢哌酮/舒巴坦、氨苄西林/舒巴坦)、碳青霉烯类(亚胺培南/西司他丁、美罗培南、比阿培南)、多黏菌素类(B 或 E)、替加环素、四环素类(米诺环素、多西环素)、氨基糖苷类(阿米卡星、异帕米星)或喹诺酮类(环丙沙星、左氧氟沙星、莫西沙星) 对非 MDR 感染, 可根据药敏结果选用 β-内酰胺类抗菌药物 对 XDR 或 PDR, 采用联合方案 舒巴坦及其合剂 + 多黏菌素, 或替加环素, 或多西环素, 或碳青霉烯类; 多黏菌素 + 碳青霉烯类; 替加环素 + 碳青霉烯类, 或多黏菌素; 舒巴坦及其合剂 + 多西环素 + 碳青霉烯类; 舒巴坦及其合剂 + 替加环素 + 碳青霉烯类; 亚胺培南/西司他丁 + 利福平 + 多黏菌素或妥布霉素 对碳青霉烯类耐药的鲍曼不动杆菌: 多黏菌素、舒巴坦及其合剂、替加环素 常用联合方案: 多黏菌素 + 舒巴坦及其合剂, 碳青霉烯类, 利福平, 氨基糖苷类, 或替加环素	对于 MDR 感染, 舒巴坦剂量可增至 6 ~ 8 g/d^[177-180], 碳青霉烯类可增加剂量、延长滴注时间^[181-182]
	嗜麦芽窄食单胞菌	可供选择的药物: 磺胺甲噁唑/甲氧苄啶、β-内酰胺酶抑制剂合剂(头孢哌酮/舒巴坦、替卡西林/克拉维酸)、氟喹诺酮类(左氧氟沙星、环丙沙星、莫西沙星)、替加环素、四环素类(米诺环素、多西环素)、头孢菌素(头孢他啶、头孢吡肟) 联合治疗方案 磺胺甲噁唑/甲氧苄啶 + 替卡西林/克拉维酸, 或头孢哌酮/舒巴坦, 或氟喹诺酮类, 或四环素类, 或头孢他啶, 或多黏菌素 氟喹诺酮类, 或多黏菌素 + 替卡西林/克拉维酸, 或头孢哌酮/舒巴坦, 或头孢他啶	联合用药适用于严重感染、XDR 或 PDR 菌感染等^[183-184] 对碳青霉烯类天然耐药, 替加环素的临床经验有限

注: MRSA: 耐甲氧西林金黄色葡萄球菌; VRE: 耐万古霉素肠球菌; CRE: 对碳青霉烯类耐药的肠杆菌科细菌; KPC: 指产 KPC 酶的肺炎克雷伯菌

3. HAP/VAP 常出现 XDR 或 PDR 菌感染, 应以早期、足量、联合为原则使用抗菌药物, 并应根据具体

的最低抑菌浓度 (minimum inhibitory concentration, MIC) 值及 PK/PD 理论, 推算出不同患者的具体给

药剂量、给药方式及给药次数等,以优化抗菌治疗效能^[185-186]。

HAP/VAP 常见耐药菌抗感染治疗方案的推荐意见见表 10。

(三) 抗感染治疗的疗效判断和疗程

HAP/VAP 抗感染疗程一般为 7 d 或以上。

1. 初步疗效判断:经验性治疗 48 ~ 72 h 应进行疗效评估。疗效判断需结合患者的临床症状和体征、影像学改变、感染标志物等实验室检查综合判断。如获得明确的病原学结果后,应尽早转为目标治疗或降阶梯治疗(由联合治疗转为单药治疗,或由广谱抗菌药物转为窄谱抗菌药物)^[187-189](ⅢC)。如治疗无效且病原学不明,需进一步进行病原学检查,并重新评估病原学,调整治疗药物。

2. 抗感染治疗的疗程:需结合患者感染的严重程度、致病菌种类和耐药性及临床疗效等因素决定。如果初始经验性抗感染治疗恰当,单一致病菌感染,对治疗的临床反应好,无肺气肿、囊性纤维化、空洞、坏死性肺炎和肺脓肿且免疫功能正常者,疗程为 7 ~ 8 d^[8]。对于初始抗感染治疗无效、病情危重、XDR 或 PDR 菌感染、肺脓肿或坏死性肺炎者,应酌情延长疗程。

3. 抗菌药物治疗的停药指征:根据患者的临床症状和体征、影像学 and 实验室检查(特别是 PCT)等结果决定停药时机(ⅢB)。

(四) 吸入性抗菌药物的治疗

在同时符合以下情况时,可尝试在全身抗菌治疗的基础上联合吸入性抗菌药物治疗:(1) HAP/VAP 是由 MDR 肺炎克雷伯菌、铜绿假单胞菌、鲍曼不动杆菌等所致;(2) 单纯全身用药肺炎部位药物分布不足,疗效不佳;(3) 选择的拟吸入的抗菌药物对致病菌敏感^[7,190-191](ⅠC)。可用于吸入的抗菌药物主要为氨基糖苷类(包括妥布霉素和阿米卡星)和多黏菌素^[7,190-193]。

评价吸入性抗菌药物的临床研究大多存在样本量小、观察人群和用药方案差异大等缺陷,静脉联合吸入治疗改善临床转归的临床证据主要集中于多黏菌素,因此,吸入治疗的有效性和安全性还有待进一步观察^[147-148,194-195]。

吸入性抗菌药物的最佳方案尚无定论。多黏菌素 E 推荐 30 ~ 60 mg 基质(相当于 100 ~ 200 万 IU),溶于 2 ~ 4 ml 生理盐水中,1 次/8 ~ 12 h^[196-197]。阿米卡星推荐 400 mg,2 次/d 或 25 mg/kg,1 次/d^[198-200];妥布霉素推荐 300 mg,1 次/12 h^[170]。药物(尤其是

多黏菌素 E)应现用现配^[197]。疗程为 14 d 或至脱机。对于机械通气患者,应使用合适的雾化装置,根据患者的病理生理特点设置适当的吸氧浓度和通气模式^[191,201]。

吸入治疗的局部不良反应主要为诱发气道痉挛,可表现为咳嗽、喘息和呼吸困难。雾化过程中需监测呼吸道症状和氧饱和度。如发生气道痉挛,轻度可停止雾化,并给予支气管舒张剂,缓解后再进行雾化;如持续或严重,应停用该药物吸入治疗。雾化氨基糖苷类和多黏菌素者应监测肾功能,有条件时可监测血药浓度。如为机械通气患者,尚需监测:(1) 气道峰压,如升高,可能是滤器堵塞或气道痉挛所致;(2) 患者精神状态,低剂量镇静剂可减轻人机对抗,在雾化结束后应及时停药。

(五) 辅助支持治疗

HAP/VAP 患者除经验性和目标性抗感染治疗外,气道分泌物引流、合理氧疗、机械通气、液体管理、血糖控制、营养支持等综合治疗措施也同等重要,尤其对重症感染患者往往可决定其预后,合理应用可使患者获益。

1. 呼吸支持技术:(1) 引流气道分泌物:及时有效地引流气道分泌物、维持呼吸道通畅是 HAP/VAP 抗感染治疗的首要措施,尤其是合并肺脓肿、脓胸或呼吸道廓清能力差的重症患者;卧床患者应定时翻身拍背,积极体位引流,防止误吸并进行积极的呼吸功能锻炼^[202];对于呼吸道廓清能力差、不能充分排痰的患者,可选用排痰机震动排痰、直接经鼻(口)或经人工气道给予刺激咳嗽及吸痰,必要时经支气管镜吸痰;无创机械通气患者分泌物较多时,尽早采用经支气管镜吸痰,有可能降低气管插管率^[203]。(2) 合理氧疗:对低氧血症及重症 HAP 患者应及时进行氧疗,保持动脉血氧饱和度(SaO_2) > 90%,下列情况需持续吸氧:呼吸频率 > 24 次/min、 PaO_2 < 60 mmHg、休克或存在严重代谢性酸中毒和组织缺氧等;Ⅰ型呼吸衰竭可给予较高浓度吸氧,吸入氧浓度(FiO_2) ≥ 35%,使 PaO_2 提升到 60 mmHg 以上或指脉氧饱和度(SpO_2) 达 90% 以上。Ⅱ型呼吸衰竭应常规给予低浓度(FiO_2 < 35%)持续吸氧,维持 PaO_2 ≥ 60 mmHg 或 SpO_2 ≥ 90%,并避免 PaCO_2 显著升高,若 PaCO_2 显著升高或 PaO_2 不能改善时应考虑其他氧疗方式。氧疗有多种方法,包括传统氧疗(经鼻导管和面罩吸氧)和经鼻高流量氧疗(high-flow nasal oxygen, HFNO)。对于重症 HAP 患者,HFNO 因吸入气体流量高,湿化好,并且可产生一定

水平的呼气末正压(positive end-expiratory pressure, PEEP),已逐渐成为重要的氧疗手段,同时作为患者脱机拔管后的序贯治疗方式,具有良好的有效性和安全性^[204-206]。(3)机械通气:对于呼吸频率异常(如 >30 次/min或 <12 次/min)、自主呼吸减弱或消失、呼吸节律严重异常伴有意识障碍、动用辅助呼吸肌或胸腹矛盾运动的 HAP 患者,在应用 HFNO 后仍不能纠正低氧血症时,应及时考虑机械通气^[207]。机械通气包括无创机械通气和有创机械通气,无创机械通气主要通过口鼻面罩或鼻罩辅助通气,适用于神志清楚、生命体征和血流动力学相对稳定且痰液较少或可清醒咳痰的患者,通常采用压力支持通气(pressure support ventilation, PSV)及双水平气道正压通气(bilevel positive airway pressure, BiPAP)等模式,通气治疗效果可通过观察症状和体征变化、人机是否同步、血气分析等监测指标判断。适当应用无创机械通气可减少气管插管及相关并发症的发生率,缩短在 ICU 中停留的时间^[208]。当患者出现明显意识异常、痰液引流不畅、血流动力学异常、血气分析提示呼吸衰竭等临床表现时,应及时更换为有创机械通气。有创机械通气主要通过气管插管(经口或经鼻)或气管切开进行通气,适用于 HAP 合并严重呼吸衰竭和(或)有生命体征异常且具有以下情况者:①不适宜采用无创机械通气,且严重低氧血症和(或)二氧化碳潴留危及生命时($\text{PaO}_2/\text{FiO}_2 < 150 \text{ mmHg}$);②气道分泌物清除障碍、误吸危险性高(如球麻痹或腹胀、呕吐)、意识障碍;③血流动力学不稳定、多器官功能衰竭;④正确使用无创机械通气仍未达到预期效果或病情恶化者。对于具有明确有创机械通气指征的患者,除非患者拒绝气管插管或气管切开,否则不宜应用无创机械通气替代有创机械通气治疗。(4)体外膜肺氧合(extracorporeal membrane oxygenation, ECMO):如果充分给予常规机械通气仍不能有效改善病情、纠正低氧血症时,应尽早考虑使用 ECMO^[209]。

2. 器官功能支持治疗:(1)血流动力学监测及液体管理:重症 HAP/VAP 患者早期可能因为发热、进食少、炎症反应等原因导致有效循环血量不足,也可能合并感染性休克,应适时动态评估血流动力学状态,及时进行液体复苏,必要时给予血管活性药物以维持平均动脉压 $>65 \text{ mmHg}$;在液体复苏阶段,当需要输注大量晶体液时,可酌情输注白蛋白。(2)控制血糖:参照规范的血糖管理方案,血糖控制的目标是 $\leq 10 \text{ mmol/L}$ 。(3)预防应激性溃疡:一般不推

荐常规使用抑酸剂预防应激性溃疡,如果患者存在应激性溃疡和消化道出血的危险因素,则需要使用胃黏膜保护剂(如硫糖铝)和抑酸剂,首选质子泵抑制剂,也可选用 H_2 -受体拮抗剂^[210],但应用抑酸剂可能增加患者 HAP/VAP 的发病率^[211]。(4)持续肾脏替代治疗(continuous renal replacement therapy, CRRT):HAP/VAP 患者使用 CRRT 的时机、操作模式、设定参数及对患者预后的影响等尚缺乏统一认识。建议 HAP/VAP 患者合并感染性休克、急性肾功能障碍时考虑进行 CRRT,有助于清除机体代谢产物、液体容量管理、纠正水电解质酸碱平衡紊乱、营养支持和清除部分炎症介质^[212]。

3. 非抗菌药物治疗:(1)糖皮质激素:HAP/VAP 患者糖皮质激素的使用时机、种类、剂量及疗程目前尚未达成共识,可借鉴我国 2016 年版 CAP 指南,建议糖皮质激素只适用于合并血流动力学不稳定的重症 HAP/VAP 患者。(2)营养支持:HAP/VAP 合并脓毒症或感染性休克的患者,应尽早启动肠内营养;如果肠内营养支持 7~10 d,摄入的能量与蛋白仍不足目标的 60%,无论患者是否存在营养不良的风险,均应给予肠外营养补充。对于无条件进行早期肠内营养(病程 7 d 内)的患者,如果没有营养不良的风险,营养风险筛查 2002(nutritional risk screening 2002, NRS-2002) ≤ 3 分,或危重病患者营养风险(nutrition risk in critically ill, NUTRIC)评分 ≤ 5 分,在发病 7 d 后开始进行肠外营养支持;如存在营养不良风险或严重营养不良的患者,应尽早开始肠外营养支持^[213-214]。(3)免疫治疗:由于缺乏临床循证医学证据,HAP/VAP 患者的免疫治疗尚有争议。重症 HAP/VAP 患者在抗感染治疗的基础上,酌情应用免疫球蛋白($0.5 \sim 1.0 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$),可能有助于控制炎症反应。免疫调节剂胸腺肽 $\alpha 1$ 对治疗脓毒症、改善免疫麻痹状态可能有一定作用^[215]。

八、预防

预防 HAP/VAP 的总体策略是尽可能减少和控制各种危险因素。所有医护工作均需遵循医疗卫生机构消毒、灭菌和医院感染控制相关的基本要求和原则,加强员工感染控制的意识教育,提高手卫生的依从性,保障医疗器具消毒灭菌,严格无菌操作,落实目标性监测,合理应用抗菌药物等。

(一)HAP 的预防

1. 预防误吸:采用半卧位(床头抬高 $30^\circ \sim 45^\circ$),床头过高时患者舒适性下降并且发生压疮风

险增加,故一般认为 $\geq 30^\circ$ 即可。合理喂食。

2. 减少上呼吸道和(或)消化道病原菌定植^[216-217]:采用氯己定(洗必泰)进行口腔护理,氯己定擦浴,选择性口咽部去污染(selective oropharyngeal decontamination, SOD),应用益生菌等。

3. 积极治疗基础疾病:加强危重症患者的营养支持治疗,及时纠正水电解质、酸碱失衡、低蛋白及高血糖等罹患感染的危险因素,加强心、肺疾病的治疗和康复,采用呼吸训练、体位引流、手法技术或机械装置等气道廓清技术(airway clearance therapy, ACT)^[218]。关注围手术期(特别是接受胸部及上腹部手术)患者的气道管理,加强呼吸道湿化并保持通畅。鼓励患者手术后早期下床活动,少用镇静剂^[219]。

4. 加强患者管理:对于器官移植、粒细胞减少症等严重免疫功能抑制患者,应进行保护性隔离;对有耐药菌(如 MRSA、CRAB、CRPA 及 CRE 等)感染或定植者,应采取接触隔离措施^[141]。

(二)VAP的预防

VAP 存在特定的危险因素和发病机制,除上述共同的预防措施外,还需要采取以下针对性的预防措施。

1. 预防误吸:除非有禁忌证,推荐接受有创机械通气的患者床头抬高 $30^\circ \sim 45^\circ$ ^[3, 217, 220](II A),并协助患者翻身拍背及震动排痰。

在气管导管的气囊上方堆积的分泌物是建立人工气道患者误吸物的主要来源,应用装有声门下分泌物吸引管的气管导管,可降低 VAP 的发生率并缩短住 ICU 的时间^[221-224],因此,推荐在预测有创通气时间超过 48 h 或 72 h 的患者使用^[3, 217](I A)。气管导管气囊的充盈压应保持不低于 25 cmH₂O (1 cmH₂O = 0.098 kPa)^[40, 217, 225](I A)。在气囊放气或拔出气管插管前尽可能清除气囊上方及口腔内的分泌物。

呼吸机管道中常有冷凝液形成,细菌易在此生长繁殖,既要避免含菌冷凝液直接流入下呼吸道而引起 VAP,也要避免其反流到湿化罐,使湿化的含菌气溶胶吸至下呼吸道,冷凝液收集瓶应始终处于管道最低位置,保持直立并及时清理。湿化罐、雾化器液体应使用灭菌水,每 24 h 倾倒更换。呼吸机外部管道及配件应一人一用一消毒或灭菌,长期使用机械通气的患者,一般推荐每周更换一次呼吸机管道,但在有肉眼可见到污渍或有故障时应及时更换^[217](II A)。

对机械通气的患者尽可能给予肠内营养^[3, 217](II B),早期肠内营养可促进肠道蠕动、刺激胃肠激素分泌、改善肠道血流灌注,有助于维持肠黏膜结构和屏障功能的完整性,减少致病菌定植和细菌移位,优于肠外营养。经鼻肠营养与经鼻胃内营养相比,前者可降低 VAP 的发病率,特别是对于存在误吸高风险的患者,但两者的病死率无差异^[226]。间断喂养和小残留量喂养可减少胃食管反流,降低肺炎的发生风险及其病死率,胃造口术也可降低 VAP 的发生率。对于接受肠内营养的无症状患者,不推荐常规监测胃残余量^[217, 227](II A)。

2. 减少定植:推荐机械通气患者常规进行口腔卫生护理^[217](II A),包括使用生理盐水、氯己定或聚维酮碘含漱液冲洗、用牙刷刷牙齿和舌面等,1 次/6~8 h;有证据提示,应用 0.12% 的氯己定溶液 15 ml, 2 次/d 进行口腔护理至拔管后 24 h,可降低 VAP 的发生率(10%~30%)。

SOD 指在口咽部使用非吸收性抗菌药物,选择性消化道去污染(selective digestive tract decontamination, SDD)指在口咽部使用并口服非吸收性抗菌药物,联合或不联合肠道外抗菌药物,清除患者口咽部及消化道可能引起继发感染的潜在病原菌。研究结果提示^[228], SOD^[229]或 SDD 可降低 HAP/VAP 的发生率及呼吸道耐药菌的定植率,但对缩短机械通气时间、减少住 ICU 时间和病死率证据不足。SDD 可能会增加耐药菌感染的风险,包括艰难梭菌感染,但缺乏长期风险的研究。对机械通气的患者应权衡利弊,谨慎使用 SOD 或 SDD^[3, 217](IIB)。

镀银气管导管可降低 VAP 的发病率,但对机械通气时间、ICU 住院时间及病死率无影响^[230],目前不常规推荐镀银气管导管^[217](II B)。

口服益生菌可降低 VAP 的发生率^[231],但并不降低患者的病死率,对存在免疫缺陷或增加菌群移位风险的胃肠道疾病等患者,应避免使用益生菌。总体上不推荐常规给予益生菌预防 VAP^[3, 217](IIB)。

预防应激性溃疡是 ICU 机械通气患者重要的治疗手段之一,临床主要应用的药物有胃黏膜保护剂(如硫糖铝)、抑酸剂(如 H₂-受体阻断剂)和质子泵抑制剂。胃黏膜保护剂对胃液 pH 值的影响不大,有利于抑制胃内细菌的生长,与抑酸剂相比较可以降低 VAP 的风险,但预防消化道出血的作用较弱。目前认为使用抑酸剂预防应激性溃疡可能增加胃肠道和气道内细菌的定植,但对 VAP 的病死率没有影响,在应用时应注意掌握指征^[232](II B)。

3. 减少使用有创通气:建立人工气道并应用机械通气是发生 VAP 最重要的危险因素,气管插管使肺炎风险增加 6~21 倍^[233],特别是重复插管或插管时间较长、频繁更换呼吸机管道可进一步增加 VAP 的风险^[216,234-235]。尽可能减少有创通气和缩短有创通气时间^[217]对预防 VAP 至关重要(I A)。

严格掌握气管插管或切开的适应证,对需要呼吸机辅助呼吸的患者应优先考虑无创通气;慢阻肺或充血性心力衰竭患者合并高碳酸血症或低氧血症时,应尽早合理应用无创正压通气,可减少气管插管^[236-237],进而减少 VAP 的发生率(I A);经鼻 HFNO 可用于各种病因导致的 I 型呼吸衰竭^[238-239]及部分轻度 II 型呼吸衰竭患者,减少气管插管和再插管率^[240](I A)。应用上述呼吸支持治疗时均需注意避免延误插管时机而加重病情。

有创通气时尽可能减少镇静剂的使用,使用期间应每日评估其使用的必要性,并尽早停用(I A),应特别注意避免使用苯二氮草类镇静剂^[241]。符合条件者应每日唤醒并实施自主呼吸试验,评估是否具备脱机、拔管的条件,以缩短机械通气时间,降低 VAP 的风险^[242](I A)。

4. 组合干预措施:目前研究认为下列核心干预措施可以明显减少接受机械通气患者的平均通气时间和住院天数,降低 VAP 的发病率、病死率和(或)费用^[217,243-252](I A)。主要措施为:(1)尽可能选用

无创呼吸支持治疗技术;(2)每天评估有创机械通气及气管插管的必要性,尽早脱机或拔管;(3)对机械通气患者尽可能避免不必要的深度镇静,确需镇静者应定期唤醒并行自主呼吸训练,每天评估镇静药使用的必要性,尽早停用;(4)给预期机械通气时间超过 48 或 72 h 的患者使用带声门下分泌物吸引的气管导管;(5)气管导管气囊的充盈压应保持不低于 25 cmH₂O;(6)无禁忌证患者应抬高床头 30°~45°;(7)加强口腔护理,推荐采用氯己定漱口液;(8)加强呼吸机内外管道的清洁消毒,推荐每周更换 1 次呼吸机管道,但在有肉眼可见污渍或有故障时应及时更换;(9)在进行与气道相关的操作时应严格遵守无菌技术操作规程;(10)鼓励并协助机械通气患者早期活动,尽早开展康复训练。

在落实上述核心措施的基础上,各 ICU 可根据自身收治患者的特点及客观条件,选择性采用下列防控措施并注意积累循证医学和预防经济学依据,如对气管插管患者早期气管切开、预防应激性溃疡、SOD/SDD、预防性使用益生菌、选用特殊材质的气管导管(如表面涂有抗菌药物、涂银或超薄聚氨酯气管导管套囊)等。封闭式气管内吸痰对 VAP 的发病率或患者的其他结局无影响^[217],但对经气溶胶或空气传播的呼吸道传染的院内感染防控具有一定的意义。

附件:本指南对 HAP/VAP 其他相关问题的认识与建议

一、医疗护理相关性肺炎

2005 年,美国 IDSA/ATS 首次提出了医疗护理相关性肺炎(h healthcare-associated pneumonia, HCAP)的概念^[2],其目的在于从社区发病的肺炎中及时识别耐药菌感染,并通过经验性广谱抗菌药物治疗改善此类耐药菌感染患者的预后,这一概念的临床应用价值早期曾得到美国大型临床研究数据的支持^[253]。但随着相关研究在世界范围内的广泛开展,对 HCAP 这一概念的争议也越来越大。2011 年欧洲下呼吸道感染诊治指南提出,现有的循证医学证据不支持在欧洲采用 HCAP 这一概念^[254]。

争议的焦点主要集中在两个方面:(1)不同 HCAP 的病原学研究结果差异较大,多数研究结果显示,HCAP 的概念并不能准确鉴别 MDR 菌感染^[255]。欧洲和亚洲地区 HCAP 中耐药菌感染的比

例普遍低于美国报道的水平^[256-261]。最近的荟萃分析结果表明,利用 HCAP 定义筛选耐药菌感染的敏感性和特异性并未达到可以临床应用的阈值^[255]。事实上,除了 HCAP 定义所提及的危险因素外,至少还有其他 10 余种可能增加肺炎患者耐药菌感染风险的危险因素,在特定受试人群中,将这些危险因素中的某几种联合起来筛选耐药菌感染,其效果往往优于 HCAP 的定义^[262]。(2)2005 年版美国 HAP/VAP 指南推荐的经验性广谱抗感染治疗方案,并不能有效改善 HCAP 患者的预后。虽然早期的研究结果曾提示 HCAP 较高的病死率可能与初始治疗未能覆盖耐药菌有关^[263-264],但近年来的多数研究结果表明,HCAP 的高病死率主要与高龄、合并症、严重基础疾病和脏器功能低下等因素有关,而与耐药菌感染并无必然联系,按照 2005 年版美国 HAP/VAP

指南建议的广谱抗菌药物治疗方案对 HCAP 进行治疗,并不能缩短 HCAP 患者的住院时间和临床稳定时间^[265]。2016 年版美国 HAP/VAP 指南修订时,全体制定者一致同意不再采用 HCAP 这一概念^[7]。

因我国医疗机构的设置与美国有很大的不同,即使在 HCAP 概念最流行的时期,我国也并没有跟风采用这一概念。本指南建议,在我国不采用 HCAP 这一概念,在肺炎患者的诊治中,应重视致病菌的区域性耐药性特点,强化对所有耐药菌感染危险因素的全面分析,而无需刻意区分患者是否属于 HCAP^[7] (IA)。

二、呼吸机相关性气管支气管炎

通常认为呼吸机相关性气管支气管炎 (ventilator-associated tracheobronchitis, VAT) 是病原微生物在下呼吸道从定植发展到引起 VAP 的中间环节之一^[266-269]。目前对于 VAT 是否是一种独立的疾病还存在争议,也无统一的诊断标准,VAT 与微生物定植、VAP 之间的准确界限仍有待于进一步明确。理论上,与 VAP 相比,VAT 无肺部浸润影,通常较少引起氧合水平的下降,远端气道标本 (PSB 或 BAL) 定量培养的细菌浓度也低于 VAP^[267-268,270]。

VAT 的致病菌、发病率及其进展为 VAP 的比例在不同研究、不同医疗机构以及同一医疗机构的不同医疗单元之间存在一定差别^[266-268,270-275]。罹患 VAT 的不利影响包括延长机械通气时间^[268,272-277]、延长 ICU 住院时间^[268,272-277]和总住院时间^[272-273],但对病死率似乎并无显著影响^[266,271,273]。近期的多项相关研究和荟萃分析结果显示,VAT 不是增加机械通气患者病死率的独立危险因素^[273],对机械通气患者的归因病死率也没有显著影响^[266]。VAT 是否需要抗感染治疗仍然存在争议^[266,273,278]。研究结果表明,恰当的全身抗感染治疗可以降低 VAT 进展为 VAP 的比例^[266,270,273],但并不能降低 VAT 的病死率^[266,273]。有关吸入性抗菌药物治疗 VAT 的临床研究数量少、质量差,依据现有的研究数据尚难以对其临床价值做出准确评价^[279-280]。

2016 年版美国 HAP/VAP 指南建议对 VAT 不必进行抗感染治疗^[7],这在某种程度上使得临床上诊断 VAT 已经失去了实际意义。本指南认为,在目前既无统一的严谨可行的 VAT 诊断标准、也缺乏抗菌药物治疗 VAT 能够有效改善机械通气患者预后的高质量临床证据之前,将 VAT 认定为一种独立疾病可能会进一步增加 ICU 中抗菌药物的使用,不利于

遏制细菌耐药性的发展,也会增加抗菌药物相关不良反应的发生率。所以,本指南建议,在我国临床工作中不采用 VAT 这一诊断,也不主张对 VAT 进行抗感染治疗 (II B)。

需要指出的是,对于其他临床征象高度疑似 VAP、病情进行性加重,但因各种原因 (如无条件或病情不允许进行胸部 CT 检查,床旁 X 线胸片又无法排除肺炎) 导致缺乏影像学依据而无法确诊 VAP 的危重患者,可以在严密监控下审慎地进行经验性抗感染治疗,而不必刻意区分是 VAT 还是已经发展到 VAP。

三、早发 HAP/VAP 与迟发 HAP/VAP

早期的研究结果显示,住院患者的气道定植菌在住院 3~4 d 后会逐渐由社区获得型转变为医院获得型^[281],与这种变化相对应,曾认为 HAP/VAP 的致病菌类型及其抗菌药物耐药情况也会因肺炎发生时的住院时间不同而有所区别^[2]。传统上,通常以住院时间 4 d 为界限,将住院 4 d 以内 (≤ 4 d) 发生的 HAP/VAP 称为早发 (early-onset) HAP/VAP,而住院 5 d 以后 (≥ 5 d) 发生的 HAP/VAP 称为迟发 (late-onset) HAP/VAP^[2]。既往认为,在早发 HAP/VAP 中,如果患者没有 MDR 菌感染的其他危险因素,其致病菌构成与社区获得性肺炎较为相似,而迟发 HAP/VAP 则主要由铜绿假单胞菌、不动杆菌属、MDR 肠杆菌科细菌或 MRSA 等耐药菌引起^[2]。但近年来国内外相继有大样本的临床研究结果发现,早发与迟发 HAP/VAP 的致病菌构成情况和核心致病菌的分离率非常近似^[18,282],MDR 菌感染在早发 HAP/VAP 中并不少见^[121,283-284]。

2005 年版美国 HAP/VAP 指南曾经将肺炎发生时的住院时间列为患者分组和确定经验性抗感染治疗方案的重要标准之一^[2],但新的临床研究证据提示,不恰当地强调住院时间长短对 HAP/VAP 病原学的影响,可能会对临床工作产生不利影响。一方面,由于低估了所谓早发 HAP/VAP 中耐药菌感染风险,可能由于治疗不充分而导致此类患者初始经验性抗感染治疗失败的风险增加;另一方面,对于迟发 HAP/VAP,如果仅仅强调发病时间的影响而忽视对其他真正耐药菌感染危险因素的具体分析,也可能导致不必要的过度治疗^[250]。目前,国内外一致认为,发生 HAP/VAP 前 90 天内经静脉注射使用过抗菌药物是导致耐药菌感染最重要的危险因素,而发病时已住院时间的长短对耐药菌感染风险的影响相对较小。

我国 1999 年发布的“医院获得性肺炎诊断和治疗指南(草案)”,由于缺乏自己的 HAP/VAP 调查数据,参考当时国外的研究结果将发病时间早晚列为 HAP 病情评价的标准之一^[1],但后来我们自己的流行病学调查结果表明,早发与迟发 HAP/VAP 中各种致病菌的分离率总体上并没有显著的差别^[18]。基于上述原因,本指南建议,在制定 HAP/VAP 的经验性治疗方案时,应重视对各种耐药菌感染危险因素的具体分析,避免单纯根据肺炎发生时已住院时间的长短来确定治疗方案(ⅡB)。

四、免疫功能抑制宿主罹患 HAP/VAP

免疫功能抑制患者罹患 HAP/VAP 与非免疫功能抑制患者有较大差别,其致病原构成、临床及影像学表现、预后转归除了与住院时间、ICU 住院情况、机械通气情况、抗菌药物使用情况等因素有关外,还受到免疫缺陷的类型、严重程度和持续时间的影响^[285-288]。

按照免疫机制受损环节区分,免疫功能抑制可分为粒细胞减少或功能障碍、体液免疫缺陷和细胞免疫缺陷三种类型^[286],某些患者可能同时存在联合免疫抑制^[286]。严重的粒细胞减少或功能障碍、严重的细胞免疫缺陷或联合免疫缺陷患者继发 HAP/VAP 时,致病原除 HAP/VAP 常见致病菌外,真菌(曲霉、肺孢子菌、隐球菌、接合菌等)、病毒(巨细胞病毒、单纯疱疹病毒、呼吸道合胞病毒等)、军团菌、诺卡菌等机会性感染较为常见^[285-291],临床上往往具有以下特点^[285-288]:起病隐匿但进展迅速,预后差,病死率高;呼吸困难和呼吸衰竭出现早、发生率高;肺内多发病变、弥漫性病变更多见;肺外突破性感染发生率高。单纯体液免疫缺陷患者中金黄色葡萄球菌、肺炎克雷伯菌、流感嗜血杆菌和铜绿假单胞菌等引起的化脓性感染较为常见,临床上具有反复发作的特点。在细胞免疫缺陷患者中,由结核分枝杆菌、非结核分枝杆菌、诺卡菌、曲霉或隐球菌导致的肺部感染往往呈亚急性或慢性病程,可表现为肺内单个或多个局限性病灶,但此类情况多见于院外感染,在 HAP/VAP 中相对少见。

由于基础疾病及各种治疗措施的干扰,免疫抑制宿主发生肺炎时临床诊断较为困难,常常需要与多种非感染性肺部浸润相鉴别^[290,292]。胸部 CT 检查除可以发现 X 线胸片不能发现的隐匿病变外,还能更加细致地显示肺部病变的影像学特点,为分析推测致病原提供线索,也可用于指导侵入性检查的实施^[290,292-294]。因此,在怀疑免疫抑制宿主罹患

HAP/VAP 时,如病情允许建议尽量安排胸部 CT 检查替代普通 X 线胸片(ⅢC)。

由于免疫功能抑制患者继发肺炎时的致病原构成比免疫功能正常者更为复杂^[285-291],所以应特别重视尽早建立正确的病原学诊断^[285-288,290,292](ⅡB)。常规的呼吸道标本涂片革兰染色镜检和普通细菌培养,往往不能满足此类肺炎病原学诊断的需要,在此基础上,还应根据患者免疫功能缺陷的类型和肺部影像学特点进一步安排针对真菌、病毒、诺卡菌、军团菌、结核分枝杆菌及非结核分枝杆菌等的病原学检查^[286,290,292],必要时可经支气管镜进行肺泡灌洗或组织活检^[295],或进行经皮肺穿刺活检^[296],以帮助明确诊断。由于免疫功能抑制继发感染对快速明确致病原有更高的要求,而且部分机会性致病原分离培养困难,因此,呼吸道标本涂片的各种特殊染色检查、致病原快速抗原检测以及核酸检测具有更为重要的诊断价值^[286,292,297-302](ⅡB)。血清特异性抗体检测无法进行早期诊断,而且在免疫功能抑制患者中假阴性比较多见,对免疫功能抑制患者感染的病原学诊断价值有限^[298,302](ⅢC)。

免疫功能抑制宿主罹患 HAP/VAP 时的初始经验性抗感染治疗应建立在对肺炎严重程度和免疫功能缺陷严重程度准确评价的基础之上。既要避免对重症感染和(或)严重免疫功能缺陷的不良预后估计不足导致治疗不充分或延误治疗,又要避免不加区分地进行“全覆盖式”的过度治疗。在分析推测可能的致病原、选择抗感染药物进行经验性治疗时,除了常规考虑肺炎发生时所在医疗单元 HAP/VAP 致病菌流行病学特点、耐药菌感染风险等因素外,还应兼顾免疫功能缺陷的类型、严重程度、持续时间以及肺部病变的影像学特点^[285-288,290,292,299]。治疗前应积极进行病原学检查,治疗过程中及时进行疗效评估,适时根据病原学检查结果对初始治疗方案进行调整。

重建免疫机制是治疗继发于免疫功能抑制的 HAP/VAP 的重要措施,必须给予足够重视^[286,290,292],具体措施包括促进粒细胞数量恢复、停止或减少使用导致免疫功能抑制的药物、补充外源性免疫活性物质、改善或控制导致免疫功能缺陷的基础疾病等(ⅢC)。

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Pneumonia (hospital-acquired): antimicrobial prescribing

NICE guideline

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Your responsibility

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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Overview

This guideline sets out an antimicrobial prescribing strategy for adults, young people, children and babies aged 72 hours and over with a confirmed diagnosis of hospital-acquired pneumonia. It does not cover ventilator-associated pneumonia. It aims to optimise antibiotic use and reduce antibiotic resistance.

See a [3-page visual summary](#) of the recommendations, including tables to support prescribing decisions.

See the [NICE guideline on pneumonia in adults](#) for other recommendations on diagnosis and management, including microbiological tests.

For managing other lower respiratory tract infections, see our web page on [respiratory conditions](#).

Who is it for?

- Healthcare professionals
- People with hospital-acquired pneumonia, their families and carers

Recommendations

1.1 *Managing hospital-acquired pneumonia*

Treatment for adults, young people and children

- 1.1.1 For adults, young people and children with symptoms or signs of pneumonia starting within 48 hours of hospital admission, follow the [NICE guideline on community-acquired pneumonia](#).
- 1.1.2 Offer an antibiotic(s) for adults, young people and children with hospital-acquired pneumonia. When choosing an antibiotic(s) (see the recommendations on [choice of antibiotic](#)), take account of:
- the severity of symptoms or signs^[1]
 - the number of days in hospital before onset of symptoms
 - the risk of developing complications, for example, if the person has a relevant comorbidity such as severe lung disease or immunosuppression
 - local hospital and ward-based antimicrobial resistance data
 - recent antibiotic use
 - recent microbiological results, including colonisation with multidrug-resistant bacteria
 - recent contact with a health or social care setting before current admission
 - the risk of adverse effects with broad-spectrum antibiotics, such as *Clostridium difficile* infection.
- 1.1.3 Start antibiotic treatment as soon as possible after establishing a diagnosis of hospital-acquired pneumonia, and certainly within 4 hours (within 1 hour if the person has suspected sepsis and meets any of the high risk criteria for this – see the [NICE guideline on sepsis](#)).
- 1.1.4 Give oral antibiotics first line if the person can take oral medicines, and the severity of their condition does not require intravenous antibiotics.
- 1.1.5 If intravenous antibiotics are given, review by 48 hours and consider switching

to oral antibiotics if possible.

- 1.1.6 Send a sample (for example, sputum sample, nasopharyngeal swab or tracheal aspirate) for microbiological testing.

Reassessment and specialist advice

- 1.1.7 When microbiological results are available:

- review the choice of antibiotic(s) and
- change the antibiotic(s) according to results, using a narrower-spectrum antibiotic, if appropriate.

- 1.1.8 Reassess adults, young people and children with hospital-acquired pneumonia if symptoms do not improve as expected or worsen rapidly or significantly.

- 1.1.9 Seek specialist advice from a microbiologist for adults, young people and children with hospital-acquired pneumonia if they have:

- symptoms that are not improving as expected with antibiotics or
- multidrug-resistant bacteria.

- 1.1.10 Follow the [NICE guideline on care of dying adults in the last days of life](#) when caring for adults with hospital-acquired pneumonia who are approaching their end of life.

See the evidence and committee discussions on [antibiotic prescribing strategies](#) and [choice of antibiotics](#).

1.2 Choice of antibiotic

- 1.2.1 When prescribing an antibiotic(s) for hospital-acquired pneumonia:

- follow table 1 for adults aged 18 years and over
- follow table 2 for children and young people under 18 years.

- 1.2.2 Consider following the [NICE guideline on community-acquired pneumonia](#) for

choice of antibiotic for adults, young people and children with symptoms or signs of pneumonia starting within days 3 to 5 of hospital admission who are not at higher risk of resistance^[2].

Table 1 Antibiotics for adults aged 18 years and over

Antibiotic ¹	Dosage and course length ²
First-choice oral antibiotic for non-severe symptoms or signs and not at higher risk of resistance³ (guided by microbiological results when available)	
Co-amoxiclav	500/125 mg 3 times a day for 5 days then review ⁴
Alternative oral antibiotics for non-severe symptoms or signs and not at higher risk of resistance³, if penicillin allergy or if co-amoxiclav unsuitable	
Antibiotic choice should be based on specialist microbiological advice and local resistance data. Options include:	
Doxycycline	200 mg on first day, then 100 mg once a day for 4 days (5-day course) then review ⁴
Cefalexin (caution in penicillin allergy)	500 mg twice or 3 times a day (can be increased to 1 g to 1.5 g 3 or 4 times a day) for 5 days then review ⁴
Co-trimoxazole ^{5,6}	960 mg twice a day for 5 days then review ⁴
Levofloxacin ⁶ (only if switching from IV levofloxacin with specialist advice; consider safety issues ⁷)	500 mg once or twice a day for 5 days then review ⁴
First-choice intravenous antibiotics if severe symptoms or signs (for example, symptoms or signs of sepsis) or at higher risk of resistance³. Review IV antibiotics by 48 hours and consider switching to oral antibiotics as above for a total of 5 days then review⁴	
Antibiotic choice should be based on specialist microbiological advice and local resistance data. Options include:	
Piperacillin with tazobactam	4.5 g 3 times a day (increased to 4.5 g 4 times a day if severe infection)
Ceftazidime	2 g 3 times a day
Ceftriaxone	2 g once a day

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Cefuroxime	750 mg 3 or 4 times a day (increased to 1.5 g 3 or 4 times a day if severe infection)
Meropenem	0.5 g to 1 g 3 times a day
Ceftazidime with avibactam	2/0.5 g 3 times a day
Levofloxacin ⁶ (consider safety issues ⁷)	500 mg once or twice a day (use higher dosage if severe infection)
Antibiotics to be added if suspected or confirmed MRSA infection (dual therapy with an IV antibiotic listed above)	
Vancomycin ^{5,8}	15 mg/kg to 20 mg/kg 2 or 3 times a day IV, adjusted according to serum vancomycin concentration (a loading dose of 25 mg/kg to 30 mg/kg can be used in seriously ill people); maximum 2 g per dose
Teicoplanin ^{5,8}	Initially 6 mg/kg every 12 hours for 3 doses, then 6 mg/kg once a day
Linezolid ⁵ (if vancomycin cannot be used; specialist advice only)	600 mg twice a day orally or IV

医院获得性肺炎（HAP）：抗菌药物处方

抗生素的选择：≥18 岁成人

抗生素	剂量和疗程
对于无严重的症状或体征以及无较高耐药风险的患者，首选的口服抗生素（可根据微生物学结果指导用药）	
阿莫西林/克拉维酸	500/125 mg，每天 3 次，连续 5 天，疗程结束后复查
如青霉素过敏或阿莫西林/克拉维酸不适用，无严重的症状或体征以及无较高耐药风险的患者可选择的口服抗生素。根据专家微生物学建议和当地耐药性数据进行选择，可选抗菌药物包括：	
多西环素	第一天 200 mg，然后每天 100 mg，连续 4 天（共 5 天疗程），疗程结束后复查
头孢氨苄（青霉素过敏患者慎用）	500 mg，每天两到三次，（可以增加至 1 到 1.5 g，一天三到四次），连续 5 天，疗程结束后复查
复方新诺明	960 mg，每天两次，连续 5 天，疗程结束后复查
左氧氟沙星（只有在专家建议下从静脉注射的左氧氟沙星改用口服左氧氟沙星，关注其安全性问题）	500 mg，每天一到两次，连续 5 天，疗程结束后复查
如果出现严重的症状或体征（如脓毒症）或耐药风险较高，则应首选 IV 类抗生素。在 48 小时内复查 IV 类抗生素，并考虑改用上述口服抗生素，共 5 天，然后复查 4。根据专家微生物学建议和当地耐药性数据进行选择，可选抗菌药物包括：	
哌拉西林/他唑巴坦	4.5 g，一天三次（如感染严重，可增加剂量至 4.5 g 一天四次）
头孢他啶	2 g，一天三次
头孢曲松	2 g，一天一次
头孢呋辛	750 mg，每日三至四次（严重感染时增加至 1.5g，每日三至四次）
美罗培南	0.5~1g，每日三次
头孢他啶/阿维巴坦	2/0.5g，每日三次
左氧氟沙星（关注其安全性问题）	500mg，每日一至两次（若感染严重，可增加剂量）
如怀疑或证实感染 MRSA，应加用抗生素（即以上列明的 IV 类抗生素的双重治疗）	
万古霉素	15 ~ 20 mg/kg，每日 2 ~ 3 次，根据血清万古霉素浓度调整剂量；严重感染时，负荷剂量为 25~30 mg/kg（最大 2 g /剂）
替考拉宁	起始治疗，6 mg/kg，每 12 小时 1 剂，连续 3 剂，然后 6 mg/kg，一天一次
利奈唑胺（如不能使用万古霉素，仅限专家建议）	600 mg，每天两次口服或 IV

- ¹ See [BNF](#) for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breastfeeding, and administering intravenous (or, where appropriate, intramuscular) antibiotics.
- ² Oral doses are for immediate-release medicines.
- ³ Higher risk of resistance includes symptoms or signs starting more than 5 days after hospital admission, relevant comorbidity such as severe lung disease or immunosuppression, recent use of broad-spectrum antibiotics, colonisation with multidrug-resistant bacteria, and recent contact with a health or social care setting before current admission.
- ⁴ Review treatment after a total of 5 days of antibiotics and consider stopping antibiotics if clinically stable.
- ⁵ See BNF for information on monitoring of patient parameters.
- ⁶ Not licensed for hospital-acquired pneumonia, so use would be [off-label](#). The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Good practice in prescribing and managing medicines and devices](#) for further information.
- ⁷ See [Medicines and Healthcare products Regulatory Agency \(MHRA\) advice](#) for restrictions and precautions for using fluoroquinolone antibiotics because of very rare reports of disabling and potentially long-lasting or irreversible side effects affecting musculoskeletal and nervous systems. Warnings include: stopping treatment at first signs of a serious adverse reaction (such as tendonitis), prescribing with special caution for people over 60 years and avoiding coadministration with a corticosteroid (March 2019).
- ⁸ See BNF for information on therapeutic drug monitoring.

Abbreviations: BNF, British national formulary; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 2 Antibiotics for children and young people under 18 years

Antibiotic ¹	Dosage and course length ²
Children under 1 month	
Antibiotic choice based on local resistance data and specialist microbiological advice	
Children aged 1 month and over	
First-choice oral antibiotic if non-severe symptoms or signs and not at higher risk of resistance ³ (guided by microbiological results when available)	

Co-amoxiclav	1 month to 11 months, 0.5 ml/kg of 125/31 suspension 3 times a day for 5 days then review⁴ 1 year to 5 years, 10 ml of 125/31 suspension⁵ 3 times a day or 0.5 ml/kg of 125/31 suspension 3 times a day for 5 days then review⁴ 6 years to 11 years, 10 ml of 250/62 suspension 3 times a day or 0.3 ml/kg of 250/62 suspension 3 times a day for 5 days then review⁴ 12 years to 17 years, 500/125 mg 3 times a day for 5 days then review⁴
Alternative oral antibiotic if non-severe symptoms or signs and not at higher risk of resistance³, for penicillin allergy or if co-amoxiclav unsuitable	
Clarithromycin	1 month to 11 years: Under 8 kg, 7.5 mg/kg twice a day for 5 days then review⁴ 8 kg to 11 kg, 62.5 mg twice a day for 5 days then review⁴ 12 kg to 19 kg, 125 mg twice a day for 5 days then review⁴ 20 kg to 29 kg, 187.5 mg twice a day for 5 days then review⁴ 30 kg to 40 kg, 250 mg twice a day for 5 days then review⁴ 12 years to 17 years, 500 mg twice a day for 5 days then review⁴
Other options may be suitable based on specialist microbiological advice and local resistance data.	
First-choice intravenous antibiotics if severe symptoms or signs (for example, symptoms or signs of sepsis) or at higher risk of resistance³. Review IV antibiotics by 48 hours and consider switching to oral antibiotics as above for a total of 5 days then review⁴	
Antibiotic choice should be based on specialist microbiological advice and local resistance data. Options include:	
Piperacillin with tazobactam	1 month to 11 years, 90 mg/kg 3 or 4 times a day (maximum 4.5 g per dose 4 times a day) 12 years to 17 years, 4.5 g 3 times a day (increased to 4.5 g 4 times a day if severe infection)
Ceftazidime	1 month to 17 years, 25 mg/kg 3 times a day (50 mg/kg 3 times a day if severe infection; maximum 6 g per day)

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Ceftriaxone	1 month to 11 years (up to 50 kg), 50 mg/kg to 80 mg/kg once a day (use dose at higher end of range if severe infection; maximum 4 g per day) 9 years to 11 years (50 kg and above), 2 g once a day 12 years to 17 years, 2 g once a day
Antibiotics to be added if suspected or confirmed MRSA infection (dual therapy with the IV antibiotic chosen from the list above)	
Teicoplanin ^{6,7}	1 month, initially 16 mg/kg for 1 dose, then 8 mg/kg once daily, subsequent dose to be given 24 hours after initial dose (doses given by IV infusion) 2 months to 11 years, initially 10 mg/kg every 12 hours IV for 3 doses, then 6 mg/kg to 10 mg/kg once daily IV 12 years to 17 years, initially 6 mg/kg every 12 hours IV for 3 doses, then 6 mg/kg once daily IV
Vancomycin ^{6,7}	1 month to 11 years, 10 mg/kg to 15 mg/kg 4 times a day IV, adjusted according to serum-vancomycin concentration 12 years to 17 years, 15 mg/kg to 20 mg/kg 2 or 3 times a day IV, adjusted according to serum-vancomycin concentration (a loading dose of 25 mg/kg to 30 mg/kg can be used in seriously ill people). Maximum 2 g per dose
Linezolid ^{6,8} (if vancomycin cannot be used; specialist advice only)	3 months to 11 years, 10 mg/kg 3 times a day orally or IV (maximum 600 mg per dose) 12 years to 17 years, 600 mg twice a day orally or IV

¹ See [BNF for children](#) for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breastfeeding, and administering intravenous (or, where appropriate, intramuscular) antibiotics.

² Oral doses are for immediate-release medicines. The age bands apply to children of average size and, in practice, the prescriber will use the age bands in conjunction with other factors such as the severity of the condition being treated and the child's size in relation to the average size of children of the same age.

³ Higher risk of resistance includes symptoms or signs starting more than 5 days after hospital admission, relevant comorbidity such as severe lung disease or immunosuppression, recent use of broad-spectrum antibiotics, colonisation with multidrug-resistant bacteria, and recent contact with a health or social care setting before current admission.

⁴ Review treatment after a total of 5 days of antibiotics and consider stopping antibiotics if clinically stable.

⁵ Or 5 ml of 250/62 suspension.

⁶ See BNF for children for information on monitoring of patient parameters.

⁷ See BNF for children for information on therapeutic drug monitoring.

⁸ Not licensed in children and young people under 18 years, so use would be [off-label](#). The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Good practice in prescribing and managing medicines and devices](#) for further information.

Abbreviations: BNFC, British national formulary for children; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.

See the evidence and committee discussions on [choice of antibiotic](#) and [antibiotic course length, dosage and route of administration](#).

^[1] At the time of publication (September 2019), no validated severity assessment tools are available for hospital-acquired pneumonia, and severity of symptoms or signs should be based on clinical judgement.

^[2] Higher risk of resistance includes relevant comorbidity (such as severe lung disease or immunosuppression), recent use of broad-spectrum antibiotics, colonisation with multidrug-resistant bacteria, and recent contact with health and social care settings before current admission.

Terms used in the guideline

Hospital-acquired pneumonia

Pneumonia that develops 48 hours or more after hospital admission and that was not incubating at hospital admission. When managed in hospital, the diagnosis is usually confirmed by chest X-ray. For the purpose of this guideline, pneumonia that develops in hospital after intubation (ventilator-associated pneumonia) is excluded from this definition.

Summary of the evidence

This is a summary of the evidence. For full details, see the [evidence review](#).

Hospital-acquired pneumonia is a lower respiratory tract infection that may be life threatening.

- Early-onset hospital-acquired pneumonia (less than 5 days after admission to hospital) is usually caused by *Streptococcus pneumoniae* and late-onset (more than 5 days after admission to hospital) is usually caused by microorganisms that are acquired in hospital, most commonly methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa* and other non-pseudomonal gram-negative bacteria.
- No evidence from systematic reviews or randomised controlled trials (RCTs) was identified in children or young people under 18 years.

Antibiotic prescribing strategies

- An antibiotic prescribing strategy (guided by results of immediate bronchoscopy with protected specimen brush sample culture) was not significantly different from immediate antibiotics for clinical cure and mortality up to 28 days in adults with hospital-acquired pneumonia (non-ventilated; [Herer et al. 2009](#)). Bronchoscopy was carried out within 24 hours of clinical diagnosis and gram-stain results (available 4 hours to 6 hours after bronchoscopy) were used to modify treatment.
- The total costs (antibiotics and bronchoscopy) of each strategy were not significantly different overall.
- An antibiotic prescribing strategy of using antibiotics with very broad antimicrobial cover (imipenem with cilastatin plus vancomycin) followed by de-escalation to a broad-spectrum antibiotic based on culture results was significantly better than empirical antibiotics for achieving adequate initial antimicrobial cover. However, there were no significant differences in clinical outcomes, including mortality up to 28 days ([Kim et al. 2012](#)). This study included non-ventilated adults with hospital-acquired pneumonia and a small proportion of adults with ventilator-associated pneumonia (8.3%).
- The overall incidence of multidrug-resistant bacteria was significantly higher with very broad antimicrobial cover followed by de-escalation, compared with empirical antibiotics.

Evidence for antibiotic prescribing strategies is based on 2 RCTs ([Herer et al. 2009](#) and [Kim et al. 2012](#)).

Committee discussion on antibiotic prescribing strategies

- The committee noted that the bronchoscopy antibiotic prescribing strategy used by Herer et al. (2009) was not consistent with clinical practice in the UK; culture results are not usually available within 24 hours and sputum cultures are more common than gram staining of bronchoscopy samples.
- The committee noted that overall there were no significant differences in clinical outcomes between the 2 prescribing strategies. Because of the lack of applicability to UK practice, and the small sample size, the committee agreed that there was insufficient evidence to show that the prescribing strategies were equivalent.
- The committee discussed evidence from Kim et al. (2012) suggesting no difference in clinical outcomes between a prescribing strategy of very-broad-spectrum antibiotics with de-escalation, compared with empirical antibiotics. However, the committee was concerned that the rate of emergence of multidrug-resistant bacteria was significantly higher with the very-broad-spectrum antibiotics followed by de-escalation strategy.
- The committee was concerned about the risk of antimicrobial resistance from using very-broad-spectrum antibiotics for longer than necessary, as well as the high rates of adverse effects in some of the included studies. Therefore, the committee concluded that a respiratory sample (for example, sputum sample, nasopharyngeal swab or tracheal aspirate) should be taken and sent for microbiological testing if possible. This reflects current practice.
- The committee agreed that when microbiological results are available, the antibiotic should be reviewed and changed accordingly (for example, if bacteria are found to be resistant), using a narrower-spectrum antibiotic, if appropriate.

Choice of antibiotics

Efficacy of antibiotics

- Overall, there were no differences in the clinical effectiveness (clinical cure or mortality) in a range of antibiotic comparisons in adults with hospital-acquired pneumonia:
 - penicillin with beta-lactamase inhibitor (piperacillin with tazobactam) compared with a carbapenem (imipenem with cilastatin; [Schmitt et al. 2006](#))
 - cephalosporin with beta-lactamase inhibitor (ceftazidime with avibactam) compared

- – with a carbapenem (meropenem; [Torres et al. 2017](#))
- tetracycline (tigecycline) compared with a carbapenem (imipenem with cilastatin; [Freire et al. 2010](#) and [Ramirez et al. 2013](#))
- fluoroquinolone (moxifloxacin) compared with a cephalosporin (ceftriaxone followed by cefuroxime; [Hoffken et al. 2007](#))
- cephalosporin (ceftobiprole) compared with cephalosporin plus oxazolidinone (ceftazidime plus linezolid; [Awad et al. 2014](#))
- glycopeptide (telavancin) compared with glycopeptide (vancomycin; [Rubinstein et al. 2011](#) reported in [Rubinstein et al. 2014](#)).

Evidence for efficacy of antibiotics is based on 6 RCTs (Schmitt et al. 2006, Torres et al. 2017, Freire et al. 2010, Ramirez et al. 2013, Hoffken et al. 2007 and Awad et al. 2014) and 1 post-hoc analysis of an RCT (Rubinstein et al. 2014).

Safety of antibiotics

- About 10% of the general population claim to have a penicillin allergy; this is often because of a skin rash that occurred while taking a course of penicillin as a child. Fewer than 10% of people who think they are allergic to penicillin are truly allergic. See the [NICE guideline on drug allergy](#) for more information.
- People with a history of immediate hypersensitivity to penicillins may also react to cephalosporins and other beta-lactam antibiotics ([BNF, August 2019](#)).
- Macrolides (for example, clarithromycin) should be used with caution in people with a predisposition to QT interval prolongation ([BNF, August 2019](#)).
- Tetracyclines (for example, doxycycline), can deposit in growing bone and teeth (by binding to calcium) causing staining and occasionally dental hypoplasia. They should not be given to pregnant or breastfeeding women, and use in children under 12 years is either contraindicated or cautioned for use in severe or life-threatening infections where there are no alternatives ([BNF, August 2019](#)).
- Co-trimoxazole is associated with rare but serious side effects including blood disorders and Stevens–Johnson syndrome. It is cautioned for use in older people because there is an increased risk of serious adverse effects, and in those with a predisposition to hyperkalaemia. Monitoring of blood counts is recommended with prolonged treatment ([BNF, August 2019](#)).

-
- Fluoroquinolones have restrictions and precautions around their use because of rare reports of disabling and potentially long-lasting or irreversible side effects affecting musculoskeletal and nervous systems ([MHRA Drug Safety Update, March 2019](#)). They may also be associated with a small increased risk of aortic aneurysm and dissection, particularly in older people ([MHRA Drug Safety Update, November 2018](#)).
 - Glycopeptide (for example, vancomycin and teicoplanin) doses are based on body weight. Therapeutic drug monitoring and monitoring of various patient parameters including blood count, urinalysis, auditory function, hepatic function and renal function is recommended depending on the particular glycopeptide ([BNF, August 2019](#)).
 - Severe optic neuropathy can occur with linezolid, particularly if used for longer than 28 days. Blood disorders have also been reported and weekly full blood counts are recommended ([BNF, August 2019](#)).
 - Overall, there were no significant differences in adverse effects in the studies between antibiotics or classes of antibiotics in people with hospital-acquired pneumonia.
 - Treatment-related adverse events were significantly higher with moxifloxacin compared with a cephalosporin (intravenous ceftriaxone then oral cefuroxime; 30% versus 16%, number needed to harm [NNH] 7 [range 3 to 84]).
 - Significantly more people stopped treatment because of adverse events with tigecycline than with imipenem with cilastatin (10.9% versus 6.6%, NNH 23 [range 12 to 150]).
 - See the [summaries of product characteristics](#) for information on contraindications, cautions, drug interactions and adverse effects of individual medicines.

Committee discussion on choice of antibiotics

- The committee agreed that prompt antibiotic treatment should be offered to everyone with hospital-acquired pneumonia.
- The committee discussed the definition of hospital-acquired pneumonia. Because it includes people with pneumonia that develops 48 hours or more after hospital admission and that was not incubating at hospital admission, the committee agreed that the [NICE guideline on community-acquired pneumonia](#) should be followed for people with symptoms or signs of pneumonia starting on days 1 or 2 after hospital admission.
- The committee discussed the timing of antibiotic treatment and was aware of current practice to offer antibiotics within 4 hours. No systematic reviews or RCTs were identified, and the committee agreed that there was no reason to change current practice. However, they noted that the timing should be within 4 hours of an established diagnosis to avoid inappropriate use of broad-spectrum antibiotics.
- The committee noted that evidence was identified in adults only, and for a limited number of head-to-head antibiotic comparisons. They agreed that recommendations for children and young people should be based on its experience and extrapolation of evidence in adults, taking account of any relevant medicines safety concerns.
- Given the clinical expertise needed for assessing and managing hospital-acquired pneumonia in very young children (under 1 month), the committee agreed that the choice of antibiotic in these children should be based on local resistance data and specialist microbiological advice.
- Overall, the limited evidence showed no differences in clinical effectiveness between different broad-spectrum antibiotics or classes of antibiotics, with some small differences in the rates of adverse effects. The committee noted the high rates of adverse events for many broad-spectrum antibiotics included in the studies.
- The committee discussed the most common causes of hospital-acquired pneumonia. They agreed that cause is often uncertain because many people do not have a microbiological diagnosis.
- They recognised that *S. pneumoniae* is the most common cause in people who develop hospital-acquired pneumonia within 5 days of hospital admission. The risk of having a multidrug-resistant infection with *P. aeruginosa*, MRSA or extended-spectrum beta-lactamases (ESBLs) increases in people who develop the infection after more than 5 days of

- being in hospital, although resistance rates vary locally.
- Therefore, the committee agreed that for people with symptoms or signs of pneumonia starting on days 3 to 5 after hospital admission who are not at high risk of resistance, it may be appropriate to follow the NICE guideline on community-acquired pneumonia for recommendations on the choice of antibiotic, based on their clinical judgement. This would give the option to treat some people with amoxicillin, which is a narrower-spectrum antibiotic with activity against *S. pneumoniae*.
- Based on experience, the committee agreed that there are several factors that need to be taken into account when choosing an antibiotic, including the severity of symptoms or signs. The committee did not know of any validated tools for assessing the severity of hospital-acquired pneumonia, and therefore agreed that this should be based on clinical judgement.
- The committee also agreed that some people are at higher risk of developing complications, for example, people with a comorbidity such as severe lung disease or immunosuppression.
- The committee recognised that, when available, local antimicrobial resistance data are an important consideration in hospital-acquired pneumonia, including at hospital and ward-based level (particularly in high-risk areas such as intensive care, high-dependency units, haematology or oncology).
- The committee also agreed that recent use of broad-spectrum antibiotics and recent contact with healthcare services before the current hospital admission were also highly likely to increase the risk of resistant pathogens.
- The committee agreed that taking account of these factors would optimise the appropriate use of broad-spectrum antibiotics and minimise the risk of antimicrobial resistance.
- The committee agreed that an antibiotic should be started empirically, so as not to delay treatment for an infection with a high-mortality risk.
- The committee agreed that the choice of antibiotic should be based on its experience of which antibiotics are effective against likely pathogens and cause the least harm, with the narrowest spectrum possible to minimise the risk of antimicrobial resistance and adverse effects. However, the committee discussed that people with severe symptoms or signs and those at higher risk of resistance will need broad-spectrum antibiotics with high activity against likely organisms.
- Based on its experience, the committee recommended **co-amoxiclav** as **first-choice**

- **antibiotic** for people with non-severe symptoms or signs who are not at higher risk of resistance; co-amoxiclav is a broad-spectrum antibiotic that combines a penicillin with a beta-lactamase inhibitor and has good activity against common pathogens, such as *S. pneumoniae* and *Haemophilus influenzae*. The committee also recognised the extensive clinical experience of its effectiveness in this population.
- For adults with non-severe symptoms or signs who are not at higher risk of resistance, with penicillin allergy or in whom co-amoxiclav is unsuitable (for example, because of local resistance data), the committee agreed that the choice of an **alternative antibiotic** should be based on local resistance data and specialist microbiological advice only. They agreed that options include:
 - doxycycline (a tetracycline)
 - cefalexin (a cephalosporin; not suitable if there is a risk of penicillin-resistant pneumococci)
 - co-trimoxazole (trimethoprim plus a sulfonamide)
 - levofloxacin (a fluoroquinolone; only to be used when switching from IV antibiotics, following specialist advice).
- Co-trimoxazole and levofloxacin are not licensed for hospital-acquired pneumonia, so use would be off-label.
- In children and young people with penicillin allergy or in whom co-amoxiclav is unsuitable, the **alternative antibiotic** is **clarithromycin** (a macrolide); this has good activity against common pathogens and is appropriate for use in children and young people. However, the committee recognised that other options may be suitable based on local resistance data and specialist microbiological advice.
- The committee agreed that specialist advice should be sought for young women who are pregnant with penicillin allergy or in whom co-amoxiclav is unsuitable, because they were not able to specify an alternative antibiotic for this population.
- Based on its experience, the committee recognised that many broad-spectrum antibiotics would be appropriate as **first-choice intravenous antibiotics** for people with severe symptoms or signs, or who are at higher risk of resistance. It agreed that the choice should be based on local resistance data and following specialist microbiological advice. Options include:

- - **piperacillin with tazobactam** (an antipseudomonal penicillin with a beta-lactamase inhibitor)
 - **ceftazidime** (a third-generation cephalosporin)
 - **ceftriaxone** (a third-generation cephalosporin)
 - **cefuroxime** (a third-generation cephalosporin; in adults)
 - **meropenem** (a carbapenem; in adults)
 - **ceftazidime with avibactam** (a third-generation cephalosporin with a beta-lactamase inhibitor; in adults)
 - **levofloxacin** (in adults).
- These antibiotics have good activity against common pathogens in this population, including multidrug-resistant *P. aeruginosa*, ESBLs and some carbapenemase-producing gram-negative bacteria.
- The committee discussed that a small number of people with hospital-acquired pneumonia may have suspected or confirmed infection with MRSA. Therefore, based on their experience, the committee agreed that for these people, 1 of the following **antibiotics** with activity against MRSA should be added to the treatment regimen:
 - **vancomycin** (a glycopeptide)
 - **teicoplanin** (a glycopeptide)
 - **linezolid** (an oxazolidinone; if vancomycin cannot be used, following specialist advice only). Linezolid is not licensed in children and young people under 18 years, so use would be off-label.
- Based on its experience, the committee recommended the same **oral antibiotics** (discussed above) for people with severe symptoms or signs or at higher risk of resistance who have initially received intravenous antibiotics, to complete the antibiotic course when intravenous antibiotics are no longer required.
- The committee recognised that hospital-acquired pneumonia requires careful monitoring. It agreed by consensus that a person's condition should be reassessed if symptoms do not improve as expected or worsen rapidly or significantly at any time.

- The committee agreed that for people with symptoms that are not improving as expected with antibiotics, or who are known to have multidrug-resistant bacteria, specialist advice from a microbiologist should be sought.

Antibiotic course length, dosage and route of administration

- No systematic reviews or RCTs were identified that compared antibiotic course lengths, dosage or route of administration.

Committee discussions on antibiotic course length, dosage and route of administration

- The committee agreed that the shortest course that is likely to be effective should be prescribed to reduce the risk of antimicrobial resistance and adverse effects from broad-spectrum antibiotics. However, hospital-acquired pneumonia is a serious infection with a high-mortality risk and needs effective treatment.
- Based on its experience and extrapolation of evidence for people with community-acquired pneumonia (see the [NICE guideline on community-acquired pneumonia](#)), the committee agreed that a total course of 5 days of antibiotics was the minimum required.
- The committee agreed that antibiotic treatment should be reviewed at 5 days. Stopping the antibiotic should be considered on an individual basis if the person is judged to be clinically stable.
- Based on its experience, the committee agreed that usual BNF and BNF for children doses for hospital-acquired pneumonia, or severe susceptible infections should be used.
- In line with the [NICE guideline on antimicrobial stewardship](#) and Public Health England's [Start smart – then focus](#), oral antibiotics should be given first line if the person can take them, and if the severity of their infection does not require intravenous antibiotics. The use of intravenous antibiotics should be reviewed by 48 hours (taking into account the person's response to treatment and any microbiological results) and switched to oral treatment where possible.
- For people with severe symptoms or signs or at higher risk of resistance, the committee agreed that intravenous antibiotics should always be given initially.

Other considerations

Medicines adherence

Medicines adherence may be a problem for some people taking antibiotics that need frequent dosing or longer treatment duration (see the [NICE guideline on medicines adherence](#)).

Resource implications

Recommended antibiotics (except ceftazidime with avibactam) are available as generic formulations. See the [Drug Tariff](#) and the [BNF](#) for costs.

See the [evidence review](#) for more information.

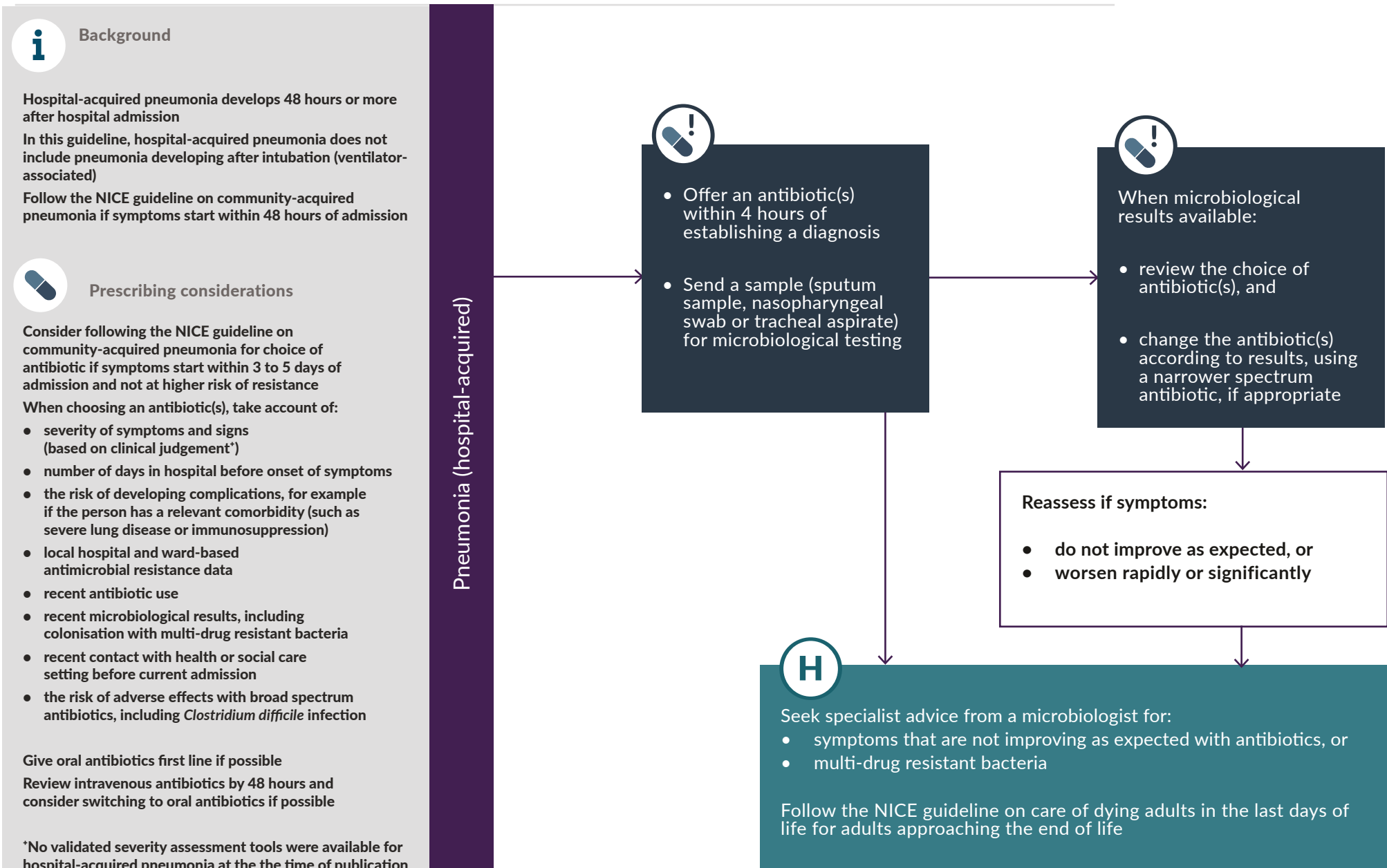
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Accreditation



Pneumonia (hospital-acquired): antimicrobial prescribing

NICE National Institute for Health and Care Excellence



When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

September 2019

Pneumonia (hospital-acquired): antimicrobial prescribing

NICE National Institute for Health and Care Excellence

Choice of antibiotic: adults aged 18 years and over

Antibiotic ¹	Dosage and course length ²
First choice oral antibiotic for non-severe symptoms or signs and not at higher risk of resistance ³ (guided by microbiological results when available)	
Co-amoxiclav	500/125 mg three times a day for 5 days then review ⁴
Alternative oral antibiotics for non-severe symptoms or signs and not at higher risk of resistance ³ , if penicillin allergy or if co-amoxiclav unsuitable. Base choice on specialist microbiological advice and local resistance data. Options include:	
Doxycycline	200 mg on first day, then 100 mg once a day for 4 days (5-day course) then review ⁴
Cefalexin (caution in penicillin allergy)	500 mg twice or three times a day (can be increased to 1 to 1.5 g three or four times a day) for 5 days then review ⁴
Co-trimoxazole ^{5,6}	960 mg twice a day for 5 days then review ⁴
Levofloxacin ⁶ (only if switching from IV levofloxacin with specialist advice; consider safety issues ⁷)	500 mg once or twice a day for 5 days then review ⁴
First choice IV antibiotics if severe symptoms or signs (for example, of sepsis) or at higher risk of resistance ³ . Review IV antibiotics by 48 hours and consider switching to oral antibiotics as above for a total of 5 days then review ⁴ . Base choice on specialist microbiological advice and local resistance data. Options include:	
Piperacillin with tazobactam	4.5 g three times a day (increased to 4.5 g four times a day if severe infection)
Ceftazidime	2 g three times a day
Ceftriaxone	2 g once a day
Cefuroxime	750 mg three or four times a day (increased to 1.5 g three or four times a day if severe infection)
Meropenem	0.5 to 1 g three times a day
Ceftazidime with avibactam	2/0.5 g three times a day
Levofloxacin ⁶ (consider safety issues ⁷)	500 mg once or twice a day (use higher dosage if severe infection)
Antibiotics to be added if suspected or confirmed MRSA infection (dual therapy with an IV antibiotic listed above)	
Vancomycin ⁵	15 to 20 mg/kg two or three times a day IV, adjusted according to serum vancomycin; loading dose of 25 to 30 mg/kg for serious illness (maximum 2 g per dose)
Teicoplanin ⁵	Initially 6 mg/kg every 12 hours for 3 doses, then 6 mg/kg once a day
Linezolid ⁵ (if vancomycin cannot be used; specialist advice only)	600 mg twice a day orally or IV

¹See [BNF](#) for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breast-feeding, and administering intravenous (or, where appropriate, intramuscular) antibiotics.

²Oral doses are for immediate-release medicines.

³Higher risk of resistance includes symptoms or signs starting more than 5 days after hospital admission, relevant comorbidity such as severe lung disease or immunosuppression, recent use of broad spectrum antibiotics, colonisation with multi-drug resistant bacteria and recent contact with health or social care setting before current admission.

⁴Review treatment after a total of 5 days of antibiotics and consider stopping the antibiotic if clinically stable.

⁵See [BNF](#) for information on monitoring of patient parameters and therapeutic drug monitoring.

⁶Not licensed for hospital-acquired pneumonia, so use is off-label. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Good practice in prescribing and managing medicines and devices](#) for further information.

⁷See [MHRA](#) advice for restrictions and precautions for using fluoroquinolones due to very rare reports of disabling and potentially long-lasting or irreversible side effects affecting musculoskeletal and nervous systems. Warnings include stopping treatment at first signs of a serious adverse reaction (such as tendonitis), prescribing with caution for people over 60 and avoiding coadministration with corticosteroids (March 2019).

医院获得性肺炎（HAP）：抗菌药物处方

抗生素的选择：≥18 岁成人

抗生素	剂量和疗程
对于无严重的症状或体征以及无较高耐药风险的患者，首选的口服抗生素（可根据微生物学结果指导用药）	
阿莫西林/克拉维酸	500/125 mg，每天 3 次，连续 5 天，疗程结束后复查
如青霉素过敏或阿莫西林/克拉维酸不适用，无严重的症状或体征以及无较高耐药风险的患者可选择的口服抗生素。根据专家微生物学建议和当地耐药性数据进行选择，可选抗菌药物包括：	
多西环素	第一天 200 mg，然后每天 100 mg，连续 4 天（共 5 天疗程），疗程结束后复查
头孢氨苄（青霉素过敏患者慎用）	500 mg，每天两到三次，（可以增加至 1 到 1.5 g，一天三到四次），连续 5 天，疗程结束后复查
复方新诺明	960 mg，每天两次，连续 5 天，疗程结束后复查
左氧氟沙星（只有在专家建议下从静脉注射的左氧氟沙星改用口服左氧氟沙星，关注其安全性问题）	500 mg，每天一到两次，连续 5 天，疗程结束后复查
如果出现严重的症状或体征（如脓毒症）或耐药风险较高，则应首选 IV 类抗生素。在 48 小时内复查 IV 类抗生素，并考虑改用上述口服抗生素，共 5 天，然后复查 4。根据专家微生物学建议和当地耐药性数据进行选择，可选抗菌药物包括：	
哌拉西林/他唑巴坦	4.5 g，一天三次（如感染严重，可增加剂量至 4.5 g 一天四次）
头孢他啶	2 g，一天三次
头孢曲松	2 g，一天一次
头孢呋辛	750 mg，每日三至四次（严重感染时增加至 1.5g，每日三至四次）
美罗培南	0.5~1g，每日三次
头孢他啶/阿维巴坦	2/0.5g，每日三次
左氧氟沙星（关注其安全性问题）	500mg，每日一至两次（若感染严重，可增加剂量）
如怀疑或证实感染 MRSA，应加用抗生素（即以上列明的 IV 类抗生素的双重治疗）	
万古霉素	15 ~ 20 mg/kg，每日 2 ~ 3 次，根据血清万古霉素浓度调整剂量；严重感染时，负荷剂量为 25~30 mg/kg（最大 2 g /剂）
替考拉宁	起始治疗，6 mg/kg，每 12 小时 1 剂，连续 3 剂，然后 6 mg/kg，一天一次
利奈唑胺（如不能使用万古霉素，仅限专家建议）	600 mg，每天两次口服或 IV

Pneumonia (hospital-acquired): antimicrobial prescribing

NICE National Institute for Health and Care Excellence

Choice of antibiotic: children and young people over 1 month and under 18 years

Antibiotic ¹	Dosage and course length ²
First choice oral antibiotic if non-severe symptoms or signs and not at higher risk of resistance ³ (guided by microbiological results when available)	
Co-amoxiclav	1 to 11 months, 0.5 ml/kg of 125/31 suspension three times a day for 5 days then review ⁴ 1 to 5 years, 10 ml of 125/31 suspension ⁵ three times a day or 0.5 ml/kg of 125/31 suspension three times a day for 5 days then review ⁴ 6 to 11 years, 10 ml of 250/62 suspension three times a day or 0.3 ml/kg of 250/62 suspension three times a day for 5 days then review ⁴ 12 to 17 years, 500/125 mg three times a day for 5 days then review ⁵
Alternative oral antibiotic if non-severe symptoms or signs and not at higher risk of resistance ³ , for penicillin allergy or if co-amoxiclav unsuitable	
Clarithromycin	1 month to 11 years: Under 8 kg, 7.5 mg/kg twice a day for 5 days then review ⁴ ; 8 to 11 kg, 62.5 mg twice a day for 5 days then review ⁴ 12 to 19 kg, 125 mg twice a day for 5 days then review ⁴ ; 20 to 29 kg, 187.5 mg twice a day for 5 days then review ⁴ 30 to 40 kg, 250 mg twice a day for 5 days then review ⁴ 12 to 17 years, 500 mg twice a day for 5 days in total then review ⁴
Other options may be suitable based on specialist microbiological advice and local resistance data	
First choice IV antibiotics if severe symptoms or signs (for example, symptoms or signs of sepsis) or at higher risk of resistance ³ . Review IV antibiotics by 48 hours and consider switching to oral antibiotics as above for a total of 5 days then review ⁴	
Antibiotic choice based on specialist microbiological advice only and local resistance data. Options include:	
Piperacillin with tazobactam	1 month to 11 years, 90 mg/kg three or four times a day (maximum 4.5 g per dose four times a day) 12 to 17 years, 4.5 g three times a day (increased to 4.5 g four times a day if severe infection)
Ceftazidime	1 month to 17 years, 25 mg/kg three times a day (50 mg/kg three times a day if severe infection; maximum 6 g per day)
Ceftriaxone	1 month to 11 years (up to 50 kg), 50 to 80 mg/kg once a day (use dose at higher end of range if severe infection; maximum 4 g per day) 9 to 11 years (50 kg and above), 2 g once a day 12 to 17 years, 2 g once a day
Antibiotics to be added if suspected or confirmed MRSA infection (dual therapy with an IV antibiotic listed above)	
Teicoplanin ^{6,7}	1 month, initially 16 mg/kg for 1 dose then 8 mg/kg once daily subsequent dose to be given 24 hours after initial dose (doses given by IV infusion) 2 months to 11 years, initially 10 mg/kg every 12 hours IV for 3 doses, then 6 to 10 mg/kg once daily IV 12 to 17 years, initially 6 mg/kg every 12 hours IV for 3 doses, then 6 mg/kg once daily IV
Vancomycin ^{6,7}	1 months to 11 years, 10 to 15 mg/kg four times a day, adjusted according to serum vancomycin; 12 to 17 years, 15 to 20 mg/kg two or three times a day, adjusted according to serum vancomycin, loading dose of 25 to 30 mg/kg for serious illness (maximum 2 g per dose)
Linezolid ⁸ (if vancomycin cannot be used; specialist advice only)	3 months to 11 years, 10 mg/kg three times a day orally or IV (maximum 600 mg per dose) 12 to 17 years, 600 mg twice a day orally or IV

¹See [BNFC](#) for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breast-feeding, and administering intravenous (or, where appropriate, intramuscular) antibiotics.

²Oral doses are for immediate-release medicines. Prescribers to use age bands with other factors such as severity and child's size in relation to the average for children of the same age.

³Higher risk of resistance includes onset of symptoms more than 5 days after hospital admission, relevant comorbidity such as severe lung disease or immunosuppression, recent use of broad spectrum antibiotics, colonisation with multi-drug resistant bacteria and recent contact with health or social care setting before current admission.

⁴Review treatment after a total of 5 days and consider stopping antibiotics if clinically stable.

⁵Or 5 ml of 250/62 suspension.

⁶See [BNFC](#) for information on monitoring of patient parameters.

⁷See [BNFC](#) for information on therapeutic drug monitoring.

⁸Linezolid is not licensed in children and young people under 18 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Good practice in prescribing and managing medicines and devices](#) for further information.

REVIEW

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The management of intra-abdominal infections from a global perspective: 2017 WSES guidelines for management of intra-abdominal infections

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Abstract

Intra-abdominal infections (IAIs) are common surgical emergencies and have been reported as major contributors to non-trauma deaths in the emergency departments worldwide.

The cornerstones of effective treatment of IAIs are early recognition, adequate source control, and appropriate antimicrobial therapy. Prompt resuscitation of patients with ongoing sepsis is of utmost importance.

In hospitals worldwide, non-acceptance of, or lack of access to, accessible evidence-based practices and guidelines result in overall poorer outcome of patients suffering IAIs.

The aim of this paper is to promote global standards of care in IAIs and update the 2013 WSES guidelines for management of intra-abdominal infections.

Keywords: Intra-abdominal infections, Sepsis, Peritonitis, Antibiotics

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Background

The world's burden of emergency surgery diseases is significant and appears to be increasing. Emergency services and acute surgical care constitute a major gap in the focus of the health sector worldwide, and several issues need to be addressed in order to promote a global dialogue on what is the most appropriate way to configure acute care surgery worldwide [1]. Although variations in the spectrum of surgical diseases are observed among and within countries, "essential" surgery and anaesthesia in emergency should be viewed as a core group of services that can be delivered within the context of universal access [1–3]. Particularly for the rural populations in low- and middle-income countries (LMICs), there are enormous gaps in access to life-saving and disability-preventing surgical services [4–6]. Furthermore, many hospitals continue to have logistic barriers associated with the application of evidence-based practice. This may lead to an overall poorer adherence to international guidelines, making them impractical to a large part of the world's population [7, 8].

Complicated intra-abdominal infections (cIAIs) are an important cause of morbidity and mortality, particularly if poorly managed. A recent multi-center observational study, conducted in 132 medical institutions worldwide during a 4-month period (October 2014–February 2015) enrolled 4553 patients with cIAIs [1]. The overall mortality in this study was 9.2% (416/4533).

The aim of these guidelines is to present an evidence-based international consensus position on the management of IAIs, from collaboration of a panel of experts, with a view to promoting the standards of care for the management of IAIs worldwide.

Methods

These guidelines have been formulated by international collaboration and discussion among an expert panel of clinicians, practicing in the field of emergency surgery. These consensus guidelines have been facilitated and coordinated by the board of the World Society of Emergency Surgery and are an update of the 2013 WSES guidelines on this topic.

The statements are formulated and graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) hierarchy of evidence from Guyatt and colleagues [9], summarized in Table 1.

Principles of sepsis control

The key factors in the effective treatment of cIAIs are (a) a prompt diagnosis, (b) adequate resuscitation, (c) early initiation of appropriate antibiotic therapy, (d) early and effective source control, and finally, (e) reassessment

of the clinical response and appropriate adjustment of the management strategy.

Abdominal sepsis represents the host's systemic inflammatory response to intra-abdominal infections. Sepsis is a dynamic process that can evolve into conditions of varying severity [10, 11]. The inflammatory response in patients with sepsis depends on the causative pathogen and the host (genetic characteristics and co-existing illnesses), with differential responses at local, regional, and systemic levels [11]. If left untreated, it may lead to the functional impairment of one or more vital organs or systems. It was previously defined that severity of illness and the inherent mortality risk escalate from sepsis, through severe sepsis and septic shock up multi-organ failure. However, differences in the spectrum of etiology and patient factors, including age and co-morbidities, make the course of sepsis different from patient to patient. Illustrating the importance of age, recent data from a consecutive, population-based cohort of patients with perforated gastroduodenal ulcer (PGDU), showed that octa- and nona-genarians with PGDU presented with fewer signs of peritonitis and had an attenuated inflammatory response [12]. HIV patients, common in sub-Saharan Africa, have an increased risk to develop sepsis due to the HIV infection itself that affects several components of the immune system involved in sepsis pathogenesis [13]. HIV causes increased susceptibility to invasive infections and affects sepsis pathogenesis caused by pre-existing activation and exhaustion of the immune system [14], and even if HIV-infected patients on antiretroviral therapy can now safely undergo major abdominal surgery with encouraging results, they are still relatively poorer than those of HIV-negative subjects [15].

Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) has recently been published [16] and updated previous classifications [17, 18]. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be represented by an increase in the Sequential (sepsis-related) Organ Failure Assessment (SOFA) score of 2 points or more. Septic shock should be defined as a subset of sepsis and should be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. The definition of severe sepsis is now superfluous. The new definition of sepsis suggests that patients with at least 2 of these 3 clinical variables: Glasgow Coma Scale score of 13 or less, systolic blood pressure of 100 mm Hg or less, and respiratory rate 22/min or greater (quick SOFA - qSOFA) may be prone

Table 1 Grading of Recommendations Assessment, Development and Evaluation (GRADE) hierarchy of evidence from Guyatt et al. [9]

Grade of recommendation	Clarity of risk/benefit	Quality of supporting evidence	Implications
1A			
Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, applies to most patients in most circumstances without reservation
1B			
Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect analyses, or imprecise conclusions) or exceptionally strong evidence from observational studies	Strong recommendation, applies to most patients in most circumstances without reservation
1C			
Strong recommendation, low-quality, or very low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but subject to change when higher quality evidence becomes available
2A			
Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on the patient, treatment circumstances, or social values
2B			
Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on the patient, treatment circumstances, or social values
2C			
Weak recommendation, low-quality, or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendation; alternative treatments may be equally reasonable and merit consideration

to a poor outcome typical of sepsis and patients with positive qSOFA should be clinically characterized as septic by SOFA score (Table 2). The SOFA score (Table 2) was proposed in 1996 by the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine [19] to objectively describe the degree of organ dysfunction over time and to evaluate morbidity in intensive care unit (ICU) in patients with sepsis. It was demonstrated to be a good indicator of prognosis in critically ill patients during the first few days of ICU admission [20].

Some concerns about the new definition of sepsis have been reported [21].

Since the first classification in 1991 [17], the definitions of sepsis, severe sepsis, and septic shock, though

imprecise, have provided to clinicians a useful framework for clinical management, stressing the need for early recognition. The new definition of sepsis requiring the presence of organ failure has lost its predictive potential and may hinder the awareness of the importance of early recognition and treatment of sepsis, de-emphasizing intervention at earlier stages when it is most treatable, and leading to a higher risk of delayed diagnosis. Early recognition of sepsis is a general principle of sepsis management and is very important in LMICs where the priorities for improving quality of care of critically ill patients are different.

Documenting the burden of critical illness in low-resource settings is challenging. In these settings, a robust triage system that quickly recognizes critically ill patients and transfers them immediately to an acute care unit are a vital component of the emergency services [22].

Moreover in many areas worldwide, there are limited resources for intensive investigations, as a consequence, any process of improving quality of sepsis care globally should focus on simple diagnostic criteria based on physical examination findings that can recognize patients needing critical care. In these settings, a feasible, low-cost method of rapidly identifying patients requiring critical care should be crucial.

Sepsis-3 definition introduces Quick SOFA (qSOFA) as a tool for identifying patients at risk of sepsis with a higher risk of hospital death both inside and outside critical care units. However, qSOFA does not define sepsis and the new sepsis definitions recommend using an increase in the SOFA score of two points or more to represent organ dysfunction. The SOFA score is potentially not accessible everywhere, especially for PaO_2 , which would require an arterial blood gas measurement.

Early warning scores utilize physiological, easy-to-measure parameters, assessing physiological parameters such as systolic blood pressure, pulse rate, respiratory rate, temperature, oxygen saturations, and level of consciousness [23].

In patients with intra-abdominal infections, early warning scores associated with abdominal signs and symptoms such as abdominal pain and abdominal rigidity can screen patients needing immediate acute care surgery.

Finally, although some patients with ongoing sepsis may not have elevated lactate levels at presentation or during their clinical course [24, 25], lactate measurement is advised as an important component of the initial evaluation of patients with sepsis. Elevated lactate levels (even if >4 mmol/l) are no longer part of organ dysfunction criteria to define sepsis. According to the new definition of sepsis, high lactate levels should be used only as one of the criteria to define septic shock.

Table 2 SOFA Score

$\text{PaO}_2/\text{FiO}_2$ (mmHg)	SOFA score
<400	1
<300	2
<200 and mechanically ventilated	3
<100 and mechanically ventilated	4
Glasgow coma scale	
13–14	1
10–12	2
6–9	3
<6	4
Mean arterial pressure OR administration of vasopressors required	SOFA score
MAP <70 mm/Hg	1
dop ≤ 5 or dob (any dose)	2
dop >5 OR epi ≤ 0.1 OR nor ≤ 0.1	3
dop >15 OR epi >0.1 OR nor >0.1	4
Bilirubin (mg/dl) [$\mu\text{mol/L}$]	
1.2–1.9 [>20 –32]	1
2.0–5.9 [33–101]	2
6.0–11.9 [102–204]	3
>12.0 [>204]	4
Platelets $\times 10^3/\mu\text{l}$	
<150	1
<100	2
<50	3
<20	4
Creatinine (mg/dl) [$\mu\text{mol/L}$] (or urine output)	
1.2–1.9 [110–170]	1
2.0–3.4 [171–298, 305]	2
3.5–4.9 [300–440] (or <500 ml/d)	3
>5.0 [>440] (or <200 ml/d)	4

Early recognition of the patient with ongoing abdominal sepsis is an essential step for an effective treatment.

Prompt administration of intravenous fluids for resuscitation is critical in patients with an ongoing sepsis. This initial resuscitation should be titrated to the clinical response, and not solely guided by a predetermined protocol. Vasopressor agents may serve to augment and assist fluid resuscitation, particularly where this therapy alone is failing (Recommendation 1A).

The data from WISS study showed that mortality was significantly affected by sepsis—mortality by sepsis status was no sepsis 1.2%, sepsis only 4.4%, severe sepsis 27.8%, and septic shock 67.8% [1].

Identifying patients with ongoing sepsis early and correcting the underlying microvascular dysfunction may improve patient outcomes. If not corrected, microvascular dysfunction can lead to global tissue hypoxia, direct tissue damage, and ultimately, organ failure [26].

Fluid therapy to improve microvascular blood flow and increase cardiac output is an essential part of the treatment of patients with sepsis. Crystalloid solutions should be the first choice because they are well tolerated and cheap [27]. They should be infused rapidly to induce a quick response but not so fast that an artificial stress response develops. They should be interrupted when no improvement of tissue perfusion occurs in response to volume loading. Basal lung crepitations may indicate fluid overload or impaired cardiac function. Recently, measuring inferior vena cava (IVC) diameter by ultrasound was suggested as a novel outcome measure to guide this resuscitative approach [28].

The Surviving Sepsis Campaign (SSC) is a joint collaboration of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine committed to reducing mortality from severe sepsis and septic shock worldwide in 2002. In 2012, the SSC updated its guidelines. SSC guidelines have been regarded as the standard of care in patients with severe sepsis and septic shock in many hospitals worldwide [29]. However, the possibility to implement the SSC guidelines has been questioned in LMICs where simple and low-cost standardized laboratory testing should be emphasized to allow accurate diagnosis, prognosis, and monitoring of treatment response [30, 31]. A study conducted as an anonymous questionnaire-based, cross-sectional survey among anaesthesia providers, suggested that the most recent SSC guidelines cannot be implemented in Africa, particularly in Sub-Sahara Africa, due to a shortage of required hospital facilities, equipment, drugs, and disposable materials [32].

The 2016 Surviving Sepsis Campaign International Guidelines for Management of Sepsis and Septic Shock was recently published [33]. Previous iterations of these guidelines aimed to treat the early hypovolemic phase of

sepsis by providing appropriate high volume resuscitation targeting central venous pressure 8–12 mm Hg, mean arterial pressure (MAP) >65 mm Hg, urine output >0.5 mL/kg/h, central venous (superior vena cava) or mixed venous oxygen saturation >70 or >65%, respectively. Since the first draft of guidelines, the basic concept of the initial resuscitation has been early goal-directed therapy (EGDT) described by Rivers in 2001, who reported that patients with severe sepsis and septic shock presenting to the emergency department had a lower mortality rate, if they received a specific 6-h resuscitation bundle of EGDT [34]. Recent randomized controlled trials (ProCESS, ARISE, and ProMiSe trials) results [35–37] have questioned River's resuscitation protocol results demonstrating that use of early goal-directed therapy for patients presenting to the emergency department with early septic shock did not reduce mortality compared with usual care.

These data indicate that an early identification and prompt administration of intravenous fluids are mandatory. However, initial resuscitation should no longer be based on a predetermined protocol but on clinical endpoints.

Hypotension is the most common indicator of inadequate perfusion. The SSC advocated a mean arterial pressure (MAP) goal of 65 mm Hg during the first 6 h of treatment. It was confirmed by a randomized controlled trial "Sepsis and Mean Arterial Pressure" (SEPSISPAM) examining high versus low MAP goals in patients with septic shock. It demonstrated that targeting a mean arterial pressure of 80–85 mm Hg, as compared with 65–70 mm Hg, in patients with septic shock undergoing resuscitation did not result in significant differences in mortality at either 28 or 90 days [38].

Particularly in patients with abdominal sepsis, requiring urgent surgical intervention, overly aggressive fluid resuscitation may increase intra-abdominal pressure and worsen the inflammatory response, which is associated with a high risk of complications [39, 40]. In patients with septic shock fluid infusion during resuscitation, bowel oedema and forced closure of the abdominal wall can cause intra-abdominal hypertension and abdominal compartment syndrome that can consequently modify pulmonary, cardiovascular, renal, splanchnic, and central nervous system physiology causing significant morbidity and mortality. Clinical endpoints in monitoring fluid volume infusions should include mean arterial pressure, skin color and capillary refill, mental status, or urinary output. Central venous access, where available, may be helpful for monitoring of central venous pressure. Simpler non-invasive devices such as tissue perfusion monitors may be more practical but are not yet widely used. Repeated measurements of IVC diameter by ultrasound can be a simple and useful method for defining fluid requirements [28].

Vasopressor agents should be administered to restore organ perfusion if fluid resuscitation fails optimizing blood flow and if hypotension persists following fluid loading. These agents should be globally available. Vasopressor and inotropic agents have increasingly become a therapeutic cornerstone for the management of sepsis. They have excitatory and inhibitory actions on the heart and vascular smooth muscle, as well as important metabolic, central nervous system, and presynaptic autonomic nervous system effects. The optimal timing of vasopressors relative to fluid infusion has been debated. Recently, a large multi-center retrospective analysis of 2849 patients with septic shock, investigators found that mortality was lowest when vasopressors were delayed by 1 h and infused from hours 1 to 6 following onset of shock [41]. Norepinephrine is now the first-line vasopressor agent used to correct hypotension in the event of septic shock [29]. Norepinephrine is more efficacious than dopamine and may be more effective for reversing hypotension in patients with septic shock [29]. Dopamine may cause more tachycardia and may be more arrhythmogenic than norepinephrine, and as an alternative vasopressor agent to norepinephrine, it should be used only in patients with low risk of tachyarrhythmias and absolute or relative bradycardia.

Dobutamine is an inotropic agent used to treat septic shock patients increasing cardiac output, stroke index, and oxygen delivery (DO_2). It has been suggested to be administered to pre-existing vasopressor therapy in the presence of myocardial dysfunction, defined as elevated cardiac filling pressures and low cardiac output. However, dobutamine increases DO_2 to supranormal values and in critically ill patients, it has raised serious questions regarding its safety in the treatment of septic shock. Because dobutamine provides direct stimulation of the β -1 adrenergic receptors, it is recognized as more problematic with regard to tachycardia and arrhythmia.

In LMICs, it may be acceptable to use adrenaline infusions as the inotrope of choice, given it is readily available, cheap, and has been shown to be equivalent to noradrenaline in septic shock [42].

Increased global availability of vasopressors together with a better understanding of their indications, pharmacodynamics, and important adverse effects are mandatory to fight sepsis worldwide.

Diagnosis

A step-up approach for diagnosis from clinical and laboratory examination, to imaging examination should be used and tailored to the hospitals resources (Recommendation 1B).

The diagnosis of intra-abdominal infections is based primarily on clinical assessment. Typically, the patient is

admitted to the emergency department with abdominal pain and a systemic inflammatory response, including fever, tachycardia, and tachypnoea. Abdominal rigidity suggests the presence of peritonitis. Hypotension and hypoperfusion signs such as lactic acidosis, oliguria, and acute alteration of mental status are indicative of ongoing sepsis.

In many countries worldwide, a large proportion of patients with diffuse peritonitis still present to the hospital with unacceptable delay. This event reduces the percentage of surviving at the lowest rates in the world [8]. In emergency departments of limited-resource hospitals, the diagnosis of intra-abdominal infections is mainly clinical; supported by basic laboratory tests like full blood count (complete blood count). Ultrasonography is sometimes done to aid diagnosis, if available. Therefore, the clinician has to improve clinical diagnosis by looking carefully for those signs and symptoms. In rural and remote areas of LMICs, diagnostic imaging is often insufficient, and in some instances, completely lacking [43]. In recent years, ultrasound use has increased worldwide, facilitated by ultrasound machines becoming smaller, more reliable, and less expensive [44]. Ultrasound is reproducible and can be easily repeated, but remains highly user-dependent, and thus, experience should be taken into account for diagnostic accuracy and reliability.

In rural areas of LMICs with limited access to surgical care and CT, plain X-ray abdomen and ultrasound can help to identify and diagnose surgical emergencies cost-effectively, allowing efficient use of resources [45, 46].

CT may be very useful especially when the diagnosis is uncertain. In high-income countries, it has become the gold standard. In 2006, a meta-analysis by Doria et al. demonstrated that CT imaging featured significantly higher sensitivity and resolution than ultrasound in studies of both children and adults with acute appendicitis [47].

Proposals of staged algorithmics with a step-up approach with CT performed after an inconclusive or negative US were proposed in the setting of acute appendicitis and acute diverticulitis [48–51].

Source control

The timing and adequacy of source control are important in the management of intra-abdominal infections; late and/or incomplete procedures may have severely adverse consequences on outcome especially in critically ill patients.

IAIs include several different pathological conditions and are usually classified into uncomplicated and complicated [52]. In uncomplicated IAIs, the infectious process only involves a single organ and does not proceed to peritoneum. Patients with such infections can be managed

with either surgical source control or with antibiotics alone. In complicated IAIs (cIAIs), the infectious process extends beyond the organ and causes either localized peritonitis or diffuse peritonitis. The treatment of patients with complicated intra-abdominal infections involves both source control and antibiotic therapy.

Peritonitis is classified into primary, secondary, or tertiary peritonitis [52]. Primary peritonitis is a diffuse bacterial infection without loss of integrity of the gastrointestinal tract in absence of an identifiable source of infection during surgical exploration; this is rare, and mainly occurs in infancy and early childhood as well as in cirrhotic patients. Secondary peritonitis, the most common form of peritonitis, is an acute peritoneal infection resulting from loss of integrity of the gastrointestinal tract or from infected viscera. It is caused by perforation of the gastrointestinal tract (e.g., perforated duodenal ulcer) by direct invasion from infected intra-abdominal viscera (e.g., gangrenous appendicitis). Anastomotic dehiscences are common causes of secondary peritonitis in the postoperative period. Tertiary peritonitis is a recurrent infection of the peritoneal cavity that follows either primary or secondary peritonitis. It is a complication of a secondary peritonitis and may be termed also “ongoing peritonitis” or “persistent” peritonitis [53, 54].

As a general principle, the most established source of infection should be totally controlled as soon as possible. However, source control requires general anaesthesia that may not be readily available in some areas of the world. In many rural areas, patients must be centralized to urban centers with the loss of much time, largely due to transport delays. Furthermore, the urgency of intervention is also affected by the rapidity of the evolution of clinical symptoms.

Source control encompasses all measures undertaken to eliminate the source of infection, reduce the bacterial inoculum, and correct or control anatomic derangements to restore normal physiologic function [55, 56]. The primary objectives of intervention include (a) determining the cause of peritonitis, (b) draining fluid collections, and (c) controlling the origin of the abdominal sepsis. This endeavor generally involves drainage of abscesses or infected fluid collections, debridement of necrotic or infected tissues, and definitive control of the source of contamination. Control of the septic source can be achieved either by surgical or non-surgical means. Non-surgical interventional procedures imply percutaneous drainages of abscesses, when it is available. Ultrasound and CT-guided percutaneous drainage of abdominal and extraperitoneal abscesses in selected patients are safe and effective [57–61]. Surgical source control includes resection or suture of a diseased or perforated viscus (e.g., diverticular perforation, gastro-duodenal perforation), removal of the infected organ (e.g., appendix, gallbladder), debridement of necrotic tissue, resection of ischemic bowel, and repair/resection

of traumatic perforations with primary anastomosis or exteriorization of the bowel.

In recent years, laparoscopy has been gaining wider acceptance in the diagnosis and treatment of intra-abdominal infections. The laparoscopic approach in the treatment of peritonitis is feasible for many emergency conditions. It has the advantage to allow, at the same time, an adequate diagnosis and appropriate treatment with a less invasive abdominal approach [62]. However, laparoscopy due to the increase of intra-abdominal pressure due to pneumoperitoneum, may have a negative effect in critically ill patients leading to acid–base balance disturbances, as well as changes in cardiovascular and pulmonary physiology [40]. Laparoscopy is still uncommon in many areas of the world for several reasons, a major one being cost. In these countries, the challenges posed by the burden of primary healthcare concerns have limited government support for development of modern tertiary healthcare facilities, and laparoscopic surgery is practiced in only a few tertiary hospitals. Innovative programs to train surgeons and develop low-cost equipment in these countries are encouraging [63]. Some studies in the literature have focused on the feasibility of implementing laparoscopic procedures in resource-poor countries, and how to overcome the challenges involved [64–66].

Etiological factors of peritonitis show a wide geographical variation and different spectrum in the various regions of the world. Table 3 summarizes the sources of infection in the recent international WISS Study [1].

Acute appendicitis

Acute appendicitis is both the most common general surgery emergency presentation, as well as the most common cause of intra-abdominal sepsis, worldwide. The

Table 3 Source of infection in 4553 patients from 132 hospitals worldwide (15 October 2014–2015 February 2015) [1]

Source of infection	Number (%)
Appendicitis	1553 (34.2)
Cholecystitis	837 (18.5)
Post-operative	387 (8.5)
Colonic non-diverticular perforation	269 (5.9)
Gastro-duodenal perforations	498 (11)
Diverticulitis	234 (5.2)
Small bowel perforation	243 (5.4)
Others	348 (7.7)
PID	50 (1.1)
Post traumatic perforation	114 (2.5)
Total	4553 (100)

WISS study [1] confirmed acute appendicitis as the most frequent cause of intra-abdominal sepsis and demonstrated that around one-third of these cases were complicated. Interestingly, the incidence of acute appendicitis varies: it is generally thought to have a low-incidence rate in sub-Saharan Africa and in many regions of Asia and Latin America. This condition once thought to be rare in many regions of the world, but appears to be increasing in many urban centers and also in LMICs, perhaps due to changes in life style and diet [65]. However, the true incidence of appendicitis in many areas of the world is unknown due to poor medical record-keeping and unreliable population census. In 2015, a retrospective study over a 4-year period in South Africa [66] reported over half (56%) were from the urban district within the city of Pietermaritzburg and the remaining 44% were from the rural health district. The median duration of illness from onset to definitive care was 4 days. Sixty percent of appendices were perforated and associated with intra-abdominal contamination. Forty percent of patients required reoperation to control intra-abdominal sepsis. Ten percent required admission to the intensive care unit. The median overall length of hospital stay was 5 days. The mortality rate was 1%. Rural patients had a longer median duration of illness (3 versus 5 days, $p < 0.001$) as well as a more advanced disease profile associated with perforation and severe intra-abdominal sepsis (19 versus 71%, $p < 0.001$).

The natural history of appendicitis has been described in three stages: (1) a normal appendix, (2) uncomplicated acute appendicitis, and (3) complicated appendicitis, according to their macroscopic and microscopic appearance and clinical relevance [67]. The high morbidity and occasional mortality associated with acute appendicitis are related to delay in presentation by patients or delay in diagnosis by the clinician. These delays may result in complications like gangrene, perforation, appendiceal mass, and peritonitis, all of which would prolong hospital stay and increase the cost of treatment.

Unfortunately, the clinical presentation of appendicitis is often inconsistent. While the clinical diagnosis may be clear in patients presenting with classic signs and symptoms, atypical presentations may result in delay in treatment. Therefore, diagnostic scoring systems have been described with the aim to provide clinical probabilities that a patient has acute appendicitis. The development of these scores may contribute to diagnosis and by easily applicable clinical criteria and simple laboratory tests a score which classifies the probability of diagnosis may be attributed to the patient. In 1986, Alvarado published his own method for the early diagnosis of acute appendicitis [68]. A score of five or six was compatible with the diagnosis of acute appendicitis, a score of seven or eight indicated a probable appendicitis, and a score of nine or ten indicated

a very probable appendicitis. The only laboratory tests needed in the initial evaluation for acute appendicitis was a complete blood count to determine if there was shift to the left or increased segmented neutrophils (more than 75%) [69]. The more recently introduced appendicitis inflammatory response (AIR) score incorporated the C-reactive protein value in its design and was developed and validated on a prospective cohort of patients with suspicion of acute appendicitis. It was based on similar values to the Alvarado score, but it also included C-reactive protein as a new variable [70].

Recently, WSES guidelines for diagnosis and treatment of acute appendicitis were published [71]

Appendectomy remains the treatment of choice also for acute appendicitis. Antibiotic therapy is a safe means of primary treatment for patients with uncomplicated acute appendicitis, but it is less effective in the long-term due to significant recurrence rates and probably needs the certainty of a CT proven diagnosis of uncomplicated appendicitis (Recommendation 1A).

Antibiotics alone may be useful to treat patients with early, non-perforated appendicitis, even if there is a risk of recurrence [71, 72]. In the APPAC (Antibiotic Therapy versus Appendectomy for Treatment of Uncomplicated Acute Appendicitis) trial recently published in JAMA [73] enrolling 530 patients with uncomplicated appendicitis confirmed by a CT-scan (257 antibiotic therapy, 273 appendectomy), the 1-year recurrence rate and appendectomy in the antibiotic group was reported as 27%. Although antibiotic therapy can be successful in selected patients with uncomplicated appendicitis, the risk of disease recurrence limits the application of this treatment strategy. Apart from this high recurrence rate, the need for additional diagnostic certainty with a CT-proven diagnosis further complicates this approach [74]. Finally, in this era of antimicrobial resistance, antibiotic overuse should be limited. For all these reasons, appendectomy has remained in international guidelines the gold-standard treatment for acute appendicitis worldwide [75].

Both open and laparoscopic appendectomies are viable approaches to surgical treatment of acute appendicitis (Recommendation 1A).

The advent of laparoscopy has modified the surgical treatment of acute appendicitis in high-income countries. In contrast, in many areas of the world, the challenges posed by the burden of primary healthcare concerns have limited support for development of modern tertiary healthcare facilities, and laparoscopic surgery is practiced in only a few tertiary hospitals. In the last years, several prospective randomized studies, meta-analyses, and systematic critical reviews have been published on the topics of laparoscopic appendectomy. Laparoscopic appendectomy is safe and effective, but open surgery still confers benefits, in particular with regard to the likelihood of

postoperative intra-abdominal abscess. In a meta-analysis by Li et al. [76] including 44 randomized controlled trials with 5292 patients laparoscopic appendectomy (LA) provided considerable benefits over open appendectomy (OA), including a shorter length of hospital stay, less postoperative pain, earlier postoperative recovery, and a lower complication rate. However, LA was associated with a slight increase in the incidence of intra-abdominal abscess, intra-operative bleeding and urinary tract infection. Sauerland et al. [77] performed a meta-analysis including 67 studies, of which 56 compared LA (with or without diagnostic laparoscopy) versus OA in adults wound infections were less likely after LA than after OA, but the incidence of intra-abdominal abscesses was increased. In a prospective study published in 2010, Tzovaras et al. found that the postoperative length of hospital stay did not differ significantly between OA and LA for men. Laparoscopic appendectomy required more time and did not offer any advantages compared with OA in men [78].

Patients with a periappendiceal abscess can be managed with percutaneous image-guided drainage in surgical departments with ready access to diagnostic and interventional radiology. When percutaneous drainage is not available surgery is suggested (Recommendation 1B).

In approximately 10% of patients, a periappendiceal abscess and inflammatory phlegmon is present at diagnosis. This is more frequently encountered in the situation of a delayed diagnosis. Clinical features of complicated appendicitis such as mass and abscess may include fever, tachycardia, palpation of mass, and extension of area of tenderness and rebound. Surgical management varies because a proportion of these cases will evolve into an ileocecal resection or a right-sided hemicolectomy if operated in the acute setting [79]. In recent years, high success rates of 76–97% [80] and low incidences of complications have been reported in patients with appendicitis associated with abscess and/or mass, after conservative management; thus, performing non-surgical treatments, such as antibiotic therapy and percutaneous drainage, during the initial period have been proven to be effective and safe [81–84]. However, a necessary condition for conservative management of these patients is an easy access to diagnostic and interventional radiology to perform a percutaneous drainage. When percutaneous drainage is not available, surgery is suggested [85, 86].

In patients treated conservatively, interval appendectomy may be not necessary following initial non-operative treatment of complicated appendicitis. However, interval appendectomies should always be performed for patients with recurrent symptoms (Recommendation 2B).

Traditionally, an interval appendectomy has been offered to patients who initially underwent a non-operative approach to their appendiceal mass. However, the role of

the interval appendectomy has been questioned, and controversy continues whether interval appendectomy is appropriate for adults with an appendiceal abscess. The main debate revolves around the recurrence rate, the complication rate of an interval appendectomy, and the potential for underlying malignancy. The results of a review by Anderson and Petzold, based mainly on retrospective studies, supported the practice of non-surgical treatment without interval appendectomy in patients with appendiceal abscess or phlegmon [81]. However, the patient should be informed about the risk of recurrence especially in the presence of appendicolith. The risk of missing another underlying condition (cancer or Crohn disease) is low, but motivates a colonoscopy in patients above the age of 40 years.

Routine use of intraoperative irrigation for appendectomies does not prevent intra-abdominal abscess formation and may be avoided (Recommendation 2B).

In 2011, a retrospective review of 176 consecutive appendectomies, open (39%) and laparoscopic (61%), at a university-affiliated tertiary care facility from July 2007 to November 2008 investigated routine use of intra-operative irrigation for appendectomies. The results did not show a decrease in postoperative intra-abdominal abscess with the use of intra-operative irrigation. Thirteen patients developed postoperative abscess: 11 with irrigation and two without irrigation. Ten of 13 patients who developed abscess were perforated; nine with irrigation and one without [87].

Acute left colonic diverticulitis

Acute sigmoid diverticulitis is a common disease of the Western World and results in a significant number of hospital admissions. Data from Western populations suggest that up to one fifth of patients with acute diverticulitis are under the age of 50 years of age [88, 89]. Recent evidence suggests that lifetime risk of developing acute left-sided colonic diverticulitis (ALCD) is only about 4% among patients with diverticulosis [90].

Recent WSES guidelines for the management of acute diverticulitis in the emergency setting were published [91].

Clinical findings of patients having ALCD include acute pain or tenderness in the left lower quadrant, which may be associated with increased inflammatory markers including C-reactive protein (CRP) and white blood cell count (WBC). However, the clinical diagnosis of ALCD lacks accuracy: in a prospective analysis [92] conducted on 802 consecutive patients that presented with abdominal pain to the emergency department, positive and negative predictive values of clinical diagnosis were 0.65 and 0.98, respectively. Additional cross-sectional imaging had a positive and negative predictive value of more than 0.95 and 0.99, respectively. Radiology

examinations improved the diagnostic accuracy in 37% of the patients, although only changed the management in 7%.

Antibiotics can be avoided in patients with CT findings of uncomplicated ALCD and without significant comorbid conditions or signs of sepsis. Patients should be clinically monitored to assess for resolution of the inflammatory processes (Recommendation 1A).

ALCD is generally divided into uncomplicated and complicated. The utility of antimicrobial therapy in acute uncomplicated diverticulitis has been a point of controversy in the international medical community [93]. In terms of clinical resolution, recent investigation demonstrates that antimicrobial treatment was not superior to withholding antibiotic therapy in patients with mild, unperforated diverticulitis. Furthermore, a multi-center randomized trial involving ten surgical departments in Sweden and one in Iceland, recruited 623 patients with computed tomography-verified acute uncomplicated left-sided diverticulitis [94], and concluded that antibiotic treatment for acute uncomplicated diverticulitis neither accelerated recovery nor prevented complications or recurrence. In these studies, the definition of uncomplicated ALCD is based on strict CT scan definitions: for example, patients with pericolic free gas or even minimal free fluid were classified as having complicated disease and were excluded from investigation [95].

On the basis of clinical conditions, patients with diverticular smaller abscesses may be treated by antibiotics alone (Recommendation 1C).

Patients with abscesses having a large diameter should be treated by percutaneous drainage and intravenous antibiotics (Recommendation 1C).

Whenever percutaneous drainage of the abscess is not feasible or not available, based on the clinical conditions patients with large abscesses can be initially treated by antibiotic therapy alone. However careful clinical monitoring is mandatory (Recommendation 1C).

Approximately 15–20% of patients admitted with ALCD have an abscess [96], and the treatment should be either antibiotics with or without percutaneous and/or surgical drainage. The use of antibiotics and percutaneous drainage in the management of diverticular abscesses facilitates single-stage operation to perform subsequently an elective sigmoidectomy. The size of 3–6 cm has been generally accepted, despite the low level of evidence, to be a reasonable limit between antimicrobial versus percutaneous drainage in the management of diverticular abscesses [96–100].

A retrospective study assessing the effectiveness of antibiotics as sole initial therapy in patients with large diverticular abscess was published in 2015 by Elagili et al. [101]. Thirty-two patients were managed by antibiotics alone while 114 underwent percutaneous drainage.

Failure of initial treatment required urgent surgery in eight patients with persistent symptoms during treatment

with antibiotics alone (25%) and in 21 patients (18%) after initial percutaneous drainage ($p = 0.21$). Patients treated with antibiotics had a significantly smaller abscess diameter (5.9 versus 7.1 cm, $p = 0.001$). Postoperative complications in patients treated with antibiotics alone were significantly less severe than after percutaneous drainage based on the Clavien-Dindo classification ($p = 0.04$).

Hartmann's procedure remains useful in the management of diffuse peritonitis in critically ill patients. However, in clinically stable patients, primary resection with anastomosis, with or without a diverting stoma, may be performed (Recommendation 1B).

Hartmann's procedure has been considered the procedure of choice in patients with generalized peritonitis and remains a safe technique for emergency colectomy in diverticular peritonitis, especially in critically ill patients and in patients with multiple co-morbidities. However, restoration of bowel continuity after Hartmann's procedure has been associated with significant morbidity [102]. In recent years, some authors have reported the role of primary resection and anastomosis with or without a diverting stoma in stable patients without comorbidity, even in the presence of diffuse peritonitis [103]. Studies comparing mortality and morbidity of Hartmann's procedure versus primary anastomosis did not show any significant differences. However, most studies had relevant selection bias as demonstrated by four systematic reviews [103–107].

Laparoscopic peritoneal lavage and drainage may not be considered the treatment of choice in patients with diffuse peritonitis (Recommendation 1A).

Recent investigation continues to define the role of laparoscopic peritoneal lavage in the treatment of ALCD, and unanswered questions remain. The latest prospective trials, including the SCANDIV, Ladies, and DILALA trials [108–111], have lacked superiority for lavage in terms of morbidity, but mortality was not compromised. A meta-analysis published in 2015 showed that in acute perforated diverticulitis with purulent peritonitis laparoscopic lavage is comparable to sigmoid resection in terms of mortality, but it is associated with a significantly higher rate of reoperations and a higher rate of intra-abdominal abscess [111]. No differences in terms of mortality were demonstrated at follow-up.

Colonic carcinoma perforation

Treatments for perforated colonic carcinoma should both stabilize the emergency condition of the peritonitis and fulfil the technical objectives of oncological intervention (Recommendation 1B).

Patients with perforated colonic carcinoma had a significantly poorer prognosis compared with patients with non-perforated colonic cancer. Colorectal cancer-induced perforation is considered an advanced stage disease due to

the potential for peritoneal dissemination of tumor cells throughout the site of perforation [112, 113].

The stage of illness, proximity of the perforation to the tumor, and the number of metastatic lymph nodes are positively correlated with reduced procedural- and cancer-free survival rates [114].

Hartmann's procedure has been widely accepted as an effective means of treating carcinoma of the left colon (with adequate R0 resection) in certain emergency scenarios [115].

Colonic perforation following colonoscopy

Patients presenting with diffuse peritonitis caused by colonoscopic perforation should undergo immediate surgical intervention, which typically involves primary repair or resection (Recommendation 1B).

Recently, the frequency of colonic perforation has increased due to routinely performed advanced therapeutic endoscopy. The recent advent of endoscopic submucosal dissection (ESD) has resulted in a high incidence of perforation, although the indication for endoscopic therapy of colorectal neoplasm has been expanded.

Over the last decade, many advancements have been streamlined to better address these perforations, yet there are no definitive guidelines for their optimal management [116].

Endoscopic management is typically used to treat colonoscopy-associated perforations if they can be closed by endoscopic clipping during colonoscopy [117–119].

Retrospective studies showed that conservative management of colonoscopic perforation could be an option for patients without overt symptoms of peritonitis or with a small defect size [120, 121].

Early exploratory laparotomy with primary closure or bowel resection has been the standard treatment of colonoscopic perforation [122]. In cases of extensive contamination, poor tissue quality and a higher complication rate, stoma, or fecal diversion after repair should be performed [123].

Iqbal et al. in a retrospective study [124] indicated that factors predicting a poor outcome included delayed diagnosis, extensive peritoneal contamination, and patients using anticoagulants ($p < .05$).

An early laparoscopic approach may be a safe and effective option for colonoscopy-related colonic perforation for experienced surgeons (Recommendation 2B).

Laparoscopic surgery is a compromise that may minimize the risks of invasive surgery as well as those of insufficiently aggressive non-operative therapy [125–128].

In the Zhang et al. study, their experience in laparoscopic direct suturing of colon perforations indicated that laparoscopic primary perforation repair was a safe and feasible repair method [127].

If the area of perforation cannot be localized laparoscopically, the surgeon should begin with a laparotomy before proceeding further [128].

Gastroduodenal peptic ulcer perforations

Gastroduodenal ulcer perforations have decreased in the last few years, largely due to the widespread adoption of medical therapies for peptic ulcer disease and decreasing incidence of helicobacter pylori infection in Western countries. However, ulcer disease is a still common emergency condition worldwide and is associated with mortality rates of up to 30% [129, 130]. The main etiologic factors include use of non-steroidal anti-inflammatory drugs (NSAIDs), steroids, smoking, *Helicobacter pylori* (*H. pylori*) and a diet high in salt. All these factors have in common that they affect acid secretion in the gastric mucosa [129]. Stress ulcers with perforation may occur in critically ill patients in intensive care, where the diagnosis may be obscured owing to lack of signs and symptoms in an unconscious or sedated patient.

Surgery is the treatment of choice for perforated peptic ulcers (Recommendation 1A).

Simple closure with or without an omental patch is a safe and effective procedure to address small perforated ulcers (<2 cm) (Recommendation 1A).

Surgery is the most effective means of source control in patients with PPU [131]. The main surgical treatment for PPU has become simple suture of the perforation site with or without the addition of an omental patch [132].

In 2010, Lo et al. conducted a study to determine if an omental patch offers any clinical benefit that is not offered by simple closure alone [133]. The study demonstrated that, in terms of leakage rates and overall surgical outcome, covering the repaired perforated peptic ulcer with an omental patch did not convey additional advantages compared to simple closure alone.

Scoring systems to predict disease severity or outcome in patients with gastroduodenal perforations are unreliable and not accurate and cannot be generalized from one population to another [133, 134].

Laparoscopic repair of perforated peptic ulcers can be a safe and effective procedure for experienced surgeons (Recommendation 1A).

Successful laparoscopic repair of perforated gastric and duodenal ulcers has been reported, though the technique has yet to be universally accepted. The literature was summarized in a recent systematic review [135]. The authors concluded that laparoscopic surgery results are not clinically different from those of open surgery. Further data is required to investigate the potentially long learning curve seen among participating surgeons.

Conservative treatment for PPU is seldom reported and restricted mostly to case reports and series, [136].

Small bowel perforations

Small bowel perforations are a less common source of peritonitis in the Western countries, compared with LMICs. In Western countries, most small intestinal perforations are due to unrecognized intestinal ischemia (mesenteric or strangulation) or inflammatory bowel disease such as Crohn disease. This pattern of disease is quite different to LMICs, where small bowel perforations are usually due to typhoid fever. Typhoid fever remains endemic in Asia, Africa, Latin America, the Caribbean, and Oceania [137]. Ileal perforation as complication of typhoid fever and enteritis is a major public health problem in many areas worldwide because of its persistent high morbidity and mortality. Typhoid ileal perforations have a mortality rate up to 60% [138]. In the CIAOW study, according to stepwise multivariate analysis, the presence of small bowel perforation was an independent variable predictive of mortality [139]. The most common clinical presentation of enteric perforation is abdominal pain and fever whereas perforation typically occurs in the third week of disease. Lack of an incidence database and poor financial resources preclude adequate prevention of this public health menace [140]. The preoperative diagnosis of perforation usually is based on findings of peritonitis in a patient with a history of prolonged febrile illness. In a prospective study, 53 consecutive patients with typhoid perforation were surgically treated; the morbidity rate for this series of procedures was 49.1%, and the most common post-operative complications included wound infection, wound dehiscence, burst abdomen, residual intra-abdominal abscesses, and entero-cutaneous fistulae. The mortality rate was 15.1% and was significantly affected by the presence of multiple perforations, severe peritoneal contamination, and burst abdomen [141].

Surgery is the treatment of choice for patients with small bowel perforations (Recommendation 1B).

In the event of small perforations, primary repair is recommended (Recommendation 1B).

There are many methods of surgical treatment of small bowel perforation, including primary closure, excision and closure, resection and primary anastomosis, limited right hemicolectomy, and stoma creation [142]. Primary repair should be performed for patients with minor symptoms and with perioperative findings of minimal peritoneal contamination of the peritoneal cavity [75]. In the setting of typhoidal perforation, although closure in two layers of single perforation with relatively healthy tissue after refreshment of the edge seems an acceptable option [143], resection of the unhealthy tissue segment with primary anastomosis of healthy edges about 10 cm on each side of the perforation is recommended [144, 145].

In delayed cases with diffuse peritonitis, there can be severe inflammation and oedema of the bowel, resulting in friable tissue which precludes anastomosis, and

therefore, an ileostomy should be performed as a life saving measure [75]. Laparoscopic management of small bowel perforations was reported, but there was no comparative study with open surgery [146].

Other infections that may rarely cause small bowel perforation in immuno-compromised patients include amoebic infection, *Clostridium difficile*, *Cytomegalovirus*, and Histoplasmosis [147–150]. Rarely, medications (NSAIDs, potassium chloride, and steroids), cancer chemotherapy and radiotherapy may lead to small bowel perforation.

Abdominal tuberculosis

Tuberculosis (TB) remains prevalent worldwide. It is considered as a global health problem by the World Health Organization and is considered the most important communicable disease in the world.

Although much of the burden is concentrated in high-burden settings in Asia and Africa, TB continues to be of concern in high-income nations. The number of tuberculosis cases has also been increasing in high-income countries, mainly because of immigration and as a consequence of acquired immunodeficiency syndrome (AIDS) and also because of the utilization of immunosuppressive drugs [151].

Abdominal involvement in tuberculosis is the most common extra-pulmonary form of this infection.

The most common site of extra pulmonary tuberculosis is the ileocecal region and terminal ileum [151].

The clinical presentation of tuberculosis is variable and non-specific, with non-pathognomonic signs and symptoms. It may mimic other infectious or inflammatory pathological diseases, and even neoplastic conditions [151, 152].

The most common complication of small bowel tuberculosis is obstruction due to the narrowing of the lumen by ileocecal tuberculosis or stricture of small intestine and perforation in ulcerative type of tuberculosis.

In the case of abdominal tuberculosis perforation resection of the affected area and anastomosis may be the treatment of choice rather than primary closure (Recommendation 1C).

Treatment of tubercular perforation of ileum depends upon the condition of the gut, general condition of the patient and number of perforations. The resection of the affected area and anastomosis may be the treatment of choice rather than primary closure [152].

Acute calculous cholecystitis

Cholelithiasis is a common disorder all over the world [153–155]. Its prevalence varies widely by region: in Western countries, the prevalence of gallstone disease reportedly ranges from approximately 7.9% in men to 16.6% in women [155]; in Asia, it ranges from

approximately 3 to 15%, is nearly non-existent (less than 5%) in Africa [156], and ranges from 4.21 to 11% in China.

Acute cholecystitis develops in 1–3% of patients with symptomatic gallstones [157].

In 2016, WSES guidelines for the management of acute calculous cholecystitis (AAC) were published [153].

The diagnosis of acute cholecystitis is made on the basis of clinical features such as right upper quadrant pain, fever, and leukocytosis and is supported by findings from relevant imaging studies. Ultrasound is the investigation of choice in patients suspected of having acute cholecystitis [158]. Ultrasound typically shows pericholecystic fluid (fluid around the gall bladder), distended gall bladder, oedematous gallbladder wall, and gall stones, and Murphy's sign can be elicited on ultrasound examination [158]. Treatment is predominantly surgical, although the timing of surgery without evidence of gangrene or perforation has been under debate in recent years. Two approaches are available for the treatment of acute cholecystitis: the early option, generally within 7 days of onset of symptoms, offers a laparoscopic cholecystectomy (LC) to provide immediate, definitive surgical treatment after establishing diagnosis and surgical fitness of the patient in the same hospital admission, while the delayed treatment option is performed in a second hospital admission after an interval of 6–12 weeks during which time the acute inflammation settles [159].

Early cholecystectomy is a safe treatment for acute cholecystitis and generally results in shorter recovery time and hospitalization compared to delayed cholecystectomies (Recommendation 1A).

Several randomized controlled trials have investigated early laparoscopic cholecystectomy (ELC) versus delayed laparoscopic cholecystectomy (DLC) and meta-analysis [160–168]. A recent meta-analysis comparing early versus delayed laparoscopic cholecystectomy for acute cholecystitis [169] reported on 16 studies, involving 1625 patients: for patients with acute cholecystitis, ELC appears as safe and effective as DLC. ELC might be associated with lower hospital costs, fewer work days lost, and greater patient satisfaction.

Among patients with uncomplicated cholecystitis, if source control is complete, no postoperative antimicrobial therapy is necessary [170].

Laparoscopic cholecystectomy is a safe and effective treatment for acute cholecystitis (Recommendation 1A).

It is the first choice for patients with acute cholecystitis where adequate resources and skill are available. Some risk factors may predict the risk for conversion to open cholecystectomy.

Multiple prospective trials have demonstrated that the laparoscopic cholecystectomy is a safe and effective

treatment for acute cholecystitis [171–174]. As a result, immediate laparoscopic cholecystectomy has largely become the therapy of choice for acute cholecystitis in operable patients. While the laparoscopic approach is usual, several risk factors predicting the need to convert to an open approach are reported. In an evaluation of preoperative risk factors as markers for conversion, a meta-analysis summarizing 11 nRCTs containing 14,645 patients, reported age >65 years, male gender, acute cholecystitis, thickened gallbladder wall, diabetes mellitus, and previous upper abdominal surgery all as significant risks, associated with increased risk of conversion [175, 176]. However, open cholecystectomy remains a feasible option, particularly in low-income countries [177], or elsewhere in the setting of resource limitations. The CIAOW study showed that open cholecystectomy, among the patients with complicated cholecystitis, was the most frequently performed procedure [139].

In LMICs, laparoscopic surgery is just evolving in tertiary centers. Despite the low volume of patients and the absence of fluoroscopy in many hospitals results in treating acute cholecystitis seem to be comparable with high volume centers [177].

Cholecystostomy is a safe and effective treatment for acute cholecystitis in critically ill and/or with multiple comorbidities and unfit for surgery patients (Recommendation 1B).

Acute cholecystitis in elderly, critically ill patients still today remains a real challenge to treat. Despite the low rate of surgical impact from the laparoscopic approach, many patients are unfit for any surgery. In this subgroup of patients, urgent cholecystostomy with or without delayed laparoscopic cholecystectomy appears to be the correct clinical approach [178–198].

Early diagnosis of gallbladder perforation and immediate surgical intervention may substantially decrease morbidity and mortality rates (Recommendation 1C).

Gallbladder perforation is an unusual complication; occasionally, acute cholecystitis, inflammation, and fulminant infection may progress to ischemic necrosis and gallbladder perforation. Prompt surgical intervention is important in decreasing morbidity and mortality rates associated with this situation. The reported incidence of gallbladder perforation in acute cholecystitis is 2–11% [190–200], and mortality in such cases is as high as 12–16% [201–204].

The gallbladder perforation is classified into three types: acute or type I-free perforation with generalized peritonitis, subacute or type II-pericholecystic abscess with localized peritonitis, and chronic or type III-cholecysto-enteric fistula [205]. Perforation of the fundus is usually free perforation leading to generalized peritonitis whereas perforation in the region of body or neck becomes covered with omentum leading to localized collection. Type I and II perforations

are reported to occur in a younger age group (around 50 years) whereas type III perforations are commonly seen in more elderly patients [200]. Type I perforations are typically encountered in patients with severe systemic disease (DM, atherosclerotic heart disease) without past history of acute cholecystitis, while type III perforation cases usually have previous history of recurrent attacks of cholecystitis [202–205]. The diagnosis is difficult and often delayed since the presentation is very much similar to acute cholecystitis. The ultrasound findings in such cases are also similar to the findings of acute cholecystitis, but visualization of the sonographic “hole sign” in the gallbladder wall can hint at the diagnosis of perforated gallbladder [206]. CT scan is more reliable in making the diagnosis as it better demonstrates the defect in the gallbladder wall in addition to pericholecystic collection and free intra-peritoneal fluid [206, 207].

Perforation is rarely diagnosed pre-operatively. Delayed surgical intervention is associated with elevated morbidity and mortality rates, increased likelihood of ICU admission, and prolonged post-operative hospitalization [208–210].

Acute cholangitis

Acute cholangitis is an infectious disease characterized by acute inflammation and infection in the bile ducts resulting from a combination of biliary obstruction and bacterial growth in bile.

Bacteria reach the biliary system either by ascent from the intestine or by the portal venous system [211]. The most common cause of cholangitis is choledocholithiasis [212].

The key elements of therapy in acute cholangitis are adequate antimicrobial treatment to avoid or manage the septic complications and biliary decompression to restore biliary drainage in case of obstruction [213]. The clinical presentation varies, and initial risk stratification is important to guide further management [214].

In severe cholangitis, an early interventional approach is absolutely essential for survival.

The type and timing of biliary drainage should be based on the severity of the clinical presentation, and the availability and feasibility of drainage techniques, such as endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), and open surgical drainage.

ERCP plays a central role in the management of biliary obstruction in patients with acute cholangitis.

Endoscopic retrograde cholangiopancreatography (ERCP) is the treatment of choice for biliary decompression in patients with moderate/severe acute cholangitis (Recommendation 1A).

A randomized controlled trial (RCT) [215] was conducted to compare endoscopic and open drainage in 82 patients with severe acute cholangitis with hypotension

and disturbed consciousness. This RCT demonstrated that the morbidity and mortality of endoscopic naso-biliary drainage (ENBD) + endoscopic sphincterotomy (EST; $n = 41$) were significantly lower than those of T-tube drainage under laparotomy ($n = 41$). The authors concluded that morbidity and mortality of endoscopic naso-biliary drainage (ENBD) + endoscopic sphincterotomy are lower than those of T-tube drainage under laparotomy.

There are various endoscopic transpapillary options available, including biliary stent or nasobiliary drain placement above the obstruction site ± sphincterotomy, all of which with their appropriate indications corresponding to disease severity and clinical context [216].

Endoscopic biliary decompression by nasobiliary catheter or indwelling stent was equally effective for patients with acute suppurative cholangitis caused by bile duct stones in a prospective randomized trial published in 2002 [217]. The indwelling stent was associated with less post-procedure discomfort and avoided the potential problem of inadvertent removal of the nasobiliary catheter.

Percutaneous biliary drainage (PTBD) should be reserved for patients in whom ERCP fails (Recommendation 1B).

There are patients in whom ERCP fails because of unsuccessful biliary cannulation, or an inaccessible papilla. In these cases, percutaneous biliary drainage (PTBD) is required. However, PTBD can lead to significant complications, including biliary peritonitis, hemobilia, pneumothorax, hematoma, liver abscesses, and patient discomfort related to the catheter [218].

In 2012, a retrospective study comparing the safety and effectiveness of endoscopic and percutaneous transhepatic biliary drainage in the treatment of acute obstructive suppurative cholangitis was reported. It confirmed the clinical efficacy of endoscopic drainage as well as its ability to facilitate subsequent endoscopic or surgical intervention [219].

Open drainage should only be used in patients for whom endoscopic or percutaneous trans-hepatic drainage is contraindicated or those in whom it has been unsuccessfully performed (Recommendation 2C).

The indication for emergent open operation for acute cholangitis is rapidly disappearing. Emergency operation for severe cholangitis carries high mortality rates.

Given the shortened length of hospitalization and the rarity of serious complications such as intra-peritoneal hemorrhage and biliary peritonitis, endoscopic drainage is preferred to open drainage [218–220].

Post-operative peritonitis

Post-operative peritonitis (PP) is a life-threatening hospital-acquired intra-abdominal infection with high rates of mortality [221, 222]. The most common cause of PP is an anastomotic leakage [223]. It is most

frequent after rectal resection [224], but it may complicate any gastrointestinal anastomosis. Treating patients with post-operative peritonitis requires supportive therapy of organ dysfunction, source control of infection, and intensive antimicrobial therapy. The diagnosis of post-operative peritonitis may be difficult because there are no absolutely specific clinical signs and laboratory tests to reject or confirm the diagnosis. The atypical clinical presentation may be responsible for a delay in diagnosis and re-intervention or reoperation.

On the basis of the clinical conditions, the size of the abscess and the access to interventional radiology, antibiotics and/or percutaneous drainage may be suggested to treat post-operative localized intra-abdominal abscesses when there are no signs of generalized peritonitis (Recommendation 2C).

Antibiotics and drainage may be the optimal means of treating post-operative localized intra-abdominal abscesses when there are no signs of generalized peritonitis. Several retrospective studies in the fields of surgery and radiology have documented the effectiveness of percutaneous drainage in the treatment of post-operative localized intra-abdominal abscesses [225].

Prompt surgical source control should be performed following diagnosis of post-operative peritonitis. Ineffective control of the septic source is associated with significantly elevated mortality rates (Recommendation 1C).

Complete surgical source control should be performed as soon as the patient has been maximally resuscitated. The inability to control the septic source is associated with an intolerably high patient mortality [222]. Organ failure and/or subsequent re-laparotomies that have been delayed for more than 24 h both result in higher rates of mortality for patients affected by post-operative intra-abdominal infections [226]. Early re-laparotomies appear to be the most effective means of treating post-operative peritonitis [227].

In 2009, a retrospective study by Chichom-Mefire et al. [228] analyzed aspects of re-operative abdominal surgery in an economically disadvantaged environment with respect to indications, operative findings, treatment modalities, and outcomes. Mortality in this series was 18%, increasingly significant when the initial operative procedure was for peritonitis and re-operation was due to septic complications. Operative re-intervention based on clinical findings was considered the favored strategy.

Pelvic inflammatory disease

Pelvic inflammatory disease (PID) is an infection of the upper part of the female reproductive genital tract, including the uterus, fallopian tubes, and adjacent pelvic structures and may spread to the abdomen causing peritonitis [229], caused by bacterial infection spreading from the vagina and cervix. Occasionally, right-upper quadrant pain

suggestive of inflammation and adhesion formation in the liver capsule (Fitz-Hugh–Curtis syndrome) can accompany pelvic inflammatory disease.

The sexually transmitted *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are present in many cases; however, microorganisms including the endogenous vaginal and cervical flora may also cause PID. Genital tract mycoplasmas, most importantly *Mycoplasma genitalium*, have recently also been implicated as a cause of acute PID [230]. The global epidemiologic profile of pelvic inflammatory disease has not been well defined. Due to financial and logistic reasons, pelvic inflammatory disease prevention programs that are based on screening are simply unavailable in most countries, where the burden of pelvic inflammatory disease may be the greatest [231].

Patients with tubo-ovarian abscess that does not respond to antibiotics should undergo surgical drainage (Recommendation 1C).

Tubo-ovarian abscesses (TOA) may be a complication of PID. In women of reproductive age, TOA is one of the most common types of pelvic abscess. TOA are classically treated with broad-spectrum antibiotics. However, if antibiotic therapy is not sufficient, surgical drainage should be performed [232–235].

Post-traumatic gastrointestinal perforations

Trauma continues to be a global major public health problem worldwide, and it is associated with high morbidity and mortality worldwide regardless of the socioeconomic status [236]. Both blunt and penetrating forces may result in bowel injury; motor vehicle crashes remain the most common, and falls the next most common, cause of blunt force trauma globally [237].

Hollow visceral injury (HVI) has a more insidious presentation in this setting, often resulting in delayed diagnoses. Clinical signs may take time to develop, and imaging investigations are not completely sensitive. In addition, other injuries may distract the patient and clinical team, and accurate and timely diagnosis is often difficult. An improved outcome is reported in these settings, where, as a result of advances in imaging modalities, patient monitoring devices and prompt intervention is possible, while poor diagnostic facilities, late presentation, as well as late intervention adversely may affect the outcome in other settings [238, 239].

Several mechanisms of bowel injury have been documented in the wake of blunt abdominal trauma. The most common injury is the posterior crushing of the bowel segment between the seat belt and vertebra or pelvis. It can result in local lacerations of the bowel wall, mural and mesenteric hematomas, transection of the bowel, localized devascularization, and full-thickness contusions. Devitalization of the areas of

contusion may subsequently result in late perforation. Colonic injuries occurred less frequently than small intestinal injuries perhaps due to its location and the lack of redundancy, which prevents the formation of closed loops. Abdominal trauma may be associated with other additional co-morbid injuries, which could complicate the management and affect the outcome. Delay in diagnosis and treatment of the HVI may result in early peritonitis, hemodynamic instability and increased mortality and morbidity.

Early surgical intervention is recommended in case of HVI (Recommendation 1C).

Repair or anastomosis of intestinal injuries should be considered in all patients. A complete diversion of the faecal stream could be considered in colorectal injuries involving all layers in the setting of multiple injuries or comorbid conditions (Recommendation 1C).

Early clinical recognition and surgical intervention is importance in case of HVI [239–241]. The accuracy of clinical examination signs in this setting remain poor. Signs include ecchymosis of the abdominal wall, increasing abdominal pain and distension are all associated with HVI [239]. A range of investigative modalities is available, including imaging techniques (plain x-ray, ultrasound, CT), and diagnostic peritoneal aspirate/lavage. However, in the presence of clinical peritonitis, surgical exploration is mandatory. Repair or anastomosis of intestinal injuries should be considered in all patients. A complete diversion of the fecal stream should be considered in colorectal injuries involving all layers in the setting of multiple injuries and resultant physiological compromise, unfavorable comorbid conditions, and perhaps in the setting of delayed diagnoses [239].

Damage control laparotomy (DCL) in the context of HVI is accepted for small bowel injury in the context of coagulopathy, while colon ligation has been debated because of high complication rates and an increased incidence of leakage; however, delayed anastomosis of colon injuries after DCL may avoid stoma creation in some patients who are not candidates for anastomosis during initial intervention [242].

Re-laparotomy strategy

Severe infection may be associated with marked inflammatory responses, which in the extreme circumstance may result in an excessive, dysfunctional immune response, with resultant physiological collapse. These shocked patients develop organ dysfunction and progress to a multiple organ dysfunction syndrome (MODS). In this case, a staged operative approach may minimize further physiological insults associated with a time and energy intense primary definitive operative strategy [243].

Apart from a staged operative approach, the clinical team may also employ a planned re-laparotomy approach to re-examine pathology and facilitate repeated debridement of contaminated tissues. However, deciding if and when to perform a re-laparotomy in cases of secondary peritonitis remains difficult. Factors indicative of progressive or persistent organ failure during early post-operative follow-up analysis are the best indicators of ongoing infection [52]. Three relaparotomy strategies are currently employed for management of abdominal sepsis following an initial laparotomy: (a) open abdomen, (b) planned re-laparotomy, and (c) on-demand re-laparotomy.

The on-demand re-laparotomy is recommended for patients with severe peritonitis because its ability to streamline healthcare resources, reduce overall medical costs, and prevent the need for further re-laparotomies (Recommendation 2A).

In 2007, van Ruler et al. published a randomized, clinical study comparing planned and on-demand re-laparotomy strategies for patients with severe peritonitis [243]. Patients in the on-demand relaparotomy group did not have a significantly lower rate of death or major peritonitis-related morbidity compared with the planned relaparotomy group, but did have a substantial reduction in relaparotomies, healthcare utilization, and medical costs. More recently, a study conducted over a 30-month period in South Africa analyzed prospectively gathered data entered into an established electronic registry comparing patients requiring planned laparotomy (PR) with patients requiring on-demand laparotomy [244]. A total of 162 patients were included, with an average age of 36 years (standard deviation 17) and 69% male predominance. Patients selected for the PR strategy had higher admission pulse rates, higher Modified Early Warning System (MEWS) scores and significantly higher rates of diffuse intra-abdominal sepsis at initial laparotomy.

The open abdomen may be a viable option for treating physiologically deranged patients with ongoing sepsis, facilitating subsequent exploration and control of abdominal contents, and preventing abdominal compartment syndrome (Recommendation 1C).

In order to define the role of OA with negative pressure therapy for improved biomediator clearance and mitigated systemic sepsis in patients with severe peritonitis a prospective trial is needed.

The OA concept is closely linked to damage control surgery. In patients with ongoing sepsis, an OA approach may be required for controlling any persistent source of infection and preventing abdominal compartment syndrome.

OA facilitates repeated abdominal exploration in the patients with severe peritonitis allowing easy second-look to control the source of infection and evacuate inflamed and toxic content, reducing the load of peritoneal

cytokines and other inflammatory substances and preventing their production by removing the source itself [245].

Temporary closure of the abdomen may be achieved by using gauze and large, impermeable, self-adhesive membrane dressings, both absorbable and non-absorbable meshes, and negative pressure therapy devices. The first and easiest method to perform a laparostomy was the application of a plastic silo (the “Bogota bag”). This system is inexpensive. However, it does not provide sufficient traction to the wound edges and allows the fascial edges to retract laterally, resulting in difficult fascial closure under significant tension, especially if the closure is delayed [243–247].

At present, negative pressure techniques (NPT) have become the most extensively employed means of temporary closure of the abdominal wall.

In 1986, Schein [246] et al. described a management technique of the open abdominal wound. It consisted of a “sandwich” composed of a Marlex mesh and an Op-Site wound dressing with interposition of suction tubes. Brock et al. in 1995 [248] described the placement of a fenestrated polyethylene sheet between the abdominal viscera and parietal peritoneum, followed by a moist towel, Kerlix gauze bandage rolls with closed suction drains or a sponge covered with an occlusive adhesive drape [245]. This method defined as the “Vacuum Pack Technique” is inexpensive, easily applied and changed, protects the viscera, prevents adhesions, removes exudate, and prevents some loss of domain [247]. Commercially prepared negative pressure dressings are available, and the initial dressing may be changed to commercial dressing, if early closure is impossible.

Rapid closure with the assistance of negative pressure therapy should be the primary objective in the management of patients with open abdomen, in order to prevent severe morbidity such as fistulae, loss of domain and massive incisional hernias (Recommendation 1B).

Severe complications including loss of the abdominal domain, fistula formation, and the development of giant incisional hernias may be observed in this procedure. Following re-exploration, the goal should be the early and definitive closure of the abdomen, in order to reduce the complications associated with an open abdomen. Early definitive closure (within 4–7 days of the initial laparostomy) is the basis of preventing or reducing the risk of complications [248–250].

A systematic review and meta-analysis to evaluate whether early fascial abdominal closure had advantages over delayed approach was published in 2014 [251]. The study confirmed the clinical advantages of early fascial closure compared with delayed closure in treatment of patients with open abdomen.

If unable to close the abdomen early, a progressive closure device may be necessary.

A systematic review and meta-analysis of the open abdomen and temporary abdominal closure techniques in non-trauma patients was recently published [252]. The best results in terms of achieving delayed fascial closure and reducing the risk of entero-atmospheric fistula were shown for NPT with continuous fascial traction. Despite that the authors concluded that the overall quality of the available evidence was poor, and uniform recommendations cannot be made.

Antimicrobial therapy

Judicious use of antimicrobials is an integral part of good clinical practice. This attitude affects therapeutic efficacy of treatment and minimizes the risks associated with the selection of resistant pathogens.

Antimicrobial resistance poses a global challenge. No single country can protect itself from the importation of resistant pathogens through travel and trade.

The global nature of antimicrobial resistance calls for a global response, both in the geographic sense and across the whole range of sectors involved. Nobody is exempt from the problem [253].

Although most surgeons are aware of the problem of antimicrobial resistance, most underestimate this problem in their own hospital. The necessity of formalized systematic approaches to the optimization of antibiotic therapy for patients with intra-abdominal infections in the setting of surgical units worldwide has become increasingly urgent.

Knowledge of regional/local rates of resistance, when it is available, should be always an essential component of the clinical decision-making process when deciding the empirical treatment of infection (Recommendation 1C).

Regional epidemiological data and resistance profiles are essential for selecting appropriate antibiotic therapy for IAIs [254, 255].

However, while high-income countries (HICs) have extensive surveillance systems to monitor antimicrobial resistance [255], in low- and middle-income countries LMIC surveillance systems have not really been established.

The Study for Monitoring Antimicrobial Resistance Trends (SMART) provides the best available evidence for the current status of cIAIs worldwide. The SMART has monitored the in vitro susceptibility patterns of clinical gram-negative bacilli to antimicrobial agents collected worldwide from intra-abdominal infections since 2002 [256, 257]. Isolates worldwide showed the highest levels of antimicrobial resistance of the global regions included the SMART study, and a trend of increasing resistance continues year by year. One particular cause for concern is the prevalence of extended-spectrum β -lactamase (ESBL)-producing Enterobacteriaceae in the clinical setting. The prevalence of ESBLs intra-abdominal infections has

steadily increased over time for in Asia, Europe, Latin America, Middle East, North America, and South Pacific [256, 257].

In addition to the expected increased resistance to beta-lactams, fluoroquinolone resistance in ESBL-positive *Escherichia coli* causing intra-abdominal infections ranges from 60 to 93% in India, China, North America, Europe, and South Africa [256, 257]. Although carbapenem activity against isolates from IAIs is also high, it is slightly lower than activity against *Klebsiella pneumoniae* isolates from urinary tract infections.

Predicting the pathogens and potential resistance patterns of a given infection begins by establishing whether the infection is community-acquired or healthcare-associated.

For patients with community-acquired intra-abdominal infections (CA-IAs), agents with a narrower spectrum of activity are preferred. However, in CA-IAI patients at risk for extended-spectrum beta-lactamases (ESBLs) producing Enterobacteriaceae infections, anti-ESBL-producer coverage may be warranted. For patients with healthcare-associated infections (HA-IAs), antibiotic regimens with broader spectra of activity are preferred (Recommendation 1B).

Initial antibiotic therapy for IAIs is typically empirical in nature because a patient with abdominal sepsis needs immediate treatment, and microbiological data (culture and susceptibility results) can require up to 48–72 h before they are available for a more detailed analysis. Selection of appropriate empiric antibiotic therapy is critical for preventing unnecessary morbidity and mortality from cIAs. The major pathogens involved in community-acquired intra-abdominal infections are usual residents of gastrointestinal flora, including *Enterobacteriaceae*, streptococci, and certain anaerobes (particularly *Bacteroides fragilis*) [75]. Narrower spectrum antimicrobial agents are appropriate for these patients [258].

In the context of intra-abdominal infections, the main resistance problem is posed by ESBL-producing *Enterobacteriaceae*, which are prevalent in hospital-acquired infections but observed in CA-IAs too [139].

Specific risk factors for ESBL-producing bacteria in community-acquired infections include recent exposure to antibiotics (particularly third generation cephalosporins or fluoroquinolones) within 90 days of IAI or known colonization with ESBL producing *Enterobacteriaceae* [253].

Although increasing overtime everywhere, carriage of ESBL producing *Enterobacteriaceae* did not evolve with the same dynamics and large intra- and inter-regional variations have been observed. Poor access to drinking water, water pollution, and a high population density are efficient drivers for ESBL producing *Enterobacteriaceae* dissemination, as for any fecally-orally transmitted diseases [259]. Reports from the Western Pacific, Eastern Mediterranean, and Southeast Asia regions showed the highest

carriage rates and the most striking recent ascending trends [259], explaining why travelers into these areas of the world are at risk of becoming colonized [260]. In contrast, rates reported in Europe never exceeded 10% [259].

HA IAIs include hospital-acquired infections (developing greater than 48 h after initial source control) but also infections in patients having recent hospitalization within 90 days, living in a skilled nursing or other long-term care facility, using aggressive medical therapies (intravenous therapy, wound dressing) at home and invasive therapies (haemodialysis, chemotherapy, radiotherapy) in outpatient clinics within 30 days of the index infection. HA-IAs are commonly caused by more resistant flora. Here, complex multidrug regimens may be necessary for first line, empiric therapy. Although transmission of multidrug resistant organisms is most frequently documented in acute care facilities, all healthcare settings are affected by the emergence and transmission of antimicrobial-resistant microbes [253].

Resistant flora may include the non-fermenting gram-negative *Pseudomonas aeruginosa*, very dangerous either in the abdominal cavity, [261] or in hepatobiliary surgery [262–265] and *Acinetobacter spp.*, ESBL-producing *K. pneumoniae*, *E. coli* and vancomycin-resistant enterococci (VRE) [266, 267].

During the last two decades, antimicrobial resistance has become a global threat to public health systems and some of the most common causes include erroneous use of antibiotics, and poor prevention and control with respect to infections. Particularly, infections caused by resistant gram-negative bacteria [253, 268] are becoming increasingly prevalent and now constitute a serious threat to public health worldwide because they are difficult to treat and are associated with high morbidity and mortality rates. Bacteria producing carbapenemases, such as *K. pneumoniae*, are rapidly emerging as a major source of multidrug-resistant infections worldwide [269–272] and pose a serious threat in clinical situations where administration of effective empiric antibiotics is essential to prevent mortality following bacteraemia and infections in immunocompromised patients. Non-fermenting gram-negative bacteria (*P. aeruginosa*, *Stenotrophomonas maltophilia*, and *Acinetobacter baumannii*) have exhibited alarming rates of increased resistance to a variety of antibiotics in health facilities worldwide. Both species are intrinsically resistant to several drugs and could acquire additional resistance to other important antimicrobial agents [253]. *P. aeruginosa* coverage is only generally recommended for patients with HA-IAs.

Among gram-positive bacteria, enterococci play a significant role in IAI. Some studies have demonstrated poor outcomes among patients with documented enterococcal infections, particularly in those with post-operative IAI where enterococci coverage should be always considered [273, 274].

The acquisition of glycopeptide resistance by enterococci has seriously affected the treatment and control of these organisms. Affected patients usually have multiple and relevant co-morbidities, with prolonged hospital stay and received long courses of broad-spectrum antibiotics [274].

The burden of multidrug-resistant organism (MDRO) infections in LMICs is difficult to quantify because in these countries, routine microbiologic culture and sensitivity testing, especially in rural hospitals, are not performed because of the lack of personnel, equipment, and financial resources. As a consequence, antimicrobial therapy is empirical and a small collection of antimicrobials may be overused. This approach, although relatively inexpensive, may increase the emergence of antimicrobial resistance and hence sub-optimal clinical outcomes [253].

Therefore, although resistance containment interventions in healthcare structures have mostly been implemented in high-income countries, there is a pressing need to intervene in the resistance pandemic also in LMIC.

In the setting of HA-IAs, post-operative peritonitis (PP) is a life-threatening hospital-acquired intra-abdominal infection with high rates of mortality and high risk for MDR infections and invasive candidiasis [275, 276]. Antimicrobial therapy between initial intervention and reoperation seems to be a significant risk factor for emergence of MDRO in patients with PP. A study by Augustin et al. [276] included all consecutive adult patients with a diagnosis of post-operative peritonitis requiring admission to a surgical intensive care unit from January 2001 to December 2004. A total of 269 bacteria were cultured in 100 patients including 41 episodes with MDRO. According to logistic regression analysis, the use of broad-spectrum antibiotics between the initial intervention and reoperation was a significant risk factor for emergence of MDRO.

In 2015, a retrospective review of patients with anastomotic leakage after colorectal cancer surgery [277], reported the use of antibiotics for more than 5 days before diagnosis of anastomosis site leakage, and diabetes mellitus were identified as independent risk factors for MDRO acquisition by multivariate analysis.

In critically ill patients antimicrobial therapy should be started as soon as possible.

In these patients to ensure timely and effective administration of antibiotics, clinicians should always consider the pathophysiological status of the patient as well as the pharmacokinetic properties of the employed antibiotics (Recommendation 1B).

An ineffective or otherwise inadequate antimicrobial regimen is one of the variables more strongly associated with unfavorable outcomes in critical ill patients [278].

Empiric antimicrobial therapy should be started as soon as possible in patients with organ dysfunction and septic shock [279].

However, apart from early timing of administration, selection of a pharmacological agent with penetration to the site of presumed infection, is necessary. Furthermore, the pathophysiological and immunological status of the patient and the pharmacokinetic properties of the chosen drugs warrant consideration. In the event of abdominal sepsis, clinicians must be aware that drug pharmacokinetics may be altered significantly in critically ill patients due to the pathophysiology of sepsis. For example, in critically ill patients, higher than standard loading doses of hydrophilic antimicrobials such as beta-lactams should be administered to ensure optimal exposure at the infection site independently of the patient's renal function because of the dilution effect [280].

Two patterns of bactericidal activity have been described for antibiotics: time-dependent activity (where the time that the plasma concentration persists above the MIC of the etiological agent is considered the major determinant for efficacy) and concentration-dependent activity (where the efficacy is mainly related to the plasma peak concentration in relation to the MIC of the microorganism). The efficacy of time-dependent antibacterial agents in severely ill patients is related primarily to the maintenance of supra-inhibitory concentrations, and therefore, multiple daily dosing or continuous infusion may be appropriate [280, 281].

On the other hand, some agents including aminoglycosides have concentration-dependent activity; therefore, for this antibiotic class, the entire daily dose should be administered in a once daily way (or with the lowest possible number of daily administrations) to achieve the highest peak plasma level and reduce the renal cortex exposure to aminoglycosides and reduces the risk of nephrotoxicity [282].

In patients with uncomplicated IAI such as uncomplicated appendicitis and uncomplicated cholecystitis, where the source of infection is treated definitively, post-operative antibiotic therapy is not necessary (Recommendation 1A).

In patients with complicated IAI undergoing an adequate source-control procedure, a short course of antibiotic therapy (3-5 d) is always recommended (Recommendation 1A).

Patients who have ongoing signs of peritonitis or systemic illness (ongoing infection) beyond 5 to 7 days of antibiotic treatment, should warrant a diagnostic investigation (Recommendation 1C).

Antibiotics should be used after a treatable infection has been recognized or if there is a high degree of suspicion of an infection. In the setting of uncomplicated acute IAIs

such as uncomplicated appendicitis or cholecystitis, single doses have the same impact as multiple doses and post operative antimicrobial therapy is not necessary if source control is adequate [170, 283–285].

In the setting of cIAIs, a short course of antibiotic therapy (3–5 days) after adequate source control is a reasonable option [170, 283–285]. The recent prospective trial by Sawyer et al. demonstrated that in patients with cIAI undergoing an adequate source control, the outcomes after approximately 4 days fixed-duration antibiotic therapy were similar to those after a longer course of antibiotics that extended until after the resolution of physiological abnormalities [286]. However, in critically ill patients with ongoing sepsis, an individualized approach should be always mandatory and patient's inflammatory response should be monitored regularly [287] and decisions to continue, narrow, or stop antimicrobial therapy must be made on the basis of clinician judgment.

Patients who have ongoing signs of peritonitis or systemic illness beyond 5–7 days of antibiotic treatment normally warrant a diagnostic investigation to determine whether additional surgical intervention is necessary to address an ongoing uncontrolled source of infection or antimicrobial treatment failure. The prolonged and inappropriate use of antibiotics appears a key factor in the rapid rise of antimicrobial resistance worldwide over the past decade [287]. A rational and appropriate use of antibiotics is particularly important both to optimize quality clinical care and to reduce selection pressure on resistant pathogens. Several strategies aiming at achieving optimal use of antimicrobial agents have been described, but it is important that surgeons know antibiotic administration minimal requirements. Without these minimal requirements, surgeons worldwide will increase the likelihood of treatment failures and antibiotic resistance.

The choice of empiric antibiotic regimens in patients with IAI should be based on the clinical condition of the patients, the individual risk for infection by resistant pathogens, and the local resistance epidemiology (Recommendation 1C).

Intra-abdominal infections may be managed with either single or multiple antibiotic regimens.

Beta-lactam/beta-lactamase inhibitor combinations have an in vitro activity against gram-positive, gram-negative, and anaerobe organisms. Amoxicillin/clavulanate is still an option in mild community acquired IAIs. Broad-spectrum activity of piperacillin/tazobactam, including anti-*P.seudomonas* effect and anaerobic coverage, still make it an interesting option for management of severe IAIs. However, the use of piperacillin/tazobactam in patients with ESBLs infections is still controversial [288, 289], even if in stable patients, it may be still a therapeutic chance.

Third generation cephalosporins including cefotaxime and ceftriaxone in association with metronidazole, may be still options for the treatment of mild IAIs.

Ceftazidime and cefoperazone are third generation cephalosporins with an activity against *P. aeruginosa*. Cefepime, is a fourth-generation cephalosporin, with broader spectrum activity than third generation cephalosporins and effective against AmpC-producing organisms [290]. For empiric therapy, also cefepime should also be combined with metronidazole because it does not possess anti-anaerobic activity [291].

Ciprofloxacin and levofloxacin are no longer appropriate choice as first-line treatment in many geographic regions because of the prevalence of fluoroquinolone resistance. However, when employed, these drugs should be used in association with metronidazole. In many current practices, the fluoroquinolones remain available for patients presenting allergy to beta-lactams, with mild intra-abdominal infections [75].

Carbapenems offer a wide spectrum of antimicrobial activity against gram-positive and gram-negative aerobic and anaerobic pathogens (with the exception of MDR-resistant gram-positive cocci). Group 1 carbapenems include ertapenem. This group has activity against extended-spectrum beta-lactamase (ESBL)-producing pathogens, but not active against *P. aeruginosa* and *Enterococcus* species. Group 2 includes imipenem/cilastatin, meropenem, and doripenem, which share activity against non-fermentative gram-negative bacilli [75].

For more than two decades, carbapenems have been considered the agents of choice for multidrug-resistant infections caused by *Enterobacteriaceae*. The recent and rapid spread *K. pneumoniae* carbapenems resistant has become a critical issue in hospitals worldwide. The use of carbapenems should be limited so as to preserve activity of this class of antibiotics because of the concern of emerging carbapenem-resistance [253].

Other options include aminoglycosides, particularly for suspected infections by gram-negative bacteria. They are effective against *P. aeruginosa*, but are ineffective against anaerobic bacteria and need association with metronidazole. Because of their toxic side effects, some guidelines did not recommend aminoglycosides for the routine empiric treatment of community-acquired IAI, reserving them for patients with allergies to beta-lactam agents or in combination with beta-lactams for treatment of IAI with suspected MDR gram-negative bacteria [292].

Tigecycline is a viable treatment option, especially in empiric therapy, for complicated IAIs due to its favorable in vitro activity against anaerobic organisms, enterococci, several ESBL- and in association carbapenemase-producing *Enterobacteriaceae*, *Acinetobacter* species, and *Stenotrophomonas maltophilia* [293–295]. It does not feature in vitro activity against *P. aeruginosa* or *P. mirabilis*. Caution is always advised for its use, in suspected bacteremia and healthcare-associated pneumonia [296].

The recent challenges of treating multidrug-resistant gram-negative infections, especially in critically ill patients, have renewed interest in the use of “old” antibiotics such as polymyxins and fosfomycin [297, 298], now routinely used for treatment of MDR bacteria in critical ill patients.

Ceftolozone/tazobactam and ceftazidime/avibactam are new antibiotics that have been approved for treatment of cIAIs (in combination with metronidazole) including infection by ESBLs producing *Enterobacteriaceae* and *P. aeruginosa*. These antimicrobials will be valuable for treating infections caused by MDR gram-negative bacteria in order to preserve carbapenems [299]. Ceftolozone/tazobactam has excellent in vitro activity against MDR *P. aeruginosa* [299]. Ceftazidime/avibactam seems to have an in vitro activity against *K. pneumoniae* carbapenemase-producing bacteria [300]. Although many reviews have been written, their precise role as empiric treatment for complicated IAI remains to be defined [301].

In table 4, antibiotics for treating patients with cIAIs as proposed by the AGORA working group are illustrated [253]. Appendices 1, 2, 3, 4 list antimicrobial regimens for management of patients with cIAIs in different settings worldwide.

Intra-operative cultures should be always performed in patients with HA-IAs or with CA- at risk for resistant pathogens or in critically ill patients. They allow expansion of the antimicrobial regimen if the initial choice is too narrow and to perform a de-escalation if the empirical regimen is too broad.

When a microorganism is identified in clinical cultures, antimicrobial susceptibility testing (AST) should always be performed and reported to guide antibiotic therapy (Recommendation 1C).

Although a lack of impact on patient outcomes by bacteriological cultures has been documented in patients with community-acquired IAI, especially in appendicitis [302, 303], the results of microbiological testing may have great importance for the choice of therapeutic strategy of every patient, in particular, in the adaptation of targeted antimicrobial treatment in patients at risk of unpredictable organisms.

Obtaining microbiological results from intra-operative culture from the site of infection has two advantages: (a) to expand antimicrobial regimen if the initial choice was too narrow and (b) to perform de-escalation of antimicrobial therapy if the empirical regimen was too broad [253].

When a microorganism is identified in clinical cultures, antimicrobial susceptibility testing (AST) should always be performed to guide antimicrobial therapy. Data are reported in the form of MIC, which is the lowest concentration of an antibiotic that inhibits visible growth of a microorganism.

The numerical MIC number, expressed as micrograms/ml, is usually reported by microbiology laboratories as a

categorical guide for clinicians, i.e., as “susceptible”, “resistant”, or “intermediate,” according to Clinical or Laboratory Standards Institute (CLSI) criteria in the USA or the European Committee for Antimicrobial Susceptibility Testing (EUCAST) criteria in Europe.

Knowledge of mechanisms of secretion of antibiotics into bile may be helpful in designing the optimal therapeutic regimen for patients with biliary-related intra-abdominal infections (Recommendation 1C).

Organisms most often isolated in biliary infections are those isolated in intra-abdominal infections including the gram-negative aerobes, *E. coli* and *K. pneumoniae* and anaerobes, especially *B. fragilis* [153]. The role of enterococci in biliary tract infections remains unclear, and specific coverage against these microorganisms is not routinely suggested for community-acquired biliary infections [153].

Although there are no clinical data to support the use of antibiotics with biliary penetration for these patients, the efficacy of antibiotics in the treatment of biliary infections may depend on effective biliary antibiotic concentrations too [153]. Obviously in patients with obstructed bile ducts, the biliary penetration of antibiotics may be poor and effective biliary concentrations are reached only in a minority of patients [153].

Antibiotics commonly used to treat biliary tract infections and their biliary penetration ability are illustrated in Table 5.

Empirical antifungal therapy for Candida species is recommended for patients with hospital-acquired IAIs, especially those with recent abdominal surgery or anastomotic leak (Recommendation 1C).

The epidemiological profile of *Candida spp* in the context of nosocomial peritonitis is incompletely defined. Its clinical presence is usually associated with poor prognosis. Empirical antifungal therapy for *Candida spp* is typically not recommended for patients with community-acquired intra-abdominal infections, with the notable exceptions of critically ill patients or immunocompromised patients (due to neutropenia or concurrent administration of immunosuppressive agents, such as glucocorticosteroids, chemotherapeutic agents, and immunomodulators) [304]. Recently, IDSA guidelines for the treatment of invasive candidiasis were developed and addressed *Candida* peritonitis [275]. IDSA guidelines suggested considering empiric antifungal therapy for patients with clinical evidence of intra-abdominal infection and significant risk factors for candidiasis, including recent abdominal surgery, anastomotic leaks, or necrotizing pancreatitis, who are doing poorly despite treatment for bacterial infections.

Preferred empiric therapy in critically ill patients or those previously exposed to an azole is an echinocandin (Caspofungin: loading dose of 70 mg, then 50 mg daily; Micafungin: 100 mg daily; Anidulafungin: loading dose of 200 mg, then 100 mg daily). However, fluconazole,

Table 4 Antibiotics for treating patients with IAIs based upon susceptibility [253]

Antibiotic	Enterococci	Ampicillin-resistant enterococci	Vancomycin-resistant enterococci	Enterobacteriaceae	ESBL-producing Enterobacteriaceae	Pseudomonas aeruginosa	Anaerobic gram-negative bacilli
Penicillins/beta-lactamase inhibitors							
Amoxicillin/clavulanate	+	—	—	+	—	—	+
Ampicillin/sulbactam	+	—	—	+	—	—	+/-
Piperacillin/tazobactam	+	—	—	+	+/-	+	+
Carbapenems							
Ertapenem	—	—	—	+	+	—	+
Imipenem/cilastatin	+/- ^a	—	—	+	+	+	+
Meropenem	—	—	—	+	+	+	+
Doripenem	—	—	—	+	+	+	+
Fluoroquinolones							
Ciprofloxacin	—	—	—	+	—	+ ^b	—
—Levofloxacin	+/-	—	—	+	—	+/-	—
Moxifloxacin	+/-	—	—	+	—	—	+/-
Cephalosporins							
Ceftriaxone	—	—	—	+	—	—	—
Ceftazidime	—	—	—	+	—	+	—
Cefepime	—	—	—	+	+/-	+	—
Ceftazidime/avibactam	—	—	—	+	+	+	—
Aminoglycosides							
Amikacin				+	+	+	—
Gentamicin				+	+	+	—
Glycylcyclines							
Tigecycline	+	+	+	+ ^c	+	—	+
5-Nitroimidazole							
Metronidazole							+
Polymyxins							
Colistimethate (Colistin)	—	—	—	+ ^d	+	+	—
Glycopeptides							
Teicoplanin	+	+	—	—	—	—	—
Vancomycin	+	+	—	—	—	—	—
Oxazolidinones							
Linezolid	+	+	+	—	—	—	—

^aImipenem/cilastatin is more active against ampicillin-susceptible enterococci than ertapenem, meropenem and doripenem
^bCiprofloxacin is more active against *P. aeruginosa* than levofloxacin
^cNot active against *Proteus*, *Morganella*, and *Providencia*
^dNot active against *Morganella*, *Proteus*, *Providencia*, *Salmonella*, *Serratia*, *Shigella*, and *Yersinia* (*Y. enterocolitica*)

600 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily, should be still considered first-line antifungal therapy, in hemodynamically stable patients who are colonized with azole susceptible *Candida* species or who have no prior exposure to azoles [275].

Conclusions

IAIs remain an important cause of morbidity and mortality in modern surgical practice worldwide. The cornerstones of effective treatment of IAIs include early and accurate diagnosis, prompt resuscitation, early and effective source

抗菌药物治疗

1. 了解地区 / 当地耐药率（当这些数据存在时），往往是选择经验性抗感染治疗临床决策部分的关键内容（推荐级别 1C）
2. 通过确定感染是社区获得性还是医院获得性来预测既定感染的病原菌和可能的耐药性。

对于社区获得性腹腔感染（CA-IAIs），更倾向于选择窄谱抗菌药物。但是，对于有产超广谱 β -内酰胺酶（ESBLs）肠杆菌感染风险的社区获得性腹腔感染患者，需要使用覆盖产 ESBLs 细菌的抗菌药物。对于医院获得性腹腔感染（HA-IAIs），需要选择广谱抗菌药物（推荐 1B）。

3. 重症患者应该尽快开始抗菌治疗。

为了确保在这些患者中及时和有效的应用抗菌药物，临床医师应该时刻考虑这些患者的病理生理状态以及所用抗菌药物的药代动力学特征（推荐级别 1B）。

4. 对于非复杂腹腔感染患者，如非复杂性阑尾炎和非复杂性胆囊炎，手术确切治疗感染源，术后的抗菌药物治疗不是必须的（推荐级别 1A）。
5. 对于复杂性腹腔感染患者且当前正在控制感染源，推荐短期应用抗菌药物治疗（3-5 天）（推荐 1A）。
6. 对于接受 5-7 天抗菌药物治疗仍然存在持续性腹膜炎体征或者全身症状的患者，应该进一步明确诊断（推荐级别 1C）。
7. 腹腔感染患者的经验性抗菌药治疗应该基于患者的临床情况，个体耐药菌感染的风险和当地耐药菌的流行病学情况（推荐级别 1C）。
8. 在医院获得性腹腔感染或者有感染耐药菌风险的社区获得性感染或者重症患者中，往往术中需要进行病原微生物培养。如果初始选择抗菌谱太窄允许抗菌药物抗菌谱扩展，以及经验性治疗抗菌谱太广可以进行抗菌药物的降级。

在临床培养中明确微生物后，往往需要开展抗菌药物敏感性检测（AST）并且报告以指导抗菌药物治疗方案的制定（推荐级别 1C）。

9. 对于抗菌药物进入胆汁的机制的认识能够帮助治疗胆汁相关腹腔感染的患者抗菌药物治疗方案的制定（推荐级别 1C）。
10. 对于医院获得性腹腔感染患者推荐经验性抗真菌治疗念珠菌，特别是近期接受腹腔手术或者存在吻合口漏的患者（推荐级别 1C）。

表 4.基于药敏结果治疗腹腔感染的抗菌药物。

抗菌药物	肠球菌	氨苄西林耐药肠球菌	万古霉素耐药肠球菌	肠杆菌科细菌	产 ESBL 肠杆菌科细菌	铜绿假单胞菌	革兰阴性厌氧菌
青霉素/β 内酰胺酶抑制剂							
阿莫西林/克拉维酸	+	-	-	+	-	-	+
氨苄西林 / 舒巴坦	+	-	-	+	-	-	+/-
哌拉西林/他唑巴坦	+	-	-	+	+/-	+	+
碳青霉烯类							
厄他培南	-	-	-	+	+	-	+
亚胺培南/ 西司他丁	+/- ^a	-	-	+	+	+	+
美罗培南	-	-	-	+	+	+	+
多立培南	-	-	-	+	+	+	+
氟喹诺酮类							
环丙沙星	-	-	-	+	-	+ ^b	-
左氧氟沙星	+/-	-	-	+	-	+/-	-
莫西沙星	+/-	-	-	+	-	-	+/-
头孢菌素类							
头孢曲松	-	-	-	+	-	-	-
头孢他啶	-	-	-	+	-	+	-
头孢吡肟	-	-	-	+	+/-	+	-
头孢洛扎/他唑巴坦	-	-	-	+	+	+	-
头孢他啶/阿维巴坦	-	-	-	+	+	+	-
氨基糖苷类							
阿米卡星				+	+	+	-
庆大霉素				+	+	+	-
甘氨酸环素类							
替加环素	+	+	+	+ ^c	+	-	+

5-硝基咪唑类

甲硝唑

+

多黏菌素类

多黏菌素 E

-

-

-

+^d

+

+

-

糖肽类

替考拉宁

+

+

-

-

-

-

-

万古霉素

+

+

-

-

-

-

-

噁唑烷酮类

利奈唑胺

+

+

+

-

-

-

-

^a 亚胺培南/ 西司他丁对氨苄西林耐药肠球菌的活性较厄他培南，美罗培南和多立培南强^b 环丙沙星对铜绿假单胞菌活性较左氧氟沙星强^c 对变形杆菌，摩根菌和普罗威登斯菌无活性^d 对摩根菌，变形杆菌，普罗威登斯菌，沙门氏菌，志贺氏菌，沙雷氏菌和耶尔森氏菌无活性

Table 5 Antibiotics commonly used to treat biliary tract infections and their biliary penetration ability [153]

Good penetration efficiency	Low penetration efficiency
Piperacillin/tazobactam	Ceftriaxone
Tigecycline	Cefotaxime
Amoxicillin/clavulanate	Meropenem
Ciprofloxacin	Ceftazidime
Ampicillin/sulbactam	Vancomycin
Cefepime	Amikacin
Levofloxacin	Gentamicin
Imipenem	

control, and initiation of appropriate antimicrobial therapy. IAs have different disease and clinical spectra in the various regions of the world, and their etiological factors show a wide geographical variation. Promoting standards of care in the managing IAs worldwide should be mandatory to grant management guidelines to all surgeons.

In Appendix 5, all the WSES recommendations are illustrated.

Appendix 1

Empiric antibiotic regimens for non-critically ill patients with community-acquired IAs. Normal renal function

Community-acquired cIAs

Non-critically ill patients

Amoxicillin/clavulanate 1.2-2.2 g 6-hourly

or

Ceftriaxone 2 g 24-hourly + Metronidazole 500 mg 6-hourly

or

Cefotaxime 2g 8-hourly + Metronidazole 500 mg 6-hourly

or

In patients with beta-lactam allergy

Ciprofloxacin 400 mg 8-hourly + Metronidazole 500 mg 6-hourly

or

Moxifloxacin 400 24-hourly

or

In patients at risk for infection with community-acquired ESBL-producing Enterobacteriaceae

Ertapenem 1 g 24 hourly

or

Tigecycline 100 mg initial dose, then 50 mg 12-hourly

Appendix 2

Empiric antibiotic regimens for critically ill patients with community-acquired IAs. Normal renal function

Community-acquired IAs

Critically ill patients

Piperacillin/Tazobactam 4.5 g 6-hourly

or
Cefepime 2 g 8-hourly + Metronidazole 500 mg 6-hourly

or

In patients at risk for infection with community-acquired ESBL-producing Enterobacteriaceae

Meropenem 1 g 8-hourly

or

Doripenem 500 mg 8-hourly

or

Imipenem/Cilastatin 1 g 8-hourly

In patients at high risk for infection with Enterococci including immunocompromised patients or patients with recent antibiotic exposure consider use of **Ampicillin 2 g 6-hourly** if the patients are not being treated with piperacillin/tazobactam or imipenem-cilastatin (active against ampicillin-susceptible enterococci)

Appendix 3

Empiric antimicrobial regimens for non-critically ill patients with healthcare-associated IAs. Normal renal function (CrCl>90 mL/min)

Healthcare-associated IAs

Non-critically ill patients

Piperacillin/Tazobactam 4.5 g 6-hourly

or

In patients at higher risk for infection with MDROs including recent antibiotic exposure, patient living in a nursing home or long-stay care with an indwelling catheter, or post-operative IAI

Meropenem 1 g 8-hourly + Ampicillin 2 g 6-hourly

or

Doripenem 500 mg 8-hourly + Ampicillin 2 g 6-hourly

or

Imipenem/Cilastatin 1 g 8-hourly

or

As a carbapenem-sparing regimen

Piperacillin/Tazobactam 4.5 g 6-hourly + Tigecycline 100 mg initial dose, then 50 mg 12-hourly

+/-

In patients at high risk for invasive candidiasis

Fluconazole 800 mg LD then 400 mg 24-hourly

In patients with documented beta-lactam allergy consider use of antibiotic combinations with **Amikacin 15–20 mg/kg 24-hourly**

Appendix 4

Empiric antimicrobial regimens for critically ill patients with healthcare-associated IAs. Normal renal function

Healthcare-associated IAs

Critically ill patients

Meropenem 1 g 8-hourly

or

Doripenem 500 mg 8-hourly

or

Imipenem/Cilastatin 1 g 8-hourly

or

As a carbapenem-sparing regimen

Ceftolozane /Tazobactam 1.5 g 8-hourly + Metro-nidazole 500 mg 6-hourly

or

Ceftazidime/Avibactam 2.5 g 8-hourly + Metro-nidazole 500 mg 6-hourly

+

Vancomycin 25–30 mg/kg loading dose then 15–20 mg/kg/dose 8-hourly

or

Teicoplanin 12 mg/kg 12-hourly times 3 loading dose then 12 mg/kg 24-hourly

or

In patients at risk for infection with vancomycin-resistant enterococci (VRE) including patients with previous enterococcal infection or colonization, immunocompromised patients, patients with long ICU stay, or recent Vancomycin exposure

Linezolid 600 mg 12-hourly

or

Daptomycin 6 mg/kg 24-hourly

+-

In patients at high risk for invasive candidiasis

Echinocandins: caspofungin (70 mg LD, then 50 mg daily), anidulafungin (200 mg LD, then 100 mg daily), micafungin (100 mg daily) or Amphotericin B Liposomal 3 mg/kg/dose 24-hourly

In patients with suspected or proven infection with MDR (non-metallo-beta-lactamase-producing) *Pseudomonas aeruginosa* consider use of antibiotic combinations with **Ceftolozane /Tazobactam**

In patients with suspected or proven infection with carbapenemase-producing *Klebsiella pneumoniae* consider use of antibiotic combinations with **Ceftazidime/Avibactam**

In patients with documented beta-lactam allergy consider use of antibiotic combinations with **Amikacin 15–20 mg/kg 24-hourly**

clinical response, and not solely guided by a predetermined protocol. Vasopressor agents may serve to augment and assist fluid resuscitation, particularly where this therapy alone is failing (Recommendation 1A).

Diagnosis

Statement 2

A step-up approach for diagnosis from clinical and laboratory examination, to imaging examination should be used and tailored to the hospitals resources (Recommendation 1B).

Source control

Statement 3

Appendectomy remains the treatment of choice also for acute appendicitis. Antibiotic therapy is a safe means of primary treatment for patients with uncomplicated acute appendicitis, but it is less effective in the long-term due to significant recurrence rates and probably needs the certainty of a CT proven diagnosis of uncomplicated appendicitis (Recommendation 1A).

Statement 4

Both open and laparoscopic appendectomies are viable approaches to surgical treatment of acute appendicitis (Recommendation 1A).

Statement 5

Patients with a periappendiceal abscess can be managed with percutaneous image-guided drainage in surgical departments with ready access to diagnostic and interventional radiology. When percutaneous drainage is not available, surgery is suggested (Recommendation 1B).

Statement 6

In patients treated conservatively, interval appendectomy may be not necessary following initial non-operative treatment of complicated appendicitis. However, interval appendectomies should always be performed for patients with recurrent symptoms (Recommendation 2B).

Statement 7

Routine use of intra-operative irrigation for appendectomies does not prevent intra-abdominal abscess formation and may be avoided (Recommendation 2B).

Statement 8

Antibiotics can be avoided in patients with CT findings of uncomplicated ALCD and without significant comorbid conditions or signs of sepsis. Patients should be clinically monitored to assess for resolution of the inflammatory processes (Recommendation 1A).

Appendix 5

WSES recommendations for management of intra-abdominal infections

Principles of sepsis control

Statement 1

Early recognition of the patient with ongoing abdominal sepsis is an essential step for an effective treatment.

Prompt administration of intravenous fluids for resuscitation is critical in patients with an ongoing sepsis. This initial resuscitation should be titrated to the

附录 1

非重症社区获得性腹腔感染患者经验性抗菌药物治疗方案（肾功能正常）

社区获得性腹腔感染

非重症患者

阿莫西林/克拉维酸 1.2-2.2 g 每 6h 一次

或

头孢曲松 2 g 每 24h 一次+甲硝唑 500 mg 每 6h 一次

或

头孢噻肟 2 g 每 8h 一次+甲硝唑 500 mg 每 6h 一次

或

对 β -内酰胺酶过敏史患者

环丙沙星 400 mg 每 8h 一次+甲硝唑 500 mg 每 6h 一次

或莫西沙星 400 mg 每 24h 一次

或

有社区获得性产 ESBL 肠杆菌感染风险的患者

厄他培南 1 g 每 24h 一次

或替加环素首剂 100 mg，之后 50 mg 每 12h 一次

附录 2

重症社区获得性腹腔感染患者的经验性抗菌药物治疗方案（肾功能正常）

社区获得性腹腔感染

重症患者

哌拉西林/他唑巴坦 4.5 g 每 6h 一次

或

头孢吡肟 2g 每 8h 一次+甲硝唑 500 mg 每 6h 一次

或

有社区获得性产 ESBL 肠杆菌感染风险的患者

美罗培南 1 g 每 8h 一次

多立培南 500 mg 每 8h 一次

或

亚胺培南/西司他丁 1 g 每 8h 一次

有肠球菌感染高风险的患者（包括免疫功能缺陷或者近期有抗菌药物暴露的患者）如未给予过哌拉西林/他唑巴坦或亚胺培南/西司他丁（对氨苄西林敏感肠球菌），则建议氨苄西林 2 g 每 6h 一次。

附录 3

非重症医疗保健相关性腹腔感染患者的经验性抗菌药物治疗方案（肾功能正常，CrCl>90 mL/min）

医疗保健相关性腹腔感染

非重症患者

哌拉西林/他唑巴坦 4.5 g 每 6h 一次

或

存在 MDR 菌感染高风险患者（包括近期抗菌药物暴露，居住于疗养院或者长期留置导管或留置针，术后 IAI）

美罗培南 1 g 每 8h 一次+氨苄西林 2 g 每 6h 一次

或

多立培南 500 mg 每 8h 一次+氨苄西林 2 g 每 6h 一次

或

亚胺培南/西司他丁 1 g 每 8h 一次

或

无碳青霉烯类备选方案

哌拉西林/他唑巴坦 4.5 g 每 6h 一次+替加环素首剂 100 mg，之后 50 mg 每 12h 一次

+/-

有侵袭性念珠菌感染高风险患者

氟康唑负荷剂量 800 mg，之后 400 mg 每 24h 一次

对于有 β -内酰胺酶过敏史患者考虑联用阿米卡星 15-20 mg/kg 每 24 小时一次

附录 4

重症医疗保健相关性腹腔感染患者的经验性抗菌药物治疗方案（肾功能正常）

医疗保健相关性腹腔感染

重症患者

美罗培南 1 g 每 8h 一次

或

多立培南 500 mg 每 8h 一次

或

亚胺培南/西司他丁 1 g 每 8h 一次

作为无碳青霉烯类备选方案

头孢洛扎/他唑巴坦 1.5 g 每 8h 一次+甲硝唑 500 mg 每 6h 一次

或

头孢他啶/阿维巴坦 2.5 g 每 8h 一次+甲硝唑 500 mg 每 6h 一次

+万古霉素负荷剂量 25-30 mg/kg，之后 15-20 mg/kg 每 8h 一次

或

替考拉宁 12 mg/kg 每 12 h 一次给予 3 次负荷剂量，之后 12 mg/kg 每 24h 一次

或

有万古霉素耐药肠球菌（VRE）感染风险患者（之前肠球菌感染或定植，免疫缺陷，长期 ICU 住院，或近期万古霉素暴露）

利奈唑胺 600 mg 每 12h 一次

或

达托霉素 6 mg/kg 每 24h 一次

有侵袭性念珠菌感染高风险患者

棘白菌素：卡泊芬净（负荷剂量 70 mg，之后每天 50 mg），阿尼芬净（负荷剂量 200 mg，之后每天 100 mg），米卡芬净（每天 100 mg）或两性霉素 B 脂质体 3 mg/kg 每 24h 一次

如怀疑或证实感染 MDR（非产金属 β -内酰胺酶）铜绿假单胞菌，考虑联合头孢洛扎/他唑巴坦

如怀疑或证实感染产碳青霉烯酶肺炎克雷伯菌，考虑联合头孢他啶/阿维巴坦

对有 β -内酰胺酶过敏史患者考虑联合阿米卡星 15-20 mg/kg 每 24 小时一次

Statement 9

On the basis of clinical conditions, patients with diverticular smaller abscesses may be treated by antibiotics alone (Recommendation 1C).

Statement 10

Patients with abscesses having a large diameter should be treated by percutaneous drainage and intravenous antibiotics (Recommendation 1C).

Statement 11

Whenever percutaneous drainage of the abscess is not feasible or not available, based on the clinical conditions patients with large abscesses can be initially treated by antibiotic therapy alone. However, careful clinical monitoring is mandatory (Recommendation 1C).

Statement 12

Hartmann's procedure remains useful in the management of diffuse peritonitis in critically ill patients. However, in clinically stable patients, primary resection with anastomosis, with or without a diverting stoma, may be performed (Recommendation 1B).

Statement 13

Laparoscopic peritoneal lavage and drainage may not be considered the treatment of choice in patients with diffuse peritonitis (Recommendation 1A).

Statement 14

Treatments for perforated colonic carcinoma should both stabilize the emergency condition of the peritonitis and fulfil the technical objectives of oncological intervention (Recommendation 1B).

Statement 15

Patients presenting with diffuse peritonitis caused by colonoscopic perforation should undergo immediate surgical intervention, which typically involves primary repair or resection (Recommendation 1B).

Statement 16

An early laparoscopic approach may be a safe and effective option for colonoscopy-related colonic perforation for experienced surgeons (Recommendation 2B).

Statement 17

Surgery is the treatment of choice for perforated peptic ulcers (Recommendation 1A).

Statement 18

Simple closure with or without an omental patch is a safe and effective procedure to address small perforated ulcers (<2 cm) (Recommendation 1A).

Statement 19

Laparoscopic repair of perforated peptic ulcers can be a safe and effective procedure for experienced surgeons (Recommendation 1A).

Statement 20

Surgery is the treatment of choice for patients with small bowel perforations (Recommendation 1B).

Statement 21

In the event of small perforations, primary repair is recommended (Recommendation 1B).

Statement 22

In the case of abdominal tuberculosis perforation, resection of the affected area and anastomosis may be the treatment of choice rather than primary closure (Recommendation 1C).

Statement 23

Early cholecystectomy is a safe treatment for acute cholecystitis and generally results in shorter recovery time and hospitalization compared to delayed cholecystectomies (Recommendation 1A).

Statement 24

Laparoscopic cholecystectomy is a safe and effective treatment for acute cholecystitis (Recommendation 1A).

It is the first choice for patients with acute cholecystitis where adequate resources and skill are available. Some risk factors may predict the risk for conversion to open cholecystectomy.

Statement 25

Cholecystostomy is a safe and effective treatment for acute cholecystitis in critically ill and/or with multiple comorbidities and unfit for surgery patients (Recommendation 1B).

Statement 26

Early diagnosis of gallbladder perforation and immediate surgical intervention may substantially decrease morbidity and mortality rates (Recommendation 1C).

Statement 27

Endoscopic retrograde cholangiopancreatography (ERCP) is the treatment of choice for biliary decompression in patients with moderate/severe acute cholangitis (Recommendation 1A).

Statement 28

Percutaneous biliary drainage (PTBD) should be reserved for patients in whom ERCP fails (Recommendation 1B).

Statement 29

Open drainage should only be used in patients for whom endoscopic or percutaneous trans-hepatic drainage is contraindicated or those in whom it has been unsuccessfully performed (Recommendation 2C).

Statement 30

On the basis of the clinical conditions, the size of the abscess and the access to interventional radiology, antibiotics, and/or percutaneous drainage may be suggested to treat post-operative localized intra-abdominal abscesses when there are no signs of generalized peritonitis (Recommendation 2C).

Statement 31

Prompt surgical source control should be performed following diagnosis of post-operative peritonitis. Ineffective control of the septic source is associated with significantly elevated mortality rates (Recommendation 1C).

Statement 32

Patients with tubo-ovarian abscess that does not respond to antibiotics should undergo surgical drainage (Recommendation 1C).

Statement 33

Early surgical intervention is recommended in case of HVI (Recommendation 1C).

Statement 34

Repair or anastomosis of intestinal injuries should be considered in all patients. A complete diversion of the fecal stream could be considered in colorectal injuries involving all layers in the setting of multiple injuries or comorbid conditions (Recommendation 1C).

Statement 35

The on-demand re-laparotomy is recommended for patients with severe peritonitis because its ability to streamline healthcare resources reduce overall medical costs and prevent the need for further re-laparotomies (Recommendation 2A).

Statement 36

The open abdomen may be a viable option for treating physiologically deranged patients with ongoing sepsis, facilitating subsequent exploration and control of abdominal contents, and preventing abdominal compartment syndrome (Recommendation 1C).

In order to define the role of OA with negative pressure therapy for improved biomediator clearance and mitigated systemic sepsis in patients with severe peritonitis, a prospective trial is needed.

Statement 37

Rapid closure with the assistance of negative pressure therapy should be the primary objective in the management of patients with open abdomen, in order to prevent severe morbidity such as fistulae, loss of domain, and massive incisional hernias (Recommendation 1B).

Antimicrobial therapy**Statement 38**

Knowledge of regional/local rates of resistance, when it is available, should be always an essential component of the clinical decision-making process when deciding the empirical treatment of infection (Recommendation 1C).

Statement 39

Predicting the pathogens and potential resistance patterns of a given infection begins by establishing whether the infection is community-acquired or hospital-acquired.

For patients with community-acquired intra-abdominal infections (CA-IAs), agents with a narrower spectrum of activity are preferred. However, in CA-IAI patients at risk for extended-spectrum beta-lactamases (ESBLs) producing *Enterobacteriaceae* infections, anti-ESBL-producer coverage may be warranted. For patients with hospital-acquired infections (HA-IAs), antibiotic regimens with broader spectra of activity are preferred (Recommendation 1B).

Statement 40

In critically ill patients, antimicrobial therapy should be started as soon as possible.

In these patients, to ensure timely and effective administration of antibiotics, clinicians should always consider the pathophysiological status of the patient as well as the pharmacokinetic properties of the employed antibiotics (Recommendation 1B).

Statement 41

In patients with uncomplicated IAI such as uncomplicated appendicitis and uncomplicated cholecystitis, where the source of infection is treated definitively, post-operative antibiotic therapy is not necessary (Recommendation 1A).

Statement 42

In patients with complicated IAI undergoing an adequate source-control procedure, a short course of antibiotic therapy (3–5 days) is always recommended (Recommendation 1A).

Statement 43

Patients who have ongoing signs of peritonitis or systemic illness (ongoing infection) beyond 5–7 days of antibiotic treatment should warrant a diagnostic investigation (Recommendation 1C).

Statement 44

The choice of empiric antibiotic regimens in patients with IAI should be based on the clinical condition of the patients, the individual risk for infection by resistant pathogens, and the local resistance epidemiology (Recommendation 1C).

Statement 45

Intra-operative cultures should be always performed in patients with HA-IAs or with CA- at risk for resistant pathogens or in critically ill patients. They allow expansion of the antimicrobial regimen if the initial choice is too narrow and to perform a de-escalation if the empirical regimen is too broad.

When a microorganism is identified in clinical cultures, antimicrobial susceptibility testing (AST) should always be performed and reported to guide antibiotic therapy (Recommendation 1C).

Statement 46

Knowledge of mechanisms of secretion of antibiotics into bile may be helpful in designing the optimal therapeutic regimen for patients with biliary-related intra-abdominal infections (Recommendation 1C).

Statement 47

Empirical antifungal therapy for *Candida* species is recommended for patients with hospital-acquired IAIs, especially those with recent abdominal surgery or anastomotic leak (Recommendation 1C).

Abbreviations

CA-IAs: Community-acquired intra-abdominal infections; HA-IAs: Hospital-acquired intra-abdominal infections; IAIs: Intra-abdominal infections; MDRO: Multidrug-resistant organism

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The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection

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Abstract

Background: Previous evidence-based guidelines on the management of intra-abdominal infection (IAI) were published by the Surgical Infection Society (SIS) in 1992, 2002, and 2010. At the time the most recent guideline was released, the plan was to update the guideline every five years to ensure the timeliness and appropriateness of the recommendations.

Methods: Based on the previous guidelines, the task force outlined a number of topics related to the treatment of patients with IAI and then developed key questions on these various topics. All questions were approached using general and specific literature searches, focusing on articles and other information published since 2008. These publications and additional materials published before 2008 were reviewed by the task force as a whole or by individual subgroups as to relevance to individual questions. Recommendations were developed by a process of iterative consensus, with all task force members voting to accept or reject each recommendation. Grading was based on the GRADE (Grades of Recommendation Assessment, Development, and Evaluation) system; the quality of the evidence was graded as high, moderate, or weak, and the strength of the recommendation was graded as strong or weak. Review of the document was performed by members of the SIS who were not on the task force. After responses were made to all critiques, the document was approved as an official guideline of the SIS by the Executive Council.

Results: This guideline summarizes the current recommendations developed by the task force on the treatment of patients who have IAI. Evidence-based recommendations have been made regarding risk assessment in individual patients; source control; the timing, selection, and duration of antimicrobial therapy; and suggested approaches to patients who fail initial therapy. Additional recommendations related to the treatment of pediatric patients with IAI have been included.

Summary: The current recommendations of the SIS regarding the treatment of patients with IAI are provided in this guideline.

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This document is available on the Surgical Infection Society website, www.sisna.org.

EXECUTIVE SUMMARY

Intra-abdominal infection (IAI) is a common disease process managed by surgical practitioners. The Surgical Infection Society (SIS) developed and disseminated guidelines for the management of these infections in 1992 [1], in 2002 [2,3], and most recently in 2010 as a joint guideline with the Infectious Diseases Society of America (IDSA) [4]. Since the 2010 guideline, additional challenges have arisen in the management of these infections, in part because of the aging of the population and the burden of chronic disease in these patients, and in part because of the increased prevalence of resistant bacteria and fungi in both the healthcare setting and the community. Nonetheless, advances in the management of these infections have also been made; newer approaches to source control are now available, as are new antibiotic agents that may meet some of the challenges posed by resistant pathogens.

To maintain the clinical relevance of the guideline, the SIS appointed a task force to revise the 2010 guideline. This task force included members of the Therapeutics and Guidelines Committee as well as additional individuals from the SIS with expertise in the subject matter. The task force selected subjects from the previous guideline for updating, developed specific questions for review, and then used the best available contemporary evidence to formulate recommendations. The task force evaluated the quality of the evidence and the strength of the recommendations using the GRADE (Grades of Recommendation Assessment, Development, and Evaluation) nomenclature, which has now become widely accepted as a standard for guidelines. Once completed, the entire document was subjected to external review by additional experts from the SIS, modified according to these reviews by consensus of the task force and sent to the Executive Council of the SIS for final approval.

All judgments regarding interpretation of this evidence and the GRADE assignments were exercised by the members of the task force and subsequent reviewers based on their individual and collective expertise, recognizing that the evidence could be interpreted differently by others. As with previous guidelines, these recommendations were designed to support clinicians in making appropriate treatment decisions and not designed to supplant the judgment of the individual practitioner [4].

1. Risk assessment

Assessing the risk of an adverse outcome in patients with IAI is important in optimizing selection of source control and antimicrobial therapy. Specific recommendations include:

- Use phenotypic and physiologic factors, including signs of sepsis or septic shock, extremes of age, and patient co-morbidities; the extent of abdominal infection and adequacy of initial source control; and the presence or persistence of resistant or opportunistic pathogens in assessing risk for treatment failure and mortality in patients with IAI (Grade 1-B).
- Characterize patients as being at either lower or higher risk for treatment failure or death, and as having either a community-acquired IAI (CA-IAI) or a healthcare or hospital-associated IAI (HA-IAI), including a post-operative infection, for purposes of planning source control and empiric antimicrobial therapy (Grade 2-C).

- Identify patients with IAI meeting Surviving Sepsis Campaign criteria for sepsis or septic shock and those having an Acute Physiology and Chronic Health Evaluation II score greater than or equal to 10 as higher-risk patients (Grade 1-B). Consider patients with at least two physiologic/phenotypic risk factors for an adverse outcome, those having diffuse peritonitis, and those having delayed or inadequate source control as potential higher-risk patients (Grade 2-B).
- Identify patients who have been hospitalized for at least 48 hours during the previous 90 days; those residing in a skilled nursing or long-term care facility during the previous 30 days; those who have received intravenous (IV) infusion therapy, wound care, or renal replacement therapy within the preceding 30 days; those who have received several days of broad-spectrum antimicrobial therapy within the previous 90 days; those who have post-operative infections; and those known to have been colonized or infected previously with a resistant pathogen as having HA-IAI and at potential risk for infection because of resistant or opportunistic organisms (Grade 2-B).

2. Source control

Source control is considered fundamental to the treatment of most patients with IAI. Specific recommendations regarding source control include:

- Routinely use a source control procedure to remove infected fluid and tissue and to prevent ongoing contamination in patients with IAI except for those patients with clinical problems for which there is clear evidence that a non-interventional approach is associated with a good clinical outcome (Grade 1-A).
- Undertake source control within 24 hours of the diagnosis of IAI, except for those infections for which clinical evidence indicates a non-interventional or delayed approach is appropriate (Grade 2-B). Undertake source control in a more urgent manner in patients with sepsis or septic shock (Grade 2-C).
- Use the least invasive approach that is able to achieve adequate source control, at least on a temporary basis, in patients with IAI (Grade 1-B).
- Consider use of alternative or temporizing approaches to source control in patients with major physiologic instability, those with diffuse infections, and those with ongoing bowel ischemia who are considered at higher risk for initial source control failure (Grade 2-B).
- Use abbreviated laparotomy and temporary abdominal closure techniques in critically ill patients with IAI if closure of the abdomen would create meaningful intra-abdominal hypertension, if the patient's physiologic reserves are severely compromised, if there is an inability to achieve adequate source control with the initial procedure, or if there is a plan for a second look laparotomy because of mesenteric ischemia (Grade 1-B).
- Do not use routine planned re-laparotomy in higher-risk patients with severe peritonitis when adequate source control can be obtained at the time of the index procedure; treat such patients with on-demand rather than scheduled re-laparotomy (Grade 1-B).
- Irrigate with crystalloid fluid to remove visible debris and gross contamination before abdominal closure in patients

undergoing laparotomy for IAI, generally limiting lavage to those areas with gross involvement (Grade 2-B).

3. Microbiologic evaluation

Microbiologic evaluation may be useful in selected patients, but is not necessary in most. Specific recommendations include:

- Do not routinely obtain peritoneal fluid cultures in lower-risk patients with CA-IAI for purposes of guiding antimicrobial therapy (Grade 1-B).
- Obtain cultures of peritoneal fluid or infected tissue in higher-risk patients with CA-IAI and in patients with HA-IAI to identify potential resistant or opportunistic pathogens (Grade 1-C).
- Consider obtaining cultures in all patients with IAI for epidemiologic purposes if adequate resources are available to aggregate and analyze the data and the information can be used to guide empiric antimicrobial therapy (Grade 2-C).

4. Intravenous antimicrobial agents

Many IV antimicrobial agents are potentially useful in the treatment of patients with IAI, as a supplement to source control. Specific recommendations regarding antimicrobial agents for the management of IAI include:

A. General principles

- Use antimicrobial regimens that have activity against the typical gram-negative Enterobacteriaceae, gram-positive cocci, and obligate anaerobes involved in these infections (Grade 1-A).

B. Aminoglycoside-based regimens

- Do not use aminoglycoside-based regimens routinely for empiric therapy (Grade 1-B). Consider use of these agents for treatment of neonatal patients and for management of IAI because of resistant gram-negative organisms in all patients, if other agents are not suitable (Grade 2-B).

C. Penicillin-β-lactamase inhibitor combinations

- Do not use ampicillin-sulbactam routinely for empiric therapy (Grade 2-B).
- Do not use IV amoxicillin-clavulanic acid routinely for empiric therapy (Grade 2-B).
- Consider use of ticarcillin-clavulanic acid as an option for empiric therapy of lower-risk adults and children, if this agent again becomes available (Grade 2-B).
- Use piperacillin-tazobactam for empiric therapy of adults and children (Grade 1-A), but reserve this agent primarily for higher-risk patients because of its broader-spectrum antimicrobial activity (Grade 2-C).

D. Cephalosporin-based regimens and cephalosporin-β-lactamase inhibitor combinations

- Do not use cefoxitin and cefotetan routinely for empiric therapy (Grade 2-B).
- Do not use cefazolin plus metronidazole routinely for empiric therapy (Grade 2-C).

- Consider use of cefuroxime plus metronidazole as an option for empiric therapy of lower-risk adults and children (Grade 2-B).
- Use cefotaxime or ceftriaxone plus metronidazole for empiric therapy of lower-risk adults and children (Grade 1-A).
- Consider use of ceftazidime plus metronidazole as an option for empiric therapy of adults and children (Grade 2-A), but reserve this regimen primarily for higher-risk patients because of its broader-spectrum antimicrobial activity (Grade 2-C).
- Use cefepime plus metronidazole for empiric therapy of adults and children (Grade 1-A), but reserve this regimen primarily for higher-risk patients because of its broader-spectrum antimicrobial activity (Grade 2-C).
- Consider use of cefoperazone-sulbactam as an option for empiric therapy of lower-risk adults and children, in areas where this agent is available (Grade 2-B).
- Consider use of ceftolozane-tazobactam plus metronidazole as an option for empiric therapy of adults (Grade 2-A), but reserve this regimen primarily for higher-risk patients strongly suspected or proven to be infected with resistant strains of *Pseudomonas aeruginosa*, for which other agents are not suitable (Grade 2-C).
- Consider use of **ceftazidime-avibactam** plus metronidazole as an option for empiric therapy of adults (Grade 2-A), but reserve this regimen primarily for higher-risk patients strongly suspected or proven to be infected with *Klebsiella pneumoniae* carbapenemase (KPC)-producing Enterobacteriaceae, for which other agents are not suitable (Grade 2-C).

E. Aztreonam-based regimen

- Consider use of aztreonam plus metronidazole plus vancomycin as an option for empiric therapy of adults and children (Grade 2-B), but reserve this regimen primarily for higher-risk patients, particularly those with serious β-lactam allergies, because of its broader-spectrum activity (Grade, 2-C).

F. Carbapenems

- Use ertapenem for empiric therapy of lower-risk adults and children (Grade 1-A).
- Use doripenem for empiric therapy of adults (Grade 1-A), but reserve this agent primarily for higher-risk patients because of its broader-spectrum antimicrobial activity (Grade 2-C). Do not use doripenem for empiric therapy of children unless no other options are available (Grade 1-C).
- Use imipenem-cilastatin or meropenem for the empiric therapy of adults and children (Grade 1-A), but reserve these agents primarily for higher-risk patients because of their broader-spectrum antimicrobial activity (Grade 2-C).

G. Fluoroquinolones and fluoroquinolone-based regimens

- Use moxifloxacin for empiric therapy of lower-risk adults, but use with caution in areas where there is a high incidence of fluoroquinolone-resistant *Escherichia coli* (Grade 1-A). Do not use moxifloxacin for the

empiric treatment of children unless no other options are available (Grade 1-C).

- Use ciprofloxacin plus metronidazole for empiric therapy of lower-risk adults with CA-IAI, but use with caution in areas where there is a high incidence of fluoroquinolone-resistant *E. coli* (Grade 1-A). Consider use of the regimen for empiric therapy of lower-risk children if other options are not suitable (Grade 2-B).
- Consider use of levofloxacin plus metronidazole as an option for empiric therapy of lower-risk adults, if use of a fluoroquinolone is warranted and it is the only fluoroquinolone available (Grade 2-C). Consider use of this regimen for empiric therapy of lower-risk children if other options are not suitable (Grade 2-C).

H. Tigecycline

- Do not use tigecycline for empiric therapy under most circumstances (Grade 1-B). Consider use of this agent for therapy of adult patients with resistant pathogens, particularly as a component of a combination regimen, if other agents are not suitable (Grade 2-B).

I. Anti-anaerobic agents

- Use metronidazole as the preferred anti-anaerobic agent in combination regimens for empiric therapy in adults and children (Grade 1-B).
- Do not use clindamycin as an anti-anaerobic agent in combination regimens for the empiric treatment in adults and children unless metronidazole cannot be used (Grade 2-B). Consider use of clindamycin in children under one month of age (Grade 2-C).

J. Anti-enterococcal and anti-staphylococcal agents

- Consider use of ampicillin for empiric or pathogen-directed therapy of susceptible enterococcal strains in higher-risk adults and children (Grade 2-B).
- Consider use of vancomycin for empiric or pathogen-directed therapy of vancomycin-susceptible *Enterococcus faecium* or methicillin-resistant *Staphylococcus aureus* (MRSA) in higher risk adults and children (Grade 2-B). Include vancomycin in aztreonam-based regimen for coverage of gram-positive organisms (Grade 2-B).
- Consider use of linezolid or daptomycin for empiric or pathogen-directed therapy of infections from vancomycin-resistant *Enterococcus* spp. (VRE) and as an alternative to vancomycin for infections from MRSA in adults and children (Grade 2-B).

K. Antifungal agents

- Do not use amphotericin B or its lipid formulations routinely for empiric or pathogen-directed management of intra-abdominal candidiasis in adults or children (Grade 2-B).
- Consider use of fluconazole for preemptive and for pathogen-directed therapy of susceptible strains of *Candida albicans* in non-critically ill adults and children (Grade 2-B).
- Consider use of voriconazole for empiric or pathogen-directed therapy of fluconazole-non-susceptible strains

of *Candida* in non-critically ill adults and in children older than one month of age (Grade 2-B).

- Use an echinocandin (anidulafungin, caspofungin, or micafungin) for empiric or pathogen-directed treatment of infections from *Candida* spp. in severely ill adults and children (Grade 1-B).

5. Oral antimicrobial agents

Substitution of oral for IV antibiotic agents in patients with IAI may be considered under selected circumstances. Specific recommendations are:

- Use selected oral agents with good bioavailability as a substitute for IV agents for therapy of patients with return of adequate gastrointestinal function. Use oral antibiotics only to complete a short course of treatment and not to prolong antimicrobial use beyond current recommendations (Grade 1-B).
- Consider use of oral amoxicillin-clavulanic acid as an option to complete a short course of antimicrobial therapy in adults and children (Grade 2-B).
- Consider use of oral moxifloxacin as an option to complete a short course of antimicrobial therapy in adults (Grade 2-B). Do not use oral moxifloxacin in children unless no other option is available (Grade 1-B).
- Use oral ciprofloxacin plus metronidazole to complete a short course of antimicrobial therapy in adults (Grade 1-B). Consider use of oral ciprofloxacin plus metronidazole to complete a short course of antimicrobial therapy in children if other options are not suitable (Grade 2-B).
- Consider use of oral levofloxacin plus metronidazole, an oral first-, second-, or third-generation cephalosporin plus metronidazole, or oral trimethoprim-sulfamethoxazole plus metronidazole as potential options to complete a short course of antibiotic therapy in adults and children if other oral agents are not suitable (Grade 2-C).

6. Selection of empiric antimicrobial therapy for adult patients with CA-IAI

The selection of specific empiric IV antimicrobial therapy for the treatment of patients with CA-IAI should be based on principles of antimicrobial stewardship, using broader-spectrum agents primarily for seriously ill patients. Specific recommendations are:

A. Lower-risk patients with CA-IAI

- Treat lower-risk patients with narrower-spectrum antimicrobial agents having activity against the usual gram-negative Enterobacteriaceae, aerobic streptococci, and obligate anaerobic micro-organisms associated with these infections (Grade 1-A). Do not routinely use broader-spectrum or additional agents to provide anti-pseudomonal, anti-enterococcal coverage (Grade 1-A), or antifungal therapy (Grade 2-B).
- Use cefotaxime or ceftriaxone plus metronidazole or ertapenem as the preferred agents for initial empiric therapy of lower-risk patients (Grade 1-A). Consider use of cefuroxime plus metronidazole or cefoperazone-sulbactam, where available, as alternatives (Grade 2-

4. 静脉抗菌药物

作为控制感染源的补充方法，许多静脉抗菌药物能有效的治疗腹腔感染。-治疗腹腔感染抗菌药物具体推荐包括：

A. 一般原则

- 在这类感染中使用对革兰阴性杆菌，革兰阳性球菌和专性厌氧菌有活性的抗菌药物（Grade 1-A）。

B. 基于氨基糖苷类药物的方案

- 氨基糖苷类药物不作为常规经验性治疗（Grade 1-B）。在新生儿患者和在耐药革兰阴性菌感染中其他药物不可用的情况下考虑使用氨基糖苷类药物（Grade 2-B）。

C. 青霉素-β-内酰胺酶抑制剂联合

- 氨苄西林/舒巴坦不作为常规经验性治疗（Grade 2-B）。
- 阿莫西林/克拉维酸不作为常规经验性治疗（Grade 2-B）。
- 在低风险的成人和儿童中，在有药物的情况下，考虑使用替卡西林/克拉维酸作为经验性治疗的选择（Grade 2-B）。
- 在成人和儿童患者中，考虑使用哌拉西林/他唑巴坦作为经验性治疗的选择（Grade 1-A），但是由于哌拉西林/他唑巴坦是广谱抗菌药物，因此主要在高风险的患者中使用（Grade 2-C）。

D. 头孢菌素为基础的联合治疗方案和头孢菌素-β-内酰胺酶抑制剂联合方案

- 头孢西丁和头孢替坦不作为常规经验性治疗（Grade 2-B）。
- 头孢唑啉+甲硝唑不作为常规经验性治疗方案（Grade 2-C）。
- 在低风险的成人和儿童中，考虑头孢呋辛+甲硝唑作为经验性治疗的选择（Grade 2-B）。
- 在低风险成人和儿童患者中，考虑头孢噻肟或头孢曲松+甲硝唑作为经验性治疗（Grade 1-A）。
- 在成人和儿童中，考虑头孢他啶+甲硝唑作为经验性治疗方案（Grade 2-A），由于它的广谱抗菌活性，主要在高风险的患者中使用（Grade 2-C）。
- 在成人和儿童中，考虑头孢吡肟作为经验性治疗方案（Grade 1-A），由于它的广谱抗菌活性，主要在高风险的患者中使用（Grade 2-C）。
- 在低风险的成人和儿童中，考虑头孢哌酮/舒巴坦作为经验性治疗的选择（Grade 2-B）。
- 考虑头孢洛扎/他唑巴坦+甲硝唑作为成人经验性治疗的选择（Grade 2-A），

但主要在高度怀疑或证实耐药铜绿假单胞菌感染及其他药物不适合的高风险患者中使用（Grade 2-C）。

- 考虑**头孢他啶/阿维巴坦**+甲硝唑作为成人经验性治疗的选择（Grade 2-A），但主要在高度怀疑或证实产肺炎克雷伯菌碳青霉烯酶（KPC）的肠杆菌感染、因无适用药物的高风险患者中使用（Grade 2-C）。

E. 基于氨曲南的治疗方案

- 在成人和儿童中，考虑氨曲南+甲硝唑+万古霉素作为经验性治疗的选择（Grade 2-B），由于这个方案广谱抗菌活性，主要在高危险患者，特别是严重 β -内酰胺类药物过敏的患者中使用（Grade 2-C）。

F. 碳青霉烯类

- 在低风险的成人和儿童中，考虑厄他培南作为经验性治疗（Grade 1-A）。
- 应用多立培南作为成人患者经验性治疗（Grade 1-A），由于它的广谱抗菌活性，主要在高风险患者中使用（Grade 2-C）。除非其他方案不可用，否则多立培南不应用于儿童患者的经验性治疗（Grade 1-C）。
- 应用亚胺培南/西司他丁或美罗培南作为成人和儿童患者经验性治疗（Grade 1-A），由于此类药物具有广谱的抗菌活性，这些药物主要在高风险的患者中使用（Grade 2-C）。

G. 氟喹诺酮类和以氟喹诺酮类为基础的联合用药的方案

- 在低风险的成人患者中，莫西沙星作为经验性治疗，但在氟喹诺酮类耐药的大肠埃希菌高流行的地区谨慎使用（Grade 1-A）。除非其他药物不可用，否则莫西沙星不用于儿童患者的经验性治疗（Grade 1-C）。
- 在社区获得性腹腔感染低风险的成人患者中使用环丙沙星+甲硝唑作为经验性治疗，但在氟喹诺酮类耐药的大肠埃希菌高流行的地区谨慎使用（Grade 1-A）。如果其他方案不可用时，考虑此方案用于低风险儿童患者的经验性治疗（Grade 2-B）。
- 在低风险的成人患者中，如果必须使用氟喹诺酮类而左氧氟沙星是唯一可用的喹诺酮类药，考虑左氧氟沙星+甲硝唑作为经验性治疗（Grade 2-C）。如果其他方案不可用时考虑此方案用于低风险儿童患者的经验性治疗（Grade 2-C）。

H. 替加环素

- 大多数情况下替加环素不作为经验性治疗的选择（Grade 1-B）。其他药物不可用时，在耐药菌感染的成人患者中考虑使用替加环素，特别是作为联合用药的一部分（Grade 2-B）。

I. 抗厌氧菌药物

- 在成人和儿童中，甲硝唑作为抗厌氧菌感染的经验性联合治疗方案的选择（Grade 1-B）。
- 除非甲硝唑不能使用，否则在成人和儿童患者的经验性联合治疗方案中，不使用克林霉素作为抗厌氧菌治疗选择（Grade 2-B）。在一月龄以下的儿童中可考虑使用克林霉素（Grade 2-C）。

J. 抗肠球菌和葡萄球菌的方案

- 在高风险的成人和儿童患者中，考虑使用氨苄西林用于经验性治疗或者敏感肠球菌的治疗（Grade 2-B）。
- 在高风险成人和儿童患者中，考虑使用万古霉素作为经验性治疗和万古霉素敏感屎肠球菌和耐甲氧西林金黄色葡萄球菌（MRSA）的目标性治疗（Grade 2-B）。在以氨曲南为基础的治疗方案中联合万古霉素以覆盖革兰阳性菌的感染（Grade 2-B）。
- 考虑使用利奈唑胺或者达托霉素作为经验性或者耐万古霉素肠球菌（VRE）的目标性治疗，并且作为成人和儿童患者 MRSA 感染的万古霉素的替代治疗药物（Grade 2-B）。

K. 抗真菌药物

- 在成人和儿童患者中，两性霉素 B 和它的脂质体不作为常规经验性或腹腔念珠菌感染的治疗（Grade 2-B）。
- 在非重症成人和儿童患者中，考虑氟康唑作为预防性和敏感白色念珠菌感染的目标性治疗（Grade 2-B）。
- 在非重症成人和大于一月龄的儿童患者中，考虑使用伏立康唑作为经验性或耐氟康唑念珠菌感染的目标性治疗方案（Grade 2-B）。
- 在重症成人和儿童患者中，使用棘白菌素（阿尼芬净，卡泊芬净，或者米卡芬净）作为念珠菌感染的经验性治疗（Grade 1-B）。

5. 口服抗菌药物

在特定的情况下，在腹腔感染患者中，考虑口服抗菌药物作为静脉治疗的替代方案。建议如下：

- 对于胃肠道功能充分恢复的患者，使用生物利用度高的口服抗菌药物作为静脉药物的替代。口服抗菌药物仅作为完成短期的治疗，不作为超出目前推荐的延长治疗（Grade 1-B）。

- 在成人和儿童患者中，考虑使用阿莫西林/克拉维酸作为完成短期抗菌药物治疗的选择（Grade 2-B）。
- 在成人患者中，考虑使用莫西沙星口服作为完成短期抗菌药物治疗的选择（Grade 2-B）。除非其他药不可用，否则在儿童患者中不推荐口服莫西沙星治疗（Grade 1-B）。
- 在成人患者中，应用口服环丙沙星+甲硝唑完成短期抗菌药物治疗（Grade 1-B）。在其他方法不可用的情况下，在儿童患者中考虑使用口服环丙沙星+甲硝唑完成短期抗菌药物治疗（Grade 2-B）。
- 在成人和儿童患者中，无其他适用药物时，考虑使用口服左氧氟沙星+甲硝唑，或一代/二代/三代头孢菌素+甲硝唑，或口服复方新诺明+甲硝唑作为完成短期抗菌治疗的选择（Grade 2-C）。

B). Use ciprofloxacin plus metronidazole or moxifloxacin monotherapy for patients who have serious β -lactam allergies (Grade 1-A). Consider use of levofloxacin plus metronidazole as an alternative if no other fluoroquinolone is available (Grade 2-C).

- Use agents recommended for lower-risk patients with perforated appendicitis, unless they meet criteria as higher-risk patients or at risk for having resistant pathogens (Grade 1-A).

B. Higher-risk patients with CA-IAI

- Treat higher-risk patients with broader-spectrum empiric antimicrobial agents to ensure coverage of less common gram-negative pathogens potentially involved in these infections (Grade 2-C).
- Use piperacillin-tazobactam, doripenem, imipenem-cilastatin, meropenem, or cefepime plus metronidazole as the preferred agents for initial empiric therapy of higher-risk patients (Grade 2-A). Consider use of ceftazidime plus metronidazole as an alternative regimen for these patients (Grade 2-B). Consider use of aztreonam plus metronidazole plus vancomycin as an option for higher-risk patients with a severe reaction to β -lactam agents (Grade 2-B). Do not add an adjunctive aminoglycoside or fluoroquinolone to a β -lactam agent for empiric treatment of higher-risk patients (Grade 1-B).
- Consider use of added ampicillin or vancomycin for empiric anti-enterococcal treatment in higher-risk patients if the patient is not being treated with piperacillin-tazobactam or imipenem-cilastatin (Grade 2-B).
- Do not use antifungal agents routinely for empiric therapy of higher-risk patients (Grade 1-B). Consider use of antifungal agents for empiric therapy of critically ill patients with an upper gastrointestinal source (Grade 2-B).

C. Other considerations for empiric antimicrobial therapy of patients with CA-IAI

- Consider use of fluoroquinolone-based regimens for initial empiric therapy of lower-risk patients who have major reactions to β -lactam antibiotics (Grade 2-B). Consider use of an aztreonam-based regimen for initial empiric therapy of higher-risk patients who have major reactions to β -lactam antibiotics (Grade 2-B). Consider use of a non-penicillin β -lactam for empiric therapy of patients for whom a severe penicillin allergy has not been documented and for whom the risk-benefit ratio is believed acceptable (Grade 2-B).
- Do not use cephalosporin-, aztreonam-, or fluoroquinolone-based regimens for empiric therapy of patients who reside in geographic areas where there is a high prevalence of extended-spectrum β -lactamase (ESBL)-producing Enterobacteriaceae in the community (Grade 1-B). Use ertapenem for empiric therapy in lower-risk patients or a broad-spectrum carbapenem for higher-risk patients who reside in such areas (Grade 1-B).
- Consider use of locally available IV or oral agents having activity against common intra-abdominal pathogens for empiric therapy in patients who reside in geographic areas where there are major resource limitations (Grade 2-C).

7. Selection of empiric antimicrobial therapy for adult patients with HA-IAI

Because patients with HA-IAI are at risk for infection from resistant organisms, additional antimicrobial agents may lessen the risk of inadequate initial therapy and subsequent treatment failure. The recommendations include:

A. General approach

- Assess patients with respect to their separate risks of infection from *Enterococcus* spp., MRSA, resistant gram-negative bacilli, and *Candida* spp. (Grade 2-B).
- Use the broader-spectrum agents recommended for higher-risk patients with CA-IAI for initial empiric therapy of patients with HA-IAI. Consider addition of other empiric agents based on the patient's risk for an infection from *Enterococcus* spp., MRSA, resistant gram-negative bacilli, and *Candida* spp. (Grade 2-B).

B. Anti-enterococcal therapy

- Identify patients with HA-IAI who have post-operative infections, recent exposure to broad-spectrum antimicrobial therapy, signs of severe sepsis or septic shock, or known to be colonized with VRE as at risk for infection with *Enterococcus* spp. (Grade 2-B).
- Consider use of vancomycin or teicoplanin for empiric therapy of HA-IAI in patients at risk for infection from *Enterococcus* spp. Consider use of linezolid or daptomycin for empiric therapy of patients known to be colonized with or at high risk for infection with VRE (Grade 2-B).

C. Anti-staphylococcal therapy

- Identify patients with HA-IAI with multiple healthcare-associated risk factors for MRSA colonization, including advanced age, co-morbid medical conditions, previous hospitalization or surgery, and significant recent exposure to antibiotic agents, or known to be colonized with MRSA at risk for infection due to MRSA (Grade 2-B).
- Consider use of vancomycin or teicoplanin, where available, or linezolid or daptomycin as alternatives, for empiric therapy of patients known to be colonized or at high risk for infection with MRSA (Grade 2-B).

D. Antibacterial therapy for resistant gram-negative organisms

- Identify patients who have received substantial previous broad-spectrum antimicrobial therapy, had prolonged hospitalizations, undergone multiple invasive interventions, or known to have been colonized or infected with a resistant gram-negative organism at risk for infection from a resistant gram-negative pathogen (Grade 2-B). Consult local epidemiologic data and antibiograms for assistance in selecting empiric antimicrobial therapy in patients considered at risk for infection with resistant gram-negative pathogens (Grade 2-B).
- Consider use of a broad-spectrum carbapenem, or ceftolozane-tazobactam or **ceftazidime-avibactam** as alternatives, for empiric therapy of patients at risk for infection with ESBL-producing Enterobacteriaceae (Grade 2-B).

- Consider use of a broad-spectrum carbapenem, with **ceftazidime-avibactam** as an alternative, for empiric therapy of patients at risk for infection with Amp C- β -lactamase-producing Enterobacteriaceae (Grade 2-B).
- Consider use of combinations of a carbapenem or **ceftazidime-avibactam** as an alternative, an aminoglycoside, a polymyxin, and/or tigecycline for empiric therapy of patients at risk for infection with carbapenem-resistant Enterobacteriaceae (Grade 2-B).
- Consider use of combinations of a β -lactam antibiotic, including ceftolozane-tazobactam, an aminoglycoside, and/or a polymyxin, for empiric therapy of patients at risk for infection with multi-drug resistant (MDR)-, extensively drug resistant (XDR)-, or pandrug resistant (PDR)-strains of *P. aeruginosa* (Grade 2-B). Consider use of combinations of a carbapenem, an aminoglycoside, a polymyxin, and/or tigecycline for empiric therapy of patients at risk for infection with MDR-, XDR-, or PDR-strains of *Acinetobacter* spp. (Grade 2-B).

E. Antifungal therapy

- Identify patients with HA-IAI because of upper gastrointestinal perforations, recurrent bowel perforations, surgically treated pancreatitis, those who have received prolonged courses of broad-spectrum antibiotic therapy, and those who are known to be heavily colonized with *Candida* at increased risk for infection from *Candida* spp. (Grade 2-B). Consider patients found to have yeast on a Gram stain of infected peritoneal fluid or tissue as having an infection with *Candida* spp. (Grade 2-B).
- Use an echinocandin (anidulafungin, caspofungin, or micafungin) for empiric therapy of severely ill patients at risk for infection with *Candida* spp. (Grade 1-B). Consider use of fluconazole for antifungal therapy of less severely ill patients at risk for infection with *Candida* spp. (Grade 2-B). Consider use of an echinocandin or voriconazole for empiric therapy of patients at risk for infection with a fluconazole-resistant strain of *Candida* (Grade 2-B).

8. Timing of antimicrobial therapy

Antimicrobial therapy for patients with IAI needs to be timed to optimize management of the infection as well as prevent secondary infections following source control.

- Initiate empiric antimicrobial therapy within one hour, if possible, once a diagnosis of IAI is made in patients presenting with sepsis or septic shock (Grade 2-B). Initiate antimicrobial therapy as soon as feasible in other patients with IAI, taking into account plans for subsequent source control (Grade 2-C).
- Re-administer an antimicrobial agent within one hour before the start of a source control procedure if two half-lives of the agent have passed at the time the intervention is initiated (Grade 1-B).

9. Dosing of antimicrobial agents in adult patients

Antimicrobial dosing in adult patients with IAI should be optimized based on the patient's physiologic conditions and co-morbidities. Specific recommendations related to antimicrobial dosing and administration include:

- Use standard dosages of antimicrobial agents for lower-risk patients who are not severely obese and who do not have substantial renal or hepatic impairment (Grade 1-B). Consider use of higher dosages of antimicrobial agents in selected higher-risk patients (Grade 2-B).
- Use adjusted dosages of antimicrobial agents, based on available clinical outcome data, standard pharmacokinetic parameters, and therapeutic drug monitoring, where applicable, in patients with significant renal impairment (Grade 2-B).
- Use adjusted dosages of selected, hepatically eliminated or metabolized antimicrobial agents in patients with substantial hepatic impairment (Grade 2-B).
- Consider use of adjusted dosages of selected antimicrobial agents, based on available clinical outcome data and pharmacokinetic parameters, in obese patients (Grade 2-B).
- Do not use prolonged or continuous infusion of β -lactam antibiotic agents routinely in all patients, but consider use of these approaches as options in critically ill patients and those at risk for infection with resistant gram-negative pathogens (Grade 2-B).

10. Duration of antimicrobial therapy

The duration of antimicrobial therapy in the patient with IAI needs to be specific for each clinical condition. Specific recommendations include:

- Do not use antibiotic agents to prevent infection in patients with severe or necrotizing pancreatitis (Grade 1-B).
- Consider deferral of antibiotic therapy in lower-risk patients with uncomplicated acute colonic diverticulitis (Grade 2-B).
- Limit antimicrobial therapy to no more than 24 hours in patients with traumatic bowel perforations operated on within 12 hours (Grade 1-A), patients with gastroduodenal perforations operated on within 24 hours (Grade 1-C), patients with acute or gangrenous appendicitis in the absence of perforation (Grade 1-A), patients with acute or gangrenous cholecystitis in the absence of perforation (Grade 1-A), and patients with ischemic, non-perforated bowel (Grade 1-C).
- Limit antimicrobial therapy to four days (96 h) in patients who have had adequate source control (Grade 1-A).
- Consider limiting antimicrobial to 5–7 days in patients with established IAI in whom a definitive source control procedure is not performed. Consider use of clinical parameters of fever, leukocytosis, and adequacy of gastrointestinal function to determine whether antimicrobial therapy can be discontinued sooner. Re-assess patients who do not respond fully to antimicrobial therapy within 5–7 days for a potential source control intervention (Grade 2-C).
- Consider limiting antimicrobial therapy to seven days in patients with secondary bacteremia because of IAI, who have undergone adequate source control and are no longer bacteremic (Grade 2-B).
- There are insufficient data to evaluate duration of therapy in patients receiving immunosuppressive medications (no recommendation).

对于耐药革兰氏阴性菌的抗菌治疗

- 对于感染产 ESBL 的肠杆菌科风险患者的经验性治疗，考虑使用广谱碳青霉烯，或头孢洛扎/他唑巴坦或头孢他啶/阿维巴坦作为替代药物 (Grade 2-B)。
- 对于感染产 Amp C- β 内酰胺酶肠杆菌科风险患者的经验性治疗，考虑使用广谱碳青霉烯类药物，以头孢他啶-阿维巴坦作为替代药物 (Grade 2-B)。
- 对于感染碳青霉烯耐药肠杆菌科风险患者的经验治疗，考虑联合使用碳青霉烯或头孢他啶/阿维巴坦作为替代药物，氨基糖苷，多粘菌素，和/或替加环素的经验疗法 (Grade 2-B)。
- 对于多重耐药 (MDR)、广泛耐药 (XDR) 或全耐药 (PDR) 铜绿假单胞菌感染风险患者的经验治疗，考虑联合使用 β 内酰胺类抗生素，包括头孢洛扎/他唑巴坦、氨基糖苷，和/或多粘菌素 (Grade 2-B)。对于感染 MDR-、XDR-或 PDR 鲍曼不动杆菌科患者的经验治疗，考虑联合使用碳青霉烯、氨基糖苷、多粘菌素，和/或替加环素 (Grade 2-B)。

11. Pathogen-directed antimicrobial therapy

Changing antimicrobial therapy based on culture results should be considered in selected patients. Specific recommendations include:

- Do not change antimicrobial therapy on the basis of culture results in lower-risk patients who have had a satisfactory clinical response to source control and empiric therapy (Grade 1-B).
- Consider modification of antimicrobial therapy in higher-risk patients if culture results identify organisms resistant to the initial empiric regimen and further antimicrobial therapy is planned (Grade 2-C).
- There are insufficient data to make a recommendation regarding modification of antimicrobial therapy in patients who have a highly resistant organism isolated as a minor component of a mixed peritoneal culture (no recommendation).
- Routinely de-escalate or streamline antimicrobial therapy in higher-risk patients to the narrowest-spectrum agent or agents having activity against the isolated micro-organisms once definitive culture results are available (Grade 1-B).

12. Treatment failure

Treatment of patients who fail initial therapy follows the same principles used in initial management of IAI. Specific recommendations include:

A. Source control for treatment failure

- Use measures of ongoing or progressive systemic inflammation or organ system dysfunction to identify patients with likely source control failure (Grade 1-B).
- Assess patients for source control failure if there is progressive organ dysfunction within the first 24–48 hours after source control, if there is no clinical improvement in organ dysfunction 48 hours or more after source control, or if there are persistent signs of inflammation 5–7 days after source control (Grade 2-C).
- Consider abdominal exploration in patients who deteriorate clinically or fail to improve within 48–72 hours of the initial procedure (Grade 2-C). Use computed tomography scanning, with percutaneous aspiration or drainage of any potentially infected fluid collections, in patients suspected of treatment failure after 48–72 hours of the initial source control procedure (Grade 1-B).
- Use the least invasive approach that will achieve definitive source control or sufficiently control the infection to allow resolution of the inflammatory response and organ dysfunction (Grade 1-B).
- Undertake further source control within 24 hours when source control failure is identified (Grade 2-C), but as soon as feasible in patients with physiologic instability or progressive organ dysfunction (Grade 2-B).
- Obtain routine peritoneal cultures in patients with source control failure so that pathogen-directed antimicrobial therapy can be utilized (Grade 1-C).

B. Antimicrobial therapy for treatment failure

- Do not routinely change antimicrobial therapy when patients have early treatment failure and undergo repeat

source control within 48 hours of the initial source control intervention (Grade 2-C). Consider altering antimicrobial therapy, using an alternative antibiotic class if feasible, in patients who have late treatment failure (Grade 2-C).

- Consider discontinuation of antimicrobial therapy in patients with clinical evidence of treatment failure but negative results of imaging studies for recurrent or persistent IAI (Grade 2-B).
- Consider a trial of further antimicrobial therapy in patients with clinical evidence of treatment failure and imaging studies showing ongoing intra-abdominal inflammation; if there is no clinical response to this antimicrobial trial within a few days, discontinue antimicrobial therapy and re-instate only if there is evidence of clinical deterioration (Grade 2-C).
- Consider continuation of antimicrobial therapy in patients with clinical evidence of treatment failure and imaging studies showing recurrent or persistent IAI, in whom further source control cannot be achieved; discontinue antimicrobial therapy when clinical signs of systemic inflammation or organ dysfunction abate (Grade 2-C). Monitor these patients for resistant pathogens, adjusting antimicrobial therapy as necessary (Grade 2-C).

13. Treatment of pediatric IAI

Management of IAI in pediatric patients with IAI follows the same general principles as treatment of adult patients. Specific recommendations on treatment of pediatric patients with IAI include:

- Use cefotaxime or ceftriaxone plus metronidazole or ertapenem as preferred agents for empiric therapy of lower-risk pediatric patients greater than one month of age (45 wks post-conceptual age, Grade 1-A). Consider use of cefuroxime plus metronidazole or cefoperazone-sulbactam, where available, as alternatives (Grade 2-B). Consider use of ciprofloxacin plus metronidazole, or levofloxacin plus metronidazole if no other fluoroquinolone is available, for empiric treatment of selected pediatric patients if other agents cannot be used, particularly for those patients with life-threatening β -lactam reactions (Grade 2-B).
- Use piperacillin-tazobactam, imipenem-cilastatin, or meropenem as the preferred agents for empiric therapy of higher-risk pediatric patients greater than one month of age (45 wks post-conceptual age) with CA-IAI (Grade 2-A) or with HA-IAI (Grade 2-B). Consider use of ceftazidime or cefepime plus metronidazole as alternatives (Grade 2-B). Consider use of aztreonam plus metronidazole plus vancomycin as an option if other agents cannot be used, particularly for those with life-threatening β -lactam reactions (Grade 2-B). Consider addition of ampicillin or vancomycin as empiric anti-enterococcal therapy of higher-risk patients if the patient is not being treated with piperacillin-tazobactam or imipenem-cilastatin (Grade 2-B).
- Limit antimicrobial therapy to five days (120 h) in pediatric patients older than one month (45 wks post-conceptual age) who have had adequate source control (Grade 1-A).

- Use oral antimicrobial agents with good bioavailability to complete a five-day course of therapy in patients with adequate source control when feasible, but do not use oral antimicrobial agents to extend total antimicrobial duration beyond five days (Grade 1-B).
- Do not use additional outpatient IV antimicrobial therapy in patients with adequate source control unless administered to complete a total antimicrobial course of five days (Grade 1-B).
- Treat pediatric patients with failure of treatment in an analogous fashion to adult patients with treatment failure (Grade 1-C). Use the least invasive means of providing adequate source control and a standard course of IV antibiotic agents, preferably with a change in the antibiotic class, to treat these patients (Grade 2-C). Do not extend a course of IV antibiotic agents beyond seven days in children with perforated appendicitis who have a post-operative abscess (Grade 1-C).
- Employ either laparotomy or peritoneal drainage as source control in addition to antimicrobial therapy for pediatric patients less than one month of age (45 wks post-conceptual age) with necrotizing enterocolitis or intestinal perforation (Grade 1-A).
- Use ampicillin, gentamicin, and either metronidazole or clindamycin; ampicillin, cefotaxime, and either metronidazole or clindamycin; or meropenem in pediatric patients less than one month of age (45 wks post-conceptual age). Consider use of vancomycin instead of ampicillin if there is suspected infection with penicillin-resistant *Enterococcus* spp. or MRSA. Consider use of fluconazole or amphotericin B if there is a suspected infection with *Candida* spp. (Grade 2-C).
- Use a 7–10 day course of antimicrobial therapy in pediatric patients less than one month of age (45 wks post-conceptual age), particularly for those with necrotizing enterocolitis (Grade 2-C).
- Use standard pediatric dosages for various antimicrobial agents for lower-risk pediatric patients with CA-IAI (Grade 1-B). Consider use of higher pediatric dosages, where applicable, for higher-risk patients with CA-IAI and those with HA-IAI (Grade 2-C).

INTRA-ABDOMINAL INFECTION (IAI) is a common disease process managed primarily by surgical practitioners. It is associated with substantial morbidity and death, despite therapeutic advances made over the past decades. Key components of the management of these infections include expeditious diagnosis, early resuscitation of the patient, timely and appropriate source control, and adequate antimicrobial therapy directed against the micro-organisms involved in the infection.

The Surgical Infection Society (SIS) has released various evidence-based guidelines for the management of these infections. The initial guideline developed by the Antimicrobial Agents Committee (now the Therapeutics and Guidelines Committee) was published in 1992 [1]. A subsequent revision based on published evidence through early 2001 was published in 2002 [2]. Accompanying this publication was a compilation of the evidence used to develop the recommendations [3]. These initial guidelines focused primarily on appropriate antimicrobial therapy for these infections. Subsequently, in 2010, a more comprehensive document written jointly by the SIS and the Infectious Diseases Society of America (IDSA) was published, which included some recommendations regarding diagnosis, initial resuscitation, and source control for these infections, as well as treatment of children with IAI [4]. This guideline revised both the 2002 SIS guideline and a similar guideline published by the IDSA in 2003 [5].

Since the 2010 guideline, additional challenges have arisen in the management of these infections. With the advancing age and increased burden of chronic disease in the population, IAI is being diagnosed more commonly and managed in patients with impaired host defenses and limited physiologic reserves. In addition, the prevalence of resistant bacteria and fungi has been growing worldwide, with resistant micro-organisms identified not only in patients whose infections arise in the healthcare setting, but also in patients in whom their infections develop in the community. This has led to declining efficacy of some antimicrobial agents traditionally used to treat these patients.

Nonetheless, advances have been made in the management of IAI as well. An increasingly standardized and successful

approach to the resuscitation of patients with sepsis, including those with IAI, has been provided through the various iterations of the Surviving Sepsis Campaign guidelines [6]. More targeted and less morbid techniques for achieving source control are being increasingly used in patients with IAI. Finally, a few newer antimicrobial agents are now available that have activity against some resistant pathogens, although the problem of resistance remains a major problem for managing nearly any type of infection.

This revision of the 2010 guideline was undertaken by a task force from the SIS including members of the Therapeutics and Guidelines Committee as well as additional individuals with expertise in the subject. Because the previous guideline did not include an in-depth evidence review, the task force elected to review not only the literature related to management of IAI published since dissemination of the 2010 guideline, but to also re-analyze the literature published between 2001 and 2008 that had been used in part for the previous revision. The guideline was also constructed in a manner such that it might be amenable for use in an algorithmic format for treating patients with IAI.

Previous guidelines have used various approaches to grading the quality of evidence and the strength of the recommendations. Increasingly, the GRADE (Grades of Recommendation Assessment, Development, and Evaluation) nomenclature has been used for guideline development. The GRADE approach calls for a clearly transparent methodology to guideline development. It also separates issues related to the quality of the evidence from the overall strength and importance of the recommendation. Evidence is characterized according to the quality of the study design and its execution, but also considers problems of consistency, directness, and potential bias in grading quality [7]. The recommendations themselves are strongly influenced by the quality of the evidence behind them, but also take into consideration the balance between desirable and undesirable effects, values and preferences in different settings, and the resources needed to fully implement the recommendation [8].

TABLE 1. CLASS OF EVIDENCE

A	High quality evidence	The evidence was primarily obtained from RCTs, meta-analyses of such trials, or methodologically sound epidemiologic studies. If the preponderance of evidence is based on studies that do not directly address the question being posed, the overall grade is downgraded to B or C. If there are conflicts in Class A data, the evidence grade is lowered to B or C, depending on the degree of conflict.
B	Moderate quality evidence	The evidence was obtained from lower quality prospective studies, retrospective case control studies, and large observational, cohort, or prevalence studies, and was based on clearly reliable data. If there are significant conflicts in Class B data, the evidence grade is lowered to C.
C	Weak quality evidence	The evidence was obtained from smaller observational studies, studies relying on retrospective or less reliable data, authoritative opinions expressed in reviews, or expert opinions of task force members.
None	Insufficient evidence	There was little or no relevant evidence to address a question, or the evidence reviewed was highly conflicting.

RCT = randomized controlled trial.

The current guideline uses this basic approach to grading the evidence and the resultant recommendations, as summarized in Tables 1 and 2. Because of the limited quantity of methodologically rigorous studies investigating key questions in the management of IAI, the task force did not undertake a detailed statistical analysis for most of these recommendations, but relied on a process of iterative consensus among task force members to develop the recommendations and their final grading.

Methods

The task force undertook a formalized process of guideline development and review, which is outlined here. This process was based on that outlined by the GRADE Working Group [9].

The initial selection of the task force chair and working group leaders was made by the Executive Council of the SIS. These individuals then named additional SIS members identified as content experts in the management of IAI to the task force, supplemented by the members from the Therapeutics and Guidelines Committee with an interest in the topic. An initial series of teleconferences and one face-to-face meeting were held in 2014 and 2015, but much of the initial and subsequent work was done via electronic mail.

Members of the task force first agreed on the scope of the guideline and developed an outline of a series of topics for

review (Table 3). Working groups then developed specific questions to be addressed under each of these topics, which were supplemented by additional suggestions from members of the task force. These questions were then refined by iterative review until a consensus was achieved on the specific questions that would be investigated.

Evidence was then collected to investigate these questions. The primary tactic employed was a systematic search of the Medline database using various strategies in an effort to identify all literature related to IAI published between 2007 and mid-2014. Abstracts of more than 8,000 articles were subjected to a first review by task force members to identify articles relevant to the current revision. These publications were combined with literature published between 2000 and 2007, which had been selected from a similar search of the Medline database performed for preparation of the previous guideline.

Secondary searches were performed to supplement the primary search when evidence was found to be lacking for examination of a specific question. The focus of such searches was prevention or management of infections other than IAI, and identification of side effects or complications related to specific antimicrobial agents or therapeutic approaches. In addition, literature relevant to the topic was identified during systematic evaluations of review articles for pertinent references, including those published as part of the *Cochrane Database of Systematic Reviews* [10].

TABLE 2. RATING SCALE FOR RECOMMENDATIONS

1	Strong recommendation	The task force concluded that the intervention is a desirable approach for the care of those patients to whom the question applies. This rating is generally based on moderate to high quality evidence. The conclusion is unlikely to be changed with future research. The magnitude of the effect is also sufficient to justify the recommendation. A strong recommendation was also used to describe interventions that are likely to have a significant effect on patient outcome, even if based on weak evidence. These recommendations are prefaced as “We recommend ...”.
2	Weak recommendation	The task force concluded that the intervention is a reasonable approach for the care of patients. Not all patients and clinicians, however, would necessarily want to follow the recommendation. A decision not to follow the recommendation is unlikely to result in a major adverse outcome. This rating was generally based on weak to moderate quality evidence. Both the magnitude of the treatment effect and its direction might be altered by future research. These recommendations are prefaced as “We suggest ...”.
None	No recommendation	The evidence was considered inadequate or too inconsistent to allow any meaningful conclusion to be reached.

TABLE 3. GUIDELINE TOPICS

Risk assessment
Source control
Microbiologic evaluation
Intravenous antimicrobial agents
Oral antimicrobial agents
Selection of empiric antimicrobial therapy for adult patients with CA-IAI
Selection of empiric antimicrobial therapy for adult patients with HA-IAI
Timing of antimicrobial therapy
Dosing of antimicrobial agents in adult patients
Duration of antimicrobial therapy
Pathogen-directed antimicrobial therapy
Treatment failure
Management of pediatric IAI

CA-IAI=community-acquired intra-abdominal infection; HA-IAI=healthcare- or hospital-acquired intra-abdominal infection; IAI=intra-abdominal infection.

Before final review of the guideline, an additional comprehensive Medline search was performed to uncover relevant articles published between 2014 and early 2016 that had not been already identified during the previous or supplementary searches. Selected publications from before 2000 were added to the database when necessary. The final literature database included 778 articles identified during the primary screening process, 565 identified via secondary and supplementary searches, and 89 identified in the final search of the most recent literature.

The literature database was screened for randomized controlled trials (RCTs) related to use of antimicrobial therapies for treatment of patients with IAI published between 2000 and 2016. These trials underwent formal review; studies that enrolled patients with multiple types of infections were reviewed if outcomes in patients with IAI were reported separately from the outcomes of all patients with infections. The RCTs related to surgical or other interventional approaches were selected for formal review only if they related to strategies for treating patients with IAI. The task force elected not to study questions related to technical aspects of managing specific disease entities, such as studies comparing laparoscopic versus open approaches for acute appendicitis.

The RCTs were reviewed by at least two members of the task force, using the criteria employed during the previous evidence review [3]. The primary end point assessed was clinical cure in the clinically evaluable population at the time point (generally a test of cure visit) specified by the specific trial design; where available, clinical cure in the modified intent-to-treat population (those receiving at least one dose of study drug) was also used. Severity of illness in the study populations was gauged by overall death, the percentage of patients having an appendiceal source of infection, and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, where reported. Quality was graded on a scale of 0–5 based on adequacy of randomization, blinding, and description of patients excluded from the study, according to the system of Jadad et al. [11]. Quality was also assessed based on whether or not patients enrolled in the trial met the criteria for complicated IAI, as specified by IDSA criteria [12]. Discrepancies between the two reviewers were resolved by a third reviewer.

Working groups were obligated to use the data from all relevant RCTs when formulating recommendations for specific questions. These data were evaluated according to GRADE criteria for precision, directness, consistency, and risk of bias [7], but formal GRADE tables were not prepared. This assessment was incorporated into the final evidence grade applied to each recommendation (Table 2).

Data from RCTs were available for only a small fraction of questions developed by the subgroups. Thus, heavy reliance was placed on data from other types of studies to formulate many recommendations. Working groups used selected publications from the literature database for these questions, with the choice of specific references being based on the perceived quality and relevance of the study to the question at hand. Because no generally accepted system exists for evaluating quality of these studies, they were not objectively graded. Summaries of RCTs and selected additional literature pertinent to treatment of IAI are provided in the Supplementary Tables, which are available on the *Surgical Infections* website (www.liebertpub.com/overview/surgical-infections/53/).

Based on these literature reviews, individual working groups drafted and graded provisional recommendations. The GRADE criteria of quality of evidence, balance between desirable and undesirable effects, values and preferences, and resource allocation [8] were used for this, emphasizing the first two criteria (Table 3). The entire task force repeatedly reviewed and refined these recommendations until a final consensus was achieved.

The guideline was then submitted to independent reviewers from the SIS who were not members of the task force. The task force responded to these critiques by either modifying the specific recommendation or leaving it unchanged, providing a detailed rationale for its decision. After a final vote was taken on all recommendations, the guideline along with supporting materials was presented to the Executive Council of the SIS for approval as an official guideline of the SIS. Documentation regarding individual votes or recusals on recommendations by task force members as well as minutes of the SIS Executive Council deliberations are maintained by the Executive Director of the SIS.

Background

1. Scope of the guideline

Intra-abdominal infection refers to a wide variety of infections encountered in clinical practice. The term, however, is used generally in the context of disease processes within the abdominal cavity treated with some type of mechanical intervention, such as a surgical procedure. It has been traditional to separate IAI into uncomplicated and complicated IAI. With some pathologic entities, however, the distinction between uncomplicated and complicated IAI becomes somewhat arbitrary, as will be more fully discussed in the subsequent section.

Past IAI guidelines have focused primarily on complicated IAI. Although the vast majority of this document emphasizes treatment of patients with complicated IAI, it also includes some recommendations relevant to the treatment of patients with uncomplicated IAI and some non-infectious disease processes that can lead to IAI. When referring to uncomplicated IAI, the guideline will usually describe the specific disease entity, such as acute appendicitis, acute cholecystitis,

or uncomplicated diverticulitis, rather than combining these disparate infections under the term “uncomplicated IAI.” Throughout the document, the term “IAI” should generally be considered synonymous with the term “complicated IAI.”

As with previous guidelines, management of certain disease entities occurring in the abdomen is not considered in this guideline, including primary peritonitis, catheter-related peritonitis, and infections in solid abdominal organs arising from hematogenous spread. Diseases developing as a result of transmural enteritis or inflammatory bowel disease, and diseases primarily involving the genitourinary tract have also been excluded.

Management of IAI generally involves expeditious diagnosis, initial resuscitation of the patient, source control, and antimicrobial therapy. Diagnosis of IAI is usually undertaken by other persons, such as emergency medicine physicians or primary care providers, and may use various approaches, depending on the actual disease entity being investigated. The task force elected not to review this subject. Initial resuscitation of the patient is frequently the responsibility of a number of persons, including surgeons as well as emergency medicine providers, anesthesiologists, and critical care physicians. Guidance on the care of the patient with sepsis and septic shock, including patients with IAI, is provided in the Surviving Sepsis Campaign guideline [6], which is currently being updated. The reader is referred to that guideline, which has been endorsed by the SIS, for further information on this topic.

As emphasized in the Surviving Sepsis Campaign guideline, early source control and provision of appropriate empiric antimicrobial therapy are key to the survival and recovery of seriously ill patients with infection, including those with IAI. The task force has elected to focus on these issues in this guideline, because these are the aspects of management most directly under the control of the surgical practitioner. Source control refers to a large variety of mechanical techniques for treating patients with IAI, with a goal of decreasing the bacterial inoculum and allowing the patient’s host defenses to control the infection. This guideline expands the discussion of source control somewhat compared to the previous guideline. Nonetheless, because of the wide variety of potential approaches to source control, only general concepts of source control are addressed, and interventional therapies for specific disease entities have been left to be addressed by more focused guidelines. Antimicrobial therapy is likewise approached from a relatively broad perspective. With the advent of increasingly resistant microbial strains in both the hospital and community environments, however, the treatment of patients with resistant or opportunistic micro-organisms has been given further weight. Finally, although initial treatment using an evidence-based approach is frequently successful, it fails in approximately 20% of patients. Patients with initial treatment failure are at increased risk for further adverse outcomes. Thus, treatment of patients with failure of treatment has been given additional emphasis in this guideline.

The goal of this document is to provide guidance to clinicians by describing reasonable approaches to the use of therapeutic modalities. An important consideration stressed in this guideline is that most management decisions should be tempered according to an individualized assessment of the patient, taking into account not only the risk of the specific

interventions being contemplated, but also the likelihood of a poor outcome if inadequate therapeutic efforts are employed. It is also important to recognize, however, that collective decisions on the use of these modalities have impacts on the healthcare system and the overall population as well. For instance, widespread use of expensive imaging or therapeutic equipment, particularly in areas of substantial resource limitations, may limit the opportunity to use other therapies of equal or greater value to the community. Hence, the task force has attempted to take into account the cost-effectiveness of certain interventions in its recommendations. Further, with regard to antimicrobial therapy, overuse of antimicrobial resources leads to the development of microbial resistance and loss of effective anti-infective agents for all. The principles of antimicrobial stewardship have therefore been stressed throughout this document.

2. Definitions

Much of the published literature regarding management of IAI uses the concept of uncomplicated and complicated IAI. Traditionally, infections limited to a hollow viscus were called uncomplicated IAI, whereas those that extended into a normally sterile area of the abdomen, such as the peritoneal cavity, mesentery, retroperitoneum, another abdominal organ, or the abdominal wall, were defined as complicated IAI [4,13]. Nonetheless, there are borderline conditions, such as localized colonic diverticulitis, which may be difficult to categorize as a complicated or uncomplicated IAI. Complicated IAI have also traditionally been described as those disorders managed with a source control procedure; in part, this has been to satisfy the requirements of regulatory bodies, such as the United States Food and Drug Administration (FDA), which require that microbiologic cultures be obtained for approval of anti-infectives for complicated IAI. Nonetheless, there are conditions, such as a peri-appendiceal phlegmon, which are clearly a complicated IAI, but may be managed without a source control procedure and microbiologic analysis.

Patients with complicated IAI may be characterized as manifesting secondary or tertiary peritonitis, single or multiple intra-abdominal abscesses, or an intra-abdominal phlegmon. Secondary peritonitis, arising as a result of perforation of a hollow viscus, is the most straightforward of these terms [4,13]. The term secondary peritonitis, however, does not always imply an infection, because peritoneal inflammation may be the result of chemical irritation in the absence of an overt infection, as may be found in patients with a perforated gastroduodenal ulcer. The term also does not convey important information about the extent of the infection—i.e., whether or not it is a localized or diffuse process—nor about the chronicity of the infection, both of which may affect prognosis.

There is much less agreement as to what constitutes tertiary peritonitis. One consensus group defined tertiary peritonitis as that which persisted or recurred more than 48 hours after apparently successful management of secondary peritonitis [14]. Many patients, however, such as those with a recurrent abscess after initial management of perforated appendicitis, could be included under this definition. This would result in a group of patients with a mixed severity of illness rather than a group of patients generally considered to be those most seriously ill as a result of IAI. Instead of

attempting to specifically define tertiary peritonitis, other authors have developed the concept that there is a continuum between secondary and tertiary peritonitis; thus, describing any specific patient as having secondary versus tertiary peritonitis is somewhat arbitrary, unless the patient is clearly at one of the extremes of the spectrum [13,15,16]. Given these variable definitions, it is unlikely that patients described as having tertiary peritonitis in various publications are necessarily comparable. Therefore, recommendations have not been made specifically for patients with tertiary peritonitis, but have been included with the recommendations regarding the most severely ill patients with IAI.

3. Microbiology of IAI

The microbiology of IAI varies according to source of the infection and whether or not the patient has been exposed to the healthcare setting; exposure to previous antimicrobial therapy may be of particular importance in this regard [17–19]. The microbiology of community-acquired IAI (CA-IAI) has been well characterized. These are generally mixed infections involving a number of enteric micro-organisms. The principal gram-negative micro-organisms cultured from infected abdominal fluid or tissue are *Escherichia coli* and, to a much lesser extent, other Enterobacteriaceae such as *Klebsiella* spp. or non-fermenting gram-negative aerobes such as *Pseudomonas aeruginosa*. Streptococci, primarily of the *Streptococcus milleri* group, are also isolated frequently; enterococci are identified much less frequently in patients with CA-IAI. Enteric anaerobes, with *Bacteroides* spp., *B. fragilis* predominating, are also common, although clinical laboratories frequently do not isolate most of anaerobic micro-organisms involved in these infections. Anaerobic micro-organisms are more prevalent for sources of infection in the distal gastrointestinal tract [18–28].

Although the prevalence of these micro-organisms in CA-IAI has not changed appreciably over time, susceptibilities of these pathogens to various antibiotics have changed, particularly in certain geographic localities. This is particularly true of Enterobacteriaceae. Globally, there is significant resistance of *E. coli* to ampicillin-sulbactam, as well as to fluoroquinolones. Further, the prevalence of extended spectrum β -lactamase-producing strains of *E. coli* and *Klebsiella* spp. among patients with IAI has been increasing in Latin America, Asia, and parts of Europe. These resistant organisms are increasingly being isolated from patients with CA-IAI, and not just from those with risk factors for healthcare-associated/hospital-acquired infection (HA-IAI) [28–31].

In patients with HA-IAI, the types of micro-organisms isolated vary to a much greater extent. Most of the pathogens isolated are still enteric flora, but other micro-organisms, such as staphylococci, are also encountered. The incidence of *E. coli* as a causative pathogen decreases somewhat, whereas the incidence of other Enterobacteriaceae, such as *Enterobacter* spp., as well as lactose-negative gram-negative bacilli, such as *P. aeruginosa* and *Acinetobacter* spp., have increased. Aerobic streptococci are found much less commonly, but other gram-positive micro-organisms, particularly *Enterococcus* spp., become much more prevalent, particularly in the post-operative setting. Staphylococci, both coagulase-negative species and *Staphylococcus aureus*, although still uncommon, are also identified more frequently in patients with HA-IAI

than those with CA-IAI. The frequency with which anaerobic micro-organisms are present in these HA-IAI may be somewhat lower than in CA-IAI, although this has been less well documented. Non-bacterial pathogens, particularly yeast such as *Candida* spp., are encountered more frequently in patients with HA-IAI, particularly if there has been previous exposure to broad-spectrum antibiotics [22–28].

Resistance of the micro-organisms involved in HA-IAI to various antimicrobial agents is quite common. This is particularly notable among patients who received multiple courses of antimicrobial therapy, who are frequently among those described as having tertiary peritonitis. Among the micro-organisms encountered in these patients are various multi-drug-resistant (MDR) gram-negative pathogens, such as *Pseudomonas* spp. and *Acinetobacter* spp., resistant gram-positive cocci, including vancomycin-resistant *Enterococcus* spp. (VRE) and methicillin-resistant *S. aureus* (MRSA), and non-*C. albicans* spp. [15,32,33].

4. General management of IAI

Once the diagnosis is made, initial management of IAI includes physiologic stabilization of the patient using intravenous (IV) fluid therapy and other modalities where warranted, an appropriate intervention to control the source of the problem, and early initiation of antimicrobial therapy directed against the likely pathogenic microbial agents [4,34]. Source control and antimicrobial therapy, however, should be individualized to a given patient based on an assessment of that patient's risk for an adverse outcome. This concept of risk stratification of therapy was introduced in previous guidelines [3–5]. As will be detailed subsequently, this risk is influenced by many different factors, some of which may have greater importance for decisions with regard to specific source control modalities and others with regard to selection of antimicrobial therapy [3,35].

After employment of source control and initiation of antimicrobial therapy, subsequent treatment of the patient with IAI will be based in large part on that patient's response to the therapeutic measures actually employed. Typically, signs and symptoms of infection will abate in patients responding favorably to initial treatment. In such patients, further interventions should be minimized, with early discontinuation of antimicrobial therapy. In contrast, patients who do not exhibit resolution of the signs and symptoms of infection within the first several days of treatment may have an ongoing or recurrent IAI, a secondary infection that is potentially the result of collateral damage from antimicrobial therapy, or a non-infectious source of inflammation. In such patients, directed diagnostic and treatment modalities are warranted and not just an extension or alteration of the current therapeutic regimen.

Recommendations

1. Risk assessment

Q 1.1. What are the important risk factors for treatment failure and death in patients with IAI?

Q 1.2. How should patient risk be categorized when making decisions regarding management of IAI, including source control and antimicrobial therapy?

Q 1.3. What specific criteria should be used to identify patients with IAI as being at lower or higher risk for treatment failure or death?

Q 1.4. How should patients be identified as having a HA-IAI or otherwise at risk for an IAI because of resistant or opportunistic pathogens?

A large number of investigators have used multivariable analyses to identify factors that predict initial treatment failure or death in patients with IAI. These publications have studied distinct patient subsets and used various definitions of treatment failure [24,26,27,36–74]. Data from individual studies are summarized in Supplementary Table A (see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/).

Not surprisingly, a wide variety of risk factors have been identified. For clarity, these risk factors have been divided into (1) those related to patient characteristics and physiologic changes associated with the infection, both at the time of presentation and after initial source control; (2) those related to the source and extent of the infection itself, as well as the adequacy and timing of source control; and (3) those related to the presence or likely presence of resistant pathogens, and whether or not initial empiric antimicrobial therapy had activity against the microbial pathogens eventually isolated. It should be emphasized that assignment of a particular clinical finding to one of these categories is somewhat arbitrary, and the categories certainly overlap to some extent. This division of risk factors, however, may have some utility in identifying specific interventions for higher-risk patients. For example, identifying the patient at risk for treatment failure because of the extensive nature of the infection within the abdominal cavity may be relevant to selecting a specific source control intervention, whereas identifying a patient at risk for an infection because of a resistant or opportunistic pathogen may suggest a different approach to antimicrobial therapy. Risk factors identified in these multivariable analyses are summarized in Table 4.

In addition to identifying patients as lower or higher risk according to these criteria, the task force has also chosen to continue the previous approach of stratifying patients as having a CA-IAI or an HA-IAI [2,4,5]. This results in a tripartite division into lower-risk patients with CA-IAI, higher-risk patients with CA-IAI, and patients with HA-IAI. This system then provides a framework for making stratified recommendations without creating undue complexity. Lower-risk patients with CA-IAI, such as those with perforated appendicitis, typically have good outcomes, with very low deaths and a 10%–20% incidence of treatment failure [26,75,76]. Outcomes in more severely ill, higher-risk patients with CA-IAI are substantially worse, with higher rates of mortality, organ system dysfunction, and treatment failure [27,38,60,77–79]. Patients with HA-IAI represent a distinct class for purposes of therapeutic recommendations. Outcomes are somewhat variable, depending on what other risk factors are present aside from having a HA-IAI, but are quite poor in a substantial number of these patients [27,38,50,52,56,58,60,77–79].

Previous guidelines suggested certain characteristics to guide patient stratification, but these had not been prospectively validated [2,4]. Other attempts have been made to establish evidence-based scoring systems for stratifying patients with IAI according to risk [55]; however, thus far, no system for classifying patients with IAI into different risk categories has gained widespread acceptance.

Definitions of sepsis, severe sepsis, and septic shock provided by the Surviving Sepsis Campaign have generally been well accepted and provide a means of identifying the most severely ill patients with IAI [6]. These definitions have undergone revision recently, and the term “severe sepsis” has been dropped. The new definitions of sepsis and septic shock are thought to correspond to patient groups with an estimated 10% and 40% overall death (Table 5) [80]. Thus, the task force recommends that patients with IAI meeting the criteria of severe sepsis or septic shock by the older criteria or of sepsis or septic shock by the newer criteria be considered higher-risk patients.

In various studies, APACHE II scores are frequently identified as the strongest predictors of outcome among all clinical variables collected [26,27,36,38,40,42–46,48,49–51,60–62,67,78,79,81]. APACHE II scores reflect both pre-morbid factors, such as patient age and chronic medical conditions, and acute changes in clinical and laboratory values because of physiologic alterations as a result of the infection. The APACHE II scores, however, require access to a large number of clinical and laboratory variables, making them difficult to calculate in an urgent situation; further, they are subject to inter-rater variability. If these scores are obtained, the task force recommends that patients with a score greater than or equal to 10 be considered at higher risk, because treatment failure rates are at least 20%–30% in this group [45,82].

Many patients with IAI will not meet criteria for sepsis or septic shock and may not be able to be assessed by APACHE II scores. Nonetheless, these patients may have a number of the risk factors for an adverse outcome. Based on the multivariable analyses summarized previously, the task force has recognized advanced age (70 years of age or greater), presence of malignant disease, major compromise of cardiovascular, hepatic, or renal function, and hypoalbuminemia as being the most consistently identified physiologic/phenotypic risk factors predicting an adverse outcome [26,36–39,42–44,48–50,55,57,59,61,62,65–67,69]. The task force has suggested that patients having two or more of these risk factors be considered higher-risk patients (Table 6).

Other characteristics related to the abdominal infection itself have also been identified as placing the patient at higher risk for an adverse outcome. The source of the infection has not been a consistent predictor of outcome in multivariable analyses [26,56,59,60,61,63]; the task force does not recommend taking this into consideration when stratifying patients for risk. Infections associated with diffuse peritonitis involving all abdominal quadrants, however, have more consistently been associated with an adverse outcome [24,57]. The Mannheim peritonitis index (MPI) includes this as a component, along with several other factors. Although infrequently obtained, an elevated MPI score is also associated with an adverse outcome [15,44,46,68,69,79,83]. A delay in source control after IAI is diagnosed [26,49,63] and an inability to achieve adequate initial source control [37,48,51,61,71,84] also correlate highly with an adverse outcome. Based on these findings, the task force has suggested that patients with diffuse peritonitis, an elevated MPI score (if obtained), and those who have delayed or inadequate initial source control be considered higher-risk patients (Table 6).

Patients infected with resistant or opportunistic microorganisms have been identified as being at increased risk for

TABLE 4. RISK FACTORS FOR ADVERSE OUTCOMES WITH INTRA-ABDOMINAL INFECTION

<i>Treatment failure</i>	<i>Death</i>
<i>Phenotypic/physiologic risk factors</i>	
Present at diagnosis	
Age [39,55]	Age [26,36,37,40,43,48,49,51,52,59,61,62,65,69]
Younger age [38,57]	Malignancy [37,48,61,62]
Male gender [51]	Significant cardiac disease [38,62]
Malignancy [67]	Significant liver disease/cirrhosis [48,50,61,62]
Peripheral vascular disease [63]	Significant renal disease/renal replacement therapy [48,61,62]
Alcohol abuse [63]	Unconsciousness [51]
Increased Charlson score [64]	Malnutrition [36]
Tachycardia [66]	Corticosteroid therapy [40]
Body mass index ≥ 29 [63]	Any medical comorbidity [24]
Elevated white blood cell count [39]	Any pre-operative organ impairment [37,44]
Hypoalbuminemia [38,55,66]	ASA score ≥ 3 [68]
Low PaO ₂ /FiO ₂ ratio [55]	ICU admission [26,62]
APACHE II score [38,45,51,67]	Temperature [62]
SAPS II score [58]	Hypoalbuminemia [38,44]
	Hypocholesterolemia [44]
	Peak lactate concentration [70]
	Peak procalcitonin concentration [70]
	APACHE II score [27,36,38,40,43,44,46,48,49,50,61,62]
	SAPS II score [58,60]
	Severe sepsis/septic shock/vasopressor use [26,43,61]
	Sequential (sepsis-related) organ failure assessment (SOFA) score [74] of 1 or greater [65,68,70]
	Any marker of disease severity [24]
Developing after initial source control	
Post-operative temperature $>39^{\circ}\text{C}$ [57]	Decreasing urinary output [72]
Post-operative tachycardia [57]	Worsening thrombocytopenia [72,73]
Low post-operative PaO ₂ /FiO ₂ ratio [57]	Worsening hyperbilirubinemia [72]
Low post-operative hemoglobin concentration [57]	Worsening Glasgow Coma Scale SOFA score [72]
Elevated post-operative serum sodium concentration [57]	Worsening renal SOFA score [72]
MODS scores [59]	MOF/MODS scores [50]
	Cardiac event [59]
	Catheter-related blood stream infection [59]
<i>Infection characteristics</i>	
Diffuse peritonitis [57]	Diffuse peritonitis [24]
Non-appendiceal source [59]	MPI score [44,46,68,69]
Presence of bowel ischemia [63]	Upper GI source [56,61]
	Biliary source [60]
	Small bowel, colonic source [26]
	Non-appendiceal source [58]
	Non-colonic source [61]
<i>Source control</i>	
Inadequate source control [51]	Inadequate source control [37,48,51,61,71]
Delayed source control [63]	Delayed source control [26,49]
Laparotomy vs. laparoscopy for source control [58]	Laparotomy vs. laparoscopy for source control [58]
	No abdominal fascial closure [50]
	Any surgical complication [50]
<i>Microbiologic characteristics</i>	
Resistant pathogen [39]	Growth of <i>Enterococcus</i> spp. in culture [49]
Growth of <i>Enterococcus</i> spp. in culture [58]	<i>Candida</i> peritonitis [56,68]
Prolonged hospitalization before source control [45]	Growth of resistant pathogens in culture [62]
HA-IAI [67]	CA-IAI [27]
<i>Antimicrobial therapy</i>	
Inadequate initial antimicrobial therapy [42,53,54]	Inadequate initial empiric antimicrobial therapy [43,58,61, 71]

ASA=American Society of Anesthesiologists; ICU=intensive care unit; APACHE=Acute Physiology and Chronic Health Evaluation; SAPS II=Simplified Acute Physiology Score II; MOF=multiple organ failure; MODS=multiple organ dysfunction syndrome; MPI=Mannheim Peritonitis Index; GI=gastrointestinal; HA-IAI=healthcare- or hospital-associated; CA-IAI=community-acquired intra-abdominal infection.

TABLE 5. SURVIVING SEPSIS CAMPAIGN CRITERIA FOR SEPSIS, SEVERE SEPSIS, AND SEPTIC SHOCK

*2012 Criteria [8]***Sepsis**

Documented or suspected infection plus some of the following:

General variables

- Fever ($>38.3^{\circ}\text{C}$)
- Hypothermia (core temperature $<36^{\circ}\text{C}$)
- Heart rate $>90/\text{min}$ or more than two SD above the normal value for age
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance ($>20\text{ mL/kg}$ over 24 h)
- Hyperglycemia (plasma glucose $>140\text{ mg/dL}$ or 7.7 mmol/L) in the absence of diabetes mellitus

Inflammatory variables

- Leukocytosis (WBC count $>12,000\text{ }\mu\text{L}$)
- Leukopenia (WBC count $<4,000\text{ }\mu\text{L}$)
- Normal WBC count with greater than 10% immature forms
- Plasma C-reactive protein more than two SD above the normal value
- Plasma procalcitonin more than two SD above the normal value

Hemodynamic variables

- Arterial hypotension (SBP $<90\text{ mm Hg}$, MAP $<70\text{ mm Hg}$, or a SBP decrease $>40\text{ mm Hg}$ in adults or less than two SD below normal for age)

Organ dysfunction variables

- Arterial hypoxemia ($\text{PaO}_2/\text{FiO}_2 <300$)
- Acute oliguria (urine output $<0.5\text{ mL/kg/h}$ for at least 2 h despite adequate fluid resuscitation)
- Creatinine increase $>0.5\text{ mg/dL}$ or $44.2\text{ }\mu\text{mol/L}$
- Coagulation abnormalities (INR >1.5 or aPTT $>60\text{ sec}$)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count $<100,000\text{ }\mu\text{L}^{-1}$)
- Hyperbilirubinemia (plasma total bilirubin $>4\text{ mg/dL}$ or $70\text{ }\mu\text{mol/L}$)

Tissue perfusion variables:

- Hyperlactatemia ($>1\text{ mmol/L}$)
- Decreased capillary refill or mottling

Severe sepsis

Sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be because of the infection):

Sepsis-induced hypotension

- Lactate above upper limits laboratory normal
- Urine output $<0.5\text{ mL/kg/h}$ for more than 2 h despite adequate fluid resuscitation
- Acute lung injury with $\text{PaO}_2/\text{FiO}_2 <250$ in the absence of pneumonia as infection source
- Acute lung injury with $\text{PaO}_2/\text{FiO}_2 <200$ in the presence of pneumonia as infection source
- Creatinine $>2.0\text{ mg/dL}$ ($176.8\text{ }\mu\text{mol/L}$)
- Bilirubin $>2\text{ mg/dL}$ ($34.2\text{ }\mu\text{mol/L}$)
- Platelet count $<100,000\text{ }\mu\text{L}$
- Coagulopathy (INR >1.5)

Septic shock

Sepsis-induced hypotension persisting despite adequate fluid resuscitation

*2016 Criteria [80]***Sepsis**

Documented or suspected infection plus either:

- (1) An acute change in the total SOFA score ≥ 2 points, or
- (2) A qSOFA score of ≥ 2 points, based on at least two of the following suspected to be because of infection:
 - Respiratory rate $\geq 22/\text{min}$
 - Altered mentation
 - Systolic blood pressure $\leq 100\text{ mm Hg}$

Septic shock

Sepsis with persisting hypotension requiring vasopressors to maintain MAP $\geq 65\text{ mm Hg}$ and having a serum lactate level $>2\text{ mmol/L}$ (18 mg/dL) despite adequate volume resuscitation.

SD=standard deviation; WBC=white blood cell; SBP=systolic blood pressure; MAP=mean arterial pressure; INR=International Normalized Ratio; aPTT=activated partial thromboplastin time; SOFA=Sequential Organ Failure Assessment; qSOFA=quick Sequential Organ Failure Assessment.

TABLE 6. FACTORS POTENTIALLY IDENTIFYING PATIENTS WITH INTRA-ABDOMINAL INFECTION AT HIGHER RISK

<i>Phenotypic/physiologic risk factors</i>
Advanced age (≥ 70 y)
Malignancy
Significant cardiovascular compromise
Significant liver disease or cirrhosis
Significant renal disease
Hypoalbuminemia
<i>Extent of infection/adequacy of initial source control</i>
Diffuse, generalized peritonitis
Elevated MPI score
Delayed initial source control
Inability to achieve adequate source control
Microbiologic characteristics
Suspected infection with resistant pathogens

MPI = Mannheim Peritonitis Index.

an adverse outcome [24,39,42,43,45,49,58,62,68]. There is a broad body of evidence that patients with HA-IAI, including patients with post-operative infections, are at increased risk for infection with resistant or opportunistic pathogens [15,17,22–24,26,32,33,62,77,85–90]. Patients who are not hospitalized, however, may nonetheless be at risk for IAI because of these micro-organisms. Patients at risk for infections with resistant or opportunistic pathogens, including IAI, include those who are known carriers of a resistant organism [91–106] and those who have had recent exposure to broad-spectrum antimicrobial therapy [17,19,99,106–123]. The task force would include such patients in the category of patients having HA-IAI (Table 7).

Patients exposed to other healthcare settings outside the hospital may also be at risk of harboring more resistant pathogens. This concept had been applied to patients with healthcare-associated pneumonia, but this concept has recently come into question [124]. Risk factors described previously included hospitalization for greater than 48 hours within the preceding 90 days, residence in a skilled nursing or other long-term care facility, and a history of home infusion therapy, home wound care, or renal replacement therapy within the preceding 30 days [125]. Unfortunately, there are little data to determine whether these risk factors identify patients at risk for IAI because of resistant pathogens. For now, the task force would suggest classifying these patients as potentially having HA-IAI, such that a decision whether or not to direct therapy against resistant pathogens would be considered.

TABLE 7. CRITERIA FOR HEALTHCARE- OR HOSPITAL-ACQUIRED INTRA-ABDOMINAL INFECTION

Infection developing greater than 48 h after initial source control.
Hospitalized for greater than 48 h during current admission or within the previous 90 d.
Residence in a skilled nursing or other long-term care facility within the previous 30 d.
Home infusion therapy, home wound care, or dialysis within the preceding 30 d.
Use of broad-spectrum antimicrobial therapy for 5 d or more during the preceding 90 d.

1.1. We recommend considering phenotypic and physiologic factors, including signs of sepsis or septic shock, extremes of age, and patient co-morbidities; the extent of abdominal infection and adequacy of initial source control; and the presence or persistence of resistant or opportunistic pathogens in assessing risk for treatment failure and death in patients with IAI (Grade 1-B).

1.2. We suggest that patients be characterized as being at either lower or higher risk for treatment failure or death and as having either CA-IAI or HA-IAI (including post-operative infection) for purposes of planning source control and empiric antimicrobial therapy (Grade 2-C).

1.3. We recommend that patients with IAI meeting Surviving Sepsis Campaign criteria for sepsis or septic shock and those having an APACHE II score greater than or equal to 10 be considered higher-risk patients (Grade 1-B). We suggest that patients having at least two physiologic/phenotypic risk factors for an adverse outcome, those having diffuse peritonitis, and those having delayed or inadequate source control also be considered higher-risk patients (Grade 2-B).

1.4. We suggest that patients who have been hospitalized for at least 48 hours during the previous 90 days; those residing in a skilled nursing or long-term care facility during the previous 30 days; those who have received IV infusion therapy, wound care, or renal replacement therapy within the preceding 30 days; those who have received several days of broad-spectrum antimicrobial therapy within the previous 90 days; those who have post-operative infections; and those known to have been colonized or infected previously with a resistant pathogen be considered as having HA-IAI and at risk for infection because of resistant or opportunistic organisms (Grade 2-B).

2. Source control

Q 2.1. What is the role of source control in the management of IAI?

Q 2.2. When should the initial source control procedure be undertaken?

Q 2.3. What procedures should be used to obtain source control in patients with IAI?

Q 2.4. What risk factors identify patients with IAI who are likely to fail initial efforts at source control?

Q 2.5. How should source control be approached in high-risk patients undergoing laparotomy?

Q 2.6. Should higher-risk patients with severe or diffuse peritonitis in whom adequate source control is achieved at the index procedure undergo planned re-laparotomy?

Q 2.7. How should intra-operative lavage be used during source control?

Source control has been summarized as drainage of infected fluid collections, debridement of necrotic infected tissue, and definitive measures to control contamination and restore normal gastrointestinal anatomy and function [34]. Source control should not only reduce bacterial and toxin load by removing the focus of infection and ongoing contamination, but also transform the local environment such that further microbial growth is impeded and host defenses can be optimized [126–130]. Studies of patients with IAI have demonstrated repeatedly that a failure to obtain adequate source control is one of the factors most strongly associated with an adverse outcome, including death (Supplementary Table B; see online supplementary

material at www.liebertpub.com/overview/surgical-infections/53/ [37,48,51,61,71,84]. Thus, even though not definitively tested using RCTs, the magnitude of the increase in death and other adverse outcomes associated with inadequate source control makes it clear that these interventions are of prime importance in treating most patients with IAI.

Although expeditious source control is the standard of care for most patients with IAI, certain highly selected patients with a localized IAI have been treated successfully with anti-infective therapy alone. Source control has been omitted or delayed in patients with acute colonic diverticulitis, when the inflammatory process extends only into the peri-colonic tissues [131,132], in patients with perforated appendicitis and a peri-appendiceal phlegmon [133–135], in selected patients with localized upper gastrointestinal perforations [136–138], and in patients with relatively small diverticular or peri-appendiceal abscesses (generally less than 3–4 cm in diameter) [131,132,139–142].

There are also some patients for whom a more delayed approach to source control is advocated. For instance, early surgical intervention is associated with increased morbidity and death in patients with infected pancreatic necrosis, and a delay in definitive therapy for days or even weeks may be warranted [128,143–145]. Outside of clinical situations in which there has been well-documented success using a non-interventional approach, however, an expeditious source control procedure is considered essential for patients with IAI. Careful clinical observation is mandatory in patients treated without source control, and patients who fail to improve on antimicrobial therapy alone should undergo a source control intervention [81,129,131,132].

There is sparse evidence regarding the ideal timing of source control interventions. Short delays may be needed to mobilize technical expertise and other resources for optimal treatment of the patient with IAI. Multivariable analyses have identified the time between diagnosis and source control as a predictor of death in patients with IAI [49,63]. One reviewer concluded that most patients with peritonitis should undergo a source control procedure within 24 hours of the diagnosis of the infection [146]. Studies of septic patients undergoing source control for IAI and other types of infection, however, suggested that delays of only 3–6 hours were associated with increased death [147,148]. Based on these limited data, the recommendations found in previous guidelines and reviews, and the opinions of the members of this task force, most patients with IAI should undergo source control within 24 hours; patients with sepsis or septic shock should undergo earlier source control, although a short delay to allow for rapid resuscitation may be needed in the hemodynamically unstable patient with sepsis [4,6,49,90,128,146].

Selection of a specific source control procedure for a given patient should be predicated both on the characteristics of the infection and the patient, as well as the availability of technical expertise at the local institution. Operative and other invasive procedures present additional stresses to patients whose physiologic reserves have already been challenged by the infection, so limiting the extent of the source control procedure may be advantageous under some circumstances. If source control is inadequate, however, persistence of the infectious insult may result in an adverse outcome. The balance between the competing demands of optimally managing the infection and ameliorating the ef-

fects of source control on the patient's physiologic function requires individualized patient assessment and careful clinical judgment [128].

The utility of less invasive source control interventions has been confirmed for many patients with IAI. A robust body of evidence has shown that percutaneous drainage of infected intra-abdominal fluid collections provides adequate source control [128,149]. Success rates range from 82%–91% in various series using these techniques [150–153]. In general, minimally invasive approaches are reasonable for most patients with localized IAI, when feasible. The efficacy of less invasive approaches for patients with more diffuse IAI is uncertain, however. Although case series had demonstrated good outcomes using laparoscopic drainage without colonic resection for the treatment of selected patients with Hinchey class III or IV diverticulitis [154–157], recent prospective trials suggested that this approach was less successful than colectomy [158,159]. Overall, based on the available evidence, the task force concluded that the least invasive intervention that will fulfill the goal of establishing adequate source control should be used preferentially in most patients with IAI. Unless clearly shown to be effective, however, less invasive approaches may not be warranted in patients with diffuse peritonitis. This echoes the recommendations from the previous guideline and those of other authors [4, 6,128,149].

The identification of certain risk factors for an adverse outcome in patients with IAI might be useful in selecting alternative approaches to source control interventions. Higher-risk patients, particularly those identified as having an acute compromise of their physiologic status, are a group of patients who might benefit from such alternative approaches [4, 6,128]. Patients with diffuse peritonitis, identified directly or through an elevated MPI score, are another such group of patients [15,24,44,46,51,57,68,69,79,81,83]; however, the utility of such observations in modifying approaches to source control remains conjectural for the most part [160].

The use of abbreviated or damage control laparotomy with delayed fascial closure is an approach that has been used to treat severely ill patients with IAI [161,162]. There are observational data supporting the use of this approach in certain patients. One such group of patients are those whose physiologic reserves are exhausted, as manifested by parameters such as pH less than 7.2, a temperature less than 35°C, or clinically evident coagulopathy [162–164]. The use of open abdominal techniques to manage or prevent abdominal compartment syndrome is also widely accepted [163–165]; this syndrome may occur in patients who have IAI with sepsis and have received large amounts of IV fluids for resuscitation. An inability to obtain full source control at the time of the index procedure is another indication for use of damage control laparotomy and temporary abdominal closure to facilitate early re-laparotomy for more definitive source control [149,162–164,166–169]. Patients with bowel ischemia may also benefit from abbreviated laparotomy and temporary abdominal closure to facilitate planned second-look procedures [162,163,166,168,169].

The use of planned or mandatory re-laparotomy had been suggested as an approach for treating all patients with severe, diffuse secondary peritonitis. A RCT comparing mandatory planned re-laparotomy to re-laparotomy based on clinical indications in patients with severe secondary peritonitis,

however, showed no significant benefit of planned re-laparotomy in terms of peritonitis-related morbidity or death (Supplementary Table C; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/); moreover, resource utilization was higher in patients undergoing mandatory re-laparotomy [170,171]. Additional, non-randomized studies have also questioned the need for planned re-laparotomy in patients with severe peritonitis when adequate source control can be achieved [149,170,172–177]. Based on these data, the task force concluded that damage control laparotomy may be useful in selected patients, but that neither this approach nor mandatory re-laparotomy should be applied universally to patients with severe, diffuse peritonitis.

Irrigation or lavage of the peritoneal cavity is widely used in the management of IAI. A review of the available data concluded that there was no overall benefit for peritoneal lavage beyond that necessary for removal of gross contamination [178]. Several more recent series and one prospective trial of patients with perforated appendicitis likewise have found that aspiration and limited irrigation to remove gross contamination were as effective as lavage [179–182]. The use of continuous post-operative lavage in patients with peritonitis has not been supported by reviews of the available evidence [178,183]. The inclusion of antibiotic agents in lavage fluid has also been used in an effort to reduce complications related to IAI. A meta-analysis of seven older studies of diverse patient populations, not all of whom had IAI, suggested that the inclusion of antibiotic agents in lavage fluid reduced post-operative septic complications, but had no effect on death. Because of the poor methodology used in these studies, however, the authors of this meta-analysis did not believe that the data supported the efficacy of antibiotic lavage, and that this remained an open question [178].

The precise definition of what constitutes adequate source control remains elusive [126]. Approaches to source control have changed as new techniques develop and evidence accumulates regarding various management options. Even when detailed descriptions of adequate source control are provided, interobserver variation in assessing source control adequacy is quite high [184,185]. Local variations in practice patterns may also lead to different, but not necessarily inappropriate, approaches to source control [185]. Given the complexity of defining adequate source control, the task force does not believe that assessments of source control adequacy in patients with IAI would be a useful performance measure by which to evaluate surgical competence.

2.1. We recommend routine use of a source control procedure to remove infected fluid and tissue and to prevent ongoing contamination in patients with IAI except for those patients with clinical problems for which clear evidence has shown that a non-interventional approach is associated with a good clinical outcome (Grade 1-A).

2.2. We suggest that source control be undertaken within 24 hours of the diagnosis of IAI, except for those infections for which clinical evidence indicates non-interventional or delayed management is appropriate (Grade 2-B). We suggest that patients with sepsis or septic shock undergo source control in a more urgent manner (Grade 2-C).

2.3. We recommend use of the least invasive approach that is able to achieve adequate source control, at least on a temporary basis, for patients with IAI (Grade 1-B).

2.4. We suggest that patients with major physiologic instability, those with diffuse infections, and those with ongoing bowel ischemia be considered at higher risk for failure of initial source control and for use of alternative or temporizing approaches to source control (Grade 2-B).

2.5. We recommend that an abbreviated laparotomy and temporary abdominal closure techniques be used in critically ill patients with IAI if closure of the abdomen would create meaningful intra-abdominal hypertension, if the patient's physiologic reserves are severely compromised, if there is an inability to achieve adequate source control with the initial procedure, or if there is a plan for a second-look laparotomy because of mesenteric ischemia (Grade 1-B).

2.6. We recommend against routine planned re-laparotomy in high-risk patients with severe peritonitis when adequate source control can be obtained at the time of the index procedure; such patients should be treated with on-demand rather than scheduled re-laparotomy (Grade 1-B).

2.7. We suggest use of irrigation with crystalloid fluid to remove visible debris and gross contamination before abdominal closure in patients with IAI, generally limiting lavage to those areas with gross involvement as an adjunct to the source control procedure (Grade 2-B).

3. Microbiologic evaluation

Q 3.1. Should cultures be obtained in lower-risk patients with CA-IAI?

Q 3.2. Should cultures be obtained in higher-risk patients with CA-IAI and those with HA-IAI?

Q 3.3. Should routine peritoneal cultures be obtained from patients with IAI for epidemiologic purposes?

The value of routine culture data in guiding antimicrobial therapy for lower-risk patients with CA-IAI has not been rigorously evaluated in prospective trials [186]. Nevertheless, a number of observational studies have suggested that these cultures rarely, if ever, provide information useful to the clinician [187–191]. The majority of lower-risk patients with CA-IAI are successfully treated with standard approaches to source control and antimicrobial therapy. When treatment failure is attributed to inadequate antimicrobial therapy in such patients, it is generally because the initial empiric regimen lacked activity against the common Enterobacteriaceae or enteric anaerobes responsible for the infection [54,187,192]. Nonetheless, the increased prevalence of extended-spectrum β -lactamase (ESBL)-producing Enterobacteriaceae strains in certain geographic areas may necessitate a modification of the recommendation against obtaining routine cultures, particularly if this phenomenon leads to a substantial increase in treatment failure in lower-risk patients with CA-IAI.

There is a greater rationale for obtaining routine peritoneal cultures in higher-risk patients with CA-IAI and those with HA-IAI. In patients with sepsis, use of appropriate antimicrobial therapy is considered essential [8]; inadequate empiric antimicrobial therapy has been associated with higher deaths in patients with sepsis, including those with IAI [43,54,58,187,193–195]. Higher-risk patients with CA-IAI may be infected with somewhat more resistant pathogens than lower-risk patients [22–24,26,27], and the likelihood of encountering resistant pathogens is substantially higher in patients with HA-IAI [15,17,22–24,26,32,33,62,77,85,87,90].

To provide adequate antimicrobial therapy to higher-risk patients, use of broad-spectrum empiric antimicrobial regimens is recommended [4,6,13,127]. To avoid excessive exposure of the patient to broad-spectrum antimicrobial therapy and potential selection of further resistant microorganisms, however, de-escalation of therapy based on culture results is also recommended [4, 6,196–198]. In addition to de-escalating antimicrobial therapy, culture and susceptibility results can be used to guide pathogen-directed therapy when an unexpected or resistant pathogen is encountered; even though such therapy may be delayed, it is still more likely to be successful than continued administration of an inappropriate empiric regimen [197,199,200].

There have been substantial increases in resistance of microbial pathogens involved in IAI to previously effective antimicrobial agents, particularly in Asia and Latin America [28–31]. Ideally, epidemiologic investigations could identify problematic pathogens in a specific geographic locale, and the results could be used to guide selection of preferred empiric antimicrobial regimens for that region [186]. To track these epidemiologic changes, culture results from an unbiased sample of patients must be obtained. Thus, culture and susceptibility data from even lower-risk patients with CA-IAI are needed, although the culture results themselves will provide little direct benefit to the patient. For such an approach to be viable, however, adequate resources are needed for aggregation, analysis, and dissemination of this information. Given the increasing incidence of resistant pathogens in both CA-IAI and HA-IAI and the limited antimicrobial armamentarium available to treat patients with such micro-organisms, such investigations will likely be increasingly vital in the future.

Optimal techniques for obtaining peritoneal cultures were reviewed in the previous guideline [4]. At least one mL of peritoneal fluid or infected tissue should be collected and placed in a suitable transport system for examination by the microbiologic laboratory. If anaerobic cultures are to be obtained, these specimens need to be sent in an anaerobic transport system. Direct inoculation of fluid specimens into blood culture bottles is an additional option. In any case, use of peritoneal swabs instead of fluid or tissue for cultures is strongly discouraged.

3.1. We do not recommend routinely obtaining peritoneal fluid cultures in lower-risk patients with CA-IAI for purposes of guiding antimicrobial therapy (Grade 1-B).

3.2. We recommend obtaining cultures of peritoneal fluid in higher-risk patients with CA-IAI and in patients with HA-IAI to identify potential resistant or opportunistic pathogens (Grade 1-C).

3.3. We suggest obtaining cultures in all patients with CA-IAI and HA-IAI if adequate resources are available to aggregate and analyze the epidemiologic data and the information can be used to guide empiric antimicrobial therapy (Grade 2-C).

4. Intravenous antimicrobial agents

A. General principles

Q 4.1. What are the general principles regarding antimicrobial therapy for patients with IAI?

Standard antimicrobial therapy for patients with IAI should include agents with activity against aerobic gram-negative Enterobacteriaceae, aerobic streptococci, and obligate enteric an-

aerobic organisms found in the gastrointestinal tract, although coverage of the latter may not be absolutely essential in patients with an upper gastrointestinal source of infection. Additional antimicrobial agents, providing coverage of less common resistant or opportunistic pathogens, may be warranted in more severely ill patients. A wide variety of antimicrobial agents have activity against these various micro-organisms. This section summarizes the task force's interpretation of the utility of various antimicrobial agents in treating patients with IAI. A synopsis of these recommendations is available in Table 8. Summaries of older RCTs evaluating antimicrobial therapy for IAI are included in the previous evidence review [3]; summaries of more recent RCTs are provided in the Supplementary Tables (see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/).

The basic principle of providing empiric antimicrobial therapy effective against gram-negative Enterobacteriaceae, aerobic streptococci, and obligate enteric anaerobic organisms in patients with IAI was described several decades ago and has been a component of all previous guidelines [1,2,4,5]. Observational studies have demonstrated an increased risk of treatment failure and death when this basic principle is not followed (Supplementary Table D; (see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [54,58,187,201,202]. A recent large database study of more than 6000 patients confirmed that patients who received regimens lacking activity against anaerobic organisms had a significantly increased rate of treatment failure compared with patients who received agents effective against both gram-negative Enterobacteriaceae and anaerobic pathogens (Supplementary Table D) [192].

4.1. We recommend use of antimicrobial regimens having activity against the typical gram-negative Enterobacteriaceae, gram-positive cocci, and obligate anaerobes involved in these infections (Grade 1-A).

B. Aminoglycoside-based regimens

Q 4.2. What is the role of aminoglycoside-based regimens in the treatment of patients with IAI?

At one time, aminoglycosides (gentamicin, tobramycin, amikacin, netilmicin), in combination with an anti-anaerobic agent (clindamycin, metronidazole) and variably with an agent active against gram-positive organisms, were considered the “gold standard” for treatment of patients with IAI. These regimens were recommended in early guidelines [1,2], but not in subsequent guidelines [4,5]. Aminoglycosides were used in four RCTs published since 2000 (Supplementary Table E (see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/)). In one, the clinical efficacy of amikacin, in combination with ceftazidime and metronidazole, was found to be inferior to cefoperazone-sulbactam [203]. No significant differences in outcome were noted in the other three studies; however, one only compared once daily to multiple daily doses of amikacin [204–206].

Two meta-analyses published since 2000 found that aminoglycoside-based regimens were inferior to comparators for treating patients with IAI (Supplementary Table F; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [207,208]. In the previous evidence review [3], four trials also showed higher treatment

TABLE 8. SUMMARY OF RECOMMENDATIONS ON INTRAVENOUS ANTIMICROBIAL AGENTS

Agent	Empiric use		*Rationale	Pathogen-directed use	Other comments
	Recommendation				
<i>Aminoglycosides</i>					
Amikacin, gentamicin, tobramycin	Not recommended		1, 2	Resistant gram-negative bacteria	Suggested for treating neonatal patients
<i>Penicillin-β-lactamase inhibitor combinations</i>					
Ampicillin-sulbactam	Not recommended		1, 3	Potentially for sulbactam-susceptible strains of <i>Acinetobacter baumannii</i>	
Amoxicillin-clavulanic acid	Not recommended		1, 3, 4		Not available in the United States
Ticarcillin-clavulanic acid	Suggested - lower-risk patients		4		Not currently available in the United States
Piperacillin-tazobactam	Recommended - higher-risk patients				
<i>Cephalosporins (including cephamycins) and cephalosporin-β-lactamase inhibitor combinations</i>					
Cefoxitin, Cefotetan	Not recommended		1, 4		Recommended for prophylaxis in colorectal procedures in SSI prevention guideline
Cefazolin	Not recommended		5		
Cefuroxime	Suggested - lower-risk patients		4		
Cefotaxime	Recommended - lower-risk patients				
Ceftriaxone	Recommended - lower-risk patients				
Ceftazidime	Suggested - higher-risk patients		4		
Cefepime	Recommended - higher-risk patients				
Cefoperazone-sulbactam	Recommended - lower-risk patients				Not available in the United States
Ceftolozane-tazobactam	Suggested - higher-risk patients			Susceptible MDR, XDR, or PDR strains of <i>Pseudomonas aeruginosa</i> .	Restrict to patients with or at risk for MDR, XDR, or PDR strains of <i>P. aeruginosa</i> .
Ceftazidime-avibactam	Suggested - higher-risk patients			KPC-producing strains of Enterobacteriaceae	Restrict to patients with or at risk for KPC-producing strains of Enterobacteriaceae
<i>Monobactam</i>					
Aztreonam	Suggested - higher-risk patients		4		Potentially useful for patients with reactions to β-lactam antibiotic agents
<i>Carbapenems</i>					
Ertapenem	Recommended - lower-risk patients			Many ESBL-producing strains of Enterobacteriaceae	Suitable for empiric use in lower-risk patients in geographic regions with a high incidence of ESBL-producing strains of Enterobacteriaceae

(continued)

TABLE 8. (CONTINUED)

Agent	Empiric use		*Rationale	Pathogen-directed use	Other comments
	Recommendation				
Doripenem	Recommended - higher-risk patients			Many ESBL-producing strains of Enterobacteriaceae	Suitable for empiric use in higher-risk patients in geographic regions with a high incidence of ESBL-producing strains of Enterobacteriaceae.
Imipenem-cilastatin	Recommended - higher-risk patients			Many ESBL-producing strains of Enterobacteriaceae	Suitable for empiric use in lower-risk patients in regions with a high incidence of ESBL-producing strains of Enterobacteriaceae
Meropenem	Recommended - higher-risk patients			Many ESBL-producing strains of Enterobacteriaceae	Suitable for empiric use in lower-risk patients in regions with a high incidence of ESBL-producing strains of Enterobacteriaceae; suggested for treating neonatal patients.
<i>Fluoroquinolones</i> Moxifloxacin	Recommended - lower-risk patients	3			For use primarily in patients with severe reactions to β -lactam antibiotic agents; use with caution in geographic areas with a high incidence of fluoroquinolone-resistant Enterobacteriaceae
Ciprofloxacin	Recommended - lower-risk patients	3			For use primarily in patients with severe reactions to β -lactam antibiotic agents; use with caution in geographic areas with a high incidence of fluoroquinolone-resistant Enterobacteriaceae
Levofloxacin	Suggested - lower-risk patients	3, 5			For use only if no other fluoroquinolone is available; use primarily in patients with severe reactions to β -lactam antibiotic agents; use with caution in geographic areas with a high incidence of fluoroquinolone-resistant Enterobacteriaceae
<i>Glycylcycline</i> Tigecycline	Not recommended	1		Resistant gram-negative bacteria other than <i>Pseudomonas</i> spp.	
<i>Anti-anaerobic agents</i> Clindamycin Metronidazole	Not recommended Recommended	2, 3			Suggested for treating neonatal patients
<i>Agents with activity against gram-positive organisms</i> Ampicillin	Suggested - higher-risk patients potentially infected with <i>Enterococcus faecalis</i>	4		<i>E. faecalis</i> if not using piperacillin-tazobactam or imipenem-cilastatin	Suggested for treating neonatal patients
Vancomycin	Suggested - higher-risk patients potentially infected with <i>E. faecium</i> or MRSA.	5		Glycopeptide-susceptible <i>E. faecium</i> or MRSA	Suggested for treating neonatal patients
Teicoplanin	Suggested - higher-risk patients potentially infected with <i>E. faecium</i> or MRSA.	5		Glycopeptide-susceptible <i>E. faecium</i> or MRSA	Not available in the United States

(continued)

TABLE 8. (CONTINUED)

<i>Agent</i>	<i>Empiric use</i>		<i>*Rationale</i>	<i>Pathogen-directed use</i>	<i>Other comments</i>
	<i>Recommendation</i>				
Daptomycin	Suggested - higher-risk patients potentially infected with VRE or as an alternative to glycopeptides for MRSA		5	VRE or as an alternative to a glycopeptide for MRSA	
Linezolid	Suggested - higher-risk patients potentially infected with VRE or as an alternative to a glycopeptide for MRSA		5	VRE or as an alternative to a glycopeptide for MRSA	
<i>Antifungal agents</i>					
Amphotericin B and lipid formulations	Not recommended		1, 2		Suggested for treating neonatal patients
Fluconazole	Suggested - non-critically ill patients potentially infected with <i>Candida albicans</i>			<i>C. albicans</i> in non-critically ill patients	Suggested for treating neonatal patients
Voriconazole	Suggested - non-critically ill patients potentially infected with fluconazole-resistant species of <i>Candida</i>		5	Fluconazole-resistant species of <i>Candida</i> in non-critically ill patients	
Anidulafungin	Recommended - higher-risk patients potentially infected with <i>Candida</i> spp.			<i>Candida</i> spp. in critically ill patients	
Caspofungin	Recommended - higher-risk patients potentially infected with <i>Candida</i> spp.			<i>Candida</i> spp. in critically ill patients	
Micafungin	Recommended - higher-risk patients potentially infected with <i>Candida</i> spp.			<i>Candida</i> spp. in critically ill patients	

*Rationale(s) for decision:

1. Efficacy concerns.
2. Toxicity concerns.
3. Increased resistance.
4. No recent randomized controlled trial data.
5. No randomized controlled trial data for intra-abdominal infection.

SSI = surgical site infection; KPC = *Klebsiella pneumoniae* carbapenemase; ESBL = extended-spectrum beta-lactamase; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant *Enterococcus* spp.

failure rates with aminoglycoside-based regimens compared with other agents [209–212], whereas one trial demonstrated superiority of an aminoglycoside-based regimen compared with ampicillin-sulbactam [213]. The nephrotoxicity and ototoxicity of these agents as well as the need for therapeutic drug monitoring further complicates their use. Given the availability of alternative agents, the task force concluded that these agents should not be used routinely for empiric therapy of patients with IAI. These agents may be useful, however, for treating patients with an infection because of a resistant gram-negative pathogen for which other classes of agents are not suitable. Unfortunately, many of these microorganisms are also resistant to aminoglycosides [28]. Aminoglycoside-based regimens are still used when treating neonatal patients with IAI, as will be discussed in Section 13.

4.2. We recommend against the routine use of aminoglycoside-based regimens for the empiric treatment of patients with IAI (Grade 1-B). We suggest that these regimens may be useful for treatment of IAI in neonatal patients and in adults and children because of resistant gram-negative organisms, if other agents are not suitable (Grade 2-B).

C. Penicillin-β-lactamase inhibitor combinations

Q 4.3a. What is the role of ampicillin-sulbactam in the treatment of patients with IAI?

Q 4.3b. What is the role of IV amoxicillin-clavulanic acid in the treatment of patients with IAI?

Q 4.3c. What is the role of ticarcillin-clavulanic acid in the treatment of patients with IAI?

Q 4.3d. What is the role of piperacillin-tazobactam in the treatment of patients with IAI?

Ampicillin-sulbactam was recommended for treatment of patients with IAI in an older guideline [2], but not in the more recent guidelines [4,5]. The RCTs evaluating the efficacy of ampicillin-sulbactam for the treatment of IAI are limited. Since 2008, two studies have been published using ampicillin-sulbactam (Supplementary Table G; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [214,215], one of which found ampicillin-sulbactam inferior to ertapenem [214]. Three older articles were previously reviewed [3], one of which found ampicillin-sulbactam inferior to a regimen of gentamicin plus clindamycin [213]. Microbiologic data have documented substantial resistance of gram-negative Enterobacteriaceae globally to ampicillin-sulbactam; in the most recent Study for Monitoring of Antimicrobial Resistance Trends (SMART) data, only 34% of hospital-associated strains and 45% of community-acquired strains of *E. coli* were susceptible to this agent [28].

Based on the clinical and microbiologic data, the task force concluded that other agents were preferable to ampicillin-sulbactam for the empiric treatment of patients with IAI. Ampicillin-sulbactam does have some activity against *A. baumannii*, primarily because of the sulbactam entity, and may have some use in pathogen-directed therapy of patients with infections from that micro-organism [216]; however, the majority of *Acinetobacter* strains isolated from patients with IAI are not susceptible [28].

The IV preparation of amoxicillin-clavulanic acid is not available for use in the United States but is available in Europe and other parts of the world. The literature search did

not identify any RCTs published since 2000 evaluating this agent. In the previous evidence review [3], one small prospective trial comparing use of IV amoxicillin-clavulanic acid plus metronidazole to IV ciprofloxacin plus metronidazole found lower success rates with the amoxicillin-clavulanic acid plus metronidazole regimen, although this difference was not statistically significant [217]. In a recent observational study of patients with peritonitis in The Netherlands, the authors concluded that amoxicillin-clavulanic acid-resistant *E. coli* was increasingly common, and that use of this agent in such patients was associated with increased death [218].

Microbiologic studies suggest that in vitro resistance of *E. coli* to amoxicillin-clavulanic acid is high; in one study, susceptibility of *E. coli* isolates from various sources to amoxicillin-clavulanic acid was 50%–51%, which was only marginally better than that of ampicillin-sulbactam (45%–47%) [219]. Because of concerns regarding efficacy and resistance of *E. coli* as well as the lack of recent RCTs on use of this agent, the task force does not support use of amoxicillin-clavulanic acid for empiric treatment of patients with IAI.

Ticarcillin-clavulanic acid had been recommended for empiric treatment of patients with IAI in previous guidelines [1,2,4,5]. Since 2000, only one small RCT has evaluated this agent (Supplementary Table G; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/). No significant differences in success rates were demonstrated comparing use of this agent with ertapenem, but only 11 clinically evaluable patients were treated with ticarcillin-clavulanic acid [220]. In the previous evidence review [3], three prospective trials demonstrated efficacy of ticarcillin-clavulanate for the treatment of lower-risk patients with IAI. Contemporary data on the activity of this agent against gram-negative pathogens found with IAI are limited. Although the activity spectrum of ticarcillin-clavulanic acid includes *P. aeruginosa*, in vitro susceptibility has declined in recent years [221]. Ticarcillin-clavulanic acid may have some activity against MDR organisms such as *A. baumannii*, although less than ampicillin/sulbactam [222], and some activity against ESBL-producing strains of Enterobacteriaceae, but less than piperacillin-tazobactam [223]. Ticarcillin-clavulanic acid is no longer available in the United States [224]. The task force concluded that this agent was acceptable for empiric treatment of patients with IAI, although other agents would be preferable because of the lack of contemporary data demonstrating efficacy of this agent. This recommendation is moot, however, unless production of it resumes.

Piperacillin-tazobactam is a commonly used agent for treating patients with IAI. It has been recommended for the treatment of higher-risk patients or those with higher severity infections in previous guidelines [2,4,5]. Six RCTs comparing this agent with other regimens for IAI have been published since 2000 (Supplementary Table G; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [225–230], one of which was reviewed previously [3]. There were no significant differences noted in the clinical success rates between patients receiving piperacillin-tazobactam and those receiving various comparators. Eight other trials evaluating this agent were reviewed previously [3], including one in severely ill patients comparing use of piperacillin-tazobactam with the combination of this agent plus an aminoglycoside. It was also concluded that

piperacillin-tazobactam was as effective as the various comparators [3]. In vitro susceptibility data generally document good activity of this agent against *E. coli*, although there has been some decline in this over the past decade. Piperacillin-tazobactam is active against many ESBL-producing Enterobacteriaceae but generally less so than carbapenems [28].

Based on the continued evidence of good efficacy of piperacillin-tazobactam, the task force recommends this agent for the treatment of patients with IAI. To avoid excessive use and potential promotion of resistance to broad-spectrum agents such as piperacillin-tazobactam, the task force suggests that this agent be reserved primarily for use in higher-risk patients.

4.3a. We suggest that ampicillin-sulbactam not be used for the empiric treatment of adults and children with IAI (Grade 2-B).

4.3b. We suggest that IV amoxicillin-clavulanic acid not be used for the empiric treatment of adults and children with IAI (Grade 2-B).

4.3c. We suggest that ticarcillin-clavulanic acid is an acceptable agent for the empiric treatment of lower-risk adults and children greater than one month of age with CA-IAI, if it is available (Grade 2-B).

4.3d. We recommend piperacillin-tazobactam as an acceptable agent for the empiric treatment of adults and children older than one month with IAI (Grade 1-A). We suggest that this agent be reserved primarily for higher-risk patients because of its broader-spectrum antimicrobial activity (Grade 2-C).

D. Cephalosporin-based regimens and cephalosporin- β -lactamase inhibitor combinations

Q 4.4a. What is the role of cephamycin antibiotic agents (cefoxitin, cefotetan) in the treatment of patients with IAI?

Q 4.4b. What is the role of cefazolin plus metronidazole in the treatment of patients with IAI?

Q 4.4c. What is the role of cefuroxime plus metronidazole in the treatment of patients with IAI?

Q 4.4d. What is the role of cefotaxime or ceftriaxone plus metronidazole in the treatment of patients with IAI?

Q 4.4e. What is the role of ceftazidime plus metronidazole in the treatment of patients with IAI?

Q 4.4f. What is the role of cefepime plus metronidazole in the treatment of patients with IAI?

Q 4.4g. What is the role of cefoperazone-sulbactam in the treatment of patients with IAI?

Q 4.4h. What is the role of ceftolozane-tazobactam plus metronidazole in the treatment of patients with IAI?

Q 4.4i. What is the role of ceftazidime-avibactam plus metronidazole in the treatment of patients with IAI?

Cephamycin antibiotic agents have been recommended variably in previous guidelines as monotherapy for the treatment of patients with IAI [1,2,4,5]. The literature search did not identify any RCTs published since 2000 that evaluated the use of these agents. In the previous evidence review [3], eight trials evaluated cefoxitin in patients with IAI, the most recent published in 1996, and three trials evaluated cefotetan, the most recent published in 1994. None of these demonstrated significant differences in clinical outcomes comparing cephamycins with other agents.

Because of the lack of contemporary data on the use of these agents, recent studies analyzing use of these antibiotic agents for surgical prophylaxis in colorectal procedures were also reviewed. One RCT found cefotetan inferior to ertapenem for this indication [231]. Two recent, large database studies found that cephamycins were less efficacious than other recommended agents for prophylaxis for colorectal procedures [232,233]. Microbiologic data indicate that about 90% of *E. coli* strains isolated from patients with IAI in North America are susceptible to cefoxitin [234], but this is lower in other parts of the world [31,235]. Resistance of anaerobic micro-organisms, including *B. fragilis*, to cephamycins is increasing, however [236,237]. A concern specific to cefoxitin is its short half-life of 0.7–1.1 hours. Because of this, intra-operative re-dosing every two hours is recommended for surgical site infection prophylaxis [238].

Overall, given the lack of contemporary data and the potential for decreased efficacy of cephamycin antibiotic agents, as reflected in the indirect evidence from studies of colorectal surgical procedure prophylaxis, the task force suggests use of regimens other than cephamycins for empiric treatment of patients with IAI. It is recognized that this conflicts with a recent guideline on surgical prophylaxis, which recommends cephamycins for appendectomy and colorectal procedures [238]. Nevertheless, because there are alternative regimens for lower-risk patients with CA-IAI, the task force believes that these should be used preferentially to cephamycins.

Unlike other cephalosporins, cephamycins have in vitro activity against many ESBL-producing Enterobacteriaceae. This suggests their potential utility in treating those resistant pathogens; however, there are virtually no data evaluating their clinical efficacy for this indication [239].

The combination of cefazolin plus metronidazole was included as a recommended regimen in some previous guidelines [4,5]. Cefazolin has been approved by the FDA for the treatment of patients with biliary tract disease, but not for management of complicated IAI. There are essentially no prospective data evaluating the efficacy of this regimen compared with others for IAI. One trial from 1989 studied this regimen in patients with complicated appendicitis but did not compare it with an alternative regimen [240]. There are two large database studies that evaluated antibiotic agents for colorectal prophylaxis, both of which suggested cefazolin plus metronidazole was efficacious for this indication [232,233]. Relatively recent data show that 92% of *E. coli* strains from patients with acute and perforated appendicitis are susceptible to cefazolin [241]. Nevertheless, because there is only indirect evidence supporting the use of cefazolin plus metronidazole for treatment of patients with IAI, the task force suggests using alternative regimens for empiric therapy.

The combination of cefuroxime plus metronidazole was also recommended in previous guidelines for the treatment of patients with IAI [2,4,5]. This recommendation was supported by three trials showing efficacy of this regimen, which were included in the previous evidence review [3]. There are no recent trials re-evaluating this regimen for IAI and relatively few recent microbiologic studies. A study of appendiceal isolates demonstrated 95% susceptibility of *E. coli* to cefuroxime [241], but a global survey of urinary isolates found only 82% susceptibility of *E. coli* to this agent [242]. The task force concluded that this regimen was acceptable for

empiric treatment of lower-risk patients with CA-IAI but suggested preferential use of other regimens for which more recent evidence is available.

The combination of a third-generation cephalosporin plus an anti-anaerobic agent has been recommended in all previous guidelines [1,2,4,5]; the 2010 guideline specifically recommended use of cefotaxime or ceftriaxone plus metronidazole for lower-risk patients with CA-IAI [4]. Cefotaxime plus metronidazole was compared with piperacillin-tazobactam in one study published since 2000 (Supplementary Table H; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/); this study demonstrated similar outcomes with either regimen [225]. The previous evidence review [3] included five studies comparing cefotaxime plus an anti-anaerobic agent with other agents. In one of these studies, success rates were significantly higher with cefotaxime plus metronidazole than with meropenem [243], whereas the opposite was true in a second study [244]. In one additional small study comparing a regimen of cefotaxime plus gentamicin plus metronidazole with ciprofloxacin plus metronidazole, the fluoroquinolone-based regimen appeared to be more efficacious [245].

Nine studies have been published since 2000 comparing ceftriaxone and a nitroimidazole (generally metronidazole) with other agents (Supplementary Table H; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [204,246–253]. Three additional trials were cited in the previous evidence review [3]. None of the more recent studies demonstrated any significant difference in outcomes between patients receiving ceftriaxone plus a nitroimidazole and those receiving the comparator; one of the older studies found ceftriaxone plus metronidazole to be superior to an aminoglycoside-based regimen.

Approximately 90% of *E. coli* obtained from patients with IAI in North America are susceptible to cefotaxime or ceftriaxone. Susceptibility rates are appreciably lower in other parts of the world, however, particularly Asia, the Middle East, and Latin America, where there is a high prevalence of ESBL-producing Enterobacteriaceae [28,31,234,235]. Based on the evidence available, the task force recommends use of cefotaxime or ceftriaxone plus metronidazole for the treatment of lower-risk patients with CA-IAI. In areas of the world where ESBL-producing *E. coli* are prevalent, however, other agents would be preferable.

Previous guidelines recommended the combination of the third-generation anti-pseudomonal cephalosporin, ceftazidime, plus metronidazole for the treatment of higher-risk patients with IAI [2,4,5]. The task force did not identify any recent RCTs evaluating ceftazidime plus metronidazole only, although one recent trial compared ceftazidime plus amikacin and metronidazole with cefoperazone/sulbactam monotherapy (Supplementary Table H; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/); this study, performed in a region where there is a high incidence of ESBL-producing *E. coli*, found greater efficacy with cefoperazone-sulbactam than the ceftazidime-based regimen [203]. In the previous review [3], two studies compared ceftazidime plus an anti-anaerobic agent to other agents; one of these demonstrated superiority of ceftazidime plus metronidazole over an aminoglycoside plus metronidazole [210]. In vitro susceptibilities of *E. coli* to ceftazidime remain greater than 90% in North America and Europe;

however, the susceptibility of this organism to ceftazidime is appreciably lower in Asia, the Middle East, and Latin America, where ESBL-producing strains of *E. coli* are prevalent [28,31,234,235].

Based on the available data, the task force suggests that ceftazidime plus metronidazole can be used for the treatment of patients with IAI, although this is graded as a weak recommendation because of the lack of contemporary data. As with most other agents with broad-spectrum activity against gram-negative organisms, this regimen should be reserved primarily for empiric treatment of higher-risk patients with IAI. A ceftazidime-based regimen should most likely be avoided in regions where there is a high prevalence of ESBL-producing Enterobacteriaceae. In general, the task force prefers use of cefepime rather than ceftazidime for those patients in whom an anti-pseudomonal cephalosporin is believed warranted.

The fourth-generation anti-pseudomonal cephalosporin, cefepime, in combination with metronidazole, was also recommended for the treatment of higher-risk patients with IAI in previous guidelines [2,4,5]. Cefepime plus metronidazole was evaluated in two RCTs published since 2000 (Supplementary Table H; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [254,255] and in two RCTs included in the previous evidence review [3]. Two of these trials demonstrated significantly higher success rates with cefepime plus metronidazole compared with imipenem-cilastatin [45,255], although this statistical difference disappeared in one study when the results were adjusted for an imbalance in the severity of illness between the study groups [45]. As with ceftazidime, microbiologic data indicate in vitro susceptibility of *E. coli* to cefepime is greater than 90% in North America and Europe but appreciably lower in Asia, the Middle East, and Latin America [28,31,234,235]. Cefepime is less susceptible to hydrolysis by AmpC β -lactamases than are other broad-spectrum cephalosporins, so it may be a therapeutic alternative to carbapenems for patients with infections because of gram-negative bacteria expressing those enzymes [256–259].

Overall, based on the available data, the task force recommends cefepime plus metronidazole for the treatment of patients with IAI. The task force suggests that this regimen be used primarily for empiric therapy of higher-risk patients because of its potent anti-pseudomonal activity.

Several combinations of a cephalosporin with a β -lactamase inhibitor are now available that may be able to overcome some the resistance mediated by ESBL enzymes. Cefoperazone-sulbactam is one such combination. This agent is not available in the United States. In one recent trial, cefoperazone-sulbactam was superior to a regimen of amikacin, ceftazidime, and metronidazole for the treatment of patients with IAI (Supplementary Table H; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/); of note, this trial took place in a region with a high prevalence of ESBL-producing Enterobacteriaceae [203]. Two additional trials using cefoperazone-sulbactam were described in the previous evidence review [3], one of which found cefoperazone-sulbactam superior to an aminoglycoside-based regimen [209].

Cefoperazone-sulbactam has activity against a number of ESBL-producing strains of *E. coli*, although this varies somewhat from country to country [260–262]. This agent has

been tested primarily in lower-risk patients with IAI. Overall, the task force concluded that cefoperazone-sulbactam is an effective agent for the treatment patients with IAI and may be of value for use in lower-risk patients with CA-IAI who live in parts of the world where the prevalence of ESBL-producing Enterobacteriaceae is appreciable.

Two new cephalosporin- β -lactamase inhibitor combinations, ceftolozane-tazobactam and ceftazidime-avibactam, used in combination with metronidazole, have been approved by the FDA for the treatment of patients with complicated IAI. These agents have also now been approved for use by the European Commission. In phase II and phase III trials, ceftolozane-tazobactam, in combination with metronidazole, appeared to have similar efficacy to meropenem for the treatment of patients with IAI (Supplementary Table H; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [263,264]. Ceftolozane-tazobactam is active in vitro against many ESBL-producing Enterobacteriaceae, although not against *K. pneumoniae* carbapenemase (KPC)-producing strains or metallo- β -lactamase (MBL)-producing strains. It is also active against many strains of *P. aeruginosa* and appears to be the most potent currently available β -lactam or β -lactam- β -lactamase inhibitor combination against this organism [265–268]. Of particular note is the substantial activity of ceftolozane-tazobactam against many MDR and extremely drug resistant (XDR) strains of *P. aeruginosa*, including strains that are resistant to ceftazidime and carbapenems [269–273].

Ceftazidime-avibactam also has an expanded, albeit somewhat different spectrum of activity against gram-negative micro-organisms. As with ceftolozane-tazobactam, the clinical efficacy of ceftazidime-avibactam in combination with metronidazole was compared with meropenem for the treatment of patients with IAI in phase II and phase III trials (Supplementary Table H; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/). Success rates in patients treated with this agent were non-inferior to those observed in patients treated with meropenem [274,275]. Ceftazidime-avibactam has activity against most strains of Enterobacteriaceae, including ESBL-producing strains and AmpC β -lactamase-producing strains. Ceftazidime-avibactam is the only currently available β -lactam- β -lactamase inhibitor combination with substantial in vitro activity against KPC-producing Enterobacteriaceae but is not active against MBL-producing micro-organisms [268,276–278]. Ceftazidime-avibactam also has good in vitro activity against *P. aeruginosa*, including a number of MDR and XDR strains [277,279].

Based on the clinical and microbiologic data, the task force concluded that both ceftolozane-tazobactam plus metronidazole and ceftazidime-avibactam plus metronidazole are acceptable regimens for the treatment of patients with IAI. Of some concern, however, was the finding that both agents were less effective than meropenem in subgroups of patients with renal impairment [275,280]. Further research will be needed to clarify the role of these agents in the treatment of patients with IAI. For now, the task force suggests that these regimens be reserved for the treatment of higher-risk patients with CA-IAI or HA-IAI who are either known or strongly suspected of being infected with one of the resistant pathogens that are uniquely susceptible to one of these agents, when other antibiotics are not suitable.

4.4a. We suggest that cefoxitin and cefotetan not be used for the empiric treatment of adults and children with IAI (Grade 2-B).

4.4b. We suggest that cefazolin plus metronidazole not be used for the empiric treatment of adults and children with IAI (Grade 2-C).

4.4c. We suggest that cefuroxime plus metronidazole is an acceptable regimen for the empiric treatment of lower-risk adults and children older than one month with CA-IAI (Grade 2-B).

4.4d. We recommend cefotaxime or ceftriaxone plus metronidazole for the empiric treatment of lower-risk adults and children older than one month with CA-IAI (Grade 1-A).

4.4e. We suggest that ceftazidime plus metronidazole is an acceptable agent for the empiric treatment of adults and children older than one month with IAI (Grade 2-A). We suggest that this regimen be reserved primarily for higher-risk patients because of its broader-spectrum antimicrobial activity (Grade 2-C).

4.4f. We recommend cefepime plus metronidazole for the empiric treatment of adults and children older than one month with IAI (Grade 1-A). We suggest that this regimen be reserved primarily for higher-risk patients because of its broader-spectrum antimicrobial activity (Grade 2-C).

4.4g. We suggest that cefoperazone-sulbactam, where available, is an acceptable agent for the empiric treatment of lower-risk adults and children older than one month with CA-IAI (Grade 2-B).

4.4h. We suggest that ceftolozane-tazobactam plus metronidazole is an acceptable regimen for the empiric treatment of adults with IAI (Grade 2-A). Because of the unique spectrum of activity of ceftolozane-tazobactam against certain ESBL-producing Enterobacteriaceae and against resistant strains of *P. aeruginosa*, we suggest this regimen be used primarily for selected patients with IAI strongly suspected or proven to be caused by one of those resistant pathogens, for whom other agents are not suitable (Grade 2-C).

4.4i. We suggest that ceftazidime/avibactam plus metronidazole is an acceptable regimen for the empiric treatment of adults with IAI (Grade 2-A). Because of the unique spectrum of activity of ceftazidime-avibactam against many ESBL-producing Enterobacteriaceae, particularly KPC-producing Enterobacteriaceae, we suggest this regimen be used primarily for selected patients with IAI strongly suspected or proven to be caused by one of those resistant pathogens, for whom other agents are not suitable (Grade 2-C).

E. Aztreonam-based regimen

Q 4.5. What is the role of an aztreonam-based regimen in the treatment of patients with IAI?

Previous guidelines recommended an aztreonam-based regimen for the treatment of patients with IAI [1,2,4,7]. There have been no RCTs published since 2000 evaluating use of this agent for the treatment of such patients. The previous evidence review [3] identified three RCTs evaluating aztreonam plus clindamycin for the treatment of patients with IAI, all of which demonstrated non-inferiority of this regimen. Aztreonam has no anti-anaerobic activity and is almost devoid of activity against gram-positive organisms [281]. The current and some previous guidelines recommend use of metronidazole rather than clindamycin as the preferred anti-anaerobic agent when

combination regimens are needed. If metronidazole is used instead of clindamycin in conjunction with aztreonam, however, the regimen lacks activity against most gram-positive cocci. Therefore, for use in patients with IAI, aztreonam should be combined with metronidazole and with an agent that has activity against aerobic gram-positive cocci, such as vancomycin.

Although aztreonam has good in vitro activity against many gram-negative bacteria, it has relatively poor activity against ESBL-producing strains of *E. coli* and *K. pneumoniae* [282]. Aztreonam appears to be safe for use in patients with serious allergic reactions to other β -lactams [283]; thus, an aztreonam-based regimen may be of utility in such patients when other β -lactam agents cannot be used.

Overall, the task force believes that the regimen of aztreonam in combination with metronidazole and vancomycin is acceptable for treatment of patients with IAI, particularly those patients with serious β -lactam allergies for whom other alternatives may not be suitable. Use of alternative agents would be preferable, however, when such an option is available, because of the lack of contemporary data on the efficacy of this combination regimen. The task force also suggests that this aztreonam-based regimen be reserved primarily for higher-risk patients, because of its broad-spectrum activity against gram-negative pathogens.

4.5. We suggest that the regimen of aztreonam plus metronidazole plus vancomycin is acceptable for the empiric treatment of adults and children older than one month with IAI (Grade 2-B). We suggest this regimen be reserved primarily for higher-risk patients, particularly those with serious β -lactam allergies, because of its broader-spectrum activity against gram-negative pathogens (Grade 2-C).

F. Carbapenem

Q 4.6a. What is the role of ertapenem in the treatment of patients with IAI?

Q 4.6b. What is the role of the broad-spectrum carbapenem, doripenem, in the treatment of patients with IAI?

Q 4.6c. What is the role of the broad-spectrum carbapenems, imipenem-cilastatin, and meropenem, in the treatment of patients with IAI?

Ertapenem was been recommended for the treatment of patients with IAI in previous guidelines [2,4,5]. The task force identified nine RCTs published since 2000 evaluating use of this agent as monotherapy for IAI (Supplementary Table I; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [205,214,220,226,228,230,246,247,284], one of which [226] was reviewed before publication in the previous evidence review [3]. Success rates with ertapenem have been similar to those of comparators except in one trial, in which ertapenem was found to be superior to ampicillin-sulbactam [214]. Ertapenem is active against the most common strains of ESBL-producing Enterobacteriaceae but is not active against KPC-producing and MBL-producing strains [265,285]. Increased use of carbapenems may lead to selection of gram-negative pathogens expressing these resistance genes. Thus far, little decline in the susceptibilities of intra-abdominal isolates of *E. coli* to carbapenems has been detected, but there have been some decrease in *K pneumoniae* susceptibilities [28]. Ertapenem does not have appreciable antibacterial activity against *Enterococcus* spp. or *P. aeruginosa* [286,287].

The task force concluded that ertapenem is an acceptable agent for monotherapy for lower-risk patients with CA-IAI. Because its spectrum of activity is narrower than that of other carbapenems, the task force recommends use of broader-spectrum carbapenems for empiric treatment of higher-risk patients with CA-IAI and those with HA-IAI, although treatment could be de-escalated to ertapenem if resistant pathogens were not identified in definitive cultures. Ertapenem is also a good option for treating patients in areas of the world where there is a high prevalence of ESBL-producing *E. coli* in the community.

The broad-spectrum carbapenems—doripenem, imipenem-cilastatin, and meropenem—have been recommended for the treatment of patients with IAI in previous guidelines as they have become available [1,2,4,5]. Doripenem was compared with meropenem for the treatment of adult patients with IAI in two large RCTs (Supplementary Table I; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [288,289]. No significant differences were observed in clinical success rates between the two carbapenems. An aborted clinical trial was also reported comparing doripenem with meropenem in pediatric patients with IAI, nearly all of whom had perforated appendicitis [290]; both agents appeared to be effective in the limited number of patients completing this trial before it was terminated. Doripenem, however, has not been approved for use in pediatric patients [291].

Imipenem-cilastatin has been evaluated in seven RCTs published since 2000 (Supplementary Table I; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [227,255,292–296] and in 19 RCTs cited in the previous evidence review [3]. In one small recent study, success rates in patients treated with imipenem-cilastatin were significantly lower than in patients treated with cefepime plus metronidazole [255]. Among studies reviewed previously, one found imipenem-cilastatin superior to comparators [211]; however, two found imipenem-cilastatin inferior to comparators [45,297], although a higher severity of illness in patients receiving imipenem-cilastatin may have accounted for the decreased efficacy observed in one trial [45].

Meropenem has also been evaluated extensively in RCTs, including eight published since 2000 (Supplementary Table I; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [263,264,274,275,288–290,292]. There were no statistically significant differences in outcomes between meropenem and comparators in these recent trials. In 11 RCTs reviewed previously [3], two found significant differences between meropenem and comparators, with one favoring meropenem and one favoring the comparator [243,244].

As with ertapenem, the broad-spectrum carbapenems generally retain activity against the common ESBL-producing strains of gram-negative bacteria, but not against KPC- or MBL-producing strains [286,287]. Increased resistance to broad-spectrum carbapenems has been observed for some gram-negative microorganisms, however, particularly *P. aeruginosa* and *A. baumannii*, which may be a reflection of increased reliance on carbapenems in areas of high prevalence of ESBL-producing bacteria [298]. Based on the available data, the task force recommends the use of doripenem, imipenem-cilastatin, or meropenem for the

treatment of adult patients with IAI, and imipenem-cilastatin or meropenem for the treatment of pediatric patients with IAI. Because of their broad-spectrum activity, their use as empiric therapy should be restricted to higher-risk patients with CA-IAI or HA-IAI.

4.6a. We recommend ertapenem for the empiric treatment of lower-risk adults and children older than one month with CA-IAI (Grade 1-A).

4.6b. We recommend doripenem for the empiric treatment of adults with IAI (Grade 1-A). We do not recommend the use of doripenem for empiric treatment of children older than one month with IAI unless no other options are available (Grade 1-C). We suggest that this agent be reserved primarily for higher-risk patients because of its broader-spectrum antimicrobial activity (Grade 2-C).

4.6c. We recommend imipenem-cilastatin and meropenem for the empiric treatment of adults and children older than one month with IAI (Grade 1-A). We suggest that these agents be reserved for higher-risk patients because of their broader-spectrum antimicrobial activity (Grade 2-C).

G. Fluoroquinolones and fluoroquinolone-based regimens

Q 4.7a. What is the role of moxifloxacin in the treatment of patients with IAI?

Q 4.7b. What is the role of ciprofloxacin plus metronidazole in the treatment of patients with IAI?

Q 4.7c. What is the role of levofloxacin plus metronidazole in the treatment of patients with IAI?

The previous guideline recommended moxifloxacin monotherapy for the treatment of patients with IAI [4]. Moxifloxacin has been evaluated in five RCTs published since 2000 (Supplementary Table J; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [215,229,250,251,284]. No significant differences were observed in success rates using moxifloxacin compared with other agents in any of these trials. A meta-analysis also found moxifloxacin monotherapy to be non-inferior to treatment with comparators (Supplementary Table K; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [299]. Moxifloxacin has not been evaluated in pediatric patients. Concerns have been raised about resistance of anaerobic micro-organisms to moxifloxacin, but a recent analysis showed no correlation between anaerobic susceptibility data and clinical outcome with use of moxifloxacin [300]. Similarly, the decreased susceptibility of *E. coli* and other gram-negative organisms to ciprofloxacin and levofloxacin [28] would be expected to apply to moxifloxacin as well. These decreases in susceptibility, however, have not led to obvious increases in failure rates in recent clinical trials.

Based on the available data, the task force still recommends use of moxifloxacin as monotherapy for lower-risk patients with CA-IAI, particularly for patients who have serious or life-threatening reactions to β -lactam antibiotic agents. Other agents would be preferable, however, if there is an appreciable prevalence of fluoroquinolone-resistant *E. coli* in the local environment.

The regimen of ciprofloxacin plus metronidazole was recommended for use in patients with IAI in previous guidelines [2,4,5]. Two RCTs evaluating ciprofloxacin plus

metronidazole have been published since 2000 (Supplementary Table J; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [247,249] these are in addition to four studies included in the previous evidence review [3]. Success rates using ciprofloxacin plus metronidazole have been equivalent to comparators in all of these studies, with two of the older studies reporting a significantly higher success rate with this regimen [245,301]. A meta-analysis of RCTs reported higher success rates with use of ciprofloxacin plus metronidazole than comparators for treatment of patients with IAI (Supplementary Table K; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [302]. Although ciprofloxacin has been approved for certain pediatric indications, concern has been expressed about potential side effects in pediatric patients. Recent reviews have concluded that this agent is relatively safe to use in children [303,304]. The increasing world-wide resistance of *E. coli* to ciprofloxacin is also of concern [28], although it has not been clearly associated with decreased clinical responses to fluoroquinolones in patients with IAI.

Based on all data, the task force concludes that ciprofloxacin plus metronidazole is a reasonable option for the treatment of lower-risk patients with CA-IAI. In geographic localities with a high prevalence of fluoroquinolone-resistant *E. coli*, however, a non-fluoroquinolone-based regimen would be preferable. For higher-risk patients, the task force believes that ciprofloxacin should be used primarily in a pathogen-directed fashion, only if peritoneal cultures reveal susceptible gram-negative micro-organisms. As with other fluoroquinolones, use of ciprofloxacin plus metronidazole may be an appropriate option in patients who cannot receive β -lactam antibiotic agents.

Levofloxacin plus metronidazole has been used for the treatment of patients with IAI, but its use has not been reported in any published RCT. Levofloxacin has not received FDA approval for treatment of patients with IAI. Based on its spectrum of activity, it would be expected to have efficacy similar to that of other recommended fluoroquinolones. Similar to ciprofloxacin, levofloxacin has been approved by the FDA for certain pediatric indications. As with other fluoroquinolones, resistance of *E. coli* to levofloxacin is increasing worldwide [28]. Because levofloxacin may be the sole fluoroquinolone on many hospital formularies, the task force has included levofloxacin plus metronidazole as an acceptable regimen for the treatment of lower-risk patients with CA-IAI. Because of the lack of data documenting its efficacy for treating patients with IAI, however, its use should be limited to situations in which patients cannot be treated with alternative agents, and levofloxacin is the only fluoroquinolone available because of formulary restrictions.

4.7a. We recommend moxifloxacin as an acceptable agent for the empiric treatment of lower-risk adults with CA-IAI, although it should be used with caution in areas of the world where there is a high incidence of fluoroquinolone-resistant E. coli (Grade 1-A). We do not recommend the use of moxifloxacin for empiric treatment of children with IAI unless no other options are available (Grade 1-C).

4.7b. We recommend ciprofloxacin plus metronidazole as an acceptable regimen for the empiric treatment of lower-risk adults with CA-IAI, although it should be used with caution in

areas of the world where there is a high incidence of fluoroquinolone-resistant *E. coli* (Grade 1-A). We suggest that ciprofloxacin plus metronidazole may be used for empiric treatment of children older than one month CA-IAI, if other options are not suitable (Grade 2-B).

4.7c. We suggest that levofloxacin plus metronidazole is an acceptable regimen for the empiric treatment of lower-risk adults with CA-IAI, if use of a fluoroquinolone is warranted and it is the only fluoroquinolone available for use (Grade 2-C). We suggest that levofloxacin plus metronidazole may be used for empiric treatment of children older than one month with IAI, if other options are not suitable (Grade 2-C).

H. Tigecycline

Q 4.8. What is the role of tigecycline in the treatment of patients with IAI?

Tigecycline is a glycylcycline that is less susceptible to some of the common mechanisms producing resistance of bacteria to tetracyclines [305]. It was recommended for empiric use in lower-risk patients with CA-IAI in the previous guideline [4]. Use of tigecycline in the treatment of patients with IAI has been described in five RCTs published since 2000 (Supplementary Table L; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [252, 253, 294–296]. None of these demonstrated any statistically significant difference in success rates between tigecycline and other agents. In meta-analyses of these RCTs, there was a trend toward lower clinical success rates with tigecycline, which did not reach statistical significance (Supplementary Table M; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [306, 307]. Aggregated data from clinical trials using tigecycline for any indication, however, revealed higher deaths in tigecycline-treated patients, which was significant in some of the analyses [306–310]. These data resulted in a black box warning from the FDA indicating that tigecycline should be reserved for situations in which other agents are not suitable.

Tigecycline has in vitro activity against many ESBL-producing strains of Enterobacteriaceae and *A. baumannii*, although not against *P. aeruginosa* [311, 312]. In observational studies, tigecycline has been successful in the treatment of patients with IAI likely to harbor resistant micro-organisms [313–315]; however, tigecycline was frequently administered in conjunction with other effective agents in these studies, so its efficacy as a single agent remains uncertain [316–318]. Tigecycline could also offer a carbapenem-sparing option for the treatment of ESBL-producing strains of Enterobacteriaceae.

Overall, the task force concluded that the possibility of lower efficacy and higher deaths argued against a continued recommendation for the routine use of tigecycline as an empiric agent to treat patients with IAI. There are clinical scenarios in which pathogen-directed use of tigecycline for the management of resistant bacteria could be an option, particularly in patients who cannot be treated with other agents, however.

4.8a. We do not recommend tigecycline for the empiric treatment of patients with IAI under most circumstances (Grade 1-B). We suggest that tigecycline may be of use in the treatment of adult patients with resistant pathogens, particularly as a component of a combination regimen, when other agents are not suitable (Grade 2-B).

I. Anti-anaerobic agents

Q 4.9a. What is the role of metronidazole as an anti-anaerobic agent in combined regimens for the treatment of patients with IAI?

Q 4.9b. What is the role of clindamycin as an anti-anaerobic agent in combined regimens for the treatment of patients with IAI?

Metronidazole is commonly used for the treatment of patients with IAI to provide anti-anaerobic activity, if the agent being used to treat gram-negative micro-organisms lacks such activity. Nearly all recent RCTs have used metronidazole as the anti-anaerobic agent in combination regimens [203–205, 225, 246, 247, 249–255, 263, 264, 274, 275, 319]. Metronidazole was also used extensively in studies reviewed previously [3]. There are no current data and only limited older data from RCTs comparing the efficacy of metronidazole with other anti-anaerobic agents; however, the breadth of studies using this agent attests to its efficacy. The development of major resistance of anaerobic micro-organisms to metronidazole has yet to be observed [236]. Overall, the task force concluded that metronidazole remains the preferred agent for management of anaerobic bacteria when combination regimens are used for the treatment of patients with IAI.

The use of clindamycin as an anti-anaerobic agent to treat patients with IAI has fallen into disfavor. Since 2000, only three RCTs using clindamycin have been published [204, 206, 320], all in pediatric patients with perforated appendicitis. Clindamycin was used much more frequently in studies published before that date [3]. Use of clindamycin for treatment of patients with IAI has been curtailed because of increased in vitro resistance of anaerobic bacteria, particularly *B. fragilis*, to this agent [236, 321] and the heightened concern for the development of *Clostridium difficile*-associated disease after exposure to clindamycin [322, 323]. Based on these considerations and the availability of alternative agents, the task force considers clindamycin to be a second-line anti-anaerobic agent in combination regimens, although it is an option if metronidazole cannot be used.

4.9a. We recommend metronidazole as the preferred anti-anaerobic agent to be used in combination regimens for the empiric treatment of IAI in adults and children older than one month (Grade 1-B).

4.9b. We suggest that clindamycin not be used as an anti-anaerobic agent in combination regimens for the empiric treatment of IAI in adults and children older than one month (Grade 2-B) unless other agents cannot be used. We suggest use of this agent is acceptable in children under one month of age (Grade 2-C).

J. Anti-enterococcal and anti-staphylococcal agents

Q 4.10a. What is the role of ampicillin in the treatment of patients with IAI?

Q 4.10b. What is the role of vancomycin in the treatment of patients with IAI?

Q 4.10c. What are the roles of linezolid and daptomycin in the treatment of patients with IAI?

Treatment of *Enterococcus* spp. should be considered in higher-risk patients with CA-IAI and those with HA-IAI. Nearly all strains of *E. faecalis*, including some strains of

vancomycin-resistant *E. faecalis*, are susceptible to ampicillin [89,324]. This agent is used frequently for the treatment of patients with serious infections because of *E. faecalis*, such as endocarditis or bacteremia [325,326]. Ampicillin has been used frequently also as a component of combination (“triple”) antibiotic therapy for IAI, particularly in pediatric patients, although its necessity for that has not been demonstrated [204,327,328]. The task force has concluded that ampicillin is an acceptable agent for managing a proven or suspected IAI because of *E. faecalis* in higher-risk patients, if the selected regimen lacks activity against that micro-organism.

In IAI, *E. faecium* is increasingly encountered as a pathogen, particularly in patients with HA-IAI. In contrast to *E. faecalis*, nearly all strains of *E. faecium* are resistant to ampicillin [89,324,329–332]. Although the incidence of VRE is increasing, vancomycin-susceptible strains of *E. faecium* can be treated with vancomycin or other glycopeptides such as teicoplanin [324,329,331,332]. The efficacy of empiric vancomycin or teicoplanin as anti-enterococcal agents in patients with IAI has not been evaluated definitively. Broad experience has been gained with use of glycopeptides to manage serious enterococcal infections, however. Therefore, the task force considers vancomycin (or teicoplanin where available) to be the first-line agent for treating most patients with HA-IAI proven or suspected to be because of vancomycin-susceptible strains of *E. faecium*.

Vancomycin should not be used as empiric anti-enterococcal therapy in patients known to be infected or considered to be at high risk for infection with VRE. Ampicillin may be an option for patients with IAI from vancomycin-resistant strains of *E. faecalis*, although susceptibilities should be monitored [333,334]. For patients with vancomycin-resistant *E. faecium*, linezolid or daptomycin are the preferred agents. Both linezolid and daptomycin have good in vitro activity against vancomycin-resistant *E. faecium* [322,329,333,335], and linezolid has been approved by the FDA for the treatment of patients with infections from this resistant pathogen. Observational studies have reported that both agents have been used successfully to treat patients with various types of infections because of VRE, including HA-IAI [115,334–337]. Recent meta-analyses of patients with VRE bacteremia suggested lower mortality rates after treatment with linezolid rather than daptomycin; however, the component studies used in these analyses were all retrospective in nature [338,339]. Because of the lack of prospective data, the task force did not attempt to indicate a preference between linezolid and daptomycin for the treatment of IAI from VRE.

Although relatively uncommon, MRSA strains are encountered in patients with HA-IAI, particularly those with post-operative HA-IAI [23,24,26,62,340–342]. There are no published studies specifically evaluating antimicrobial therapy for the treatment of patients with IAI involving MRSA. For patients with serious infections from MRSA, a glycopeptide is frequently described as the preferred agent [334,343–345]. Thus, vancomycin or teicoplanin (where available) would be appropriate choices for empiric therapy of HA-IAI when MRSA is a suspected or proven pathogen. Concerns have been expressed, however, about the efficacy of glycopeptides for managing MRSA infections [345–349] and the nephrotoxicity of these agents [350–352]. Among other agents with activity against MRSA [345,353–355], the task

force considered linezolid and daptomycin to be the most reasonable alternatives. Linezolid is at least as effective as vancomycin for the management of infections from MRSA, with some data suggesting superiority [344,348,355–358]. There are some observational data describing successful use of linezolid to treat patients with IAI from MRSA [336]. Daptomycin, likewise, appears to be equivalent to vancomycin for the management of serious MRSA infections [337,354,359] and could be used to treat patients with IAI from MRSA.

4.10a. We suggest that ampicillin may be used for treatment of IAI in adults and children to provide pathogen-directed therapy against susceptible enterococcal strains (Grade 2-B).

4.10b. We suggest that vancomycin may be used for treatment of IAI in adults and children to provide empiric or pathogen-directed therapy for suspected or proven infections from vancomycin-susceptible *E. faecium* or methicillin-resistant *S. aureus* (MRSA) (Grade 2-B). We suggest inclusion of vancomycin in an aztreonam-based regimen for coverage of gram-positive organisms (Grade 2-B).

4.10c. We suggest that linezolid and daptomycin may be used for management of IAI in adults and children to provide empiric or pathogen-directed therapy for suspected or proven infections from vancomycin-resistant *Enterococcus* spp., and as an alternative to vancomycin for suspected or proven infections because of MRSA (Grade 2-B).

K. Antifungal agents

Q 4.11a. What is the role of amphotericin B and its lipid formulations in the treatment of patients with IAI?

Q 4.11b. What is the role of fluconazole in the treatment of patients with IAI?

Q 4.11c. What is the role of voriconazole in the treatment of patients with IAI?

Q 4.11d. What is the role of echinocandins (anidulafungin, caspofungin, micafungin) in the treatment of patients with IAI?

The antifungal agents most commonly used to treat patients with HA-IAI because of *Candida* spp. include the polyene amphotericin B and its various formulations; azoles, including fluconazole and voriconazole; and echinocandins, including anidulafungin, caspofungin, and micafungin. Most RCTs evaluating these agents have enrolled primarily patients with candidemia and only limited numbers of patients with candidal IAI. In a number of these RCTs, outcomes of these latter patients have not been reported separately.

Use of amphotericin B has fallen into disfavor because of toxicity, despite the development of alternative formulations designed to combat that problem [360]. Two RCTs published since 2000 reported lower success rates in small numbers of adult patients with intra-abdominal candidiasis treated with either amphotericin B or liposomal amphotericin B versus those treated with caspofungin or micafungin (Supplementary Table N; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [361,362]. In a previously reviewed study [3], success rates in treating a confirmed candidal IAI appeared higher with amphotericin B than with fluconazole, but only very small numbers of patients were treated with either agent [363]. Among all patients with invasive candidal infections, a meta-analysis found no overall difference in treatment failure comparing amphotericin B

formulations with echinocandins or azoles, but a better safety profile with echinocandins and less nephrotoxicity with fluconazole [364].

Fluconazole has been used extensively to treat patients with intra-abdominal candidal infections, but there are only limited new prospective data regarding this use. One RCT found higher success rates with anidulafungin compared with fluconazole in patients with invasive candidiasis, primarily from an abdominal source (Supplementary Table N; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [365]. In the previous evidence review [3], one RCT showed that pre-emptive administration of fluconazole was more effective than placebo for preventing *Candida* peritonitis [366]; however, as indicated above, another RCT suggested fluconazole was less effective than amphotericin B in a very limited number of patients with abdominal candidiasis [363]. In patients with any type of candidal infection, the meta-analysis by Gafter-Gvili et al. [364] identified a trend toward higher treatment failure rates with use of fluconazole, but this did not reach statistical significance.

There are few data available regarding management of intra-abdominal candidiasis with other azoles. Voriconazole has better in vitro activity than fluconazole against *C. glabrata* and *C. krusei*, although not all strains are susceptible [367–369]. Voriconazole appeared to be equivalent to amphotericin B followed by fluconazole for the management of candidal infections in non-neutropenic patients, but the results in the very small number of patients with invasive candidiasis rather than candidemia were not reported separately [370].

Several RCTs have suggested that echinocandins are at least as effective as other agents for the treatment of patients with IAI from *Candida* spp. [361,362,365,371]. An uncontrolled trial of pre-emptive caspofungin suggested that this prevented an overt clinical infection from *Candida* in nearly all patients [372]. For the management of candidal infections in general, caspofungin and micafungin appear to be non-inferior to amphotericin B formulations, and anidulafungin may be superior to fluconazole [364,373]. Adverse events appear to be lower with echinocandins than with polyenes or azoles. A cost-effectiveness analysis has suggested lower overall costs with use of an echinocandin compared with other agents, because of reduced adverse events, including persistent infection [374]. Guidelines by the IDSA recommend use of echinocandins over fluconazole in patients with moderately severe to severe illness from *Candida* [375].

Overall, the task force concluded that echinocandins can be recommended for the treatment of severely ill patients suspected or proven to have an IAI from *Candida*. Fluconazole can be used to treat less severely ill patients infected with *C. albicans*, but voriconazole or an echinocandin would be preferred for the treatment of patients infected with fluconazole-resistant species of *Candida*. Because less toxic alternatives are available, the task force does not recommend routine use of polyenes for treatment of patients with candidal IAI.

4.11a. We do not recommend routine use of amphotericin B or its lipid formulations for empiric or pathogen-directed treatment of adults or children with intra-abdominal candidiasis (Grade 2-B).

4.11b. We suggest use of fluconazole for pre-emptive management of IAI in non-critically ill adults and children

who are at high risk for intra-abdominal candidiasis, and for pathogen-directed treatment of non-critically ill patients infected with susceptible strains of C. albicans (Grade 2-B).

4.11c. We suggest use of voriconazole for empiric or pathogen-directed management of IAI in non-critically ill adults and children older than one month who are suspected or proven to be infected with strains of Candida that are not susceptible to fluconazole (Grade 2-B).

4.11d. We recommend an echinocandin (anidulafungin, caspofungin, or micafungin) for empiric or pathogen-directed management of IAI in severely ill adults and children older than one month who are suspected or proven to be infected with Candida spp. (Grade 1-B).

5. Oral antimicrobial agents

Q 5.1. When can oral antimicrobial agents be used in the treatment of patients with IAI?

Q 5.2a. What is the role of oral amoxicillin-clavulanic acid in the treatment of patients with IAI?

Q 5.2b. What is the role of oral moxifloxacin in the treatment of patients with IAI?

Q 5.2c. What is the role of oral ciprofloxacin plus metronidazole in the treatment of patients with IAI?

Q 5.2d. What other oral antimicrobial agents can potentially be used for the treatment of patients with IAI?

An accepted principle of antimicrobial stewardship is conversion from IV to oral anti-infective agents when the patient's condition permits [196]. This principle can be applied to patients with IAI as well and was recommended in previous guidelines [2,4,5]. As with IV antimicrobial agents, oral agents should have activity against the common aerobic gram-negative bacilli, gram-positive cocci, and anaerobic micro-organisms involved in these infections. Although the use of oral agents in patients with IAI is frequently not feasible immediately after a source control procedure because of gastrointestinal intolerance, it is often possible to switch the patient to oral agents later, once the patient has return of gastrointestinal function.

A number of RCTs have permitted use of oral antibiotics as a substitute for IV antibiotics. Only a few of these have directly tested the hypothesis that a switch to oral agents is equivalent to use of exclusive IV therapy for patients with IAI. In two studies, pediatric subjects were randomized to a regimen of IV antibiotics only or to a regimen of IV antibiotics in which a switch to oral amoxicillin-clavulanic acid was allowed after three or four days of IV therapy (Supplementary Table O; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [319,320]. An older study, reviewed previously [3], randomized one group of patients to an arm in which oral ciprofloxacin plus metronidazole was permitted as continuation therapy [376]. Outcomes were similar in patients allowed the oral switch and those who received IV antibiotics only.

Indirect evidence in support of a switch to oral antibiotic agents has come from additional RCTs in which patients were allowed to receive oral agents [215,217,229,245–247,249,251,288,289,301,377]. It should be noted that many of these trials allowed for prolonged antimicrobial therapy, well beyond the previous recommendation of a maximum four to seven days of total antimicrobial therapy [2,4] or the current recommendation of a maximum of four days in adult

patients or five days in pediatric patients (Sections 10 and 13). Thus, much of these data on use of oral antimicrobial therapy are irrelevant to current recommendations. Patients in these RCTs were frequently switched to oral agents different from the IV ones they had received, and in some cases to oral agents from an entirely different class of antibiotic. Thus, there does not appear to be an obligatory need to continue the same agent or agents when making a switch to oral therapy. Overall, the task force concluded that use of oral antimicrobial therapy is a valid option, but only if it shortens the course of IV therapy, and not if it is used to prolong the total duration of antimicrobial therapy beyond current recommendations.

Oral amoxicillin-clavulanic acid was directly evaluated as step-down therapy in two small RCTs of pediatric patients with perforated appendicitis [319,320], and allowed as step-down therapy in a number of other trials [217,229,251, 288,301,320,377]. No increase in treatment failure was observed in patients who were switched to this oral agent. There is a relatively high prevalence of *E. coli* resistant to amoxicillin-clavulanic acid throughout the world, however [219]. Thus, the task force would recommend some caution when using this agent for oral step-down therapy, and it should not be used if culture results reveal a resistant organism.

A switch from IV to oral moxifloxacin was permitted in several RCTs testing this agent [214,228,250]. There was no indication of any adverse events associated with a switch to oral moxifloxacin therapy. No trials directly compared patients permitted oral therapy with those assigned to receive IV therapy only, however. Use of oral moxifloxacin has not been studied in pediatric patients with IAI.

One relatively large RCT included in the previous evidence review [3] directly compared patients permitted a switch to oral ciprofloxacin plus metronidazole with patients who received IV therapy only with ciprofloxacin plus metronidazole or with imipenem-cilastatin. No significant differences in outcome were demonstrated between any of the study groups [376]. Additional trials also permitted a switch to oral ciprofloxacin plus metronidazole as an option [217,245–247,249,301]. Clinical outcomes were not adversely affected by this switch to oral agents. Use of oral ciprofloxacin in pediatric patients appears to be relatively safe [303,304] and can be considered when other agents are not suitable.

There is relatively scant evidence with regard to the use of other oral agents for the treatment of patients with IAI. Oral first-, second-, and third-generation cephalosporins, including cephalexin, cefadroxil, cephadrine, cefuroxime, cefaclor, cefprozil, cefdinir, and cefpodoxime, in combination with metronidazole, are potential options, as they have reasonable activity against non-ESBL-producing strains of *E. coli* [378–385]. One small RCT found no adverse effect of a change from IV therapy to oral cephalexin, but this switch occurred fairly late during a prolonged course of antibiotic treatment [386]. Oral levofloxacin in combination with metronidazole is also a potential option, but there are no published RCTs describing use of either IV or oral levofloxacin in patients with IAI. Use of oral trimethoprim-sulfamethoxazole plus metronidazole as continuation therapy appeared to be successful in two observational studies in pediatric patients, but this switch also occurred fairly late in the antibiotic course [387,388].

5.1. We recommend use of selected oral agents with good bioavailability as a substitute for IV agents in the treatment of

patients with IAI when the patient has return of adequate gastrointestinal function. Oral antibiotics should only be used to complete a short course of treatment and not to prolong antimicrobial use beyond current recommendations for duration of therapy (Grade 1-B).

5.2a. We suggest use of oral amoxicillin-clavulanic acid as an acceptable regimen to complete a short course of antimicrobial therapy for the treatment of IAI in adults and children older than one month with IAI (Grade 2-B).

5.2b. We suggest use of oral moxifloxacin as an acceptable regimen to complete a short course of antimicrobial therapy for the treatment of IAI in adults (Grade 2-B). We do not recommend the use of oral moxifloxacin for the treatment of IAI in children, unless no other option is available (Grade 1-B).

5.2c. We recommend use of oral ciprofloxacin plus metronidazole as an acceptable regimen to complete a short course of antimicrobial therapy for the treatment of IAI in adults (Grade 1-B). We suggest that oral ciprofloxacin plus metronidazole may be used to complete a short course of antimicrobial therapy for the treatment of IAI in children older than one month, if other options are not suitable (Grade 2-B).

5.2d. We suggest that oral levofloxacin plus metronidazole, an oral first-, second-, or third-generation cephalosporin plus metronidazole, or oral trimethoprim-sulfamethoxazole plus metronidazole are potential regimens that could be used selectively to complete a short course of antibiotic therapy for the treatment of IAI in adults and children older than one month, if other oral agents are not suitable (Grade 2-C).

6. Selection of empiric antimicrobial therapy for adult patients with CA-IAI

A. Lower-risk patients with CA-IAI

Q 6.1. What are the general principles for selection of empiric antimicrobial therapy of CA-IAI in lower-risk patients?

Q 6.2a. What are the preferred agents for initial empiric antimicrobial therapy of CA-IAI in lower-risk patients?

Q 6.2b. Should patients with perforated appendicitis be treated with different empiric antimicrobial agents than other lower-risk patients with CA-IAI?

The established principle of antimicrobial therapy for patients with IAI has been to administer agents with activity against gram-negative Enterobacteriaceae, aerobic streptococci, and obligate enteric anaerobes [1,2,4,5]. As detailed in Section 4, a large number of antimicrobial agents or regimens meet these criteria, with efficacy information about many of them available from RCTs. In these clinical trials, lower-risk patients with CA-IAI have predominated, even in those evaluating broad-spectrum antimicrobial regimens [3,389]. Based on these trials, the breadth of antimicrobial coverage does not appear to have a major impact on clinical outcomes in lower-risk patients with CA-IAI. Several RCTs published since 2000 have compared regimens with and without anti-pseudomonal activity [204,205,220,225,228–230,294–296] and with or without anti-enterococcal activity [204,205,225,228–230,252, 255,274].

By and large, these trials have not demonstrated significant differences in outcome when comparing narrow-spectrum and broad-spectrum regimens. A detailed meta-analysis concluded that antimicrobial regimens used for secondary peritonitis were all essentially equivalent [390]. A large database study

did not identify any major differences in outcome comparing narrow-spectrum regimens with broad-spectrum regimens, as long as the regimen covered standard gram-negative Enterobacteriaceae and obligate anaerobes [192].

There are relatively little data available regarding use of antifungal agents in lower-risk patients with CA-IAI. Typically, RCTs have not permitted concomitant use of antifungal therapy. Treatment failures attributed to a lack of antifungal coverage, however, have rarely been evident in these trials. Moreover, microbiologic studies indicate that isolation of *Candida* spp. is quite uncommon in patients with CA-IAI [21,24,391–394].

Based on these data, the task force supports previous guidelines on avoiding use of broad-spectrum antimicrobial therapy, including antifungal therapy, in lower-risk patients with CA-IAI. Limiting the exposure of lower-risk patients with CA-IAI to broad-spectrum antimicrobial therapy would be consistent with the goals of antimicrobial stewardship programs [196,395,396]. In keeping with the goal of using narrow-spectrum agents for lower-risk patients with CA-IAI, the task force recommends use of agents that may not have much activity against *Pseudomonas* spp. or *Enterococcus* spp. These include ertapenem as monotherapy, and cefotaxime or ceftriaxone with metronidazole as combination therapy. Where available, cefoperazone-sulbactam is also an option. The use of cefuroxime plus metronidazole is reasonable but has been less well supported by contemporary data. Ticarcillin-clavulanic acid would be acceptable but will now only be an option if production resumes.

Use of fluoroquinolone-based regimens requires additional consideration. The finding that nearly 30% of *E. coli* strains isolated from patients with IAI in North America are resistant to fluoroquinolones is of concern [28], although the prevalence of resistant strains in lower-risk patients with CA-IAI may be lower than this. Recent clinical studies have described good results using moxifloxacin alone or ciprofloxacin plus metronidazole in patients with CA-IAI, despite being performed while there was increasing in vitro resistance of Enterobacteriaceae to fluoroquinolones [215,229,247,249–251,284]. Thus, the task force recommends moxifloxacin or ciprofloxacin plus metronidazole for use in lower-risk patients with CA-IAI, but would prefer that such use be restricted primarily to patients with contraindications to the use of β -lactam antibiotics. A paucity of data exists supporting use of levofloxacin plus metronidazole for treatment of patients with IAI, and it has not been approved by the FDA for this indication. Because it may be the only fluoroquinolone available on some hospital formularies, however, the regimen of levofloxacin plus metronidazole is acceptable under those circumstances.

Table 9 outlines these recommendations for selection of empiric antimicrobial therapy in lower-risk patients with CA-IAI. In regions of the world where there is a much higher prevalence of fluoroquinolone-resistant and ESBL-producing strains of Enterobacteriaceae in the community [28,235,397], these recommendations would likely need to be modified, as will be discussed further in Section C under recommendations 6.6.

Perforated appendicitis is usually the most common cause of IAI among participants in clinical trials [3]. Overall deaths are lower in these patients than in patients with IAI from other sources, even after adjusting for age and co-morbidities [59,75,187,398]. Post-operative infections, however, including intra-abdominal abscesses, occur in a substantial number

TABLE 9. RECOMMENDED EMPIRIC ANTIMICROBIAL REGIMENS FOR PATIENTS WITH COMMUNITY-ACQUIRED INTRA-ABDOMINAL INFECTION

<i>Lower-risk patients</i> ^{a,b}	<i>Higher-risk patients</i>
Single agents	
Ertapenem	Piperacillin-tazobactam
Moxifloxacin ^c	Doripenem ^f
	Imipenem-cilastatin
	Meropenem ^f
Combination regimens	
Cefotaxime or ceftriaxone plus metronidazole ^d	Cefepime plus metronidazole ^{f,g}
Ciprofloxacin plus metronidazole ^{c,e}	Aztreonam plus metronidazole plus vancomycin ^h

^aTicarcillin-clavulanate is no longer available in the United States.

^bCefoperazone-sulbactam is also an option, where available.

^cUse of fluoroquinolones is suggested primarily for patients with significant reactions to β -lactam antibiotic agents.

^dCefuroxime plus metronidazole is also an option, but is less well supported by contemporary data.

^eIf levofloxacin is the only fluoroquinolone available on a formulary, it may be substituted for ciprofloxacin. There is little evidence with regard to its efficacy, and it is not approved by the Food and Drug Administration for treatment of patients with complicated intra-abdominal infection.

^fUse of an agent such as ampicillin or vancomycin effective against *Enterococcus* spp. can be considered in patients with severe sepsis-septic shock and other higher-risk patients who receive doripenem or meropenem, and should be added to a cephalosporin-based regimen.

^gCeftazidime plus metronidazole is also an option, but is less well supported by contemporary data.

^hAztreonam plus metronidazole plus vancomycin is an option for patients with significant reactions to β -lactam antibiotic agents, but is less well supported by contemporary data.

of patients with appendiceal perforations [187,399–401]. These treatment failures are associated with longer hospitalizations and increased use of resources [192]. Thus, the task force believes that the same antimicrobial regimens outlined for use in lower-risk patients with CA-IAI apply to lower-risk patients with perforated appendicitis, and that potentially lower cost but inferior regimens should not be substituted.

6.1. We recommend treatment of CA-IAI in lower-risk patients with narrower-spectrum antimicrobial agents having activity against the usual gram-negative Enterobacteriaceae, aerobic streptococci, and obligate anaerobic microorganisms associated with these infections (Grade 1-A). We recommend against the use of broader-spectrum or additional agents specifically to provide anti-pseudomonal or anti-enterococcal coverage (Grade 1-A). We suggest that antifungal coverage is unnecessary for management of CA-IAI in lower-risk patients (Grade 2-B).

6.2a. We recommend cefotaxime or ceftriaxone plus metronidazole or ertapenem as the preferred antimicrobial agents for the management of CA-IAI in lower-risk patients (Grade 1-A). We recommend ciprofloxacin plus metronidazole or moxifloxacin monotherapy for the management of CA-IAI in lower-risk patients who have serious β -lactam allergies (Grade 1-A), and suggest levofloxacin plus metronidazole as an alternative if no other fluoroquinolone is available (Grade 2-C). We suggest use of cefuroxime plus metronidazole (Grade

2-B), or cefoperazone-sulbactam, where available (Grade 2-B), as alternative empiric antimicrobial regimens for the management of CA-IAI in lower-risk patients.

6.2b. We recommend treatment of patients with perforated appendicitis with the same agents or regimens recommended for other lower-risk patients with CA-IAI, unless they meet criteria identifying them as higher-risk patients or at risk for having resistant pathogens (Grade 1-A).

B. Higher risk patients with CA-IAI

Q 6.3. What are the general principles for selection of empiric antimicrobial therapy of CA-IAI in higher-risk patients?

Q 6.4a. What are the preferred agents for initial empiric antimicrobial therapy of CA-IAI in higher-risk patients?

Q 6.4b. Should empiric anti-enterococcal therapy be used to treat CA-IAI in higher-risk patients?

Q 6.4c. Should empiric antifungal therapy be used to treat CA-IAI in higher-risk patients?

Inadequate antimicrobial therapy has been associated with higher deaths in patients with sepsis and septic shock from any source [193–195]. A number of studies have also demonstrated an association of inadequate antimicrobial therapy with worse outcomes in patients with IAI [43,54,58,71,187,194], although this finding has not been replicated by all investigators [18,402,403]. The infecting flora of higher-risk patients with CA-IAI are generally similar to those of lower-risk patients. Some patients with CA-IAI, however, are infected with pathogens such as *Enterobacter* spp., *P. aeruginosa* and *Enterococcus* spp., which are resistant to the narrower-spectrum agents recommended for use in lower-risk patients [22–24,26,27]. Higher-risk patients infected with these pathogens might therefore receive inadequate antimicrobial therapy if narrower-spectrum agents were used.

A limited number of observational studies have suggested that the failure to treat seriously ill patients infected with micro-organisms such as *Enterococcus* spp. and *P. aeruginosa* does result in higher deaths [24,111,330,404]. The task force therefore suggests that higher-risk patients with CA-IAI, particularly those with sepsis or septic shock, receive broader-spectrum empiric antimicrobial therapy to minimize the risk of inadequate initial therapy. The agents that have been included in this category are piperacillin-tazobactam, the broad-spectrum carbapenems, imipenem-cilastatin, meropenem, and doripenem, and cefepime plus metronidazole. The use of ceftazidime plus metronidazole is an option, although less well supported by contemporary data. Similarly, the use of aztreonam plus metronidazole plus vancomycin can be considered, particularly for patients with severe β -lactam reactions, although it too has not been evaluated in recent publications (Table 9).

Previous guidelines did not support the use of combination gram-negative therapy when treating higher-risk patients with CA-IAI. MDR gram-negative pathogens are uncommon in higher-risk patients with CA-IAI [24]. Two RCTs published since 2000 did not find the combination of an aminoglycoside with a cephalosporin to be any more efficacious than use of a cephalosporin-based regimen alone, although different agents were used in each arm of these trials [203,254]. Another large RCT did not identify any improvement in outcome with addition of moxifloxacin to meropenem for treat-

ment of patients with sepsis; this study included a large number of patients with IAI, but did not report the results of those patients separately [405]. A recent meta-analysis did not find any benefit of combination regimens on outcomes in patients with bacteremia because of *P. aeruginosa* [406]. Two randomized trials included in the previous evidence review [3] did not demonstrate any improvement in outcome with addition of an aminoglycoside to a β -lactam antibiotic agent in severely ill patients with IAI [22,407]. The task force, therefore, does not believe that combination gram-negative therapy is necessary for empiric treatment of higher-risk patients with CA-IAI.

Although there is strong evidence that anti-enterococcal therapy is unnecessary in lower-risk patients with CA-IAI, it is less clear if this applies to higher-risk patients with CA-IAI. Most of the evidence is derived from observational studies. The frequency with which *Enterococcus* spp. is isolated appears to be increased in higher-risk as compared with lower-risk patients with CA-IAI [27,89,408]. Isolation of *Enterococcus* spp. has also been associated with worse clinical outcomes, including death, in some studies of higher-risk patients with CA-IAI [24,27,111]. Thus, the task force concluded that there is rationale for providing empiric anti-enterococcal coverage in seriously ill patients with CA-IAI.

Although both *E. faecalis* and *E. faecium* have been isolated from peritoneal cultures of patients with CA-IAI, *E. faecalis* predominates [24,26]. Thus, coverage of *E. faecalis* is likely to be the primary concern when potentially using an anti-enterococcal agent to treat higher-risk patients with CA-IAI. Ampicillin and piperacillin generally have good activity against *E. faecalis* in vitro [89,324,409]. Among the broad-spectrum carbapenems, imipenem-cilastatin also has good in vitro activity, but doripenem and particularly meropenem have somewhat less activity [329,332,409–411]. Based on these data, the task force judged piperacillin-tazobactam or imipenem-cilastatin, and the regimen of aztreonam, metronidazole, and vancomycin as adequate for empiric treatment of *Enterococcus* spp. in higher-risk patients with CA-IAI. With use of other broad-spectrum carbapenems, addition of ampicillin or vancomycin could be considered. Supplemental ampicillin or vancomycin for coverage of *E. faecalis* should be added routinely to combinations of cefepime or ceftazidime with metronidazole, because these regimens lack anti-enterococcal coverage. Routine therapy directed against *E. faecium* was not considered necessary for higher-risk patients with CA-IAI, but if there were a high suspicion that this organism was a component of the infecting flora, supplemental vancomycin should be used.

It is also uncertain whether the recommendation against use of empiric antifungal therapy in lower-risk patients with CA-IAI should apply to higher-risk patients with CA-IAI. Observational studies have provided somewhat contradictory findings as to whether or not isolation of *Candida* is associated with increased deaths in critically ill patients with CA-IAI [56,412]. One RCT, which included critically ill patients with both CA-IAI and HA-IAI, did not find empiric use of fluconazole associated with any improvement in outcome [413]. Retrospective studies have also failed to document a benefit to routine use of empiric antifungal therapy in patients with CA-IAI [27,414]. Thus, in agreement with other authorities [56,415], the task force believes that routine antifungal therapy is unnecessary for most higher-risk patients with CA-IAI.

Critically ill patients with CA-IAI from upper gastrointestinal perforations, however, have a particularly high incidence of *Candida* peritonitis [110,416,417], and the overall deaths in these patients is quite high [412,418]. A retrospective study of patients with gastroduodenal perforations suggested that delayed antifungal therapy contributed to increased deaths [416]. Based on these limited data, the task force suggested that empiric antifungal therapy be considered for critically ill patients with CA-IAI because of upper gastrointestinal perforations.

6.3. We suggest treatment of CA-IAI in higher-risk patients with broader-spectrum empiric antimicrobial agents to ensure coverage of less common gram-negative pathogens potentially involved in these infections (Grade 2-C).

6.4a. We suggest piperacillin-tazobactam, imipenem-cilastatin, meropenem, doripenem, or cefepime plus metronidazole as the preferred antimicrobial agents for empiric treatment of CA-IAI in higher-risk patients (Grade 2-A). We suggest ceftazidime plus metronidazole as an alternative regimen for these patients (Grade 2-B). We suggest aztreonam plus metronidazole plus vancomycin for empiric treatment of patients with a severe reaction to β -lactam agents (Grade 2-B). We do not recommend addition of an adjunctive aminoglycoside or fluoroquinolone to a β -lactam agent for empiric management of CA-IAI in higher-risk patients (Grade 1-B).

6.4b. We suggest addition of ampicillin or vancomycin for empiric anti-enterococcal management of CA-IAI in higher-risk patients, if the patient is not being treated with piperacillin-tazobactam or imipenem-cilastatin (Grade 2-B).

6.4c. We do not recommend routine use of empiric antifungal therapy for management of CA-IAI in higher-risk patients (Grade 1-B). We suggest empiric use of antifungal therapy for management of CA-IAI in critically ill patients with an upper gastrointestinal source (Grade 2-B).

C. Other considerations for empiric antimicrobial therapy of patients with CA-IAI

Q 6.5. What agents can be used for initial empiric antimicrobial therapy of CA-IAI in patients with major reactions to β -lactam antibiotics?

Q 6.6. What agents can be used for initial empiric antimicrobial therapy of CA-IAI in patients who reside in geographic areas with a high prevalence of ESBL-producing Enterobacteriaceae in the community?

Q 6.7. What agents can be used for initial empiric antimicrobial therapy of CA-IAI in patients who reside in geographic areas where there are major resource limitations precluding use of recommended antimicrobial agents?

Antibiotic selection may be problematic in patients with hypersensitivity reactions to β -lactam antibiotic agents. Although 5%–10% of patients report a history of a reaction to penicillin, anaphylactic reactions are uncommon. Moreover, the majority of patients reporting a penicillin allergy do not in actuality have one [283,419,420]. Cross-reactivity between various β -lactam agents is relatively uncommon, and monobactams and carbapenems are generally safe to use in almost all patients with reactions to penicillins or cephalosporins, even those with serious reactions [283,421,422]. Nonetheless, frequently there is a reluctance on the part of clinicians to

prescribe a β -lactam antibiotic agent to any patient with even a very vague history of a penicillin or other β -lactam allergy.

Based on the review of this evidence and expert opinion, the task force has identified a fluoroquinolone-based regimen as a reasonable option for initial empiric treatment of lower-risk patients with CA-IAI who have a serious reaction to β -lactam antibiotic agents. If the patient cannot receive a fluoroquinolone antibiotic agent, a β -lactam antibiotic agent with a low potential for cross-reaction with the agent producing the allergy could be considered. Non- β -lactam alternatives such as an aminoglycoside plus metronidazole or tigecycline are also options, but the potential for decreased efficacy of these alternative agents is a concern.

For higher-risk patients with CA-IAI, alternatives to β -lactam antibiotic agents may be quite limited because of efficacy concerns. The task force has selected aztreonam plus metronidazole plus vancomycin as a reasonable alternative for patients with severe β -lactam reactions, because aztreonam has almost no cross-reactivity with other β -lactam antibiotic agents. A β -lactam from a different class could also be considered, given the relatively low cross-reactivity between β -lactams. Use of a fluoroquinolone-based regimen is a less-attractive option, because of the relatively widespread prevalence of fluoroquinolone-resistant Enterobacteriaceae. The potential for decreased efficacy of aminoglycoside-based regimens and tigecycline would also argue against their use as monotherapy for management of CA-IAI in higher-risk patients with severe β -lactam reactions.

The increasing prevalence of ESBL-producing Enterobacteriaceae in parts of Latin America, Asia, and Southern Europe makes selection of empiric antimicrobial therapy for patients with CA-IAI in those regions more problematic. Common ESBL-producing strains should be considered resistant to aztreonam and most cephalosporins other than cephamycins regardless of in vitro testing. Moreover, ESBL-producing Enterobacteriaceae are frequently resistant to cephamycins and to fluoroquinolones through other mechanisms [29,235,397,423,424–428]. Susceptibilities of ESBL-producing strains of Enterobacteriaceae to tigecycline are generally high, although susceptibilities to piperacillin-tazobactam and amikacin are somewhat more variable [28,235,241,429,430]. Carbapenems have reliable activity against most ESBL-producing Enterobacteriaceae except for those producing carbapenemases [28,29,235,431].

Based on these data, the task force considers ertapenem to be the best option for empiric treatment of lower-risk patients with CA-IAI in regions where there is a high likelihood that ESBL-producing Enterobacteriaceae are components of the infection. Tigecycline or an aminoglycoside-based regimen is an alternative, although less preferable because of efficacy concerns. Where available, cefoperazone-sulbactam is another potential option, especially since one RCT demonstrated its efficacy in managing IAI in a region where there is a high prevalence of ESBL-producing Enterobacteriaceae [203]. Based on in vitro susceptibility patterns, most cephalosporins, including cephamycins, aztreonam, and fluoroquinolones, would not be good options [423,424,432]. Nonetheless, recent RCTs have not generally demonstrated higher clinical failure rates in patients with IAI who were treated with agents that have poorer activity against ESBL-producing micro-organisms [203,205,214,220,246,252,253, 255,284,293].

Based on the principle of ensuring adequate initial empiric antimicrobial therapy, the task force would select a broad-spectrum carbapenem as the first choice in treating higher-risk patients with CA-IAI who reside in regions with a high prevalence of ESBL-producing Enterobacteriaceae in the community [423,424,432]. Another option could be piperacillin-tazobactam [309], although many authorities advise caution with its use [423,424,432,433]. The potential for decreased efficacy of aminoglycosides and tigecycline for treating higher-risk patients with CA-IAI argues against their use as empiric therapy. Based on in vitro susceptibility profiles and limited clinical data, ceftolozane-tazobactam and ceftazidime-avibactam could be options for empiric therapy [263, 264,266,274–276], but these agents are not yet available in many parts of the world where there is a high prevalence of ESBL-producing Enterobacteriaceae. Because heavy use of carbapenems has been associated with selection of carbapenemase-producing gram-negative bacilli [298,432, 434,435], de-escalation from empiric carbapenem therapy should be undertaken, whenever possible.

Limitations on the availability of antimicrobial resources in many parts of the world may preclude use of recommended antibiotic regimens to treat patients with IAI. Although the task force recommendations are based primarily on evidence of efficacy, the absolute risk of a worse outcome with use of a non-recommended regimen compared with a recommended regimen may be relatively small, as illustrated in meta-analyses comparing use of aminoglycoside-based regimens to other regimens [207,208]. Inadequate source control is much more likely than selection of a specific empiric antimicrobial regimen to lead to an adverse outcome in patients with IAI [51,61,71,436]. Thus, ensuring access to appropriate source control may have a larger impact than providing ideal, but expensive antimicrobial agents in areas of resource limitations.

Non-recommended agents or regimens such as ampicillin-sulbactam, amoxicillin-clavulanate, cefoxitin, cefotetan, or cefazolin or aminoglycosides in combination with metronidazole or clindamycin have an appropriate spectrum of activity for treating patients with IAI and could be used if available. Recommended oral agents would also be lower-cost alternatives to more expensive IV agents. Nonetheless, the potential for decreased efficacy or increased side effects related to use of non-recommended agents could negate any of the cost benefits from using less expensive pharmaceuticals.

6.5. We suggest use of a fluoroquinolone-based regimen for initial empiric antimicrobial therapy of CA-IAI in lower-risk patients who have had major reactions to β -lactam antibiotic agents (Grade 2-B). We suggest use of an aztreonam-based regimen for initial empiric therapy of CA-IAI in higher-risk patients who have had major reactions to β -lactam antibiotic agents (Grade 2-B). We suggest that a non-penicillin β -lactam may be used for empiric antimicrobial therapy of CA-IAI in patients for whom a severe penicillin allergy has not been documented and for whom the risk-benefit ratio is believed acceptable (Grade 2-B).

6.6. We recommend against empiric use of most cephalosporin-, aztreonam-, or fluoroquinolone-based regimens for empiric antimicrobial therapy of CA-IAI in patients who reside in geographic areas where there is a high prevalence of ESBL-producing Enterobacteriaceae in the community

(Grade 1-B). We recommend use of ertapenem for empiric antimicrobial therapy of CA-IAI in lower-risk patients or a broad-spectrum carbapenem (doripenem, imipenem-cilastatin, or meropenem) for CA-IAI in higher-risk patients who reside in such areas (Grade 1-B).

6.7. We suggest that locally available IV or oral agents having activity against common intra-abdominal pathogens be used for empiric antimicrobial therapy of CA-IAI in patients who reside in geographic areas where there are major resource limitations (Grade 2-C).

7. Selection of empiric antimicrobial therapy for adult patients with HA-IAI

A. General approach

Q 7.1a. How should patients with HA-IAI be assessed with respect to their risk of infection with resistant or opportunistic pathogens?

Q 7.1b. What agents can be used for initial empiric antimicrobial therapy of HA-IAI in patients who are identified as being at risk of resistant pathogens?

The criteria for identifying patients with HA-IAI were discussed in Section 1 and are listed in Table 7. Epidemiologic studies have identified a number of risk factors identifying patients with HA-IAI at risk for harboring resistant or opportunistic pathogens [15,17,19,22–24,26,32,33,62,77,79, 85–90,110,340,417,418]. The task force believes that *Enterococcus* spp., MRSA, resistant gram-negative bacilli, and *Candida* spp. are the resistant or opportunistic pathogens of primary concern for purposes of prescribing antimicrobial therapy. It is therefore suggested that a patient be assessed individually as to his or her risk of infection with each of these distinct micro-organisms. Knowledge of the local microbial ecology as well as the patient's exposure to previous antimicrobial therapy will also influence antimicrobial selection.

Because of the wide variety of infecting micro-organisms in patients with HA-IAI and the frequency with which these pathogens are resistant to antimicrobial agents, these patients are at risk for a worse outcome because of inadequate empiric antimicrobial therapy [43,54,58,187,193–195]. At a minimum, the task force believes that patients with HA-IAI should receive the empiric antimicrobial regimens described for use in higher-risk patients with CA-IAI. The recommended agents include piperacillin-tazobactam, cefepime plus metronidazole, or a broad-spectrum carbapenem; ceftazidime plus metronidazole or aztreonam plus metronidazole plus vancomycin are potential alternatives (Table 10). The potential pathogenic role of enterococci in post-operative infections probably warrants use of an empiric anti-enterococcal agent in most of these patients as well. Addition of other agents to this basic regimen should be predicated on the individualized assessment of the patient's risk for resistant gram-positive, resistant gram-negative, or fungal pathogens [17,18,33,62,197,241,437,438].

7.1a. We suggest that all patients with HA-IAI be assessed with respect to their separate risks of infection from Enterococcus spp., MRSA, resistant gram-negative bacilli, and Candida spp. (Grade 2-B).

7.1b. We suggest that broader-spectrum agents or regimens described for use in higher-risk patients with CA-IAI be used for the initial empiric antimicrobial therapy of patients

TABLE 10. SUMMARY OF EMPIRIC ANTIMICROBIAL THERAPY FOR PATIENTS WITH HEALTHCARE- OR HOSPITAL-ACQUIRED INTRA-ABDOMINAL INFECTION

<i>General approach</i>	
Piperacillin-tazobactam, doripenem, imipenem-cilastatin, meropenem, or cefepime plus metronidazole, with ceftazidime plus metronidazole and aztreonam plus metronidazole plus vancomycin as potential alternatives	
<i>Supplemental agents</i>	
Potential pathogen	Recommendations
<i>Enterococcus faecalis</i>	Addition of ampicillin or vancomycin if not using piperacillin-tazobactam or imipenem-cilastatin
<i>Enterococcus faecium</i>	Vancomycin or teicoplanin
Vancomycin-resistant <i>Enterococcus</i> spp.	Daptomycin or linezolid
MRSA	Vancomycin, teicoplanin, daptomycin, or linezolid
ESBL-producing or AmpC- β -lactamase-producing Enterobacteriaceae	Use of a broad-spectrum carbapenem
KPC-producing Enterobacteriaceae	Combination therapy with a broad-spectrum carbapenem plus an aminoglycoside, polymyxin, or tigecycline; or ceftazidime-avibactam
MDR strains of <i>Pseudomonas aeruginosa</i>	Combination therapy with an aminoglycoside plus colistin, or ceftolozane-tazobactam or ceftazidime-avibactam
MDR strains of <i>Acinetobacter baumannii</i>	Combination therapy with a broad-spectrum carbapenem plus an aminoglycoside, polymyxin, or tigecycline
<i>Candida albicans</i>	An echinocandin (anidulafungin, caspofungin, micafungin) for critically ill patients, fluconazole for less critically ill patients
Non- <i>C. albicans</i> spp.	An echinocandin

MRSA = methicillin-resistant *Staphylococcus aureus*; ESBL = extended-spectrum beta-lactamase; KPC = *Klebsiella pneumoniae* carbapenemase.

with HA-IAI. Other empiric agents should be added to the regimen according to the assessment of the patient's risk for an infection from *Enterococcus* spp., MRSA, resistant gram-negative bacilli, and *Candida* spp. (Grade 2-B).

B. Anti-enterococcal therapy

Q 7.2a. How should patients with HA-IAI be assessed with respect to their risk of infection because of *Enterococcus* spp.?

Q 7.2b. Which agents can be used for initial empiric antimicrobial therapy of HA-IAI in patients considered at risk for infection with *Enterococcus* spp.?

Enterococci are common opportunistic micro-organisms isolated from patients with HA-IAI, although their pathogenic role in IAI is still a matter of some debate. Isolation of enterococci has been associated with a higher risk for an adverse outcome in many, but not all studies [24,27,49,58,86,88,89,119,403,408]. Patients in whom HA-IAI develops after an abdominal operation appear to be at particular risk for infection from *Enterococcus* spp. [26,86,88,89,439], as are patients who have received previous broad-spectrum antibiotic therapy [111,119]. Other risk factors for isolation of enterococci in patients with IAI include co-morbid conditions such as heart disease, chronic obstructive pulmonary disease, and malignancy; higher APACHE II, Simplified Acute Physiology Score (SAPS) II, or Sequential Organ Failure Assessment (SOFA) scores; previous hepatobiliary instrumentation; a history of solid organ transplantation, particularly liver transplantation; and immunosuppressive therapy [88,89,111,119,439].

Both *E. faecalis* and *E. faecium* are encountered relatively frequently in patients with HA-IAI, with the latter micro-organism accounting for a substantial proportion of these enterococcal isolates [24,26,106,119,408,439,440]. Moreover, VRE is being identified increasingly in patients with enterococcal infections, including HA-IAI, in several areas of

the world [26,115,441,442]. Recent reports suggest that VRE accounts for more than one-third of enterococcal infections in the United States, with most of these because of vancomycin-resistant *E. faecium* [102,106]. The risk of an infection from VRE is much higher in patients already colonized with VRE [93,96,102,103,106]. Risk factors for colonization and infection with VRE also include a prolonged hospital length of stay, particularly in the intensive care unit, previous surgical procedures, a high severity of illness or extensive comorbidities, and substantial previous exposure to broad-spectrum antibiotic therapy [102,103,106,115]. Solid organ transplant patients, especially liver transplant patients, are a particularly high-risk group of patients for VRE colonization and infection [103,115,443].

There are conflicting data as to whether or not timely anti-enterococcal therapy improves outcomes in patients infected with enterococci [49,86,89,111,119,408,411]. Methodologically robust trials of anti-enterococcal therapy in higher-risk patients are lacking. Because of the potential for poor outcomes with a failure to provide adequate antimicrobial therapy, however, the task force supports use of anti-enterococcal therapy in patients with HA-IAI identified as being at risk for infection with *Enterococcus* spp. This therapy should be selected on the basis of the likely species and strains that will be encountered.

Because of the higher risk that *E. faecium* is a pathogen in patients with HA-IAI, empiric anti-enterococcal therapy should be directed against both *E. faecalis* and *E. faecium*. Glycopeptides generally have good activity against non-VRE strains of *E. faecalis* and *E. faecium*, whereas β -lactam antibiotic agents typically lack activity against *E. faecium* [324,329,331,332,409,444]. Therefore, the task force suggests use of vancomycin or teicoplanin for patients with HA-IAI at risk for infection with *Enterococcus* spp. For patients with HA-IAI considered at high risk for infection from VRE, however, the task force suggests use of empiric linezolid or daptomycin.

These agents generally have good activity against VRE, with linezolid having been approved by the FDA for management of such infections [93,106,115,333,335,445]. Tigecycline also has good in vitro activity against VRE, but there are only limited clinical data regarding use of this agent for patients with HA-IAI because of VRE [443,446,447]. These suggestions for anti-enterococcal therapy in patients with HA-IAI are summarized in Table 10. With empiric use of any type of anti-enterococcal agent, treatment should be discontinued or de-escalated if a resistant enterococcal strain is not identified in definitive cultures.

7.2a. We suggest that patients with HA-IAI who have a post-operative infection, have had substantial recent exposure to broad-spectrum antimicrobial therapy, who manifest signs of severe sepsis or septic shock, or who are known to be colonized with VRE be considered at risk for infection from Enterococcus spp. (Grade 2-B).

7.2b. We suggest vancomycin or teicoplanin for empiric antimicrobial therapy of HA-IAI in patients considered at risk for an infection from Enterococcus spp. We suggest use of linezolid or daptomycin for management of HA-IAI in patients known to be colonized with VRE or considered at high risk for infection from this organism (Grade 2-B).

C. Anti-staphylococcal therapy

Q 7.3a. How should patients with HA-IAI be assessed with respect to their risk of infection with MRSA?

Q 7.3b. Which agents can be used for initial empiric antimicrobial therapy of HA-IAI in patients considered to be at risk for infection with MRSA?

Staphylococci are not common pathogens in IAI. Coagulase-negative staphylococci are most often described in the context of tertiary peritonitis or recurrent IAI, although their pathogenic role is uncertain [32,85,90,448]. *S. aureus* is rarely isolated from peritoneal cultures of patients with CA-IAI [23,24,27,62], but is found somewhat more frequently in cultures from patients with HA-IAI; many of these isolates are resistant to methicillin [23,24,27,62,340,341,342].

Patients colonized with MRSA are at risk for invasive MRSA infections [94,97,98,100], including post-operative HA-IAI [340]. Risk factors for MRSA colonization, which overlap with those for HAI in general, include advanced age, female gender, major medical co-morbidities, previous exposure to healthcare-associated pathogens, residence in a long-term care facility, recent hospitalization, recent surgery, and a history of recent exposure to antibiotic agents [100,449–451]. The task force suggests that patients known to be colonized with MRSA and those who have several risk factors for MRSA colonization be considered at risk for HA-IAI because of MRSA.

There are no published studies specifically evaluating antimicrobial therapy for IAI related to MRSA. Glycopeptides are the agents prescribed most commonly for patients with serious infections from MRSA [334,343–345,358]. Thus, vancomycin or teicoplanin (where available) could be used for empiric therapy of HA-IAI if MRSA is a suspected pathogen. The higher dosages of vancomycin advocated for managing infections from MRSA [344,452] may be leading to higher rates of nephrotoxicity with this agent, however [350–352]. In addition, the overall efficacy of vancomycin for serious MRSA infections has been called into question [345–348].

Thus, use of different agents for first-line therapy of MRSA infections should also be considered [353–355]. Both linezolid and daptomycin appear to have efficacy at least equivalent to vancomycin for managing serious infections from this organism and have been used successfully in patients with IAI [344,348,354–359]. Based on these data, the task force believes that vancomycin, teicoplanin (where available), linezolid, and daptomycin are options for the empiric treatment of patients with HA-IAI when MRSA is a suspected pathogen (Table 10). The task force did not encounter sufficient published data regarding management of serious MRSA infections with other agents active against this organism, including ceftaroline, tigecycline, telavancin, dalbavancin, and oritavancin, to make any recommendation regarding use of these agents.

7.3a. We suggest that patients with HA-IAI known to be colonized with MRSA and those with multiple healthcare-associated risk factors for MRSA colonization, including advanced age, co-morbid medical conditions, previous hospitalization or surgery, and significant recent exposure to antibiotic agents, be considered at risk for infection from MRSA (Grade 2-B).

7.3b. We suggest vancomycin or teicoplanin, where available, or linezolid or daptomycin as alternatives, for empiric antimicrobial therapy of HA-IAI in patients known to be colonized with MRSA or considered at high risk for infection from this organism (Grade 2-B).

D. Antibacterial therapy for resistant gram-negative organisms

Q 7.4a. Which patients with HA-IAI should be considered at risk for infection from resistant gram-negative pathogens?

Q 7.4b. What other factors should be considered in selecting empiric antimicrobial therapy for patients with HA-IAI from suspected resistant gram-negative pathogens?

Q 7.4c. What agents can be used for empiric antimicrobial therapy of HA-IAI in patients considered at risk for resistant Enterobacteriaceae?

Q 7.4d. What agents can be used for empiric antimicrobial therapy of HA-IAI in patients considered at risk for MDR, or XDR, or pan-drug-resistant (PDR) strains of *P. aeruginosa* or *Acinetobacter* spp.?

Compared with patients with CA-IAI, those with HA-IAI are infected with a much wider variety of gram-negative pathogens, many of which are resistant to various antibiotic agents [437,453]. Although *E. coli* is still the most common gram-negative pathogen identified in HA-IAI, other Enterobacteriaceae, such as *Enterobacter* spp., and non-lactose-fermenting gram-negative pathogens, such as *P. aeruginosa* and *A. baumannii*, are encountered with some frequency [22–28,33,62,454]. These pathogens develop resistance to antibiotic agents through a variety of mechanisms, including production of an ESBL or an aminoglycoside-modifying enzyme, elaboration of efflux pumps, loss of porins, or target site modifications. Simultaneous resistance to several classes of antibiotic agents is relatively common with many of these gram-negative bacteria [239,256,285,317,432,455–458].

The risk factors for HA-IAI because of resistant gram-negative pathogens mirror those for HA-IAI in general. Hospitalization, recent medical interventions, and pre-existing

medical co-morbidities are all associated with infection from these resistant microorganisms [17–19,62,104,439]. Numerous studies have also closely linked previous broad-spectrum antimicrobial therapy with colonization or infection because of resistant gram-negative organisms [17–19,99,112–114,116–118,120–123]. Unfortunately, these risk factors are quite non-specific and are probably only useful in the extreme for identifying patients with HA-IAI likely to be infected with one of these pathogens. Patients known to be previously colonized or infected with a resistant gram-negative organism, however, can be suspected of having HA-IAI because of that agent. Routine surveillance for resistant gram-negative organisms, however, is rarely performed [91,92,95,99,101,104,105], so this information will only be available for a minority of patients with HA-IAI.

The local microbial ecology may be the most important aspect to consider in evaluating the risk that a patient with HA-IAI is infected with a resistant gram-negative micro-organism. Strains of these resistant bacteria are endemic in certain geographic locales [239,432,434,435,437,453,455,459,460]; this phenomenon may extend to the individual institution or even to a specific unit within that institution [461–463]. Thus, updated hospital- or unit-specific antibiograms, where available, may help determine when a patient with HA-IAI is at risk for infection with a specific resistant gram-negative pathogen [194,462,463]. Overall, the task force believes that risk factors such as prolonged hospitalization, multiple medical interventions, previous broad-spectrum antimicrobial therapy, or a history of colonization or infection with resistant micro-organisms should be considered along with local epidemiologic information in identifying patients with HA-IAI at risk for infection from resistant gram-negative pathogens.

Selection of empiric antimicrobial therapy for HA-IAI will be based not only on the general risk that the patient is infected with a resistant gram-negative micro-organism, but also on the specific risk for a given pathogen or pathogens. The goal is to select an empiric regimen likely to be active against the resistant pathogens the patient may carry, so that the risk of inadequate antimicrobial therapy is minimized. The task force has concluded that the agents with broad-spectrum activity against gram-negative micro-organisms that were recommended for treatment of higher-risk patients (Table 10) form the basis for empiric therapy of patients with HA-IAI. Alternative or additional agents for gram-negative coverage may be warranted, however, if the patient is at risk for an MDR- or XDR-pathogen.

Patients with HA-IAI are at risk for infections with ESBL-producing Enterobacteriaceae, although the risk of this is highest in certain geographic regions of the world, such as Asia and Latin America [28,29,31]. Carbapenems are generally considered the empiric agents of choice for treating patients with the most common ESBL-producing Enterobacteriaceae (Table 10) [309,464–466]. To avoid excessive carbapenem use, however, de-escalation to other agents, such as piperacillin-tazobactam, cefepime, an aminoglycoside, a cephamycin, a fluoroquinolone, or tigecycline, can be considered once susceptibilities are known. Unfortunately, with the exception of tigecycline, ESBL-producing Enterobacteriaceae are frequently resistant to these other agents [206,257,423,424,432,467]. Both ceftolozane-tazobactam and ceftazidime-avibactam have shown efficacy in treating patients with IAI caused by ESBL-producing Enterobacteriaceae, par-

ticularly *E. coli*, but clinical experience with these agents is still limited [263,264,274,275].

Patients with HA-IAI who have had extensive exposure to the hospital environment and broad-spectrum antimicrobial therapy may be infected with AmpC- β -lactamase-producing strains of *Enterobacter* spp. or other Enterobacteriaceae. There is relatively little published experience regarding management of these organisms in patients with HA-IAI. Broad-spectrum carbapenems are generally considered the treatment of choice for patients with bacteremia and other infections because of AmpC- β -lactamase-producing gram-negative pathogens, and would likely be effective in patients with HA-IAI from these resistant strains (Table 10) [256–259,315,468]. Cefepime has been described as an option to treat patients with these pathogens, despite the recognized propensity of other cephalosporins to serve as inducers of these enzymes [257–259,468]. Other agents, including tigecycline, aminoglycosides, and fluoroquinolones, may have activity against AmpC- β -lactamase-producing organisms, but little information is available regarding their clinical efficacy [256,257]. Ceftazidime-avibactam has good in vitro activity against AmpC- β -lactamase-producing Enterobacteriaceae [277,469,470], and ceftolozane-tazobactam has activity against 70% of these strains [265], but clinical experience using these agents to treat AmpC- β -lactamase-producing gram-negative pathogens is quite limited.

Carbapenemase-producing gram-negative bacteria present an even greater challenge to the clinician. There is a paucity of evidence regarding treatment of patients with HA-IAI who are infected with these pathogens. Most of the available literature relates to the treatment of patients with bacteremia from carbapenemase-producing Enterobacteriaceae, particularly *K. pneumoniae*. For treatment of KPC-producing strains, the combination of a carbapenem with an aminoglycoside, a polymyxin, or tigecycline has been associated with the highest efficacy, at least when the minimum inhibitory concentration (MIC) to carbapenems is not too high [316,317,471,472]. Ceftazidime-avibactam has activity against KPC-producing strains of Enterobacteriaceae and thus may provide an option for treating patients with HA-IAI because of this organism (Table 10) [276,469]. Treatment of patients with MBL-producing Enterobacteriaceae is more problematic, because these bacteria are resistant to nearly all β -lactam antibiotic agents, although aztreonam may be an exception. Combination therapy, using agents such as a polymyxin, tigecycline, or fosfomycin, among others, is generally advocated [434,473].

Some patients with HA-IAI may be infected with MDR, XDR, or PDR strains of gram-negative bacteria such as *Pseudomonas* spp. and *Acinetobacter* spp. [474]. These highly resistant micro-organisms may be found in patients characterized as having tertiary peritonitis [33,87,475]. Selection of empiric therapy in these patients is individualized, based on previous culture and susceptibility data, the patient's history of previous antimicrobial exposure, and the type of resistant pathogens encountered in the local environment. For these MDR, XDR, and PDR pathogens, combination regimens are generally used. Depending on the suspected micro-organism, this may or may not include a broad-spectrum β -lactam antibiotic agent, an aminoglycoside, a polymyxin, tigecycline (not applicable for *Pseudomonas*), rifampin, or fosfomycin (Table 10) [318,476–481].

Ceftolozane-tazobactam has activity against many MDR and XDR strains of *Pseudomonas* resistant to other β -lactam antibiotic agents [265,266]; ceftazidime-avibactam may also have some enhanced activity against these strains as well [277,279]. These newer agents, however, are not particularly active against *Acinetobacter* spp. Experience with these agents in critically ill patients is still quite limited. Overall, no ideal regimen has been identified for managing HA-IAI in patients infected with these highly resistant pathogens.

7.4a. We suggest that patients with HA-IAI who have received substantial previous broad-spectrum antimicrobial therapy, have had prolonged hospitalizations, have undergone multiple invasive interventions, or are known to have been colonized or infected with a resistant gram-negative organism be considered at risk for infection from a resistant gram-negative pathogen (Grade 2-B).

7.4b. We suggest use of local epidemiologic data and antibiograms for selecting empiric antimicrobial therapy of HA-IAI in patients considered at risk for infection with resistant gram-negative pathogens (Grade 2-B).

7.4c. We suggest a broad-spectrum carbapenem, with ceftolozane-tazobactam or ceftazidime-avibactam as potential alternatives, for empiric antimicrobial therapy of HA-IAI in patients considered at risk for infection with ESBL-producing Enterobacteriaceae (Grade 2-B). We suggest a broad-spectrum carbapenem, with ceftazidime-avibactam as a potential alternative, for empiric antimicrobial therapy of HA-IAI in patients considered at risk for infection with AmpC- β -lactamase-producing Enterobacteriaceae (Grade 2-B). We suggest combinations of a carbapenem with an aminoglycoside, a polymyxin, and/or tigecycline, or ceftazidime-avibactam as an alternative, for empiric antimicrobial therapy of HA-IAI in patients considered at risk for infection with carbapenem-resistant Enterobacteriaceae (Grade 2-B).

7.4d. We suggest combinations of a β -lactam, including ceftolozane-tazobactam, an aminoglycoside, and/or a polymyxin, for empiric antimicrobial therapy of HA-IAI in patients considered at risk for infection from MDR, XDR, or PDR strains of *P. aeruginosa* (Grade 2-B). We suggest combinations of a carbapenem, an aminoglycoside, a polymyxin, and/or tigecycline for empiric antimicrobial therapy of HA-IAI in patients considered at risk for infection from MDR, XDR, or PDR strains of *Acinetobacter* spp. (Grade 2-B).

E. Antifungal therapy

Q 7.5a. Which patients with HA-IAI should be considered at risk for infection from *Candida* spp.?

Q 7.5b. What agents can be used for empiric antifungal therapy of HA-IAI in patients considered at risk for a candidal infection?

Risk factors for invasive candidal infections in hospitalized patients, particularly critically ill patients, include a previous surgical procedure, a history of broad-spectrum antimicrobial therapy, pancreatitis, use of parenteral nutrition, presence of invasive catheters, medical co-morbidities including diabetes mellitus, cardiac disease, renal failure, or immunosuppression, and multiple sites of colonization with *Candida* spp. [416,482–489]. These risk factors are generally derived from studies of patients with candidemia and may not be directly applicable to patients with HA-IAI. Studies that have

more closely examined specific risk factors for *Candida* peritonitis have identified recurrent gastrointestinal perforations [490], upper gastrointestinal perforations [110,413,416,417], surgically treated pancreatitis [490], and previous receipt of antimicrobial therapy [107–110] as predisposing factors for HA-IAI from *Candida* spp. Colonization with *Candida* at multiple sites has been used to identify patients at high risk of an invasive candidal infection [490–493], but the utility of this observation has been disputed [494].

Mortality rates of 20%–64% have been recorded in patients with HA-IAI from *Candida* spp., with at least some of the deaths being directly attributed to the candidal infection itself [56,109,412,413,418,483,495,496]. Delays in effective antifungal therapy have been associated with increased deaths in patients with candidemia and other invasive candidal infections, particularly those with septic shock [56,375,412,415,489].

Antifungal agents applicable to the empiric treatment of patients with HA-IAI potentially because of *Candida* spp. include the polyenes (amphotericin B in its various formulations), triazoles (fluconazole and voriconazole), and echinocandins (anidulafungin, caspofungin, and micafungin). Evidence from RCTs and a meta-analysis suggest that echinocandins are more efficacious than triazoles and less toxic than polyenes when treating patients with candidal infections, particularly those who are critically ill [361,362,364,365,371–373].

Although these clinical trials primarily enrolled subjects with candidemia, not *Candida* peritonitis, the task force believes these findings should apply to severely ill patients with HA-IAI potentially from *Candida*. Thus, an echinocandin is recommended for empiric treatment of these patients with HA-IAI. Nonetheless, fluconazole was effective at preventing *Candida* peritonitis when used preemptively in patients at high risk for an infection with this organism [366]. For patients who are less critically ill, the task force suggests that empiric fluconazole should suffice in most patients. Historically, amphotericin B was the primary antifungal agent used to treat patients with intra-abdominal candidiasis; however, use of this agent has fallen into disfavor because of its toxicity [360,364]. It is not currently recommended except when other, less toxic, agents cannot be used to manage the infection [497–501].

Although *C. albicans* is the most common yeast found with IAI, non-*C. albicans* species, including *C. glabrata*, *C. parapsilosis*, and *C. tropicalis*, are isolated with increasing frequency [375,502–504]. *Candida glabrata* may be intrinsically resistant or demonstrate dose-dependent susceptibility to fluconazole; voriconazole has much better activity against this organism [505]. The echinocandins are highly active against nearly all *Candida* spp. Thus, voriconazole or an echinocandin are options in patients at risk for or known to be colonized or infected with a fluconazole-resistant species of *Candida* [367–369,505].

7.5a. We suggest that patients with HA-IAI because of upper gastrointestinal perforations, recurrent bowel perforations, or surgically treated pancreatitis, those who have received prolonged courses of broad-spectrum antibiotic therapy, and those who are known to be heavily colonized with *Candida* be considered at increased risk for infection from *Candida* spp. (Grade 2-B). We suggest that patients with HA-IAI found to have yeast on a Gram stain of infected peritoneal fluid or tissue be considered to have a candidal infection (Grade 2-B).

7.5b. We recommend an echinocandin (anidulafungin, caspofungin, or micafungin) for empiric antifungal therapy of HA-IAI in severely ill patients considered at risk for infection from *Candida* spp. (Grade 1-B). We suggest fluconazole can be used for empiric antifungal therapy in less severely ill patients with HA-IAI considered at risk for infection from *Candida* spp. (Grade 2-B). We suggest an echinocandin or voriconazole for empiric antifungal therapy of patients with HA-IAI considered at risk for infection because of a fluconazole-resistant non-*C. albicans* strain (Grade 2-B).

8. Timing of antimicrobial therapy

Q 8.1. When should antimicrobial therapy be initiated in patients with a diagnosis of IAI?

Q 8.2. Should additional antimicrobial therapy be administered to patients undergoing source control procedures for IAI who are already receiving empiric antimicrobial therapy?

There is little definitive evidence on the timing of antimicrobial therapy for patients with IAI. In patients with sepsis or septic shock, a substantial proportion of whom present with IAI, several cohort and retrospective studies have demonstrated increased deaths if antimicrobial therapy is delayed [506–508]. Based on these data, the Surviving Sepsis Campaign recommends initiation of antimicrobial therapy within one hour of identifying a patient with sepsis or septic shock [6]. Nonetheless, some studies have failed to find an association between a delay of antimicrobial therapy and death for up to five hours in such patients [509–512]. Although these conflicting data question whether a one-hour time window should be considered a rigid standard for delivering anti-infective therapy once the diagnosis of IAI with sepsis has been made, the task force believes that early administration of antimicrobial agents represents a reasonable goal. It also needs to be recognized, however, that there are additional priorities in the acute management of IAI with sepsis, such as preparing the patient for definitive source control.

There are little data with regard to antimicrobial timing for patients with IAI who do not meet sepsis criteria. In general, the task force believes it is reasonable to initiate antimicrobial therapy as soon as feasible in these patients, as had been recommended in the previous guideline [4]. Withholding antimicrobial therapy until definitive peritoneal cultures can be obtained is not justified, because of the prolonged delay in effective antimicrobial therapy that could entail.

There are also important considerations with regard to timing of antimicrobial delivery relative to a source control procedure. Even though an established infection is already present in patients with IAI, the general principles of antimicrobial prophylaxis for surgical procedures still apply. Guidelines for prevention of surgical site infection specify administration of most prophylactic antibiotics within one hour of the surgical incision to ensure that adequate blood and tissue concentrations are present [238,513–515]. A number of observational studies have provided evidence in support of this recommendation [516–520].

A patient with IAI may have had an antimicrobial agent administered several hours before a source control procedure, however. Under those circumstances, adequate serum and tissue concentrations of the agent may not be present during that procedure. Therefore, the task force recommends re-

administration of an anti-infective agent at the time of a source control intervention if more than two half-lives have elapsed since the previous dose. This is based on surgical site infection prevention guidelines recommending re-dosing of prophylactic agents intra-operatively if the length of the procedure exceeds two half-lives of the agent in question [238,514,521,522]. Because dissemination of pathogenic micro-organisms may occur during less-invasive source control procedures as well, it seems reasonable to adhere to this recommendation for source control interventions other than operative procedures. The task force also endorses re-administration of antibiotics intra-operatively during source control if two antibiotic half-lives have elapsed since the previous dose.

8.1. We suggest initiation of empiric antimicrobial therapy within one hour or as soon as possible thereafter of the time the diagnosis of IAI is made in patients presenting with sepsis or septic shock (Grade 2-B). We also suggest initiation of antimicrobial therapy as soon as feasible in other patients with IAI, taking into account plans for subsequent source control (Grade 2-C).

8.2. We recommend re-administration of an antimicrobial agent within one hour before the start of a source control procedure for IAI if two half-lives of the agent will have passed at the time the intervention is initiated (Grade 1-B).

9. Dosing of antimicrobial agents in adult patients

Q 9.1. What dosages of antimicrobial agents should be used for management of IAI in adult patients?

Q 9.2. Should adjusted dosages of antimicrobial agents be used for management of IAI in adult patients who have substantial renal impairment?

Q 9.3. Should adjusted dosages of antimicrobial agents be used for management of IAI in adult patients who have substantial hepatic impairment?

Q 9.4. Should adjusted dosages of antimicrobial agents be used for management of IAI in obese patients?

Q 9.5. Should alternative dosing schedules, such as prolonged or continuous infusion of selected agents, be used for management of IAI in critically ill patients or those infected with resistant pathogens?

Standard dosing recommendations for antimicrobial agents used in the treatment of patients with IAI are listed in Table 11. These dosing recommendations have been derived from the information published in RCTs (see Supplementary Tables; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) and supplemental publications describing individual agents, from the prescribing information for specific antimicrobials approved by the FDA [523], and from a standard pharmacology text [524]. For lower-risk patients with CA-IAI who do not have substantial renal or hepatic impairment or severe obesity, the task force believes these dosage recommendations should be fairly accurate, because they reflect dosing from clinical trials primarily enrolling lower-risk subjects without major organ impairment [3,389].

Critically ill patients may benefit from adjusted dosing of many antimicrobial agents. The evidence supporting this for patients with IAI is mostly indirect, however. Critical illness may impact the volume of distribution (Vd) and clearance of

TABLE 11. DOSING OF ANTIMICROBIAL AGENTS

<i>Agent</i>	<i>Standard dose</i>	<i>Renal dose</i>
<i>Aminoglycosides</i>		
Amikacin	7.5 mg/kg IV q8-12h	7.5 mg/kg IV q12-72h based on serum drug levels
Gentamicin	1.5-2.5 mg/kg IV q8h-12h; 4-7 mg/kg IV q24h	1.5-2.5 mg/kg IV q12-48h based on serum drug levels
Tobramycin	1.5-2 mg/kg IV q8h; 4-7 mg/kg IV q24h	1.5-2 mg/kg IV q12-72h based on serum drug levels
<i>Penicillin/β-lactamase inhibitor combinations</i>		
Ampicillin-sulbactam	1.5-3 g IV q6h	1.5-3 g IV q12-24h
Amoxicillin-clavulanate	1.2 g IV q6-8h	1.2 g IV, then 0.6 g IV q12-24h
Ticarcillin-clavulanate (not currently available)	3.1 g IV q6h	1-2 g IV q12-24h
Piperacillin-tazobactam	3.375-4.5 g IV q6h	2.25 g IV q6-8h
<i>Cephalosporins (including cephamycins) and cephalosporin-β-lactamase inhibitor combinations</i>		
Cefoxitin	1-2 g IV q6h	0.5-1 g IV q8-48h
Cefotetan	1-2 g IV q12h	0.5-1 g IV q12-24h
Cefazolin	1-2 g IV q8h	1 g q12-24h
Cefuroxime	1.5 g IV q8h	0.75 g IV q12-24h
Cefotaxime	1-2 g IV q6-8h	0.5-1 g IV q8-24h
Ceftriaxone	1-2 g IV q24h	No dosing adjustment; check blood levels with dialysis
Ceftazidime	1-2 g IV q8h	0.5-1 g IV q12-24h
Cefepime	1-2 g IV q12h	0.5-2 g IV q24h
Cefoperazone-sulbactam: 1:1 ratio	1-2 g IV q12h	No dosing adjustment; maximum daily sulbactam dosage of 1-2 g depending on degree of renal impairment
2:1 ratio	1.5-3 g IV q12h	
Ceftolozane-tazobactam	1.5 g IV q8h	750 mg IV q8h or 375 mg IV q8h depending on degree of renal impairment
Ceftazidime-avibactam	2.5 g IV q8h	0.94-1.25 g IV q8-48h depending on degree of renal impairment
<i>Monobactam</i>		
Aztreonam	1-2 g IV q8h	1-2 g IV, then 0.5-1 g IV q6-12h
<i>Carbapenems</i>		
Ertapenem	1 g IV q24h	0.5 g IV q24h
Doripenem	0.5 g IV q8h	0.25-0.5 g IV q8-12h
Imipenem-cilastatin	0.5-1 g IV q6-8h	0.125-0.5 g IV q6-12h
Meropenem	1-2 g IV q8h	0.5-1 g IV q12-24h
<i>Fluoroquinolones</i>		
Moxifloxacin	400 mg IV q24h	No dosing adjustment
Ciprofloxacin	400 mg IV q12h	200-400 mg IV q18-24h
Levofloxacin	500-750 mg IV q24h	250-750 mg IV q24-48h
<i>Glycylcycline</i>		
Tigecycline	100 mg IV, then 50 mg IV q12h	No dosing adjustment
<i>Anti-anaerobic agents</i>		
Clindamycin	600-900 mg IV q6-12h	No dosing adjustment
Metronidazole	1 g IV, then 0.5 g IV q6-8h	No dosing adjustment
<i>Agents with activity against gram-positive organisms</i>		
Ampicillin	1-2 g IV q4-6h	Reduce frequency of dosing to q6h-q24h depending on degree of renal impairment
Daptomycin	4-6 mg/kg q24h	4-6 mg/kg q48h
Linezolid	600 mg IV q12h	No dosing adjustment
Teicoplanin	400 mg IV q12h × 3 doses, then 400 mg IV q24h	Reduction of daily dosage to one-half to one-third depending on degree of renal impairment
Vancomycin	10-20 mg/kg IV q12h	10-20 mg/kg IV q24h with subsequent dosing based on serum drug levels
<i>Antifungal agents: Azoles</i>		
Fluconazole	400 mg IV q24h, then 200 mg IV q24h	200 mg IV q24h, then 100 mg IV q24h or after hemodialysis
Voriconazole	6 mg/kg q12h × 2 doses, then 3-4 mg/kg q12h	IV formulation not recommended because of accumulation of SBEC (sulfobutyl ether beta-cyclodextrin sodium) vehicle
<i>Antifungal agents: Echinocandins</i>		
Anidulafungin	200 mg IV, then 100 mg IV q24h	No dosing adjustment
Caspofungin	70 mg IV, then 50 mg IV q24h	No dosing adjustment
Micafungin	100 mg IV q24h	No dosing adjustment
<i>Antifungal agents: Polyenes</i>		
Amphotericin B deoxycholate	1-1.5 mg/kg IV q24h	1-1.5 mg/kg IV q48h
Amphotericin B lipid complex, liposomal amphotericin B	5 mg/kg IV q24h	No dosing adjustment

IV = intravenous.

antimicrobial agents. The Vd for hydrophilic antibiotic agents, such as β -lactams, aminoglycosides, and glycopeptides, may be expanded as a result of administration of large volumes of IV fluids, and further exacerbated by fluid shifts into the extravascular space [525–527]. Increased renal clearance of antibiotic agents may also occur in some critically ill patients [525,526,528]. These alterations could lead to suboptimal blood or tissue concentrations, with the potential for treatment failure if the infection is because of less susceptible pathogens [525–529]. For β -lactams, aminoglycosides, tigecycline, vancomycin, and polymyxins, some clinical studies have found improved outcomes in selected critically ill patients treated with higher dosages or shorter dosing intervals, particularly in those patients infected with less susceptible organisms [478–480,525,526,530,531].

Thus, the task force believes that altered antimicrobial dosing regimens, including higher initial loading doses, may be useful in selected patients with IAI. Critically ill patients, however, may also have impaired renal function, leading to decreased antibiotic clearance, and a risk for antibiotic toxicity [525–528,532]. Therefore, use of higher dosages or altered dosing intervals in critically ill patients with IAI needs to be individualized.

Dosing adjustments of antimicrobial agents cleared primarily by renal elimination are frequently necessary in patients with IAI who have impaired kidney function. Most antimicrobial agents do not require dosage adjustments until the glomerular filtration rate (GFR) decreases below 60 mL/min. The GFR is typically estimated according to the Cockcroft-Gault formula [533,534], which relies on serum creatinine measurements. Other methods for determining estimated GFR (eGFR) are available, which may be preferable to the Cockcroft-Gault method; however, these also lack accuracy and precision, particularly in critically ill patients [535–537]. Because the eGFR heavily influences dosing of antimicrobial agents in patients with renal impairment, the treating clinician should be aware of pitfalls associated with these calculations of eGFR.

In general, the initial dosage of most antimicrobial agents should not be altered in patients with impaired renal function, because initial drug concentrations will primarily reflect Vd and not clearance [526,527,538,539]. Subsequent dosing of antimicrobial agents will typically be altered according to the eGFR [539]. Table 11 provides general recommendations for antimicrobial dosing adjustments in patients with impaired kidney function [523,526,539].

Antimicrobial dosing adjustments in patients with renal dysfunction can be expedited using therapeutic drug moni-

toring [527,539]. Commercial assays are commonly available for the measurement of blood concentrations of vancomycin and aminoglycosides, although not for most other antibiotic agents. Therapeutic drug monitoring may be of particular value when the GFR fluctuates during the course of antimicrobial therapy. Antimicrobial dosing in patients with renal dysfunction can also be facilitated by consultation with a clinical pharmacist familiar with use of antimicrobial agents. This may be particularly important in patients undergoing various forms of renal replacement therapy, such as intermittent hemodialysis or continuous veno-venous hemofiltration-dialysis. Specific recommendations for antimicrobial dosing in patients undergoing renal replacement therapy are beyond the scope of this guideline, but several reviews provide information on this subject [527,536,538–540].

There is far less information available regarding antimicrobial dosage adjustments in patients with hepatic dysfunction. Liver disease has an impact primarily on the dosing of antibiotic agents cleared by hepatic metabolism; thus, hepatic dysfunction can lead to accumulation of certain anti-infective agents and a risk of associated toxicity [528,541,542]. Table 12 summarizes recommendations made by Halilovic and Heintz [542] for dosing of some hepatically cleared antibiotic agents used in the treatment of patients with IAI.

Alternative dosing regimens for obese patients should also be considered. Obesity may have a major impact on the Vd of antimicrobial agents. In general, the Vd of hydrophilic antibiotic agents correlates better with the lean body mass or ideal body weight, whereas the Vd of lipophilic antibiotic agents correlates better with total body weight. For many antibiotic agents of interest, an adjusted body weight calculation, which adds a percentage of the excess body weight to the ideal body weight, has been used to predict Vd [543–548]. Obese patients with a higher Vd may benefit from a higher initial dose of a given antimicrobial agent.

Renal clearance of antibiotic agents can also be affected by obesity. In the absence of intrinsic renal disease, obesity generally produces an increase in creatinine clearance. Standard equations for creatinine clearance, however, such as the Cockcroft-Gault formula [533], may produce misleading values [545,549], and corrective formulas, such as the Salazar-Corcoran equations [550], have not been fully validated [551]. Calculations of eGFR may be particularly prone to error in critically ill obese patients [535,543,545], making dosage adjustments in these patients quite problematic.

Recommendations based on pharmacokinetic principles have been developed for the dosing of individual antibiotic

TABLE 12. ANTIMICROBIAL DOSAGE ADJUSTMENTS IN PATIENTS WITH CIRRHOSIS

<i>Agent</i>	<i>Suggested adjustment</i>
Cefotaxime	No dosage adjustment
Ceftriaxone	Consider 50% reduction in patients with Child-Pugh class C cirrhosis
Moxifloxacin	No dosage adjustment
Ciprofloxacin	No dosage adjustment
Tigecycline	Decrease maintenance dosage to 25 mg q12h in patients with Child-Pugh class C cirrhosis; no change in initial loading dosage
Metronidazole	Decrease dosage to 500 mg q12–24h in patients with Child-Pugh class A, B, or C cirrhosis
Clindamycin	Decrease dosage by 50% in patients with Child-Pugh class C cirrhosis
Linezolid	No dosage adjustment; use cautiously in patients with Child-Pugh class C cirrhosis

TABLE 13. ANTIMICROBIAL DOSAGE ADJUSTMENTS IN OBESE PATIENTS

<i>Agent</i>	<i>Suggested Adjustment</i>
Aminoglycosides	Base dosage on adjusted body weight (ideal body weight plus 40% of the excess weight above ideal weight)
β -lactam/ β -lactamase inhibitor combination	Use dosages at the higher end of treatment range, or use standard dosages with therapeutic drug monitoring in critically ill obese patients
Cephalosporin	Use of dosages at the higher end of treatment ranges, or use standard dosages with therapeutic drug monitoring in critically ill obese patients
Fluoroquinolones	Use dosages at the higher end of treatment ranges, or base dosage on adjusted body weight (ideal body weight plus 45% of the excess over ideal body weight)
Clindamycin	Use higher dosages up to 4.8 g/d in patients with a body mass index greater than 40 kg/m ²
Vancomycin	Base dosage on actual body weight, with limitation of the total dose to 4g/d
Linezolid	Dosage adjustment for obesity not currently recommended
Daptomycin	Base dosage on total body weight

agents or classes in obese patients. These include aminoglycosides [543–545,548,552–556], various β -lactam antibiotic agents [531,543–546,556–563], fluoroquinolones [543,544,548,556,564–569], clindamycin [548,569], vancomycin [344,452,544,545,548,556], linezolid [570,571], and daptomycin [545,548,556,572,573]. Suggestions for dosing of these antibiotic agents in obese patients are summarized in Table 13. As of yet, however, there are little data documenting improvements in clinical outcomes with use of these alternative dosing strategies. In fact, obesity has not been uniformly identified as a significant risk factor for an adverse outcome in patients with IAI [574,575].

Continuous or prolonged (over 3–4 h) antibiotic infusion, as opposed to intermittent infusion (over 30–60 min), is a therapeutic tactic designed to take advantage of the pharmacokinetic and pharmacodynamic properties of specific antibiotic agents to maximize their clinical efficacy. The primary class of antibiotic agents that has been assessed using continuous or prolonged infusion are β -lactams. The main pharmacodynamic parameter believed to be important in a bacteriologic response to β -lactams is the time that the local concentration is above the MIC of the specific bacterium (ideally, 40% or more of the dosing interval). This time is enhanced by continuous or prolonged infusion [576–580]. One study in patients with IAI found that continuous infusion of cefotaxime resulted in peritoneal fluid concentrations of the antibiotic at least five times greater than the MICs of the infecting Enterobacteriaceae [581].

Meta-analyses comparing continuous or prolonged antibiotic infusion to conventional intermittent infusion in a broad range of patients with various types of infections have come to conflicting conclusions with regard to the efficacy of this approach, however [579,580,582]. A recent large RCT of patients with severe sepsis, 25% of whom had an abdominal source, did not demonstrate any advantage to continuous infusion; results in patients with IAI were not reported separately [583]. A single RCT comparing continuous versus intermittent infusion of piperacillin-tazobactam in patients with IAI (Supplementary Table P; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) also did not demonstrate any advantage to the continuous infusion approach [584]. A separate analysis of pharmacokinetic and pharmacodynamic parameters and the MICs of the isolated pathogens in this trial suggested that either ap-

proach would likely have sufficed in these patients, however [585]. Thus, while continuous or prolonged antibiotic infusion appears safe and effective for patients with IAI, it remains unknown if there is a demonstrable clinical benefit to its use. The task force believes that this approach could be considered when treating potentially less susceptible strains of gram-negative pathogens in critically ill patients with IAI.

9.1. *We recommend use of standard dosages of antimicrobial agents for lower-risk patients with CA-IAI who are not severely obese and who do not have substantial renal or hepatic impairment (Grade 1-B). We suggest use of higher dosages of antimicrobial agents for selected higher-risk patients with CA-IAI or HA-IAI (Grade 2-B).*

9.2. *We suggest use of adjusted dosages of antimicrobial agents, based on available clinical outcome data, standard pharmacokinetic parameters, and therapeutic drug monitoring, where applicable, for management of IAI in patients with significant renal impairment (Grade 2-B).*

9.3. *We suggest use of adjusted dosages of selected, hepatically cleared antimicrobial agents for management of IAI in patients who have substantial hepatic impairment (Grade 2-B).*

9.4. *We suggest use of adjusted dosages of selected antimicrobial agents, based on available clinical outcome data and pharmacokinetic parameters, for management of IAI in obese patients (Grade 2-B).*

9.5. *We suggest that prolonged or continuous infusion of β -lactam antibiotic agents does not need to be used routinely for treatment of patients with IAI, but is an option for management of IAI in critically ill patients and those at risk for infection with resistant gram-negative pathogens (Grade 2-B).*

10. Duration of antimicrobial therapy

Q 10.1a. Should antibiotic agents be given to patients with severe or necrotizing pancreatitis who do not have a documented peri-pancreatic infection?

Q 10.1b. Should antibiotic agents be given to patients with uncomplicated acute colonic diverticulitis?

Q 10.2. Which patients should be considered to have intra-abdominal contamination only, and receive antimicrobial therapy for no greater than 24 hours?

Q 10.3a. What should the duration of antimicrobial therapy be for patients with established IAI?

Q 10.3b. What should the duration of antimicrobial therapy be for patients with established IAI in whom a definitive source control was not performed?

Q 10.4. Should patients with secondary bacteremia from IAI receive a longer course of antimicrobial therapy?

Q 10.5. Should immunosuppressed patients with IAI receive longer courses of antimicrobial therapy?

Limiting the duration of antimicrobial therapy in patients with IAI and other infections is an important antimicrobial stewardship measure. Short duration therapy should decrease the development of antimicrobial resistance as well as lessen the chance that the patient will have an adverse reaction to an antimicrobial agent [197,529,586]. Antimicrobial agents have been given to patients with or at risk for IAI for a number of reasons, including prevention of infection in patients with a non-infectious inflammatory process such as acute pancreatitis, peri-operatively for an uncomplicated IAI such as non-perforated appendicitis, for intra-abdominal contamination that has occurred as a result of trauma or iatrogenic injury, or for an established complicated IAI.

The use of antibiotic agents to prevent infection in patients with severe or necrotizing pancreatitis had been advocated previously. Six RCTs of antibiotic prophylaxis for patients with severe pancreatitis have been published since 2000 (Supplementary Table Q; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [587–592]. None showed any impact on death or on most measures of morbidity, although two showed a decrease in the incidence of infection, mainly extra-pancreatic infections [588,590]. Recent meta-analyses of these and earlier studies have, for the most part, demonstrated little benefit to the use of antimicrobial agents in patients with severe or necrotizing pancreatitis who do not have an established infection (Supplementary Table R; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [593–598].

One meta-analysis showed a survival benefit with use of prophylactic antibiotic agents, but only if cohort studies were included along with RCTs [599]. Other meta-analyses have suggested some reductions in rates of secondary pancreatic infection, need for operative intervention, occurrence of non-pancreatic infections, or hospital length of stay, but without changes in deaths or other global outcomes [600–603]. These benefits, however, were not detected when analyzing only higher quality or more recent studies [598,604]. Concerns have also been raised about increased bacterial resistance as a result of treating patients with severe pancreatitis with prophylactic antimicrobials [109,588,589]. Based on the lack of clear efficacy and the potential risk of increased bacterial resistance, the task force recommends against use of antibiotic agents to prevent infection in patients with severe or necrotizing pancreatitis.

The need for antibiotic agents in the management of uncomplicated acute sigmoid diverticulitis has come into question. Two retrospective studies found that many patients with acute colonic diverticulitis could be treated entirely without antibiotic agents [605,606]. A subsequent large RCT of this hypothesis (Supplementary Table S; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) found no differences in outcomes in patients with uncomplicated, left-sided diverticulitis who

received antibiotic agents and IV hydration versus those who received IV hydration alone [607]. A recent Cochrane review suggests that antibiotic agents may not be necessary, although calling for additional high quality trials [608]. Thus, omitting use of antimicrobial therapy in selected lower-risk patients with acute, uncomplicated sigmoid diverticulitis appears to be a reasonable option. It would be premature to conclude, however, that this approach should be used in higher-risk patients, such as those receiving immunosuppressive therapy.

Many patients, such as patients with penetrating abdominal trauma, present with intra-abdominal contamination without having an established IAI at the time of a surgical procedure. Antimicrobial use for such patients falls into a gray area between surgical prophylaxis and treatment for IAI. Guidelines for surgical prophylaxis generally recommend no more than 24 hours of antibiotic therapy to prevent surgical site infection [238,515]; in fact, the need for any post-operative antibiotic administration has been questioned [609,610].

Several lines of evidence support limiting peri-operative antibiotic therapy to no more than 24 hours in patients with intra-abdominal contamination, even though such patients are at increased risk for infection. In three RCTs included in the previous evidence review [3], infectious outcomes were similar in patients with abdominal contamination as a result of traumatic injury treated with 24 hours compared with five days of antibiotic therapy post-operatively [611–613]. The duration of intra-abdominal contamination previously defined as differentiating contamination from an established infection was 24 hours for an upper gastrointestinal (stomach, duodenal, biliary) source and 12 hours for a lower gastrointestinal (small bowel, colon) source [2,4]. There is also evidence that post-operative antibiotic therapy can be limited to no more than 24 h in patients with uncomplicated IAI.

Recent RCTs (Supplementary Table T; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) have found no benefit to more than 24 hours of antibiotic therapy in patients with non-perforated appendicitis and patients undergoing cholecystectomy for acute cholecystitis [614,615]. Older, allocation-based studies reviewed previously [3] demonstrated similar rates of post-operative infection in patients with non-perforated or ischemic gastrointestinal processes treated with peri-operative antibiotic agents only compared with historical controls receiving more prolonged courses of therapy [616,617]. Therefore, for most patients undergoing source control for intra-abdominal contamination without an established infection or for an uncomplicated IAI in which the source control procedure can completely eradicate the infection, the task force concluded that antimicrobial use should be limited to no more than 24 hours.

There are increasingly strong data that duration of antimicrobial therapy for patients with established IAI can be somewhat shorter than had been used in the past. Older studies suggested no differences in outcome comparing five days with longer courses of antimicrobial therapy for patients with gastrointestinal perforations who had adequate source control [616–618]. More recent retrospective cohort studies have also found no significant differences in the rates of post-operative infections in patients with complicated appendicitis who received shorter duration of antimicrobial therapy

(generally less than five days) versus longer duration therapy (five days or more) [619,620]. In fact, some retrospective studies suggested that patients receiving prolonged antimicrobial therapy for IAI were at increased risk of secondary infections and death [621,622].

Two recent RCTs (Supplementary Table U, see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) also support a decreased duration of therapy for IAI. A smaller study found three days of antibiotic therapy was as effective as five or more days of therapy in patients with mild to moderate IAI, 50% of whom had perforated appendicitis [623]. A larger RCT supported by the SIS (the STOP-IT trial) demonstrated that a fixed four-day course of antimicrobial therapy was as effective as a longer, symptom-based duration of therapy (average of eight days of antimicrobial therapy). Importantly, this latter trial restricted the number of patients with complicated appendicitis to 15%. In addition, the mean APACHE II score was approximately 10, suggesting the patients in this trial were more severely ill than those in many prospective trials of antimicrobial therapy that have used a longer duration of therapy [82]. Overall, the results of this and other studies suggest that a 4-day duration of therapy is adequate for most patients with IAI.

The duration of antimicrobial therapy for patients with IAI treated without a source control procedure (such as those with complicated diverticulitis or a peri-appendiceal phlegmon managed non-operatively) is open to question. Most patients selected for non-operative management are likely lower-risk patients who have robust host defenses, which allows them to locally control the infection. There are very little data on standardized approaches to antimicrobial therapy in such patients; even when antibiotic duration is described, the rationale for a given duration is rarely discussed. Previous studies have shown that resolution of fever, leukocytosis, and paralytic ileus is associated with a high likelihood of treatment success in patients with IAI who undergo definitive source control [624,625], making it reasonable to discontinue anti-infective agents at that time. The consensus of the task force was that lower risk-patients who did not undergo definitive source control could have antimicrobial therapy discontinued at the time of resolution of these symptoms and did not have to undergo a prolonged course of therapy. If signs of infection persisted after five to seven days, however, those patients should be considered to have had treatment failure and undergo imaging and other studies to determine whether or not a definitive source control should be undertaken.

There is a wide variation in the duration of antimicrobial therapy for treatment of patients with secondary bacteremia, including that from an abdominal source [626]. Recent studies suggest that patients with transient secondary blood stream infections do not need more than seven days of antibiotic treatment. One study of critically ill patients with secondary blood stream infections, including those from a peritoneal source, found no difference in outcomes among patients receiving shorter (seven days or fewer) versus longer courses of antimicrobial therapy [627]. A systematic review and meta-analysis of duration of antibiotic therapy among critically ill patients with secondary bacteremia also found that patients who received shorter courses of anti-infective therapy, generally defined as seven or fewer days, had out-

comes similar to patients receiving longer courses of therapy [628]. Thus, the task force has suggested that patients with transient bacteremia because of IAI can have antimicrobial therapy limited to seven days.

There are some patients with IAI for whom shorter-course antimicrobial therapy might not necessarily be appropriate. One group of patients at higher risk for treatment failure are those who receive immunosuppressive medications, such as patients who have undergone solid organ transplant procedures. These patients are frequently treated with prolonged antimicrobial therapy for any infection, including IAI. Definitive data are not available to draw any conclusions as to the efficacy of shorter courses of antimicrobial therapy in these patients. It is also uncertain if short course therapy should be used in critically ill patients with severe sepsis and septic shock. Although the STOP-IT trial did not demonstrate any benefit of prolonged antimicrobial therapy in any subgroup of patients, including those with an APACHE II score greater than 10 [82], relatively few severely ill patients with sepsis or septic shock were enrolled in the trial. There is anecdotal evidence that stopping antimicrobial therapy in critically ill patients with uncontrolled tertiary peritonitis may lead to increased deaths [629]; however, such patients may actually be experiencing treatment failure, for which further anti-infective treatment would generally be warranted. Overall, the task force has concluded that shorter course antimicrobial therapy can be used in most patients with IAI, but that some caution may be needed when applying this principle to immunosuppressed patients or those with ongoing signs of sepsis or septic shock.

10.1a. We recommend against the use of antibiotic agents to prevent infection in patients with severe or necrotizing pancreatitis (Grade 1-B).

10.1b. We suggest that antibiotic therapy may not be necessary for the treatment of lower-risk patients with uncomplicated acute colonic diverticulitis (Grade 2-B).

10.2. We recommend that antimicrobial therapy be limited to 24 hours in patients with traumatic bowel perforations operated on within 12 hours (Grade 1-A), patients with gastroduodenal perforations operated on within 24 hours (Grade 1-C), patients with acute or gangrenous appendicitis in the absence of perforation (Grade 1-A), patients with acute or gangrenous cholecystitis in the absence of perforation (Grade 1-A), or patients with ischemic, non-perforated bowel (Grade 1-C).

10.3a. We recommend no more than four full days (96 h) of antimicrobial therapy for patients with IAI who had an adequate source control procedure (Grade 1-A).

10.3b. We suggest that no more than 5–7 days of antimicrobial therapy be provided to patients with established IAI in whom a definitive source control procedure is not performed. We suggest that clinical parameters, including fever, leukocytosis, and adequacy of gastrointestinal function, be assessed periodically to determine whether antimicrobial therapy can be discontinued sooner. We suggest that patients who do not respond fully to antimicrobial therapy within 5–7 days be reassessed for a potential source control intervention (Grade 2-C).

10.4. We suggest that most patients with secondary bacteremia because of IAI who have undergone adequate source control and are no longer bacteremic can have antimicrobial therapy discontinued after seven days (Grade 2-B).

10.5. *There are insufficient data to evaluate duration of therapy in patients receiving immunosuppressive medications (no recommendation).*

11. Pathogen-directed antimicrobial therapy

Q 11.1a. Should lower-risk patients with CA-IAI have antimicrobial therapy changed on the basis of culture results?

Q 11.1b. Should higher-risk patients with CA-IAI and those with HA-IAI have antimicrobial therapy changed on the basis of culture results?

Q 11.1c. Can treatment of patients with highly resistant organisms, isolated as part of a mixed peritoneal culture in patients with HA-IAI, be deferred?

Q 11.2. Should antimicrobial therapy be de-escalated or streamlined on the basis of culture results in patients with IAI?

The use of culture data to guide antimicrobial therapy is an established principle for the treatment of patients with infectious diseases [6,197,200]. It is unclear, however, whether this principle should be applied routinely to patients with IAI. Indirect evidence provides little support for routine pathogen-directed therapy in lower-risk patients with CA-IAI. As discussed in Section 3, routine cultures in these patients have been found to provide little benefit, suggesting that altering therapy on the basis of those results would have little impact [186,188–191,630]. Further, recent RCTs have not identified higher failure rates in lower-risk patients who receive a narrower-spectrum versus a broader-spectrum antimicrobial regimen, despite the occasional isolation of micro-organisms resistant to a narrower-spectrum agent [215,225,226,228–230,249–253,294,295,300]. Finally, the use of shorter courses of antimicrobial therapy [82,623], as recommended in the previous Section, would make use of pathogen-directed therapy moot in many lower-risk patients with IAI. Therefore, the task force does not believe that routine pathogen-directed antimicrobial therapy is necessary in lower-risk patients who are making a satisfactory response to empiric therapy. Alteration of the antimicrobial regimen is appropriate, however, in patients who do not respond to initial therapy and are classified as having treatment failure, discussed further in Section 12.

There may be a greater rationale for providing pathogen-directed therapy to higher-risk patients with CA-IAI and HA-IAI. Altering an initially inadequate antimicrobial regimen according to culture results appeared to be important in patients with pneumonia or bacteremia, although results were not as good in those patients as they were in those whose initial empiric regimen provided adequate coverage [197,199,200]. There is relatively little direct evidence as to whether this approach also applies to higher-risk patients with IAI. One retrospective study found that altering an initially inadequate antimicrobial regimen did not improve outcomes in patients with IAI, although not all of the patients in the study would be considered at higher risk [49]. Nonetheless, based on the potential deleterious consequences of inadequate antimicrobial therapy in higher-risk patients, the task force believes it is reasonable to adjust that therapy on the basis of culture results in higher-risk patients with CA-IAI or HA-IAI. As with lower-risk patients, however, this is probably unnecessary in patients who are nearing completion

of a course of therapy and have already exhibited satisfactory clinical responses.

Peritoneal cultures from some higher-risk patients may reveal a highly resistant micro-organism along with larger numbers of less resistant pathogens. It is uncertain whether a definitive antimicrobial regimen must be active against all of the isolated micro-organisms or just against the predominant ones. Published information specifically examining this question does not exist. The task force has therefore not made any recommendation on this question.

De-escalation or streamlining of antimicrobial therapy may be an option for higher-risk patients with CA-IAI and those with HA-IAI once definitive culture results are available. De-escalation may include conversion from a broader-spectrum to a narrower-spectrum antibiotic agent, eliminating duplicative agents if a single agent will suffice to manage the isolated organisms, and discontinuation of agents effective against gram-positive, gram-negative, or fungal pathogen if those micro-organisms are not isolated. In selected patients, changing to an oral rather than an IV agent may also be an option [197]. Several studies have described de-escalation in critically ill patients with sepsis from an abdominal source, although not all have reported the results in patients with IAI separately [146,198,631–636]. Importantly, none of these studies have identified any adverse effects of de-escalation, and some have suggested decreased deaths in patients who underwent de-escalation [146,198,635]. Based on the available data, the task force recommends that de-escalation or streamlining of antimicrobial therapy be employed whenever feasible.

11.1a. We recommend against changing antimicrobial therapy on the basis of culture results in lower-risk patients with CA-IAI who have a satisfactory clinical response to source control and empiric antimicrobial therapy (Grade 1-B).

11.1b. We suggest modifying antimicrobial therapy in higher-risk patients with CA-IAI and HA-IAI if culture results identified organisms resistant to the initial empiric regimen and further antimicrobial therapy is planned (Grade 2-C).

11.1c. There are insufficient data to make any recommendation regarding modification of antimicrobial therapy in patients with HA-IAI who have a highly resistant organism isolated as a minor component of a mixed peritoneal culture (no recommendation).

11.2. We recommend routinely de-escalating or streamlining antimicrobial therapy in higher-risk patients with CA-IAI and HA-IAI to the narrowest-spectrum agent or agents having activity against the isolated micro-organisms, once definitive culture results are available (Grade 1-B).

12. Treatment failure

A. Source control for treatment failure

Q 12.1a. What are the clinical indicators of source control failure in patients with IAI?

Q 12.1b. When should patients with IAI be assessed for source control failure?

Q 12.1c. What diagnostic maneuvers should be undertaken in patients who are suspected of having source control failure?

Q 12.1d. What therapeutic approach should be undertaken with patients with failure of initial source control?

Q 12.1e. When should further source control procedures be undertaken in patients considered to have a treatment failure?

Q 12.1f. Should abdominal fluid or tissue cultures be obtained in patients with treatment failure?

After initial source control, the clinician may be faced with the task of recognizing and developing a therapeutic plan for patients who fail that intervention. The diagnosis of source control failure may be problematic. Symptoms and signs of recurrent or ongoing IAI, such as abdominal pain, rebound tenderness, ileus, fever, or leukocytosis, are not specific, being quite common in all post-operative patients. Further, these signs may not be present in some patients with recurrent or ongoing IAI. Use of risk factors to identify patients with source control failure, such as those outlined in Section 1, are also insufficient to make a diagnosis in patients with source control failure. Source control failure will actually develop in only a fraction of these higher-risk patients, particularly when the initial procedure was considered adequate [172].

Several studies have demonstrated that changes in physiologic parameters and other clinical problems that become manifest at or beyond post-operative day two are far more predictive of source control failure than the patient status at the time of the initial source control procedure. Adverse trends in individual measures of heart rate, temperature, the ratio of the arterial partial pressure of oxygen to the fractional inspired oxygen concentration ($\text{PaO}_2:\text{F}_i\text{O}_2$), C-reactive protein level, procalcitonin level, SAPS II or multiple organ failure (MOF) or multiple organ dysfunction syndrome (MODS) scores, the development of a fascial dehiscence, or the finding of inadequacy of empiric antimicrobial coverage are all associated with a higher risk of source control failure [15,32,50,57,70,81,637,638]. Thus, the task force would recommend using these temporal signals to help identify patients with a high likelihood of failed source control.

Models combining trends in various risk factors or physiologic scores may have greater potential for predicting source control failure, although none of the current models provide high certainty. Serial MODS scores were used as triggers for on-demand re-laparotomy in one RCT, but there was still a relatively high 31% rate of negative re-laparotomy [170]. A related study found that the combination of changes in several physiologic parameters predicted a positive re-laparotomy, but even the best model had an overall accuracy of approximately 80% [57]. Thus, although the decision to intervene in a patient with presumed source control failure may be aided by use of such models, clinical acumen still needs to be exercised to accurately identify patients with source control failure.

Death is significantly higher in patients with IAI who have a failure of the index source control procedure [48,51,61,71,84,126,637,639]. Moreover, the time to re-operation may be a further determinate of outcome, with therapeutic delays greater than 24–48 hours being associated with increased deaths [51,81]. Thus, early identification of the patient with source control failure through diagnostic imaging or re-laparotomy would be beneficial. Negative diagnostic studies or re-laparotomies, however, may lead to complications as well as increases in resource utilization. The opinion of the task force is that diagnostic investigation or therapeutic interventions should be strongly considered in patients who

have progressive deterioration or no improvement in inflammatory markers or signs of organ function 48 hours after the index intervention, and in those patients who show evidence of ongoing inflammation 5–7 days after the index procedure.

In most patients, the imaging study of choice to investigate treatment failure is contrast-enhanced computed tomographic (CT) imaging [640–642]. The CT scans are generally quite sensitive in detecting infected intra-abdominal fluid collections, particularly when compared with physical examination, laboratory studies, and other imaging modalities [643–645]. The CT scans, however, do not necessarily differentiate infected from uninfected post-operative fluid collections [646–648]. The CT scans may also be less useful for detecting infections because of early anastomotic leaks [649,650]. It has generally been accepted that the utility of contrast-enhanced CT scans increases the longer it is after initial source control. One report suggested, however, that a good diagnostic yield is obtained even at 3–7 days after the index procedure with current generation CT scanners [651]. Nonetheless, because of the risk of false negative imaging in patients with IAI who have early treatment failure, excessive reliance should not be placed solely on CT scanning to determine the need for re-intervention.

Optimal re-intervention in patients with source control failure, as with the index source control procedure, should include measures directed at the elimination, drainage, or control of infected fluid and tissue collections and the prevention of ongoing contamination. Operative morbidity, however, is generally high in patients with source control failure, particularly in those who have already undergone extensive abdominal operations. Thus, when feasible, use of less invasive procedures should be considered. For localized fluid collections, percutaneous drainage is generally recommended [128,149]. Even when complete source elimination is not technically possible, however, less invasive techniques may still be beneficial as temporizing measures, as has been demonstrated for patients with widespread infected pancreatitis [143–145,652]. Overall, the task force supports the concept that some attempt at source control should be undertaken in patients with recurrent or ongoing IAI, because outcomes in these patients are poor in the absence of source control, even with continuation of antimicrobial therapy. The nature of that source control procedure, however, needs to be individually tailored to the patient, taking into consideration both the risks and benefits of the proposed intervention.

There are scant data regarding timing of source control for IAI in patients with treatment failure. The task force believes that undertaking source control within 24 hours of diagnosis is appropriate based on the limited data available [49,146]. In critically ill patients with treatment failure following an index procedure, however, the time to re-operation appears to be a determinate of outcome [51,81,147,148]. Thus, when treatment failure is established in a critically ill patient, efforts to achieve source control should be undertaken as expeditiously as possible.

Patients with source control failure are typically at risk for infections with more resistant pathogens than those who have CA-IAI and may be at risk for highly resistant micro-organisms if they have had significant exposure to the healthcare environment and particularly previous antimicrobial therapy

[17,22–24,26,27,32,43,62,86,88,89]. Inadequate empiric antimicrobial therapy has been independently associated with death in these patients [43,54,58,187,193–195]. Thus, there is a rationale for obtaining peritoneal cultures in patients with source control failure, just as there is generally for any higher-risk patient with IAI. These data are essential for pathogen-directed therapy [42,197,199,200], and may provide the basis for de-escalation of initially broad-spectrum antimicrobial therapy [4,6,196–198].

12.1a. We recommend using measures of ongoing or progressive systemic inflammation or organ system dysfunction to identify patients with likely source control failure (Grade 1-B).

12.1b. We suggest that patients be assessed for source control failure if there is progressive organ dysfunction within the first 24–48 hours after source control, if there is no clinical improvement in organ dysfunction 48 hours or more after source control, or if there are persistent signs of inflammation 5–7 days after source control (Grade 2-C).

12.1c. We suggest that patients who clinically deteriorate or fail to improve within 48–72 hours of the initial procedure be considered for abdominal exploration (Grade 2-C). We recommend that patients suspected of treatment failure after 48–72 hours of the initial source control procedure undergo CT scanning, with percutaneous aspiration or drainage of any potentially infected fluid collections (Grade 1-B).

12.1d. We recommend utilization of the least invasive approach that will either achieve definitive source control or will sufficiently control the infection such that there is resolution of the inflammatory response and organ dysfunction (Grade 1-B).

12.1e. We suggest that further source control be undertaken within 24 hours when failure of source control is identified (Grade 2-C). We suggest that patients with physiologic instability or progressive organ dysfunction should undergo further source control as soon as feasible (Grade 2-B).

12.1f. We recommend obtaining peritoneal cultures routinely in patients with source control failure, such that pathogen-directed antimicrobial therapy can be utilized (Grade 1-C).

B. Antimicrobial therapy for treatment failure

Q 12.2a. How should antimicrobial therapy be approached in patients with IAI who have treatment failure?

Q 12.2b. How should antimicrobial therapy be approached in patients with IAI who have clinical evidence of treatment failure but have negative imaging studies for persistent or recurrent IAI?

Q 12.2c. How should antimicrobial therapy be approached in patients with IAI who have clinical evidence of treatment failure and imaging studies showing inflammation but no discrete intra-abdominal source of infection amenable to source control?

Q 12.2d. How should antimicrobial therapy be approached in patients with IAI who have clinical evidence of treatment failure and imaging studies showing persistent or recurrent IAI, but in whom adequate source control cannot be achieved?

Early treatment failure in patients with IAI, occurring within 48 hours of source control, is typically the result of an unsuccessful initial intervention and not to a failure of anti-

microbial therapy. The limited amount of anti-infective agents these patients have received is unlikely to have exerted much selection pressure on the pathogens that predominated at the time of the index procedure. In contrast, patients with late treatment failure, occurring after 48 hours, are likely to have a somewhat more resistant microbial flora because of longer-duration antimicrobial therapy. The differences between the micro-organisms associated with CA-IAI and HA-IAI attest to this selection pressure [15,22–28,32,33]. The consensus of the task force is that continuation of previous antimicrobial therapy is appropriate in most patients with IAI who experience early treatment failure. Broader-spectrum empiric antimicrobial therapy, however, tailored to the expected risk of resistant pathogens, should be provided to patients with late treatment failure; if feasible, a switch in the class of antibiotic agents being administered should be considered.

Although successful management of IAI is usually heralded by resolution of fever, leukocytosis, and gastrointestinal dysfunction, these signs may persist in some patients, even in the absence of ongoing infection [653,654]. Patients who have persistent signs of inflammation should undergo diagnostic investigations to determine whether there is recurrent or persistent IAI, or an alternate source of infection. If diagnostic studies have negative results, further antimicrobial therapy for IAI is not generally warranted. Retrospective analyses have indicated that use of prolonged antibiotic courses, even in patients with ongoing fever or leukocytosis, does not provide any benefit [618,621,622].

Prospective studies using procalcitonin measurements to determine length of antimicrobial therapy also provided indirect evidence that treatment could be safely discontinued, even if not all signs of inflammation had resolved [655,656]. Moreover, the recent STOP-IT trial found that patients with IAI randomized to antimicrobial therapy continued two days beyond resolution of fever, leukocytosis, and ileus fared no better than patients randomized to having antibiotic agents stopped at four days, whether or not these signs were still present; this finding applied even to patients with higher APACHE II scores [82]. Taken together, these data support the task force's suggestion that antimicrobial therapy be discontinued in patients with IAI who have some clinical signs of treatment failure but whose imaging studies show no clear infectious source.

Imaging studies may be equivocal in some patients who have ongoing fever, leukocytosis, or ileus after an initial course of antimicrobial therapy for IAI. These studies may not identify a discrete source of infection, but may show areas of ongoing inflammation or small fluid collections within the abdomen, which cannot be accessed percutaneously. The importance of these findings is obscure. The task force did not identify any substantive body of literature that addresses therapeutic approaches for such patients. Antimicrobial therapy alone, however, has been used for treating patients with some localized inflammatory processes because of IAI, such as a peri-appendiceal phlegmon or a small intra-abdominal abscess related to diverticular or appendiceal disease [131–135,140–142]. Based on these considerations, the task force suggests that selected patients with clinical signs of treatment failure whose diagnostic studies show ongoing inflammation may receive a trial course of repeat antimicrobial therapy, preferably using agents distinct from those administered initially. Once this brief course of

antimicrobial therapy is completed, however, the patient should not be given further anti-infective agents unless there is clear evidence of clinical deterioration or an imaging study documents progression of the inflammatory process.

Further source control should be the first consideration for treating patients with recurrent or persistent IAI identified by imaging studies. Further intervention may not be feasible, however, if the risk of surgical re-exploration is excessive and less invasive techniques cannot address the source of the infection. A decision made by the patient or a surrogate may also preclude further attempts at source control. The only option for these patients, then, is further antimicrobial therapy. There are few data regarding optimal anti-infective treatment of these patients. The task force suggested approach is based, in part, on current management practices for patients with infected pancreatitis. If at all possible, antimicrobial therapy should be guided by microbiologic data; potentially, cultures can be obtained by diagnostic techniques such as a fine needle aspiration when definitive source control is not an option [657,658]. Patients should be followed clinically and undergo repeat imaging studies while on antimicrobial therapy. If the patient's clinical examination improves substantially or if imaging studies reveal that the infection has abated, antimicrobial therapy can be discontinued. If subsequent imaging studies or a change in the patient's condition make source control a viable option, a procedure should be attempted. Periodic cessation of antimicrobial therapy should be attempted at intervals, even in the setting of persistent systemic inflammation, because indefinite treatment with antimicrobial agents will likely lead to development of resistant organisms. Nonetheless, antimicrobial therapy should not be discontinued in certain patients with IAI, particularly critically ill patients with uncontrolled tertiary peritonitis or worsening sepsis with organ failure [8,629].

12.2a. We suggest that patients with IAI who have early treatment failure and undergo repeat source control within 48 hours of the initial source control intervention do not need to have antimicrobial therapy changed (Grade 2-C). We suggest that patients with IAI who have late treatment failure should have antimicrobial therapy changed to agents appropriate for HA-IAI; if feasible, the class of antibiotic being provided should be switched (Grade 2-C).

12.2b. We suggest that patients with IAI who have clinical evidence of treatment failure but negative imaging studies for recurrent or persistent IAI have antimicrobial therapy discontinued (Grade 2-B).

12.2c. We suggest that patients with IAI who have clinical evidence of treatment failure and imaging studies showing ongoing intra-abdominal inflammation undergo a trial of additional antimicrobial agents appropriate for HA-IAI, using a different class of agents if feasible; if there is no clinical response to this antimicrobial trial within a few days, antimicrobial therapy should be discontinued, and only reinstated if there is evidence of clinical deterioration (Grade 2-C).

12.2d. We suggest that patients with IAI who have clinical evidence of treatment failure and imaging studies showing recurrent or persistent IAI, but in whom further source control cannot be achieved, have antimicrobial therapy continued; antimicrobial therapy should be discontinued when clinical signs of systemic inflammation or organ dysfunction abate

(Grade 2-C). We suggest that these patients be monitored for resistant pathogens, with antimicrobial therapy adjusted as necessary to treat such pathogens (Grade 2-C).

13. Treatment of pediatric IAI

Q 13.1a. What are the preferred agents for initial empiric antimicrobial therapy of lower-risk pediatric patients older than one month (45 wks post-conceptual age) with CA- IAI?

Q 13.1b. What are the preferred agents for initial empiric antimicrobial therapy of higher-risk pediatric patients older than one month (45 wks post-conceptual age) with CA-IAI and those with HA-IAI?

Q 13.2a. What should the duration of antimicrobial therapy be for pediatric patients older than one month (45 wks post-conceptual age) with IAI?

Q 13.2b. Should supplemental oral antimicrobial therapy be provided to pediatric patients with IAI after they have received IV therapy?

Q 13.2c. Should outpatient IV antimicrobial therapy be provided to pediatric patients with IAI who can be discharged from the hospital?

Q 13.3. How should treatment failure be managed in pediatric patients with IAI?

Q 13.4a. How should pediatric patients less than one month old (45 wks post-conceptual age) with necrotizing enterocolitis (NEC) or intestinal perforation be treated?

Q 13.4b. What are the preferred antimicrobial agents for initial empiric therapy of pediatric patients less than one month old (45 wks post-conceptual age) with IAI?

Q 13.4c. What should be the duration of antimicrobial therapy for pediatric patients with IAI less than one month old (45 wks post-conceptual age)?

Q 13.5. What dosages of antimicrobial agents should be used for treatment of pediatric patients with IAI?

The most common IAI encountered in children outside of the neonatal age group is complicated appendicitis; IAI from other sources is observed much less frequently [659]. As with adults, empiric antimicrobial therapy directed against gram-negative Enterobacteriaceae and anaerobic bacteria is appropriate for children with perforated appendicitis and other types of IAI [660,661]. Previously, a combination of ampicillin, an aminoglycoside, and an anti-anaerobic agent was considered the gold standard in treating pediatric patients with IAI. Numerous studies, however, have demonstrated efficacy of other antimicrobial regimens for managing IAI in these patients [328,661]. RCTs published before 2000 are included in the previous evidence review [3], and newer studies are summarized in Supplementary Table V; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/. These RCTs support use of ticarcillin-clavulanic acid [220,662,663], piperacillin-tazobactam [225,327], ertapenem [205,214,220], imipenem-cilastatin [664,665], meropenem [290,666], cefoperazone-sulbactam [203], and combinations of cefotaxime [225,667], ceftriaxone [204,212,319,668], or ceftazidime [210] with metronidazole or clindamycin. In addition, cefuroxime has been approved for use in pediatric patients [523], and cefepime [669] and aztreonam [670] have efficacy for managing

serious pediatric infections, although studies have not specifically addressed their use in pediatric IAI.

Age-based restrictions to use of fluoroquinolone antibiotic agents in pediatric patients were advocated in the past. Investigational studies documented cartilage injury in weight-bearing joints of juvenile canines [671,672], although the importance of these findings was uncertain. A systematic review of the literature suggested that any musculoskeletal adverse events developing in pediatric patients were reversible [303]. The American Association of Pediatrics Committee on Infectious Diseases has recommended the use of fluoroquinolones in certain clinical scenarios, and many centers have adopted this practice [304]. The task force has therefore suggested that ciprofloxacin with metronidazole can be used as an alternative regimen for treating pediatric patients with IAI when other regimens are not suitable, particularly in patients who have major reactions to β -lactam antibiotic agents.

As with adult patients, data demonstrating superiority of any specific antimicrobial regimen for the management of IAI in pediatric patients are lacking [328]. Thus, the task force recommendations regarding selection of specific antimicrobial agents are based on factors such as toxicity, convenience, and cost, with particular emphasis placed on considerations of antimicrobial stewardship. For CA-IAI in lower-risk pediatric patients older than one month, monotherapy with ertapenem or combination therapy with cefotaxime or ceftriaxone plus metronidazole are recommended. An alternative regimen, not nearly as well investigated, is cefuroxime plus metronidazole. The use of ciprofloxacin plus metronidazole can be considered in patients with severe β -lactam reactions (Table 14). The use of aminoglycoside-based regimens is discouraged, because of evidence of decreased efficacy [207,208] as well as the toxicity associated with these agents.

Although recommended by some, the task force does not advocate use of routine anti-pseudomonal coverage for

lower-risk pediatric patients with CA-IAI. *Pseudomonas* spp. has been isolated with variable frequency from peritoneal cultures of pediatric patients with complicated appendicitis. One series identified *P. aeruginosa* in 31% of such cultures [673], but the incidence was substantially lower in other series [20,393,674]. In addition, RCTs have not demonstrated improved outcomes in pediatric patients receiving regimens with anti-pseudomonal coverage compared with patients receiving regimens without that coverage [203,205,220,226,675].

There is minimal evidence with regard to antimicrobial therapy of higher-risk children with CA-IAI or those with HA-IAI. The task force suggests that recommendations for higher-risk pediatric patients parallel those for higher-risk adult patients. Broader-spectrum empiric therapy should be provided initially in pediatric patients with severe sepsis or septic shock, because of the potential for inadequate therapy if a more resistant organism, such as *Pseudomonas* spp., is encountered. Use of piperacillin-tazobactam, imipenem-cilastatin, or meropenem is suggested in these patients. Alternative regimens, not as well studied in pediatric patients, include ceftazidime or cefepime plus metronidazole. Additional coverage of *Enterococcus* spp., MRSA, MDR gram-negative bacilli, or yeast should be considered in pediatric patients with HA-IAI, if they have risk factors for infection with those resistant micro-organisms.

Previously, pediatric patients were frequently prescribed seven or more days of IV antibiotic therapy after source control for perforated appendicitis or other types of IAI [387,673]. A recent RCT indicated that five days of IV antimicrobial therapy was sufficient for these patients (Supplementary Table W; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [319]. Other authorities have advocated earlier discontinuation of antimicrobial therapy in pediatric patients with IAI, either based on a fixed duration of therapy or resolution of clinical signs of infection [328,661,676,677]. Although RCTs have found that a 3–4 day course of antimicrobial therapy is adequate in adult patients [82,214,623], the task force recommends a five-day total duration of antimicrobial therapy in pediatric patients with IAI, because of the lack of evidence on shorter-duration therapy in those patients.

There is increasing acceptance of the option to transition pediatric patients to oral antibiotic agents once they are afebrile and tolerating a regular diet. Two RCTs in pediatric patients found a switch to oral amoxicillin-clavulanic acid equivalent to use of IV therapy only (Supplementary Table O; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) [319,320]. Other retrospective studies suggested this agent or a combination of trimethoprim-sulfamethoxazole plus metronidazole were adequate to complete a course of antimicrobial therapy [387,388].

There are no data, however, indicating that administering oral antibiotic agents after completing a full course of IV antibiotic agents provides any additional benefit [319,677]. Thus, oral antibiotic agents should be used only to complete a recommended five-day course of antimicrobial therapy and not to extend therapy beyond that [328,678]. Similarly, because there are no data suggesting a benefit of additional IV antibiotic agents beyond five days [319,661,678], the use of outpatient IV antimicrobial therapy would generally be

TABLE 14. RECOMMENDED EMPIRIC ANTIMICROBIAL REGIMENS FOR PEDIATRIC PATIENTS OLDER THAN ONE MONTH WITH COMMUNITY-ACQUIRED INTRA-ABDOMINAL INFECTION*

Lower-risk patients	Higher-risk patients
<i>Preferred regimens</i>	
Cefotaxime or ceftriaxone plus metronidazole	Piperacillin-tazobactam
Ertapenem	Imipenem-cilastatin
	Meropenem
<i>Alternative regimens</i>	
Cefuroxime plus metronidazole	Ceftazidime or cefepime plus metronidazole ^a
	Aztreonam plus metronidazole plus vancomycin
<i>Optional regimens</i>	
Ciprofloxacin or levofloxacin plus metronidazole	

*More than 45 weeks post-conceptual age.

^aUse of an agent effective against *Enterococcus* spp. is suggested in patients with severe sepsis/septic shock who receive a cephalosporin-based regimen.

unnecessary for most pediatric patients with IAI. Outpatient IV therapy to complete a five-day course could be considered in the infrequent patient with IAI because of a resistant organism for which no oral agent was suitable. Overall, in the absence of treatment failure, the task force recommends against use of additional oral or IV antibiotic agents beyond five days in pediatric patients with IAI.

In pediatric IAI, complications developing after management of perforated appendicitis are the most common examples of treatment failure. One large observational study documented a 13% risk of an intra-abdominal abscess in pediatric patients with perforated appendicitis [677]. Percutaneous drainage of an abscess provides adequate source control, although small abscesses may be treatable with antibiotic agents alone [679,680]. Further antimicrobial therapy should follow the principles outlined previously for adult patients with treatment failure. There is no evidence that prolonged antimicrobial therapy benefits pediatric patients with a post-operative abscess. In the presence of adequate source control, the task force suggests no more than seven days of antimicrobial therapy for treatment failure in children. These patients may be converted to oral therapy to complete their course of therapy [319], as is done for children with primary IAI. In the absence of adequate source control, however, such as in patients with continued soilage of the abdomen from an appendiceal stump leak, more prolonged antimicrobial therapy may be warranted, with the proviso that definitive source control should be attempted whenever feasible.

IAI in neonatal patients develops most commonly as a result of NEC or spontaneous intestinal perforation; other etiologies, such as post-operative IAI, are also encountered [659]. Source control in premature infants is generally considered imperative. Both laparotomy with resection and peritoneal drainage have been used, however, to treat patients with spontaneous and NEC-induced intestinal perforations [681]. Two RCTs (Supplementary Table X; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) comparing these two approaches showed no differences in mortality; however, considerably different rates of salvage laparotomy were observed in patients treated with initial peritoneal drainage in the two studies [682,683].

There is little prospective evidence regarding optimal antimicrobial therapy for infants with IAI. A few RCTs comparing antibiotic regimens for patients with NEC have been published, but these have evaluated primarily treatment of patients with clinical evidence of NEC without overt perforation; the studies have not addressed directly antimicrobial therapy of patients with established IAI due to intestinal perforation [684]. Thus, recommendations for antimicrobial therapy are based primarily on indirect evidence from studies of NEC and expert opinion [685–687]. In general, the task force believes that antimicrobial therapy in neonatal patients with IAI should conform to the general principles outlined for treatment of HA-IAI. Multi-drug combinations have frequently been used in this high-risk population [688], but monotherapy providing equivalent broad-spectrum gram-negative coverage is acceptable. Selective addition of agents with activity against enterococci, MRSA, and yeast should be considered in patients with risk factors for these resistant organisms, most commonly previous broad-spectrum antibiotic use. Vancomycin has been used for infections suspected to be from MRSA or ampicillin-resistant enterococci.

TABLE 15. SUMMARY OF EMPIRIC ANTIMICROBIAL THERAPY FOR PEDIATRIC PATIENTS LESS THAN ONE MONTH OLD WITH INTRA-ABDOMINAL INFECTION*

<i>General recommendation</i>	
Ampicillin, gentamicin, plus metronidazole	
Ampicillin, cefotaxime, plus metronidazole	
Meropenem	
<i>Additional agents</i>	
<i>Potential pathogen</i>	<i>Suggestion</i>
<i>Enterococcus</i> spp.	Use of ampicillin if <i>E. faecalis</i> is suspected, or use of vancomycin instead of ampicillin if a penicillin-resistant <i>Enterococcus</i> spp. is suspected
MRSA	Use of vancomycin if MRSA suspected
<i>Candida</i> spp.	Use of amphotericin B or fluconazole

*Less than 45 weeks post-conceptual age.

MRSA = methicillin-resistant *Staphylococcus aureus*.

Amphotericin B and fluconazole have been prescribed for fungal peritonitis. Once source control has been achieved, the task force suggests that antimicrobial therapy be continued for 7–10 days. These consensus recommendations for antimicrobial treatment of neonatal patients up to one month of age with IAI are shown in Table 15.

Dosing recommendations for pediatric patients both younger and older than one month are listed in Table 16. Where possible, these dosing recommendations are derived from RCTs (Supplementary Table X; see online supplementary material at www.liebertpub.com/overview/surgical-infections/53/) performed in pediatric patients. Other sources include the prescribing information for specific antimicrobial agents approved by the FDA [523] and a standard pharmacology text [524]. As with adult patients, standard dosing is appropriate for nearly all lower-risk children with CA-IAI. Higher doses, however, may be reasonable in critically ill pediatric patients, who may have an increased volume of distribution and/or accelerated clearance of antimicrobial agents. Optimal dosing of many antimicrobial agents in the neonatal age group is extrapolated from data on older children, because pharmacokinetic studies on these younger patients are frequently lacking.

13.1a. We recommend ertapenem or a combination of cefotaxime or ceftriaxone plus metronidazole for empiric antimicrobial therapy of CA-IAI in lower-risk pediatric patients older than one month (45 wks post-conceptual age) (Grade 1-A). We suggest cefuroxime plus metronidazole as an alternative regimen for empiric treatment of these pediatric patients (Grade 2-B). We suggest ciprofloxacin or levofloxacin plus metronidazole as acceptable regimens for empiric treatment of selected pediatric patients with IAI if other agents cannot be used, particularly for those pediatric patients with life-threatening β -lactam reactions (Grade 2-B). We suggest cefoperazone-sulbactam, where it is available, as an acceptable option for empiric therapy of CA-IAI in lower-risk pediatric patients (Grade 2-B).

13.1b. We suggest piperacillin-tazobactam, imipenem-cilastatin, or meropenem for empiric antimicrobial therapy of CA-IAI in higher-risk pediatric patients older than one month (45 wks post-conceptual age) (Grade 2-A). We also

TABLE 16. DOSAGES OF ANTIMICROBIAL AGENTS FOR PEDIATRIC PATIENTS

Agent	Age	
	Children older than one month of age ^a	Term infants to one month of age ^a
<i>Aminoglycosides</i>		
Amikacin	5–7.5 mg/kg IV q8h	4-5 mg/kg IV q24–48h
Gentamicin	2.5 mg/kg IV q8h	
Tobramycin	2–2.5 mg/kg IV q8h	
<i>Aminopenicillin</i>		
Ampicillin	100–400 mg/kg/d IV in divided doses q6h	50 mg/kg IV q6–12h
<i>β-lactamase/β-lactamase inhibitor combinations</i>		
Ampicillin-sulbactam	100–200 mg ampicillin/kg/d IV in divided doses q6h	50 mg/kg IV q8–12h
Ticarcillin-clavulanate (Not currently available)	200–300 mg/kg/d IV in divided doses q4–6h	
Piperacillin-tazobactam	240–300 mg/kg/d IV in divided doses q6–8h	
<i>Cephalosporins</i>		
Cefoxitin	80–160 mg/kg/d IV in divided doses q6–8h	50 mg/kg IV q8–12h
Cefotetan	20–40 mg/kg IV q12h	
Cefazolin	25–50 mg/kg in 3–4 divided doses q6-8h	
Cefuroxime	75-200 mg/kg/d IV in divided doses q6–8h	
Cefotaxime	50–180 mg/kg/d IV in divided doses q4–6h for patients <50 kg; adult dosages for patients >50 kg	
Ceftriaxone	50–100 mg/kg/d IV in 1–2 divided doses	
Ceftazidime	30–50 mg/kg IV q8h	
Cefepime	50 mg/kg IV q12h (≤16 y and ≤40 kg); adult dosages for >16 y or >40 kg)	
<i>Cephalosporin/β-lactamase inhibitor combination</i>		
Cefoperazone-sulbactam:		
1:1 ratio	40–80 mg/kg/d divided q6–12h	
2:1 ratio	30–60 mg/kg/d divided q6-12h	
<i>Monobactam</i>		
Aztreonam	30 mg/kg IV q6–8h (>9 mo)	
<i>Carbapenems</i>		
Ertapenem	15 mg/kg IV q12h (≤12 y); adult dosages for >12 y	20 mg/kg IV q8–12h
Imipenem/cilastatin	15–25 mg/kg IV q6h	
Meropenem	30–120 mg/kg/d IV in divided doses q8h	
<i>Fluoroquinolones</i>		
Ciprofloxacin	20–30 mg/kg/d IV in divided doses q12h	5–7.5 mg/kg IV q8–12h
Levofloxacin	10 mg/kg IV q12h (6 mo to 5 y); 10 mg/kg IV q24h (≥5 y)	
<i>Anti-anaerobic agents</i>		
Clindamycin	20–40 mg/kg/d IV in 3–4 divided doses	5–7.5 mg/kg IV q8–12h
Metronidazole	22.5–40 mg/kg/d IV in divided doses q8h	15 mg/kg IV q12–24h
<i>Agents with activity against resistant gram-positive organisms</i>		
Vancomycin	10 mg/kg IV q6h	10–15 mg/kg IV q8-12h
Teicoplanin	10 mg/kg IV q8–12h × 3 doses, then 6–10 mg/kg IV q24h	
Linezolid	10 mg/kg IV q8h (<12 y)	
<i>Antifungal agents</i>		
Amphotericin B deoxycholate	1–1.5 mg/kg IV q24h	1 mg/kg/d IV or 1.5 mg/kg IV q48h
Amphotericin B lipid complex, amphotericin B, colloidal dispersion, liposomal amphotericin B	5 mg/kg IV q24h	5 mg/kg IV q24h
Caspofungin	70 mg/m ² IV x 1 dose, then 50 mg/m ² q24h	3–12 mg/kg IV q24h
Fluconazole	3–12 mg/kg IV q24h	

^aOlder or younger than 45 weeks post-conceptual age.
IV = intravenous.

suggest these agents for empiric therapy of HA-IAI in pediatric patients (Grade 2-B). We suggest ceftazidime or cefepime plus metronidazole as alternative regimens for empiric treatment of CA-IAI or HA-IAI in these pediatric patients (Grade 2-B). We suggest aztreonam plus metronidazole plus vancomycin as an acceptable regimen for empiric treatment of selected pediatric patients if other agents cannot be used, particularly for pediatric patients with life-threatening β -lactam reactions (Grade 2-B). We suggest addition of ampicillin or vancomycin as empiric anti-enterococcal therapy of CA-IAI in higher-risk patients and those with HA-IAI if the patient is not being treated with piperacillin-tazobactam or imipenem-cilastatin (Grade 2-B).

13.2a. We recommend no more than five full days (120 h) of antimicrobial therapy of IAI in pediatric patients older than one month (45 wks post-conceptual age) who have had adequate source control (Grade 1-A).

13.2b. We recommend against use of additional oral antimicrobial therapy for IAI in pediatric patients who have had adequate source control, unless given to complete a total antimicrobial course of five days (Grade 1-B).

13.2c. We recommend against use of additional outpatient IV antimicrobial therapy for IAI in pediatric patients who have had adequate source control, unless given to complete a total antimicrobial course of five days (Grade 1-B).

13.3. We recommend that pediatric patients with treatment failure be managed in an analogous fashion to adult patients with treatment failure (Grade 1-C). We suggest using the least invasive means of providing adequate source control and using a standard course of IV antibiotic agents; a change in antibiotic class may be considered in these patients (Grade 2-C). We recommend against use of IV antibiotic agents beyond seven days for children with perforated appendicitis who have a post-operative abscess (Grade 1-C).

13.4a. We recommend either laparotomy or peritoneal drainage as source control in addition to antimicrobial therapy for pediatric patients less than one month of age (45 wks post-conceptual age) with NEC or intestinal perforation (Grade 1-A).

13.4b. We suggest use of ampicillin, gentamicin, and metronidazole or clindamycin; ampicillin, cefotaxime, and metronidazole or clindamycin; or meropenem in pediatric patients less than one month of age (45 wks post-conceptual age) with IAI. Vancomycin may be used instead of ampicillin if there is suspected infection with penicillin-resistant *Enterococcus* spp. or MRSA. Fluconazole or amphotericin B can be added if there is a suspected infection with *Candida* spp. (Grade 2-C).

13.4c. We suggest a 7–10 day course of antimicrobial therapy for pediatric patients less than one month of age (45 wks post-conceptual age), particularly for those with NEC (Grade 2-C).

13.5. We recommend use of standard pediatric dosages for various antimicrobial agents for lower-risk pediatric patients with CA-IAI (Grade 1-B). We suggest use of higher pediatric dosages, where applicable, for higher-risk patients with CA-IAI and those with HA-IAI (Grade 2-C).

Recommendations for Future Investigations

The development of this revised guideline for the management of IAI has uncovered numerous problems for which data are inadequate to allow firm conclusions. Key questions

remain both with respect to optimal source control and to utilization of antimicrobial therapy in patients with IAI.

Many recommendations in these guidelines are stratified based on the perceived risk that a given patient will have an adverse outcome. An adverse outcome has been defined variably in the literature and may refer to treatment failure or to death. Treatment failure, in turn, has been variably defined, ranging from persistent signs of infection to a need for further invasive interventions for source control. At present, a simple tool for calculating risk of either treatment failure or death does not yet exist.

One goal of future investigations would be to construct and validate simple, reliable tools for assessing risk of source control failure and death, such that they can be utilized for planning source control and antimicrobial therapy at the point of care. Relatively simple, revised criteria for identifying patients with sepsis or septic shock have been proposed by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine [80], which may simplify the identification of patients with IAI who have sepsis or septic shock. For purposes of treating patients with IAI, however, additional measures are needed, because not all higher-risk patients with IAI meet these revised criteria for sepsis or septic shock.

Options for source control in patients with IAI continue to evolve. Relatively few new procedures have been evaluated prospectively. There is little doubt that less invasive procedures can provide adequate source control for patients with IAI, and that extensive procedures performed to maximize source control may produce greater morbidity and death than less extensive procedures. Nonetheless, less invasive source control measures may not lead to improved patient outcomes. New procedures should be adequately investigated and not adopted prematurely for patient care. An example is the current controversy over the use of less invasive procedures for managing Hinchey Stage III and IV complicated diverticulitis [154–159].

Given the wide variety of potential source control interventions that could be tested, it is unrealistic to expect RCTs can be used to analyze even a small fraction of these approaches. Non-randomized cohort studies, however, can provide valuable information, particularly if care is taken to ensure that control patients are carefully matched with regard to prognostic factors. The use of large, multi-institutional databases, such as that obtained from the Complicated Intra-Abdominal Infection Observational Study, can facilitate these observations and make them more generalizable [26,438]. The SIS and similar organizations should consider developing similar databases to analyze best practices with regard to source control.

The principles of antimicrobial therapy for patients with IAI are well established. The increasing prevalence of ESBL-producing and fluoroquinolone-resistant strains of *E. coli* and other gram-negative organisms in patients with IAI, however, could have a major impact on antimicrobial selection [28]. These resistance concerns extend to patients with CA-IAI as well as those with HA-IAI. As of yet, it is unclear whether the outcomes of lower-risk patients with CA-IAI will significantly worsen because of these resistant organisms. Although data from a number of RCTs suggest that narrower-spectrum empiric antimicrobial agents are still effective in these patients [204,205,220,225,228–230,252,255,294–296], larger-scale, contemporary investigations are needed to determine the impact of this increasing resistance on outcomes in patients with IAI.

Future investigations should focus on preventing the number of deaths in higher-risk patients, both those with CA-IAI and those with HA-IAI. In general, the adequacy of initial empiric antimicrobial therapy has been thought to have a major impact on the deaths and morbidity of higher-risk patients [43,54,58,71,187,193–195]. This guideline recommends use of empiric anti-enterococcal and antifungal therapy in many of these patients, and also recommends use of empiric agents that have broader-spectrum activity against gram-negative pathogens. The increase in resistant microorganisms makes the selection of appropriate empiric antimicrobial agents for these patients more difficult, but overuse of broad-spectrum agents may lead to even greater resistance problems. The hypothesis that outcomes in severely ill patients with IAI are improved by using broader-spectrum empiric antimicrobial effective against all the expected pathogens should be evaluated prospectively through a methodologically sound trial to determine whether empiric use of broad-spectrum antimicrobial agents, as well as anti-enterococcal, anti-MRSA, and antifungal agents, is actually necessary. To better examine this hypothesis, RCTs of new antimicrobial agents with activity against resistant microorganisms should include adequate numbers of severely ill patients likely to harbor such resistant pathogens.

There are relatively few new anti-infective agents on the horizon that are likely to overcome these resistance problems, and none is likely to be a panacea. Among newer agents undergoing investigation, published phase II data are available only for the use of eravacycline and imipenem-cilastatin with relabactam in patients with IAI [689,690]. Most patients with IAI will therefore continue to be treated with conventional antimicrobial agents. The application of the principles of antimicrobial stewardship will be of utmost importance in conserving these antimicrobial resources. Stratification of empiric antimicrobial therapy according to patient risk and de-escalation of broad-spectrum therapy once culture results have been obtained have been emphasized in this guideline as approaches to antimicrobial stewardship. There is a strong potential, however, that newer diagnostic microbiologic modalities, which provide information on the presence of important pathogens within hours rather than days, will allow earlier deployment of pathogen-directed antimicrobial therapy. As these methodologies mature, prospective studies should be undertaken to document their potential benefits not only in improving outcomes in patients with IAI, but also in decreasing use of broad-spectrum empiric anti-infective therapy.

Other means of promoting antimicrobial stewardship have also been endorsed with these recommendations. Decreasing the duration of antimicrobial therapy to the minimum necessary to achieve a maximal clinical benefit is another fundamental principle of antimicrobial stewardship. The SIS STOP-IT trial has provided valuable data indicating that duration of therapy can be safely limited in adult patients with IAI [82]. Limiting duration of antimicrobial therapy even further, for example, to two days in patients with perforated appendicitis, has been proposed [617]; this hypothesis could be evaluated rigorously in future studies.

Optimizing dosing of antimicrobial agents provides another means of conserving antimicrobial resources. Altered pharmacokinetic parameters are common in critically ill patients, including those with IAI, with resultant underdosing and overdosing of anti-infective agents. The use of extended

infusions to optimize pharmacodynamics of these agents is an attractive approach, but has not yet shown to have clear clinical benefits in patients with IAI. Optimization of antimicrobial dosing for patients at the extremes of age, obese patients, and those with renal or hepatic impairment has not been investigated sufficiently; such studies should be considered, because these are common risk factors in the most severely ill patients with IAI.

Patients with treatment failure are at substantially increased risk for morbidity and death. The ideal means of providing source control in these patients has not been fully elucidated. There are clearly trade-offs between less aggressive approaches, which may lead to incomplete source control, and more invasive approaches, which may lead to excess procedural morbidity and death. The development of more standardized approaches to source control in these patients could potentially improve the outcomes of these severely ill patients.

There are also numerous questions related to the treatment of pediatric patients with IAI. The use of less invasive procedures for source control in pediatric patients with IAI is becoming widespread. Careful evaluation as to the efficacy of these interventions should be ongoing. Although there is good evidence that non-aminoglycoside-based antimicrobial regimens provide equivalent if not superior results in most pediatric patients with IAI, aminoglycoside-based regimens continue to be widely used in neonatal patients. Studies of alternative regimens are needed to avoid the potential side effects of these agents. Another important question is whether or not antimicrobial therapy can be limited further in pediatric patients with IAI; extended duration therapy is still frequently used in these patients.

Although this guideline has focused on the management of patients with IAI, ongoing investigations into the pathophysiology of IAI should not be discounted. These investigations may provide an avenue toward novel ways of treating patients with these infections. The pioneering studies performed nearly 50 years ago on the importance of both aerobic gram-negative bacilli and anaerobic organisms in the pathophysiology of IAI led directly to the principles used today for providing antimicrobial therapy to these patients. Currently, some of the most exciting work relates to the role of the gastrointestinal microbiome as a contributor to both illness and health. With the advent of increasingly sophisticated tools to identify the wide variety of microorganisms associated with gastrointestinal tract pathology, our understanding of the intricate relationship between the resident microbial population and the host will be greatly amplified. It would not be unexpected that antimicrobial therapy and potentially source control approaches for patients with IAI will be modified through the use of this knowledge. It is even possible that future therapy of IAI could involve use of probiotic agents to restore a healthy internal ecosystem within the gastrointestinal tract, rather than the antibiotic agents currently used.

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Treatment of infections caused by multidrug-resistant Gram-negative bacteria: report of the British Society for Antimicrobial Chemotherapy/Healthcare Infection Society/British Infection Association Joint Working Party†

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The Working Party makes more than 100 tabulated recommendations in antimicrobial prescribing for the treatment of infections caused by multidrug-resistant (MDR) Gram-negative bacteria (GNB) and suggest further research, and algorithms for hospital and community antimicrobial usage in urinary infection. The international definition of MDR is complex, unsatisfactory and hinders the setting and monitoring of improvement programmes. We give a new definition of multiresistance. The background information on the mechanisms, global spread and UK prevalence of antibiotic prescribing and resistance has been systematically reviewed. The treatment options available in hospitals using intravenous antibiotics and in primary care using oral agents have been reviewed, ending with a consideration of antibiotic stewardship and recommendations. The guidance has been derived from current peer-reviewed publications and expert opinion with open consultation. Methods for systematic review were NICE compliant and in accordance with the SIGN 50 Handbook; critical appraisal was applied using AGREE II. Published guidelines were used as part of the evidence base and to support expert consensus. The guidance includes recommendations for stakeholders (including prescribers) and antibiotic-specific recommendations. The clinical efficacy of different agents is critically reviewed. We found there are very few good-quality comparative randomized clinical trials to support treatment regimens, particularly for licensed older agents. Susceptibility testing of MDR GNB causing infection to guide treatment needs critical enhancements. Meropenem- or imipenem-resistant Enterobacteriaceae should have their carbapenem MICs tested urgently, and any carbapenemase class should be identified: mandatory reporting of these isolates from all anatomical sites and specimens would improve risk assessments. Broth microdilution methods should be adopted for colistin susceptibility testing. Antimicrobial stewardship programmes should be instituted in all care settings, based on resistance rates and audit of compliance with guidelines, but should be augmented by improved surveillance of outcome in Gram-negative bacteraemia, and feedback to prescribers. Local and national surveillance of antibiotic use, resistance and outcomes should be supported and antibiotic prescribing guidelines should be informed by these data. The diagnosis and treatment of both presumptive and confirmed cases of infection by GNB should be improved. This guidance, with infection control to arrest increases in MDR, should be used to improve the outcome of infections with such strains. Anticipated users include medical, scientific, nursing, antimicrobial pharmacy and paramedical staff where they can be adapted for local use.

†NICE has accredited the process used by the Healthcare Infection Society to produce the 'Treatment of infections caused by multidrug-resistant Gram-negative bacteria: report of the British Society for Antimicrobial Chemotherapy/Healthcare Infection Society/British Infection Association Joint Working Party' guidelines. Accreditation is valid for 5 years from March 2015. More information on accreditation can be viewed at <http://www.nice.org.uk/about/what-we-do/accreditation>.



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Lay summary

Multidrug-resistant (MDR) Gram-negative bacteria (GNB) are bacteria (or germs) that remain susceptible to only one or two antibiotics. Gram-negative bacteria usually live in the gut (or in the environment), where they do no harm, but can appear and cause infection at other body sites that normally lack any bacteria, for example in the bladder or blood. This especially occurs in patients who are made vulnerable by underlying disease, injury or hospitalization. MDR GNB may be acquired from other patients who have

received antibiotics. Infections caused by MDR GNB are difficult to treat and so may cause more prolonged symptoms in the site of infection and can cause additional complications such as pneumonia or infection in the blood. This can prolong the length of stay in hospital, and in some cases can cause death. Some types of MDR GNB, *Acinetobacter* spp. for example, can be carried on the skin rather than in the gut, again with no obvious signs or symptoms. 'Colonization' describes carriage of bacteria on body surfaces or in the gut without infection. When patients develop infection and require antibiotic treatment, selecting the correct antibiotic can be difficult. This report provides advice on the best choices among the antibiotics currently available.

1. Introduction

This guidance has been prepared by a joint Working Party of the British Society for Antimicrobial Chemotherapy (BSAC), the Healthcare Infection Society (HIS) and the British Infection Association (BIA) to advise on the treatment of infections caused by MDR Gram-negative bacteria. It also describes best practice in antimicrobial prescribing. There is an accompanying guideline describing appropriate infection prevention and control precautions, including hand hygiene, equipment and environmental cleaning and guidance on screening for MDR GNB.³ The infection control and prevention guideline should be used in conjunction with the present document. There is a glossary of technical terms (Appendix 1, available as [Supplementary data](#) at JAC Online).

The Working Party comprised a group of medical microbiologists and scientists, infectious disease physicians, infection control practitioners, epidemiologists, and patient representatives nominated by the Societies. The patient representatives were lay members and had direct experience of the treatment of healthcare-associated infections through personal experience, membership of SURF (Healthcare-acquired Infection Service Users Research Forum), patient charities or through involvement in the development of NICE guidelines. The representatives were: Susan Bennett, Member of Health Care Acquired Infections, Service Users Research Forum, Leicester, UK; Jennifer Bostock, Member of Health Care Acquired Infections, Service Users Research Forum, Leicester, UK; and Maria Cann, Trustee, MRSA Action, Kirkham, UK.

They were involved in the preparation of the remit of the Working Party ([Supplementary data](#) Appendix 3), were invited to all meetings, invited to comment on the final draft prepared by the authors and endorsed the final version.

2. Guideline development team

2.1 Guideline advisory group

Phil Wiffen, Cochrane Pain, Palliative and Supportive Care Group Pain Research, Churchill Hospital Oxford, Nuffield Department of Clinical Neurosciences, Oxford. Karla Soares-Wieser, Enhance Reviews, Ltd, Wantage.

2.2 Responsibility for guidelines

The views expressed in this publication are those of the authors and have been endorsed by the three sponsoring societies following consultation. Patient representatives confirmed the guidelines

addressed the questions raised in setting the Working Party's remit.

3. The Working Party Report

Date of publication: March 2018.

3.1 What is the Working Party Report?

This Report is a set of recommendations covering the treatment of infections caused by MDR GNB (i.e. herein defined as susceptible to only one or two different antibiotics). Strains internationally defined as MDR GNB by possession of resistance to three or more classes of antibiotics can nevertheless be treated with a wide range of antibiotics so we argue the case for a re-definition below (see Section 6.2).

The Working Party recommendations have been developed systematically through a multi-professional group and are based on published evidence. They should be used to develop local protocols for acute and long-term healthcare settings.

3.2 Why do we need a Working Party Report for these infections?

MDR GNB have become more prevalent internationally, including in the UK and Europe. The increased use of broad-spectrum agents encourages their proliferation.⁴ The spread of these bacteria causes infections that can increase the length of hospital stay and adversely affect the quality of life of patients. Public awareness has been increasing, and the relative lack of new antimicrobial agents to treat infections due to GNB has resulted in the formulation of the 5 year Antimicrobial Resistance Strategy by the UK Department of Health.⁵ Outbreaks are associated with considerable physical, psychological and financial costs. Evidence-based treatment regimens are effective in improving the outcome of infections due to these bacteria.

3.3 What is the purpose of the Report's recommendations?

The Report describes appropriate antimicrobial chemotherapy for infections due to MDR GNB.

3.4 What is the scope of these guidelines?

We examine the background information on the mechanisms, global spread, and UK prevalence of resistance, prescribing, and then discuss treatment (i) in hospitals using antibiotics intravenously and (ii) in primary care using agents given orally, ending with a consideration of antibiotic stewardship. Data (and doses, where given) usually refer to adults as there are few data for children and neonates. Extrapolation from adult data for β -lactams seems reasonably secure but this is not necessarily the case for other agents. Another set of guidelines considers appropriate infection control principles, best practice hand hygiene, screening and environmental cleaning.³ For the detailed scope for this guideline see Appendix 2.5 and for the review questions see Appendix 3.7 (both in the [Supplementary data](#)).

3.5 What is the evidence for these guidelines?

In the preparation of these recommendations, systematic reviews were performed of peer-reviewed research using the searches show in Appendix 4. Expert opinion was also derived from published guidelines subjected to validated appraisal.² Evidence was assessed for methodological quality and clinical applicability according to protocols of the Scottish Intercollegiate Guidelines Network (SIGN) initially using SIGN 2011¹ guidelines and then updating this as the work continued in order to comply with the SIGN 2014 guidance.⁶

3.6 Who developed these guidelines?

A group of medical microbiologists, scientists, infectious disease physicians, infection control practitioners, epidemiologists and patient representatives.

3.7 Who are these guidelines for?

Any hospital or general practitioner can use these guidelines and adapt them for local use. Expected users include clinical medical, nursing, antimicrobial pharmacy and paramedical staff. Paediatric licences and formulation may limit the suitability of some of the discussed agents for children and neonates. Where there are specific issues relating to dosage, outcome or toxicity that are outside current licence information, these are discussed. The guidelines should be used to improve the treatment of both presumptive and confirmed cases of infection by MDR GNB.

3.8 How are the guidelines structured?

Most areas (defined by questions) comprise an introduction, a summary of the evidence base with levels and a recommendation graded according to the available evidence. The guidelines are not organized by clinical indication.

3.9 How frequently are the guidelines reviewed and updated?

The guidelines will be reviewed and updated every 4 years if warranted by sufficient changes in the evidence or by the availability of new agents or formulations.

3.10 Aim

The primary aim of the review was to assess the current evidence for antimicrobial prescribing in the treatment of MDR Gram-negative infections. The secondary aims were: (i) to evaluate the efficacy of antibiotics to treat community and hospital infections caused by MDR GNB; and (ii) to evaluate the impact of educating and providing support to professionals and patients to reduce unnecessary use of antibiotics, leading to a reduction in the selective pressure for resistance, thereby assisting antibiotic stewardship.

4. Summary of guidelines

The guidance has been derived from current best peer-reviewed publications and expert opinion. Each recommendation is graded according to standard grades¹ and is associated with a class of supporting evidence, or it is presented as a Good Practice Point.

General recommendations for stakeholders, including prescribers, are made in Table 1. Specific antibiotic recommendations are made in Table 2.

4.1 How can the guidelines be used to improve clinical effectiveness?

The guidelines can be used to direct and formulate antibiotic policies and to aid the prescribing practice of infection specialists and other clinicians. They provide a framework for clinical audit tools for quality improvement.

4.2 How much will implementation of the guidelines cost?

The majority of the antimicrobial agents that are described in these guidelines are generic and are currently widely used. Newer β -lactam/ β -lactamase inhibitors (BL/BLIs) are more expensive than older BL/BLIs and most alternatives to carbapenems against MDR GNB are also more expensive. Extra financial support will be required for the surveillance of outcomes of bacteraemia. Implementation of these guidelines should enable better-focused therapy, with no increase in drug utilization and possibly a modest decrease.

4.3 Summary of suggested audit measures

Patients with infections with MDR GNB should receive empirical (best guess) or definitive (i.e. after results of laboratory tests) appropriate antibiotic treatment (alone or in combination) and the former should be active in at least 80% of cases. It is important to note that the basis on which resistance was defined was changed by EUCAST from predicting failed clinical response to deviation from the normal susceptibility of the species. In an era of multiple resistance, continuing to select for such resistant strains even when the patient has clinically responded to antibiotics to which the organism is resistant is undesirable. Control groups with infections at the same site and caused by the same species, but not MDR, or infections without known aetiology should not receive definitive treatment reserved for patients with MDR GNB. This audit should be conducted first for bacteraemias.

To reduce total antibiotic consumption, measured as defined daily doses.

Quarterly use of carbapenems and piperacillin/tazobactam should be reduced if either is in the top quintile/1000 patient days as assessed in each quarter. Specialist and tertiary care units may have special needs and should be excluded from the quintile assessment. Reductions of use in such units should be undertaken but should be tailored by consideration of their speciality case mix.

Trimethoprim use should be reduced and nitrofurantoin use increased in primary care.

Risk assessment tools for colonization and infection with MDR GNB in patients should be developed for the UK and put in place in all settings. Only infected patients known to be, or at risk of being (by these assessments), colonized with these bacteria should receive empirical treatment with drugs reserved for MDR GNB.

No antibiotic prescriptions for treating the elderly with asymptomatic bacteriuria (ASB), or urinary tract infection (UTI) in the

Table 1. Summary of recommendations for stakeholders including prescribers

Organization	Recommendation	Strength
Central public health authorities	Central public health departments or the Chief Medical Officers should receive bacteraemia data from the jurisdictions of trusts and CCGs or equivalent primary care organizations bacteraemia data in their localities annually. They should ensure computerized record linkage to provide dates of death. They should ensure information is categorized by locality (separately for hospitals and for community with associated separate wider healthcare data), date of onset or acquisition, organism, specific antibiotic resistance and pattern, and mortality rate. These data should be made available, for open interrogation, with rolling cumulative data within the health service.	Strong for
	Make publicly available tabulated incidence and outcome data for bacteraemia giving hospital onset data by region and hospital, and for community and wider healthcare onset data by CCG or equivalent primary care organizations. Correlate these data with similar analysed and tabulated annual data on total antibiotic use and organisms and antibiotic resistance in clinical infections.	Good practice
	Consider central production of unbiased national or regional data on true resistance rates in community-onset localized or systemic infections to guide national community antibiotic recommendations.	Strong for
Commissioning and quality organizations	Continuously monitor bacteraemia outcomes and antibiotic resistance by organism and devise improvement programmes for both.	Good practice
	Provide and use active feedback of monitoring to prescribers and nursing staff, ensuring optimization of clinical, microbiological and antimicrobial prescribing outcomes. Use audit and feedback to reduce inappropriate antimicrobial use in the community and wider healthcare.	Conditional for
	Use persuasive and restrictive interventions to reduce the total antibiotic consumption, particularly broad-spectrum antibiotics in the community and care home setting.	Strong
	Ensure production of local guidelines for empirical and definitive antibiotic use, regularly updated for community-, wider healthcare- and hospital-onset infections and audit compliance with these.	Conditional for
Hospital and primary care: general	Provide an ongoing antimicrobial stewardship programme in all care settings, based on resistance rates, with audit of compliance, with guidelines, surveillance of outcome and active feedback.	Strong
	Identify through horizon scanning and make available new antimicrobials that may be required to treat MDR GNB. Monitor use through formulary/drug and therapeutics committees.	Conditional for
	Use restrictive prescribing policies to acutely reduce the incidence of infection or colonization with MDR GNB; thereafter, maintain persuasive and restrictive approaches and monitor to check whether gains persist.	Strong for
	Integrate hospital IT to deliver annually linked data for each bacteraemia, including patient demographics, whether the bacteraemia's onset was in the community, wider healthcare or hospital, antibiotic resistances of isolate, antibiotics prescribed, and maximum early warning score or occurrence of septic shock, and if possible defined time-limited (not admission-limited) mortality. Use these integrated data to review the adequacy of treatment of infection in communities and hospitals.	Good practice
Hospital and primary care treatment of UTI	Inspect up-to-date national and local antibiotic surveillance when compiling local antibiotic guidelines on treatment of UTI. Follow local guidance on what antibiotics to prescribe.	Strong for
	For an elderly patient, do NOT send urine for culture or start empirical antibiotics unless there are specific symptoms or signs of UTI and none elsewhere. Use the algorithm in Figure 5 to decide whether to do this in elderly patients, especially in those with dementia.	Conditional for
	Do not prescribe antibiotics in asymptomatic bacteriuria (ASB) in the elderly with, or without, an indwelling catheter.	Strong for
	Always consider the positive and negative predictive value of specific symptoms before sending urine for culture or starting antibiotics for a UTI. Base decision on when to prescribe (whatever the age) primarily on symptoms. Use dipstick tests, if no catheter is present, to confirm the diagnosis, before prescribing, especially when symptoms are mild or not localized.	Strong for
	If there are risk factors for MDR GNB or previous presence of MDR GNB and the patient is symptomatic, send a urine specimen for culture and susceptibility.	Strong for
	Building on previous work, predictive scoring should be developed for the presence of ESBL-producing <i>E. coli</i> in primary care and on admission to hospital to restrict the need to prescribe carbapenems and other antimicrobial agents generally active against ESBLs.	Strong for

Continued

Treatment of infections caused by MDR Gram-negative bacteria

Table 1. Continued

Organization	Recommendation	Strength
Primary care prescriber for UTI	Need to quantify risks of infection with/carriage of extraintestinal pathogenic <i>E. coli</i> and of <i>Klebsiella</i> spp. resistant to all antibiotics and relate to time since travel to countries with high prevalence of MDR GNB and incorporate in risk assessments for clinical infection with MDR GNB in the community and on admission to hospital to guide therapy.	Strong for
	If defined risk factors for MDR GNB are present avoid cephalosporins, quinolones, trimethoprim and co-amoxiclav in treatment of lower UTIs unless the pathogens are confirmed to be susceptible.	Strong for
	Personalize empirical chemotherapy for each patient by considering current features of bacteraemia, risk factors for antibiotic resistance and past susceptibility testing, including the presence of MDR GNB in the patient, hospital unit, nursing home or community.	Conditional for
	In pyelonephritis always collect a urine sample before treatment. MDR GNB are unlikely to respond to oral treatment so consider risk factors for MDR GNB, including travel. Use an active oral agent only if patient is well enough and if known to have had ciprofloxacin-, trimethoprim- or co-amoxiclav-susceptible MDR GNB in last month.	Conditional for
	If the patient has pyelonephritis and risk factors for MDR GNB, start, if hospitalization not required, empirical intravenous therapy with ertapenem if OPAT therapy available. This will treat ESBL- and AmpC-producing Enterobacteriaceae. If hospitalization required for this or OPAT not available, admit for meropenem, temocillin or ceftolozane/tazobactam if no evidence of CPE organism. If the patient is penicillin hypersensitive then the hospital may use amikacin or meropenem, or if only susceptible isolates in the past, gentamicin. If carbapenem-resistant bacteria are, or have been, present, base treatment on susceptibility testing of recent or current isolates.	Strong for
	Locally assess the true rate of resistance and determine from this when changes to guideline recommendations for empirical therapy for UTI in guidelines are necessary, including recommendations where the risk of antibiotic-resistant bacteraemia is high.	Conditional for
	Always inform the patient or their carer(s) on what to look out for and how to re-consult if symptoms worsen or do not improve as community-onset <i>E. coli</i> bacteraemias of urinary origin are increasing.	Strong for
	In younger women with acute uncomplicated UTI, only consider MDR GNB in choosing empirical treatment if there are risk factors (see Section 8.4) or recent foreign travel to countries where such strains are highly prevalent.	Strong for
	Use fosfomycin, nitrofurantoin or pivmecillinam, guided where possible (i) by susceptibility testing and (ii) by this guideline's recommendation on choice, dosing and duration, for uncomplicated lower UTI where MDR GNB are suspected.	Strong for
	Use nitrofurantoin for 5 days with MDR GNB. Alternatively use fosfomycin trometamol 3 g orally as single dose, and repeat on third day only if MDR GNB confirmed to improve bacteriological cure. Pivmecillinam alone at 200 mg three times daily for 7 days may be a third-line choice but consider combination use with amoxicillin/clavulanate depending on clinical trial results at the time.	Conditional for
	Review outcome data linked to antibiotic prescribing to improve quality of care in the community and care homes.	Conditional for
	To reduce recurrent UTI, consider firstly the option of pre-prescribed standby antibiotics to take when symptoms begin, rather than daily or post-coital antibiotic prophylaxis. Where prophylaxis is used successfully for recurrent infection in adults limit use to 6 months.	Conditional for
	Avoid antibiotic prophylaxis for urinary catheter insertion or changes unless there is previous history of symptomatic UTI with the procedure, insertion of incontinence implant, or trauma at catheterization.	Conditional for

Table 2. Summary recommendations for specific antibiotics

Antibiotic	Recommendation	Grading
Amikacin	Modernize use of amikacin, which has improved activity, with development of validated nomograms. Ensure assays are readily available before repeat doses and consider, because of the risks of toxicity, the practicality of monitoring with audiograms.	Conditional for
Amoxicillin/clavulanate	Use for lower UTI due to known ESBL-producing bacteria only if current isolates, or if using empirically, recent isolates, are fully susceptible.	Conditional for
Ampicillin/sulbactam	Could use against some carbapenem-resistant apparently sulbactam-susceptible <i>A. baumannii</i> isolates. Caution needed in the UK because of a higher range of MICs. Absence of a break-point prevents categorization as susceptible/resistant.	Conditional for
Aztreonam	Do not use aztreonam alone empirically if MDR GNB or Gram-positive or anaerobic pathogens are suspected.	Strong against
	Do not use aztreonam for CTX-M ESBL- or AmpC-producing bacteria even if these appear susceptible <i>in vitro</i> .	Strong against
	Use aztreonam for MBL- or OXA-48-producing strains if it is certain that they do not produce ESBLs or AmpC.	Strong for
	Research usefulness of aztreonam in combination with avibactam for bacteria producing MBLs with ESBL/AmpC enzymes and for those with other carbapenemases.	Conditional for research
Cefepime	Could use cefepime to treat infection caused by ESBL- or AmpC-producing bacteria if susceptible at the EUCAST breakpoint of MIC ≤ 1 mg/L	Conditional for
	Do not use cefepime even at increased dose for isolates with (i) MIC of 2–8 mg/L (CLSI 'susceptible dose dependent') or (ii) MIC 2–4 mg/L (EUCAST intermediate), or (iii) strains with stable derepression of AmpC or (iv) strains that produce both AmpC and ESBLs.	Strong against
	Do not use cefepime to treat infection caused by CPE.	Strong against
Cefixime and other oral cephalosporins	Do not used for treating infection caused by ESBL, AmpC and CPE.	Conditional
Cefoxitin	Confirmation needed of its usefulness as a carbapenem-sparing agent for inpatients to empirically treat urinary infection or use definitively for infections caused by CTX-M-15-producing <i>E. coli</i> ; its short serum half-life means it is unsuitable for OPAT and probably it has insufficient advantage to displace existing agents.	Research and trials
Ceftazidime	Use ceftazidime for susceptible infections with <i>P. aeruginosa</i> including quinolone-resistant or some imipenem-resistant strains.	Strong for
	Do not use ceftazidime to treat infections due to ESBL- or AmpC-producing Enterobacteriaceae or CPE (other than OXA-48 producers), even if <i>in vitro</i> tests suggest the isolate is susceptible.	Conditional against
Ceftazidime/avibactam	Could use ceftazidime/avibactam as an alternative to carbapenems for infection with ESBL- and AmpC-producing Enterobacteriaceae but alternatives may be cheaper.	Conditional for
	Evaluate further ceftazidime/avibactam use alone or in combination when non-MBL carbapenemase-producing organisms cause infection. KPC-3-producing <i>Klebsiella</i> are vulnerable to mutations in the enzyme causing resistance.	Research and trials
	Consider whether ceftazidime/avibactam should be used with a carbapenem or colistin to treat infections with KPC-3 producers based on latest evidence at the time of use.	Research and trials
	Do not use for treating infection with anaerobes or bacteria producing MBLs: these are resistant.	Strong against
Ceftolozane/tazobactam	Use ceftolozane/tazobactam to treat susceptible infections with <i>P. aeruginosa</i> resistant to ceftazidime.	Conditional for
	Conduct clinical trials in <i>P. aeruginosa</i> infections in cystic fibrosis.	Research and trials
	Use ceftolozane-tazobactam as an alternative to carbapenems to treat urinary or intra-abdominal infection involving ESBL-producing <i>E. coli</i> . Caution may be needed when treating infections with ESBL-producing <i>Klebsiella</i> spp. owing to a higher resistance rate.	Conditional for
	Do not use for infections due to AmpC- or CPE or MBL/ESBL-producing <i>P. aeruginosa</i> .	Strong against
Ertapenem	Use ertapenem to treat serious infections with ESBL and AmpC-producing Enterobacteriaceae.	Strong for
	Apply antibiotic stewardship to use of all carbapenems to minimize the risk of developing resistance either by acquisition of carbapenemase-producing strains or by porin loss.	Strong for
	Prefer carbapenem OPAT of susceptible infections in view of the once-daily dosing regimen.	Conditional for
Fluoroquinolones	Could use orally to treat UTI caused by MDR GNB that are susceptible.	Conditional for

Continued

Table 2. *Continued*

Antibiotic	Recommendation	Grading
Fosfomycin	Use in the treatment of lower UTI due to MDR Enterobacteriaceae. Oral formulation available is useful for ESBL producers after repeated recurrence after nitrofurantoin and potentially for carbapenemase producers.	Conditional for
	Consider dosage and trials of oral formulation for upper UTI.	Research and trials
	Consider parenteral fosfomycin, probably in combination, as part of salvage treatment for susceptible MDR GNB; clear indications for use are not yet established. Potential drug of last resort.	Research and trials
	Need comparative clinical trials to establish optimal indications for, and optimal use of, oral and parenteral drug.	Research and trials
	Carry out ongoing local and national surveillance of use and resistance because of previous emergence of bacterial resistance in populations and the drug's potential as an important parenteral agent.	Strong for
Gentamicin	Could use gentamicin empirically in the UK if the likelihood of MDR GNB is low.	Conditional for
	Could use gentamicin as a carbapenem-sparing agent for urinary, intra-abdominal and bacteraemic infections due to ESBL-producing <i>E. coli</i> when susceptibility is confirmed but do not use empirically if the risk of MDR GNB is raised.	Conditional for
	Could use gentamicin in combinations for urinary, intra-abdominal and bacteraemic infections due to gentamicin-susceptible KPC-producing <i>Klebsiella</i> spp. if strain is resistant to colistin and meropenem (see Section 7.18).	Conditional for
	Use once-daily dosage of gentamicin or tobramycin if no renal impairment, followed by measurement of levels 6–14 h post-dose and adjust repeat dosage by reference to the appropriate 7 or 5 mg/kg nomogram. Consider increased risks of toxicity if there is co-administration of nephrotoxic or ototoxic drugs.	Strong for
Imipenem and meropenem	Use meropenem or imipenem or ertapenem to treat serious infections with ESBL and AmpC-producing Enterobacteriaceae.	Strong for
	Apply antibiotic stewardship to use of all carbapenems to minimize the risk of developing resistance either by acquisition of carbapenemase-producing strains or, with ertapenem, by porin loss.	Strong for
	Do not use imipenem to treat susceptible <i>Pseudomonas</i> infections.	Conditional for
	Introduce in the UK mandatory reporting of meropenem- or imipenem-resistant Enterobacteriaceae from all anatomical sites and specimens.	Strong for
	Test all meropenem- or imipenem-resistant isolates of Enterobacteriaceae immediately for the precise level of resistance and for an indication of the responsible class of carbapenemase. Submit to agreed reference laboratories to determine susceptibility to a wide range of potentially active agents, including, as appropriate, colistin, ceftazidime/avibactam, temocillin, aminoglycosides, fosfomycin and tigecycline.	Strong for
Nitrofurantoin	Consider use of continuous infusion meropenem in combination at dose determined by nomogram if infection with KPC carbapenemase-producing <i>Klebsiella</i> with MIC of >8 and <64 mg/L.	Research and trials
	Could use nitrofurantoin for 5 days to treat uncomplicated, lower UTIs with nitrofurantoin-susceptible MDR <i>E. coli</i> (not Proteaeae or <i>P. aeruginosa</i>).	Strong for
	Do not use repeatedly if there is moderate renal impairment (eGFR <45 mL/min/1.73 m ²), or in long-term courses, as these are associated with rare unwanted pulmonary effects.	Conditional against
	Use alternative agents if there are repeated recurrences with MDR GNB but do not anticipate the emergence of resistance in <i>E. coli</i> infections on a single recurrence as selection for resistant strains in the urine or faecal flora is rare.	Conditional for
	Need comparative studies of nitrofurantoin and other active antimicrobials in patients with ESBL-producing <i>E. coli</i> and <i>Klebsiella</i> spp.	Research and trials
Piperacillin/tazobactam	Use for infections with known ESBL-producing bacteria only if current isolates, or, if using empirically, isolates from the recent past, are fully susceptible by EUCAST criteria.	Conditional for
	Consider definitive use of piperacillin/tazobactam to treat infections caused by <i>P. aeruginosa</i> if susceptible by EUCAST criteria.	Conditional for

Continued

Table 2. Continued

Antibiotic	Recommendation	Grading
Pivmecillinam	Consideration should be given to reducing the mecillinam EUCAST breakpoint for classification of susceptibility.	Conditional for
	Treat lower UTI due to ESBL-negative <i>E. coli</i> with pivmecillinam at 200 mg three times daily; do not use for infections caused by Proteaceae, <i>Klebsiella</i> or <i>Pseudomonas</i> .	Conditional for
	Some ESBL-producing <i>E. coli</i> respond, but efficacy is poor against CTX-M-15 and OXA-1 enzyme producers: dosing at 400 mg three times daily may be no more effective. Consider combination of the lower dose with 375 mg three times daily amoxicillin/clavulanate for follow-on to parenteral therapy for such infections in hospital or OPAT.	Conditional for
	Requires clinical comparative trials in the public interest (i) alone or together with amoxicillin/clavulanate for UTIs due to ESBL-producing organisms, including particularly those producing CTX-M-15 enzymes, (ii) in uncomplicated lower UTI generally against fosfomycin trometamol and nitrofurantoin as the relative advantages of these drugs have not been directly compared over the last 10 years as MDR GNB have become more problematic.	Trials and research
Polymyxins (including colistin)	Reserve intravenous colistin for infections due to polymyxin-susceptible but multiresistant bacteria and preferably use in combination with other agents.	Conditional for
	Give careful consideration to use of higher dosage regimens in critically ill patients.	Conditional for
	Use colistin with meropenem to treat susceptible KPC-producing <i>Klebsiella</i> spp. if the meropenem MIC is ≤ 8 mg/L and consider higher meropenem dose by continuous infusion if the MIC is > 8 and ≤ 32 mg/L.	Conditional for
	Consider colistin with aminoglycosides or tigecycline in infections with strains producing KPC or other carbapenemases, which are susceptible to these but resistant to meropenem with MIC > 32 mg/L.	Conditional for
	Closely monitor renal function especially in the elderly, those receiving high intravenous doses for prolonged periods and those on concomitant nephrotoxic agents, e.g. aminoglycosides.	Strong for
	Reconsider use of polymyxins in selective digestive decontamination regimens as these agents are now important last therapeutic options against CPE and are more threatened by resistance than previously appreciated.	Good practice
	Need research on optimal rapid and practical methods of susceptibility testing outside intrinsically resistant groups such as Proteaceae and <i>Serratia</i> spp.	Research and trials
	Aerosolized colistin dry powder should be used in cystic fibrosis according to NICE guidelines. Use in combination in ventilator-associated pneumonia may be considered pending further trials without methodological flaws.	Conditional for
Temocillin	Use alone for UTIs and associated bacteraemia caused by AmpC- or ESBL-producing Enterobacteriaceae.	Conditional for
	Continuous infusion or thrice-daily dosing may be desirable for systemic infections with ESBL- or AmpC-producing bacteria.	Research and trials
	Could use for UTIs with KPC-producing Enterobacteriaceae but not for OXA-48 or MBL producers, on basis of published <i>in vitro</i> data.	Research and trials
Tigecycline	Could use tigecycline in combination in the treatment of multiresistant soft tissue and intra-abdominal infections.	Conditional for
	Use alone in hospital-acquired respiratory infections is unlicensed and not advised as outcomes with current dosing are not clearly satisfactory in <i>Acinetobacter</i> and MDR GNB infections.	Conditional against
	Use in combinations in hospital-acquired respiratory infections: precise combinations depend on the antibiotic susceptibility of the MDR GNB causing the infection.	Research and trials
	Use higher-than-licensed dosing such as 100 mg twice daily for infections due to MDR GNB in critical care.	Conditional for
	Investigate if higher dosing counters the unexpectedly high mortality seen even in infections due to strains apparently susceptible <i>in vitro</i> .	Research and trials
Tobramycin	Avoid tobramycin for MDR Enterobacteriaceae because of risk of resistance due to AAC(6')-I and AAC (6')-Ib-cr.	Conditional against
	Use tobramycin in preference to other aminoglycosides for susceptible <i>Pseudomonas</i> infection.	Conditional for Strong for

Continued

Table 2. *Continued*

Antibiotic	Recommendation	Grading
Trimethoprim	Use once-daily dosage of tobramycin if no renal impairment followed by measurement of levels 6–14 h post-dose and adjust repeat dosage by reference to nomogram.	
	Do not use trimethoprim in treating MDR GNB or treatment failures with other agents unless <i>in vitro</i> susceptibility has been demonstrated.	Strong against
	Do not use trimethoprim to treat lower UTIs as a first-line agent. Only consider use if there are no risk factors for resistance, or if confirmed <i>in vitro</i> susceptibility.	Conditional against
Trimethoprim/ sulfamethoxazole	Use in treatment of infections due to susceptible <i>S. maltophilia</i> and consider in infections due to <i>Achromobacter</i> spp., <i>Alcaligenes</i> spp., <i>Burkholderia</i> spp., <i>Chryseobacterium</i> spp. and <i>Elizabethkingia</i> spp.	Conditional for

presence of a urinary catheter unless bacteraemia or renal infection is suspected.

No antibiotic prophylaxis for urinary catheter insertion or change unless previous history of symptomatic UTI associated with a change of catheter, or if there is trauma during catheter insertion, or if a urinary continence device has been inserted.

Gram-negative bacteraemia incidence should be decreased and outcomes should be improved in cases which developed in primary care, wider healthcare settings, and secondary and tertiary units.

Enhancements to surveillance should be planned and supported by information technology (IT) that allows record linkage and simplification of surveillance from the laboratory to national level.

4.4 E-learning tools

Continuing professional development questions and model answers are listed for self-assessment in Appendix 5.

5. Methodology

5.1 Evidence appraisal

Methods were in accordance with SIGN 50 and Cochrane Collaboration criteria^{1,7} and critical appraisal was applied using AGREE II.² Accepted guidelines were used as part of the evidence base and to support expert consensus. Questions for review (see Appendix 3.7) were derived from the Working Party Group, which included patient representatives in accordance with Patient Intervention Comparison Outcome (PICO).⁶

K. Soares-Wiesner of Enhance Reviews Ltd and Dr P. Wiffen of Pain Research and Nuffield Department of Clinical Neurosciences, Oxford University, used a systematic review process. Guidelines and research studies were identified for each search question. Systematic reviews, randomized controlled trials (RCTs) and observational studies were included. The latter comprised cohort non-RCTs, controlled 'before and after' studies, and interrupted time series. All languages were searched. Search strategies for each area are given in the sections below and in Appendix 4. MeSH headings and free-text terms were used in the Cochrane Library (Issue 11, 2012), Medline (1946–2012), Embase (1980–2012) and Cumulated Index of Nursing and Allied Health Literature (CINAHL) (1984–2012). On 23 May 2014, an update search was conducted

on Medline alone using the same strategy for references after 1 January 2013. Reference lists of included studies were searched. Additional references were added in October 2016 and June 2017 to cover specific issues. Two review authors independently screened all citations and abstracts identified, and screened full reports of potentially eligible studies (those that addressed the review questions in primary or systematic secondary research, or a clinical, *in vitro* or in-use study). Disagreements were resolved by discussion, and rationales for exclusion of studies were documented. Pre-tested data extraction forms were used, and study characteristics and results collected. Data were extracted from observational studies for multiple effect estimates: these included the number of cases analysed, adjusted and unadjusted effect estimates, with standard error or 95% CI, confounding variables and methods used to adjust the analysis. If available, data were extracted from contingency tables. Risk of bias was assessed using SIGN critical appraisal checklists. Interrupted time series were assessed using the Cochrane Effective Practice and Organisation of Care (EPoC) Group.^{6,8} Quality was judged by report of details of protection against secular changes (intervention independent of other changes) and detection bias (blinded assessment of primary outcomes and completeness of data). For outbreak patterns associated with particular pathogens, the Working Party made additional searches of descriptive studies to extract effective treatments for infections caused by bacteria with specific resistance.

5.2 Data analysis and interpretation

Clinical outcomes were mortality, effectiveness of treatment and length of hospital stay. Microbial outcome measures were decreases in the prevalence of MDR GNB or decreases in colonization or infection by specific GNB. Risk ratios (RRs) were used for dichotomous variables, and mean differences with 95% CI were used for continuous variables.⁹ Analyses were performed in Revman 5.22.¹⁰ SIGN summary tables were used. Evidence tables and judgement reports were presented and discussed by the Working Party and the guidelines were prepared according to the nature and applicability of the evidence, patient preference and acceptability and likely costs. The level of evidence was as defined by SIGN (Table 3), and the strength of recommendation was based upon Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Table 4).¹¹ The grading relates to the strength of the supporting evidence and predictive power of the

表 2.特殊抗菌药物的推荐总结

抗菌药物	推荐	推荐等级
阿米卡星	随着已验证列线图的发展，现代使用的阿米卡星抗菌活性有所增强。在重复给药的时候确保能够监测药物浓度，并且由于它的毒性，考虑检测听力图的实用性。	有条件的推荐
阿莫西林/克拉维酸	用于近期分离产 ESBL 菌感染的下尿路感染或者用于近期分离细菌全部敏感的经验性治疗。	有条件的推荐
氨苄西林/舒巴坦	能够用于碳青霉烯类耐药但是舒巴坦敏感的鲍曼不动杆菌感染的治疗。英国由于 MICs 值范围大，使用时要谨慎。缺乏敏感/耐药的折点。	有条件的推荐
氨曲南	怀疑 MDR GNB 或革兰阳性菌或厌氧菌感染时不单独使用氨曲南用于经验性治疗。	强烈反对
	即使体外药敏结果敏感，氨曲南不用于产 CTX-M ECBL 或产 AmpC 细菌感染	强烈反对
	如果明确细菌不产 ESBL 或 AmpC，氨曲南可用于治疗产 MBL 或 OXA-48 细菌感染的治疗	强烈支持
	研究发现氨曲南联合阿维巴坦治疗产 MBLs 和 ESBL/AmpC 酶以及其他碳青霉烯酶的细菌感染有效	有条件的推荐，仅用于研究
头孢吡肟	对于 EUCAST 折点 MIC≤1 mg/L 的产 ESBL 或 AmpC 细菌感染，可以使用头孢吡肟治疗	有条件的推荐
	即使增加头孢吡肟剂量也不用于下列感染治疗：(i) MIC 2-8 mg/L (CLSI 剂量依赖性敏感) 或 (ii) MIC 2-4 mg/L (EUCAST 中介)，或 (iii) AmpC 稳定下降的菌株，或 (iv) 同时产 AmpC 和 ESBLs 的菌株。	强烈反对
	头孢吡肟不用于治疗产碳青霉烯酶肠杆菌科细菌 (CPE) 感染	强烈反对
头孢克肟和其他口服头孢菌素	不用于治疗产 ESBL，AmpC 和 CPE 细菌的感染	有条件的反对
头孢西丁	作为碳青霉烯类替代经验性治疗尿路感染的住院患者或者治疗由产 CTX-M-15 大肠埃希菌引起的感染的有效性需要进一步确认；它的半衰期较短意味着对于治疗门诊	用于研究和试验

	胃肠外抗菌药物（OPAT）不稳定，并且它的优势不足以替代其他抗菌药物。	
头孢他啶	应用头孢他啶治疗敏感铜绿假单胞菌感染包括喹诺酮类耐药或一些亚胺培南耐药的菌株	强烈支持
	头孢他啶不用于治疗产 ESBL 或 AmpC 肠杆菌或 CPE（除了产 OXA-48）细菌的感染，即使体外药敏结果显示敏感	有条件的反对
头孢他啶/阿维巴坦	头孢他啶/阿维巴坦可以作为碳青霉烯类替代治疗产 ESBL 或 AmpC 肠杆菌科细菌感染但是头孢他啶/阿维巴坦价格可能更便宜	有条件的支持
	产非 MBL 碳青霉烯酶细菌感染，需要进一步评价头孢他啶/阿维巴坦单用或者联合应用疗效。在酶引起的耐药突变株中产 KPC-3 肺克伯雷菌容易对其耐药。	用于研究和试验
	基于最新的证据，考虑是否使用头孢他啶/阿维巴坦联合碳青霉烯类或者多黏菌素治疗产 KPC-3 酶细菌的感染	用于研究和试验
	不用于治疗厌氧菌或产 MBLs 细菌感染：这些细菌对头孢他啶/阿维巴坦耐药	强烈反对
头孢洛扎/他唑巴坦	应用头孢洛扎/他唑巴坦治疗头孢洛扎/他唑巴坦敏感和头孢他啶耐药铜绿假单胞菌的感染	有条件的推荐
	在肺囊性纤维化铜绿假单胞菌感染患者中开展临床试验	用于研究和试验
	头孢洛扎/他唑巴坦作为碳青霉烯类替代治疗尿路感染或者包括产 ESBL 大肠埃希菌感染在内的腹腔感染。由于对产 ESBL 肺炎克雷伯菌有更高耐药率，因此用于治疗这类感染需谨慎。	有条件的推荐
	不用于治疗产 AmpC 或 CPE 或产 MBL/ESBL 铜绿假单胞菌的感染	强烈反对
厄他培南	厄他培南用于治疗产 ESBL 和 AmpC 肠杆菌的严重感染。	强烈支持
	在使用所有碳青霉烯类时加强抗菌药物应用管理，以减小细菌产生碳青霉烯酶和孔蛋白丢失而耐药的风险。	强烈支持
	对于敏感菌感染，每日一次给药方案用于门诊胃肠外抗菌药物治疗（OPAT）更优。	有条件的推荐
氟喹诺酮类	能够通过口服给药治疗敏感的 MDR GNB 引起的感染	有条件的推荐

磷霉素	用于治疗 MDR 肠杆菌科细菌引起的下尿路感染。口服制剂对治疗呋喃妥因引起的反复复发产 ESBL 和可能产碳青霉烯酶的细菌感染有效。	有条件的推荐
	考虑口服制剂治疗上尿路感染的剂量和方案	用于研究和试验
	考虑胃肠外磷霉素和联合应用作为敏感 MDR GNB 的补救治疗；明确的应用指征尚不确定。最后一道防线潜在的治疗药物。	用于研究和试验
	对于口服和胃肠外给药，需要对照试验来确定最佳的使用指征和优化给药。	用于研究和试验
	由于之前人群中出现细菌耐药性以及该药物作为重要的肠胃外药物的潜力，因此需要对地区和国家耐药性进行持续监测。	强烈支持
庆大霉素	在英国如果 MDR GNB 的可能性低的时候，庆大霉素可以用于经验性的治疗。	有条件的支持
	敏感性确定的情况下可以使用庆大霉素作为碳青霉烯类替代治疗产 ESBL 细菌引起的尿路感染，腹腔感染和菌血症，但是如果 MDR GNB 风险增加的时候不用于经验性的治疗。	有条件的支持
	如果产 KPC 肺炎克雷伯菌对多黏菌素和美罗培南耐药，对庆大霉素敏感，可以使用庆大霉素治疗此类细菌引起的尿路感染，腹腔感染和菌血症（见 7.18）。	有条件的支持
	肾功能正常时采用庆大霉素或妥布霉素每日一次给药，给药后 6-14 h 监测药物浓度，根据 7 或 5 mg/kg 列线图法调整重复给药剂量。联用肾毒性和耳毒性药物时需要考虑毒性增加的风险。	强烈支持
亚胺培南和美罗培南	亚胺培南或美罗培南或厄他培南用于治疗产 ESBL 和 AmpC 肠杆菌的严重感染。	强烈支持
	在使用所有碳青霉烯类时加强抗菌药物应用管理，以减小细菌产生碳青霉烯酶和孔蛋白丢失（厄他培南）而耐药的风险。	强烈支持
	亚胺培南不用于治疗敏感假单胞菌感染。	有条件的支持

	在英国对所有解剖部位和培养标本中美罗培南或亚胺培南耐药的肠杆菌强制上报。	强烈支持
	立即检测所有亚胺培南或美罗培南耐药的肠杆菌以明确耐药水平和碳青霉烯酶的类别。提交给规定的实验室以确定潜在药物的活性，包括多黏菌素， 头孢他啶/阿维巴坦 ，替莫西林，氨基糖苷类，磷霉素和替加环素。	强烈支持
	对于 MIC>8 和 MIC<64 mg/L 产 KPC 肺炎克雷伯菌感染，考虑联合美罗培南连续输注并且采用列线图法计算剂量。	用于研究和试验
呋喃妥英	呋喃妥因 5 天治疗呋喃妥因敏感的多重耐药大肠埃希菌引起的非复杂性，下尿路感染（非变形杆菌和铜绿假单胞菌）。	强烈支持
	在中度肾功能不全的患者中（eGFR<45 mL/min/1.73m ² ），不能重复使用呋喃妥因或者从长期来看，其可能造成罕见的肺部损伤。	有条件的反对
	如果存在 MDR GNB 的反复复发则使用其他药物治疗，但是不能预测大肠埃希菌单次复发后就出现耐药，因为尿液和粪便中的耐药菌治疗选择比较少。	有条件的支持
	需要对照研究比较呋喃妥因和其他活性抗菌药物治疗产 ESBL 大肠埃希菌和肺炎克雷伯菌感染的疗效。	用于研究和试验
哌拉西林/他唑巴坦	根据 EUCAST 标准，仅仅在目前培养的细菌或者最近分离的细菌完全敏感的情况下，治疗已知产 ESBL 细菌感染。	有条件的推荐
	如果根据 EUCAST 标准，考虑使用哌拉西林/他唑巴坦治疗铜绿假单胞菌的感染。	有条件的推荐
匹美西林	考虑降低美西林 EUCAST 折点进行敏感性分类。	有条件的推荐
	匹美西林 200 mg 每日 3 次治疗由产 ESBL 大肠埃希菌引起的下尿路感染；不用于治疗变形杆菌，克雷伯菌或假单胞菌引起的感染。	有条件的推荐
	治疗某些产 ESBL 的大肠埃希菌有效，但对产 CTX-M-15 和 OXA-1 酶的细菌感染疗效差；400mg 每日三次的抗菌疗效可能不够。考虑较低剂量联合阿莫西林/克拉维酸	有条件的推荐

	375mg 每日三次用于此类院内感染或门诊胃肠外治疗 (OPAT) 。	
	对于公众利益，需要进行临床对照试验 (i) 单用或与阿莫西林/克拉维酸联用治疗产 ESBL 细菌引起的尿路感染，特别是那些产生 CTX-M-15 酶的细菌，(ii) 在非复杂性的下尿路感染中，由于 MDR GNB 感染变得越来越棘手，在过去的 10 年没有研究直接比较磷霉素氨丁三醇，呋喃妥因这些药物的优势。	用于试验和研究
多黏菌素（包括黏菌素）	静脉应用黏菌素用于治疗黏菌素敏感的多重耐药细菌，优先与其他药物联用	有条件的推荐
	在重症患者中谨慎考虑应用更高剂量的给药方案。	有条件的推荐
	如果美罗培南 MIC 为 ≤ 8 mg/L，使用黏菌素与美罗培南联合治疗敏感产 KPC 的克雷伯菌属，如果美罗培南 MIC 为 > 8 和 ≤ 32 mg/L，则考虑通过连续输注更高剂量的美罗培南。	有条件的推荐
	考虑黏菌素联合氨基糖苷类或替加环素治疗产 KPC 或其他碳青霉烯酶的菌株感染，这些菌株对以上药物敏感但对美罗培南耐药 MIC > 32 mg/L.	有条件的推荐
	密切监测肾功能，尤其是老年人，长期接受高静脉注射剂量的患者和合用肾毒性药物的患者，例如：氨基糖苷类。	强烈支持
	重新考虑在选择性消化净化方案中使用黏菌素，因为这些药物现在是治疗 CPE 感染的最后选择，并且耐药性威胁比之前认识的更严重。	良好的实践
	需要研究最优的快速和实用的敏感性测试方法，如变形杆菌和沙雷氏菌等具有体外内在耐药性细菌。	用于研究和试验
	根据 NICE 指南，雾化黏菌素干粉应用于囊性纤维化。在呼吸机相关肺炎中的应用问题，暂未解决，需要进一步无方法学缺陷的临床研究证据。	有条件的推荐
替莫西林	单用治疗尿路感染和产 AmpC 或产 ESBL 的肠杆菌科引起的菌血症。	有条件的推荐

	连续输注或每日三次给药治疗产 ESBL 或 AmpC 细菌的全身性感染。	用于研究和试验
	根据发表的体外数据，可用于产 KPC 的肠杆菌引起的尿路感染，但不可用于产 OXA-48 或 MBL 细菌感染。	用于研究和试验
替加环素	可联合使用替加环素治疗多重耐药软组织感染和腹腔感染。	有条件的推荐
	未批准单用治疗医院获得性呼吸道感染，并且在不动杆菌和 MDR GNB 感染中，由于当前剂量疗效不满意，所以不推荐。	有条件的反对
	在医院获得性呼吸道感染中联合使用：根据感染的 MDR GNB 的药敏结果搭配联合用药的组合。	用于研究和试验
	使用超说明书剂量如 100 mg 每日两次治疗重症监护室 MDR GNB 引起的感染。	有条件的推荐
	观察高剂量是否能够降低体外实验敏感菌株引起的高死亡率。	用于研究和试验
妥布霉素	由于 AAC(6')-I 和 AAC(6')-Ib-cr 产生的耐药性风险，所以避免妥布霉素治疗 MDR 肠杆菌感染。	有条件的反对
	对于敏感假单胞菌感染，优先使用妥布霉素而不是其他氨基糖苷类。	有条件的支持
	如果没有肾功能不全，则使用每日一次剂量的妥布霉素，然后在给药后 6-14 小时测量药物水平，并参照列线图调整重复剂量。	强烈的支持
甲氧苄啶	除非已证实体外药敏活性，否则不使用甲氧苄啶联合其他药物治疗 MDR GNB 失败的感染。	强烈的反对
	甲氧苄氨嘧啶不作为治疗下尿路感染的一线药物。只有在没有耐药风险或体外药敏实验确定的情况下才考虑使用。	有条件的反对
甲氧苄啶/ 磺胺甲恶唑	用于治疗敏感的嗜麦芽窄食单胞菌引起的感染，考虑用于无色杆菌属，产碱杆菌属，伯克霍尔德氏菌属，金黄杆菌属和脑膜脓毒性菌属引起感染的治疗。	有条件的支持

Table 3. Levels of evidence for intervention studies¹

Score	Description
1++	High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews or RCTs with a low risk of bias.
1–	Meta-analyses, systematic reviews or RCTs with a high risk of bias. ^a
2++	High-quality systematic reviews of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
	Interrupted time series with a control group: (i) there is a clearly defined point in time when the intervention occurred; and (ii) at least three data points before and three data points after the intervention.
2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal OR controlled before-after studies with two or more intervention and control sites.
2–	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal. Interrupted time series without a parallel control group: (i) there is a clearly defined point in time when the intervention occurred; and (ii) at least three data points before and three data points after the intervention. Controlled before-after studies with one intervention and one control site.
3	Non-analytical studies (e.g. uncontrolled before-after studies, case reports, case series).
4	Expert opinion. Legislation.

^aStudies with an evidence level of 1– and 2– should not be used as a basis for making a recommendation.

Table 4. Grading of recommendations¹¹

Grading	Recommendation
Undesirable consequences clearly outweigh desirable consequences	Strong recommendation against
Undesirable consequences probably outweigh desirable consequences	Conditional recommendation against
Balance between desirable and undesirable consequences is closely balanced or uncertain	Recommendation for research <i>and possibly</i> conditional recommendation for use restricted to trials
Desirable consequences probably outweigh undesirable consequences	Conditional recommendation for
Desirable consequences clearly outweigh undesirable consequences	Strong recommendation for

study designs, rather than the importance of the recommendation. Any disagreements between members were resolved by discussion. For some areas and recommendations, only expert opinion is available; in such cases, a good practice recommendation has been made. A flow chart of the systematic review process is given in Figure 1.

5.3 Consultation process

These guidelines were opened to consultation with circulation to the stakeholders listed (see Appendix 6). The draft report was placed on the BSAC web site for 1 month in June 2016 for open consultation. Views were invited on format, content, local applicability, patient acceptability and recommendations. The Working Party considered and collated comments, and agreed revisions.

6. Rationale for recommendations

6.1 Usage

It is beyond the scope of this guideline to define optimal quantitative usage of antibiotics by hospital beds or community populations and the UK is not an exceptionally high antibiotic user in international terms. Equally, measures to reduce antibiotic usage

will depend on what apparent over-usage is occurring in any community or hospital department. For this reason, the assessment of reduction measures whilst based on comparative epidemiology must also consider both clinical outcome measures and usage at the local level. Suggestions for reducing overall usage must therefore be largely implemented at the local level where risk to patients and benefit can be adequately assessed, and they lie beyond the practical scope of this guideline.

6.2 What is the definition of multidrug-resistant Gram-negative bacteria?

Multidrug resistant (MDR) is a vexed term. From 1980 it was used to mean ‘resistant to multiple agents’ without the number or types of agents being specified. More recently the European Centre for Disease Prevention and Control (ECDC) has attempted to formalize the term as ‘resistant to three or more antibiotic classes’, whilst extremely drug resistant (XDR) is ‘susceptible only to one or two drug classes. These definitions, based on those for tuberculosis, are epidemiologically attractive, but can prove to be impractical. An international consensus is difficult to achieve, as not all products are available and tested by laboratories in all countries, and there is no universal testing policy for laboratories (which make

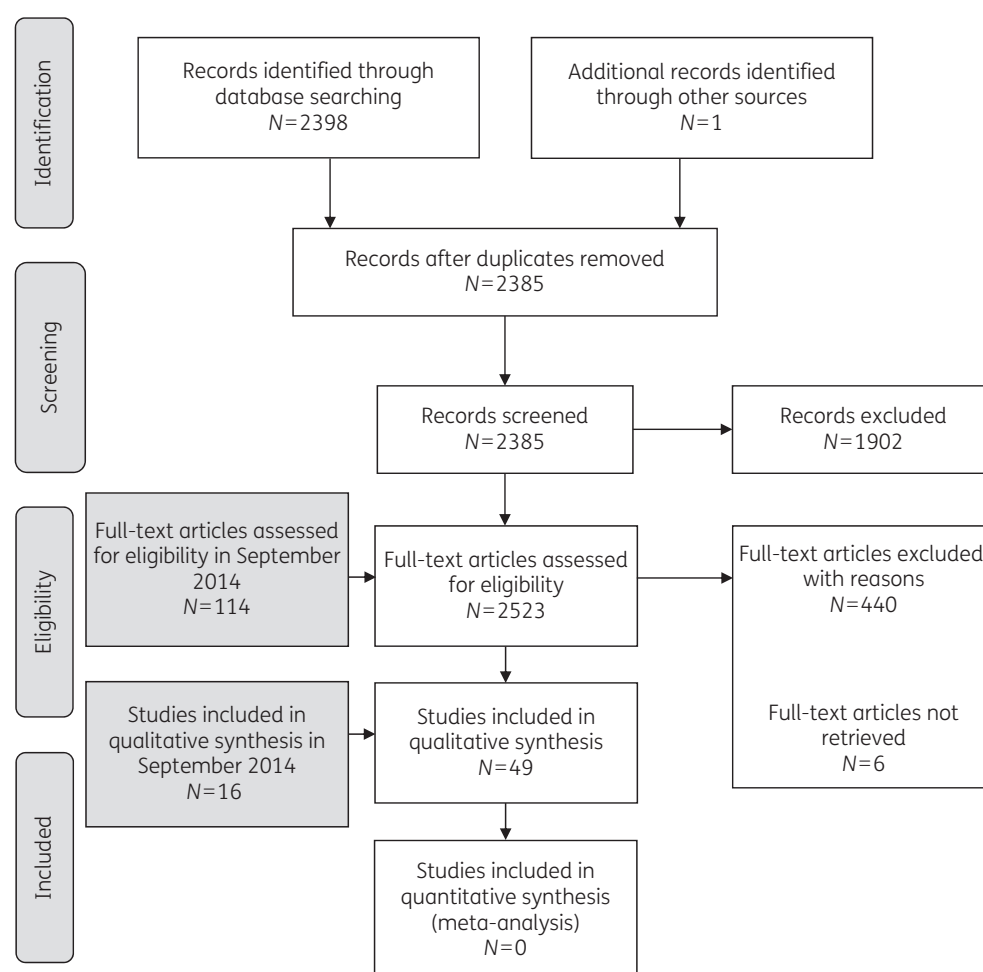


Figure 1. Flow chart of systematic review.

pragmatic decisions on what to test). Some antibiotic resistances are now very common and stable, e.g. to ampicillin and sulphonamides, so they are seldom tested for, but if they are present the organism needs only one further resistance to count as MDR GNB by the ‘three classes of resistance’ rule. There also is scope for disagreement on which antibiotics should be considered as separate classes; for example, monobactams behave similarly to oxyiminocephalosporins in respect of most resistance mechanisms but very differently in the case of metallo-lactamases (MBLs).

Difficulties arise also if *in vitro* ‘susceptibility’ is poorly defined, e.g. with the absence of EUCAST breakpoints, as for e.g. (i) *Acinetobacter* spp. and sulbactam, and (ii) temocillin. Furthermore, differences between European (EUCAST) and US (CLSI or FDA) breakpoints can affect fundamentally whether isolates are regarded as MDR or XDR. These inconsistencies will have an effect on the recruitment and classification of patients in clinical trials. Separate breakpoints for urinary isolates, although needed to take account of high urinary concentrations with some antibiotics, also complicate assessments. Lack of laboratory uniformity in breakpoints can make comparisons and data aggregation meaningless. For example, EUCAST and CLSI breakpoints differ for piperacillin/tazobactam and amoxicillin/clavulanate. EUCAST defines Enterobacteriaceae isolates as piperacillin/

tazobactam susceptible if they have an MIC ≤ 8 mg/L [resistance (R) >16 mg/L] compared with $\leq 16+4$ mg/L (R $\geq 128+4$ mg/L) in CLSI guidance. For amoxicillin/clavulanate susceptibility is defined by EUCAST as $\leq 8+2$ mg/L (R >8 mg/L (or $32+2$ mg/L for uncomplicated UTI) and by CLSI as $\leq 8+4$ mg/L (R $\geq 32+16$ mg/L). The FDA regard *Pseudomonas aeruginosa* isolates as susceptible to piperacillin/tazobactam if the MIC is ≤ 64 mg/L (the historical CLSI breakpoint for piperacillin) whereas EUCAST and CLSI now consider the breakpoint should be susceptibility (S) $\leq 16+4$ mg/L. The EUCAST and CLSI definitions have changed with time and from previous national guidelines, e.g. the pre-EUCAST BSAC breakpoint for amoxicillin/clavulanate in systemic infections was $8+4$ mg/L. Cefepime is a further example of an antibiotic with breakpoint changes: the old CLSI breakpoint for Enterobacteriaceae was ≤ 8 mg/L but is now ≤ 2 mg/L based on 1 g twice daily doses. Organisms with MICs of 4 or 8 mg/L are viewed as being ‘susceptible but dose-dependent’ by CLSI. EUCAST categorizes an MIC ≤ 1 mg/L as susceptible and >4 mg/L as resistant. A failure rate of 83% in a prospective trial of cephalosporins for ‘susceptible’ serious infections due to ESBL-producing *Klebsiella* spp. and *Escherichia coli* partly reflected the use of high breakpoints.¹² Breakpoint differences and changes over time in the categorization of isolates with the same MIC as ‘susceptible’ or

'resistant' profoundly challenge conclusions in the clinical literature, including reports of regulatory trials on the response to be expected of infections due to 'susceptible' or 'resistant' strains or indeed which patients have been included in trials where susceptibility of the organism is a selection criterion.

For all these reasons, the international definitions have not led to better surveillance of MDR strains and their usefulness must still be questioned. In our literature search routines, we have employed the international definitions but have had to augment these with literature on specific resistances. A useful pragmatic approach to the definition of MDR is to consider oral and parenteral drugs separately. The reason being that oral drugs will be largely used in the primary care setting and parenteral drugs in secondary care. Furthermore, one should base definitions on susceptibility rather than resistance as the former is more likely to be sought clinically by further testing with MDR strains. This gives a basis for alternative definitions for MDR. For oral drugs, multiresistance can usefully be defined as a bacterium susceptible to only one or no readily available oral agent active against infections systemically or in the upper urinary tract. This definition is vulnerable to the introduction of new, or newly re-licensed, oral agents, but this is appropriate and may emphasize the importance of new agents to the licensing authorities. By this definition the following would be classed as multiresistant isolates for the community: (i) *E. coli* resistant to co-amoxiclav (amoxicillin with clavulanic acid), oral cephalosporins, quinolones and trimethoprim but susceptible to nitrofurantoin, mecillinam and fosfomycin. Although providing options in cystitis, these oral agents lack evidence of achieving systemically active concentrations and efficacy in upper and complicated UTIs, which is particularly relevant if these are caused by ESBL- and AmpC-producing strains; (ii) *P. aeruginosa* resistant to quinolones. This approach could be modified to exclude agents where the mutation frequency is sufficiently high so that resistance commonly emerges during treatment.

For parenteral antibiotics a similar approach can be considered. Susceptibility to oral agents that have no licensed, or available, parenteral form, e.g. pivmecillinam and nitrofurantoin, should not be taken into account. Specific agents to which impaired susceptibility might be significant include carbapenems, relevant cephalosporins (cefotaxime for Enterobacteriaceae, ceftazidime for *P. aeruginosa*), aztreonam, ceftolozane/tazobactam, ceftazidime/avibactam, temocillin, piperacillin/tazobactam, colistin, quinolones, fosfomycin, tigecycline and aminoglycosides (including amikacin). Given this greater number of agents and the paucity of new pipeline antibiotics active against Gram-negative bacteria, it is pragmatic to consider 'multiresistant' as isolates where only two, or fewer, unrelated antibiotics are active against the bacterium. By such a definition the following would be considered multiresistant isolates in hospitals:

- (i) *Acinetobacter baumannii* susceptible to two or fewer of meropenem or imipenem, (third-generation cephalosporins), piperacillin/tazobactam, (tigecycline), aminoglycosides, quinolones, (trimethoprim), colistin, where agents in brackets lack EUCAST breakpoints.
- (ii) *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. that are susceptible to two or fewer of carbapenems, third-generation cephalosporins, including with β -lactamase inhibitors, piperacillin/tazobactam,

temocillin, tigecycline, aminoglycosides, quinolones, trimethoprim or colistin.

- (iii) *Proteus* spp., *Morganella* spp. and *Providencia* spp. that are resistant to third-generation cephalosporin, piperacillin/tazobactam, and aminoglycosides and susceptible only to carbapenems, and the new BL/BLI combinations (ceftolozane/tazobactam or ceftazidime/avibactam). Unlike the species considered in (ii) above, these Proteaceae are inherently resistant to tigecycline and colistin.

The following would not be regarded as multiresistant:

- (i) *E. coli* that is susceptible to carbapenems, ceftolozane/tazobactam, ceftazidime/avibactam, colistin and fosfomycin but resistant to unprotected third-generation cephalosporins, co-amoxiclav, piperacillin/tazobactam, quinolones and trimethoprim.

The effect of new parenteral antibiotic introductions on the definition of MDR GNB in hospitals is illustrated by the licensing of ceftazidime/avibactam and the availability of parenteral fosfomycin. Both drugs join temocillin, tigecycline or colistin as potentially effective agents against some Enterobacteriaceae with KPC carbapenemases. Such strains would no longer be classified as MDR GNB by our definition. Clearly, acquired resistance of KPC-producing strains to colistin, ceftazidime/avibactam, fosfomycin and tigecycline may all arise so some will be MDR GNB and some will not. From a therapeutic view this is probably appropriate, although all should remain major targets for infection control, given the cost of new agents and the need to conserve their usefulness, along with plasmid-mediated transmission of *bla*_{KPC} gene and transmission of their host strains. The use of alternative β -lactams or new BL/BLIs rather than carbapenems may be expensive but might reduce the selective pressure for carbapenem-resistant MDR GNB. These antimicrobials, with activities against organisms with different β -lactamases, may have differential effects on the prevalence of particular β -lactamases and other carbapenem-resistant bacteria. They may select more for MBLs that are particularly resistant to β -lactams, which will limit their ultimate usefulness in a locality. The activity of different β -lactamase inhibitors against, and stability of β -lactams to, different β -lactamases is shown in Table 5.

The difficulty in international surveillance of MDR GNB need not preclude the establishment of surveillance for specific organism-antibiotic resistance combinations. This has been adopted by PHE for the English Surveillance Programme for Antibiotic Use and Resistance (ESPAUR) and is weighted towards resistance to third-generation cephalosporins, quinolones and carbapenems of *E. coli*, *Klebsiella* spp. and *P. aeruginosa*.

6.3 What is the global epidemiology of MDR GNB?

6.3.1 Origins and impact of multiresistance

Resistance to multiple agents can develop via successive mutations, through the dissemination of multiresistance plasmids/genes (e.g. transposons), or through a combination of both processes. Resistance narrows antibiotic choices for definitive therapy. More critically, it increases the likelihood that empirical therapy will prove ineffective, increasing mortality in septic patients.

Table 5. Stability of various β -lactam antibiotics and different inhibitor activities against important β -lactamases found in MDR GNB

Compound	Enterobacteriaceae					Acinetobacter		Burkholderia		Pseudomonas	
	AmpC	TEM ESBL	SHV- ESBL	CTX-M ESBL	OXA-1	OXA-48	KPC	IMP/VIM/NDM	native		OXA- 23/24/58
Inhibitors											
clavulanate	not inhibited	inhibited	inhibited	inhibited	weak inhibition	not inhibited	not inhibited	not inhibited	not inhibited	not inhibited	
sulbactam	not inhibited	inhibited	inhibited	inhibited	weak inhibition	not inhibited	not inhibited	not inhibited	not inhibited	not inhibited	
tazobactam	not inhibited ^a	inhibited	inhibited	inhibited	weak inhibition	not inhibited	not inhibited	not inhibited	not inhibited	not inhibited	
avibactam	inhibited	inhibited	inhibited	inhibited	?	inhibited	inhibited ^b	not inhibited	not inhibited	not inhibited	
β-Lactams											
temocillin	stable	stable	stable	stable	stable	labile	moderately stable	labile	inherently inactive	inherently inactive	variable
piperacillin	labile ^c	labile	labile	labile	labile	labile	labile	labile	acquired R near	labile	variable
ceftazidime	labile ^c	labile	labile	labile	stable	stable	labile	labile	universal acquired R near	labile	variable
MEM/IPM	stable	stable	stable	stable	stable	labile	labile	labile	active	labile	variable
ertapenem	moderately stable ^c	stable	stable	stable	stable	labile	labile	labile	inherently inactive	inherently inactive	inherently inactive
aztreonam	labile ^c	labile	labile	labile	stable	labile	labile	stable	inherently inactive	inherently inactive	inherently inactive
mecillinam	stable	moderately stable	labile	moderately stable	stable	labile	labile	labile	inherently inactive	inherently inactive	inherently inactive

MEM/IPM, meropenem/imipenem. R, resistance.

^aExcept *Morganella morganii*.

^bInhibition not reliable with KPC-3.

^cMay appear active if AmpC is inducible, as induces weakly.

Plasmids are the main source of MDR in Enterobacteriaceae and *Acinetobacter* spp., except for mutations in DNA gyrase genes *gyrA/B* conferring fluoroquinolone resistance, mutational up-regulation of *arcA/B*-mediated efflux compromising tigecycline, and for mutational derepression of AmpC β -lactamases giving resistance to third-generation cephalosporins in *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp. and *Morganella morganii*.^{13,14} By contrast, sequential accumulation of mutations is paramount in *Pseudomonas* spp.

A recent review has discussed the emergence of specific resistant lineages and the role of different plasmid groups in emerging resistance problems in *E. coli*.¹⁵ Some clones have spread widely for reasons that are not clear. Resistance may increase their competitiveness, but some strains are adept at acquiring MDR. Several strands of evidence support this view. First, some 'high-risk clones', e.g. *E. coli* ST131, frequently acquire diverse resistance determinants, including different ESBLs, AmpC and even carbapenemases.¹⁶ Second, there is co-selection of hypermutability with resistance in *P. aeruginosa* in patients with cystic fibrosis, facilitating development of further resistance. Third, it is commonplace for plasmids and resistance islands to carry multiple genes encoding resistance to an antibiotic via two or more different mechanisms not all of which can remain under effective selection pressure. Fourth, the presence of toxin-antitoxin systems in plasmids may prevent loss of plasmids even when selective pressure is removed.¹⁷ Fifth, integrons, which provide efficient gene-capture and expression systems, and which are now frequent in plasmids but were not present prior to the widespread use of antibiotics, provide a mechanism whereby resistance acquisition has accelerated. Finally, the presence of MDR GNB in the environment, including foodstuffs and water sources, provides important pathways for amplification and the spread of some resistance genes to man.^{18,19,20-23}

Until recently, environmental sources of carbapenemase genes did not appear to exist but the description of high levels of NDM-producing *E. coli* in chicken in China²⁴ suggests this position will not be maintained with current international practices and biosecurity of food as a source. Surprisingly, the ST131 clone of *E. coli* did not seem to have significant environmental sources in its initial spread, although it has now been described occasionally in chickens.^{25,26}

6.3.2 Epidemiological trends among MDR Enterobacteriaceae: cephalosporin and quinolone resistance

Countries historically varied in the prevalence of different CTX-M ESBLs conferring cephalosporin resistance and in the plasmids encoding these enzymes.²⁷ The prevalence of different CTX-M enzymes has changed with time and latterly in Europe and North America CTX-M-15 has become the dominant enzyme, often associated with *E. coli* ST131.²⁸ Whole-genome sequencing (WGS) suggests that the acquisition of CTX-M enzymes occurred a number of times in clade C of *E. coli* ST131.²⁹ Frequent co-carriage of OXA-1 penicillinases impairs susceptibility to combinations of clavulanate and tazobactam with penicillins. Ceftolozane appears stable to this OXA-1 enzyme. Other factors associated with the rise of MDR Enterobacteriaceae include the spread of plasmids encoding AmpC β -lactamase. These seem around 10-fold less frequent than plasmids encoding ESBLs in the UK,³⁰ although more recently in

Canada a plasmid-mediated AmpC enzyme (CMY-2, which shares a promoter gene, *ISEcp1*, with CTX-M-15) was almost half as common as ESBL production and one-third of such strains belonged to *E. coli* ST131.³¹ Distinguishing AmpC and ESBL cephalosporin-resistant strains is important epidemiologically and in routine testing, although both EUCAST and CLSI do not recommend it for guiding treatment.³² However early information on AmpC/ESBL status in Enterobacteriaceae may predict resistance/susceptibility to ceftolozane/tazobactam. Mutations can augment MDR: for example, porin loss can engender resistance to ertapenem (and, sometimes, other carbapenems) in ESBL- and AmpC-producing Enterobacteriaceae.

6.3.3 Carbapenem resistance

Carbapenem resistance was initially slow to emerge in Enterobacteriaceae but is now steadily increasing, and mediated more and more by acquired carbapenemases (predominantly by KPC, VIM, IMP, NDM and OXA-48-like types).³³⁻³⁶ Internationally there has been a considerable spread of *K. pneumoniae* clonal complex (CC) 258 isolates with KPC carbapenemases. The rise of NDM and OXA-48 carbapenemases is more often associated with the spread of their encoding plasmids or transposons among bacterial strains. Carbapenem resistance due to ESBL or AmpC enzymes combined with OmpK35 porin loss may lead to treatment failure but is often unstable and may impose a fitness cost on bacteria, meaning that spread of such strains among patients is rare, though not unknown.³³ Loss of the OmpK36 porin conferred resistance to new carbapenem- β -lactamase inhibitor combinations, relebactam with imipenem/cilastatin³⁷ and meropenem with vaborbactam.³⁸ Resistance conferred by acquired carbapenemases is of much greater concern, and is generally associated with considerable resistance to other agents.

Data from EARS-Net suggest that the prevalence of carbapenem-resistant Enterobacteriaceae causing bacteraemia markedly increased in most parts of Europe between 2013 and 2015.³⁹ European prevalence of carbapenem-resistant *K. pneumoniae* was higher than 5% in 2015 (and much higher in some of the countries)⁴⁰ in Greece, Italy, Cyprus and Romania. In Greece, the proportion of bloodstream *K. pneumoniae* isolates resistant to carbapenems increased from 27.8% in 2005 to 62.3% in 2014. VIM enzymes dominated early in this period but were replaced by KPC types, often carried by CC258. The rise of carbapenem-resistant *K. pneumoniae* in Italy has been dramatic and recent: from 1% of bacteraemias in 2009 to 15% in 2010 and 32.3% in 2014. This increase again is mainly due to CC258 *K. pneumoniae* with KPC enzymes.⁴¹ This clone also spread widely earlier in the USA⁴² and then in Israel,⁴³ where an aggressive, nationwide infection control intervention was successful in bringing it under control.^{44,45} In Romania the major problem is *K. pneumoniae* producing OXA-48 carbapenemase.⁴⁶

Outbreaks of carbapenemase-producing Enterobacteriaceae (CPE) have been reported in many other parts of the world, including all US states⁴⁷ (where KPC enzymes dominate), South Asia (predominantly NDM enzymes), the Middle East (OXA-48), Brazil and Colombia (KPC).^{36,48} The MBL IMP-4 has spread widely in China, often together with KPC-2. IMP-4, without KPC, is the dominant carbapenemase in Australia. Further global spread is to be expected⁴⁹ as IMP-4 has now been observed in South London

(unpublished observations, D. M. Livermore). In the absence of comprehensive international prevalence data for infection and carriage, risk factors for CPE are difficult to derive, but seem to include travel to high-prevalence areas, notably including the Indian subcontinent for NDM producers, and exposure to health-care and antimicrobials.³³ Travel locations are becoming convergent with those where ESBLs are prevalent. Case-number trigger points for carbapenem-resistant isolates and regional coordination in control action has recently been modelled in the USA to show the high importance of early intervention with effective control measures⁵⁰ for *K. pneumoniae* strains and other Enterobacteriaceae. Carbapenem resistance in Enterobacteriaceae has been associated with increased attributable mortality, probably owing to the greater likelihood that initial empirical therapy proves inadequate.^{33,51,52}

6.3.4 Global resistance issues with oral drugs with low resistance rates in the UK

A 2008 study of clinical isolates from women aged 18–65 years with symptoms of uncomplicated lower UTI in 10 countries found susceptibility rates above 90% only for fosfomycin (98%), mecillinam (96%) and nitrofurantoin (95%).⁵³ Nitrofurantoin resistance in *E. coli* as assessed in European and Canadian isolates collected in 1999–2000 and 2007–08 was associated with a very diverse range of sequence types, although many strains showed multiple resistances: mecillinam resistance was similarly diverse but not associated with multiple resistance.⁵⁴ A further study from Munster and Seattle suggests nitrofurantoin resistance is particularly common in ST58.⁵⁵ Nitrofurantoin resistance is now described in 11% of the dominant H30 sub-clone of ST131,⁵⁶ suggesting the drug may be selective in the upper intestine, although this drug does not usually eliminate Enterobacteriaceae from the faecal flora of patients receiving it. In Canada, nitrofurantoin resistance rates in ESBL-producing *E. coli* were 16% but in ESBL-producing *Klebsiella* spp. were 71% (nosocomial) and 93% (non-nosocomial).⁵⁷ Well-described mutations in nitrofurantoin reductases confer resistance and plasmid-mediated resistance due to an efflux pump (*oqxAB*) has recently been described from Hong Kong.⁵⁸ This efflux pump and its encoding plasmid (with the *oqxAB* gene flanked by IS26 insertion sequences) was found in 26/103 nitrofurantoin-resistant or -intermediate human isolates (by CLSI criteria) and was more common in ESBL-producing isolates. The combination of *oqxAB* with the nitroreductase genes caused high-level nitrofurantoin resistance. This two-level resistance process is analogous to the hypothetical role of AAC-6'-Ib-cr in aiding the emergence of quinolone resistance by chromosomal mutation. Notably, *oqxAB* also mediates resistance to mequindox, which is used in China as a growth promoter in animal feed. In China 322/1123 veterinary isolates of *E. coli* carried this gene but these mainly belonged to phylogroups A and B1, which are less associated with extraintestinal pathogenicity in man.⁵⁹

Fosfomycin use has been complicated by the emergence of resistance in some populations.⁶⁰ In Spain, when use increased some 50% between 2005 and 2008, resistance rates in CTX-M-15 ESBL-producing *E. coli* rose to 16% and among all ESBL-producing isolates increased from 4.4% in 2005 to 11.4% in 2009. The increase was particularly associated with nursing homes.⁶¹ Fosfomycin resistance developed in *E. coli* ST131 (previously

present there but not typed)⁶² and was not associated with described mutational mechanisms of fosfomycin resistance.⁶³ Such mutations involve inactivation of genes encoding the hexose and triose sugar phosphate transport, impairing drug uptake. A different mechanism is present in the acquired *fosA* gene, which encodes a drug-inactivating metalloglutathione transferase.⁶⁰ Fosfomycin resistance was present in 2009–10 in 7.8% of human *E. coli* in mainland China and approximately half of this was due to *fosA*₃.⁶⁴ A recent survey of food animals in Hong Kong found plasmid-mediated *fosA* to be increasing in frequency and associated with CTX-M ESBL-encoding plasmids.⁶⁵ A recent Chinese survey of isolates collected from 2010 to 2013 detected fosfomycin resistance in 12% of ESBL-producing *Klebsiella* and 169/278 (61%) of KPC-producing *K. pneumoniae*: 94 KPC-producing strains carried *fosA*₃ flanked by two IS26 insertions and were clonally related.⁶⁶ Similar genetic findings were made in non-clonally related *E. coli* and *Klebsiella* sp. in Korea.⁶⁷

Mecillinam resistance is said to remain uncommon in the clinic, at 5%–7% of ESBL-producing *E. coli* in Sweden.⁶⁸ In a wider European study overall susceptibility was similar, with 4.8% resistance in *E. coli* from uncomplicated UTI, although gradually rising,⁶⁹ notably in Spain, where the proportion of resistant strains rose from 1% in 2000 to 6.5% in 2014.

6.4 How do MDR Enterobacteriaceae differ from non-fermenters in terms of their prevalence and associated resistance genes?

Carbapenem resistance is more common in non-fermenting GNB than in Enterobacteriaceae. In *A. baumannii*, by the year 2000 it was common to encounter isolates resistant to all treatment options except carbapenems, colistin and tigecycline. Subsequently, carbapenem resistance has proliferated, reaching ~30% of bloodstream isolates. It is largely associated with acquired OXA-23, -40 or -58-like carbapenemases or with insertion-sequence-mediated up-regulation of the chromosomal OXA-51-like carbapenemase. The strain structure of *A. baumannii* is extremely clonal, making it difficult, without a history of patient transfers, to distinguish place-to-place spread from repeated independent selection of lineage variants that were previously circulating at low frequency. UK *A. baumannii* isolates producing OXA-23 carbapenemases often co-produce *ArmA*-encoded 16S ribosomal methyltransferases conferring pan-aminoglycoside resistance. MDR *Acinetobacter* spp. largely cause outbreaks in ICU settings,^{70–72} whereas carbapenem-resistant Enterobacteriaceae, principally *E. coli* and *Klebsiella* spp., cause infection in a wider group of patients, and have far greater potential to spread rapidly when introduced into wider patient populations.^{36,44,45,48,73,74}

Most UK *P. aeruginosa* remain susceptible to β -lactams, including ceftazidime, piperacillin/tazobactam and carbapenems, aminoglycosides and fluoroquinolones, with resistance rates of 5%–10% for these agents; and <1% for ceftolozane/tazobactam.⁷⁵ Nevertheless, single MDR lineages, some with carbapenemases, have persisted in a few UK hospitals for up to 9 years, causing multiple infections widely scattered over time and possibly reflecting colonization of the hospital water systems. The most frequently encountered carbapenemase is VIM, which may be plasmid mediated, with multiple gene copies conferring high-level meropenem resistance,⁷⁶ but is usually integron associated. IMP-9, another

MBL, is as common as VIM in China,⁷⁷ and has been shown to be derived (as probably are many carbapenemase genes) from environmental bacteria by horizontal gene transfer.⁷⁸ MDR is also a major problem in *P. aeruginosa* from cystic fibrosis patients, with resistance increasing over time in the individual patient's lung microflora. MDR profiles are extremely variable even within widely successful cystic fibrosis lineages, e.g. the Liverpool Epidemic Strain, which has circulated in multiple cystic fibrosis patients and units. Rates of carbapenem resistance in *P. aeruginosa* vary greatly across Europe, with high rates in Eastern Europe; Lithuania, Poland, Slovakia, Hungary, Croatia, Romania, Bulgaria and Greece all have rates of resistance >25% and sometimes >50%.⁴⁰ More generally, these rates of resistance show a gradient, rising from north-west to south-east Europe, with extensive spread of carbapenemase-producing clones in Belarus, Kazakhstan and Russia, which are outside the EU surveillance area.⁷⁹ In contrast to Enterobacteriaceae, rates of resistance to carbapenems are generally higher than those to ceftazidime, piperacillin/tazobactam or aminoglycosides.

6.5 Prevalence of antibiotic resistance in Gram-negative bacilli in the UK and relevant antibiotic prescribing

There are no epidemiological reports in the UK that specifically study defined MDR GNB. In this section, we discuss information on resistance to individual antibiotics and, where available, their associated resistances. Analysis is complex. Different reports from English, Welsh, Northern Irish and Scottish devolved administrations need to be drawn together to give a UK summary: bacteria and antibiotic resistances do not respect national boundaries.

Reduced prescribing may be followed by reduced resistance (see Section 11.1) but this is not invariable at a national level. Such reduced resistance has not occurred as older antibiotics (e.g. sulphonamides and streptomycin) have been abandoned,⁸⁰ perhaps because of resistance linkage and for reasons already discussed (see Section 6.3). Reduced prescribing may reduce the likelihood of new resistance becoming prevalent but this is only a hypothesis set within the modern issues of travel and migration, which may import and spread resistance. Overall antibiotic consumption in England has fallen by 4.5% between 2012 and 2015 to 21.8 DDDs/1000 population/day. It has yet to decline in general practice to the levels seen in 2010. After 5 years of increases in prescribing, hospital antibiotic use declined by 5% in 2014 from 5190 to 4933 DDDs/1000 admissions and is now at approximately 2010 and 2011 levels. This decrease is concentrated in teaching hospitals, which may reflect their case-mix or different pressures in other hospitals.⁴

In Scotland antibiotic use in primary care fell for the third consecutive year in 2015 (by 2.4%) and is now 9.5% lower than the peak rate of use in 2012. The level of prescribing was related to population deprivation scores and to residence in nursing homes where antibiotic use among those aged over 65 years was 83% higher than for similarly aged patients not resident in nursing homes.⁸¹ Since 2012, antibiotic use in Scottish nursing homes has fallen by 7.8% compared with 5.1% in all patients aged >65 years. Nevertheless, hospital use rose by 3.5% and is now 9.9% higher than it was in 2012. The rate of 5880 DDDs/1000 admissions is now 19% higher than in England.⁸¹ Of course, this may reflect use of less-selective combination regimens such as penicillin,

metronidazole and gentamicin rather than the number of days a patient receives antibiotics, which is a weakness both of using DDDs and the number of admissions to estimate the number of people exposed to an individual antibiotic. Although England has the lowest antibiotic consumption in the UK, Scottish hospitals show significantly less consumption of carbapenems and piperacillin/tazobactam.

Information on primary and secondary care prescribing for Wales for 2015^{82,83} is only available at the level of health board and hospital, respectively, and has not been reported as aggregate totals.

An overview of current antibiotic resistance in Gram-negative serious infections in the UK can be secured in various ways. The BSAC Bacteraemia Surveillance Programme (<http://www.bsac.surv.org>) provides historical and current information with a marked time lag for centrally tested isolates from a restricted sample of 24–40 hospitals and can be examined on a national or regional basis by species. It has an archive of organisms that can be studied in retrospect, which is an important strength. Other surveillance depends on collection of local data rather than isolates. In England reporting is mandatory for all cases of *E. coli* bacteraemia which has improved case ascertainment. Mandatory data are needed for *Klebsiella*, other Enterobacteriaceae and Proteaceae, *Acinetobacter* spp. and *P. aeruginosa* if early national interventions in emerging problems are to be reliably assessed. Mandatory reporting of MRSA bacteraemia in England was established in 2001 and has improved with more comprehensive data capture from 2005 onwards. Health Protection Scotland now has mandatory reporting of *E. coli* bacteraemia but other species of Gram-negative bacilli are only reported across the UK on a voluntary basis. Such voluntary laboratory reporting of all bacteraemias has been in place since the Devonport incident of contaminated intravenous infusions in 1972 and is believed now to capture data for 82% of all bacteraemias. These data include antibiotic susceptibility data that have not been present in mandatory data. The collection of voluntary and mandatory data suggests that voluntary reporting should be replaced by mandatory reporting as soon as possible to reduce the laboratory workload. Most laboratories in England and Wales examining human samples now download bacteria identified and their antibiotic susceptibilities irrespective of anatomical site to regional and national repositories, where trends but not additional information, e.g. demographic details of patients' residence etc., can be analysed.

Bacteraemia due to *E. coli* has increased over the last 10 years in England and Wales, and analysis of the dataset showed that receipt of antibiotics in the 4 weeks preceding bacteraemia was the most important risk factor, followed by age over 65 years, and occurrence during summer months.⁸⁴ A study by the *E. coli* subgroup of the UK Department of Health's Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare-Associated Infection on the first 891 cases of *E. coli* bacteraemia with enhanced surveillance data are available in Committee papers for 28 March 2014 online.⁸⁵ This showed that urinary catheterization was a factor in only 10% of cases but that 72% of episodes from a urogenital source involved individuals aged ≥65 years. A urogenital infection had been treated in 310/891 (34.8%) cases in the 4 weeks preceding bacteraemia and this sub-population differed very significantly in its antibiotic resistances. Resistance in this subpopulation to ciprofloxacin was 80% versus 17% overall, 76.9% versus 39% to trimethoprim, and 49.3% versus 45% to co-amoxiclav. The third-generation

cephalosporin resistance rate in the population overall was 10% but no figure was provided for the resistance rate in this sub-population treated. Although the rates for ciprofloxacin seem surprising, the figures show a marked selection for multiply resistant, if not necessarily MDR, strains because of either failed treatment that did not cover the multiresistant organisms or selection of resistant organisms in the gut flora that subsequently caused a urinary infection that then progressed to bacteraemia. Approximately half of the bacteraemias appeared to be associated only with a lower UTI but this probably represents symptomatically silent upper UTI giving rise to bacteraemia, either initially or through spread to the upper tract despite treatment. The implication of this important study is that failure to give effective antibiotics may be the reason for 70% of *E. coli* bacteraemias, whilst 30% of cases are associated with antibiotic resistance and, possibly, directly with treatment failure. The former requires detailed study, which is beyond the scope of this guideline. The consistent use of an active antibiotic regimen for those either aged >65 years or with signs and symptoms of an upper UTI would make a sizeable contribution to the target of a 50% reduction in the rate of *E. coli* bacteraemias by 2020 that was announced by the then UK Prime Minister at the Japan 2016 G7 meeting.⁸⁶ This enhanced surveillance study has now been analysed and published.⁸⁷ Most patients (69.6%) were aged over 65 years. Most patients (68.3%) had a positive blood culture taken within 24 h of admission but 46.7% of these had a healthcare exposure within the previous month and 546 out of these 930 (58.7% of this subgroup, 31.5% overall) had received antibiotics in the preceding month. In 281 there was a clear urinary focus for the bacteraemia, for which 145 had received antibiotics (most commonly trimethoprim or co-amoxiclav). The largest independent risk factor for a bacteraemia's focus being the urogenital tract was previous treatment for UTI within 4 weeks of the bacteraemia's onset [adjusted odds ratio (aOR) 10.7 (95% CI 3.6–8.1)] but details of antibiotic resistance in this subpopulation for the whole study was not given. Twenty one percent of patients had either a urinary catheter *in situ* or had one inserted, removed or manipulated in the previous 7 days. Since the 2014 initial report, PHE has changed its recommendation for first-line treatment of UTI in all but those under 50 years from trimethoprim to nitrofurantoin, which is a urinary antiseptic that is only effective for treating lower UTI, although it can be effective for preventing pyelonephritis associated with bacteriuria of pregnancy. It is too early to tell whether this will be effective in reducing bacteraemia or whether an oral combination regimen that attains systemically active concentrations will be necessary to achieve the desired outcome. The UK Advisory Committee on Antimicrobial Prescribing, Resistance, and Healthcare Associated Infection (APRHAI) on 28 March 2014 opined that in suspected pyelonephritis or upper UTI the patient should be admitted if (i) ciprofloxacin, piperacillin/tazobactam or co-amoxiclav had been used in the previous 2 months and (ii) the patient's symptoms worsened or did not improve in the 12–48 h after prescription. In UK strains of *E. coli* ST131 from various sources collected in 2011–12, when O16 and non-typeable strains are excluded, there is evidence that trimethoprim resistance occurs in at least 69% of CTX-M-positive strains, which constituted 32% of recent UK strains studied but 39%, at most, of CTX-M-negative strains.⁸⁸ All CTX-M producers were ciprofloxacin resistant and 71% of non-CTX-M producers were quinolone resistant. Quinolones are not therefore useful if ST131 strains are prevalent even if these strains are not carrying ESBLs.

A study reported that sequence-typed *E. coli* isolates from the BSAC Bacteraemia Surveillance Programme showed that the significant change in *E. coli* bacteraemia was almost exclusively due to an increase in clonal complexes 12, 69, 73, 95 and 131.⁸⁴ This reflects the sequence types in these clonal complexes. The clonal complexes, which each may contain more than one sequence type, belong to phylogroups B2 and D, which have the virulence factors associated with extraintestinal spread. Phylogroup A and B1 strains, which may be more antibiotic resistant, are usually confined to the gut and lack these virulence factors. CC131, unlike the other CCs, includes multiresistant isolates (of ST131) hosting CTX-M ESBLs, almost invariably now with resistance to quinolones.⁸⁴ In a 2010–12 Yorkshire study of bacteraemias 129/768 were ST131 (39/129 ESBL producers), confirming the importance of ST131 strains even in the absence of production of ESBLs. One hundred and forty-two of 768 were ST73 (3/142 ESBL producers), 81 were ST69 (1 an ESBL producer), 73 were ST95 (1 an ESBL producer), 31 were ST12 (no ESBL producer, quinolone-resistant) and 27 ST127 (no ESBL producers or quinolone-resistant strains).⁸⁹ Phylogroup D-ST69 strains (which include the previously designated clonal group A) were not fluoroquinolone resistant in a recent Italian study,⁹⁰ although they were commonly detected in Italy in a previous cystitis study.⁹¹ ST69 is usually ampicillin, trimethoprim and sulfamethoxazole resistant. Quinolone-resistant D-ST69 strains were also uncommon in a Spanish survey with isolates from 2009 accounting for 3% of quinolone-resistant strains respectively, compared with 26% for O25:H4-B2 ST131 strains.⁹² We did not consider it feasible to introduce control measures for ST131 when preparing our earlier guidance on infection control³ and indeed cephalosporin resistance has spread into many other STs.⁹³

More recent data from 2012 to 2014 on antibiotic resistance in *E. coli* bacteraemia in England were collected on 82% (54 301/66 512) of cases recorded by mandatory surveillance by record-linking with the national records of all bacterial isolates. Seventy-four percent were classified as community onset whereas 16% of cases occurred 7 or more days after hospital admission. Antibiotic resistances reported were 8439 (18.4%) to ciprofloxacin, 4256 (10.4%) to third-generation cephalosporin, 4694 (10.2%) to piperacillin/tazobactam, 4770 (9.7%) to gentamicin and 91 (0.2%) to carbapenems.⁹⁴ Non-susceptibility to quinolones and cephalosporins decreased by 10% and 11% respectively over the 2 years in hospital-onset cases, whereas third-generation cephalosporin resistance increased by 10% in community-onset cases. Trends in hospital or community onset changes in antibiotic susceptibility in other species, such as *Klebsiella*, are precluded by lack of mandatory surveillance of bacteraemia.

A 12 year single-centre study in England suggested that the increase in *E. coli* bacteraemias was essentially confined to ciprofloxacin, co-amoxiclav, cefotaxime and aminoglycoside resistance and accompanied a similar change in urinary isolates.⁹⁵ The major rise in cephalosporin and MDR *E. coli* in the UK occurred between 2000 and 2007, largely reflecting the spread of IncF (pEK499 or similar) plasmids, and was associated initially with the internationally successful *E. coli* ST131 lineage with chromosomal fluoroquinolone resistance. These *IncF* plasmids encoding the CTX-M-15 β -lactamase, along with resistances to trimethoprim, sulphonamides, tetracyclines and aminoglycosides [often associated with *aac(6')-Ib-cr*, also augmenting ciprofloxacin resistance],

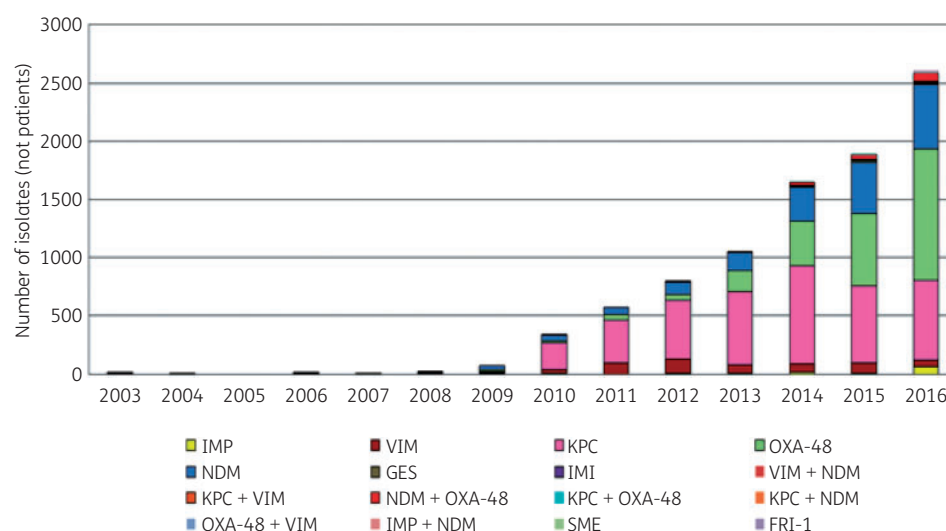


Figure 2. Carbapenemase-producing Enterobacteriaceae submitted to and confirmed by PHE-AMRHAI Colindale from laboratories in England. In a national context, a regional non-PHE centre in an area of KPC endemicity became active in 2014 and did not submit or report isolates. Courtesy of Dr Katie Hopkins, Public Health England.

also spread in other *E. coli* sequence types and other Enterobacteriaceae, notably *K. pneumoniae*. Since approximately 2007 (the date varies with the species and resistance) the rise of cephalosporin- and fluoroquinolone-resistant Enterobacteriaceae has slowed and fluctuated (*E. coli*) or reversed (*Klebsiella* spp. and *Enterobacter* spp.) in the UK, though not in continental Europe.⁹⁶ This shift in percentage resistance may reflect the reduction in prescribing of cephalosporins and quinolones in the UK, predicated not only by the Enterobacteriaceae problem but also by concern about *Clostridium difficile*. It is important to know if this reflects an absolute decrease in numbers. Some data suggest that increased quinolone use largely mirrored the selection of such strains.⁹⁷ An increase in quinolone resistance in bacteraemias preceded the arrival of ESBL-producing strains. Cephalosporin use in England is now reported to be the lowest in Europe.^{4,98} Cephalosporin usage fell by a further 9.2% between 2012 and 2015 following larger previous declines from a peak in 2006–07 because of the national *C. difficile* problems. From 2012 to 2015, oral cefalexin use fell by 25.7% but parenteral cefotaxime use by only 1.6%, whilst parenteral ceftriaxone use increased by 37.4%, probably reflecting use of this once-daily antibiotic in outpatient parenteral antibiotic therapy.⁴ The microbiological need for preferring this broad-spectrum agent to teicoplanin or daptomycin, which are only active against Gram-positive bacteria, should be critically reassessed.

General practice quinolone use in terms of DDDs/1000 inhabitants/day has fallen consistently since 2012, reducing by 3.6% between 2014 and 2015. However, the national overall usage of ciprofloxacin has declined only slightly, from approximately 0.48 DDDs/1000 inhabitants/day in 2012 to 0.43 in 2015: quinolone use in hospitals has increased despite an 18.4% incidence of ciprofloxacin resistance in *E. coli* bacteraemia.⁹⁴ A 53.6% rise in the respiratory quinolone levofloxacin, which is the L-isomer of ofloxacin, seems unjustifiable but reflects a recommendation for use in penicillin-allergic patients with pneumonia. A similar increase (50.3%) was seen in Scotland, accompanied by a 17% increase in

ofloxacin use. An English target of a 10% reduction on 2013–14 levels of cephalosporin, quinolone and co-amoxiclav use in primary care or a reduction in use to be below the 2013–14 median value (11.3%) of Clinical Commissioning Groups (CCGs) for antibiotic prescribing of these agents, was achieved in 189/209 CCGs.⁴ Prescribing of these antibiotics is substantially lower in Scotland and is not the subject of targets. Scottish reductions in primary care use in 2015 were 4.9% for co-amoxiclav, 5.8% for fluoroquinolones and 6.0% for cephalosporins, with an 8% overall reduction in use.⁸¹

Despite these reductions, cephalosporin and quinolone resistances continue to be seen frequently in UK bloodstream and urinary *E. coli* and *K. pneumoniae* isolates, with significant circulation in older patients who move between hospitals, nursing homes and the community, and who have frequent exposure to cross-infection and antibiotics. Resistance to both quinolones and third-generation cephalosporins in *E. coli* bacteraemias is concentrated in those aged ≥ 65 years in England and is at least twice as prevalent in those aged over 74 years compared with those aged 65–74 years.⁴ An Italian scoring system for carriage of ESBL-producing organisms has not been tested in the UK or modelled to see if the group of patients at risk of carrying these strains on admission to hospital is increasing.⁹⁹

The total number of *E. coli* bacteraemias in England, and therefore the absolute burden of resistance, continues to rise – by 4.6% from 35659 to 37310 between 2014 and 2015 in England.⁴ The same publication notes an increase in *Klebsiella* bacteraemias by 9% over the same period. Over the period from 2000 to 2014 the incidence of *E. coli* bacteraemia in England has risen inexorably from 20 to 50 cases/100000 population.⁹⁴

In England, rates of resistance to piperacillin/tazobactam are said to have increased in *E. coli* bacteraemias from 8.5% to 11.7% and in *Klebsiella* spp. bacteraemias from 12.6% to 18.5% over the period from 2011 to 2015.⁴ Equivalent rises in resistance to co-amoxiclav from 31% to 42% in *E. coli* bacteraemias and 18.7% to

28.2% in *Klebsiella* spp. bacteraemias have occurred over the same period.

Record linkage for *E. coli* bacteraemias between 2012 and 2014 showed piperacillin/tazobactam resistance increasing by 15.1% for hospital-onset cases compared with 8.7% for community-onset cases.⁹⁴ This study also revealed significant variations in resistance rates by age and sex. Similar trends were seen in Scotland, with an 8.6% increase for piperacillin tazobactam resistance and 6.1% for co-amoxiclav resistance in *E. coli* bloodstream isolates and 14.8% and 28.7%, respectively in *Klebsiella* spp. in 2015. Changes from CLSI to EUCAST criteria may have produced these large rises in resistance in Scotland (see Section 6.2), but there were no changes in EUCAST criteria for these antibiotics between 2013 and 2015⁸¹ and in England few laboratories use CLSI criteria. In Wales 11/18 hospitals in 2015 recorded an increase in piperacillin/tazobactam resistance in *E. coli*.¹⁰⁰ In England piperacillin/tazobactam use rose linearly by 62% between 2010 and 2015 to 135 DDDs/1000 admissions across all hospital types.⁴ In Scotland, use fell by 7.9% in 2015.⁸¹

These changes are important. The main antibiotics used in a recent prospective study in 10 English hospitals of treatment of Gram-negative bacteraemia were co-amoxiclav in 32% of patients and piperacillin/tazobactam in 34%.¹⁰¹ Despite empirical therapy being inactive against responsible organisms based on *in vitro* tests in 34% of cases, all-cause mortality was said to be low, 8% assessed at 7 days and 15% at 30 days. Given the increasing resistance rates and use, explorations of comparative outcome in relation to resistance and use are needed at each national level and also by source of infection (see Section 11.2). Mortality in *E. coli* bacteraemia throughout England was measured between July 2011 and June 2012 as 18.2% at 30 days or 10.34/100000 population in 1 year. These data were derived by record linkage of *E. coli* bacteraemia cases mandatorily reported to PHE, voluntary reporting of antibiotic susceptibilities on all isolates to PHE, and records at the Office for National Statistics Death Registrations and at the NHS Spine.¹⁰² Mortality is high as compared with Finland (8%) and inpatient-only mortality in Canada (11%) and New Zealand (9%). Analysis showed important associated features: 30% of deaths occurred on, or on the day after, the blood sample was taken and 76.3% within 14 days making the separate mortality analysis of community-onset and hospital-onset bacteraemia important. Overall 19174/26216 (73.1%) patients had their bacteraemia recorded within 1 day of admission. Mortality was higher (34.0%) if a respiratory focus of infection was diagnosed or the focus of infection was unknown (25.9%) than if a urogenital focus was diagnosed (13.2%). No information was available on the antibiotics prescribed, precluding any test of whether higher mortality was correlated with failure to provide adequate Gram-negative cover in suspected respiratory or unknown foci of infection; moreover, there were no audit data to show if the reported foci of infection were supported by evidence. A recent audit of coding and diagnosis of pneumonia by the British Thoracic Society did not support the diagnosis in 15.8% of cases and noted a 14.3% rate of mortality in this group.¹⁰³ At a population level the high burden of urogenital-related infection for *E. coli* was such as to make this the largest cause of deaths, even though mortality in this group was lower. The lower rate of mortality with urogenital infection correlates with information in an earlier study, which showed that the excess mortality for bacteraemia with ESBL-producing

Enterobacteriaceae was confined to non-urinary infections.¹⁰⁴ The study by Abernethy and colleagues¹⁰² identified a urogenital source for 55.3% of community-onset cases of bacteraemia and 45.1% of healthcare-onset cases. In 17.3% of cases the source was unknown. Mortality was lowest in those aged 1–44 years (5.4%) versus those aged 45–84 (17.9%) and >85 years (25.2%). Mortality rates varied by the susceptibility of the isolated causative bacterium; ciprofloxacin susceptible 17.0% (95% CI 16.4%–17.5%), ciprofloxacin intermediate or resistant 21.9% (95% CI 20.5%–23.2%); cephalosporin susceptible 17.5% (95% CI 16.9%–18.1%), cephalosporin intermediate or resistant 21.3% (95% CI 19.4%–23.2%). The inclusion of a factor in the adjusted model to allow for hospital- and case-mix-related mortality eliminated any significance from the difference in mortality by cephalosporin susceptibility. Cephalosporins are unlikely to have been used in infections due to ESBL-producing organisms in England, but piperacillin/tazobactam may have been used and the absence of a difference in mortality may reflect some improved outcome in urinary infection, despite the presence of bacteraemia. Different cephalosporins are not equally associated with *C. difficile*.¹⁰⁵ Oral first-generation cephalosporins would be useful in early treatment. It might be appropriate, whilst keeping *C. difficile* under review, to abandon downward pressure on the whole class of antibiotics and introduce a cephalosporin-specific approach. There were no data on mortality in relation to susceptibility to piperacillin/tazobactam, co-amoxiclav or aminoglycosides: carbapenem resistance rates were too low for robust assessment.

Resistance to any one of quinolones, cephalosporins or carbapenems was associated with a 30% increase in mortality. The association of increased mortality in quinolone-resistant strains needs explanation and it is not clear if this relates to hospital case-mix. Furthermore, if reduced use of oral quinolones is attempted, care is needed in the controversial area of prophylaxis in neutropenia, where quinolones are widely used. Studies of withdrawing quinolones for this indication show an increase in Gram-negative bacteraemia with susceptible strains without any diminution, at least initially, in resistant strains,^{106–108} and recent Cochrane reviews support the efficacy of quinolone prophylaxis.^{109,110}

Rates of carbapenemase production by Enterobacteriaceae (<2%) remain low in the UK but reference laboratory submissions of these organisms are growing annually (Figure 2), with many of the isolates coming from clinical rather than screening samples. It is noteworthy that surveillance of carbapenem-resistant strains depends on voluntary submission to reference laboratories and that regional molecular testing necessary for rapid turnaround has not been converted into national surveillance.⁴ Given the importance of reducing carbapenem resistance, consideration should be given to introducing mandatory reporting of all isolates of carbapenem-resistant Enterobacteriaceae so the evolving picture can be properly assessed. English data suggest the proportion of carbapenem-resistant *Klebsiella* spp. rose from 0.2% to 1.1% between 2011 and 2015.⁴ There are pockets of local endemicity, especially of *K. pneumoniae* and other Enterobacteriaceae, with KPC enzymes around Manchester or with VIM and OXA-48 in north Cheshire. These have persisted for 5–6 years (D. M. Livermore, unpublished data). Many other sites, notably London teaching hospitals, are currently being repeatedly challenged with a diversity of carbapenemase producers, many imported from overseas. CC258

K. pneumoniae with KPC carbapenemase remains rare in the UK, despite repeated introduction, and the greater issue, particularly in north-west England, is dissemination of plasmids encoding KPC carbapenemases among different *K. pneumoniae* and Enterobacteriaceae. Carbapenem-resistant isolates submitted to reference laboratories in Scotland increased from 47 in 2014 to 63 in 2015.⁸¹ The dual loss of both quinolone and cephalosporin susceptibility has driven increased usage of carbapenems, particularly meropenem, from some 75 DDDs/1000 admissions in 2010 to 104 DDDs/1000 admissions in 2015 in England, a 38.6% increase, but in 2015 the increase was only 1%.^{4,81} In Scotland the picture is different; there was a 6.5% increase in use of carbapenems between 2014 and 2015 but this is now only 9.3% higher than in 2012.

Phenotypic information on aminoglycoside susceptibility is available. Frequent gentamicin resistance was noted in ESBL-producing strains of *E. coli* from all sites in one region, representative of the UK, with resistance rates of 48.7% for *E. coli* ST131 and 55.1% for *E. coli* non-ST131.⁹³ The record linkage data previously discussed shows that overall gentamicin resistance rates (i.e. irrespective of ESBL production) varied by region between 5.5% and 15.4% in the years 2012–14 and that the overall rate in community-onset cases was 8.6%.⁹⁴ The region with lowest rate of resistance had a 34% higher incidence of *E. coli* bacteraemias than that with the highest rates, which suggests the possibility of dilution of the denominator by an increase in more susceptible bacteraemias (e.g. ST73 in northern England). In Wales in 2015 only 5/18 hospitals reported gentamicin resistance rates less than 8.6% in *E. coli* bacteraemia and two had rates over 20%.¹⁰⁰ Rates of 8.6%–15% would seem too high for empirical use of gentamicin alone. However, the 8.6% rate of gentamicin resistance in community-onset bacteraemia is very similar to the 8.7% resistance rate to piperacillin/tazobactam, which is widely used alone.⁹⁴ National data on amikacin are hard to interpret because fewer laboratories test it in addition to gentamicin and the amount of testing that is second line because of resistance on first-line testing remains unresolved, potentially skewing the data. Nevertheless, as expected, amikacin resistance is rarer than gentamicin resistance (2% in 2015) in England.⁴

Rates of co-resistance in bacteraemia isolates for 2015 for gentamicin and third-generation cephalosporins were 4.6% for *E. coli* and 5.9% for *Klebsiella* spp. compared with resistance rates to third-generation cephalosporins alone of 7.5% and 5.2%, suggesting some useful activity for gentamicin against ESBL-producing *E. coli* but less against ESBL-producing *Klebsiella* spp. Rates of co-resistance in bacteraemia isolates for 2015 to gentamicin with co-amoxiclav are 7.8% in both *E. coli* and *Klebsiella* spp. compared with resistance rates to co-amoxiclav alone of 35.2% and 19.3%.⁴ This confirms the potential utility of an aminoglycoside compared with co-amoxiclav alone for both *E. coli* and *Klebsiella* spp. bacteraemias. The same data source indicates a somewhat different situation with ciprofloxacin/gentamicin combinations. For *E. coli* and *Klebsiella* spp. rates of co-resistance were respectively 6.8% and 5.8% whereas resistance to ciprofloxacin alone occurred in 11.8% and 5.0%, suggesting that addition of an aminoglycoside was seldom advantageous in *Klebsiella* infection. Overall these co-resistance data⁴ suggest only a modest improvement on gentamicin monotherapy and the benefit compared with the harm of continuing selection of resistance by the non-aminoglycoside may not be great.

Consumption of aminoglycosides is now low in England in hospital inpatients (approximately 0.08 DDDs/1000 population/day) and fell in 2015. By contrast, use rose in Scotland by 5.9%, becoming 16.9% more frequent than in 2012. Falls in use are likely to reflect concern about resistance in ESBL producers and about potential toxicity; they may also reflect a change in clinical contacts with microbiologists as antibiotic assays are increasingly undertaken by clinical chemistry departments. A comparison with Scotland to understand the differences would be informative.

Bacteraemia represents a group of community infections selected for virulence factors sometimes but not always by antibiotics. Antibiotic resistance in Gram-negative infections in the community was thought, even a decade ago, to be quite uncommon in the UK. A historical European study of acute, community-acquired, uncomplicated, non-recurrent UTI in 2008 caused by *E. coli* involved 12 general practices in the UK and enrolled 200 unselected women aged 18–65 years. Resistance was rare to mecillinam (1%), nitrofurantoin (0%), fosfomycin (0.5%) amoxicillin/clavulanic acid (2.0%) and ciprofloxacin (0.5%), but commoner to amoxicillin (32%), sulfamethoxazole (26%), trimethoprim (15%) and trimethoprim/sulfamethoxazole (14%).¹¹¹ In that survey the co-amoxiclav resistance rate seems low in relation to the amoxicillin resistance rate. Reported resistance rates to co-amoxiclav in lower urinary infections have increased since the time of that study partly because of the substitution of EUCAST's (32+2 mg/L) breakpoint for the previous BSAC (16+8 mg/L) value. A contemporaneous UK study with a large community sample reported 12.0% resistance to co-amoxiclav versus 54% for ampicillin.¹¹² Welsh data in 2014 report the following resistance rates in 'coliforms' from urine in different communities: co-amoxiclav 12.9% (range 5.1%–25.4%), third-generation cephalosporin (ESBL) 6.8% (range 3.3%–17.9%), nitrofurantoin 10.0% (range 8.7%–22.4%), trimethoprim 36.7% (range 30.3–41.8%) and fluoroquinolone 10% (range 7.6%–16.4%).¹¹³ A 2010–13 large UK study¹¹⁴ of all community urinary isolates from a UK region with a population of 5.6 million found that by 2013 resistance to third-generation cephalosporins in *E. coli* had risen to 5.5% and ciprofloxacin resistance to 15.5%; for *Klebsiella* spp. the cephalosporin resistance rate was higher at 10.1%. Only 0.06% of the *E. coli* isolates were reported as resistant to one or more carbapenems, as were 0.32% of the *Klebsiella* spp. isolates. In this regional survey, VIM enzymes were found in *Pseudomonas* spp., whereas among *E. coli* and *Klebsiella* spp. 16 had NDM genes, 5 KPC and 2 OXA-48. These findings support the view that carbapenemases are rare in the community in the UK. A further study of isolates in the same English region over the period 2007–14 showed, after de-duplication, 69 with *bla*_{NDM}, 26 with *bla*_{KPC}, 16 with *bla*_{OXA-48-like} and 7 with *bla*_{VIM}.¹¹⁵

A historical audit of urine samples taken at presentation from primary and secondary care in South London before the widest dissemination of ESBL-positive *E. coli* ST131 occurred, found that 22.6% of isolates were resistant to trimethoprim, 43.3% to amoxicillin and 10.3% to nitrofurantoin.¹¹⁶ Since this audit, resistance to trimethoprim has slowly risen across the UK, and in Wales is significantly commoner in isolates from patients over 65 years. Trimethoprim resistance rates vary widely by CCG in England. In 2011 it ranged in these from 16.3% to 66.7% but by 2015 in 86% of CCGs it was >25% with an almost uniform median of 29% in CCGs.^{4,82} The reason for these variations in a minority of CCGs

remains uncertain. In Wales resistance rates of 38.2% overall are currently reported. A caveat is that high resistance rates may reflect selective testing of previously treated patients in the community and different local policies for submitting samples, and the true rate of resistance to trimethoprim in patients presenting in the community with uncomplicated UTI may be lower than current figures suggest.¹¹⁷ Trimethoprim use in England fell by 14.5% between 2014 and 2015, reversing the increase seen between 2012 and 2014. This fall should be many times larger in 2016 if there is expeditious compliance with the PHE recommendation in 2014 to substitute nitrofurantoin for trimethoprim as the first-line antimicrobial for cystitis in the older patient. A Swedish trimethoprim-sparing switch in one region resulted in an 86% decline in trimethoprim use between 2004 and 2006.¹¹⁸ In 2015 in England rates of trimethoprim prescribing were approximately 1.1 DDDs/1000 population/day compared with 0.8 DDDs/1000 population for nitrofurantoin.⁴

UK data on resistance to nitrofurantoin, fosfomycin and mecillinam is scanty. In a single-centre study nitrofurantoin resistance was commoner in *Klebsiella* spp. of community origin (around 15%) than in *E. coli* (3%).¹¹⁹ English national data for the second quarter of 2016 suggest resistance in *E. coli* in community UTIs varied with CCG between 0.3% and 12.8% with a median of 3.8%,⁴ whilst in Scotland 5.9% of isolates tested in 2015 showed nitrofurantoin resistance.⁸¹ Nitrofurantoin resistance is also common in UK CPE isolates.¹²⁰ Proteaceae are inherently resistant to nitrofurantoin and data on their prevalence in UTI and resistance linkage for nitrofurantoin resistance in England are needed given the recommendation to use this antimicrobial first line (see Section 9.1 for previous experience of changes in prevalent phylogroups and STs of *E. coli*). There are no recent data on fosfomycin resistance in the UK. A survey of fosfomycin resistance in Leeds found *fosA* in two urinary tract isolates collected months after its UK introduction in 1994 despite a lack of use in the study hospital.¹²¹ In the same publication, a study of foods in Leeds in 1995 identified two Enterobacteriaceae isolates carrying *fosA* in vegetables imported from Spain. Fosfomycin resistance (MIC ≥ 64 mg/L was present in 32/81 strains of CPE in 2011; 27 of these were *Klebsiella* spp.¹²⁰ In Wales, only 6.2% of cefpodoxime-resistant *E. coli* (i.e. probably ESBL- and AmpC-producing strains) were apparently resistant to mecillinam,¹²² but this is discussed further later in the article (see Section 9.4).

The impact of the successful clone ST131 clone of *E. coli* on multiple resistances has been assessed. In one 2011 UK study, resistance rates in ESBL-producing *E. coli* ST131 (mostly with CTX-M-15 enzyme) compared with non-ST131 (producing CTX-M-15 or CTX-M-14) were 99% versus 83%, respectively, for ciprofloxacin and 92% versus 86% for trimethoprim.⁹³ Fluoroquinolone resistance alleles *gyrA/B* and *parC* are characteristic on WGS of the Clade C of *E. coli* ST131, which is almost exclusively the clade carrying CTX-M ESBLs.²⁹

There is no reliable information on acquired colistin resistance. Usage sharply increased by 30% between 2013 and 2015 in England, entirely in specialist and teaching hospitals.⁴ Given: (i) the growing use of colistin as a drug of last resort; (ii) the prevalence of colistin resistance in KPC-producing *Klebsiella pneumoniae*, especially in Italy, but also in the USA; (iii) the lack of mandatory surveillance of *Klebsiella* spp.; and (iv) the recognition of plasmid-mediated colistin resistance due to *mcr1* and *mcr2*, there is an urgent need for enhanced surveillance of colistin resistance at a

national level.⁴ *mcr1* has been found in isolates from British pigs¹²³ but is widespread in the European food chain, including additionally turkeys and veal calves,¹²⁴ and *mcr2* has been found in pork and cattle products.¹²⁵

6.6 What impact have returning travellers made on UK epidemiology?

Whilst mutational resistances often emerge locally, strains with acquired resistance genes are often clearly imported to the UK from other countries. Examples include MDR *K. pneumoniae* with OXA-48 carbapenemases with Libyan conflict casualties and with patient transfers from elsewhere in the Middle East; *K. pneumoniae* with KPC carbapenemases from Greece and Israel and, most significantly, Enterobacteriaceae with the NDM MBL from south Asia and China.¹²⁶ Colonization of travellers may be frequent, although precise rates are largely unknown. A systematic review confirms travel to certain areas is a significant risk factor.¹²⁷ Most data concern ESBL-producing strains and there is a notable dearth of information on other important resistances, including to aminoglycosides, carbapenems, colistin and fosfomycin. Nevertheless, an Australian study suggests that travel-associated aminoglycoside and quinolone resistance may be even commoner than travel-associated cephalosporin resistance.¹²⁸ Interestingly, prolonged carriage was significantly associated with the pathogenic phylogroups B2 and D rather than A and B1 but strains of ST131 were rare even with Asian travel. A Canadian study showed that bacteraemia due to CTX-M-14 ESBL-producing *E. coli* was associated with travel to Europe and Africa whilst CTX-M-15-producing strains were associated with travel to Asia.¹²⁹ Analysis of risk factors in Norway for new cases of ESBL-producing infection was undertaken in a case-control study of adults who had been resident for 1 year or more, with no previous hospital or nursing home residence >24 h in the previous 31 days. It identified as risk factors travel to Asia, the Middle East or Africa within the past 6 weeks (OR 2.1, 95% CI 1.4–3.2) or 6 weeks to 24 months (OR 2.3, 95% CI 1.1–4.4), recent use of fluoroquinolones (OR 1.6, 95% CI 1.1–2.3) or recent use of β -lactams other than pivmecillinam (OR 5.0, 95% CI 2.1–12), diabetes (OR 3.2, 95% CI 1.0–11) and freshwater swimming in the last year (OR 2.1, 95% CI 1.0–4.0) were all associated with UTI due to ESBL-producing *E. coli* or *Klebsiella* spp. Factors associated with decreased risk were the number of fish meals/week (OR 0.68/fish meal, 95% CI 0.51–0.90) and increasing age (OR 0.89/5 year increase, 95% CI 0.82–0.97). Almost 1 in 4 (23%) ESBL-positive patients had travelled to the risk countries within the previous 6 weeks and 39% in the 6 week to 24 month period compared with 1% and 19%, respectively. Travel to Europe (11% and 67% in ESBL producers and 7% and 57% in non-ESBL producers), America or Oceania (including Japan) was not a risk factor.¹³⁰ This emphasizes that there is a longer-term effect of travel or migration that is often not considered. A placebo-controlled trial of ciprofloxacin to prevent traveller's diarrhoea showed that prophylaxis selected for quinolone- and other drug-resistant GNB, suggesting that such practices need review.¹³¹ Previous travel to destinations where resistance is prevalent is a risk factor for acquired MDR bacteria and should be considered in respect of empirical therapy. However, many patients with MDR organisms lack any relevant travel and it is not known if their organisms represent spread from carriers, especially in the same household, who have a history

of high-risk travel,^{132–134} or who have asymptotically acquired the organism in hospital.

The most significant impact that the movement of people can have on the problem of resistance in Gram-negative bacteria is the maintenance of higher levels of resistance in commensal bacteria after return from high-incidence areas. Data on faecal carriage rates may mislead when compared with correlates of clinical infection since it will include phylogroup A and B1 strains of lower pathogenicity than the B2 and D strains seen commonly in urinary and bacteraemia.¹³⁵ Tangden in Sweden showed that 7/8 previously uncolonized travellers to South Asia and 10/32 to East Asia returned with carriage of ESBL *E. coli*.¹³⁶ One study in Birmingham (UK) showed that 22% of individuals with names of Middle Eastern or south Asian origin had faecal carriage of CTX-M ESBL-producing *E. coli* compared with 8.1% in those with names of European origin.¹³⁷ A recent large-scale survey studying 2430 healthy individuals in four areas in England found similar carriage rates of 25% and 5.6%, respectively. In a multivariable logistic regression model the percentage contribution made to risk of colonization was apportioned. Being born in South Asia (India, Pakistan, Bangladesh) or coming from those countries contributed 26.6%, and travel to those countries 12.1%. In contrast, being born in UK of UK origin contributed 9.9% and travel to all other parts of the world 17.8%.⁵¹⁹ Hence, the choice of antibiotics for empirical treatment may need to take into account recent travel history and cultural background.

The second ESPAUR report (2016)⁴ includes details from a research study of faecal carriage rates of ESBL-producing Enterobacteriaceae in England. This showed variations in carriage from 4.9% in Shropshire to 16% in Heart of Birmingham Primary Care Trust with intermediate rates in Southampton and Newham (East London). Risk factors in this study included birth in India, Pakistan, Bangladesh, Sri Lanka, Afghanistan (which collectively accounted for 24% of all carriage) or the Middle East (including Egypt, Iraq, Saudi Arabia and other countries in the Persian Gulf) and travel in the last year to Africa, South Asia (Indian subcontinent and Afghanistan), South-East Asia [Thailand, Burma, Cambodia, Laos, Malaysia, Singapore or Pacific Asia (including Vietnam, Korea, China)] or South or Central America (WHO regions). Until control measures reduce prevalence the following countries are also risk factors for either ESBL carriage or carbapenemase acquisition or both: the Eastern Mediterranean (the Balkans, Greece, Cyprus, Turkey, and Syria) and Eastern Europe and Russia, Belarus and Kazakhstan, and Italy.

There is a need for further studies with controls (non-travellers from different households of the same ethnic background) on the carriage of antibiotic-resistant *E. coli*, with strain typing and phylogroup allocation to better predict the potential for extraintestinal infection. This is further reviewed elsewhere. Studies are needed also of *Klebsiella* spp. and on the time elapsed since travel to specified locations of high prevalence. Information on healthcare and antibiotic exposure is required as well as details of many non-ESBL antibiotic resistance mechanisms.

Evidence

There is a clear indication of association of infection with ESBL-producing *E. coli* and travel. There is no information on other

antibiotic resistances in association with travel and minimal information on carriage duration after travel.

Evidence level: 3

Recommendation

Need to quantify risks of infection with/carriage of extraintestinal pathogenic *E. coli* and of *Klebsiella* spp. resistant to all antibiotics and relate to time since travel to countries with high prevalence of MDR GNB and incorporate in risk assessments for clinical infection with MDR GNB in the community and on admission to hospital to guide therapy.

Grading: Strong recommendation for

6.7 What is the clinical importance of carbapenemase-versus CTX-M- and AmpC-producing strains?

ESBL-producing Enterobacteriaceae, MDR *P. aeruginosa*, and *A. baumannii* are associated with increased mortality, length of stay and expense in most but not all studies evaluating the impact of antibiotic resistance in GNB.^{138,139} Nevertheless, variability in the setting (mainly ICU), study design, organisms included (most notably, which Enterobacteriaceae species), resistance profile and site of infection make the studies difficult to compare.^{138,139} Fluoroquinolone resistance in *P. aeruginosa* was associated with increased hospital costs, and, if associated with imipenem resistance (MDR strains), increased mortality.¹⁴⁰ Four of eight studies in one review of MDR strains of *P. aeruginosa* showed increased mortality.¹³⁸ With *A. baumannii*, carbapenem resistance was generally associated with increased length of stay and expense of care; mortality was generally increased, most clearly if bloodstream infection was involved.^{138,139} However, two studies of MDR (but carbapenem-susceptible) *A. baumannii* did not identify a significant increase in mortality, whereas studies of carbapenem resistance in *A. baumannii* consistently identify a significant increase in mortality only partly due to use of inactive carbapenems.^{139,141–143}

More recently, studies have emerged evaluating the impact of carbapenem resistance in Enterobacteriaceae.¹⁴⁴ Pooled analysis of nine studies comparing mortality in Enterobacteriaceae infections including bacteraemia found that mortality was more than 2-fold higher when infections were caused by CPE. Broad-spectrum antibiotics other than carbapenems can select for colonization (detectable by active surveillance) that precedes later infection with bacteria resistant to a range of other antibiotics because of linkage with multiple resistance factors.^{145–149} Carbapenem resistance in *Acinetobacter* spp. is similarly linked with multiple resistances that can be selected for by antibiotics that are not carbapenems, and can be detected as colonization prior to development of infection,¹⁵⁰ this is likely to be the case with Enterobacteriaceae.

Carbapenem resistance is an increasing problem in *Enterobacter* spp. in the absence of carbapenemases. In *E. aerogenes* ertapenem resistance is associated with loss of Omp35, a porin, and meropenem resistance with loss of Omp36 together with derepressed overproduction of AmpC.¹⁵¹

Bacteria producing CTX-M are of international importance. In the community they are usually MDR with few and hitherto

little-used antibiotics offering the sole effective treatment. The spread of these strains requires widespread changes in primary care prescribing practice, which can be slow to take effect. Further, systemic infection with these strains usually requires parenteral drugs involving additional hospital admissions or outpatient parenteral antibiotics. Particular successful clones such as *E. coli* ST131 and ST69 are frequently involved. The fundamental reason for the success of these clones remains obscure and strategies to counter their spread nationally and internationally have so far been based on antibiotic restriction alone.

AmpC-producing strains of Enterobacteriaceae were a problem when third-generation cephalosporins and monobactams were widely used because stable derepression of this enzyme occurred by mutation at the regulatory gene *ampD*¹³ in *Enterobacter* spp., *Serratia* spp., *Citrobacter freundii* and *Morganella morganii*. Selection of such mutants during cephalosporin treatment of bacteraemia with these species can cause treatment failure.^{152,153} Amoxicillin/clavulanate, both components of which are strong inducers of AmpC in such species, is not active against such species but piperacillin, although inactive against derepressed mutants, seems less prone than third-generation cephalosporins to select such strains from the induced population. Genes encoding AmpC enzymes have also escaped to plasmids that have spread into *E. coli*; such plasmid-carrying strains are widespread in foodstuffs. The main enzyme is CMY-2. In the UK it remains considerably rarer than ESBLs.³⁰ Cefepime is more stable to AmpC than other third-generation cephalosporins but in *Enterobacter cloacae* high-level cefepime resistance is associated with mutation in AmpC.¹⁵¹ Carbapenems and temocillin are active against AmpC- β -lactamase whether of chromosomal or plasmid origin but ertapenem is more labile and, if OmpK35 porin loss occurs, resistance arises from this enzyme's action.

7. Intravenous treatment options for MDR GNB: what is the efficacy of carbapenems, temocillin, fosfomycin, colistin and other antibiotics against specific MDR GNB and what are the recommended antibiotics for secondary/tertiary care?

The evidence base (and grading) for all agents is generally weak, as most studies were retrospective case series, only rarely including a comparator agent. Our suggestions for intravenous treatment are summarized in the algorithm in Figure 3. Each intravenous agent is further considered individually.

7.1 Carbapenems

Carbapenems should be regarded as the drugs of choice for serious infections with ESBL-producing Enterobacteriaceae¹⁵⁴ and they are the drugs of choice for the empirical therapy of patients with serious sepsis caused by GNB, depending on local resistance rates and clinical experience.

Meropenem was found to be narrowly superior to imipenem/cilastatin (cilastatin prevents degradation of imipenem by urinary and ileal dehydropeptidase) in both clinical and bacteriological outcomes in one meta-analysis of 27 RCTs.¹⁵⁵ The clinical response rates (complete remission or improvement in signs and symptoms

of sepsis) for meropenem and imipenem were 91.4% and 87.2%, whereas bacteriological response rates were 85.1% and 82.8%, respectively. There was no significant difference in mortality in the nine trials reporting data (7.4% for meropenem, 9.7% for imipenem). Meropenem and imipenem (sometimes referred to as 'Group 2' carbapenems, based upon activity against Gram-negative non-fermentative bacteria) are typically preferred to ertapenem for the empirical treatment of bacteraemias (often arising from the urinary tract) because of their broader spectrum (see below). A switch to ertapenem may be rational with susceptible isolates if it leads to earlier discharge with outpatient parenteral antimicrobial therapy (OPAT) but without this it is not a mechanism for reducing selection for carbapenem resistance. In Singapore, de-escalation of meropenem regimens by infectious disease physicians (including, in a small proportion, de-escalation to ertapenem) was associated with no increase in clinical failure rates or hospital mortality, reduced duration of carbapenem treatment from 8 to 6 days, less diarrhoea and *C. difficile* infection and less acquisition of carbapenem-resistant *A. baumannii*.¹⁵⁶

Meropenem or imipenem select respectively for carbapenem-resistant Gram-negative organisms, including pre-existing carbapenem-resistant *A. baumannii*,¹⁵⁷ and porin *oprD* mutants, the commonest mechanism of imipenem resistance, arising during imipenem treatment of *P. aeruginosa*.¹⁵⁸ Overproduction of AmpC-type enzymes, and efflux pumps (which are common), are implicated in meropenem resistance in *P. aeruginosa*: MBLs, usually of a VIM type, occur but are much less common.¹⁵⁹ A multi-centre Spanish study of isolates in 2008 from *P. aeruginosa* bacteraemia showed similar resistance rates to piperacillin/tazobactam, ceftazidime and meropenem. Meropenem resistance was more commonly associated with MexB or MexY and AmpC overexpression whereas resistance to piperacillin/tazobactam and ceftazidime was more commonly associated with AmpC overexpression alone, making non-carbapenems preferable agents for avoidance of MDR strains. Nevertheless, AmpC overexpression was associated with quinolone resistance, which, with aminoglycoside resistance, is already known to be associated with efflux pumps.¹⁶⁰ Whilst both imipenem and meropenem have a similar spectrum of activity, use of imipenem has declined and meropenem is now the most widely prescribed carbapenem in the UK.¹⁵⁴

Widespread usage, particularly internationally, has driven the emergence of resistance and careful and considered empirical usage is essential. If the bacteria responsible for the infection are subsequently shown to produce neither ESBLs nor AmpC β -lactamase, carbapenem use should reasonably be stepped down to narrower-spectrum agents. An Italian cohort study across five hospitals showed that rectal carriage of KPC-producing *Klebsiella* was predictive of bacteraemia with such strains in the subsequent 2 years; sensitivity and specificity were 93% and 42% respectively; positive and negative predictive values were 29% and 93% respectively. Bacteraemia was associated with ICU admission, invasive abdominal procedures, cancer chemotherapy or radiation therapy and the number of colonization sites.¹⁶¹ This suggests that screening may play a role in anticipating a requirement for treatment other than carbapenems active against such strains, but this will not necessarily apply to other bacteria with carbapenemases.

The ominous changes and increase in meropenem resistance in Enterobacteriaceae in the UK (shown in Section 8.4), and the

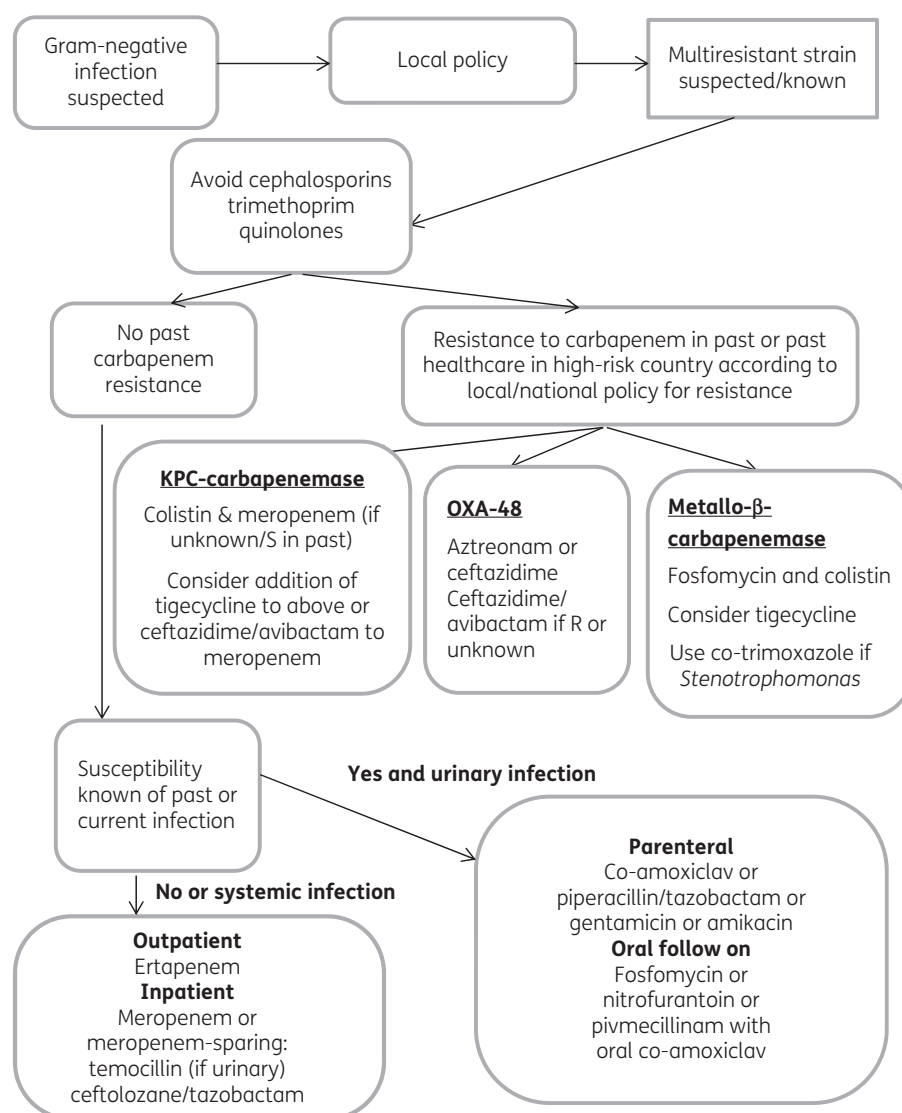


Figure 3. Suggested algorithm for the treatment of MDR Gram-negative bacterial infections admitted to UK hospitals.

clinical importance of such resistance and the need to know the resistance mechanism so that appropriate chemotherapy can be used, mean that an accurate overall view of the emerging picture is essential if appropriate action is to be taken. We include recommendations on this epidemiological matter because of its importance. We recommend the introduction of mandatory reporting of carbapenem-resistant Enterobacteriaceae from all anatomical sites and specimens. Such isolates should be tested contemporaneously to determine the responsible carbapenemase and the meropenem MIC. Isolates should be submitted to reference laboratories to determine susceptibility to a wider range of appropriate agents and for those agents, such as colistin or ceftazidime/avibactam, for which susceptibility testing is technically demanding. The determination of susceptibilities is a part of essential surveillance. Appropriate patient treatment also depends on performing these susceptibility tests in an expeditious manner but the methodology required may be beyond the scope of most routine diagnostic laboratories.

Ertapenem is licensed in Europe for the treatment of intra-abdominal and gynaecological infections and community-acquired pneumonia. In the rest of the world, including in the USA, it is also licensed for skin and skin structure infections and for complicated UTIs (for which it is widely used 'off-label' in the UK). Ertapenem shares the broad spectrum of imipenem and meropenem against Enterobacteriaceae, some Gram-positive species and anaerobes, but is inactive against *Acinetobacter* spp. and *P. aeruginosa*.¹⁶² It is sometimes called a Group 1 carbapenem on this basis. Its main benefit is its once-daily mode of administration.

Use of ertapenem for the treatment of infections caused by Enterobacteriaceae is less well established than for imipenem or meropenem but it has good *in vitro* activity. A retrospective cohort study compared outcomes of bacteraemias due to ESBL-producing *E. coli* and *K. pneumoniae* treated with ertapenem and Group 2 carbapenems. Outcomes were equivalent between patients (mortality rates of 6% and 18%, respectively; $P = 0.18$).

However, more patients treated with Group 2 carbapenems had severe sepsis/septic shock/multi-organ failure: 5/49 (10.2%) for ertapenem versus 36/109 (33.3%) for other carbapenems (OR 0.23, 95% CI 0.08–0.62; $P < 0.002$), suggesting clinicians were more likely to treat ‘sicker’ patients with a Group 2 carbapenem than ertapenem.¹⁶³ A retrospective study in Taiwan evaluated 251 patients with bacteraemia caused by ESBL-producing *E. coli* and *K. pneumoniae* isolates treated with a carbapenem.¹⁶⁴ Two hundred and thirty patients received carbapenems appropriately (57 ertapenem, 136 imipenem and 37 meropenem): 21 received carbapenems inappropriately (18 received ertapenem and 3 imipenem when the MICs were respectively >0.5 and >1 mg/L). Among the isolates, rates of susceptibility to ertapenem (MIC ≤ 0.5 mg/L EUCAST) were 83.8% in *E. coli* and 76.4% in *Klebsiella* spp. and those to meropenem were 100% and 99.3%. Sepsis-related mortality varied if the lower CLSI breakpoint for susceptibility (≤ 0.25 mg/L) was used. By this criterion, mortality was 5.3% (3/57) in those patients infected with an ertapenem-susceptible strain versus 33% (6/18) for an ertapenem non-susceptible isolate if they were treated with ertapenem. If categorization was based on the EUCAST MIC breakpoints ≤ 0.5 or >0.5 mg/L, there was no significant difference in mortality. Propensity matching of patients showed that patients with isolates that were ertapenem non-susceptible by CLSI criteria had a similar raised mortality if treated with imipenem or meropenem but numbers were small. A recently published multinational retrospective cohort study of 195 patients given empirical carbapenem and 509 given targeted therapy for bacteraemia with ESBL-producing Enterobacteriaceae found ertapenem to be equivalent to other carbapenems.¹⁶⁵ The authors recognized that as in other similar studies ertapenem was more frequently used in lower-risk patients and that more studies are needed in severely ill patient populations.

Resistance (MIC ≥ 1 mg/L) and high-level resistance (taken here as MIC 16 mg/L) by EUCAST breakpoints to ertapenem in *Klebsiella* spp. and *Enterobacter* spp. were well recognized before CPE began to spread and were associated with combinations of a β -lactamase (often a CTX-M ESBL in *Klebsiella* spp. or AmpC in *Enterobacter* spp.) plus impermeability due to OmpK35 porin loss. Despite the results of Lee *et al.*,¹⁶⁴ imipenem and meropenem appear to remain active against most isolates with low-level ertapenem resistance caused by these mechanisms but with raised MICs compared with normal levels for the species. An *in vitro* study showed the frequent emergence of this type of resistance in ESBL-producing *E. coli* in a pharmacokinetic model¹⁶⁶ but most resistant isolates are *Klebsiella* spp. or *Enterobacter* spp., not *E. coli*. In a survey of UK isolates in 2007 only one of 95 ertapenem-resistant isolates of *K. pneumoniae* produced a defined carbapenemase, namely IMP-1, with the remainder inferred to have impermeability-mediated resistance (porin loss).¹⁶⁷ However, this situation has changed radically as KPC, OXA-48 and NDM are enzymes now regularly encountered in the UK.^{168,169} A retrospective case-control study from the eastern USA found that risk factors for infection caused by ertapenem-resistant Enterobacteriaceae with such impermeability-mediated resistance included exposure to any antibiotic (not just β -lactams and carbapenems) during the 30 days before a positive culture result.¹⁷⁰ A study from Singapore found that hospitalization and fluoroquinolone treatment were predictors for the appearance of ertapenem-resistant imipenem-susceptible variants.¹⁷¹

The use of ertapenem has no detrimental effect in terms of selecting for *P. aeruginosa*.¹⁷² Results from 10 clinical studies showed that use of ertapenem did not result in decreased susceptibility to carbapenems in *Pseudomonas* spp. This was confirmed in a study of hospitals in Queensland.¹⁷³ A further study found that one hospital's use of ertapenem was balanced by less use of imipenem and ciprofloxacin, and this may have contributed to a reduced prevalence of resistance of *P. aeruginosa* to imipenem.¹⁷⁴ In contrast to these findings a study in Singapore associated increasing consumption of ertapenem with a rising incidence density of carbapenem-resistant *P. aeruginosa*.¹⁷⁵ Ertapenem use had no impact on the susceptibility of *A. baumannii* to imipenem.¹⁷⁶

Prolonged infusion therapy with meropenem for MDR GNB including carbapenem-resistant organisms has been advocated on pharmacokinetic grounds in children for *A. baumannii*, *P. aeruginosa* and Enterobacteriaceae with meropenem MICs up to 8 mg/L.¹⁷⁷ There is a general trend towards considering continuous infusion of β -lactams in critically ill patients with severe Gram-negative sepsis (see Section 7.18).¹⁷⁸ Continuous infusion meropenem has been assessed in 375 obese patients for its ability to produce steady-state levels above the MIC at levels from 2 to >16 mg/L.¹⁷⁹ Dosing nomograms to sustain this had previously been constructed in critical care patients.¹⁸⁰

Meropenem combined with vaborbactam (RPX7009), a boronic-acid-derived β -lactamase inhibitor, is progressing through Phase 3 trials and may cover Enterobacteriaceae strains producing KPC carbapenemases but not those with MBLs or OXA-48-like enzymes. Some isolates with OmpK36 porin loss (see Sections 6.3.3 and 6.7) are resistant.³⁸ Relebactam in combination with imipenem/cilastatin is entering Phase 3 trials with trials against imipenem-resistant bacteria compared with a combination of colistin and imipenem/cilastatin and a comparative study against piperacillin/tazobactam in ventilator-associated pneumonia. Phase 2 studies are as yet unpublished. *In vitro* studies show no enhanced activity against *Acinetobacter* spp. but activity against KPC-producing *K. pneumoniae* (unless it has an OmpK36 porin loss, which is responsible for meropenem resistance; see Sections 6.3.3 and 6.7), and many but not all *P. aeruginosa* with enhanced AmpC production and depressed *oprD*.³⁷

Evidence

Carbapenems are drug of choice for treatment of serious infection with Enterobacteriaceae including those producing ESBLs or AmpC.

Evidence level: 1+

Imipenem use is associated with emergence of resistance in *P. aeruginosa*.

Evidence level: 3

Ertapenem treatment is associated with emergence of resistance via porin loss in ESBL- and AmpC-producing *Klebsiella* spp. and *Enterobacter* spp.

Evidence level: 3

Recommendations

- Use meropenem, imipenem or ertapenem to treat serious infections with ESBL and AmpC-producing Enterobacteriaceae. Grading: Strong recommendation for

- Apply antibiotic stewardship to use of all carbapenems to minimize the risk of developing resistance either by acquisition of carbapenemase-producing strains or, with ertapenem, by porin loss.
Grading: Strong recommendation for
- Do not use imipenem to treat susceptible *Pseudomonas* infections.
Grading: Conditional recommendation against use
- Introduce in the UK mandatory reporting of meropenem- or imipenem-resistant Enterobacteriaceae from all anatomical sites and specimens.
Grading: Strong recommendation for
- Test immediately for the precise level of meropenem resistance and for an indication of the responsible class of carbapenemase (e.g. MBL/KPC/OXA48-like) all meropenem- or imipenem-resistant isolates of Enterobacteriaceae. Submit to agreed reference laboratories to determine susceptibility to a wide range of potentially active agents, including, as appropriate, colistin, ceftazidime/avibactam, temocillin, aminoglycosides, fosfomycin and tigecycline.
Grading: Strong recommendation for
- Prefer ertapenem for OPAT of susceptible infections in view of the once-daily dosing regimen.
Grading: Conditional recommendation for

7.2 Ceftazidime

Observational studies of ceftazidime-susceptible ESBL-producing *E. coli* and *Klebsiella* spp. infections treated with ceftazidime frequently show treatment failure, mainly during bacteraemias.^{12,181–184} One study of seven patients treated with ceftazidime in China suggested useful activity but this may reflect the type of ESBL; CTX-M-14, -27 and -9 enzymes predominate in parts of China (and Spain) and have weak activity against ceftazidime as compared with CTX-M-15 enzymes with lower ceftazidime MICs. The higher CLSI susceptible breakpoint (≤ 4 mg/L) was found to classify 34% of CTX-M-positive *E. coli* as susceptible to ceftazidime with normal inocula. Most CTX-M-14 isolates became resistant at higher inocula.¹⁸⁵ The EUCAST breakpoint for susceptibility is <1 mg/L, reducing this problem. Early problems arose with apparent ceftazidime susceptibility by disc testing of CTX-M-15-producing *E. coli* ST131 isolates in the UK down-regulated by an IS26 insertion between promoter and structural gene.¹⁸⁶ Ceftazidime is active against some OXA-48-producing CPE, principally those that do not co-produce ESBLs or AmpC enzymes. Ceftazidime retains activity against many isolates of *P. aeruginosa*, including in the presence of mutation to imipenem or ciprofloxacin resistance.¹⁸⁷ However, strains with derepressed class C (AmpC) β -lactamases or strongly up-regulated efflux mechanisms are resistant, as are strains producing MBLs, other carbapenemases or ESBLs.

Evidence

Ceftazidime is usually ineffective in treating multiresistant infections with Enterobacteriaceae except against some OXA-48 carbapenemase-producing strains.

Evidence level: 3

Ceftazidime remains useful for infections due to quinolone or imipenem-resistant *P. aeruginosa*.

Evidence level: 3

Recommendations

- Use ceftazidime for susceptible infections with *P. aeruginosa* including quinolone- or some imipenem-resistant strains.
Grading: Strong recommendation for
- Do not use ceftazidime to treat infections due to ESBL- or AmpC-producing Enterobacteriaceae or CPE (other than OXA-48 producers), even if *in vitro* tests suggest the isolate is susceptible.
Grading: Conditional recommendation against use

7.3 Ceftazidime/avibactam

Ceftazidime has recently been combined with the β -lactamase inhibitor avibactam. This combination has broad Gram-negative activity including Enterobacteriaceae and *P. aeruginosa*. Ceftazidime-susceptible bacteria remain susceptible to the combination, but avibactam protects additionally against class A (TEM, SHV, CTX-M, KPC) class C (AmpC) and some class D (OXA) β -lactamases.^{188–192} Ceftazidime/avibactam has no inhibitory activity against the MBLs (NDM-1, IMP and VIM) but it is the first BL/BLI combination to retain activity against KPC-2 carbapenemase-producing and most OXA-48 carbapenemase-producing strains. Ceftazidime/avibactam has minimal activity against *Acinetobacter* spp., anaerobic or Gram-positive organisms.^{190,193,194} A recent susceptibility study that included 120 KPC-producing Enterobacteriaceae collected from US hospitals found that ceftazidime/avibactam had MIC_{50/90} values of 0.5/2 mg/L.¹⁹⁵ The first case series of use of ceftazidime/avibactam against carbapenem-resistant Enterobacteriaceae has recently been published.¹⁹⁶ Among 37 patients with severe infections due to these organisms, 31 had strains with KPC carbapenemases. Resistance to ceftazidime/avibactam emerged independently in three cases infected by *K. pneumoniae* ST258 with KPC-3 enzymes. In two of these isolates meropenem MICs were reduced ≥ 4 -fold to the susceptible range in parallel with the rise in ceftazidime/avibactam MICs. The overall clinical success rate was 59% of patients whilst microbiological failure occurred in 10 patients, including the 3 patients where resistant mutants were selected. An earlier epidemiological study had shown that ceftazidime/avibactam median MICs of ceftazidime/avibactam are higher for KPC-3-producing isolates than those with KPC-2 enzymes, although it was unclear if this represents enzyme specificity or quantity.¹⁹⁷ Isolates that produce KPC-3 enzyme are internationally widespread, including in South America and Southern Europe. Ceftazidime/avibactam-resistant isolates with similar or identical mutations can be selected *in vitro*.¹⁹⁸ The mechanism involves the enzyme becoming a stronger ceftazidime-destroying enzyme, not in it becoming avibactam resistant. The licensing of avibactam (a non- β -lactam β -lactamase inhibitor) with ceftazidime offers a new choice where organisms that produce both AmpC and an ESBL, or KPC2 carbapenemase cause systemic infection.

In Phase 2 double-blind randomized trials, the efficacy of ceftazidime/avibactam was similar to that of imipenem/cilastatin in the treatment of complicated UTI (19/27 and 21/35 respectively).¹⁹⁹ A Phase 3 RCT of doripenem versus ceftazidime/avibactam in complicated UTI or pyelonephritis, with patients not selected for antibiotic resistance, showed equivalence with microbiological eradication in 304/393 (77.4%) in the ceftazidime/avibactam arm and 296/417 (71%) in the doripenem arm.²⁰⁰ Efficacy combined with metronidazole was similar to meropenem in an RCT of 203

patients with intra-abdominal infection.²⁰¹ A Phase 3 RCT comparison of meropenem against ceftazidime/avibactam with metronidazole in 1066 complicated intra-abdominal infections, with the exclusion of a standardized set of highest-mortality surgical indications, again showed equivalence.²⁰² On ITT analysis response rates were 82.5% to the ceftazidime/avibactam or metronidazole combination and 84.9% to meropenem. There was no difference in patient outcome in the combination arm if a ceftazidime-resistant strain of Enterobacteriaceae was present or absent. Only one case of *C. difficile* was recognized in either arm of the study. An RCT of ceftazidime/avibactam and metronidazole against meropenem of 333 patients, largely with patients with complicated UTI but with some patients treated for intra-abdominal infections, all with infections with ceftazidime-resistant Enterobacteriaceae or *P. aeruginosa*, showed 91% response rates at a test-of-cure visit.²⁰³ None of these patients was infected with carbapenemase-producing strains.

Evidence

Ceftazidime/avibactam has similar efficacy to carbapenems in abdominal and complicated UTI, the former requiring combination of ceftazidime/avibactam with metronidazole.

Evidence level: 1+

Although clinical experience is limited in MDR GNB largely to ceftazidime-resistant organisms in complicated UTI, it would be expected to be effective when OXA-48-producing MDR GNB cause infection.

Evidence level: 4

Clinical experience against *Klebsiella* spp. producing KPC carbapenemase is limited but, ominously, efficacy is only some 60% with resistance emerging in 10% of treated patients.

Evidence level: 2+

Recommendations

- Could use ceftazidime/avibactam as an alternative to carbapenems for infection with ESBL- and AmpC-producing Enterobacteriaceae but alternatives may be cheaper.
Grading: Conditional recommendation for
- Evaluate further ceftazidime/avibactam use alone or in combination when non-MBL carbapenemase-producing organisms cause infection. KPC-3-producing *Klebsiella* spp. are vulnerable to mutations in the *bla*_{KPC-3} gene causing resistance.
Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials
- Do not use for treating infection with anaerobes or bacteria producing MBLs: these are resistant.
Grading: Strong recommendation against

7.4 Ceftolozane/tazobactam

Ceftolozane is an oxyimino-cephalosporin that has been combined with tazobactam. Ceftolozane/tazobactam is active against many Gram-negative organisms, including Enterobacteriaceae and *P. aeruginosa*.^{193,204,205} It is active against *P. aeruginosa* isolates that are resistant to standard agents such as ceftazidime because of derepressed AmpC β -lactamases or up-regulated efflux. In terms of MIC, ceftolozane is the most active β -lactam against *P. aeruginosa*, with resistance (MIC 4 mg/L EUCAST) largely confined to those with MBLs or unusual ESBLs such as VEB and GES

types. MIC_{50/90} values against 310 MDR isolates of *P. aeruginosa* were 2/8 mg/L.²⁰⁵ Activity against *Acinetobacter* spp. is variable.¹⁹³ Ceftolozane/tazobactam has *in vitro* activity against Enterobacteriaceae producing ESBLs including most TEM, SHV, and CTX-M types.^{205–207} Since oxyimino-cephalosporins are stable to the inhibitor-resistant OXA-1 enzyme, ceftolozane is not compromised by co-production of this enzyme in CTX-M-15-producing Enterobacteriaceae as happens with piperacillin/tazobactam. Activity is less against ESBL-producing *Klebsiella* spp., possibly owing to high ESBL levels arising from production of additional SHV enzymes.²⁰⁸ Activity against Enterobacteriaceae with copious AmpC enzyme is variable, but many *Enterobacter* spp. with derepressed AmpC are resistant. The combination has no activity against strains with MBLs (NDM-1, IMP and VIM) or against those with KPC carbapenemases. Ceftazidime-resistant strains with OXA-48-like enzymes are mostly resistant: ceftazidime-susceptible OXA-48 producers are susceptible to ceftolozane/tazobactam (D. M. Livermore, unpublished data).

Ceftolozane/tazobactam therefore has potentially different uses from ceftazidime/avibactam and should not be used in infections due to AmpC- or KPC-producing Enterobacteriaceae. The absence of clinical comparisons of piperacillin/tazobactam and ceftolozane/tazobactam means that choices must be made on *in vitro* grounds. The apparent enhanced activity of ceftolozane/tazobactam against strains that co-produce the enzyme OXA-1, including the internationally prevalent *E. coli* ST131 lineage, needs full laboratory and clinical verification but may make this drug more likely to produce clinical cure. Caution on clinical outcome is necessary because of the potential, as with ceftazidime/avibactam, for superinfection with *C. difficile*. Ceftolozane activity against *P. aeruginosa* including ceftazidime-resistant strains *in vitro* may offer clinical advantages where MDR *Pseudomonas* infections are a problem, such as in cystic fibrosis,²⁰⁹ but this needs confirmation in a clinical trial. Optimal dosing in cystic fibrosis needs to be established but the drug's pharmacokinetics appears to be the same as in unaffected patients.²¹⁰

Ceftolozane/tazobactam is licensed, at present, for complicated intra-abdominal infection and complicated urinary tract infection.²¹¹ In a prospective, randomized, double-blind trial, 993 hospitalized patients with complicated intra-abdominal infection received either ceftolozane/tazobactam (1.5 g q8h iv) plus metronidazole, or meropenem (1 g q8h iv) for 4–14 days.²¹² Non-inferiority was demonstrated overall and MIC was not related to outcome. In 50 patients an ESBL-producing organism was isolated. In these patients, the clinical cure rate was 95.8% (23/24) in the ceftolozane/tazobactam plus metronidazole group and 88.5% (23/26) in the meropenem group. In patients with CTX-M-14/15 ESBL-producing Enterobacteriaceae, clinical cure was observed in 13 of 13 (100%) and 8 of 11 (72.7%) patients, respectively. A double-dummy, double-blinded RCT compared ceftolozane/tazobactam against levofloxacin in 1083 patients with complicated UTI.²¹³ Patients received ceftolozane/tazobactam (1.5 g q8h iv) or intravenous levofloxacin (750 mg q24h). The majority of participants (82%) had pyelonephritis. Overall, ceftolozane/tazobactam was found to be non-inferior in clinical and superior in microbiological outcome to levofloxacin therapy. In the ITT population, 20/731 (2.7%) of Gram-negative pathogens were resistant to ceftolozane/tazobactam at baseline, whereas 195/731 (26.7%) were resistant to levofloxacin. Two (0.3%) of 594 *E. coli* isolates were resistant to

ceftolozane/tazobactam and 144/594 (24.2%) were resistant to levofloxacin. For patients with levofloxacin-resistant uropathogens (based on CLSI criteria) clinical cure was seen in 90 (90.0%) of 100 patients in the ceftolozane/tazobactam group compared (surprisingly) with 86/112 (76.8%) in the levofloxacin group. In patients with ESBL-producing uropathogens, cure with ceftolozane/tazobactam was 55/61 (90.2%) compared with 42/57 (73.7%) for levofloxacin (95% CI 2.6–30.2). Treatment choice in complicated UTI and pyelonephritis involving MDR GNB between piperacillin/tazobactam, carbapenems, ceftolozane/tazobactam, temocillin or ceftazidime/avibactam depends on the bacteria present and their patterns of susceptibility.

Evidence

Ceftolozane/tazobactam is not active against CPE strains, excepting ceftazidime-susceptible OXA-48 producers, but otherwise, when combined with metronidazole, is non-inferior to meropenem in intra-abdominal infection.

Evidence level: 1+

Ceftolozane/tazobactam is non-inferior to intravenous levofloxacin in complicated UTIs, including those caused by ESBL-producing *E. coli* (most of which are resistant to levofloxacin).

Evidence level: 2–

Ceftolozane/tazobactam is the most active β -lactam *in vitro* against *P. aeruginosa*.

Evidence level: 4

Recommendations

- Use ceftolozane/tazobactam to treat susceptible *P. aeruginosa* infections resistant to ceftazidime.
Grading: Conditional recommendation for
- Conduct clinical trials in *P. aeruginosa* infections in cystic fibrosis.
Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials
- Use ceftolozane/tazobactam as an alternative to carbapenems to treat urinary or intra-abdominal infection involving ESBL-producing *E. coli*. Caution may be needed when treating infection due to ESBL-producing *Klebsiella* spp. owing to a higher resistance rate.
Grading: Conditional recommendation for
- Do not use for infections due to AmpC- or carbapenemase-producing Enterobacteriaceae or MBL/ESBL-producing *P. aeruginosa*.
Grading: Strong recommendation against use

7.5 Aztreonam

Aztreonam is labile to AmpC and ESBL enzymes. It is stable to MBLs and OXA-48-like carbapenemases but most Enterobacteriaceae with these enzymes also express ESBLs or AmpC, which confer resistance.^{214,215} Isolates with MBLs or OXA-48 and no ESBL or AmpC production may be susceptible (those with OXA-48 alone are likely also to be susceptible to ceftazidime and ceftolozane/tazobactam). At EUCAST breakpoints ($S \leq 1$ mg/L, $R > 16$ mg/L) most *P. aeruginosa* are intermediate in susceptibility and the drug is usually less active than ceftazidime or ceftolozane/tazobactam except against MBL producers resistant to all other β -lactams, which may be intermediate (rarely susceptible) to aztreonam.

An aztreonam/avibactam combination is in Phase 2 development. This creates a combination with very promising activity against Enterobacteriaceae with MBLs, OXA-48, AmpC, ESBLs and other β -lactamases (including AmpC, OXA-1 and CTX-M class).^{214,215,216}

Evidence

Aztreonam is not active against Gram-negative bacteria producing ESBLs, AmpC or KPC carbapenemase; it is only moderately active against *P. aeruginosa*.

Evidence level: 4

It is stable to MBLs but strains possessing these often have ESBL or AmpC as well, resulting in resistance. Similar limitations apply to strains with OXA-48-like enzymes.

Evidence level: 3

Combination with a β -lactamase inhibitor such as avibactam would potentially make aztreonam useful against MBL (NDM, IMP and VIM)-producing bacteria that also have ESBLs or AmpC enzymes.

Evidence level: 4

Recommendations

- Do not use aztreonam alone empirically if MDR GNB or Gram-positive or anaerobic pathogens are suspected.
Grading: Strong recommendation against use
- Do not use aztreonam for CTX-M ESBL- or AmpC-producing bacteria even if these appear susceptible *in vitro*.
Grading: Strong recommendation against use
- Use aztreonam for MBL- or OXA-48-producing strains if it is certain that they do not produce ESBLs or AmpC.
Grading: Conditional recommendation for
- Research usefulness of aztreonam in combination with avibactam for bacteria producing MBLs with ESBL/AmpC enzymes and for those with other carbapenemases.
Grading: Recommendation for research

7.6 Cefepime

Cefepime is not available in the UK. It appeared to be active *in vitro* against ESBL-producing Enterobacteriaceae, especially when the old NCCLS/CLSI breakpoint of ≤ 8 mg/L was used. A retrospective, case-controlled study compared the clinical and microbiological responses for 10 infections due to ESBL-producing *Klebsiella* spp. and *E. coli* from a non-urinary source with 20 matched controls receiving cefepime for non-ESBL strains. Four patients with ESBL producers had strains that were resistant to cefepime by broth microdilution MIC, one of whom responded: three of the remaining six with strains then regarded as susceptible (NCCLS/CLSI breakpoint MIC ≤ 8 mg/L) failed on treatment. Patients receiving cefepime for infection with ESBL-producing bacteria were 9.7 times more likely to have an unsuccessful clinical and microbiological response than those with non-ESBL-producing bacteria.²¹⁷ A randomized evaluator-controlled trial of ICU patients compared cefepime with imipenem for the treatment of hospital-acquired pneumonia. The failure rate was 31% in the cefepime group compared with 0% in the imipenem group. Cefepime MICs of 2–4 mg/L, then interpreted as susceptible by the NCCLS/CLSI breakpoint of ≤ 8 mg/L but now regarded as susceptible dose-dependent by

current CLSI and intermediate by EUCAST criteria, were noted in strains from treatment failures.²¹⁸ A retrospective case-control study of cefepime-susceptible bacteraemia caused by ESBL producers in the period 2012–17 compared 30 day mortality amongst 17 patients treated with cefepime versus 161 cases treated with a carbapenem.²¹⁹ Mortality in the cefepime group was 58.8% versus 16.8% for carbapenem treatment and, in multivariate analysis, cefepime treatment was strongly associated with mortality (OR 9.9, 95% CI 2.8–319; $P=0.001$). Mortality with cefepime in definitive treatment was also related to MIC, being 16.7% (1/6) in those with an MIC ≤ 1 mg/L, 45% (5/11) in those with an MIC of 2–8 mg/L and 100% (4/4) in those with an MIC of ≥ 16 mg/L.²²⁰ In a retrospective study of 305 adults with monomicrobial *E. cloacae* infections, those with MICs of 4–8 mg/L (i.e. with CLSI dose-dependent susceptibility and straddling the EUCAST intermediate/resistant breakpoint) had significantly higher mortality than those treated with a carbapenem (71.4% versus 18.2%; $P=0.045$).¹⁴ Fifty-eight percent of strains in the cefepime-treated group produced an ESBL in addition to AmpC. In those definitively treated with cefepime, ESBL production (16/40 versus 3/32; $P=0.006$) and susceptible dose-dependent strains (10/16 versus 9/56; $P\leq 0.001$) were independently associated on multivariate analysis with increased mortality.¹⁴ ESBL production was more frequent in those strains with cefepime MICs of 4–8 mg/L (32/36 compared with 61/138 with MIC ≤ 2 mg/L; $P\leq 0.001$). Mortality was not reduced even when high-dose regimens (2 g q8h iv) were used. Mortality in infections due to ESBL non-producers (with median MICs of 0.5 mg/L) treated with definitive cefepime was similar to that in those that received definitive carbapenem therapy (9/56 versus 16/72; $P=0.5$). This study demonstrates the efficacy of cefepime against the presumptive AmpC producer *E. cloacae* but only in the absence of additional ESBL production or absence of MIC 2 mg/L. Nevertheless, in another retrospective study between 2005 and 2007, for bacteraemia due to ESBL-producing pathogens, receipt of empirical cefepime alone ($n=43$) was associated with increased mortality compared with cefepime combination ($n=69$) or carbapenem combination ($n=44$) regimens: mortality was unlinked to MIC, being 5/13 for those with organisms having MIC ≤ 2 mg/L, 2/6 for those having MICs of 4 or 8 mg/L and 10/24 for those having MICs ≥ 16 mg/L.²²¹

The concept of 'susceptible dose dependent' isolates of Enterobacteriaceae was suggested by CLSI in order to maximize cefepime use and spare carbapenems, but these findings suggest this is unwise. A recent systematic review did not support the use of cefepime in empirical therapy of critically ill patients when ESBL-producing *E. coli* or *Klebsiella* spp. infection is suspected. Even in patients with ESBL strains susceptible to cefepime (≤ 2 mg/L CLSI; <1 mg/L EUCAST), treatment failure can be seen.²²⁰

Evidence

Cefepime has a higher failure rate in treatment of infections due to ESBL-producing GNB than carbapenems unless cefepime MICs are ≤ 1 mg/L.

Evidence level: 2+

Bacteraemia due to *E. cloacae* strains without ESBLs and with MIC ≥ 2 mg/L <8 mg/L can be successfully treated with cefepime.

Evidence level 2+

Recommendations

- Could use cefepime to treat infection caused by ESBL- or AmpC-producing bacteria if susceptible to the EUCAST breakpoint of MIC ≤ 1 mg/L.
Grading: Conditional recommendation for
- Do not use cefepime even at increased dose for isolates with (i) MIC of 2–8 mg/L (CLSI 'susceptible dose dependent') or (ii) MIC 2–4 mg/L (EUCAST intermediate) or (iii) strains that produce both AmpC and ESBLs.
Grading: Strong recommendation against use
- Do not use cefepime to treat infection caused by CPE.
Grading: Strong recommendation against use

7.7 Cefoxitin

Cefoxitin, the original parenteral cephamycin, was developed by Merck and is now a generic. It is no longer available in Europe but has several suppliers in the USA. Cefoxitin was licensed at the same time as second-generation cephalosporins such as cefuroxime but differs in having activity against gut *Bacteroides* spp. but minimal activity against *Haemophilus influenzae*. Cefoxitin is on the list of forgotten antibiotics that may be useful against MDR GNB.²²² It is active against ESBL-producing *E. coli* but is not active against AmpC-inducible species of Enterobacteriaceae, e.g. *Enterobacter* spp., *C. freundii*, *Serratia* spp., *M. morganii* and *Providencia stuartii*, nor against *P. aeruginosa*. Cefoxitin differs from temocillin (which has a 6- α -methoxy group corresponding to the 7- α -methoxy group of cefoxitin) in having activity against Gram-positive bacteria including penicillin-susceptible *Streptococcus pneumoniae* and methicillin-susceptible *Staphylococcus aureus*, which may be advantageous if a urinary infection is diagnosed but the patient actually has infection due to these organisms elsewhere.

EUCAST no longer cites MIC breakpoints but BSAC had a breakpoint of S <8 mg/L and R >8 mg/L. Typical MICs for *E. coli* and *Klebsiella* spp. are slightly below this level, meaning that small reductions in susceptibility can confer resistance. These can arise by reductions in permeability or (in *E. coli* only) by mutation in promoter or attenuator sequences for *ampC*. Cefoxitin resistance is very common in the Middle East, India and China. In a multicentre study of 1762 isolates from urinary infection in the Asia-Pacific region 50.3% of strains were resistant to cefoxitin.²²³ Resistance also occurs in *E. coli* and *Klebsiella* spp., from plasmid-mediated AmpC production. Porin loss combined with other mechanisms of β -lactam resistance, such as ESBL production, is described as emerging during treatment of some *Klebsiella* infections (see Sections 6.3.3 and 6.7).

Cefoxitin is used in selective media for *C. difficile* and would be expected to trigger infection with this pathogen. In one recent study antibiotic prophylaxis with cefoxitin was an independent risk factor for *C. difficile* infection.²²⁴ The absolute frequency at which this will occur relative to other antibiotics is not known.

In murine models of pyelonephritis cefoxitin was effective against an OXA-1- and CTX-M-15-producing transconjugant *E. coli*²²⁵ and in combination with fosfomycin prevented selection for fosfomycin-resistant mutants.²²⁶ Only one human trial of cefoxitin against current ESBL producers has been reported. In that 2015 French study, largely of urinary and catheter-related bacteraemia, 30/33 patients responded in the first 48 h and 20/24 patients responded who were evaluable at follow-up. Six microbiological failures were documented with

emergence of resistance in two patients with *Klebsiella* infection.²²⁷ A pharmacological model suggests 1 h infusion of 2 g four times daily would be effective.²²⁸

Although cefoxitin appears active against CTX-M-15-producing *E. coli* and *Klebsiella* spp., it lacks temocillin's activity against strains with copious inducible, derepressed²²⁹ or plasmid-mediated AmpC. Cefoxitin may be more prone than temocillin to select *C. difficile*.²³⁰ Temocillin, unlike cefoxitin, has no Gram-positive spectrum so in empirical use in the elderly where it is not clear if the urinary tract or the chest/skin is the source of infection, it may need supplementation with another antibiotic. It is not clear if cefoxitin's reintroduction would offer any sustainable or competitive advantage apart from its carbapenem-sparing capacity as its four-times daily intravenous dosing makes it only usable in inpatient treatment, not OPAT.

Evidence

Cefoxitin is an intravenous cephamycin antibiotic, formerly licensed in the UK. Inducible, derepressed or plasmid-mediated AmpC production confers resistance, as does porin loss, especially in association with ESBL production. Nevertheless, *in vitro*, animal and human studies indicate activity against ESBL-producing strains of *E. coli* and *Klebsiella* spp. Treatment can be complicated by emergence of resistance due to porin loss.

Evidence level: 3.

Recommendations

- Could use as a carbapenem-sparing agent for infections caused by CTX-M-15-producing *E. coli* but is only suitable for inpatient use, not OPAT, because of the short serum half-life. Narrower Gram-negative spectrum than temocillin so less suitable for empirical use in UTI.

Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials

7.8 Temocillin

Temocillin is a semi-synthetic 6- α -methoxy derivative of ticarcillin that is highly stable to most β -lactamases except MBLs (e.g. IMP, NDM and VIM) and OXA-48-like enzymes. It lacks activity against anaerobes, Gram-positive bacteria and most Gram-negative non-fermenters such as *P. aeruginosa* and *Acinetobacter* spp. It retains *in vitro* activity against ESBL- and AmpC-producing Enterobacteriaceae^{231,232} and some KPC-producing *E. coli* and *Klebsiella pneumoniae*,²³³ and *Burkholderia cepacia* complex.²³⁴ It is active against Enterobacteriaceae strains whose AmpC production is stably derepressed.²³⁵ No EUCAST breakpoint for susceptibility to the drug has yet been published but the CA-SFM has a rate of $S \leq 8$ mg/L, $R > 8$ mg/L and the BSAC had a systemic value of $S \leq 8$ mg/L, $R > 8$ mg/L and an uncomplicated UTI value of $S \leq 32$ mg/L, $R > 32$ mg/L. MICs of temocillin for KPC-producing bacteria are in the range of 4–32 mg/L (mode 16 mg/L). In a lethal mouse model of intra-abdominal infection using strains of KPC-producing *E. coli*, temocillin was effective against KPC-2.²³⁶ Temocillin has poor activity against carbapenem-resistant isolates of Enterobacteriaceae lacking carbapenemases—presumptively due to porin loss.²³⁷ This antibiotic has no activity against OXA-48- or MBL-producing strains.²³⁸ Caution is also needed in predicting results of treatment of systemic infections from *in vitro* susceptibility and further trials of

temocillin alone at defined and possibly greater doses than the licensed 2 g twice daily are necessary. Outcomes should be correlated with MIC.

At present, clinical studies are limited to non-comparative series. The largest multicentre study (non-randomized retrospective case series) involved 92 patients who were treated with at least 3 days of therapy.²³⁹ Urinary tract and bacteraemia (42 episodes each) were the most frequent indications followed by hospital-acquired pneumonia. Dosages of ≥ 4 g/day, rather than 1 g twice daily, were associated with improved outcome. Patients with strains producing AmpC or ESBL enzymes responded microbiologically in 23/27 or 18/22 cases in respectively UTI or bacteraemia. Higher dosage regimens, including 2 g three times daily and 6 g by continuous infusion, and use in veno-venous haemofiltration are reported in the literature with suggestions that these improve efficacy in critically ill patients. These data have led to a modification of the licensed posology with the usual dose increased to 4 g/day and the higher dose, particularly in critically ill patients, to 6 g/day.²⁴⁰ In a retrospective case review of bacteraemia caused by KPC-producing Enterobacteriaceae, 14/14 patients treated with temocillin either alone or in combination survived, whereas 6/30 treated similarly with tigecycline died.²⁴¹ Two studies have been published on the use of temocillin in cystic fibrosis patients with *B. cepacia* complex and sometimes *P. aeruginosa*. Both were retrospective non-randomized audits, the first showing equivalence of combinations of temocillin with tobramycin versus other agents with tobramycin against *Burkholderia cenocepacia* and the second showing that 18/32 courses of temocillin resulted in improvement in the patient's infection.^{242,243}

Evidence

Temocillin at a dose of 2 g twice daily is an effective and well tolerated drug for UTI and bacteraemia with AmpC- or ESBL-producing bacterial infection.

Evidence level: 3

Although *in vitro* work suggests activity against many KPC-producing bacteria, there is little published clinical evidence to support this. Respiratory infections, including CF infections with *B. cepacia*, and other sites of systemic infection requires further clinical trials.

Evidence level: 4

Recommendations

- Use alone for UTIs and associated bacteraemia caused by AmpC- or ESBL- producing Enterobacteriaceae.
Grading: Conditional recommendation for
- Continuous infusion or thrice-daily dosing may be desirable for systemic infections with ESBL- or AmpC-producing bacteria.
Grading: Recommendation for research and possible conditional recommendation for use restricted to trials
- Could use for UTIs with KPC-producing Enterobacteriaceae but not for OXA-48 or MBL producers, on basis of published *in vitro* data.
Grading: Recommendation for research and possible conditional recommendation for use restricted to trials

7.9 Ampicillin/sulbactam

Sulbactam has *in vitro* microbiological activity against some strains of *A. baumannii*, including some carbapenem-resistant lineages.

Microbiological studies showed that sulbactam alone (without ampicillin) was active against these bacteria.²⁴⁴ In an uncontrolled study, 42 patients with infections caused by MDR *A. baumannii* were treated with sulbactam or ampicillin/sulbactam. Eighteen received sulbactam alone and 24 received ampicillin/sulbactam; no difference in cure rate was observed between the two groups. Another study compared ampicillin/sulbactam with colistin therapy in a retrospective review of patients who had nosocomial infections caused by carbapenem-resistant *Acinetobacter* spp. from 1996 to 2004.²⁴⁵ Eighty-two patients received polymyxins and 85 were treated with ampicillin/sulbactam. The authors concluded that ampicillin/sulbactam appeared to be more efficacious than polymyxins. More generally, and predictably, multivariate analysis found that prognostic factors for in-hospital mortality were older age, septic shock and higher APACHE II score. A small retrospective non-blinded trial compared treatment with ampicillin/sulbactam versus imipenem and tried also to address the benefit of combining ampicillin/sulbactam with colistin. There was no difference in outcome.^{246,247} Two small RCTs have tried to assess differences in dosing regimens and efficacy compared with colistin.^{248,249} Overall the evidence base is poor and interpretation is difficult without consideration of the MIC for the organism. In context, sulbactam MICs for most UK isolates of carbapenem-resistant *A. baumannii* are 16–32 mg/L, implying poor rates of susceptibility (D. M. Livermore, unpublished data).

Evidence

Ampicillin/sulbactam appears effective in treating infections due to some carbapenem-resistant *Acinetobacter* spp. but many isolates in the UK have relatively high sulbactam MICs.

Evidence level: 3

Recommendations

- Could use against some carbapenem-resistant, apparently sulbactam-susceptible *A. baumannii* isolates. Caution needed in the UK because of a higher range of MICs. Absence of a breakpoint prevents categorization as susceptible/resistant. Grading: Conditional recommendation for

7.10 Co-amoxiclav

Co-amoxiclav is a combination of the broad-spectrum amoxicillin with the β -lactamase inhibitor clavulanic acid. Co-amoxiclav is known to select for Enterobacteriaceae resistant to the clavulanate component as well as amoxicillin in the gastrointestinal flora.²⁵⁰ Co-amoxiclav has been successfully used to treat UTIs due to ESBL producers, as described in case reports and an observational study.^{251,252} The cure rate among 37 patients with cystitis treated with co-amoxiclav was 93% for those with susceptible isolates (MIC ≤ 8 mg/L) and 56% for those with intermediate or resistant isolates (MIC ≥ 16 mg/L) ($P = 0.02$).²⁵¹ The study was performed in Spain, where many ESBL producers have CTX-M-14 enzyme; in the UK more have CTX-M-15 and many of these co-produce OXA-1, an inhibitor-resistant penicillinase, raising co-amoxiclav MICs to the intermediate or resistant range. Furthermore, MIC determinations were done with a β -lactam: β -lactamase inhibitor ratio of 2:1 and higher MICs would likely be obtained using the fixed clavulanate concentration of

2 mg/L now advocated by EUCAST. The outcomes for bacteraemias treated with co-amoxiclav or piperacillin/tazobactam have been reviewed and the findings are discussed in the section on piperacillin/tazobactam (Section 7.11).²⁵³

Evidence

These studies suggest that co-amoxiclav is effective in lower UTIs caused by ESBL-producing bacteria but efficacy was only reliably predicted in strains where these organisms were fully susceptible *in vitro* and lacked co-production of OXA-1 β -lactamase.

Evidence level: 3

Recommendations

- Use for lower UTI due to known ESBL-producing bacteria only if current isolates, or, if using empirically, recent isolates, are fully susceptible. Grading: Conditional recommendation for

7.11 Piperacillin/tazobactam

Different susceptibility standards are used worldwide and so correlations of mortality with *in vitro* susceptibility cannot be reliably transferred between countries. EUCAST regards more isolates as resistant than CLSI. Some countries, such as the UK, have a higher prevalence of Enterobacteriaceae with CTX-M-15 and, in *E. coli*, OXA-1 β -lactamase, and these are more resistant than the CTX-M-14 ESBL producers circulating, for example, in Spain. This may critically affect the validity of evidence collected from different laboratories and hospitals about the adequacy of these combinations against ESBL-producing bacteria.

The use of piperacillin/tazobactam for treating bacteraemias caused by ESBL-producing bacteria consequently remains contentious. One recent retrospective analysis of 331 patients in a US hospital with bacteraemia due to ESBL-producing bacteria suggested carbapenems were superior to piperacillin/tazobactam.²⁵⁴ One hundred and three (48%) patients received piperacillin/tazobactam empirically and 110 (52%) received carbapenems empirically. The adjusted risk of death was 1.92 times higher for patients receiving empirical piperacillin/tazobactam compared with empirical carbapenem therapy. Another retrospective study of bacteraemic patients with ESBL-producing *P. mirabilis* compared the outcomes of patients treated with piperacillin/tazobactam or a carbapenem for at least 48 h.²⁵⁵ Forty-seven patients with available clinical data were studied, of whom 34 were included. Only 11% of strains were imipenem susceptible but MICs of the drug for Proteaeae typically clustered around the breakpoint. The overall 30 day mortality rate was 29.8%. Three of 21 patients treated with carbapenems (all imipenem) died within 30 days (all in hospital) versus 4/13 treated with piperacillin/tazobactam, a non-significant difference. Furthermore, among those treated with piperacillin/tazobactam, the mortality rate was lower in those infected by the isolates with lower piperacillin/tazobactam MICs ($\leq 0.5/4$ mg/L) when compared with isolates with MICs of $\geq 1/4$ mg/L (0/7 versus 3/5; $P = 0.045$). A study of 39 episodes of bacteraemia due to ESBL-producing *E. coli* from Spain found a statistically significant reduction in 30 day mortality in infections from non-urinary sources if the MIC was ≤ 2 mg/L (0/11) compared with those strains with higher MIC (7/17).²⁵⁶ This suggests that even the current EUCAST

breakpoints (S <8 mg/L, R >16 mg/L) are too high to give guidance on clinical response. An analysis of patients with bacteraemias due to ESBL-producing *E. coli* was performed to assess the efficacy of combinations of piperacillin/tazobactam or co-amoxiclav compared with carbapenems.²⁵³ Mortality in patients treated with such BL/BLI combinations or carbapenem was compared in two cohorts: empirical therapy and definitive therapy. Mortality rates at day 30 for those treated with BL/BLI versus carbapenems were 9.7% versus 19.4% for empirical therapy and 9.3% versus 16.7% for definitive therapy respectively. After adjustment for confounders, no association was found between either empirical therapy or definitive therapy and increased mortality. The study suggested that co-amoxiclav and piperacillin/tazobactam may be suitable alternatives to carbapenems for treating patients with bacteraemias due to ESBL-producing *E. coli* but only in the minority that were susceptible *in vitro*. The study was not randomized, and confounding due to unmeasured variables may have occurred. This retrospective observational study has been repeated on a multinational basis and extended to 627 patients and showed that BL/BLI combinations were statistically as effective as carbapenems in empirical and directed therapy against ESBL-producing Gram-negative bacteraemia.²⁵⁷ A subset of 207 patients had the ESBL genes of their pathogens examined by PCR: 42 were identified as CTX-M-15, 27 as CTX-M-1, 31 as CTX-M-14 and 18 as CTX-M-9. No details were given of response rates in relation to the presence of specific resistance genes and co-production of OXA enzymes was not sought. In another study co-amoxiclav and piperacillin/tazobactam susceptibility of the bacteria causing bacteraemia, particularly for *E. coli* ST131, were not correlated: 51% of the isolates also had OXA-1 and 90% of isolates were reported susceptible to piperacillin/tazobactam versus 26% susceptible to co-amoxiclav by CLSI criteria.²⁵⁸ Such discrepancies with different BL/BLIs may relate to whether the EUCAST or CLSI breakpoints are used, as the MICs for many isolates with a combination of CTX-M-15 and OXA-1 enzymes cluster around 16 mg/L. The relationship of the BL/BLI used and its MIC for the infecting strain with efficacy in lower UTIs (where urinary concentrations are higher than in serum) or bacteraemia needs to be established. More generally, individual drug/inhibitor combinations must be separately studied for efficacy, and related to both the β -lactamase genes present and *in vitro* susceptibility. As American commentators have pointed out,²⁵⁹ it is important to note the dosing regimen when considering the response to piperacillin/tazobactam of many ESBLs. Many Spanish studies used piperacillin/tazobactam at 4.5 g q6h, not the usual licensed UK dose of 4.5 g q8h. For β -lactams, increasing the time above the MIC substantially decreases mortality.²⁶⁰ It is possible that more frequent dosing would achieve this. More materially, this can be achieved with continuous infusion, albeit with higher daily drug dosage (which might breach targets to reduce use) and could be considered to increase efficacy of piperacillin/tazobactam. It cannot be anticipated with biliary excretion whether this will change selection pressure for superinfecting organisms or *C. difficile* in the gastrointestinal flora.

A retrospective case review of empirical treatment of bacteraemia caused by ESBL-producing *E. coli* or ESBL-producing *Klebsiella* spp. showed a mortality rate of 18/70 (25.7%) when patients received carbapenems. If they received piperacillin/tazobactam 8/44 (18.2%) died if the strain was retrospectively susceptible by CLSI criteria, but 3/6 died if the strain was resistant or intermediate.

Similarly, if they received co-amoxiclav 3/40 (7.5%) died if the strain was retrospectively susceptible by CLSI criteria, but 10/27 (37%) died if the strain was resistant or intermediate to piperacillin/tazobactam.²⁶¹ Data on the genotypes of the ESBL producers present were not provided.

The findings of all these studies cannot be simply applied to the UK, where many ESBL-producing strains are more resistant than CTX-M-14, as they co-produce CTX-M-15 and OXA-1 β -lactamases, with the latter enzyme compromising susceptibility to piperacillin/tazobactam. Variable dosing further complicates the picture.

Piperacillin/tazobactam is commonly used to treat infections caused by *P. aeruginosa*. A retrospective cohort study of bacteraemic patients showed that in 34 episodes of bacteraemia caused by strains with a piperacillin/tazobactam MIC of 32 or 64 mg/L, the 30 day mortality was significantly greater than that for controls given other appropriate therapy.²⁶² At the time, CLSI defined strains as susceptible if they had an MIC of ≤ 64 mg/L whereas EUCAST, then as now, has a breakpoint for susceptibility of $\leq 16+4$ mg/L and for resistance $>16+4$ mg/L.

Evidence

Could use piperacillin/tazobactam in some bloodstream infections where ESBL producers appear susceptible *in vitro* but mortality may be higher than with carbapenems.

Evidence level: 2–

Mortality when piperacillin/tazobactam is used in bloodstream infection due to ESBL-producing Enterobacteriaceae without regard to *in vitro* susceptibility appears higher than with carbapenems.

Evidence level: 2+

In vitro susceptibilities by EUCAST and CLSI recommendations on what is a susceptible organism differ for Enterobacteriaceae but only 2-fold. There is no good analysis of the impact of this difference in relation to: (i) strain MIC; (ii) clinical outcome of infections at different sites; and (iii) different ESBL genotypes.

Evidence level: 4

Breakpoints for piperacillin/tazobactam against Enterobacteriaceae have changed with time. Better outcomes may be seen with isolates that are much more susceptible (MIC ≤ 2 mg/L) than the currently agreed piperacillin/tazobactam Enterobacteriaceae breakpoints (EUCAST S if MIC $\leq 8+4$ mg/L, R if MIC $16+4$ mg/L; CLSI S if MIC $\leq 16+4$ mg/L, R if MIC $\geq 128+4$ mg/L).

Evidence level: 3

Recommendations

- Use for infections with known ESBL-producing bacteria only if current isolates, or, if using empirically, isolates from the recent past, are fully susceptible.
Grading: Conditional recommendation for
- Consider definitive use of piperacillin/tazobactam to treat infections caused by *P. aeruginosa* if susceptible by EUCAST standards.
Grading: Conditional recommendation for

7.12 Aminoglycosides

Parenteral broad-spectrum aminoglycosides are potentially important carbapenem-sparing drugs for infections due to MDR-GNB. Three such antibiotics, gentamicin, tobramycin and amikacin,

remain available in the UK following the withdrawal of netilmicin and sisomicin. These antibiotics have intrinsic activity against all *P. aeruginosa*, *Acinetobacter* spp. and Enterobacteriaceae, but plasmid-borne resistance (and chromosomal resistance in *Providencia* spp. and *Serratia* spp.) now limits their spectrum. Resistance is mostly due to: (i) bacterial aminoglycoside-modifying enzymes, which acetylate, phosphorylate or adenylylate vulnerable hydroxyl or amino groups; or (ii) 16S ribosomal methyltransferases, which alter the binding site for aminoglycosides. The latter mechanism produces pan-resistance to aminoglycosides except the veterinary product apramycin.²⁶³ By contrast, the vulnerability of aminoglycosides to modifying enzymes varies, with amikacin inactivated by fewer enzymes than gentamicin or tobramycin.²⁶⁴ Initially aminoglycoside-modifying enzymes were restricted to certain species but integron and transposon carriage have mediated their wide dissemination.

Amikacin evades AAC(3) and AAC(2') enzymes but remains vulnerable to AAC(6')-I as does tobramycin. AAC(6')-Ib-cr arose from AAC(6')-Ib by the substitutions Trp102Arg and Asp179Tyr and can acetylate ciprofloxacin (but not levofloxacin) as well as aminoglycosides causing their deactivation. This enzyme, formerly rare in the UK,²⁶⁵ is commonly found in *E. coli* ST131. Amikacin MICs typically are raised to just below the susceptible breakpoint. Such reductions nevertheless may be important since efficacy of aminoglycosides is proportional to the ratio of peak concentration to MIC.²⁶⁶ EUCAST currently suggests that reports on isolates with this enzyme are edited to amikacin resistant but this is under review. In contrast to other common aminoglycoside-modifying enzymes, AAC(6')-I spares gentamicin. Aminoglycoside-nucleotidyl transferases (ANT-6, ANT-9, ANT-4', ANT-2'' and ANT-3'') do not confer amikacin resistance nor [except APH (3)-V1, which is mostly confined to *A. baumannii*] do aminoglycoside phosphotransferases in Gram-negative species.

Overall the resistance rate to gentamicin in community-onset *E. coli* bacteraemia in 2012–14 was 8.6%. This is a similar figure to the 8.7% resistance rate to piperacillin/tazobactam in community-onset cases. Such data must be considered when empirically treating probable Gram-negative bacteraemia of likely urinary or unknown origin.⁹⁴ In the 1980s, parenteral aminoglycoside therapy rarely selected for resistant Enterobacteriaceae in the gut flora,²⁶⁷ but oral aminoglycosides given for selective digestive decontamination in haematological malignancy frequently did so²⁶⁸ and continued to do so over a 20 year period once resistance emerged, even when combined with oral colistin.²⁶⁹

There is limited surveillance of the genotypic distribution of aminoglycoside-modifying enzymes except in specific strains and in those with other resistances (e.g. ESBL producers). Little is known of travel associations beyond those with gentamicin and tobramycin (but to a lesser extent amikacin) associated with acquisition of ESBL or carbapenemase producers, for which there are clear links with travel.²⁷⁰

Aminoglycoside activity against *P. aeruginosa* varies between patients with cystic fibrosis, where aminoglycosides continue to be heavily used, and patients with other comorbidities. Resistance due to efflux pumps and permeability defects is common, as well as aminoglycoside-modifying enzymes. Tobramycin, which has greater intrinsic activity than gentamicin against this species (offsetting its lower activity against Enterobacteriaceae) and which causes less toxicity than gentamicin, continues to be the

aminoglycoside most likely to remain active. A recent meta-analysis continues to suggest that use of β -lactam/aminoglycoside combinations in the absence of cystic fibrosis offers no statistically significant advantage in terms of outcome compared with use of an active β -lactam alone.²⁷¹

A new aminoglycoside, plazomicin (ACHN 490, Achaeogen),^{272,273,274} has completed clinical trials. This evades modification by almost all aminoglycoside-modifying enzymes except the AAC(2') chromosomal enzymes of *Providencia* spp. It is, however, compromised by the plasmid-mediated ArmA and Rmt 16S ribosomal methyltransferases, which are currently rare in UK MDR GNB except in Enterobacteriaceae strains producing NDM-1 carbapenemase²⁶³ or OXA-23 carbapenemase-producing *A. baumannii*, which have spread globally over the last 10 years.

Aminoglycosides have a narrow margin between being effective and toxic to the auditory and vestibular apparatus or to the kidneys. They fell from favour as broader-spectrum β -lactams were developed. For acceptably safe use, intervals between doses are increased, usually to a minimum of once daily, but with doses related to renal clearance and MIC and the presumption of a post-antibiotic effect. If the dosage is based on the patient's weight it is possible, using a nomogram, to model the likely blood concentration at varying intervals after the dose. Measuring plasma levels between 6 and 14 h after the dose, usually now by immunoassay, and relating these levels to the nomogram permits more precise dosing intervals than those determined by measuring renal function. Nomograms for gentamicin and tobramycin at doses of 7 mg/kg²⁷⁵ and 5 mg/kg²⁷⁶ in adults have been constructed and their use is associated with a low incidence of detected ototoxicity (3/2184 cases in the former). The dosage recommendation for amikacin is 15 mg/kg/day, reflecting that amikacin MICs are 2- to 4-fold higher than gentamicin MICs for susceptible strains. Much higher incidences of toxicity with all aminoglycosides are well recorded and it is still common to encounter in the UK deficiencies in: (i) weight-related dosage; (ii) dosage interval, especially if there is renal impairment; (iii) measuring levels in every case; and (iv) taking blood for assay at the correct interval after dosing and recording both the time of administration and time of sample collection to enable later interpretation of assay results by other staff. Validation of expected and achieved serum levels has been undertaken for the 7 mg/kg dose but not for the 5 mg/kg dose, which is based on exclusion of some patients considered in the former study. There is no validated nomogram for amikacin²⁷⁷ and immunoassays for this antibiotic are not widely available on automated immunoassay platforms. There are no trial data on amikacin use in *E. coli* ST131. Vestibular toxicity with all aminoglycosides commonly presents after the drug has been stopped and the patient has left hospital.^{278,279} Toxicity can occur after normal courses of five daily doses or even a single dose.²⁷⁸ Auditory toxicity is initially often subclinical, requiring audiograms to detect it. The true incidence of toxicity is difficult to determine. Renal toxicity can be measured by quantitative renal function tests or qualitative urinary renal tubular enzymes. These critical steps to safe use, as determined by case follow-up after the patient has left hospital, have not yet been assessed for plazomicin, although there are no described cases of toxicity yet in clinical trials. In older studies before the adoption of once-daily regimens and weight-related dosage, auditory toxicity appears to have been commoner with amikacin than gentamicin, whilst vestibular toxicity rates were not

significantly different;²⁸⁰ toxicity was commoner with increasing age, paralleling a decline in renal function.²⁸¹ This creates an issue, insofar as infections with MDR GNB and ESBL producers occur more frequently among those aged over 65 years and especially over 75 years. It is noteworthy that one recent Scottish national intervention in surgery as part of targeted antimicrobial stewardship measures to reduce the incidence of *C. difficile* by 30% in 2 years was to substitute use of gentamicin for cephalosporins in prophylaxis in surgery. In Tayside, an interrupted time series with segmented regression in 7666 patients undergoing orthopaedic surgery (excluding fractured neck of femur), where two doses of flucloxacillin 1 g and one dose of 4 mg/kg gentamicin were substituted for cefuroxime was performed. An unacceptable 94% increase in acute kidney injury in gentamicin-treated patients occurred and the gentamicin use was stopped.²⁸² Patients undergoing implant surgery had a mean age of 71 years and 36% had received non-steroidal anti-inflammatory drugs in the last year and 38% received a diuretic, which are known cofactors for gentamicin nephrotoxicity, but this was adjusted for in the study. One-year mortality was higher in the acute kidney injury group (20.8% versus 8.2%). There was no association of acute kidney injury in a further 4816 patients in other surgical specialties where gentamicin was substituted. It is not certain whether the effect was due to gentamicin, flucloxacillin, or the combination, or whether all patients additionally received gentamicin bone cement.

Evidence

Aminoglycosides retain activity against a similar proportion of Enterobacteriaceae to piperacillin/tazobactam (8.6%–8.7%). However, approximately 50% of ESBL-producing *E. coli* in the UK are resistant to gentamicin and more to tobramycin.

Evidence level: 3

Overall resistance rates to amikacin are lower than to gentamicin and tobramycin in the UK. However, bacteria producing AAC(6') are usually amikacin resistant and bacteria producing the AAC(6')-Ib-cr enzymes, including many *E. coli* ST131, often have reduced amikacin susceptibility. Strains producing NDM carbapenemase often carry 16S ribosomal methyltransferases that confer high-level pan-resistance to aminoglycosides, including amikacin and plazomicin. 16S ribosomal methyltransferases are also frequent in UK *A. baumannii*.

Evidence level: 3

Plazomicin, a new aminoglycoside, evades almost all aminoglycoside-modifying enzymes but is inactive if 16S ribosomal methyltransferases are present. It has recently completed a Phase 3 RCT with superiority to meropenem in complicated UTI, so far reported only in a press release.

Evidence level: 3

Historically, parenteral aminoglycosides rarely proved selective for resistance among Enterobacteriaceae in the faecal flora. However, because of resistance linkage and carriage on transposons and integrons, aminoglycoside resistance may be selected by use of other antibiotics.

Evidence level: 3

Evidence from travel-associated ESBL producers suggests that aminoglycoside resistance may also be travel associated. The co-carriage of 16S ribosomal methyltransferases by strains with NDM carbapenemase linked to the Indian subcontinent is noteworthy.

Evidence level: 3

The narrow therapeutic index of aminoglycosides demands attention to the detail of weight-related dosing and frequency of doses, collection of blood at an appropriate time for assays, and the careful interpretation of antibiotic assays by nomograms. These actions are essential for adequately safe management of patients treated with gentamicin and tobramycin. Similar modern safety measures are likely to be necessary for amikacin and plazomicin but nomograms are not, and assays may not be widely available.

Evidence level: 4

When strains are susceptible and safety measures are well organized and reviewed in hospitals, gentamicin and tobramycin are useful carbapenem-sparing agents for definitive treatment.

Evidence level: 4

Recommendations

- Could use gentamicin empirically in the UK if the likelihood of MDR GNB is low.
Grading: Conditional recommendation for
- Could use gentamicin as a carbapenem-sparing agent for urinary, intra-abdominal and bacteraemic infections due to ESBL-producing *E. coli* when susceptibility is confirmed but do not use empirically if the risk of MDR GNB is raised.
Grading: Conditional recommendation for
- Could use gentamicin in combinations for urinary, intra-abdominal and bacteraemic infections due to gentamicin-susceptible KPC-producing *Klebsiella* spp. if strain is resistant to colistin and meropenem (see Section 7.18).
Grading: Conditional recommendation for
- Use once-daily dosing of gentamicin if no renal impairment, followed by measurement of levels 6–14 h post-dose and adjust repeat dosage by reference to the appropriate 7 or 5 mg/kg nomogram. Consider increased risks of toxicity if there is co-administration of nephrotoxic or ototoxic drugs.
Grading: Strong recommendation for
- Avoid tobramycin for MDR Enterobacteriaceae because of risk of resistance due to AAC(6')-I and AAC(6')-Ib-cr.
Grading: Conditional recommendation against use
- Use tobramycin in preference to other aminoglycosides for susceptible *Pseudomonas* infection.
Grading: Conditional recommendation for
- Use once-daily dosing of tobramycin if no renal impairment, followed by measurement of levels 6–14 h post-dose and adjust repeat dosage by reference to nomogram.
Grading: Strong recommendation for
- Modernize use of amikacin, which has improved activity, with development of validated nomograms. Ensure assays are readily available before repeat doses and consider, because of the risks of toxicity, the practicality of monitoring with audiograms.
Grading: Conditional recommendation for

7.13 Polymyxins

The polymyxins are a group of five chemically different bactericidal antibiotics (polymyxins A to E). Only polymyxin B and polymyxin E (colistin) have been used in clinical practice. Intravenously administered colistin methane sulfonate is most widely used, and requires conversion in the body to the active colistin molecule.

Polymyxins have a wide spectrum of activity against Gram-negative organisms, including most Enterobacteriaceae, *A. baumannii*, *P. aeruginosa* and *Stenotrophomonas maltophilia*, but are inactive against *B. cepacia*, *Proteus* spp., *Providencia* spp., *Morganella* spp. and *Serratia marcescens*. Resistance to colistin occurs in some *P. aeruginosa* isolates²⁸³ but remains rare and almost exclusive to cystic fibrosis isolates. Acquired colistin resistance is generally rare but has become common in *K. pneumoniae* in Italy. Colistin heteroresistance is defined as the emergence of resistance to colistin in a subpopulation of an otherwise susceptible (MIC of ≤ 2 mg/L) population.²⁸⁴ This may be related to exposure to suboptimal polymyxin concentrations. Detection of resistance or heteroresistance is difficult,⁵⁰⁶ and is reviewed elsewhere.⁵⁰⁷

Etest[®], disc diffusion, Microscan[®]²⁸⁵ and VITEK2[®] detection methods are currently unreliable,²⁸⁶ and data for Phoenix[®] are only published for *A. baumannii*. A comparison of broth microdilution (BMD) was made with VITEK2[®], Sensititre[™] and Etest[®] using a collection of 76 Enterobacteriaceae, including 21 MCR-1-positive strains.⁵⁰⁸ Both Etest[®] and VITEK2[®] performed poorly against BMD with very major error (VME) rates of 12% (Etest[®]) and 36% (VITEK2[®]) for colistin.⁵⁰⁸ Poor performance of both Phoenix[®] and VITEK2[®] with substantial under-reporting of resistance has been reported when using these systems for testing *Acinetobacter baumannii*.⁵⁰⁹

The difficulty of detecting colistin resistance in routine laboratories was evident in a recent US study.²⁸⁷ Resistance to gentamicin was rarer and tigecycline resistance commoner in colistin-resistant isolates. Colistin resistance was associated with increased hospital mortality. Most colistin resistance is chromosomally mediated, involving various mutations that modulate two-component regulatory systems (e.g. *pmrAB*, *phoPQ* and its negative regulator *mgrB* in the case of *K. pneumoniae*), leading to modification of lipid A with moieties such as phosphoethanolamine or 4-amino-4-arabinose, or in rare instances to total loss of the lipopolysaccharide.²⁸⁸ Of concern is the recent reporting of plasmid-mediated polymyxin resistance lipid A-modifying enzymes (MCR-1 and -2) that confer resistance in Enterobacteriaceae.²⁴ MCR-1 was first found in China but is now being detected worldwide, mainly in Enterobacteriaceae of animal origin but also in occasional human isolates. It remains much rarer than mutational resistance. China plans to stop use of 8000 tons of colistin in animal feed from April 2017. A recent study shows *mcr-1* genes are very widespread (50%–100%) in chicken in hatcheries, commercial farms and supermarkets and a slaughterhouse in Shandong. Although testing of hatcheries was negative, NDM carbapenemase-producing *E. coli* were recovered from 21.8% of samples; 23% of carbapenem-resistant *E. coli* tested MCR-1 positive and multiple sequence types and NDM subtypes were found.²⁸⁹ There are widespread reports of MCR-1 in the European (including UK) food chain.⁵¹⁰

Synergy studies suggested many years ago^{290–294} that polymyxins, trimethoprim and sulphonamides might be useful together in therapy, and these studies need repeating with other agents and newer strains.

Pharmacokinetic and pharmacodynamic data have been limited, particularly in critically ill patients. Polymyxins were developed before the advent of contemporary drug evaluation. Colistin methanesulfonate is an inactive prodrug converted *in vivo* to the active

drug and different brands may produce different concentrations of active drug. Data suggested drug concentrations are very variable and dosing in excess of data-sheet recommendations may be required commonly on the basis of pharmacokinetic parameters.²⁹⁵ Recently the FDA and EMA have made new, but different, recommendations for intravenous colistin in patients with various degrees of renal function. These have been assessed using data from 162 adult critically ill patients with varying renal function. A comparison showed that adequate serum levels with impaired renal function were more likely to be attained with European guidelines and a later paper suggests that in the critically ill target concentrations are difficult to achieve if creatinine clearance is ≥ 80 mL/min/1.73 m².^{296,297} Data are also now available on the implications of haemodialysis.²⁹⁸ Therapeutic drug monitoring is advisable, if available, and depends critically on maintaining stability of the drug in separated plasma.

Colistin can be given intravenously, or in respiratory infection via the aerosol route (typically in patients with cystic fibrosis, either alone or combined with intravenous administration), or intrathecally.

Polymyxin B or colistin sulphate can be given orally as a non-absorbed major component of selective digestive decontamination regimens. Selective digestive decontamination has been widely used for general infection prevention in neutropenia and intensive care. Polymyxins given orally were widely added in haematology to aminoglycosides, trimethoprim/sulfamethoxazole²⁹⁹ or ciprofloxacin²⁶⁹ to prevent emergence of resistance and in ICUs to parenteral cephalosporins and oral tobramycin.³⁰⁰ Recent findings that colistin resistance is difficult to detect accurately and that its frequency is usually underestimated, the clear emergence in China and elsewhere of plasmid-mediated resistance and the emergence of colistin resistance in KPC-producing *Klebsiella* spp. in Italy, China and the USA imply that it can no longer be relied on to prevent emergence of resistant strains in patients who have strains that are already frequently resistant to the drugs to which it was added for protection. Use of colistin in all patients in such a unit might well now become a mechanism for selection for XDR GNB or indeed pan-drug resistant MDR GNB in the critical care and haematology units where it is used. This is an enduringly controversial area³⁰¹ which we do not have space to fully review, but such selection of colistin resistance in ESBL-producing *Klebsiella* spp. in an ICU has already been reported.³⁰² We consider that continued use of colistin-containing decontamination regimens should be reviewed urgently within specialties³⁰³ and at the local level, and in our judgement its use is now unwise.

Clinical reports and reviews of experience with colistin are relatively encouraging, with side effects (principally nephrotoxicity and neurotoxicity) observed less often than expected from historical data.^{304–309} These studies are summarized in Table 6. In Italy strict rules for the use of colistin are advocated to stop the spread of colistin-resistant KPC-producing *Klebsiella* spp., which have increased 3-fold in 4 years among bacteraemic patients. A case-control study of this guidance showed associations of resistance with previous colistin therapy, previous colonization or infection with KPC-producing *Klebsiella* spp., and a Charlson comorbidity score >3 (all of which were associated with mortality) and also with neutropenia and more than three hospitalizations.³¹⁰

The addition of aerosolized to intravenous colistin has been compared with intravenous colistin alone for the treatment of

Table 6. Studies of the efficacy of colistin

Study	No. of patients	Conditions treated	Pathogens	Duration (mean)	Outcome
Levin et al. 1999 ³⁰⁵	59	VAP 33%; UTI 20%; BSI 15%; CNS 8%	<i>A. baumannii</i> 65%; <i>P. aeruginosa</i> 35%	12 days	58% success overall. Worst in pneumonia group (25%)
Garnacho-Montero et al. 2003 ³⁰⁴	21	VAP 100%	<i>A. baumannii</i> 100%	14 days	57% success
Linden et al. 2003 ³⁰⁶	23	VAP 78%; BSI 35%; intra-abdominal 26%	<i>P. aeruginosa</i> 100%	17 days	61% favourable
Markou et al. 2003 ³⁰⁷	24	VAP 63%; catheter related 12%; meningitis 4%	<i>A. baumannii</i> 24%; <i>P. aeruginosa</i> 76%	13.5 days	73% success
Michalopoulos et al. 2005 ³⁰⁸	43	VAP 73%; BSI 33%	<i>A. baumannii</i> 19%; <i>P. aeruginosa</i> 81%	18.6 days	69% clinical cure
Reina et al. 2005 ³⁰⁹	55	VAP 53%; UTI 18%; BSI 16%	<i>A. baumannii</i> 65%; <i>P. aeruginosa</i> 35%	13 days	15% cure on day 6 of treatment
Koomanachai et al. 2007 ⁵⁰⁵	78	VAP 58%; BSI 10%	<i>A. baumannii</i> 91%; <i>P. aeruginosa</i> 9%	12 days	81% clinical response

BSI, bloodstream infection; VAP, ventilator-associated pneumonia.

ventilator-associated pneumonia in several studies. Korbila and colleagues³¹¹ demonstrated an improvement in outcome with the addition of aerosolized colistin but no benefit was demonstrated in another study.³¹² Both had methodological flaws. NICE has recently reviewed the usefulness of aerosolized colistin or tobramycin dry powders in patients with cystic fibrosis and concluded there were some patients who would benefit from colistin dry powder and there would be cost reduction.³¹³

Polymyxin B is more toxic than colistin (polymyxin E) but has the advantage of not requiring subject-variable conversion to an active form. A recent retrospective cohort study compared 45 patients with *P. aeruginosa* bacteraemia treated with polymyxin B at a median dose of 141±54 mg/day usually in two divided doses: 11 received >200 mg/day. Eighty-eight patients were treated with a comparator (typically a β -lactam). The in-hospital mortality was 66% in the arm treated with polymyxin B versus 28% for those treated with a comparator, even when matched for mechanical ventilation and sepsis score, suggesting polymyxin B was inferior.³¹⁴ This was regardless of dosing regimens. A higher dose (≥ 200 mg/day) of polymyxin B was found to be associated with reduced mortality but increased renal impairment in another retrospective cohort study.³¹⁵ We do not recommend use of polymyxin B in the light of these results.

Combinations including colistin are more effective than monotherapy in treating infections with *K. pneumoniae* carbapenemase (KPC)-producing organisms (see Section 7.18).^{316,317}

Nephrotoxicity and neurotoxicity are the principal side effects associated with parenteral administration of polymyxins. The toxicity demonstrated in earlier studies was almost certainly related to lack of understanding of the drug's pharmacokinetics/pharmacodynamics (PK/PD) and the use of inappropriate doses.³¹⁸ Studies now suggest that age, high doses, prolonged courses, concomitant vancomycin, hypoalbuminaemia and non-steroidal anti-inflammatory drugs, are independent risk factors for nephrotoxicity^{319,320} and it is likely that other nephrotoxic drugs are also associated. Monitoring renal function closely is essential for

patients receiving colistin. Recent expert opinion suggests the risk-benefit ratio should be carefully considered, with strategies applied to reduce toxicity.³²¹ There is no information on the relationship of dose with reversible neurotoxicity or encephalopathy; in a recent large paediatric series they occurred in 2% of patients.³²²

There are gaps in our knowledge about these agents. Although they were developed some 70 years ago they have only recently been used extensively. Much of the current knowledge is summarized in the Prato consensus report.³²³

Dosing of intravenous colistin remains contentious. In adult cystic fibrosis patients, colistin is typically given at a standard dose of 2 MU q8h. However, evidence is emerging that higher-dose regimens may be more appropriate in the ICU setting (with therapeutic drug monitoring: to target a peak of 5–15 mg/L and a trough of 2–6 mg/L). A recent study of significant infections caused by a range of MDR GNB suggested that a loading dose of 9 MU followed by 4.5 MU q12h (reduced in renal impairment) was effective (23/28 responses) and resulted in a reversible mild renal injury in only five patients.³²⁴ Further clinical and PK/PD studies are required to confirm appropriate regimens, including in relation to a loading dose, combination therapy and the need for monitoring. In the meantime EMA guidance should be followed.

Evidence

Colistin is effective in treatment of infections caused by MDR GNB with low mortality at higher-than-previous, but well-controlled dosage.

Evidence level: 3

The role of loading doses of colistin, monitoring of serum levels and optimal combination therapy are inadequately researched.

Evidence level: 4

Use of aerosolized colistin dry powder has recently been accepted by NICE in cystic fibrosis.

Evidence level: 3

Use of aerosolized colistin dry powder in ventilator-associated pneumonia as an addition to intravenous chemotherapy appears useful.

Evidence level: 3

The dose relationship of colistin nephrotoxicity and the rarer neurotoxicity and encephalopathy require investigation.

Evidence level: 4

Recommendations

- Reserve intravenous polymyxins for infections due to susceptible multiresistant strains and preferably use them in combination with other agents.
Grading: Conditional recommendation for
- Give careful consideration to use of higher dosage regimens in critically ill patients.
Grading: Conditional recommendation for
- Closely monitor renal function, especially in the elderly, those receiving high intravenous doses for prolonged periods and those on concomitant nephrotoxic agents, e.g. aminoglycosides.
Grading: Strong recommendation for
- Reconsider use of polymyxins in selective digestive decontamination regimens as these agents are now important last therapeutic options against CPE and are more threatened by resistance than previously appreciated.
Grading: Good practice point
- Need research on optimal rapid and practical methods of susceptibility testing outside intrinsically resistant groups such as *Proteaceae* and *Serratia* spp.
Grading: Recommendations for research
- Aerosolized colistin dry powder should be used in cystic fibrosis according to NICE guidelines. Use in combination in ventilator-associated pneumonia may be considered pending further trials without methodological flaws.
Grading: Conditional recommendation for

7.14 Fluoroquinolones

Fluoroquinolones suppress susceptible Enterobacteriaceae in the intestinal flora and also select for quinolone-resistant MDR GNB.^{250,131} Such suppression has been used in neutropenic patients alone or with colistin.²⁶⁹ The continued efficacy of this combination in suppression and non-selection of resistance to either agent needs re-establishing, with the increasing recognition of colistin resistance that may well emerge alongside existing quinolone resistance. Prophylaxis with quinolones alone in neutropenia against susceptible bacteraemia seems effective even when quinolone resistance levels in the treated population reach a high level. Trials of withdrawing prophylaxis have been reported and show problematic increases in Gram-negative bacteraemia (see Section 6.5).

Fluoroquinolones (intravenous and oral) may be suitable for complicated UTIs due to ESBL-producing Enterobacteriaceae if there is no resistance *in vitro*; however, most ESBL-producing strains in the UK are resistant to fluoroquinolones, including ciprofloxacin and levofloxacin. Furthermore, quinolone resistance without ESBL production is now frequent, particularly in the multiply resistant if not MDR *E. coli* ST131.⁸⁹ Newer quinolones in development are unlikely to provide substantial additional benefits over ciprofloxacin for infections due to Gram-negative pathogens.

Three observational clinical studies have assessed the relative merits of quinolones and carbapenems for serious infections due to ESBL-producing organisms.^{181,325,326} Two of these found that carbapenems were superior to quinolones, although most strains were quinolone susceptible, whereas one study found equivalent effectiveness.

Fluoroquinolones have been used to treat infections caused by *S. maltophilia*; however, resistance is not uncommon, so combination with one or more of trimethoprim/sulfamethoxazole, ceftazidime or tigecycline has been proposed.³²⁷ These combinations have not been shown to offer any advantages over trimethoprim/sulfamethoxazole alone.

A wide range of resistance mechanisms exist; high-level resistance almost always involves mutations in the genes encoding subunits of the target enzymes, DNA gyrase and topoisomerase IV (*gyrA* and *parC* respectively), but reduced susceptibility can arise from plasmid-acquired genes e.g. *aac(6')-Ib-cr*, *oqxAB*, *qnrA*, etc. or via up-regulation of outer-membrane efflux pumps and porin loss.³²⁸

Evidence

Quinolones are effective in treatment of complicated UTI caused by susceptible ESBL-producing Gram-negative bacteria, but resistance is common and limits their usefulness.

Evidence level: 2+

Recommendations

- Could use orally to treat UTI caused by MDR GNB that are susceptible.
Grading: Conditional recommendation for

7.15 Tigecycline and eravacycline

Tigecycline is a semisynthetic glycylglycine derivative of minocycline and like other tetracyclines is bacteriostatic.³²⁹ The main determinant of acquired plasmid-mediated resistance to older tetracyclines in Gram-negative bacteria, namely active efflux by Tet pumps, is overcome by steric hindrance by a large substituent group. Tigecycline has *in vitro* activity against most Enterobacteriaceae except *Proteaceae*, i.e. *Proteus* spp., *Providencia* spp. and *M. morganii*. MICs for *A. baumannii* (including many carbapenem-resistant strains) and *S. maltophilia* are low (mostly 0.25–2 mg/L) but there are no breakpoints or convincing efficacy studies. In common with other tetracyclines, tigecycline lacks useful activity against *P. aeruginosa*. Tigecycline is vulnerable to the chromosomal resistance–modulation–cell division (RND) multidrug efflux pumps, including MexXY–OprM of *P. aeruginosa*, and the AcrAB pump found in *Proteus mirabilis*, which explains the intrinsic resistance of these species.^{330,331}

Whilst tigecycline-resistant isolates of Enterobacteriaceae have been described from treatment-naïve patients, another potential problem is the development of resistance during treatment of infections with Enterobacteriaceae and *Acinetobacter* spp. by the mutational up-regulation of RND pumps, but the frequency is unclear, particularly when used in combination.^{332–336} Use of tigecycline is an independent predictor of emergence of tigecycline resistance when treating multiresistant *K. pneumoniae* infection.³³⁷ Further studies are required, possibly including

different dosing regimens and in combination with other agents. Tigecycline has a potential to favour superinfections by *P. aeruginosa*, Proteaceae³³⁸ and sometimes *Klebsiella* spp.;^{337,339} again, these aspects require further investigation.

Subject to the earlier caveat about the lack of breakpoints, tigecycline has *in vitro* activity against *S. maltophilia*, and susceptibility rates of >87% have been reported.³⁴⁰ However, there is little clinical experience with the drug in treating infections caused by this organism.

Intravenous tigecycline is licensed for the treatment of complicated skin and soft tissue infections and complicated intra-abdominal infections.^{341,342} However, the US FDA issued a warning describing an increased mortality risk with its use when compared with other drugs.^{343,344} The highest risk was in patients treated for ventilator-associated pneumonia, which was not a licensed indication. However even in FDA-approved uses there was a higher risk of death among patients given tigecycline compared with those given other antibacterial drugs.^{345,346} There are no RCTs comparing tigecycline with polymyxins, fosfomycin, sulbactam and other antibiotics against infections due to MDR GNB, alone or in combinations.³⁴⁷ Several meta-analyses examine the efficacy and safety of tigecycline in general (not just against MDR GNB) and these reported conflicting findings. One very recent analysis reviews the earlier studies and includes a number of new trials. Clinical success rates were lower than comparator for hospital-acquired pneumonia and diabetic foot infection, with increased gastrointestinal adverse events and higher all-cause mortality, probably due to reduced efficacy.³⁴⁸

Further work on tigecycline is needed, as its efficacy in ventilator-associated pneumonia might be improved using higher doses (i.e. 200 mg initially and then 100 mg twice daily); an increase in adverse events was not seen with this regimen.³⁴⁹ Tigecycline in combination with other antibiotics (e.g. carbapenems and polymyxins) is a potentially valuable approach for infections caused by carbapenemase-producing *Klebsiella* spp., as shown by Tumbarello et al.³⁵⁰ In this retrospective cohort study, largely of infections due to strains with KPC-3 carbapenemase, 9/19 patients survived on tigecycline monotherapy, 0/11 on colistin monotherapy and 16/23 with tigecycline and colistin combinations. Two comparisons of monotherapy and combination therapy for infections with carbapenemase-producing *Klebsiella* spp. give further survival data on monotherapy: survival in one study was 71/116 for tigecycline and 70/132 for colistin³¹⁶ and in the other study 16/27 for tigecycline and 12/22 for colistin.³⁵¹

Whilst the *in vitro* data support use of tigecycline in respiratory infection, there is poor correlation between the laboratory results and clinical outcome.^{334,352,353}

Eravacycline is a novel intravenous fluorocycline with a similar spectrum to tigecycline. It showed non-inferiority to ertapenem in a Phase 3 trial of complicated intra-abdominal infection but failed to show non-inferiority to levofloxacin in an intravenous/oral switch Phase 3 trial of complicated UTI.^{354–356}

Evidence

The role of tigecycline remains uncertain in the treatment of infections due to MDR GNB.

Evidence level: 1 –

Recommendations

- Could use tigecycline in combination in the treatment of multi-resistant soft tissue and intra-abdominal infections.
Grading: Conditional recommendation for
- Use alone in hospital-acquired respiratory infections is unlicensed and not advised with licensed dosing, as outcomes are not clearly satisfactory in *Acinetobacter* and MDR GNB infections.
Grading: Conditional recommendation against
- Use in combinations in hospital-acquired respiratory infections; precise combinations depend on the antibiotic susceptibility of the MDR GNB causing the infection.
Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials
- Use higher than licensed dosing, such as 100 mg twice daily, for infections due to MDR GNB in critical care.
Grading: Conditional recommendation for
- Investigate whether higher dosing counters the unexpectedly high mortality seen even in infections due to strains apparently susceptible *in vitro*.
Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials

7.16 Fosfomycin

Fosfomycin, a strongly hydrophilic phosphonic acid (unrelated to aminoglycoside or macrolide antibiotics), inhibits the addition of phosphoenol-pyruvate to *N*-acetyl-glucosamine in synthesis of the bacterial cell wall. Fosfomycin MICs for *E. coli* vary from 1 to 4 mg/L; those for *Klebsiella* spp. are higher at 2–64 mg/L. EUCAST breakpoints for both intravenous and oral formulations are $S \leq 32$ mg/L, $R > 32$ mg/L, available for *E. coli* only. *M. morganii* and *Bacteroides* spp. are inherently resistant and activity against *P. aeruginosa* is controversial, particularly in combination. The drug is otherwise very broad in its spectrum. Fosfomycin was active against 72% of Enterobacteriaceae resistant to carbapenems in a German study.³⁵⁷ *In vitro* testing with discs required the addition of glucose-6-phosphate to the disc. In this study there were 22% major discrepancies between agar dilution in medium containing glucose-6-phosphate and disc or Etest testing and it is not clear if glucose-6-phosphate was present in discs and MIC gradient strips, an area for quality control development. There are similarly no published details on the reliability of automated susceptibility testing methods.

Fosfomycin trometamol is used as an oral treatment for patients with uncomplicated lower UTI due to fosfomycin-susceptible organisms resistant to first-line agents. At the conventional dosage of 3 g on a single occasion, this oral formulation gives an adequate urinary concentration for 2 days (see Section 9.3). An earlier oral product was a calcium salt, only 30%–40% of which was absorbed: this gave peak plasma levels of 7–9 mg/L 4 h after a 3 g dose. The trometamol salt that replaced this is better absorbed (60% bioavailable), reaching peak plasma levels of 32 mg/L 2 h after a 3 g dose).

Experience with intravenous fosfomycin disodium (not a trometamol formulation) is limited in the UK, where it has only recently been introduced, specifically for treatment of infection with multi-resistant bacteria. It has been more widely used elsewhere in Europe. The intravenous sodium salt reaches levels of 25 mg/L

after a 1 g dose. A very early single open comparison of 38 patients with acute pyelonephritis showed that 7 days of intravenous fosfomycin 2 g q6h achieved only a 44% response rate;³⁵⁸ the authors therefore concluded the drug had no role in pyelonephritis; the oral trometamol salt has never been examined for pyelonephritis. Intravenous dosage with MDR GNB is now usually at 24 g/day in three divided doses but dosage reduction is needed in renal impairment as the drug is exclusively renally excreted, unchanged. The formulation has a high sodium load and the most frequently encountered side effect is hypokalaemia (26% patients).³⁵⁹ Fosfomycin exhibits excellent penetration into tissue after an intravenous dose as it is a small (138 Da) molecule with negligible protein binding; it also has a long serum half-life of 4–8 h.³⁶⁰

A prospective salvage study of 11 ICU patients with serious infections caused by carbapenem-resistant *K. pneumoniae* reported an all-cause mortality of 2/11, although analysis of the claimed successes is complicated because six patients were also treated with colistin and three with gentamicin.³⁶¹ A larger outcome study of 48 patients (mainly with ventilator-associated pneumonia) infected with KPC-producing *K. pneumoniae* and to a lesser extent VIM-producing *P. aeruginosa* reported clinical success when fosfomycin was used mainly in combination with colistin or tigecycline in 54.2% patients and 28 day all-cause mortality of 37.5%.³⁶² Of 15 patients with colistin-, tigecycline-, aminoglycoside- and carbapenem-resistant KPC-producing *Klebsiella* infection (one with an additional carbapenem-resistant *P. aeruginosa*), 9 responded to fosfomycin combinations and in 8 microbiological eradication was achieved.

The use of intravenous fosfomycin has been reviewed extensively. Clinical cure was described in 1242/1529 patients (81.2%) overall (for both Gram-positive and Gram-negative pathogens).³⁶³ Most of the Gram-negative infections in this series were due to *P. aeruginosa* (which most would regard as resistant), but also included infections due to *Enterobacter* spp., *Klebsiella* spp., *E. coli*, *Proteus* spp. and *Salmonella typhi*. Most patients also received concomitant antibiotics, so again interpretation is difficult. A wide variety of infections was treated and fosfomycin was well tolerated. Despite *in vitro* resistance to fosfomycin, most patients with infections caused by *P. aeruginosa* improved, although this may reflect concomitant antibiotics.

Further detailed studies of the parenteral form used alone in single indications (such as UTI and ventilator-associated pneumonia) are required to establish its relative efficacy and usefulness for specific MDR GNB. Similarly, in combination therapy comparisons of specific combinations are required.

Evidence

Further details and regimens for the oral formulation are given in Section 9.3.

The parenteral formulation may be a valuable treatment alternative for infections due to MDR GNB including carbapenemase- and MBL-producing strains. However, further detailed comparative trial experience is necessary to determine its optimal use.

Evidence level: 3

Recommendations

- Consider parenteral fosfomycin, probably in combination, as part of salvage treatment for susceptible MDR GNB: clear

indications for use are not yet established.

Grading: Conditional recommendation for

- Need comparative clinical trials to establish optimal indications for, and optimal use of, parenteral fosfomycin, a potential drug of last resort against MDR GNB.

Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials

7.17 Trimethoprim/sulfamethoxazole

Trimethoprim/sulfamethoxazole (available as intravenous and oral formulations) has *in vitro* activity against *S. maltophilia*³⁴⁰ and some less-frequently encountered non-fermenting Gram-negative bacilli (e.g. *Achromobacter* spp., *Alcaligenes* spp., *Burkholderia* spp., *Chryseobacterium* spp. and *Elizabethkingia* spp.).³⁶⁴ These species have inherent resistance to most other antibiotics and often produce MBLs. *Stenotrophomonas* spp. typically have similar percentage susceptibility at the CLSI breakpoint to sulphonamides alone and trimethoprim/sulfamethoxazole but are resistant to trimethoprim alone. The combination has greater *in vitro* potency than either trimethoprim or sulfamethoxazole. A similar comment applies to *Achromobacter* spp. and with few exceptions to *Alcaligenes* spp., *Chryseobacterium* spp. and *Elizabethkingia* spp.³⁶⁴ These genera are susceptible to trimethoprim and more strains of these genera and *Burkholderia* spp. are susceptible to trimethoprim/sulfamethoxazole than either component alone.³⁶⁴ The clinical use of sulphonamides alone against non-fermenters has not been explored and the combination of trimethoprim/sulfamethoxazole is usually used in *S. maltophilia* infections and, for simplicity, against those due to these other unusual species. Problems occur with disc susceptibility testing of *S. maltophilia* and there are few data on the performance of automated susceptibility systems. Trailing endpoints are frequent and results vary with the temperature of incubation and the susceptibility testing medium used. Occasional resistance to trimethoprim/sulfamethoxazole is not well understood in these non-fermenters but resistance to trimethoprim/sulfamethoxazole caused via the *sulI* gene has been described repeatedly in *S. maltophilia*.³⁶⁵ A recent systematic review suggested that some strains of *Acinetobacter* spp. are susceptible to trimethoprim/sulfamethoxazole and that use against this genus can be guided by *in vitro* testing.³⁶⁶ However, over half the UK strains of *A. baumannii* show high-level resistance.³⁶⁴

Evidence

Trimethoprim/sulfamethoxazole has wide *in vitro* activity against *S. maltophilia*, *Achromobacter* spp., *Alcaligenes* spp., *Burkholderia* spp., *Chryseobacterium* spp. and *Elizabethkingia* spp. Susceptibility testing methods for these organisms are not well established but some *S. maltophilia* have resistance to trimethoprim and sulfamethoxazole. Carbapenem resistance is inherent to most of these species.

Evidence level: 3

Recommendations

- Use in treatment of infections due to susceptible *S. maltophilia* and consider in infections due to *Achromobacter* spp., *Alcaligenes* spp., *Burkholderia* spp., *Chryseobacterium* spp. and

Elizabethkingia spp.

Grading: Conditional recommendation for

7.18 Intravenous combination therapy for infections due to carbapenemase producers

Although results of RCTs will become available, most of the current evidence for the advantage of combination therapy for carbapenem-resistant infections derives from observational studies and reports mainly focus on severely ill patients or those where the pathogen has reduced susceptibility to colistin.³⁶⁷ An international working group report recommended combinations including a carbapenem as optimal treatment but only in settings where NDM carbapenemases are infrequent.³⁶⁸ However, retrospective studies are liable to bias in that investigators have no control over antibiotic use.

Different studies and reviews of combination therapy have reached contradictory conclusions. One systematic review identified that evidence for combination treatment was poor quality and inherently biased, being based on small observational studies with heterogeneity of: (i) antibiotic choice and activity against responsible pathogens; (ii) antibiotic dosage; and (iii) severity of illness.³⁶⁹ These authors concluded that any benefit in outcome between monotherapy with colistin and combination of colistin with other agents (aminoglycoside, tigecycline, carbapenem or rifampicin) was uncertain. There were methodological problems in the studies reviewed. Another systematic review³⁷⁰ which lacked quality assessments likewise found only observational studies with marked heterogeneity, and suggested no proven benefit in terms of mortality between combination treatment and monotherapy except for three more homogeneous studies exclusively of bacteraemias due to KPC-producing *Klebsiella* spp. in critically ill patients, which are worth detailed consideration.^{350,371,372}

Firstly, Tumbarello et al.³⁵⁰ in a three-centre retrospective cohort study found 16/23 patients survived with tigecycline and colistin combinations and 12/14 with colistin/tigecycline/carbapenem combinations compared with 11/22 with colistin monotherapy and 10/19 with tigecycline monotherapy. Secondly, Qureshi et al.³⁷¹ in a two-centre retrospective cohort study showed that 3/7 receiving polymyxin monotherapy, 1/5 receiving tigecycline monotherapy, 2/4 receiving carbapenem monotherapy and 2/3 other antibiotics as monotherapy survived 28 days compared with 5/6 receiving colistin combinations and 6/6 receiving tigecycline combinations. Thirdly, Zarkotou et al.³⁷² noted 3/7 survivals with colistin, 3/5 with tigecycline and 0/1 on carbapenem, all as monotherapy, compared with 9/9 receiving combined tigecycline and colistin, 3/3 receiving tigecycline and carbapenems and 8/8 among those treated with other combinations. Two studies of bacteraemias involving VIM-1 producers considered in this review produced even less interpretable results. A third systematic review of polymyxin treatment found mortality at 30 days was lower in patients given combination treatment.³⁷³ A 2017 systematic review and meta-analysis favours combination use of polymyxins.³⁷⁴

Given this background, conclusions from further individual non-RCT studies must be interpreted with caution, but some support combination treatment. A larger retrospective cohort study of 661 infections caused by KPC carbapenemase-producing strains of *K. pneumoniae* reported improved survival in patients treated with two or more active drugs versus those given monotherapy.³¹⁶ Mortality at 14 days in bacteraemias with an unknown or non-

urinary source was 52.8% with monotherapy and 34.1% with combination treatment. A similar result with 49.1% and 24.8% mortality respectively was seen with lower respiratory tract infection. There was no significant difference in bacteraemias from a known urinary source. Overall death rates on monotherapy were 62/132 (47%) with colistin, 45/116 (39%) with tigecycline and 28/70 (40%) with gentamicin. With two-drug therapy mortality was 38/134 (28%) and with three-drug therapy it was 67/217 (31%). Only the use of meropenem in a combination produced a statistically significant improvement to 54/205 (26%). Use of meropenem was associated with lower mortality only if the MIC was ≤ 8 mg/L, as was the case for 37% of the isolates. Colistin resistance was significantly associated with increased mortality. Overall, combinations including tigecycline, colistin and meropenem were associated with the lowest mortality (12.5%, OR 0.11, 95% CI 0.02–0.69). Epidemiologically, overall colistin, tigecycline and gentamicin resistance rates were 11%, 9% and 6% in 2010 but by 2014 were 21%, 27% and 25%.

A further review including some previously reviewed studies suggested superiority of combination therapy over monotherapy, with mortality rates of 27.4% versus 38.7% respectively. Again, carbapenem-containing regimens had the lowest mortality (18.8%) and this was associated with isolates that were not resistant by the EUCAST breakpoint.³⁷⁵ Similar findings were reported in a retrospective observational study of 205 bacteraemias caused by carbapenemase-producing *K. pneumoniae*.³⁵¹ Combination therapy was associated with a lower mortality rate of 27% compared with 44% for monotherapy, 11/27 with tigecycline, 10/22 with colistin and 7/12 with carbapenems. The difference in mortality was most marked in the more severe cases. Furthermore, mortality with a carbapenem-containing combination was 19.3% (6/31) compared with 30.6% (22/72) without a carbapenem (5/16 in those treated with tigecycline and colistin alone). Mortality on carbapenem-containing regimens in this study was lower only if the carbapenem MIC was ≤ 8 mg/L. The authors comment that 40% of isolates with MICs by Etest ≤ 8 mg/L were found resistant by automated testing. These studies suggest: (i) that KPC-carbapenemase-producing *Klebsiella* spp. commonly appear meropenem susceptible *in vitro*; and (ii) that treatment combinations containing conventionally dosed carbapenems are advisable in such cases with lower MICs.

Much higher doses of meropenem by continuous infusion can also be used (see Section 7.1). This extends the MIC range of strains that can be treated. Continuous infusion therapy of meropenem with doses up to 13.2 g daily with levels optimized by therapeutic drug monitoring when used in combinations (mainly with colistin and tigecycline) were associated with 73% clinical cures in patients with KPC-producing *K. pneumoniae* with MIC 16 to <64 mg/L.³⁷⁶ These are better outcomes in treatment of more-resistant KPC-producing *Klebsiella* than apparent in earlier studies of these more-resistant KPC-producing *Klebsiella*. Direct comparisons have not been made including comparison with high-dose continuous infusion meropenem alone. The application of this approach to other carbapenem-resistant isolates with MICs within the attainable range has not been assessed.

Anecdotal reports suggest double carbapenem combinations of ertapenem plus either meropenem or doripenem can be effective as last-resort treatment for infections due to *K. pneumoniae* producing KPC carbapenemase but not those with NDM enzymes.

This is perhaps because ertapenem binds tightly to the KPC enzyme, acting as an inhibitory substrate and thereby protecting the meropenem or doripenem.^{377,378}

In cases where the *Klebsiella* spp. strain was resistant to colistin and carbapenems, the use of gentamicin in combination with various agents was independently associated with reduced mortality in a retrospective cohort study.³⁷⁹ However, this was in the epidemiological context of a clonal *K. pneumoniae* ST512 (CC258) lineage with a KPC enzyme. This lineage commonly has the AAC(6')-Ib enzyme, which confers resistance to amikacin but largely spares gentamicin; it is unlikely to be true for isolates with NDM carbapenemases, which mostly have ArmA or Rmt ribosomal methyltransferases, conferring high-level resistance to all standard aminoglycosides, including gentamicin and plazomicin. Plazomicin might have a future role with non-NDM-producing, gentamicin-resistant strains.

Evidence for efficacy of tigecycline in combination largely derives from observational studies but microbiological cure rates with monotherapy are lower than clinical cure rates and mortality rates are high. Pooled results from five observational studies suggested a clinical response rate of 77% (567/733) for all patients and 81% (329/408) for tigecycline monotherapy in the treatment of complicated intra-abdominal infection.³⁸⁰ Another review of five observational studies of uncomplicated soft tissue and intra-abdominal infection with tigecycline similarly found monotherapy was effective.³⁸¹ These studies contain no data on response by resistances present and studies were with the licensed dose of 50 mg twice daily.

In an open-label RCT of treatment of ventilator-associated or hospital-acquired pneumonia caused by MDR *Acinetobacter* spp., addition of rifampicin to colistin did not affect 30 day mortality or length of hospital stay, but was associated with a higher rate of microbiological eradication.³⁸² A retrospective observational study of 251 bloodstream infections treated with colistin, colistin/sulbactam, colistin/carbapenem or another colistin combination reached the similar conclusion that mortality was not affected but microbiological eradication was higher with combination treatment.³⁸³ Another observational study of 101 patients with MDR *Acinetobacter* infections did not show any improvement in mortality rates for combination therapy (e.g. colistin plus tigecycline or carbapenem plus tigecycline) over a single agent (usually colistin) but the group size in this study was small.³⁸⁴

In the case of MDR *Pseudomonas* infections a prospective cohort study showed no outcome advantage in combination versus monotherapy.³⁸⁵ Combination therapy with aminoglycosides did not reduce the development of resistance.³⁸⁶ Fosfomycin in combination with tigecycline or colistin was effective in 54% of 48 patients with infections with MDR GNB, some of whom had *Pseudomonas* infection.³⁶²

The recent introduction of ceftazidime/avibactam and the possibilities of using this in treatment may change the need to use combination treatment for some KPC- or ceftazidime-resistant OXA-48 carbapenemase-producing strains.

Evidence

Two of four systematic reviews do not show a benefit of combination therapy over monotherapy.

Evidence level: 2++

In infections with KPC-carbapenemase producing *Klebsiella* spp., combination therapy including meropenem is associated with lower mortality than colistin monotherapy if the meropenem MIC is <8 mg/L but this was not the case with strains with higher MICs unless continuous infusion therapy with higher than licensed doses was used (see Section 7.1). Combinations with other agents such as tigecycline or an aminoglycoside to which carbapenemase-producing strains are susceptible also seem advantageous, but only the expected results of a new RCT will resolve this.

Evidence level: 3

Paul et al.³⁶⁹ detail the hazards of bias in favour of combination therapy that arise without an RCT. Data from a subset with bacteraemia with *Klebsiella* spp. producing KPC carbapenemases in the second systematic review performed by Falagas et al.³⁷⁰ suggest that in treatment of carbapenem-resistant Enterobacteriaceae infection, colistin used in combination with other agents is associated with a lower mortality than colistin alone, and this is also a finding in the review of Ni et al.³⁷³

Evidence level: 1+

The evidence that tigecycline combinations, including other antibiotics active against Enterobacteriaceae, are more effective than tigecycline alone in intra-abdominal infections is poor.

Evidence level: 1–

Ertapenem in combination with meropenem may be effective as salvage therapy for infections with KPC carbapenemase producers but the evidence is very weak.

Evidence level: 3

In treatment of MDR *Acinetobacter* respiratory infections, addition of rifampicin to colistin does not affect 30 day mortality.

Evidence level: 1+

Recommendations

- Use colistin with meropenem to treat susceptible KPC-producing *Klebsiella* infection if the meropenem MIC is ≤ 8 mg/L and consider a higher meropenem dose by continuous infusion if the MIC is > 8 and ≤ 32 mg/L.

Grading: Conditional recommendation for

- Consider colistin with aminoglycosides or tigecycline in infections with strains producing other carbapenemases or KPC strains that are susceptible to these agents but resistant to meropenem.

Grading: Conditional recommendation for

- Consider whether ceftazidime/avibactam should be used with a carbapenem or colistin to treat infections with KPC-3 producers based on latest evidence at the time of use.

Grading: recommendation for research and possibly conditional recommendation for use restricted to trials

8. Oral agents for secondary/tertiary care treatment

8.1 Mecillinam and pivmecillinam

Pivmecillinam (the oral form of mecillinam) can be considered alone as oral therapy for lower UTI caused by AmpC-producing Enterobacteriaceae. The antibiotic is not active against carbapenemase producers. It has been suggested to be active against ESBL-producing *E. coli*. Patients with infections with such strains referred from the community for intravenous treatment with carbapenems

might be considered for oral follow-on therapy with pivmecillinam alone for UTI because of mecillinam's apparent activity *in vitro*. However, additional measures are desirable and this oral treatment is dealt with under community use (see Section 9.4 for more detail). Patients should be carefully monitored both clinically and microbiologically if pivmecillinam is prescribed alone in hospital for infections involving ESBL producers as treatment failure is a risk.

8.2 Cefixime and oral cephalosporins

Cefixime is an oral third-generation cephalosporin that has been used as an oral switch for patients with pyelonephritis. Among uropathogenic Enterobacteriaceae, it is not active alone against ESBL-producing *E. coli* because of their multiple resistances, including quinolones,³⁸⁷ but is useful if ESBL-producing organisms or CPE are not present. Cefixime could be used in combination with co-amoxiclav against ESBL-producing Enterobacteriaceae, as supported by *in vitro* data.³⁸⁸ Data from transconjugant *E. coli* further suggest that cefixime plus clavulanate is effective against strains producing CTX-M-15 enzyme, which have higher cefixime MICs than strains producing CTX-M-9 enzyme.³⁸⁹ Other oral cephalosporins, including cefdinir, ceftibuten and cefpodoxime, also showed synergy with clavulanate, whereas sulbactam was less effective as a potentiator. Cefixime, with or without clavulanate, was not active against AmpC-producing organisms nor would it be expected to be active against CPE. Consequently cefixime/co-amoxiclav combinations should not be used against cephalosporin-resistant organisms without tests to distinguish AmpC and ESBL production. No clinical trials of cefixime together with clavulanate or amoxicillin/clavulanate against ESBL-producing *E. coli* have been published. Cefixime is detectable in faeces after administration. Other cephalosporins, e.g. cefalexin, which are fully absorbed, are not detectable in faeces and less frequently provoke *C. difficile*, may be better partners for clavulanate, although *in vitro* data to support this combination are lacking.¹⁰⁵ Synergy *in vitro* between cephalosporins and mecillinam because of their different target penicillin-binding proteins is likely, and synergy of cefalexin with fosfomycin (earlier known as alafosfalin or fosfonomycin), another cell-wall active antibiotic, is also recorded.³⁹⁰

Evidence

Cefixime with clavulanate, which is not available commercially, has reliable *in vitro* activity against ESBL-producing *E. coli* and *Klebsiella* spp. (not *Enterobacter* spp., where AmpC will cause resistance). Cefixime is not useful alone against MDR GNB and no clinical studies with oral cephalosporins and clavulanate or amoxicillin/clavulanate have been published.

Evidence level: 3

Recommendations

- Do not use cefixime or other oral cephalosporins alone for treating infections caused by ESBL-, AmpC- or carbapenemase-producing Enterobacteriaceae.
Grading: Conditional recommendation against use
- Oral cephalosporins need clinical trials with clavulanate (alone or with amoxicillin) against ESBL-producing *E. coli* UTI.
Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials

8.3 What are the recommended antibiotics for community care, including care homes?

Most MDR GNB infections encountered in the community involve the urinary tract. As described earlier, ESBL-producing isolates of Enterobacteriaceae are a significant and growing problem, whereas there are few community infections in the UK involving CPE. There are no published RCTs of antibiotic treatment of UTIs due to ESBL-producing organisms in the community or care homes. Recommendations must rely on observational studies of ESBL-producing GNB, or RCTs of effectiveness of antibiotics against UTIs caused by GNB lacking ESBLs.

8.4 What are the risk factors for patients with urinary tract infections caused by MDR GNB in the UK?

In order to help the assessment of patients we reviewed risk factors for MDR GNB and suitable oral agents for acute uncomplicated and complicated UTIs. Prospective and retrospective epidemiological studies identified several risk factors for carriage of ESBL-producing *E. coli*.^{99,136,184,391–393,394,395} Patients are at increased risk if they have:

- Recurrent UTI
- Persistent urinary symptoms after an initial antibiotic
- Over 7 days hospital admission in the last 6 months
- Residence in a care home
- Recent travel and especially healthcare in a country with increased antimicrobial resistance.
- Previously known UTI (within 1 year) caused by bacteria resistant to amoxicillin/clavulanate, cephalosporins or quinolone or recent treatment with these agents.³⁹⁶

There are no UK data validating an Italian scoring system devised and tested in 2009 for carriage of ESBL-producing bacteria on admission to hospital or incorporating information on travel, overseas healthcare in the previous 2 years or migration. The Italian scoring system identifies risk based on hospitalization within the previous 12 months (OR 5.69, 95% CI 2.94–10.99), transfer from another healthcare facility (OR 5.61, 95% CI 1.65–19.08), Charlson comorbidity score >4 (OR 3.80, 95% CI 1.90–7.59), β -lactam or fluoroquinolone prescription within the previous 3 months (OR 3.68, 95% CI 1.96–6.91), recent urinary catheterization (OR 3.52, 95% CI 1.96–6.91) and age >70 years (OR 3.20, 95% CI 1.79–5.70).⁹⁹ This model of risk factors has been re-assessed in the USA to see if it can be used to realistically restrict the need for carbapenem treatment to an identifiable high-risk subgroup.³⁹⁷ In the US evaluation, risk factors for community-onset clinical infection involving MDR GNB diagnosed within 48 h of admission were: hospitalization (OR 2.63, 95% CI 1.323–5.41), inter-hospital transfer (OR 5.30, 95% CI 2.67–10.71), urinary catheterization (OR 6.89, 95% CI 3.62–13.38), β -lactam or quinolone prescription (OR 3.47, 95% CI 1.91–6.41) and additionally immunosuppression in the preceding 3 months (OR 2.34, 95% CI 1.14–4.8). Age over 70 was not a risk factor but age was not examined as a continuous variable. In this model, the sensitivity and specificity were $\geq 94\%$ and $\leq 65\%$ for scores of ≤ 3 and $\leq 58\%$ and $\geq 95\%$ for scores of 8 or above. Urinary catheterization was also a risk factor

in a Spanish study.³⁹⁸ A further paired US retrospective case-control study compared infections with CTX-M ESBL-producing *E. coli* infections with *E. coli* lacking CTX-M enzymes with uninfected controls; carbapenemase producers were excluded. Patients with infections with CTX-M producers were more likely to be male, have dementia or dependency, have higher median Charlson scores, receive H2 antagonists and have exposure to healthcare settings.³⁹³ Recent antibiotics did not differ between the two groups, except that trimethoprim/sulfamethoxazole use was commoner in the non CTX-M-producing group. Exposure to immunosuppressives was also commoner in the CTX-M group. A similar 75%–77% of strains were present within 48 h of admission. When patients with strains producing CTX-M-ESBLs were compared with controls, the former had a higher incidence of comorbidity (Charlson score ≥ 5), and were more often resident in nursing homes with greater exposure to healthcare and more indwelling urinary catheters. They were more likely to be receiving H2 antagonists or proton pump inhibitors and to have exposure to oxyimino cephalosporins within the last 3 months.

Evidence

Quoted rates of resistance in the community are biased to an unknown extent by infection occurring shortly after hospital discharge, care home cross-infection, an excess of treatment failures represented in the samples tested and an unknown proportion of patients with risk factors and recent antibiotic use.

Evidence level: 2–

UK surveillance suggests MDR GNB remain uncommon in community UTIs, with few carbapenemase producers.

Evidence level: 3

Empirical antibiotic choice for lower UTI can be guided by the presence of established risk factors for a multiresistant organism.

Evidence level: 2+

Predictive models have been established in Italy and the USA for ESBL-producing *E. coli* infections and colonization on admission to hospital, but these have not been validated in the UK nor do they consider travel-, migration- or household-associated risks.

Evidence level: 2+

Recommendations

- In younger women with acute uncomplicated UTI, only consider MDR GNB in choosing empirical treatment if there are risk factors or recent foreign travel to countries where such strains are highly prevalent.
Grading: Strong recommendation for
- If the defined risk factors for MDR GNB are present avoid cephalosporins, quinolones, trimethoprim and co-amoxiclav in treatment of lower UTIs unless the pathogens are confirmed to be susceptible.
Grading: Strong recommendation against use
- Building on previous work, predictive scoring should be developed in the UK for the presence of ESBL-producing *E. coli* in primary care and on admission to hospital to restrict the need to prescribe carbapenems and other antimicrobial agents generally active against ESBL-producing organisms.
Grading: Strong recommendation for

9. Which oral antibiotics are preferred for use in treating uncomplicated UTIs due to MDR GNB in the community?

9.1 Trimethoprim

Owing to increasing resistance, trimethoprim is no longer the suggested first-line empirical therapy for post-menopausal women and older men in PHE guidance and nitrofurantoin is advised instead. In Wales trimethoprim remained until 2016 the suggested first-line empirical therapy for uncomplicated UTI in the community except for the elderly and for patients who have received antibiotics in the preceding 3 months.

Following advice to decrease trimethoprim use, an 86% reduction in trimethoprim use was seen in a Swedish region (hospitals and community) from 2004 to 2006 with a compensatory increase in nitrofurantoin, pivmecillinam and ciprofloxacin use. This programme resulted in no overall change in trimethoprim resistance. Before the intervention, trimethoprim resistance was more prevalent in *E. coli* phylogroups A, B1 and D than in phylogroup B2 strains, although rates were high in ST131, which belongs to phylogroup B2. There was a marked change after the intervention in the distribution of resistance between phylogroups and associated sequence types, with an increase in the trimethoprim resistance in phylogroup B2 (including ST131) and a decrease in trimethoprim resistance in phylogroup A and B1 strains (which seldom cause extraintestinal infection) and to a lesser extent in phylogroup D. Trimethoprim resistance was associated with a change in prevalence of *dfra1*. Resistance to other antibiotics, including those substituted for trimethoprim increased in phylogroup A and B1 strains.¹¹⁸ Amongst 273 urine isolates of *E. coli* collected in 2006 versus the same number collected in 2004, strains of ST69 (which includes the former clonal group A), ST12 and unusual strains became more prevalent, increasing respectively from 4.8% to 8.1%, from 2.6% to 4.8% and from 42% to 51%. By contrast strains of ST131, ST127, and ST80 declined in prevalence from 4.8% to 2.2%, 8.1% to 3.7% and 5.1% to 1.1%. There were statistically significant increases in trimethoprim resistance rates in the strains of ST131 and ST127. This would suggest that in types ST131 and ST127 susceptible strains were eliminated by the antibiotics substituted for trimethoprim (quinolones, pivmecillinam and nitrofurantoin) but because of resistance linkage trimethoprim resistance increased in these sequence types. Information is lacking on ST80. The increase in strains ST69 and ST12 suggests they may have been selected by the antibiotics substituted for trimethoprim, but it is not clear which antibiotics would have this effect as these STs are usually only resistant to ampicillin and, in the case of ST69, trimethoprim. In a structured survey of extraintestinal strains from US veterans in 2011, quinolone-resistant ST131 accounted for 78% of quinolone-resistant strains, which constituted 29% of reported strains overall. It accounted for 56% of trimethoprim-resistant strains and 52% of quinolone- and trimethoprim-resistant strains.³⁹⁹ This suggests that quinolones have the potential to select against trimethoprim-susceptible ST131 strains, decreasing in the Swedish intervention study the overall prevalence at that time but potentially selecting for later increased prevalence of the ST131. Thus, because of resistance linkage, community-wide change in use of a single antibiotic may unpredictably change the epidemiology and the prevalence of antibiotic resistance in more

pathogenic phylogroups. It cannot be assumed that risk factors for multiresistance or the likelihood of success with an antibiotic in reinfection or recurrent infection will stay the same after abandonment of trimethoprim as a first-line agent. This aspect of change needs urgent study.

Trimethoprim-resistant strains are much more frequently resistant to amoxicillin than trimethoprim-susceptible strains and this is a feature of ST69. Trimethoprim resistance rates in ESBL-producing *E. coli* in 2010 in the West Midlands were between 86% and 92% depending on whether the strain was not, or was, ST131. Ciprofloxacin resistance is also usual in these strains.⁹³ Trimethoprim consequently is a poor choice for patients with treatment failures on amoxicillin with, or without, clavulanate, cephalosporins or quinolones who require an urgent prescription before samples can be tested for antibiotic susceptibilities.

More generally, trimethoprim should not be used as empirical treatment for UTI if there are risk factors for an antibiotic-resistant bacterium unless: (i) susceptibility has been confirmed in the previous month; (ii) there are no new risk factors for resistance; and (iii) there have been no treatment failures with trimethoprim. In the absence of resistance, trimethoprim attains excellent bacteriological cure: 2 weeks after completion of treatment 94% of women using a 3 day course achieved bacteriological cure compared with 97% of those using a 10 day course ($n = 135$).⁴⁰⁰

Evidence

Trimethoprim use has not been explored as a risk factor for MDR GNB infection but resistance is common generally and very common in ESBL-producing bacteria. Trimethoprim is no longer recommended as a first-line antibiotic choice for post-menopausal women and older men with UTI and has little place in treatment of infection due to MDR GNB.

Evidence level: 3

3 day courses are almost as effective as longer courses in bacteriological cure of susceptible infections.

Evidence level: 1+

Recommendations

- Do not use trimethoprim in treating MDR GNB or treatment failures with other agents unless *in vitro* susceptibility has been demonstrated.
Grading: Strong recommendation against use
- Do not use trimethoprim to treat lower UTIs as a first-line agent if ≥ 50 years old. Only consider use if there are no risk factors for resistance, or if *in vitro* susceptibility is confirmed.
Grading: Conditional recommendation against use

9.2 Nitrofurantoin

Nitrofurantoin is widely used for acute uncomplicated UTI in the community, and is now the recommended first-line treatment in England. It attains only low concentrations in renal tissue and the bloodstream and should not be used if pyelonephritis or bacteraemia is suspected; treatment may fail if used for ascending infection.⁴⁰¹ Nitrofurantoin resistance is inherent in *Proteus* spp., *M. Morganii*, *Providencia* spp. and *Serratia* spp. and the drug may not be effective in the alkaline urine produced by urease-producing bacteria such as these and possibly *Staphylococcus saprophyticus*,

which is apparently susceptible *in vitro* but also produces large amounts of urease. Nitrofurantoin resistance is very common in CPE.¹²⁰

In early studies nitrofurantoin had a minimal effect on rectal flora and a recent metagenomics study supports this.^{402,403} Resistant strains of *E. coli* and increased numbers of Proteaeae may be detected in the faecal flora^{404,405} but UTIs breaking through prophylaxis in recurrent infection are usually due to strains that remain susceptible, unlike the situation with trimethoprim.^{404,405} Recurrent UTIs after nitrofurantoin treatment of ESBL-producing *E. coli* may reflect relapse or recurrent infection arising from persistent carriage in the gastrointestinal flora; these possibilities cannot easily be distinguished. Frequent recurrence of UTI due to ESBL strains may justify using an alternative antibiotic regimen such as fosfomycin, or amoxicillin/clavulanate with pivmecillinam, with a greater theoretical chance of changing the gastrointestinal flora, which may act as the source for reinfection.

If a patient has a reduced glomerular filtration rate (GFR), urinary concentrations of nitrofurantoin may be too low to be effective. Estimated GFR (eGFR) frequently declines with age, on average by between 6 and 9 mL/min/1.73 m² per decade. Around half of women over 75 years and men over 85 years have an eGFR under 60 mL/min/1.73 m², which used to be the lower limit for use of nitrofurantoin.⁴⁰¹ In a cohort study of lower UTI in 21317 women treated with nitrofurantoin and 7926 treated with trimethoprim, there was no greater risk of nitrofurantoin treatment failure in patients with creatinine clearance of 30–50 mL/min; however, the risk of pulmonary adverse events was significantly increased with creatinine clearance < 50 mL/min (HR 4.1, 95% CI 0.31–13.09).⁴⁰⁶ In 2014, and in the context of increasing antibiotic resistance to trimethoprim in the UK, the Medicine and Healthcare Regulatory Agency (MHRA) reviewed the evidence for use of nitrofurantoin in reduced renal function.⁴⁰⁷ They concluded on evidence^{401,406} that the eGFR below which nitrofurantoin should not be used could be lowered to 45 mL/min/1.73 m². The MHRA further stated that a short course (3–7 days) may be used with caution in patients with an eGFR of 30–44 mL/min/1.73 m², but only advocates prescribing in such patients for lower UTIs with suspected or proven MDR pathogens when the benefits of nitrofurantoin are considered to outweigh the risks of side effects. Long-term or repeated courses of nitrofurantoin are associated with severe pulmonary fibrosis.⁴⁰⁸ Nevertheless, 219 courses of prophylaxis for 1 year for recurrent UTI in normal patients were not associated with a single case, so this unwanted effect may be rare under controlled conditions where the drug is very effective.⁴⁰⁵ Nitrofurantoin is poorly tolerated by some patients, but the modified-release form has fewer side effects.⁴⁰⁹ When used in this formulation, an open RCT over 20 years ago ($n = 538$) found that nitrofurantoin had equivalent clinical cure rates to trimethoprim/sulfamethoxazole and trimethoprim (both given for 7 days) in a group of patients with acute uncomplicated lower UTI.⁴⁰⁹ The rate of gastrointestinal adverse effects was similar between groups (7%–8%). At this time the rate of nitrofurantoin resistance across all pathogens isolated was 3.9% whereas the rate of trimethoprim resistance was 12.5%. Trimethoprim but not nitrofurantoin resistance is now far commoner.

A recent review and meta-analysis suggested nitrofurantoin had a similar clinical cure rate to comparators but with a 5 rather than 3 day course for nitrofurantoin apparently producing better

cure rates.⁴¹⁰ However 5 and 3 day courses have not been directly compared in adequate numbers and the PHE has not recommended 5 day courses. We consider in MDR GNB UTI that course lengths should be those that produce the best rates of bacteriological cure. There is no convincing evidence that shorter courses are equivalent to longer courses specifically in MDR GNB infections nor that the risk of serious unwanted effects is increased with longer courses. Whether such longer courses should be used more generally for nitrofurantoin is therefore unresolved. Unwanted effects in the systematic review were mainly gastrointestinal and no pulmonary events were reported, although this may reflect short follow-up periods.⁴¹⁰ There are no specific studies of nitrofurantoin in UTI caused by ESBL-producing organisms, but UTIs that are susceptible to nitrofurantoin have a similar response rate irrespective of ESBL production. However, ESBL-producing members of the *E. coli* ST131 clone, which are common in the UK and elsewhere, often have urinary virulence factors that are associated with recurrence, infection of the upper urinary tract and bacteraemia,⁴¹¹ and when infection reaches the upper tract nitrofurantoin is ineffective. Nitrofurantoin resistance has appeared in this sequence type (see Section 6.3.4). Further comparative studies in UTIs due to ESBL-producing *E. coli* are needed.

Evidence

Nitrofurantoin is effective in lower, uncomplicated UTI and resistance rates remain low in *E. coli*, although new plasmid-mediated mechanisms of resistance are now described. Mechanisms of acquired resistance in the UK, including in travellers, have not been studied recently. Resistance is intrinsic in *Proteus* spp. and *Serratia* spp.

Evidence level: 1+

There is usually no change in faecal Enterobacteriaceae during or immediately after use. Breakthrough infection, when the drug is used prophylactically, remains susceptible, unlike with trimethoprim.

Evidence level: 3

Nitrofurantoin's activity is reduced in alkaline urine.

Evidence level: 4

Use of nitrofurantoin in moderate renal impairment, as seen with increasing age, has been controversial, but unrestricted use down to an eGFR of >45 mL/min may be acceptable.

Evidence level: 1+

Use in moderate renal impairment or in long-term/repeated courses may be associated, albeit rarely, with serious pulmonary unwanted effects.

Evidence level: 3

5 day, not 3 day, courses are recommended for susceptible ESBL-producing *E. coli*.

Evidence level: 1+

Recommendations

- Could use nitrofurantoin for 5 days to treat uncomplicated lower UTIs with nitrofurantoin-susceptible MDR *E. coli* (not Proteae or *P. aeruginosa*).
Grading: Strong recommendation for
- Do not use repeatedly if there is moderate renal impairment, or in long-term courses, as these are associated with rare unwanted pulmonary effects.
Grading: Conditional recommendation against

- Use alternative agents if there are repeated recurrences with MDR GNB but do not anticipate the emergence of resistance in *E. coli* infections on a single recurrence as selection for resistant strains in the urine or faecal flora is rare.

Grading: Conditional recommendation for

- Need comparative studies of nitrofurantoin and other active antimicrobials in patients with ESBL-producing *E. coli* and *Klebsiella* spp.

Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials

9.3 Fosfomycin trometamol

Fosfomycin has not been widely used in the UK, where the oral form was available between February 1994 and 1996; it was thereafter withdrawn and not marketed for nearly two decades until 2013. Its use elsewhere in Europe has been associated with clinical success in lower UTIs. Fosfomycin suppresses Enterobacteriaceae in the faecal flora of 60% of patients by day 3 after a single dose but this rapidly drops to 30% at days 10–14: in contrast, nitrofurantoin does not suppress these organisms.⁴⁰³

Oral fosfomycin should be administered while fasting or 2 or 3 h before meals, as food can slow its absorption, leading to lower concentrations in the urine.⁴¹² Oral fosfomycin is licensed solely for the treatment of uncomplicated cystitis. A single oral dose of 3 g results in a plasma C_{max} of 22–32 mg/L and a urine maximum concentration (U_{max}) of 1053–445 mg/L.⁴¹³ The urinary concentration remains inhibitory for *E. coli* for at least 48 h. In elderly patients with a mean GFR of 40 mL/min, concentrations after 24 h exceeded those reported for healthy young subjects but there was considerable variation in excretion rates.⁴¹⁴

Treatment with a 3 g single dose of fosfomycin trometamol was associated with clinical success rates (defined as the resolution of symptoms after treatment) between 77.8% and 94.2% in four observational studies (some complicated and some receiving more than one dose) of treatment of lower UTI due to multiresistant bacteria.⁴¹⁵ Oral fosfomycin trometamol has been used successfully for prophylaxis of pyelonephritis in patients with ASB in pregnancy, and there are reports of its use, sometimes in combination, in chronic prostatitis. The use and kinetics of fosfomycin have recently been extensively reviewed following its re-introduction to Canada.⁴¹³

Evidence

Fosfomycin is effective and well tolerated in treatment of UTI but the oral drug has only been studied in lower UTI.

Evidence level: 2++

Plasmid and chromosomally mediated resistance has emerged in populations where fosfomycin is widely used.

Evidence level: 2–

Recommendations

- Use in the treatment of lower UTI due to MDR Enterobacteriaceae. Oral formulation available. Useful for infections with ESBL producers or carbapenemase producers. No trials of oral formulation for upper UTI.
Grading: Strong recommendation for

- Carry out ongoing local and national surveillance of use and resistance because of previous emergence of bacterial resistance in populations and the drug's potential as an important parenteral agent.
Grading: Strong recommendation for

9.4 Mecillinam and pivmecillinam

Pivmecillinam is an oral inactive ester and prodrug that is converted to microbiologically active mecillinam after intestinal absorption. Mecillinam has *in vitro* activity against most Enterobacteriaceae (including those with copious AmpC and some with ESBLs), but innate resistance occurs in *Proteus* spp., *M. morganii*, *Providencia* spp., some *Serratia* spp. and most non-fermenters, including *Acinetobacter* spp. and *P. aeruginosa*. Mecillinam has no activity against enterococci or *S. saprophyticus*.

Some TEM and SHV ESBLs confer clear resistance^{389,416} and an inoculum effect on testing is common for other ESBL producers.⁴¹⁷ In one study of ESBL-producing *E. coli* the MIC₅₀ by agar dilution was 1 mg/L with an inoculum of 10⁴ cfu/spot but the MIC₉₀ was 4 mg/L.⁴¹⁸ Experiments with *E. coli* transconjugants showed that mecillinam MICs rose to 8 mg/L when CTX-M-15 or -3 was present but only to 0.25–0.5 mg/L with CTX-M-9 or -14. Combination with clavulanate reduced all mecillinam MICs for ESBL producers (except SHV-4) to ≤4 mg/L at high inocula and ≤2 mg/L with the usual light inocula.³⁸⁹ In another study of combination with clavulanate,⁴¹⁸ 47/48 ESBL producers were susceptible to mecillinam. Most of these produced CTX-M-3 (found in Northern Ireland) not the commoner CTX-M-15 enzymes usual in England, Wales and Scotland. There was no difference between the MICs for transconjugants producing CTX-M-3 and -15 in the earlier study. Synergy with clavulanate was detected in 40%–60.4% of ESBL-producing isolates depending on the method of assessment. When a high inoculum was used, there was a marked inoculum effect, raising the MIC of mecillinam alone but not that of mecillinam plus clavulanate. This study needs to be repeated with *E. coli* ST131 strains producing CTX-M-15 enzyme and also often OXA-1, which is not inhibited by clavulanate but said to have little activity against mecillinam.

Mutants resistant to mecillinam by non-ESBL mechanisms can readily be obtained by laboratory selection. These show mutations in many different cellular functions.⁶⁸ However, a recent study of mecillinam-resistant clinical isolates found them all to have mutations leading to inactivation of the *cysB* gene. Reduced cysteine biosynthesis results in accumulation of the transcriptional regulator guanosine 3'-diphosphate 5'-diphosphate (ppGpp) so that the mecillinam-targeted PBP2 becomes non-essential.⁴¹⁹ Addition of cysteine to the growth medium *in vitro* reversed the resistance to mecillinam for such mutants, raising possible issues with regard to current *in vitro* testing media.

Mecillinam is inactive against Enterobacteriaceae with KPC enzymes but some published data suggest *in vitro* activity against isolates with OXA-48-like enzymes^{68,389} and even some with NDM-1 enzymes, as reflected in an MIC₅₀ of 4 mg/L for NDM carbapenemase-producing *E. coli*,⁴²⁰ although this low value is disputed by others (D. M. Livermore, unpublished data).

Pivmecillinam at 200 mg three times daily only produces sustained inhibition in Monte Carlo simulations if the mecillinam MIC is ≤0.25 mg/L, suggesting a higher dose or lower EUCAST breakpoint

may be required to produce and predict clinical response, respectively.⁴²¹

Pivmecillinam is used mainly for lower UTI, where it has similar short-term symptomatic efficacy to amoxicillin and trimethoprim/sulfamethoxazole if organisms are susceptible^{422,423} and also to norfloxacin in 3 or 7 day regimens.⁴²⁴ Seven day pivmecillinam regimens are associated with more frequent clinical success than 3 day regimens.⁴²⁵ Pivmecillinam prophylaxis in children with vesicoureteric reflux markedly reduced faecal *E. coli* and urinary breakthrough with *E. coli*; unlike nitrofurantoin, breakthrough infection with enterococci was common, reflecting different *in vitro* resistance.⁴²⁶ Urinary concentrations are very high.⁴²⁷

Clinical trials of pivmecillinam against ESBL-producing Enterobacteriaceae are limited to case series. In one small trial pivmecillinam was used alone with 30/39 patients receiving 400 mg three times daily and 9/39 receiving 200 mg three times daily. Dosage did not clearly affect the cure rates regardless of whether the UTI was complicated. Twenty-eight patients were noted to have calculi, prostatic hypertrophy or urinary catheters (i.e. complicated UTI) and six of these were bacteriological failures. Two other bacteriological failures were seen among the remaining 11 patients. Bacteriological cure was attained in 31/39 (79% overall), but five relapsed; clinical cure was attained in 16/19 patients but the rest were lost to follow-up.⁴²⁸ There is no theoretical, trial or practice evidence to support a regimen with a loading dose of 400 mg followed by 200 mg three times daily, which has been recommended in the UK as a compromise.⁴²⁹ A population-based Norwegian study of pivmecillinam treatment of community-acquired UTIs examined the impact of MICs and ESBL production in *E. coli*; it is not clear whether this was restricted to uncomplicated lower UTIs, for which, alone, pivmecillinam is licensed.⁴³⁰ A total of 343 patients were included, of whom 158 (46%) were treated with pivmecillinam. Eighty-one patients had infections caused by ESBL-producing *E. coli*, and 41 (51%) received pivmecillinam as the primary treatment, usually at a dose of 200 mg three times daily for at least 7 days. Mecillinam MICs were higher for ESBL producers than non-producers: 68% of strains had CTX-M Group 1 enzymes (including CTX-M-15) and 28% had Group 9 enzymes (including CTX-M-9 and -14). Treatment failure was (atypically) defined as a new antibiotic prescription appropriate for UTI within 2 weeks of the initial therapy or failure to clinically improve. Clinical treatment failure with pivmecillinam was observed in 18 (44%) patients infected by ESBL-producing strains and in 16 (14%) patients with ESBL non-producing strains. Mecillinam MICs for isolates from treatment failures (*n* = 34, 18 ESBLs) averaged 2 mg/L (range 1–4 mg/L) compared with MICs of <1 mg/L for all isolates from treatment successes (*n* = 124, 23 ESBLs). Treatment failures occurred in 50% of cases with mecillinam MICs of 2 mg/L, rising to 63% at MICs of 4 mg/L. This compares with a EUCAST breakpoint of S ≤8 mg/L, R >8 mg/L for mecillinam, again suggesting inadequate levels or too high a breakpoint. Multivariate analysis showed that ESBL status (OR 3.2, 95% CI 1.3–7.8; *P* = 0.009) and increased MIC of mecillinam (OR 2.0 for each doubling value of MIC, 95% CI 1.4–3.0; *P* < 0.001) were associated with pivmecillinam treatment failure. Treatment failure rates above 25% were associated with mecillinam MICs ≥2 mg/L for ESBL producers and >4 mg/L for isolates lacking ESBL. From the transconjugant study cited earlier it is likely that UK CTX-M-15-producing isolates will be in this more-resistant category and will

respond poorly if pivmecillinam is used alone. This study must be seen also in the context of the earlier studies on the doses necessary to achieve adequate urinary concentrations.

There has been controversy over whether studies should be repeated with higher doses, such as 400 mg three times daily, but a more effective action to improve cure rates may be combined use of a regimen of 200 mg three times daily together with amoxicillin/clavulanate at 375 mg three times daily. We recommend this combination if oral pivmecillinam follow-on therapy is prescribed following hospital or OPAT intravenous treatment for UTI involving an ESBL producer. Co-administration of amoxicillin/clavulanate may not only provide efficacy via inhibition of ESBL but also 10- to 100-fold bactericidal synergy by combining amoxicillin's action on PBP1 and 3 and mecillinam's action on PBP2.⁴³¹

Future use of co-amoxiclav, rather than clavulanate without amoxicillin, in combination with mecillinam is partly supported by a high-quality double-blind multicentre RCT of mecillinam and ampicillin-congeners without clavulanate in pyelonephritis in 1995, in the era before CTX-M enzymes. Equivalent results to cefotaxime/cefadroxil were achieved with an oral switch from parenteral mecillinam (no longer available) and ampicillin to pivmecillinam (at 400 mg three times daily) plus an oral ampicillin prodrug, suggesting that synergy of amoxicillin and pivmecillinam potentially would be clinically useful in follow-on therapy for pyelonephritis. In modern circumstances, including against ESBL producers, this efficacy might be restored by protecting both mecillinam and amoxicillin by using them with clavulanate. A clinical success rate of 93% for pivmecillinam as against 53% with pivampicillin in a study in 1986 of pyelonephritis suggests the drug has activity in the upper urinary tract.⁴³² However, it is important to note that clinical trials of the combination of amoxicillin/clavulanate with pivmecillinam have never been undertaken in pyelonephritis, and pivmecillinam has no licence for pyelonephritis.

Further clinical comparative studies with outcome data are urgently required for pivmecillinam, with and without clavulanate (probably administered as amoxicillin/clavulanate), for both complicated (including upper urinary tract) and lower UTI against ESBL producers. Amoxicillin/clavulanate, unlike clavulanate alone, is available and licensed for upper UTI. These trials would determine pivmecillinam's role and its potential to reduce the need for hospitalization or OPAT admissions to administer intravenous agents active against ESBL producers.

Pivmecillinam is claimed to have a minimal effect on the intestinal and vaginal flora of the host with little selection for resistant bacteria, vaginal *Candida* or *C. difficile*.⁴³³ However, the earlier study⁴²⁶ suggests it markedly reduces faecal *E. coli*, at least in children. In an *in vitro* human gut model, it did not elicit *C. difficile* germination, proliferation or toxin production, suggesting that superinfection with this pathogen should be rare if the drug is used alone.⁴³⁴ Clinical studies with pivmecillinam/amoxicillin/clavulanate regimens should include studies on persistence of ESBL-producing *E. coli* gut colonization and new infections with *C. difficile*.

Overall there are uncertainties about how pivmecillinam should best be used in the modern era. The drug has very valuable potential and these uncertainties need resolution by large clinical trials, which are now urgent. Selection for resistant strains (such as SHV producers) in the interim would be unfortunate and for this reason we await further substantive trials and action and do not include its use alone in our general recommendations.

Evidence

Pivmecillinam is a prodrug for mecillinam and is the sole oral β -lactam (excluding tebipenem and faropenem, which are available only in Asia) with some activity against ESBL- and AmpC-producing organisms. It has a European licence, and is widely and effectively used for lower UTI in some countries. Parenteral mecillinam has been manufactured in the past but is now unavailable.

Evidence level: 2++

Pivmecillinam has no published clinical trials against CPE and *in vitro* activity appears poor or non-existent.

Evidence level: 4

Urinary levels following doses of 200 mg three times daily are inadequate to inhibit some ESBL-producing MDR GNB, including some with CTX-M-15 considered susceptible by the current EUCAST breakpoint ($S \leq 8$ mg/L).

Evidence level: 3

Failure rates with 200 mg of pivmecillinam three times daily used alone against lower UTIs due to ESBL-producing *E. coli* are too high to recommend regular use in such infections. A higher dose, 400 mg three times daily, has been proposed but there is no convincing evidence to show it is more effective. Comparative studies with fosfomycin have not been reported but there are no suggestions of such ESBL-related failures in existing fosfomycin studies in the absence of resistance.

Evidence level: 3

There are inadequate trial data to support the use of pivmecillinam in *Klebsiella* infection, especially where the strain responsible produces ESBLs.

Evidence level: 4

In vitro evidence and early trials of combination with ampicillin or pivampicillin suggest that a useful measure to increase efficacy would be combination with amoxicillin as well as clavulanate (see below).

Evidence level: 2+

In vitro studies suggest that clavulanate (available clinically only as amoxicillin/clavulanate) would protect mecillinam from destruction by ESBLs and lower its MICs for Enterobacteriaceae. If pivmecillinam is prescribed as follow-on to OPAT or inpatient treatment, use of the combination is recommended.

Evidence level: 3

Clinical trials of pivmecillinam alone versus pivmecillinam with amoxicillin/clavulanate in lower UTI would be in the public interest. These should be sized to give information on efficacy against ESBL-producing bacteria and should include studies on the bowel flora and associated recurrence rates and *C. difficile*. If results of combination treatment are satisfactory, consideration should be given to trials in upper UTI, including economic assessment against OPAT treatment. Comparative trials with nitrofurantoin or fosfomycin trometamol for MDR GNB lower UTI are also required.

Evidence level: 4

Recommendations

- Consideration should be given to reducing the mecillinam EUCAST breakpoint for classification of susceptibility.
Grading: Conditional recommendation for
- Treat lower UTI due to ESBL-negative *E. coli* with pivmecillinam at 200 mg three times daily; do not use for infections caused by Proteaeae, *Klebsiella* or *Pseudomonas*. Some ESBL-producing

E. coli respond, but efficacy is poor against CTX-M-15 enzyme producers: dosing at 400 mg three times daily may be no more effective. Consider combination of the 200 mg dose with 375 mg amoxicillin/clavulanate for follow-on to parenteral therapy for such infections in hospital or OPAT.

Grading: Conditional recommendation for

- Requires clinical comparative trials in UTI in the public interest: (i) alone or together with amoxicillin/clavulanate for UTI involving ESBL-producing organisms, including particularly those producing CTX-M-15 enzymes; (ii) in uncomplicated lower UTI generally compared with fosfomycin trometamol and nitrofurantoin, as the relative advantages of these drugs have not been directly compared by industry over the last 10 years as MDR GNB have become more problematic.

Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials

10. Managing urinary tract infection

10.1 Diagnosis and the need for treatment or prophylaxis

Because UTIs are the major group of infections due to antibiotic-resistant Gram-negative infections in primary care, we have chosen to make specific recommendations about their diagnosis and about specific antibiotic stewardship.

Good practice in differentiating urinary infections from other infections and asymptomatic bacteriuria is vital to reduce the unnecessary use of antibiotics. When clinical variables were examined in a validation study⁴³⁵ of a previously derived predictive dipstick rule, based on having nitrite or both leucocytes and blood,⁴³⁶ the positive predictive value for urinary infection was 82% for women with all three of cloudy urine, dysuria and nocturia. The negative predictive value for urinary infection was 67% when none of these three features was present.⁴³⁶ When individual clinical features were considered alone, cloudy urine or dysuria was predictive of UTI, but nocturia or smelly urine was not,⁴³⁵ which brings into question its value in the assessment above of the combination of cloudy urine, dysuria and nocturia. In women aged 17–70 years with uncomplicated UTI, the negative predictive value when nitrite, leucocytes and blood are ALL negative was 76%.⁴³⁵ The positive predictive value for having nitrite alone or nitrite together with either blood or leucocytes was 92%.⁴³⁵ A systematic review of diagnostic studies found that the presence of vaginal discharge or vaginal irritation reduced the probability of urinary infection to 20%–30%.⁴³⁷

Several different studies have shown the prevalence of asymptomatic bacteriuria is about 6% in men and 16% in women aged over 65 years⁴³⁸ and is higher in older age groups and in the institutionalized elderly. In a cohort study, 1173 elderly female residents without catheters in care homes were followed for 9 years with urine cultures every 6 months.⁴³⁹ No relationship was found between ever having had asymptomatic bacteriuria and death after adjusting for covariates (HR 1.10, 95% CI, 0.78–1.55). The death rate in the group who never had asymptomatic bacteriuria was similar to that in those who had bacteriuria but either received no treatment or were treated ($P > 0.2$).⁴³⁹ The lack of benefit in treating asymptomatic bacteriuria was confirmed in another smaller study: neither mortality nor the frequency of symptomatic

episodes was reduced, but for every three women with asymptomatic bacteriuria in a care home given antibiotics (the type was not specified in this study), one experienced adverse effects (such as rash or gastrointestinal symptoms).⁴⁴⁰ Cumulatively, 3%–6% of people acquire bacteriuria per day of urinary catheterization even with best practice for insertion and care of the catheter, and therefore many older people with long-term catheters have bacteriuria.^{441,442} Intermittent catheterization is associated with a lower incidence of asymptomatic bacteriuria than long-term catheterization.⁴⁴³ Catheterized patients should only receive antibiotic treatment when they are systemically symptomatic, to reduce the risk of colonization by antibiotic-resistant bacteria.^{441,442} Differentiating UTI from asymptomatic bacteriuria can be particularly challenging in elderly patients with dementia as they cannot always describe their symptoms. A positive urine culture or dipstick test will not differentiate between UTI and ASB.⁴³⁹ Patients with asymptomatic bacteriuria may have white blood cells in the urine just as in true infection. In older patients, including those with dementia, diagnosis should be based on a full clinical assessment, including vital signs.

A Canadian RCT of a diagnostic and treatment algorithm for UTI implemented in care homes, using a multifaceted approach, reduced antibiotics for urinary indications by 31% compared with control care homes, with no increase in hospital admissions or mortality.⁴⁴⁴ Patients were considered for antibiotic treatment based primarily on presence of fever greater than 37.9°C or 1.5°C increase above baseline on at least two occasions over last 12 h and one or more signs of UTI.⁴⁴⁴ The full algorithm used is shown in Figure 5. Fewer courses of antibiotics for suspected UTIs per 1000 resident days were prescribed in the intervention nursing homes than in control care homes (1.17 versus 1.59 courses per 1000 resident days). Antimicrobials for suspected UTI represented 28.4% of all courses of drugs prescribed in the intervention nursing homes compared with 38.6% prescribed in the control care homes (weighted mean difference –9.6%, 95% CI –16.9% to –2.4%). No significant difference was found in admissions to hospital or mortality between the study arms.

In recurrent UTI, deciding whether to give prophylaxis is a balance between the benefits of reducing symptomatic relapse and pyelonephritis versus side effects and the risks of selecting antibiotic resistance. Guidance is based on a systematic review of 19 trials. Nightly prophylaxis in non-pregnant women with recurrent urinary infection showed that prophylaxis reduced the relative risk (RR) of having one microbiological recurrence by 5-fold (RR 0.21, 95% CI 0.13–0.34), giving a number-needed to treat (NNT) of 1.85 over 6–12 months.⁴⁴⁵ However, adverse effects occurred, particularly following nitrofurantoin, and 30% of women did not adhere to treatment. Any benefit was lost as soon as the prophylaxis stopped. Post-coital antibiotics were equally effective as nightly prophylaxis.^{445,446} Previous studies before the rise in resistance showed the same effect with post-coital single-dose cefalexin when used for recurrent urinary infection in pregnancy.⁴⁴⁷ If recurrence is not too frequent it may be better to provide the patient with standby nitrofurantoin, to take as soon as symptoms occur; this approach was shown to result in less use of antibiotics and intuitively should result in less antibiotic resistance. Studies with cefalexin before the rise of ESBLs showed a slight increase in use, with post-coital cefalexin offset considerably by antibiotics used in treatment of UTI recurrences.⁴⁴⁸ The offset needs to be taken into

account in individual patients if standby nitrofurantoin is used. Prophylaxis, if used, can usually be stopped after a year without a resumption of the recurrences⁴⁰⁵ and there are now European guidelines that this review should be made at 6 months.⁴⁴⁹ The increase in trimethoprim resistance makes prophylaxis with this drug less suitable than it was and prolonged nitrofurantoin is associated with an increased risk of unwanted pulmonary damage, although this is rare. Patients on prophylaxis for >6 months should be reviewed. If the patient wishes to continue with a prophylactic regimen, consideration should be given in advance as to which antibiotic would be appropriately substituted for trimethoprim, nitrofurantoin or indeed ciprofloxacin (which can also be used in prophylaxis), if resistance develops or a breakthrough infection occurs. Persisting with an agent where breakthrough with a resistant strain has occurred will be ineffective. Cranberry juice prophylaxis is less effective in preventing breakthrough infection but co-trimoxazole generates more multiple resistance in breakthrough strains.⁴⁵⁰ Prophylaxis with β -lactam antibiotics commonly selects for resistant Enterobacteriaceae in the faecal flora and is not recommended.⁴⁵¹ There are relevant studies of prophylaxis after symptomatic UTI in infants who show similar problems with emergence of resistance on continuous prophylactic antibiotics, including resistance to cephalosporins due to ESBL production.^{452,511}

NICE notes that prophylactic antibiotics given at catheter change or insertion do not reduce infections in those with urological conditions and recommends that they should not be used;⁴⁵³ such use for any indication contributes to pressure on emergence of resistance and should be avoided. NICE recommends that clinicians should consider antibiotic prophylaxis at change of catheter for patients who: (i) have a history of symptomatic UTI after catheter change; or (ii) experience trauma during catheterization (frank haematuria after catheterization or two or more attempts of catheterization). Placement of an incontinence implant is also an indication for short-term prophylaxis but the recent insertion of an orthopaedic implant is not.

Evidence

Specific symptoms and signs hitherto accepted as characteristic of urinary infection have different predictive values.

Evidence level: 1+

In women with uncomplicated urinary infection the highest positive predictive value for strip testing was for having nitrite alone or nitrite with either positive leucocyte esterase or blood.

Evidence level 1+

There is no patient benefit in treating asymptomatic bacteriuria except in pregnancy.

Evidence level: 1+

Using an algorithm based on fever and at least one sign of urinary infection reduces the number of antibiotic prescriptions in nursing homes.

Evidence level: 3

Treatment or prophylaxis with antibiotics in catheterized patients increases colonization by antibiotic-resistant strains.

Evidence level: 1+

Prophylactic antibiotics given short-term at catheter change or insertion do not reduce infections but are indicated with specific

criteria of: (i) traumatic catheterization; (ii) previous severe symptomatic infection on catheter change; or (iii) to cover placement of a urinary continence implant.

Evidence level: 4

In recurrent UTI, antibiotic prophylaxis is very effective whether given daily (Evidence level: 1++) or post-coitally (Evidence level: 1+) but an alternative is to consider pre-prescribed standby antibiotics to take at the onset of symptoms.

Evidence level 4.

If prophylaxis is used and effective it should be usually restricted to 6 months prescription.

Evidence level 3

Previous resistances or breakthrough of resistant isolates on prophylaxis should preclude use of an agent and consideration should be given to unwanted effects with long courses and what antibiotic would be chosen for breakthroughs.

Evidence level 4

Recommendations

- Always consider the positive and negative predictive value of specific symptoms before sending urine for culture or starting antibiotics for a UTI. Use dipstick tests, if no catheter is present, to confirm the diagnosis before prescribing, especially when symptoms are mild or not localized.
Grading: Strong recommendation for
- For an elderly patient, do NOT send urine for culture or start empirical antibiotics unless there are specific symptoms or signs of UTI and none elsewhere. Use the algorithm in Figure 5 to decide whether to do this in elderly patients, especially in those with dementia.
Grading: Conditional recommendation for
- Do not prescribe antibiotics in ASB in the elderly with or without an indwelling catheter.
Grading: Strong recommendation for
- Avoid antibiotic prophylaxis for urinary catheter insertion or changes unless there is previous history of symptomatic UTI with the procedure, insertion of incontinence implant, or trauma at catheterization.
Grading: Conditional recommendation for
- To reduce recurrent UTI, consider first the option of pre-prescribed standby antibiotics to take when symptoms begin, rather than daily or post-coital antibiotic prophylaxis.
Grading: Conditional recommendation for
- Where prophylaxis is used successfully for recurrent infection in adults limit use to 6 months.
Grading: Conditional recommendation for

10.2 Choosing a suitable antibiotic

Choosing an antibiotic to which a uropathogen is susceptible is important, as UTI symptoms resolve more slowly when an inappropriate antibiotic is given.⁴⁵⁴ All patients should be given advice on when to seek further medical advice, i.e. if their symptoms worsen (even if, after taking antibiotics, on the same day) or do not improve after several days. Treating patients with infections due to MDR GNB in the community is a challenge as oral antimicrobial treatment is preferred. ESBL-producing bacteria are generally resistant to trimethoprim, ciprofloxacin, amoxicillin and cephalosporins; susceptibility to amoxicillin/clavulanate is variable and

interpretation by the laboratory is affected by different breakpoints used formerly by BSAC, and currently by EUCAST, or CLSI.

Local community antibiotic guidance should be informed by national and local surveillance data. An algorithm on choices based on the individual agents discussed is given in Figure 4. Choosing between fosfomycin, pivmecillinam and nitrofurantoin is difficult as there are no direct comparisons of these three antibiotics in infections due to ESBL-producing organisms. High failure rates with pivmecillinam may be due to the precise ESBL present and not using the drug in combination with amoxicillin/clavulanate, or possibly inadequate dosage: optimal ways to use the drug now in the UK have not been proven. In urinary infections due to non-ESBL-producing organisms, nitrofurantoin for 3 days (or 7 days, which is not significantly different from the results of a 5 day course)⁴¹⁰ and a single dose of fosfomycin have similar efficacy.^{455,456}

In a systematic review of the length of antibiotic treatment for acute uncomplicated urinary infection before the rise in prevalence of ESBL-producing Enterobacteriaceae, therapy for 3 days, delivered in the case of fosfomycin trometamol by a single 3 g dose, was similarly effective to prolonged therapy in achieving symptomatic cure for cystitis.⁵¹² However, in this systematic review bacteriological failure rates in the subgroup of trials where the same antibiotic was used in both short and long treatment arms of the trial were higher in the short-duration arms (RR 1.37, 95% CI 1.07–1.74; $P = 0.01$). After a single dose of fosfomycin, high concentrations are usually maintained in the urine for 2 days. This is usually curative in uncomplicated UTI in women, but for infection due to confirmed ESBL producers, or in males, a second dose on the third day has been suggested to promote bacteriological cure.⁴⁵⁷ On the same basis 7 not 3 days of nitrofurantoin would be recommended for confirmed ESBL-producing bacteria and 7 days for pivmecillinam regimens. Although frequently used as an endpoint in regulatory trials, it is uncertain if bacteriological cure immediately after treatment is of any long-term clinical or bacteriological significance in patients with UTIs involving MDR GNB, but the precautionary principle of adequate elimination of infections with MDR GNB would suggest regimens for best bacteriological cure should be followed in such cases. Eight studies in the systematic review included pivmecillinam at various doses and durations. An analysis of *E. coli* strains from persistent or relapsed infection after pivmecillinam showed an increased frequency of phylogenetic group B2 (which includes ST131) and showed that, when matched by virulence factors, 7 days of treatment was preferable to 3 days of therapy because it was less likely to be followed by persistence or relapse.⁴⁵⁸ Studies of urinary infection with strains producing the CTX-M-15-ESBL suggest that pivmecillinam alone at 200 mg three times daily is inadequate treatment. *In vitro* studies suggesting use with amoxicillin/clavulanate have not been followed by clinical trials.

Based on evidence collected before the spread of ESBL-producing strains, nitrofurantoin (100 mg twice daily) should be given for 3 days, not 7 days, for fully susceptible strains. No trials of nitrofurantoin 100 mg twice daily with ESBL-producing strains have been published, although the antibiotic is widely used. Efficacy, relapse/recurrence rates or incidence of spread to the upper urinary tract or bloodstream are all uncertain and no studies have been published on the emergence of resistance during or after treatment or in relapses. MDR *Klebsiella* spp., but not *E. coli*, are commonly resistant to nitrofurantoin but the mechanisms for resistance in the UK have not been investigated recently.

Evidence

Local community antibiotic guidance on empirical treatment of urinary infection should be informed by national and local surveillance data.

Evidence level: 4

In lower uncomplicated UTI where risk factors for MDR GNB are present these four treatment options can be used rather than trimethoprim:

(i) Fosfomycin trometamol.

Evidence level: 2+

(ii) Nitrofurantoin (unless patient's eGFR is less than 45 mL/min/1.73 m²).

Evidence level: 2+

(iii) Pivmecillinam, but *in vitro* and clinical data suggest this is less successful than fosfomycin trometamol or nitrofurantoin for ESBL-producing bacteria likely to be present in the UK.

Evidence level: 3

(iv) Another other relevant antibiotic if the causative organism is confirmed as susceptible.

Evidence level: 4

Recommendations

- Inspect up-to-date national and local antibiotic surveillance when compiling local antibiotic guidelines on treatment of UTI. Grading: Strong recommendation for
- If there are risk factors for MDR GNB or previous presence of MDR GNB and the patient is symptomatic, send a urine specimen for culture and susceptibility testing. Grading: Strong recommendation for
- Always inform the patient or their carer(s) on what to look out for and how to re-consult if symptoms worsen or do not improve as community-onset *E. coli* bacteraemias of urinary origin are increasing. Grading: Strong recommendation for
- Use fosfomycin, or nitrofurantoin or as third-line choice pivmecillinam, guided where possible by: (i) susceptibility testing; and (ii) this guideline's recommendation on choice, combinations, dosing and duration, for uncomplicated lower UTI where MDR GNB are suspected. Grading: Strong recommendation for
- Use nitrofurantoin for 5 days with MDR GNB. Alternatively use fosfomycin trometamol 3 g orally as a single dose, and repeat on the third day only if MDR GNB are confirmed to improve bacteriological cure. Pivmecillinam at 200 mg three times daily for 7 days may be a third-line choice but consider combination use with amoxicillin/clavulanate. Clinical trial results on pivmecillinam for MDR GNB in the UK are urgently required. Grading: Conditional recommendation for

10.3 Treatment of pyelonephritis and complicated UTI caused by MDR GNB

Whenever resistant pathogens are anticipated, it is essential to send a urine specimen for culture and susceptibility testing before empirical treatment and such specimens will be useful in this condition even if resistant pathogens are not anticipated.

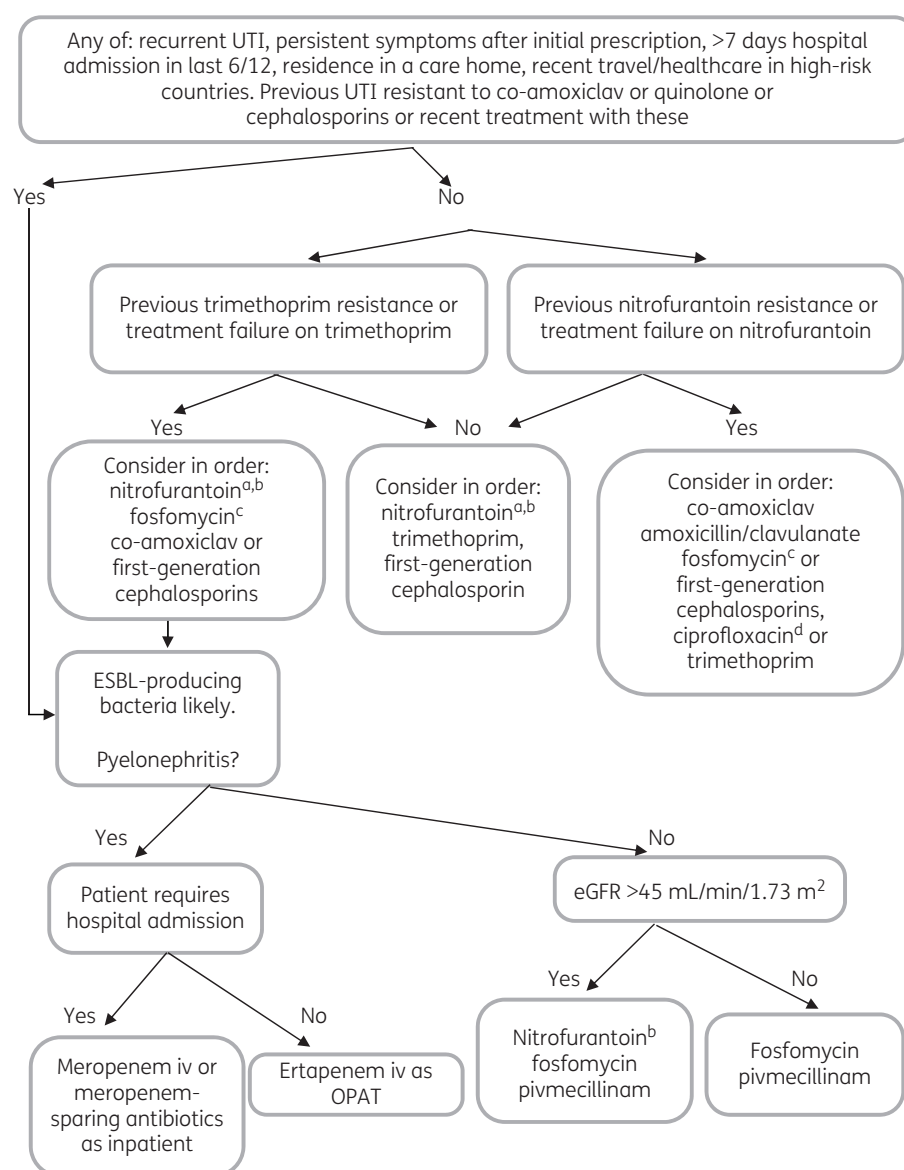


Figure 4. Suggested algorithm for the treatment of UTI in the UK community likely to be due to MDR GNB. ^aNot nitrofurantoin if pyelonephritis or eGFR <45 mL/min or age <50 years. ^bCaution regarding prolonged/frequently repeated courses. ^cNot fosfomycin if pyelonephritis. ^dUnlike co-amoxiclav, first-generation cephalosporins, fosfomycin and pivmecillinam, ciprofloxacin is generally active against *Proteus vulgaris*, *Morganella* and *Providencia*.

As nitrofurantoin, pivmecillinam and oral fosfomycin are currently considered inappropriate in suspected or confirmed pyelonephritis, intravenous ertapenem (unlicensed in Europe for this indication) should be given in an OPAT setting to treat patients with pyelonephritis confirmed or suspected to be caused by ESBL-producing pathogens that are resistant to trimethoprim and quinolones.^{163,164} If the patient requires admission to hospital, meropenem or, depending on costs and local policy, ceftolozane/tazobactam or temocillin should be given for infection due to ESBL-producing strains. Piperacillin/tazobactam may be considered if the isolate has been shown to be susceptible. Amikacin might be considered but activity may be impaired if AAC(6')-Ib-cr is produced. In practice strains with this enzyme may be reported as either susceptible or resistant and the enzyme cannot easily be

detected: no trials of amikacin use against such strains have been reported. Measuring amikacin levels promptly and adjusting doses is less likely to be easily supportable than use of gentamicin, but the latter is unsuitable for infection with ESBL producers unless susceptibility is known.

Ceftazidime/avibactam or non- β -lactam agents in combination perhaps with meropenem should be considered for infections with CPE (Figure 4). Temocillin may have a place for more susceptible strains with KPC carbapenemases but this has not been established by trials; it does not have a role against strains with MBLs or OXA-48-like carbapenemases. Such factors and choices are important when empirically treating pyelonephritis caused by probable or confirmed MDR GNB as this may be complicated by bacteraemia.⁹⁴

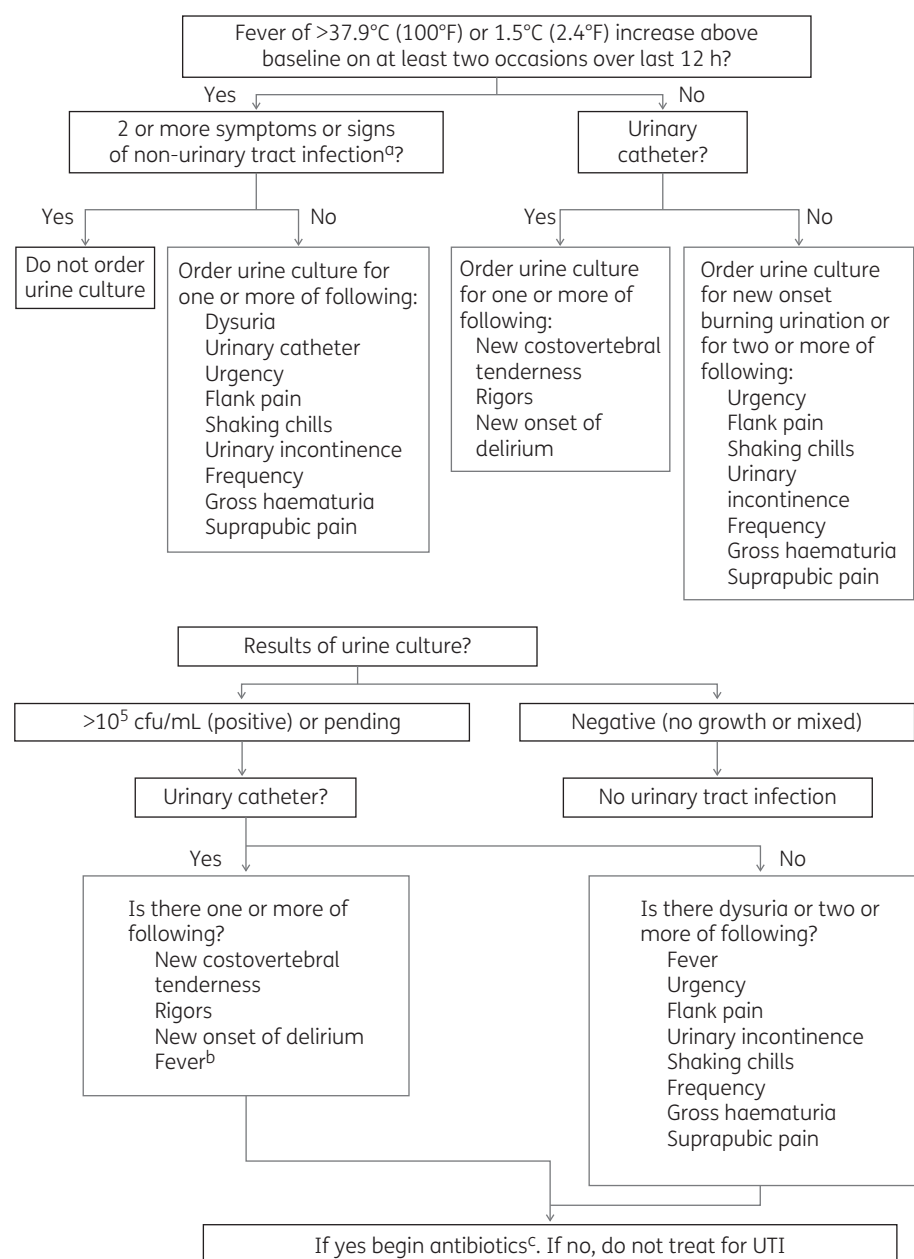


Figure 5. Diagnostic algorithm for ordering urine cultures and starting antibiotics if positive for nursing home residents in the intervention arm in the Loeb trial.⁴⁴⁴ Reproduced from ‘Effect of a multifaceted intervention on number of antimicrobial prescriptions for suspected urinary tract infections in residents of nursing homes: cluster randomized controlled trial’ *BMJ* 2005; **331**: 669, with permission from BMJ Publishing Group Ltd.⁴⁴⁴ ^aRespiratory symptoms include increased shortness of breath, increased cough, increased sputum production and new pleuritic chest pain. Gastrointestinal symptoms include nausea or vomiting, new abdominal pain and new onset of diarrhoea. Skin and soft tissue symptoms include new redness, warmth, swelling and purulent drainage. ^b>37.9°C (100°F) or 1.5°C (2.4°F) above baseline on two occasions over last 12 h. ^cStop antibiotics if urine culture is negative or no pyuria is present.

If a patient with pyelonephritis due to ESBL-producing bacteria has penicillin or cephalosporin hypersensitivity, there are two alternative strategies. Firstly meropenem can be given despite a risk of cross-allergenicity, which is now thought to be largely hypothetical. In this case caution must be exercised, with appropriate drugs ready to treat any severe acute reaction. This seems to be safe.¹⁵⁴ Alternatively, urgent susceptibility tests by automated methods should be performed. Depending on any previous results for the

patient’s isolates, intravenous gentamicin or amikacin (which has more auditory than vestibular toxicity but a lower resistance rate than gentamicin) may initially be used until a less-toxic antibiotic can be identified from the concurrent susceptibility testing. Trimethoprim, ciprofloxacin or co-amoxiclav can be used in pyelonephritis if the pathogen is known to be susceptible (or a susceptible organism has been isolated in the preceding month with a satisfactory therapeutic response). A retrospective cohort study of

community-onset acute pyelonephritis due to ESBL-producing *E. coli* compared 85 patients receiving carbapenems with 67 receiving other agents to which the infecting bacterium was susceptible *in vitro*. There was no difference in rates of clinical or microbiological failure.⁴⁵⁹ A randomized double-blind controlled trial showed that 7 days of ciprofloxacin 500 mg twice daily was as effective as 14 days of trimethoprim/sulfamethoxazole against susceptible organisms. However, trimethoprim and quinolone resistance are now common and therefore none of these agents remains suitable for empirical use in any case of pyelonephritis.⁴⁶⁰ The substitution of OPAT therapy for oral antibiotic use in early pyelonephritis has not been costed for its effects on services.

Evidence

Pending antibiotic susceptibility testing, patients at increased risk of MDR GNB and suspected of pyelonephritis or complicated UTIs (i.e. indwelling catheter, recent urinary instrumentation, renal stones, prostatic obstruction, diabetes, immunosuppression, pregnancy, functional or anatomical urological abnormality)⁴³⁷ can be treated empirically with:

- (i) OPAT with intravenous ertapenem.
Evidence level: 2+
- (ii) Admission for (a) intravenous meropenem, temocillin or ceftolozane/tazobactam if infected by ESBL-producing *E. coli* or *Klebsiella* spp.; (b) intravenous fosfomycin and colistin with or without meropenem or ceftazidime/avibactam therapy if infected by a susceptible carbapenemase producer.
Evidence level: 1+
If hypersensitive to penicillin treat with meropenem with caution or gentamicin (if no past evidence of resistance) or amikacin.
Evidence level: 4
- (iii) Trimethoprim, ciprofloxacin or co-amoxiclav if urine testing shows an organism that was susceptible in the preceding month and there has been no history of clinical failure.
Evidence level: 1+

Recommendations

- In pyelonephritis always collect a urine sample before treatment. MDR GNB are unlikely to respond to oral treatment so consider risk factors for an MDR isolate, including travel. Use an active oral agent only if the patient is well enough and if known to have had ciprofloxacin-, trimethoprim- or co-amoxiclav-susceptible MDR GNB in last month.
Grading: Conditional recommendation for
- If the patient has pyelonephritis and risk factors for MDR GNB, start, if hospitalization not required, empirical intravenous therapy with ertapenem if OPAT therapy available. This will treat ESBL- and AmpC-producing Enterobacteriaceae. If the patient needs hospitalization, or OPAT is not available, admit for meropenem, temocillin or ceftolozane/tazobactam if no evidence of a CPE organism. If the patient is penicillin hypersensitive then the hospital may use amikacin or meropenem, or if only susceptible isolates in the past, gentamicin. If carbapenem-resistant bacteria are, or have been, present, base treatment on susceptibility testing of recent or current isolates.
Grading: Strong recommendation for

10.4 What is the threshold level of resistance for changing the choice of empirical treatment for UTIs?

Most patients with UTI are treated empirically, particularly in a first episode of lower UTI. Failure of empirical therapy, particularly in complicated UTI (e.g. pyelonephritis), is a common source of Gram-negative bacteraemia where increased 30 day mortality is associated with ineffective empirical therapy,^{256,461} though perhaps only in patients with sepsis syndrome. The probability of ineffective empirical therapy would be predicted to increase as the proportion of ESBL-producing, or carbapenem-resistant, bacteria rises. Older narrower-spectrum antibiotics may be recommended for empirical use in order to slow the emergence of resistance. One group of authors asserts that the right of future patients to come to less harm outweighs the right of the present patient to share in decisions on antibiotic treatment,⁴⁶² but this is a view many do not share. There is no agreement within the Working Party on the threshold resistance rate to an antibiotic that would justify substitution of other agents, nor on the degree to which routine laboratory testing of submitted samples overestimates the 'true' resistance rate.⁴⁶³ Rates of 20% have been suggested as justifying a change of empirical treatment in UTI. Confounders are: (i) that resistance rates are affected by duplicates within the series, including when infection control sampling is intensive;⁴⁶⁴ (ii) a bias towards performing culture and susceptibility only for difficult/unresponsive cases; (iii) sequential testing of second-line agents only for resistant strains according to local laboratory policy;¹¹⁷ and (iv) differences in breakpoints between laboratories. These sources of variation may justify central susceptibility testing of all UTI from sentinel groups of general practitioners (GPs) in regions for national surveillance purposes or requirements for national notification and annual updating of method changes and assessment of their effects.⁴⁶⁵ Local and regional variations exist in resistance rates for ESBLs as demonstrated by regional and national surveys. Quinolone resistance rates in *E. coli* are below 20% in most reported susceptibility surveys but resistance in bacteraemia is associated with increased mortality and with the ST131 group of strains, which have an unrivalled ability to acquire other resistances. The risk of selection for resistance with a switch from trimethoprim leads us not to recommend their widespread use.

When the probability of bacteraemia arising from UTI rises, a lower threshold for altering normal treatment to cover a resistant strain is needed owing to the greater risk to the individual patient. A threshold of <5% resistance may be appropriate for higher-risk situations.

Evidence

There are no accurate current figures on the prevalence of antibiotic resistance in UTI. Routine clinical data are subject to sample bias. These probably lead to overestimated resistance.

Evidence level: 2–

A threshold of 20% true resistance has been suggested as an indication to change 'first-line' empirical treatment of lower UTI. A lower threshold of, perhaps, 5% is appropriate when the risk of the patient becoming bacteraemic is increased. The Working Party consider that, in the absence of accurate national resistance surveillance, these or similar thresholds presently can only be applied at a local laboratory level with (i) careful de-duplication,

(ii) precisely understood testing policies, and (iii) consistent local methodology.

Evidence level: 4

Recommendations

- Locally assess the true rate of resistance and determine from this when changes to guideline recommendations for empirical therapy in UTI are necessary, including recommendations where the risk of antibiotic-resistant bacteraemia is high.
Grading: Conditional recommendation for
- Personalize empirical chemotherapy for each patient by considering current features of bacteraemia, risk factors for antibiotic resistance and past susceptibility testing, including the presence of MDR GNB in the patient or unit.
Grading: Conditional recommendation for

11. What effect does good antibiotic stewardship have on rates of MDR GNB?

11.1 The impact of good antibiotic stewardship in secondary/tertiary care facilities

The evidence base and practice of antibiotic stewardship in the UK has been recently promulgated in the PHE 'Guidelines for Antimicrobial Prescribing and Stewardship Competencies'⁴⁶⁶ and the guidance from NICE Guideline 15 'Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use'.⁴⁶⁷ This report will focus on aspects of stewardship that pertain to MDR GNB: more general aspects can be found also in the above sources. A Cochrane systematic review showed that interventions to reduce excessive antibiotic prescribing to hospital inpatients might reduce antimicrobial resistance and that interventions to increase effective prescribing can improve clinical outcome.⁴⁶⁸ Of the 89 studies cited to 2009 (reporting 95 interventions), 56 were interrupted time series (ITS), 25 were RCTs, 5 were controlled before-after studies (CBAs) and three were controlled clinical trials (CCTs). The reporting of outcomes was very variable (only 13/25 RCTs reported on mortality and only 5 on readmissions), complicating the comparative assessment of studies. Interventions that enhanced the quality of prescribing in patients (defined softly as prescribing in accordance with guidelines) with any infection had no effect on mortality whereas interventions to increase compliance with evidence-based guidelines in community-acquired pneumonia, usually due to Gram-positive *S. pneumoniae*, were associated with reduced mortality. Reducing prescribing for all indications, determined as excessive by reference to evidence-based guidelines, was associated with increased re-admission but not with increased mortality or length of stay. Restrictive and persuasive interventions were associated with improved prescribing outcomes based on median outcome effect (proportion of subjects with an improvement or change in antibiotic selection, dose, route or duration versus control). Multifaceted interventions were common but not necessarily more effective than simple interactions. Most (80/95, 84%) of the interventions targeted the antibiotic prescribed (choice of antibiotic, timing of first dose and route of administration). The remaining 15/95 interventions aimed to change exposure of patients to antibiotics by targeting the decision to treat or the duration of treatment. Only

nine studies reported the effect of interventions on colonization or infection with antibiotic-resistant Gram-negative bacteria. Seven of these were ITSs, with a median effect size of 4.7%.^{469–474}

Although most studies reported >25% reduction in colonization/infection with resistant Gram-negative bacteria, the confidence intervals were wide and in two studies the effects were not statistically significant^{471,475} and one crossover study of cycling empirical gentamicin, ceftazidime and piperacillin/tazobactam showed an unintended increase of 39% in colonization with GNB resistant to any of the target drugs.⁴⁷⁶ One cluster CCT in neonatal units showed, as intended, a reduction from baseline in colonization/infection of 68% by cefotaxime-resistant organisms, predominantly *E. cloacae*, when the initial empirical treatment was penicillin and tobramycin rather than ampicillin/cefotaxime.⁴⁷⁷ That study, the only one of the nine to report on mortality, showed a small increase in mortality when penicillin and tobramycin was substituted for cefotaxime/ampicillin in matched neonatal units. A 2017 update of this Cochrane review⁴⁷⁸ concluded that there was still no statistically significant evidence that antibiotic stewardship reduced multiple antibiotic resistance, although the impact on *C. difficile* is undoubted. Additionally this updated unwanted effects from stewardship interventions, including an aminoglycoside substitution producing acute kidney injury²⁸² (see Section 7.12) and studies where there was consequent delay in instituting antibiotics. Furthermore, some studies reported a disruption of interaction between physicians and infection specialists as guidelines were used more frequently. Nevertheless, an editorial on this review called for stewardship to be adopted in every healthcare institution.⁴⁷⁹ One must now consider the homogeneity and quality of local hospital guidelines, given guideline compliance is being used as a criterion of good stewardship.

In the 2013 Cochrane review,⁴⁶⁸ 11 studies of attempts to reduce excessive prescribing reported data on mortality with no significant overall effect seen (and this continued to be the case in the 2017 revision).⁵¹³ Interestingly, one of the ITS studies examined the impact of a switch from penicillin and gentamicin to penicillin and amikacin in a neonatal unit with gentamicin-resistant *E. cloacae* infections and showed a reduction in gentamicin-resistant *E. cloacae* but an increase in *E. aerogenes* and enterococci.⁴⁷⁴

Kaki et al.⁴⁸⁰ produced another systematic review of antibiotic stewardship programmes, limited to the critical care unit. These included three RCTs, three ITSs and 18 uncontrolled before-and-after studies. Introduction of various antibiotic stewardship interventions led to 11%–38% reductions in antimicrobial DDDs/1000 patient-days (except in a single study that found an increase of 6%), and lower total antimicrobial costs. Stewardship programmes led to shorter average duration of antibiotic therapy, less inappropriate use and fewer antibiotic-related adverse events. They also found some reductions in antimicrobial resistance rates extending beyond 6 months.

A meta-analysis of 52 ITSs was used to compare restrictive versus persuasive interventions.⁴⁶⁸ Restrictive interventions had significantly greater impact on prescribing outcomes at 1 month (32%, 95% CI 2%–61%; $P=0.03$) and on microbial outcomes at 6 months (53%, 95% CI 31%–75%; $P=0.001$) but there were no significant differences at 12 or 24 months. Clinical outcome data were limited, with 11 studies reporting on all-cause mortality but with no defined time-boundary, 4 studies showing increased

mortality and 7 finding decreased mortality, giving a non-significant overall effect (0.92, 95% CI 0.81–1.06; $P = 0.25$).

In the USA, the Department of Veterans Affairs (VA) recently commissioned a systematic review of antimicrobial stewardship programmes (ASPs).^{481,482} The key findings have been published and the reader is referred to these publications for details.^{483,484} To avoid duplication, the VA systematic review only included papers meeting their eligibility criteria but not included in the 2013 Cochrane review. The review reported mixed results for clinical/microbial outcomes and overall improvement in prescribing. Because (i) few studies of different interventions reported each outcome, (ii) there was inconsistency across studies and (iii) there was medium/high risk of bias, the strength of evidence for all clinical outcomes was low: no single ASP was found to be superior but amongst studies since 2000 the greatest body of evidence of effectiveness was for decreasing inappropriate or increasing appropriate antibiotic use. Effects were seen across all species of Gram-negative bacteria and broad-spectrum antimicrobials.

There are individual studies of high quality. Introduction of a stewardship programme in one US hospital reduced the use of broad-spectrum agents, and was associated with a reduction in hospital-acquired infections caused by MDR GNB from 37% to 8% over 6 years.⁴⁸⁵ Similarly, resistance in *P. aeruginosa* declined when state guidelines on stewardship were implemented using a computerized programme in an Australian ICU.⁴⁸⁶ In another study in Israel, a carbapenem-restriction policy was used as part of a successful infection control strategy also including emergency department flagging of colonized or infected patients, building an isolation facility, eradication of clusters, and environmental and personnel hand cultures, with rectal screening of 8376 patients. This was effective in controlling an outbreak of carbapenem-resistant *K. pneumoniae*. Although there was a significant reduction in meropenem use, prescription of colistin rose.⁴⁸⁷ Restriction of use of some antibiotics may need, or lead to, use of a diversity of other agents and even introduction of newly available antibiotics or appropriate use of older agents. These aspects also need to be subject to stewardship with appropriate actions in responsible bodies within hospitals and reporting to users. This can be complex and time consuming. Some effective interventions are simple; for example, a high-quality study compared 8 and 15 day antibiotic treatment of ventilator-associated pneumonia ($n = 401$) and did not find any difference in mortality or unfavourable outcome. Patients who received 8 days of treatment had significantly less emergence of MDR pathogens (42% versus 62%; $P = 0.04$) but had a higher recurrence rate if they initially had non-fermenting organisms as pathogen [40.6% versus 25.4% (risk difference 15.2%), 95% CI 3.9%–26.6%].⁴⁸⁸

Effective antibiotic stewardship requires the use of timely bacterial antimicrobial susceptibility testing. Relatively simple phenotypic tests, such as a comprehensive antibiogram by automated methods, screening for resistance in bacteraemia isolates by direct disc testing,⁵¹⁴ double disc diffusion tests for ESBL, and biochemical carbapenemase detection, can provide useful information for treatment and infection control purposes.⁵¹⁵ Automated diagnostic tests for bacterial identification (e.g. MALDI-TOF) and PCR-based resistance gene detection (e.g. Cepheid® for carbapenemase and ESBL detection) can provide even more detailed information within the same day for MDR GNB. More rapid susceptibility

testing methods for resistance detection are being developed. Further information may be found in recent reviews.^{515–518}

This information together with promptly administered appropriate antibiotics is likely to improve prognosis. All UK laboratories should have access to the phenotypic and basic genotypic methods described above within their resources. As a performance measure, overall time elapsed from sample collection to administration of treatment appropriate to the bacterial susceptibility can and should be assessed and repeatedly audited against what could best be achieved with modern methods. Particular attention should be paid to MDR GNB as defined either for community- or hospital-originating strains. Audit of outcomes associated with bacteraemia provides an objective measure of the appropriateness of antimicrobial treatment, particularly for MDR GNB.

The deployment of antibiotic stewardship programmes is variable, as shown by a survey of 660 hospitals in 67 countries.⁴⁸⁹ That study included the first data from sites in Asia, Africa and South America, many with considerable problems with MDR GNB. There is an urgent need for the adoption of an international antibiotic stewardship timetable.

Evidence

Up-to-date local resistance and outcome surveillance data are needed to inform guidelines on empirical antibiotic advice and must be persuasive to medical and nursing staff, to all prescribers and to pharmacists advising on guidelines.

Evidence level: 4

Interventions intended to decrease prescribing that is excessive (by reference to guidelines) for specific antibiotics have been associated with reductions in both colonization and infections caused by carbapenem, aminoglycoside or cephalosporin-resistant bacteria, but this is not a consistent finding across all stewardship initiatives.

Evidence level: 2++

Restrictive rather than persuasive prescribing interventions cause a significant short-term change in prescribing and there is scanty evidence that they may contribute to reductions in the prevalence of resistant GNB. Persuasive prescribing interventions should also be used and are as effective over a 1–2 year period.

Evidence level: 2++

Clinical outcome data on infections that is linked to antibiotic prescribing should be collected as well as data on resistance and prescriptions of antimicrobials to ensure stewardship approaches do not degrade outcomes, and ensure high and consistent standards between hospitals.

Evidence level: 2++

Audit and feedback should be used to reduce antimicrobial use in hospitals. Local and national advice on which antibiotics to prescribe are a useful standard against which to conduct audits and to explore clinical and microbiological outcomes.

Evidence level: 4

Recommendations

- Provide an on-going antimicrobial stewardship programme in all care settings, based on resistance rates, with audit of compliance with guidelines, surveillance of outcomes, and

active feedback.

Grading: Strong recommendation for

- Use restrictive prescribing policies to acutely reduce the incidence of infection, or colonization, with MDR GNB; thereafter, maintain persuasive and restrictive approaches and monitor to check whether gains persist.

Grading: Strong recommendation for

- Identify through horizon scanning, and make available, new antimicrobials that may be required to treat MDR GNB. Monitor their use through formulary/drug and therapeutics committees.

Grading: Conditional recommendation for

11.2 The national monitoring of good antibiotic stewardship in secondary/tertiary care facilities

Antibiotic therapy differs from other treatment in man in being directed against diverse and frequently unknown organisms and in exercising selection for resistant organisms; these change the potential target for drug action and may then cause infection either in the same or other patients. Treatment options for infections due to MDR GNB are restricted and failure to deploy appropriate treatment in these infections may be associated with a poor outcome whereas excessive use of a single agent in a hospital or unit is more likely to select for superinfection caused by resistant organisms. The clinical governance of antibiotic policies is therefore a balance between treatment of the individual and management of the community's antibiotic armamentarium.

Antibiotic use and the prevalence of MDR GNB are now widely monitored in communities and hospitals but (i) monitoring use does not indicate whether use was appropriate, and (ii) monitoring the accumulative prevalence of resistant strains is no guide to the incidence rate of new cases caused by MDR GNB. Root cause analysis of individual cases is burdensome and very complex if it is intended to relate to outcome. It also runs the risk of bias with regard to outcome unless the proportions of resistant or susceptible organisms that are examined match the overall population. It does not produce reliable statistically comparable data between institutions to support good practice. Nevertheless, such comparisons were used with MRSA bacteraemia and *C. difficile* in the past in the UK, but these are acute events unlike the chronic prevalence of antibiotic-resistant strains.

Clinical trials early in a product's availability offer guidance on efficacy against susceptible organisms and, with some agents, an indication of potential for selection for resistance. However, antibiotic efficacy is not usually sustained as resistance emerges, and unlike other classes of drug, early clinical trials become less relevant with the passage of time. Anticipating when empirical therapy should include coverage against MDR GNB is difficult but is a key part of local guidelines. Recommendations that (i) limit use of broad-spectrum drugs such as carbapenems or (ii) reserve particular agents for patients with MDR GNB present in infections that have a potential high mortality need also to consider the potential hazard of poor clinical outcomes.

Despite assistance from other professions, deployment of infection and microbiology specialists into surveillance and away from patient care is frequent, and mundane tasks in surveillance employing specialists should be reduced to a minimum, without excessively compromising data quality. Routine national reporting

systems on bacteraemia in the UK should be routinely linked to public health date-of-death data held nationally for each person by the Office for National Statistics, as has been described in one study restricted to *E. coli* bacteraemia.¹⁰² Such linked information should be fed back annually to, and within, individual hospitals and summarized findings should be provided to hospitals to enable comparisons of performance. Incidence and mortality rates in bacteraemia at the local level would provide key assurance on the prevention of systemic infections and the quality of outcomes. If these data on outcome were provided by patients, it would provide a focus to examine and attempt to reduce the increasing incidence of bacteraemias and their associated mortality. Furthermore, these data would ensure locally that overall and specific audit could be made of the antibiotic resistance in organisms and the antibiotics actually deployed to treat the serious infections that they caused. Added to existing data, such audit and source information could nationally and locally identify locations where there is high mortality either in primary or secondary/tertiary care, enabling appropriate investigation and action to be taken locally. A crucial foundation has already been organized in England and Scotland via mandatory reporting of bacteraemia data for *E. coli* which specifically include, *inter alia*, data on community or hospital onset and nursing home residency entered locally by laboratories. In England, laboratories voluntarily and automatically (via computer links) submit antibiotic susceptibility data for 82% (54 301/66 512 over 2 years) of cases of *E. coli* bacteraemia reported by the mandatory programme, which does not itself capture susceptibility data. This could be built upon to deliver local and nationally useful data on outcome by antibiotic resistance.⁹⁴ Furthermore, this process should be expanded to capture mortality information on other important bacteraemias, e.g. *Klebsiella* spp., where prevalence is increasing and resistance is a major global threat, or indeed to all bacteraemias. Reduction in the absolute number of associated deaths from bacteraemia may well involve changes other than in chemotherapy, provided audit suggests chemotherapy is actively employed and appropriate. This requires multidisciplinary joint engagement and clinical management expertise in the community quite as much as in hospital to avoid sepsis and improve its management. A decrease in prevalence of bacteraemia and MDR within such infections is one aspect of this. Quantitative reduction in the number of deaths, and not changes in the comparative position of hospitals and communities in their respective peer groups, should be the focus.

Bacteraemias should be assigned reliably as being of community-, wider healthcare- or hospital-onset so that responsibility can be assigned and accepted for performance by relevant commissioning groups, public health services and hospitals. Whilst the date of sampling of bacteraemia can be recorded, patients may become colonized by the causative bacterium much earlier and the exact timing of acquisition usually cannot be proven from existing laboratory records. IT coordination and shared responsibility across the health economy is needed to access the last date of discharge from hospital, which may be a practical proxy for date of colonization in cases of apparent community acquisition that are actually hospital-acquired. Where care does not involve transfer to a tertiary centre and the patient is not being admitted to multiple hospitals in a conurbation, such information should already be available in many localities, but non-automated extraction is time consuming. It is important for securing improvement that the

bacteria isolated from bacteraemias can be related to likely acquisition in hospital, wider healthcare or community and not simply to onset in hospital or community and that responsibility for resistant strains falls accurately on hospitals or community commissioners of healthcare. Targeting reductions in MDR GNB in potentially life-threatening infection is problematic because of variations between community populations in ethnic origin associated apparently with antibiotic resistance such as ESBL production.^{4,137} For this reason a simple process of commissioned reduction in resistance may be unachievable in some communities and their associated hospitals.

Residence in a nursing home is a marker of healthcare acquisition, not general community acquisition, and nursing-home patients should be separately and reliably categorized. Dates of hospital discharge of patients admitted from nursing homes may be relevant to intervention if the patient has moved between the nursing home and hospital recently—say within the last 2 years.

Tertiary and international referral in some hospitals (including referrals from armed forces deployed overseas⁴⁹⁰), even if the hospitals are not formally categorized as specialist hospitals, may also skew their resistance profile towards multiple resistance,^{491,492} so it is important to keep a balance between recognizing that this may be a reason for high resistance rates and ensuring that such resistant strains should be, as they always have been, a target for effective infection control. Again for this reason, targeting antibiotic resistance reduction appropriately within a national context may be more straightforward if it is directed at a local level.

Dates of collection of blood cultures, as recorded in laboratory computer systems, may be distorted by entry of default dates of registration on Monday mornings after submission of samples from Friday night on wards. There is no information on the frequency of this problem but it is time consuming to retrospectively correct or prospectively avoid. An interval of <3 days since admission is recommended for defining 'community onset' as more practical than the 48 h limit suggested internationally and probably without important consequence, if permitted. This should be investigated if the mandatory programme is expanded as recommended. Laboratory data should not be reported multiple times and should utilize as little manual entry as possible and hospital trusts should ensure the automated transfer of data from laboratory systems to monitoring bodies. Information transfer should be frequent. However in the presence of good infection control and absence of an ongoing MDR GNB outbreak, annual batch processing of mortality linkage and annual central audit should be adequate in most hospitals for governance monitoring of hospitals, and this would be adequate to support changes to infection management, including antibiotic policy (which are seldom made more frequently). Not only good performance in reducing antibiotic use but also better-than-average performance in bacteraemia reduction and better outcomes in bacteraemia (including that which is antibiotic resistant) should be rewarded.

Such laboratory-based extended surveillance of all bacteraemias would address: (i) the diversity of organisms and, at a local level, the match to antibiotics prescribed (which itself could be centrally reported, if pharmacy systems and laboratory systems are linked by patient/NHS number and then ordered by concatenated patient/NHS number and reversed Julian date); (ii) the usual, but not invariable, progression in antibiotic resistance rates; and (iii) the need for organizations to make changes to prescribing

policy with document control, feedback to clinicians and corporate responsibility of CCGs and hospitals for infection management. To address bacterial species- and resistance-specific aspects in any locality, analysis (including trend analysis) of data cumulated over 5 years may be needed to avoid problems with small numbers of some pathogens. Individual hospitals need more local as well as the existing national data to systematically analyse, explain and address unsatisfactory outcomes. The already striking increase in incidence of *E. coli* bacteraemia, often in patients being admitted from the community, will probably increase further with better ascertainment of sepsis. Commissioning attention needs to be paid to the appropriateness of prior chemotherapy (i.e. for UTIs in the community) to attempt to reduce such rising incidence and associated mortality. Owing to the rise of MDR GNB, central monitoring of, and action on, informatics is required in all hospitals. Collation of information is required to explain clinical and resistance outcomes by patient and to plan action in hospital- and community-onset cases. Early Warning Scores, which are required for such analysis, are frequently now available on computerized systems to monitor vital signs. Separate patient-based prescribing systems record the date of prescription and antibiotics given. Laboratory data systems record: (i) the date of collection of the first positive blood culture for an organism-episode from a patient; and (ii) the organism and its antimicrobial susceptibilities. These datasets should be linked electronically along with, from hospital patient administration systems, the admission date, the date of last hospital discharge and place of residence (i.e. home or residential care). Early Warning Scores of 6 or more within 3 days of the bacteraemia indicate a poorer prognosis in bacteraemia, but these data are collected continuously and may be difficult to link as single values. The most difficult area to address is usually the unequivocal assessment of outcome. Mortality is associated with poor functional state and comorbidities, which may link to age and have been assessed automatically from computerized discharge records of diagnoses (ICDs or diagnosis-related group codes) in the USA⁴⁹³ and France.⁴⁹⁴ Defining mortality at a point less than 30 days after bacteraemia could tighten linkages to resistance and inappropriate prescribing, and should be studied. Acute renal injury is also a useful outcome measure, as is subsequent development of *C. difficile* infection within 28 days. Sometimes these linkages can be made expediently without linking systems by exporting data and linking it in databases or spreadsheets, but the mechanics of this should not be dependent directly and solely on infection specialists, although they must advise on what should be done.

Quality and commissioning organizations should ensure hospitals are collecting and analysing all such data to explain and improve their results in the treatment of serious infections such as bacteraemia, not just those with MDR GNB. Particular scrutiny of year-on-year improvement in outcome of bacteraemia and reduction in prevalence according to onset in hospital or the community is needed both in CCGs and hospitals. Application of enhanced definitions of place of likely acquisition, together with the Working Party's definitions of multiresistance as applied to hospitals and the community and within the context of the local communities population make-up, may explain the reasons for, and sometimes enable multifaceted action on, problematic multiple resistance as a whole health economy approach. Hospital-, community-health-care- and community-onset bacteraemia therefore require separate analysis.

Evidence

Key components of an effective antimicrobial stewardship programme are consistent effort and audit of outcome by specialists with full communication and support from electronic prescribing/ laboratory and clinical records. Computerized systems can and should be integrated. Also required are full accountability of responsible organizations for occurrence of serious infections and the outcomes of treating them. Accurate information is required on serious infections with MDR GNB but must not be assessed in isolation.

Evidence level: 2+

Hospital or community antibiotic use (by DDDs, or perhaps better in the context of resistance selection, number of patients exposed to each agent) should be reviewed locally together with antibiotic resistance data. These datasets are available from pharmacy and microbiology systems respectively. Audit on compliance with local guidelines can be undertaken, but this provides no assurance on clinical outcome in severe infections; these require comparison with performance of other similar institutions and analysis to ensure the quality of care.

Evidence level: 2++

Extended surveillance of bacteraemia with appropriate record linkage both centrally and in the hospital would provide clinical outcome assurance in the most severe infections and also a means of comparing improvement in hospitals and communities. Furthermore, this would lead to a sharp focus on improvements to antibiotic guidance, usage and infection control

Evidence level: 2+

Recommendations

- Ensure production of local guidelines for empirical and definitive antibiotic use, regularly updated for community-, wider healthcare- and hospital-onset infections, and audit compliance with these.

Grading: Conditional recommendation for

- Integrate hospital IT to deliver annually linked data for each bacteraemia, including patient demographics, whether the bacteraemia's onset was in the community, wider healthcare or hospital, antibiotic resistances of isolates, antibiotics prescribed, and maximum early warning score or occurrence of septic shock, and, if possible, defined time-limited (not admission-limited) mortality. Use these integrated data to review the adequacy of treatment of infection in communities and hospitals.

Grading: Good practice recommendation

- Central public health departments or the Chief Medical Officers should receive bacteraemia data from the jurisdictions of Trusts and CCGs or equivalent primary care organizations annually. They should ensure computerized record linkage gives dates of death that can be added to, organism, specific antibiotic resistance and pattern, date of collection, nursing home residency, and optionally local records on last hospital discharge before bacteraemia. These data should be made available, for open interrogation and downloading, with rolling cumulative data within the health service. They should ensure mortality rate is categorized by locality (separately for hospitals and for community with associated separate wider healthcare data).

Grading: Strong recommendation for

- Make publicly available tabulated incidence and outcome data for bacteraemia, giving hospital onset data by region and hospital, and, for community and wider healthcare outcome data, by CCG or equivalent primary care organization. Correlate these data with similar analysed and tabulated annual data on total antibiotic use and organism and antibiotic resistance in clinical infections.

Grading: Good practice recommendation

- Continuously monitor bacteraemia outcomes and antibiotic resistance by organism and devise improvement programmes for both, locally and appropriately within health economies.

Grading: Good practice recommendation

- Consider central production of unbiased national or regional data on true resistance rates in community-onset localized or systemic infections to guide national community antibiotic recommendations.

Grading: Strong recommendation for

11.3 Antibiotic stewardship in the community and care homes to reduce MDR Gram-negative infections

Several RCTs in UK communities have shown that prescribing has been improved by multifaceted interventions that included (i) general practice staff education and (ii) education of the patient through improving communication during the doctor-patient consultation.^{495,496} There have also been several Cochrane reviews that included studies in hospitals, but which should be transferable to the community and care homes, aiming to improve antibiotic prescribing. In one Cochrane review, restrictive interventions (selective reporting of laboratory susceptibilities, formulary restriction, and antibiotic policy change strategies) had a greater effect in the short term in reducing use of broad-spectrum antibiotics than persuasive interventions (distribution of educational materials; educational meetings; local consensus processes; educational outreach visits; local opinion leaders; reminders provided verbally, on paper or on computer; audit and feedback). However, both were equally effective in controlling antibiotic use and antimicrobial resistance after 6 months.⁴⁶⁸ In a separate Cochrane review, printed educational materials alone had an effect on the practice of healthcare professionals and patient health outcomes.⁴⁹⁷ Based on seven RCTs and 54 outcomes, the median absolute risk difference in categorical practice outcomes was 0.02 when printed educational materials were compared with no intervention (range from 0 to +0.11).⁴⁹⁷ Other Cochrane reviews show multifaceted interventions are more effective. Moreover, interventions that are based on cognitive theories and consider personal attitudes, subjective norms and perceived behavioural controls (confidence and other barriers) are more likely to be successful, e.g. posters raise awareness and change subjective norms but are ineffective when used alone.

In an audit and feedback process, an individual's professional practice or performance is measured and then compared with professional standards or targets. The results of this comparison are then fed back to the individual. In general practices this will probably be via the medicine manager, local GP prescribing champions or in collaboration with local microbiologists. The aim is to encourage the individual to follow professional standards.⁴⁹⁸ A Cochrane review considered 82 comparisons from 49 studies of any healthcare interventions in which audit and feedback were core and evaluated effects on professional practice.⁴⁹⁸ There was a median

4.3% increase in healthcare professionals' compliance with desired practice (IQR 0.5%–16%) when: (i) baseline performance was low; (ii) the source was a supervisor or colleague; (iii) it was provided more than once; (iv) it was delivered in both verbal and written formats; and (v) when it included both explicit targets and an action plan. In addition, the effect size varied based on the clinical behaviour targeted by the intervention.⁴⁹⁸ An RCT evaluating a multifaceted intervention in English general practice that was aimed at improving antibiotic prescribing included feedback of practice level data on antibiotic prescribing and resistance: this led to a 4.2% fall in total antibiotic use.⁴⁹⁵ In some parts of the UK, audit with action plans, and intense infection control measures, have been associated with falls in quinolone and cephalosporin use and resistance.^{4,499} Incentives attached to action plans can be very effective but, without personal attitude changes, the change may reverse when the incentive is reduced.⁵⁰⁰ Any audit indicators need to be well monitored, as implementation of an effective multiple-intervention strategy achieved no reduction of antibiotic prescription rates when deployed at a larger scale in general practice: the authors attributed the failure to a less tight monitoring of the intervention and audit.⁵⁰¹ It is necessary to demonstrate by further study that such interventions can be effective at practice or hospital unit/hospital level.

Relevant outcomes, which should be monitored, include mortality from systemic infections such as bacteraemia, hospital admission, emergency room attendance, requirement for outpatient parenteral antibiotic therapy, re-consultation in person or by telephone, time-limited re-prescription of antibiotics and microbiological and clinical persistence of infection.

Evidence

Restrictive and persuasive interventions are equally effective in controlling antibiotic use and antimicrobial resistance and a multifaceted approach is most effective.

Evidence level: 1+

Audit and feedback interventions result in an increase in healthcare professionals' compliance with desired practice.

Evidence level: 1++

Local and national surveillance data are needed to determine appropriate empirical antibiotic guidelines.

Evidence level: 3

Collection and analysis of outcome data are important in assessment of measures needed to improve the management of infection and to reduce the increase in antibiotic use and resistance.

Evidence level 2+

Recommendations

- Use persuasive and restrictive interventions to reduce the total antibiotic consumption, particularly broad-spectrum antibiotics in the community and care homes.
Grading: Strong recommendation for
- Provide and use active feedback of monitoring to prescribers and nursing staff, ensuring optimization of clinical, microbiological and antimicrobial prescribing outcomes. Use audit and feedback to reduce inappropriate antimicrobial use in the community and wider healthcare.
Grading: Strong recommendation for

- Review outcome data linked to antibiotic prescribing to improve quality of care in the community and care homes.
Grading: Conditional recommendation for

12. Conclusions

The selection of antibiotics for the treatment of infections caused by GNB has always been difficult. Following the introduction of the first antibiotics with activity against GNB, such as tetracycline, chloramphenicol and streptomycin, introduced in the late 1940s, resistance in *E. coli* causing UTI was observed at rates of 5%–10% as early as 1953.⁵⁰² Subsequently it emerged that Enterobacteriaceae can exchange and re-assort antibiotic resistance genes with great ease via plasmids, transposons, integrons and other mobile, or potentially mobile, genetic elements. This meant that resistances to antimicrobials no longer being used were easily and stably maintained as the relevant resistance genes commonly become genetically linked. These linked resistances became transferable to a wider and more versatile range of strains.

As each class of new agent was introduced, so resistance negated its reliable empirical use for the treatment of serious sepsis and also undermined any future reliance on the older agents. This is exemplified in the UK by the rise of plasmid-mediated TEM β -lactamase conferring resistance to ampicillin in the 1960s, aminoglycoside-modifying enzymes conferring gentamicin resistance in the 1970s, extended-spectrum TEM and SHV β -lactamases conferring cephalosporin resistance in the 1980s and, beginning in the 1990s, CTX-M ESBLs, DNA gyrase mutations and dihydrofolate reductases conferring resistance to third-generation cephalosporins, fluoroquinolones and trimethoprim, respectively. We are now facing a similar process with carbapenems and polymyxins.

The bacterial ability to maintain older resistances may undermine any benefit from the introduction of more resolute antibiotic stewardship. Over-reliance on stewardship as the sole strategy for reducing MDR GNB may not be productive, although reductions in antibiotic use, if they are substantial enough to reduce selection in the human microflora for resistant strains, are welcome. Use of a diversity of agents focused on proven bacterial infection may be more important than restricting⁴⁷⁸ entirely the use of certain antibiotics and classes. Empirical prescribing based on generic clinical diagnoses will also need to be safely reduced.

Because of widely differing usage of antibiotics active against GNB in both medicine and agriculture in different parts of the globe since the 1980s, we have created widely differing rates of occurrence of MDR GNB in these different locations and in some cases between food animals and man. Furthermore, the increasing recognition of reservoirs of pathogenic *E. coli* and *Klebsiella* spp. in different animal species suggests that animal husbandry quality and control of these strains may be variable. Higher rates of MDR GNB pose therapeutic problems for these countries. In addition, over the last decade the movement of people, goods and food has resulted in countries such as the UK meeting unpredictable and alarming appearances of MDR GNB by importation.⁴⁹ Imported food-producing animals from overseas founder stock, and food-stuffs, need to be free of important antibiotic resistance in GNB to just as great an extent as returned travellers for biosecurity and as a foundation for enhanced antimicrobial stewardship.

In order to produce relevant guidelines for the empirical treatment of infections caused by MDR GNB, an understanding of the

local epidemiology and susceptibility patterns is essential. The unpredictability of horizontal gene transfer and nosocomial spread may necessitate specific guidelines being produced for individual hospitals/communities. The present guideline has attempted to assess the relative clinical efficacy of different agents. We have found very few good-quality clinical trials to support treatment regimens, particularly for licensed older agents, formerly little used, that have been re-introduced into regular use. Finding a mechanism to address this deficit in trials much more rapidly is an important overarching research objective as the existing pattern of industry-sponsored initial regulatory trials fails to address the need.

It is self-evident that selection of antibiotic treatment based on susceptibility testing is the optimum strategy for treating infections caused by MDR GNB. The initiative to develop and deploy molecular and rapid phenotypic susceptibility testing methods will help refine antibiotic usage. Any additional expense must be funded within the healthcare system for these to be introduced. Risk factor, rule-based prescribing for MDR GNB is unlikely to be sufficiently predictive alone for the reasons outlined above but risk assessment of travel, household spread, and screening on admission to hospitals needs urgent improvement. However, we have attempted to present an evidence base and suggestions to support the development of local prescribing policies and possibly for the future application of such technologies and overall improvement in outcomes.

Over-reliance on empirical piperacillin/tazobactam and, for treatment failure, meropenem has driven and will drive selection for resistance to these agents, and UK health policy is attempting to contain this upsurge in usage. For patients presenting with serious sepsis convincingly caused by GNB and in the absence of prior exposure to healthcare in countries/hospitals with endemic CPE, carbapenems remain the best empirical therapy, with early and embedded shift to alternative definitive treatment. The overall prevalence of resistance in *E. coli* alone to piperacillin/tazobactam or gentamicin (approximately 10%) is the basis for this superiority of carbapenems, although factors such as aminoglycoside toxicity and *C. difficile* risk must be considered. Combinations of these agents or cephalosporins without β -lactamase inhibitors increase antibiotic use and are unlikely to produce adequate activity against ESBLs because of resistance linkage. Algorithms for predicting accurately the presence of ESBLs need urgent validation in the UK health service so piperacillin/tazobactam or gentamicin can be safely used to provide Gram-negative cover in their absence, and cephalosporin/BLI combinations in their presence thus diversify antibiotic use in serious infections within a stewardship framework. Use of piperacillin/tazobactam or existing licensed aminoglycosides as empirical therapy where ESBL-producing strains are prevalent, such as after overseas travel or hospitalization, in communities where such travel has been frequent, and with hospital or nursing home exposure, is unwise. Historical evidence suggests these agents continue to be appropriate for sepsis if these risk factors are not implicated.

In England, use of the Commissioning for Quality and Innovation (CQUIN) payments framework (or public health control of institutions and community healthcare) needs to be sensitive to the requirement to have safe effective antibiotics to use in sepsis caused by non-MDR GNB, which remain the majority of GNB causing serious infections in UK hospitals. The role and utility of the latest generation of BL/BLI combinations is yet to fully emerge. The

early reports of emergence of resistance to ceftazidime/avibactam in KPC-3-producing carbapenem-resistant Enterobacteriaceae is ominous.⁵⁰³ Nevertheless, at the moment new BL/BLIs and fosfomycin offer the only immediate new help to treat the latest MDR GNB, particularly for carbapenemase producers and ESBL-producing GNB. Further development of BLI combinations for oral use is an urgent need in primary care.

Initiatives are being put in place to address the paucity of new agents but it will take time for these agents to be produced and their success is by no means inevitable. A greater emphasis in communities should be given to the better use of existing treatments for effective treatment of complicated and upper UTI with prevention of bacteraemia, and in hospitals to an auditable improved outcome in well-defined groups of patients with life-threatening Gram-negative infections such as bacteraemia. This effort should match the attention given to reducing inappropriate use of wide-spectrum agents for less important infections and should ensure that reductions in antibiotic use are appropriate and do not adversely affect patients. Computerized support to spare infection professional time is necessary locally for surveillance of bacteraemia to focus attention on improvements in performance in life-threatening infection.

Greater research and deployment efforts in the area of very rapid diagnostics to guide immediate prescribing are needed. In the healthcare environment, stopping spread of infection with MDR GNBs is of paramount importance and such infection control measures have been dealt with comprehensively in another Working Party publication.³

The greatest long-term threat arises from the fundamental epidemiology of GNB, with their large faecal reservoirs in both humans and food animals leading to dissemination into the environment.²¹ This leads to unpredictable acquisition by individuals, with high rates of commensal carriage and subsequent infection. Not only antibiotic control in man but parallel control of use of the same agents in food animals is important. This is exemplified by use of colistin, mequindox and fosfomycin⁵⁰⁴ in food animals in China and other parts of the world, and consequent emergence of plasmid-mediated colistin, nitrofurantoin and fosfomycin resistance mediated by *mcr-1*, *oqxAB* and modified nitroreductases, and *fosA* as discussed previously (see Section 6.3.4). The close association of NDM MBL with connections with the Indian subcontinent is likely to change with the demonstration of this carbapenemase in poultry, farm workers, flies and wild birds in Shandong, China.²⁸⁹ Practical measures to contain human importations of carbapenemases but also assessment and potentially prevention of any spread in foodstuffs are urgent at this early stage. Variations in the prevalence of MDR GNB in different localities and cultural backgrounds even within the UK need to be further explored and considered in empirical therapy. Separate effects of migration, travel, household cross-colonization/infection and food consumption need to be rapidly studied to make risk assessments practical and effective.

Internationally, public health hygiene measures to reduce faecal-oral transmission, such as clean water initiatives and sewerage and irrigation systems to prevent transmission, are of major importance. Foodstuffs, including imports, should be regulated for the presence of GNB resistant to third-generation cephalosporins, quinolones and possibly in the future carbapenems. Failure to address these under-recognized threats will undo our ability to treat

infections caused by MDR GNB. If we do not control human and agricultural use of antibiotics and the spread of MDR GNB from faeces back into humans and food animals as a consistent multifaceted, global-scale public-health programme we will suffer greatly.

13. Further research and development

Apart from research needed for new compounds and formulations in the antibiotic pipeline, there are numerous areas which require research with a 5 year horizon for completion.

- Diagnostic tests and/or serum markers should be formally and comprehensively assessed for safety and efficacy as aids in deciding when to start and stop antimicrobial treatment, particularly in critically ill patients and those with haematological malignancies.
- Develop and introduce new cheap, rapid, and preferably bedside, diagnostic tests for important multiple antibiotic-resistant organisms in urine and blood.
- Undertake RCT studies of antimicrobial agents (both new and old) in the treatment of Gram-negative infection in areas where multiresistance is likely, e.g. admissions units, critical care and urology in hospitals and in treatment of infections due to ESBL-producing bacteria in the community. Identified research areas in this guideline include:

- (i) Use of continuous-infusion meropenem at dose determined by nomogram if infection with KPC carbapenemase-producing *Klebsiella* with MIC of >8 and <64 mg/L.
- (ii) Use of temocillin for non-urinary infections with trials to establish the optimal dosage.
- (iii) Use of temocillin alone, or in combination, in UTIs caused by Enterobacteriaceae with KPC enzyme.
- (iv) Use of ceftazidime/avibactam alone when non-MBL carbapenemase-producing organisms cause infection in comparison with alternatives, including combination therapy.
- (v) Use of ceftolozane/tazobactam in *P. aeruginosa* infections in cystic fibrosis.
- (vi) *In vitro* and *in vivo* research to identify the usefulness of aztreonam in combination with avibactam for infections due to Enterobacteriaceae with MBLs and other carbapenemases.
- (vii) Research into the role of loading doses of colistin, monitoring of serum levels and optimal combination therapy.
- (viii) Research into use of polymyxin-containing and non-containing selective digestive decontamination regimens and the prevalence of newly identified polymyxin resistance mechanisms.
- (ix) Optimal rapid and practical methods of colistin susceptibility testing outside intrinsically resistant species such as Proteaceae and *Serratia* spp.
- (x) Higher dosing studies with tigecycline to investigate if the unexpectedly high mortality in infections with strains that are apparently susceptible *in vitro* can be reduced.
- (xi) Optimal use of high-dose tigecycline in combinations in hospital-acquired respiratory infections.
- (xii) Specific system-based and resistance-mechanism-based indications for use of parenteral fosfomycin, in infections due to MDR GNB.

- (xiii) Cefixime (or other oral cephalosporin) with clavulanate (alone or with amoxicillin) against ESBL-producing *E. coli* UTI.
- (xiv) Nitrofurantoin versus fosfomycin trometamol versus pivmecillinam (with or without amoxicillin/clavulanate) in patients with ESBL-producing *E. coli* and *Klebsiella* spp.
- (xv) Use of meropenem, temocillin or ceftolozane/tazobactam in community-onset pyelonephritis where hospitalization is required and where MDR GNB excluding CPE are, or are likely to be, present. These studies should include assessment of meropenem or aminoglycosides if the patient describes penicillin hypersensitivity.

- Undertake surveillance in both the hospital and community populations, and households of newly detected colonized individuals, for incidence of known mechanisms of resistance and the emergence of novel resistance mechanisms to currently used antimicrobials. Link this surveillance to travel, prior hospitalization as inpatient, or residential healthcare.
- Develop new models of licensing and funding of antimicrobials for treating MDR GNB infections. Develop non-microbial therapies for MRGNB (e.g. phage, antibacterial peptides, etc.)

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Supplementary data

Appendices 1–7 (glossary, remit and related NICE guidelines, guideline development process, systematic review, CPD material, consultation stakeholders and response from stakeholders) are available as [Supplementary data](#) at JAC Online.

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· 译文 ·

编者按： 为帮助临床医师诊断与治疗广泛耐药革兰阴性杆菌（XDR-GNB）感染，制定合理的给药方案，我国22位临床、临床微生物学与临床药理学多学科专家共同编写了XDR-GNB感染抗菌治疗专家共识，发表在Clinical Microbiology and Infection (CMI), 2016, 22(Suppl 1): s15-s25。现将此共识翻译为中文，以方便国内读者阅读、理解。XDR-GNB感染是近年来出现的感染病临床问题，尽管参阅了大量近年来有关XDR-GNB感染诊治的国内外临床与实验研究文献，但可用于这类感染的抗菌药物少，治疗方案往往缺乏大系列前瞻性临床数据的支持，在临床应用中应该根据感染患者的临床情况加以灵活运用。

广泛耐药革兰阴性菌感染的实验诊断、抗菌治疗及医院感染控制：中国专家共识

王明贵 译

摘要： 广泛耐药革兰阴性杆菌（XDR-GNB），是指除1~2类抗菌药物（主要指多黏菌素和替加环素）外，几乎对所有类别抗菌药物均不敏感的革兰阴性杆菌。XDR-GNB 常见于肠杆菌科细菌、鲍曼不动杆菌、铜绿假单胞菌和嗜麦芽窄食单胞菌等。近年来，中国 XDR-GNB 的发生率呈不断上升趋势，由于缺乏有效的治疗药物，XDR-GNB 感染成为公共卫生安全的一大威胁。我国有关感染的临床、微生物学及临床药理学专家们就 XDR-GNB 感染的实验室诊断、临床诊疗和医院感染控制等问题深入讨论，形成此共识。其中细菌药敏试验的抗菌药物品种及结果判定标准遵循美国临床和实验室标准化协会（CLSI）、欧洲抗菌药物敏感性试验委员会（EUCAST）或美国食品与药物监督管理局（FDA）的指南。研究提示长疗程使用广谱抗菌药物是引发 XDR-GNB 感染最重要的危险因素。根据现有的临床研究和实验室数据，共识提供治疗各种 XDR-GNB 感染的联合用药推荐方案，其中常用的抗菌药物有替加环素、多黏菌素、碳青霉烯类、氨基糖苷类和磷霉素等。同时建议实行严格的感染控制措施，包括手卫生、接触隔离、主动筛查、环境消毒、去定植和抗菌药物应用管理等遏制 XDR-GNB 感染的传播。

关键词： 广泛耐药； 肠杆菌科细菌； 鲍曼不动杆菌； 铜绿假单胞菌； 嗜麦芽窄食单胞菌； 抗菌治疗

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Laboratory diagnosis, clinical management and infection control of the infections caused by extensively drug-resistant Gram-negative bacilli: a Chinese consensus statement

Chinese XDR Consensus Working Group, X.Guan, L.He, B.Hu, J.Hu, X.Huang, G.Lai, Y.Li, Y.Liu, Y.Ni, H.Qiu, Z.Shao, Y.Shi, M.Wang, R.Wang, D.Wu, C.Xie, Y.Xu, F.Yang, K.Yu, Y.Yu, J.Zhang and C.Zhuo

细菌耐药性已成为影响人类健康的主要威

胁之一^[1]。广泛耐药（extensively drug resistant, XDR）是指除对1、2类抗菌药物敏感外，细菌对几乎所有类别抗菌药物不敏感的现象。XDR 常发生于革兰阴性杆菌（XDR 革兰阴性菌以下简称为 XDR-GNB），常见菌种有：肠杆菌科细菌、鲍曼不动杆菌、铜绿假单胞菌及嗜麦芽窄食单胞菌。

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用于 XDR 细菌感染的有效治疗药物很少，且缺乏大系列的临床对照研究资料。抗菌药物单药治疗（包括多黏菌素类及替加环素）的疗效往往并不满意，多需要联合用药。由于 XDR 细菌感染多发生于有严重基础疾病、免疫缺陷和 / 或长期反复使用广谱抗菌药物的患者，导致预后差，成为当前细菌感染领域极为棘手的问题。本共识经国内有关感染病诊治的临床、微生物学及临床药理学专家们的多次深入讨论、修改而形成，期望有助于 XDR 细菌感染的临床诊治。

需要注意的是，临床标本特别是痰标本中分离到 XDR-GNB 者，应首先区分其为感染抑或定植，本共识仅适用于 XDR-GNB 感染患者，定植者无使用抗菌药物指证。

1 多重耐药（MDR）、XDR、全耐药（PDR）的定义

2012 年由欧洲与美国疾病预防控制中心（CDC）共同发起，欧美多国专家参与制定了一个 MDR、XDR 及 PDR 定义的共识^[2]，目前国内外多参照此共识对不同程度细菌耐药进行定义。耐药是指获得性耐药，不包括天然耐药（如铜绿假单胞菌及嗜麦芽窄食单胞菌对头孢噻肟为天然耐药）。

MDR：对在抗菌谱范围内的 3 类或 3 类以上抗菌药物不敏感（包括耐药和中介）。在推荐进行

药敏测定的每类抗菌药物中，至少 1 个品种不敏感，即认为此类抗菌药物耐药。

XDR：除 1~2 类抗菌药物（主要指多黏菌素类和替加环素）外，几乎对所有类别抗菌药物不敏感（抗菌药物类别耐药的确定同 MDR）。

PDR：对目前临床应用的所有类别抗菌药物中的所有品种均不敏感。

由于不同时期、不同国家使用的抗菌药物品种不同，PDR、XDR 的概念是动态变化的，例如原先对所有抗菌药物耐药的 PDR 鲍曼不动杆菌，如果对近年新上市的替加环素敏感，则应重新定义为 XDR。

2 耐药菌的表型测定

临床微生物实验室采用多种实验方法包括纸片扩散法、琼脂稀释法、微量肉汤稀释法或各种商品化检测系统，对临床分离菌进行药物敏感性检测。不同细菌需要测定药敏的抗菌药物品种不同，各类细菌药敏测试的抗菌药物品种选择及药敏结果判定折点通常参照美国临床和实验室标准化协会（CLSI）^[3]指南，某些 CLSI 无折点的抗菌药物，也可参照欧洲抗菌药物敏感性试验委员会（EUCAST）^[4]或美国食品与药品监督管理局（FDA）的指南。各类常见革兰阴性菌推荐检测的抗菌药物种类见表 1。

表 1 推荐革兰阴性菌药敏试验的抗菌药物种类

抗菌药物种类 ^a	抗菌药物品种	肠杆菌科细菌	铜绿假单胞菌	鲍曼不动杆菌	嗜麦芽窄食单胞菌
青霉素类	氨苄西林	+	-	-	-
β 内酰胺酶抑制剂合剂	阿莫西林-克拉维酸	+	-	-	-
	氨苄西林-舒巴坦	+	-	+	-
	头孢哌酮-舒巴坦或替卡西林-克拉维酸	+	+	+	+
	哌拉西林-他唑巴坦	+	+	+	-
第三和第四代头孢菌素	头孢噻肟或头孢曲松	+	-	+	-
	头孢他啶	+	+	+	+
	头孢吡肟	+	+	+	-
单环酰胺类	氨曲南	+	+	-	-
头霉素类	头孢西丁或头孢美唑	+	-	-	-
碳青霉烯类	厄他培南	+	-	-	-
	亚胺培南	+	+	+	-
	美罗培南	+	+	+	-
氨基糖苷类	庆大霉素	+	+	+	-
	阿米卡星	+	+	+	-
氟喹诺酮类	环丙沙星	+	+	+	-
	左氧氟沙星	+	+	+	+

表 1 (续)

抗菌药物种类 ^a	抗菌药物品种	肠杆菌科细菌	铜绿假单胞菌	鲍曼不动杆菌	嗜麦芽窄食单胞菌
磺胺类	甲氧苄啶-磺胺甲噁唑	+	-	+	+
氯霉素类	氯霉素	+	-	-	+
多黏菌素类	多黏菌素 E (黏菌素) 或多黏菌素 B	+	+	+	-
四环素类	多西环素	+	-	+	-
	米诺环素	+	-	+	+
甘酰胺环素类	替加环素	+	-	+	+
其他	磷霉素	+	+	-	-

^a 青霉素类、β 内酰胺酶抑制剂合剂、第三和第四代头孢菌素、单环酰胺类、头霉素类、碳青霉烯类分别作为一类抗菌药物。+：代表推荐检测该抗菌药物敏感性；-：代表该药物对此菌种没有抗菌活性，不推荐进行检测。

根据获得的药敏结果，分析不敏感（耐药及中介）抗菌药物的种类，判定菌株是否为 MDR、XDR 或 PDR。对于 XDR 菌株，尽可能测定抗菌药物对细菌的 MIC 值或纸片法测量抑菌圈直径，以作为联合抗菌药物选择及剂量确定的依据。

细菌的某些特殊耐药机制对于判定是否为 XDR 菌株有一定的预测作用，例如产碳青霉烯酶是碳青霉烯类耐药肠杆菌科细菌（CRE）的主要耐药机制，通过碳青霉烯酶的检测可确定细菌是否为 CRE。碳青霉烯酶的检测方法分为表型检测及分子生物学检测，表型检测主要包括改良 Hodge 试验、抑制剂法、双纸片协同法等，表型检测具有操作简单、经济实用等优点，易于在常规实验室开展，但不能快速报告结果，不能提供酶的具体型别；基于 PCR 及其测序是目前公认的检测碳青霉烯酶基因的“金标准”；此外，利用商品化微阵列芯片或基质辅助激光解析电离飞行时间质谱（MALDI-TOF）也可检测碳青霉烯酶。

3 XDR-GNB 的耐药机制

肠杆菌科细菌 XDR 表型主要由产碳青霉烯酶引起^[5-7]，某些菌株可同时产超广谱 β 内酰胺酶（ESBL）^[6] 和 / 或 AmpC 酶，及存在外排泵过度表达^[7] 或膜孔蛋白突变^[8] 而导致耐药。我国肠杆菌科细菌所产碳青霉烯酶的常见类型为 β 内酰胺酶中 A 类 KPC 酶（KPC-2），金属酶 IMP、VIM 及 NDM-1 少见。

鲍曼不动杆菌耐药机制复杂，通常同时具有多种耐药机制，包括产生多种 β 内酰胺酶、细胞膜通透性降低和外排泵表达增高^[9]。XDR 菌株多产生碳青霉烯酶，我国鲍曼不动杆菌临床菌株产生的碳青霉烯酶主要包括 OXA 类酶（如 OXA-23）、金属酶（IMP、VIM 和 NDM）和 A 类酶（KPC 和

GES）^[10]，也可同时存在外排泵（AdeABC）高表达。

XDR 铜绿假单胞菌通常由多种耐药机制共同作用所致^[11-12]，包括产生多种 β 内酰胺酶（尤其是碳青霉烯酶）、外排泵高表达、靶位改变和外膜蛋白改变，生物膜的形成对抗菌药物的体内敏感性也有重要影响。我国铜绿假单胞菌对碳青霉烯类的耐药机制主要是膜孔蛋白（OprD2）缺失，加上外排泵（Mex-Opr）高表达及产生金属酶（如 IMP，VIM，NDM）等。

嗜麦芽窄食单胞菌对多类抗菌药物如碳青霉烯类药物天然耐药，存在多种染色体、质粒、转座子、整合子介导的获得性耐药机制，包括多种 β 内酰胺酶的产生、多重耐药外排泵、外膜通透性降低、与喹诺酮类相关的 SmQnr 决定簇、DNA 旋转酶基因突变等^[13-14]。

4 XDR-GNB 的流行病学特点

4.1 XDR 检出率高

CHINET 数据显示，我国 2008—2014 年 XDR 鲍曼不动杆菌的检出率为 15%~21%，XDR 铜绿假单胞菌为 1.5%~2.1%^[15]，鲍曼不动杆菌对亚胺培南的耐药率由 2005 年的 31% 上升至 2014 年 62%^[16]。

4.2 XDR 检出率上升迅速

XDR 肠杆菌科细菌主要发生于肺炎克雷伯菌。CHINET 数据显示，我国 XDR 肺炎克雷伯菌的检出率由 2008 年的 0.3% 上升至 2014 年的 3.2%^[15]。监测网的数据通常统计 CRE 的检出率，我国肺炎克雷伯菌中 CRE（对美罗培南耐药）检出率由 2005 年的 2.9% 上升至 2014 年的 13.4%^[16]。CRE 不仅检出率上升迅速，而且所致感染的病死率高，故美国 CDC 细菌耐药威胁报告中将其列为最高级别“紧急威胁”^[1]。

4.3 XDR 检出率存在地区差异

欧洲抗菌药物耐药监测网 (EARS-Net) 2012 年数据显示, 革兰阴性菌对碳青霉烯类耐药率在欧洲不同国家中有显著差异, 肺炎克雷伯菌 0 (7 个欧洲国家) ~60.5% (希腊), 鲍曼不动杆菌 0 (挪威) ~87.8% (意大利), 铜绿假单胞菌 3.2% (马尔他) ~51.2% (罗马尼亚) [17]。

血培养分离菌中 XDR 鲍曼不动杆菌的检出率我国华南地区为 5.8%, 西南及西北地区为 20.4%~20.6%; 碳青霉烯类耐药肺炎克雷伯菌的检出率东北地区为 1%, 而华东地区为 9.2% [18]。

4.4 XDR 检出率存在病区差异

XDR-GNB 在部分医院中有相对集中的趋势, XDR 肺炎克雷伯菌主要分布于 ICU、烧伤科病房或神经外科病房; XDR 鲍曼不动杆菌主要分布于 ICU 或烧伤科病房 [19]。提示 XDR-GNB 在某些病区, 尤其是 ICU、烧伤科、神经外科和老年病房等可能存在耐药克隆的传播, 应引起高度重视。

5 XDR-GNB 感染的危险因素及临床特征

临床分离到 XDR-GNB 时, 首先应区分感染与定植, 只有感染患者才需要使用抗菌药物治疗。区分感染与定植往往是困难的, 主要从下述几方面鉴别: 送检标本的种类及临床标本是否合格 (临床微生物室应通过痰涂片确定痰标本的质量), 进行定量或半定量培养时菌落数是否达到要求, 是否多次培养到同一种细菌及相同耐药表型, 患者是否有感染的临床表现, 是否有 XDR-GNB 细菌感染的危险因素等 [20]。在 XDR-GNB 中, 鲍曼不动杆菌、铜绿假单胞菌和嗜麦芽窄食单胞菌定植的概率较高, 特别是痰标本分离到上述细菌时定植的可能性更大。肺炎克雷伯菌等肠杆菌科细菌的致病性较强, 定植概率相对较低, 临床标本分离到 XDR 肠杆菌科细菌时应引起重视。

5.1 XDR 肠杆菌科细菌感染

最常见的 XDR 肠杆菌科细菌为肺炎克雷伯菌, 其次为大肠埃希菌等。常见感染部位为肺部、尿路、腹腔、血流及皮肤软组织等。出现 XDR 肠杆菌科细菌感染的危险因素包括: 严重原发病、老年人、近期广谱抗菌药物 (特别是氟喹诺酮类和碳青霉烯类) 的使用、入住 ICU、血液肿瘤等疾患、实质脏器或造血干细胞移植、外科大手术及留置导管及引流管等 [21-23]。XDR 肠杆菌科细菌可寄殖于肠道长达数月, 导致耐药菌在医院内传播, 部分

可导致临床感染 [22]。

5.2 XDR 不动杆菌属感染

XDR 不动杆菌属感染主要发生在 ICU 使用机械通气的患者, 不动杆菌属为医院获得性肺炎 (HAP) 最常见分离菌, 对碳青霉烯类耐药率高 [24]。痰培养检出不动杆菌属细菌需鉴别系感染或定植。鲍曼不动杆菌血流感染常继发于肺部感染、腹腔感染及留置导管感染等。血培养有鲍曼不动杆菌生长时应及时寻找原发感染灶及可能的迁徙病灶。鲍曼不动杆菌引起的皮肤软组织感染多发生于有糖尿病等基础疾病、手术或外伤等患者, 外伤并有水接触史者多见。XDR 鲍曼不动杆菌中枢神经系统感染, 除来源于手术等侵袭性操作外, 呼吸道尤其是呼吸机的使用是重要传播途径 [25]。XDR 鲍曼不动杆菌感染的危险因素包括全身麻醉、入住 ICU、以往住院史及前期多种抗菌药物的使用史 [25]。

5.3 XDR 铜绿假单胞菌感染

铜绿假单胞菌常引起肺部感染、血流感染、皮肤软组织感染、腹腔感染和尿路感染等。XDR 铜绿假单胞菌感染的易感因素包括慢性阻塞性肺疾病 (COPD)、支气管扩张、住院时间长、使用机械通气、病情危重 (APACHE II 评分 >16 分)、不合理的抗菌药物单药使用等 [26-27]。氟喹诺酮类药物的使用是产生 XDR 铜绿假单胞菌感染的独立危险因素 [27]。

5.4 XDR 嗜麦芽窄食单胞菌感染

嗜麦芽窄食单胞菌常引起肺部感染、腹腔感染、尿路感染等, 感染危险因素包括严重基础疾病、长期入住 ICU、辅助机械通气时间 >7 d、气管切开以及使用广谱抗菌药物 (如碳青霉烯类、广谱头孢菌素和氟喹诺酮类) 等, 在抗菌药物使用过程中可筛选出嗜麦芽窄食单胞菌 XDR 或 PDR 菌株 [28-29]。氟喹诺酮类、哌拉西林-他唑巴坦、碳青霉烯类等抗菌药物的使用可增加细菌对氟喹诺酮类和甲氧苄啶-磺胺甲噁唑等药物的耐药性 [29]。嗜麦芽窄食单胞菌对碳青霉烯类天然耐药, 使用该类药物会促进细菌生长、加重感染 [30]。

6 XDR-GNB 感染的抗菌治疗

6.1 XDR-GNB 感染的抗菌治疗原则

①临床标本中分离到 XDR-GNB, 特别是痰标本中培养出 XDR 鲍曼不动杆菌或嗜麦芽窄食单胞菌时, 首先应结合临床表现区分是感染还是定植, 或为混合感染的病原菌之一。②尽量根据药敏试

验结果选择敏感抗菌药物；或选择呈中介或接近中介敏感或有较小抑菌圈的抗菌药物，大剂量联合治疗。③联合用药，XDR-GNB 感染常需联合使用抗菌药物。④根据药动学/药效学（PK/PD）原理优化给药方案，例如增加给药剂量、延长时间依赖性 β 内酰胺类抗生素的滴注时间。⑤肝、肾功能异常或老年患者，抗菌药物的剂量应适当减少；一些高血流动力学导致排泄快、高血容量患者需适当增加剂量。⑥消除感染危险因素，积极处理原发疾病。⑦抗菌药物治疗的疗程长短取决于感染的严重程度、患者的基础疾病、抗菌药物对 XDR 菌株的杀菌作用等多方面因素。

6.2 治疗 XDR-GNB 感染的常用抗菌药物

6.2.1 替加环素（tigecycline） 为首个甘氨酸类抗菌药物。对 CRE、XDR 鲍曼不动杆菌等具抗菌活性。2011 年全球分离菌株的药敏结果显示，碳青霉烯类耐药克雷伯菌属和不动杆菌属对其敏感率分别为 98% 和 90%；嗜麦芽窄食单胞菌对其敏感率为 92%^[31]。近期各地报告鲍曼不动杆菌的敏感率差异大^[32]，需根据药敏情况选用。本品对铜绿假单胞菌无抗菌活性。由于组织分布广，血药浓度低，该药不宜单药治疗血流感染等严重感染。对于 XDR 菌株引起的感染常需与其他抗菌药物联用^[22]。2012 年本品在我国上市以来，临床上主要用于 XDR 鲍曼不动杆菌、XDR 肠杆菌科细菌所致的呼吸道、皮肤软组织及腹腔等感染，常与头孢哌酮-舒巴坦、碳青霉烯类、氨基糖苷类等联合应用，国外常与多黏菌素联合^[33]。替加环素对甲氧苄啶-磺胺甲噁唑耐药菌株仍具有体外抗菌活性，可作为嗜麦芽窄食单胞菌感染的联合治疗药物之一，但临床资料不多^[34-35]。常用给药方案为首剂 100 mg，之后 50 mg 每 12 小时 1 次静脉滴注。初步研究提示，增加替加环素的给药剂量可提高其治疗重症感染或难治性感染的疗效^[36]，如医院获得性肺炎^[37]、呼吸机相关性肺炎^[38]、复杂性腹腔感染等，但有待于进一步的临床资料积累。主要不良反应为胃肠道反应。

6.2.2 多黏菌素类 包括多黏菌素 B 及多黏菌素 E（colistin，黏菌素）。多黏菌素类对各类 XDR-GNB 具良好体外抗菌活性，与碳青霉烯类、喹诺酮类、哌拉西林-他唑巴坦、替加环素、多西环素等抗菌药物联合大多表现为协同抗菌作用^[39-43]。但嗜麦芽窄食单胞菌对其敏感率相对较低，为 68%~79%^[34, 43]，MDR 菌株的敏感率仅为

37.5%^[44]。多黏菌素类与碳青霉烯类、替加环素、磷霉素、舒巴坦等联合，用于各类 XDR-GNB 包括 XDR 铜绿假单胞菌、CRE 及碳青霉烯类耐药鲍曼不动杆菌感染的治疗^[45]。多黏菌素类临床应用需要注意的问题为：该类药物存在明显异质性耐药^[45]，对鲍曼不动杆菌的防突变浓度（MPC）高^[46]，因此不推荐单独应用。该类药物的肾毒性及神经系统不良反应发生率较高，对于老年、肾功能减退等患者需特别注意进行肾功能监测。

国际上推荐的剂量为黏菌素甲磺酸盐（colistimethate sodium，CMS）每日 2.5~5 mg/kg（按基质计），分 2~4 次静脉滴注^[47]。剂量换算为黏菌素 100 万 U 相当于黏菌素基质（colistin-base activity，CBA）30 mg，相当于 CMS 80 mg。由于两种黏菌素的毫克表示方式容易引起混淆，造成给药剂量的错误，而引起严重的安全事件。2013 年 Prato 多黏菌素类共识建议统一使用基质 CBA 计量，不再使用 CMS 计量^[48]。黏菌素每日剂量不超过 900 万 U（欧洲）或 300 mg（5 mg/kg）基质（美国）。多黏菌素 B 每日给药量为 1.5~2.5 mg/kg，分 2 次静脉滴注。黏菌素基质 30~60 mg 溶于 3~4 mL 生理盐水中每天 2 次雾化吸入，联合全身用药治疗 XDR 耐药菌肺部感染。我国迫切需要至少有一种多黏菌素类（黏菌素或多黏菌素 B）能够提供临床使用，用于 XDR 和 PDR 革兰阴性菌感染的治疗。

6.2.3 舒巴坦及含舒巴坦的合剂 β 内酰胺酶抑制剂舒巴坦对不动杆菌属具抗菌作用，故含舒巴坦合剂对不动杆菌属具有良好的抗菌活性。2014 年 CHINET 数据显示，不动杆菌属对头孢哌酮-舒巴坦的耐药率为 37.7%^[15-16]。国际上常使用氨苄西林-舒巴坦，国内多使用头孢哌酮-舒巴坦治疗 MDR 和 XDR 鲍曼不动杆菌感染。通常舒巴坦推荐剂量为 ≤ 4.0 g/d，对 MDR 鲍曼不动杆菌和 XDR 鲍曼不动杆菌感染国际上推荐剂量可增加至 6.0 g/d^[47]，甚至 8.0 g/d。肾功能减退患者，需减少给药剂量。

（1）舒巴坦：目前我国也有舒巴坦单药制剂，舒巴坦可与其他抗菌药物如碳青霉烯类合用^[49]治疗 XDR 鲍曼不动杆菌引起的感染。

（2）头孢哌酮-舒巴坦：常用剂量为 3.0 g（头孢哌酮 2.0 g + 舒巴坦 1.0 g）每 8 小时 1 次或每 6 小时 1 次，静脉滴注。治疗 XDR 鲍曼不动杆菌感染常与替加环素、米诺环素（或多西环素）^[50-51]、碳青霉烯类或氨基糖苷类等药物联合用药。

6.2.4 碳青霉烯类 近年来鲍曼不动杆菌对碳青

霉烯类抗生素耐药率上升迅速,在我国其耐药率约 60%;肺炎克雷伯菌对其耐药率超过 10%。通常碳青霉烯类不单独用于 XDR-GNB 感染的治疗,但碳青霉烯类与其他抗菌药物具协同作用,协同比例分别为:多黏菌素类 75%、替加环素 50%、氨苄西林-舒巴坦 42% 及阿米卡星 42%^[52];多项临床研究提示碳青霉烯类与其他抗菌药物如多黏菌素的联合方案治疗 CRE 感染的疗效优于单药或其他联合方案^[22, 53-55]。碳青霉烯类用于治疗 CRE 感染应符合以下条件:① MIC $\leq$ 8 mg/L,②大剂量(如美罗培南 2 g 每 8 小时 1 次)给药,③延长每剂静脉滴注时间至 2~3 h^[22, 54, 56]。对于 XDR 或 PDR 菌株,尽量测定碳青霉烯类的 MIC 值或抑菌圈大小,以供临床考虑碳青霉烯类是否可作为联合用药。常用的品种为美罗培南和亚胺培南,不包括厄他培南(因后者对不动杆菌属及铜绿假单胞菌无抗菌活性,同时每天 1 g 的推荐剂量太低)。碳青霉烯类常与多黏菌素类、替加环素、磷霉素、利福平等联合应用^[52, 57]。

6.2.5 氨基糖苷类 有研究显示氨基糖苷类单用治疗碳青霉烯类耐药肺炎克雷伯菌感染(80% 为血流感染)取得较好的疗效^[22],这类药物多与其他抗菌药物联合应用治疗 XDR 肠杆菌科细菌、铜绿假单胞菌和鲍曼不动杆菌感染^[41-42, 58]。国外推荐阿米卡星或异帕米星每天 15 mg/kg。因未开展血药浓度监测,国内所用剂量大多低于国际推荐剂量,对于肾功能正常的 XDR-GNB 严重感染患者,推荐 0.8 g 每天 1 次或分 2 次给药。用药期间应密切监测肾功能及尿常规。鉴于氨基糖苷类治疗耐药革兰阴性菌临床应用的增多以及推荐使用较高的给药剂量,在中国建立该类药物的血药浓度监测方法及其临床应用十分必要。

6.2.6 磷霉素 国际上有多项研究报道,CRE 体外对磷霉素的敏感率高,如西班牙为 95%,对产金属酶者敏感率为 83%^[59]。国内 CRE 菌株对磷霉素的敏感率为 40%^[60]。但临床资料有限。有报道在 48 例碳青霉烯类耐药肺炎克雷伯菌或 XDR 铜绿假单胞菌的 ICU 感染患者中,静脉用磷霉素与黏菌素或替加环素联合治疗的临床有效率为 54.2%,细菌清除率为 56.3%,最常见的不良反应为低血钾^[61]。磷霉素单用可在疗程中出现耐药,通常与多黏菌素类、替加环素、碳青霉烯类、氨基糖苷类等联合治疗 XDR-GNB 感染^[61]。磷霉素的给药剂量为 8 g 每 8 小时 1 次或 6 g 每 6 小时 1

次静脉滴注。在我国,磷霉素常与万古霉素联合治疗 MRSA 或肠球菌属感染,但目前用于 XDR-GNB 感染的联合用药有明显上升趋势。

6.2.7 四环素类 米诺环素对鲍曼不动杆菌具良好抗菌活性,2014 年 CHINET 监测中耐药率为 49.7%;嗜麦芽窄食单胞菌对其耐药率低,为 2.1%^[15]。米诺环素为少数几个推荐作为治疗嗜麦芽窄食单胞菌感染的抗菌药物之一。美国 FDA 批准米诺环素注射剂用于鲍曼不动杆菌的治疗,给药方案为米诺环素 100 mg 每 12 小时 1 次静脉滴注,但临床资料不多。国内目前无米诺环素注射剂型,可使用口服片剂或多西环素注射剂(剂量同米诺环素)与其他抗菌药联合治疗 XDR 鲍曼不动杆菌^[39, 50-51]及嗜麦芽窄食单胞菌^[34-35, 44]感染,但临床资料很少。

6.2.8 喹诺酮类 环丙沙星、左氧氟沙星对铜绿假单胞菌具良好抗菌活性,莫西沙星对嗜麦芽窄食单胞菌的体外抗菌活性优于环丙沙星和左氧氟沙星^[34-35]。2005—2014 年 CHINET 数据显示嗜麦芽窄食单胞菌对左氧氟沙星的耐药率为 9.0%~16.4%,2014 年铜绿假单胞菌对环丙沙星的耐药率为 14.9%^[15]。喹诺酮类可与 β 内酰胺类、氨基糖苷类、多黏菌素类等联合用于 XDR 铜绿假单胞菌^[62]、嗜麦芽窄食单胞菌^[34-35]感染的治疗。治疗 XDR-GNB 感染,环丙沙星每日 0.6~1.2 g,分 2~3 次静脉给药;左氧氟沙星成人常用量为每次 0.5 g 或 0.75 g,每日 1 次静脉滴注或口服;莫西沙星成人 0.4 g,每日 1 次静脉滴注。

6.2.9 甲氧苄啶-磺胺甲噁唑 甲氧苄啶-磺胺甲噁唑对嗜麦芽窄食单胞菌具较好体外抗菌活性,国内外报道该菌对其耐药率均低于 10%^[15, 34, 43]。MDR 嗜麦芽窄食单胞菌对其敏感率 87%,与米诺环素、头孢他啶等联合对 MDR 菌株显示部分协同抗菌活性^[44]。甲氧苄啶-磺胺甲噁唑为治疗嗜麦芽窄食单胞菌感染的首选药物^[34-35]。该药对少数 XDR 鲍曼不动杆菌及 CRE 菌株也具抗菌活性,可用于联合治疗,但临床资料少。

甲氧苄啶-磺胺甲噁唑在国内只有口服片剂,通常每次 2 片,每日 2 次口服,治疗 XDR-GNB 感染可适当增加剂量,2~3 片,每日 2~3 次口服;对留置胃管者,可鼻饲给药。用药期间,注意补充足够的水分(多饮水或静脉补液),可与碳酸氢钠同服,碱化尿液;复查尿常规(注意血尿情况)。

6.2.10 其他 利福平体外对鲍曼不动杆菌具一定抗菌活性,可与碳青霉烯类联合用于 XDR 鲍曼

不动杆菌感染的治疗^[63]。但近期的一项随机对照临床试验显示，黏菌素联合利福平与黏菌素单独使用相比，并不降低 30 d 病死率^[64]。少数 XDR-GNB 包括产 NDM-1 肠杆菌科细菌对氨基糖苷类^[65]，可用于联合治疗。

6.2.11 新抗菌药物 美国 FDA 分别于 2014 年 12 月和 2015 年 2 月批准 2 个新的 β 内酰胺酶抑制剂合剂 ceftolozane-他唑巴坦和**头孢他啶-阿维巴坦**上市，均适用于复杂性腹腔感染及尿路感染。阿维巴坦为人工合成的 β 内酰胺酶抑制剂，除 ESBL 外，对 AmpC、部分 D 类 β 内酰胺酶如 OXA-48 及丝氨酸碳青霉烯酶 KPC 具抑制作用^[66]。Ⅱ期随机对照临床试验显示，头孢他啶-阿维巴坦与甲硝唑联合治疗复杂性腹腔感染的疗效及不良反应与美罗培南相仿^[67]。

Ceftolozane 为与头孢他啶结构相似的新头孢菌素，对铜绿假单胞菌的抗菌作用增强^[68]。Ⅱ期临床试验显示，ceftolozane-他唑巴坦联合甲硝唑治疗复杂性腹腔感染的临床及微生物学疗效与美罗培南相仿^[69]。

6.3 XDR-GNB 感染的抗菌药物联合治疗方案

XDR-GNB 细菌感染可供选择的抗菌药物很

少，该类细菌对替加环素及多黏菌素类的敏感率相对较高，但临床研究显示两者单用的治疗失败率均较高，应尽量避免单药应用。XDR-GNB 感染通常采用 2 种或 3 种药物联合治疗，但临床资料多数为个例报告或小规模病例对照研究，尚需更多、更可靠的临床资料予以支持^[70]。有报道用于 XDR-GNB 感染的联合治疗方案见表 2。

7 XDR-GNB 医院感染的防控

XDR-GNB 感染增多是抗菌药物选择压力、耐药基因水平传播和耐药克隆菌株传播共同作用的结果。必须将医院感染防控措施与抗菌药物临床应用管理相结合才能有效阻遏 XDR-GNB 传播、减少耐药菌感染^[22, 71-72]。

7.1 手卫生

手卫生是减少交叉感染、避免医务人员成为耐药菌传播媒介的最基本、最有效、最经济的策略。在接触 XDR 感染患者前后必须洗手或使用快速消毒液擦手^[72]。

7.2 接触隔离

临床微生物室检获 XDR-GNB 后应及时通知病区，病区对感染 XDR-GNB 患者实施接触隔离，

表 2 治疗 XDR-GNB 感染的抗菌药物联合用药方案

XDR-GNB	2 种药物联合	3 种药物联合
XDR 肠杆菌科细菌 ^[22, 33, 36, 53, 61]	以替加环素为基础的联合： 替加环素 + 氨基糖苷类 ^a 替加环素 + 碳青霉烯类 ^b 替加环素 + 磷霉素 替加环素 + 多黏菌素 以多黏菌素为基础的联合： 多黏菌素 + 碳青霉烯类 ^b 多黏菌素 + 替加环素 多黏菌素 + 磷霉素 多黏菌素 + 氨基糖苷类 ^a 其他联合： 磷霉素 + 氨基糖苷类 ^a （头孢他啶或头孢吡肟）+ 阿莫西林-克拉维酸 氨基糖苷类 + 氨基糖苷类 ^a	替加环素 + 多黏菌素 + 碳青霉烯类 ^b
XDR 鲍曼不动杆菌 ^[39, 47, 49-50, 64]	以舒巴坦及其合剂为基础的联合： （头孢哌酮-舒巴坦或氨苄西林-舒巴坦）+ 替加环素 （头孢哌酮-舒巴坦或氨苄西林-舒巴坦）+ 多西环素 舒巴坦 + 碳青霉烯类 ^b 以替加环素为基础的联合： 替加环素 + （头孢哌酮-舒巴坦或氨苄西林-舒巴坦） 替加环素 + 碳青霉烯类 ^b 替加环素 + 多黏菌素 以多黏菌素为基础的联合： 多黏菌素 + 碳青霉烯类 ^b 多黏菌素 + 替加环素	头孢哌酮-舒巴坦 + 替加环素 + 碳青霉烯类 ^b 头孢哌酮-舒巴坦 + 多西环素 + 碳青霉烯类 ^b 亚胺培南 + 利福平 + （多黏菌素或妥布霉素）

表 2 (续)

XDR-GNB	2 种药物联合	3 种药物联合
XDR 铜绿假单胞菌 ^{c[40-42, 61]}	以多黏菌素为基础的联合： 多黏菌素 + 抗铜绿假单胞菌 β 内酰胺类 ^d 多黏菌素 + 环丙沙星 多黏菌素 + 磷霉素 多黏菌素 + 利福平 以抗铜绿假单胞菌 β 内酰胺类为基础的联合： 抗铜绿假单胞菌 β 内酰胺类 ^d + 氨基糖苷类 ^a 抗铜绿假单胞菌 β 内酰胺类 ^d + 环丙沙星 抗铜绿假单胞菌 β 内酰胺类 ^d + 磷霉素 以环丙沙星为基础的联合： 环丙沙星 + 抗铜绿假单胞菌 β 内酰胺类 ^d 环丙沙星 + 氨基糖苷类 ^a 双 β 内酰胺类联合： (头孢他啶或氨曲南) + 哌拉西林-他唑巴坦 头孢他啶 + 头孢哌酮-舒巴坦 氨曲南 + 头孢他啶	多黏菌素 + 抗铜绿假单胞菌 β 内酰胺类 ^d + 环丙沙星 多黏菌素 + 抗铜绿假单胞菌 β 内酰胺类 ^d + 磷霉素 多黏菌素静脉滴注 + 碳青霉烯类 + 多黏菌素雾化吸入 氨曲南 + 头孢他啶 + 阿米卡星
XDR 嗜麦芽窄食单胞菌 ^{e[34-35, 44]}	以甲氧苄啶-磺胺甲噁唑为基础的联合： 甲氧苄啶-磺胺甲噁唑 + (替卡西林-克拉维酸或头孢哌酮-舒巴坦) 甲氧苄啶-磺胺甲噁唑 + 氟喹诺酮类 ^f 甲氧苄啶-磺胺甲噁唑 + 米诺环素 甲氧苄啶-磺胺甲噁唑 + 头孢他啶 甲氧苄啶-磺胺甲噁唑 + 多黏菌素 以喹诺酮类为基础的联合： 氟喹诺酮类 ^f + 甲氧苄啶-磺胺甲噁唑 氟喹诺酮类 ^f + (替卡西林-克拉维酸或头孢哌酮-舒巴坦) 氟喹诺酮类 ^f + 头孢他啶 以多黏菌素为基础的联合： 多黏菌素 + 替卡西林-克拉维酸 多黏菌素 + 甲氧苄啶-磺胺甲噁唑	

^a 氨基糖苷类包括阿米卡星、异帕米星等；^b 碳青霉烯类包括美罗培南、亚胺培南等，不包括厄他培南；^c 多为 MDR 或 XDR 铜绿假单胞菌的体外研究结果或临床病例报道，联合方案的临床资料少；^d 抗铜绿假单胞菌 β 内酰胺类：即抗铜绿假单胞菌 β 内酰胺类，包括碳青霉烯类（美罗培南、亚胺培南）、头孢他啶、头孢吡肟、氨曲南、哌拉西林-他唑巴坦、头孢哌酮-舒巴坦；^e 多为 MDR 嗜麦芽窄食单胞菌的体外研究结果或临床病例报道，联合方案的临床资料很少；^f 氟喹诺酮类包括环丙沙星、左氧氟沙星和莫西沙星。

保证 XDR-GNB 感染患者专用血压计、听诊器、体温计和输液泵等设备^[71]。在 XDR-GNB 感染患者转科、转院或离开病室作辅助检查时应进行交班和警示^[73]。

7.3 主动筛查

在 ICU 等 XDR-GNB 感染高发病区，对新入院患者和住院患者肛周、直肠、伤口分泌物、鼻咽部、气道分泌物等部位采样，以常规或快速诊断方法及时发现耐药菌定植并对患者采取隔离措施^[72]。必要时通过分子流行病学手段追踪传播途径，为阻断耐药菌传播提供依据^[74]。

7.4 环境表面消毒

对医院环境尤其医患频繁接触的物体表面进行定期、充分消毒^[72, 75]，并以荧光标记或 ATP 生物荧光监测等方法监测消毒效果，阻断耐药菌传播。

7.5 去定植

对 XDR-GNB 定植患者采取全身氯已定擦浴，有助于减少导管相关血流感染^[76]。

7.6 抗菌药物临床应用管理

(1) 严格掌握抗菌药物应用指征，通过分级管理限制抗菌药物使用，制定各医疗机构的治疗指南或方案，指导和规范抗菌药物的应用。

(2) 制定合理的抗菌药物处方集，保证临床需要抗菌药物包括新抗菌药物的供应。鉴于抗菌药物轮替使用对阻遏细菌耐药性增长作用的循证医学证据存在争议^[77]，应慎重考虑在医疗机构或特定病区停用某类抗菌药物。

有关 CRE 医院感染的控制，近期以色列报道一个成功的经验^[78]：采取全国性综合干预措施包括主动监测、统一检测和报告流程、隔离患者、急症

患者专职护理、对医疗机构遵守感控指南进行监管,从而有效控制 CRE 传播,急症医疗机构的 CRE 发生率由 2007 年 3 月的 55.5 例/10 万人日(patient-days)降至 2008 年 5 月的 11.7 例/10 万人日($P<0.001$)。

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表 5B 多重耐药革兰阴性杆菌全身性感染的治疗建议

本表推荐方案多未经 FDA 批准 (NAI)。推荐方案是综合体外试验、动物模型、临床观察和临床试验结果而给出的。特殊感染参见表 1，药物参见表 10A

病原菌	耐 药	首选治疗方案	备选治疗方案	说 明
鲍曼不动杆菌	所有 β 内酰胺类 (舒巴坦除外)、氨基糖苷类、氟喹诺酮类、TMP-SMX	敏感：头孢吡肟、头孢他啶、氨苄西林-舒巴坦 耐药：美罗培南或亚胺培南	危重症：美罗培南+氨苄西林-舒巴坦+米诺环素+多黏菌素 B (UTI：多黏菌素)	治疗肺炎需联合多黏菌素 50 ~ 75mg bid，雾化吸入。多黏菌素+利福平的临床试验失败 (CID 75 : 349, 2013)。存在多种耐药机制
产超广谱 β 内酰胺酶 (ESBL) 大肠杆菌、肺炎克雷伯杆菌、肠杆菌科和铜绿假单胞菌	所有头孢菌素、氟喹诺酮类、氨基糖苷类和 TMP-SMX	美罗培南或亚胺培南	Ceftolozane-舒巴坦* 头孢他啶-阿维巴坦* 美罗培南-万巴巴坦*	哌拉西林-他唑巴坦的结果布不一致：即使体外敏感，临床也可能失败。泌尿道感染：呋喃妥因、磷霉素
产 OXA-48 的肠杆菌科	所有青霉素类、氟喹诺酮、氨基糖苷类、TMP-SMX	敏感：头孢吡肟、头孢他啶	危重症：头孢他啶-阿维巴坦+氨曲南	在环地中海区域常见
产 KPC (丝氨酸碳青霉烯酶) 的肠杆菌科	所有青霉素类、头孢菌素、氨基糖苷类、碳青霉烯类、氟喹诺酮、氨基糖苷类、TMP-SMX	头孢他啶-阿维巴坦*，美罗培南-万巴巴坦	美罗培南+多黏菌素 B (治疗泌尿道感染用多黏菌素)	治疗肺炎需联合多黏菌素 50 ~ 75mg bid，雾化吸入。有厄他培南+美罗培南治疗成功的报道 (JAC 69 : 1718, 2014)
产金属碳青霉烯酶的革兰阴性杆菌	所有 β 内酰胺类 (氨曲南除外)、氟喹诺酮、氨基糖苷类、TMP-SMX	头孢他啶-阿维巴坦*+氨曲南	美罗培南+多黏菌素 B	治疗肺炎需联合多黏菌素 50 ~ 75mg bid，雾化吸入
嗜麦芽窄食单胞菌	所有 β 内酰胺类、氟喹诺酮、氨基糖苷类	TMP-SMX	如体外敏感：氟喹诺酮	替卡西林-克拉维酸不再生产 参见：Sem Respir CCM 36 : 60, 2015

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中华医学会器官移植学分会



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【摘要】 为了进一步规范实体器官移植术后耐药菌感染的诊断和治疗，中华医学会器官移植学分会组织器官移植学专家和感染学专家，从实体器官移植术后耐药菌感染的情况、国内细菌感染及耐药情况、多重耐药菌感染的抗生素治疗等方面，制订实体器官移植术后耐药菌感染的诊疗技术规范。

【关键词】 器官移植；感染；耐药菌；多重耐药；泛耐药；全耐药；耐甲氧西林金黄色葡萄球菌；泛耐药鲍曼不动杆菌；替加环素

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随着抗菌药物的广泛应用，细菌的耐药性也不断增强。在过去的20多年，出现了许多新的多重耐药（multidrug-resistant, MDR）、泛耐药（extensively drug-resistant, XDR）甚至全耐药（pandrug-resistant, PDR）的“超级细菌”，给器官移植医学带来了巨大的挑战。与普通细菌相比，耐药菌感染后相关并发症多、死亡率高。作为免疫缺陷人群，实体器官移植（solid organ transplantation, SOT）受者一旦发生MDR细菌感染，病死率高达40.4%；其中，40%的患者将面临移植切除的风险，多数患者死于重度感染引发的呼吸衰竭或脓毒血症。

1 SOT术后耐药菌感染的情况

1.1 耐药菌感染基本定义

（1）MDR：细菌对常用7大类的抗菌药物中3类或3类以上耐药；（2）XDR：细菌对常用抗菌药物几乎全部耐药，革兰阴性杆菌仅对黏菌素和替加环素敏感，革兰阳性球菌仅对糖肽类或利奈唑胺敏感；（3）PDR：细菌对所有常用抗菌药物全部耐药。

1.2 SOT术后感染的常见耐药菌

SOT术后常见的MDR细菌包括革兰染色阴性杆菌及阳性球菌。常见阴性杆菌主要包括泛耐药鲍曼

不动杆菌（pandrug-resistant *acinetobacter baumannii*, PDRAB）、泛耐药铜绿假单胞菌（pandrug-resistant *pseudomonas aeruginosa*, PDRPA）、产超广谱β-内酰胺酶（extended spectrum β-lactamases, ESBLs）的肠杆菌、耐碳青霉烯类的肺炎克雷伯杆菌（carbapenem-resistant *Klebsiella pneumoniae*, CRKP）等；常见阳性球菌主要包括耐甲氧西林金黄色葡萄球菌（methicillin-resistant *staphylococcus aureus*, MRSA）、耐万古霉素肠球菌（vancomycin-resistant *enterococcus*, VRE）^[1]。常见的感染部位多为肺部感染、伤口周围感染、泌尿系统感染（肾盂肾炎、膀胱炎）、血流感染、腹腔感染等^[2]。

1.3 SOT术后耐药菌感染的危险因素

大剂量免疫抑制剂的应用、广谱抗菌药物的应用、血液透析、移植后并发症（肾功能不全、胆道感染或梗阻等）、留观重症监护室（intensive care unit, ICU）时间与气管插管时间过长（≥72 h）、再次手术以及接受心脏死亡器官捐献（donation after cardiac death, DCD）的受者、老年受者（>60岁）、术前90 d内使用过抗生素治疗、近期住院时间≥5 d等均是SOT术后感染的危险因素^[3-5]。另外，还包括供者来源性感染（donor-derived infection, DDI），其多发生在移植术后1个月以内，发生率约为0.2%~1.7%，

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部分为 MDR 细菌^[6]。国内多中心数据显示, 肾移植术后 DDI 发生率为 1.15%, 肝移植术后 DDI 发生率为 0.23%, SOT 术后 DDI 总发生率为 0.92%, 其中 80% 为 MDR 细菌^[7]。

2 国内细菌感染及耐药情况

2.1 国内细菌的检测情况概述

近年来, 以革兰阴性杆菌为代表的 MDR 细菌检出率呈快速上升趋势, 为临床抗感染治疗带来了巨大挑战^[8]。中国细菌耐药监测网的数据显示: 2017 年共收集临床分离细菌 190 610 株, 其中革兰阳性菌 55 649 株, 占 29.2%, 革兰阴性菌 134 951 株, 占 70.8% (图 1)^[9]。标本分布中, 痰液等呼吸道标本占 40.0%、尿液标本占 19.2%、血液标本占 15.2%、伤口脓液标本占 11.7% 等 (图 2)。在总体菌株的分离率中, 肠杆菌科细菌占有所有分离菌株的 43.3%, 其中最多见者依次为大肠埃希菌、肺炎克雷伯菌 (图 3)。

2.2 国内细菌感染数据及耐药情况

SOT 受者的围手术期及术后早期感染主要为院内获得性, 其感染菌种多为 MDR 的革兰阴性杆菌。根据中国细菌耐药监测网的数据, 除了肠杆菌科中的大肠埃希菌, 不发酵糖的革兰阴性杆菌占有所有分离菌株的 24.1%, 其中最多见者依次为鲍曼不动杆菌 (38.3%)、铜绿假单胞菌 (36.0%)、嗜麦芽窄食单胞菌 (11.9%)。另外, 近年来革兰阳性球菌的分离率逐年上升 (图 4), 最多见者依次为金黄色葡萄球菌、肠球菌属和凝固酶阴性葡萄球菌 (coagulase negative staphylococcus, CNS)。其中, 甲氧西林耐药菌株的分离率逐年增加; 2017 年国内的数据显示,

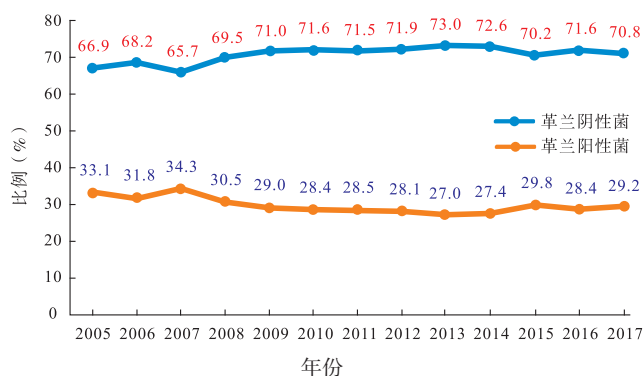


图 1 历年革兰阴性菌和革兰阳性菌菌株数及所占比例
Figure 1 Strains and proportion of Gram-negative and Gram-positive bacteria in the past years

MRSA 和耐甲氧西林 CNS (methicillin-resistant CNS, MRCNS) 的平均检出率分别达到 80.3% 和 35.3%。甲氧西林耐药株对大环内酯类、氨基苷类和喹诺酮类等多数抗菌药物的耐药率均显著高于甲氧西林敏感株。作为免疫缺陷人群, SOT 受者的甲氧西林耐药菌株尤其是 MRSA 的感染不容忽视^[9]。

肠杆菌科细菌中, 大肠埃希菌不仅是总体标本中的首位菌株, 而且是尿液标本中的首位菌株 (图 5)。因此, 肾移植术后预防用药或 SOT 术后尿路感染的治疗用药, 初始应选择主要针对肠杆菌科的抗生素, 尤其是大肠埃希菌。大肠埃希菌对 11 种常用抗菌药物的总耐药率如图 6 所示。大肠埃希菌对替加环素、3 种碳青霉烯类和阿米卡星的耐药率最低, 为 0.2%~2.8%, 对两种酶抑制剂复合剂 (哌拉西林钠-他唑巴坦钠和头孢哌酮钠-舒巴坦钠) 的耐药率分别为 4.7% 和 6.4%。产生碳青霉烯酶或新德里金属-β-内酰胺酶 (New Delhi metallo-β-lactamase, NDM)-1 是肠杆菌科细菌对碳青霉烯类抗生素最主要的耐药机制, 且不同人群来源和不同地区来源菌株的耐药机制有所不同。从地域分布看, 与南方相比, 我国北方医院临床分离的耐碳青霉烯类肠杆菌科 (carbapenem-resistant enterococcus, CRE) 菌株中产 NDM-1 菌株多些, 而产肺炎克雷伯菌碳青霉烯酶 (*Klebsiella pneumoniae* carbapenemase, KPC) 型菌株少些^[10]。

2.3 特殊 MDR 细菌的变迁情况

针对 SOT 受者、尤其是并发肺部感染的受者,

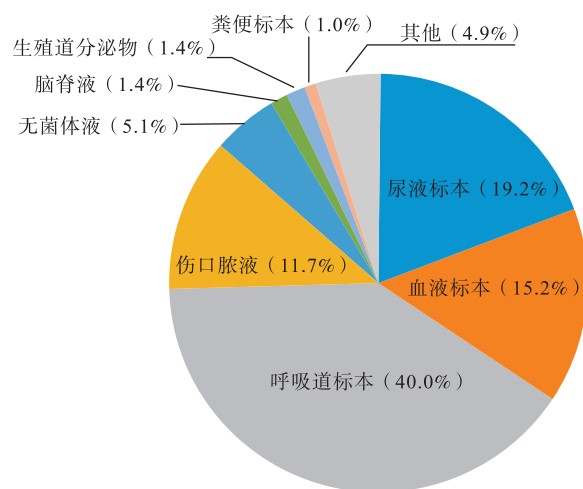


图 2 190 610 株临床分离菌在各类标本中的分布
Figure 2 Distribution of 190 610 strains of clinical isolates bacteria in various specimens

需要更加高度关注的是肺炎克雷伯菌，其每年的分离率呈稳步上升趋势。根据我国耐药细菌监测网的数据，2017 年的呼吸道分泌物中，肺炎克雷伯菌跃居首位，替代了既往多年鲍曼不动杆菌占有的首位（图 7）^[11]。而且，肺炎克雷伯菌对多种抗生素的耐药率也显著上升（图 8）^[12]。近年来，对 CRE，尤其是其中的 CRKP 感染的发生率逐年增加，严重威胁 SOT 受者的存活率^[13-14]。我国 CRKP 的耐药率从 2005 年的 3% 左右上升到了 2018 年的 28.6%，耐药率上升幅度高达 9 倍。在不同的医院，CRKP 对碳青霉烯类的耐药率不同，耐药率最高者 $\geq 50\%$ 。因此，针对此类超级耐药细菌的感染，实验室需要增做其它可能有效的抗菌药物如多黏菌素、替加环素、头孢他啶-阿维巴坦的药敏及联合药敏试验，同时关注多黏菌素和替加环

素的药敏试验方法问题，力求准确^[15-16]。目前，我国已有产苯唑西林水解酶（oxacillin hydrolase, OXA）型碳青霉烯酶肺炎克雷伯菌所致感染的克隆菌株流行的报道^[17-18]。

3 MDR 细菌感染的抗生素治疗

3.1 治疗原则

（1）尽量根据药敏结果选择敏感抗生素，当所有药物均不敏感时，选择最低抑菌浓度（minimum inhibitory concentration, MIC）较接近敏感折点的药物；（2）MDR 革兰阴性菌的治疗不仅需要增加抗生素的剂量，而且需要联合用药，但同时注意根据患者的年龄、肝肾功能及体表面积进行相应调整；（3）根据药动学和药代学原理设定给药方案，如增加给药剂量

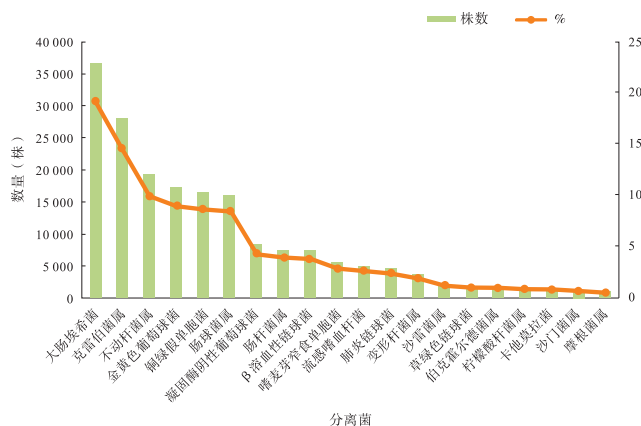


图 3 2017 年主要临床分离菌分布（前 20 位）

Figure 3 Distribution of major clinical isolates of bacteria in 2017 (top 20)

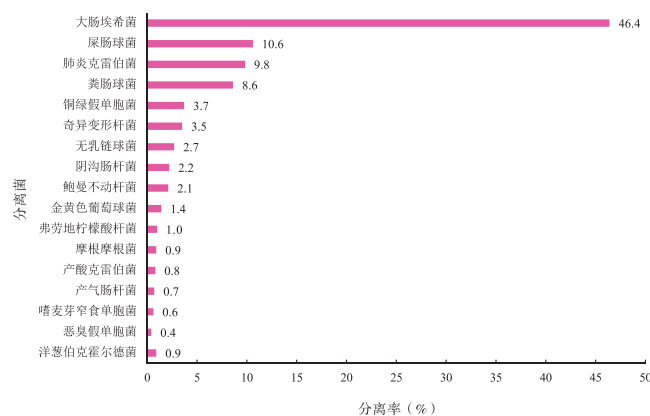


图 5 36 635 株尿道标本分离菌主要菌种分布

Figure 5 Distribution of main bacteria isolated from 36 635 strains of urethral specimens

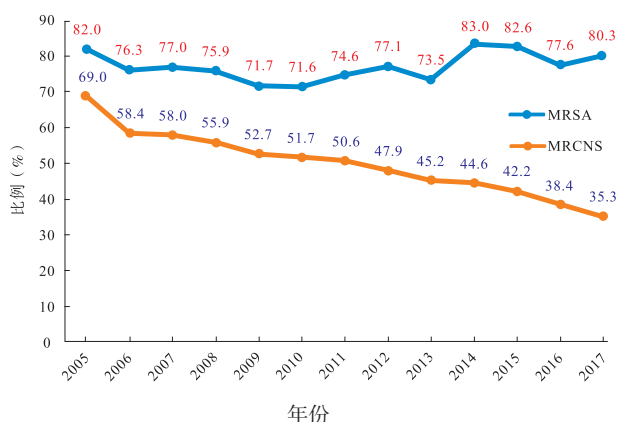


图 4 MRSA 和 MRCNS 的检出率近 13 年变迁

Figure 4 Changes of detection rate of MRSA and MRCNS in the past 13 years

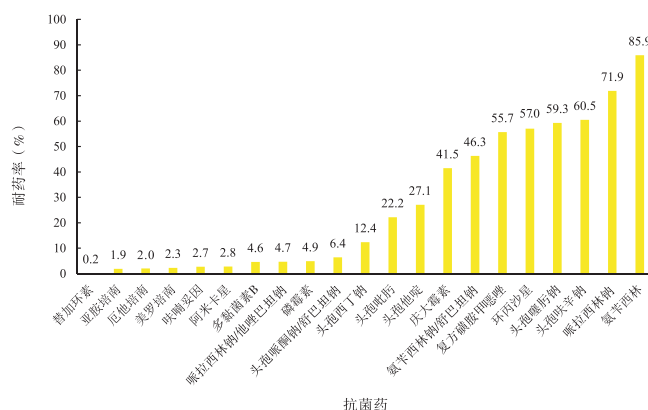


图 6 36 735 株大肠埃希菌对抗菌药的耐药率

Figure 6 Drug resistance rate of 36 735 strains of *Escherichia coli* to antimicrobial agents

或次数,延长抗生素滴注时间等;(4)积极处理原发病,控制感染源(引流积液及移除被污染的设备),尽可能消除感染的危险因素^[19-21]。

3.2 MDR 感染的常用药物

临床上常见用于治疗 MDR 细菌感染的药物包括:甘氨酸环类、多黏菌素、 β -内酰胺酶抑制剂、碳青霉烯类、氨基苷类、磷霉素、四环素类、喹诺酮类。

3.2.1 替加环素 替加环素是首个甘氨酸环类抗生素,可以有效抑制细菌蛋白质的合成,对耐碳青霉烯类细菌仍具有抗菌活性。目前,肺炎克雷伯杆菌属菌株对替加环素具有较高的敏感性。产 ESBLs 及碳青霉烯酶类耐药菌株对替加环素的敏感率与非产 ESBLs 及碳青霉烯酶类的敏感菌株相仿,临床主要用于 CRE、XDR 鲍曼不动杆菌或其它肠杆菌科细菌所致的呼吸道、皮肤软组织及腹腔感染。但替加环素组织分布广,血药浓度低,不适合单药治疗血流感染,一般推荐两药或三药联合,常与多黏菌素类、碳青霉烯类、氨基苷类等联合。由于替加环素在脑脊液及尿液中的血药浓度较低,一般不推荐用于中枢神经系统感染和泌尿道感染。对 XDR 菌株感染的治疗常需与其他抗菌药物如碳青霉烯类、氨基苷类、多黏菌素等联合应用。鉴于替加环素药敏存在地区差异性,建议各地根据药敏结果合理选用。替加环素常用的给药方案为:首剂 100 mg,之后 50~75 mg (每日 2 次)静脉滴注。CRE 导致肺炎的治疗推荐剂量为:首剂 200 mg,之后 100 mg (每日 2 次)静脉滴注。

3.2.2 多黏菌素 多黏菌素可分为两种:多黏菌素 B 和黏菌素(多黏菌素 E);前者只能用于静脉滴注,后

者既可以静脉滴注,亦可以雾化吸入。多黏菌素主要用于各类 XDR 革兰阴性菌的治疗,尤其是鲍曼不动杆菌及铜绿假单胞菌。由于该药存在明显的异质性耐药,不推荐单独应用,常需联合应用其他抗菌药物,如碳青霉烯类、替加环素、磷霉素等,可表现为协同抗菌作用。在肾功能正常患者中多黏菌素 E 甲磺酸钠给药方案为多黏菌素 E 基质(CBA) 2.5~5.0 mg/(kg·d),分 2~4 次静脉滴注。剂量换算为多黏菌素基质 15 mg=多黏菌素 E 甲磺酸盐冻干粉 40 mg=多黏菌素 E 活性成分 50 万单位。多黏菌素 B 硫酸盐每日给药量为 1.5~2.5 mg/kg,分 2 次静脉滴注。该类药物的肾毒性及神经毒性不良反应发生率高,对于移植肾功能不全的患者或老年人需要注意监测肾功能,必要时需调整剂量。

3.2.3 β -内酰胺酶抑制剂及合剂 此类药物多以合剂形式出现,代表药物包括头孢哌酮钠-舒巴坦钠、哌拉西林钠-他唑巴坦钠、替卡西林钠-克拉维酸钾、头孢他啶-阿维巴坦。 β -内酰胺酶抑制剂能够抑制 β -内酰胺酶对 β -内酰胺类抗生素的水解作用,临床常用于覆盖常见耐药阴性杆菌,包括碳青霉烯类耐药的铜绿假单胞菌、产 ESBLs 的大肠埃希菌和肠球菌等。药物常用剂量为 3.0 g (头孢哌酮钠 2.0 g+舒巴坦 1.0 g),每日 3~4 次,静脉滴注。通常舒巴坦的推荐剂量为 4.0 g/d,在治疗 MDR 鲍曼不动杆菌时,剂量上限可增加至 6.0~9.0 g/d,并且延长每次静脉给药的时间至 2 h,同时可以联合碳青霉烯类、多黏菌素等药物。头孢他啶-阿维巴坦作为一种新的酶抑制剂复合制剂,即将在中国上市,其在美国和欧洲获

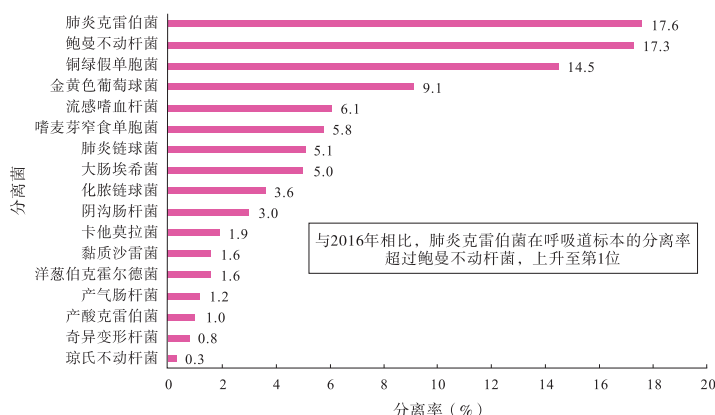


图7 76 333 株呼吸道标本分离菌主要菌种分布

Figure 7 Distribution of major bacteria isolated from 76 333 strains of respiratory tract specimens

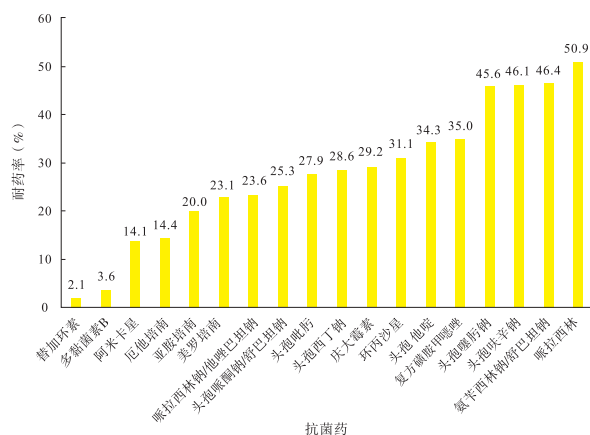


图8 27 977 株肺炎克雷伯菌对抗生素的耐药率

Figure 8 Antibiotic resistance rate of 27 977 strains of *Klebsiella pneumoniae*

得的适应证主要是：复杂的腹腔感染、复杂的尿路感染（包括急性肾盂肾炎）、医院获得性肺炎（包括呼吸机相关肺炎），以及对头孢他啶单药耐药或 MDR 革兰阴性杆菌导致的感染。该药在欧美国家上市后的临床研究显示，对于 MDR 肠杆菌属及铜绿假单胞菌等导致的感染，初始治疗失败者，予头孢他啶 - 阿维巴坦（2.5 g，每日 3 次，静脉滴注）进行补救性治疗，临床有效率可达 60% 以上。

3.2.4 碳青霉烯类 碳青霉烯类抗生素常用的品种包括美罗培南、亚胺培南 - 西司他丁钠、多尼培南和帕尼培南 - 倍他米隆。碳青霉烯类药物对各种革兰阳性球菌、革兰阴性杆菌和多数厌氧菌具有强大的抗菌活性，包括产 ESBLs 和 AmpC β - 内酰胺酶的致病菌，但是嗜麦芽窄食假单胞菌对其天然耐药。

3.2.5 氨基苷类 氨基苷类的常用品种有阿米卡星、异帕米星及妥布霉素。氨基苷类抗生素对 CRE 的血流感染有较好的疗效，这类药物多用于与其它药物联合治疗泛耐药肠杆菌科、铜绿假单胞菌及鲍曼不动杆菌的感染。阿米卡星或异帕米星的推荐剂量为 15 mg/kg，分 1~2 次给药。由于氨基苷类药物具有较强的肾毒性和耳毒性，用药期间应监测肾功能及尿常规，并监控患者的听力状态。

3.2.6 磷霉素 磷霉素是美国感染病协会（Infectious Disease Society of America, IDSA）指南推荐的治疗 CRE 的二线用药，并且磷霉素可与多黏菌素、替加环素、碳青霉烯类、氨基苷类等联合治疗泛耐药菌引起的感染。国内 CRE 对磷霉素的敏感率为 40%~50%。推荐给药方案为 8 g（每日 3 次）或 6 g（每日 4 次），静脉滴注。

3.2.7 四环素类 米诺环素对鲍曼不动杆菌、嗜麦芽窄食单胞菌均具有良好的抗菌效果。2017 年中国细菌耐药监测网检测米诺环素的耐药率为 40% 左右。推荐给药方案为首剂 200 mg，之后 100 mg（每日 2 次），口服用药。

3.2.8 喹诺酮类 临床常用的喹诺酮类抗生素包括左氧氟沙星、莫西沙星、加替沙星和环丙沙星。但对于假单胞菌具有良好的抗菌活性的主要是左氧氟沙星和环丙沙星。可与 β - 内酰胺类、氨基苷类、多黏菌素等联用治疗 PDRPA 和嗜麦芽窄食单胞菌的感染。

3.3 不同 MDR 细菌的抗生素使用

导致 SOT 受者感染的细菌，主要为 MDR 的革兰阴性杆菌；但是，痰培养的结果为 MDR 的革兰阴

性杆菌，则应该结合临床首先判断是定植菌还是责任致病菌，若是责任致病菌，则按照大剂量、联合用药的原则予以相应抗生素治疗。如培养结果为鲍曼不动杆菌，则应该选择以下列几种药物为基础的联合用药原则：舒巴坦或其合剂为基础的联合用药、多黏菌素为基础的联合用药、或替加环素为基础的联合用药。对于铜绿假单胞菌导致的感染，建议依据抗菌药物敏感性选择一种抗菌药物明确治疗。在 PDRPA 广泛流行机构，日常药敏试验必须包含多黏菌素类。不动杆菌属导致的感染，如果仅对多黏菌素类敏感，建议静脉给予多黏菌素 B 或多黏菌素 E；如果是肺部感染，建议同时辅助吸入多黏菌素 E。由于广谱抗生素碳青霉烯类抗生素的普遍使用，呼吸道标本培养到嗜麦芽窄食单胞菌的几率显著升高，因此，也需要首先判断是定植菌还是耐药菌，一旦判断是嗜麦芽窄食单胞菌导致的肺部感染或其它部位的感染，一般首选复方磺胺甲噁唑，其它药物有替卡西林钠 - 克拉维酸钾、头孢哌酮钠 - 舒巴坦、左氧氟沙星或环丙沙星、黏菌素等。对于 CRE 导致的感染，建议给予替加环素、多黏菌素或头孢他啶 - 阿维巴坦。厌氧菌感染一般选择青霉素（脆弱拟杆菌除外）、甲硝唑、克林霉素，严重者可以选择碳青霉烯类。若培养结果为革兰阳性球菌中的 MRSA，一般选择万古霉素、利奈唑胺、替考拉宁或替加环素；若培养结果为 VRE，一般选择利奈唑胺或替考拉宁等。具体抗生素的选择根据药敏结果，与常规抗生素的使用原则相同。

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Management of multidrug resistant Gram-negative bacilli infections in solid organ transplant recipients: SET/GESITRA-SEIMC/REIPI recommendations[☆]



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Abbreviations: BLBLI, β -lactam/ β -lactamase inhibitor combination; BOS, bronchiolitis obliterans syndrome; BSI, bloodstream infection; CPE, carbapenemase-producing *Enterobacteriaceae*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant *Enterobacteriaceae*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CSKP, carbapenem-susceptible *Klebsiella pneumoniae*; ESBL, extended-spectrum β -lactamases; GNB, Gram-negative bacilli; HCAP, healthcare-associated pneumonia; HCV, hepatitis C virus; HT, heart transplantation; ICU, intensive care unit; KPC-Kp, KPC-producing *K. pneumoniae*; KT, kidney transplantation; LT, liver transplantation; LuT, lung transplantation; MBL, metallo- β -lactamase; MDR, multidrug resistant; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; PDR, pandrug-resistant; RCT, randomized controlled trials; SOT, solid organ transplantation; SSI, surgical site infection; UTI, urinary tract infection; VAP, ventilator-associated pneumonia; VRE, glycopeptide-resistant *Enterococcus* spp.; XDR, extensive drug-resistant.

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ABSTRACT

Solid organ transplant (SOT) recipients are especially at risk of developing infections by multidrug resistant (MDR) Gram-negative bacilli (GNB), as they are frequently exposed to antibiotics and the healthcare setting, and are regularly subject to invasive procedures. Nevertheless, no recommendations concerning prevention and treatment are available. A panel of experts revised the available evidence; this document summarizes their recommendations: (1) it is important to characterize the isolate's phenotypic and genotypic resistance profile; (2) overall, donor colonization should not constitute a contraindication to transplantation, although active infected kidney and lung grafts should be avoided; (3) recipient colonization is associated with an increased risk of infection, but is not a contraindication to transplantation; (4) different surgical prophylaxis regimens are not recommended for patients colonized with carbapenem-resistant GNB; (5) timely detection of carriers, contact isolation precautions, hand hygiene compliance and antibiotic control policies are important preventive measures; (6) there is not sufficient data to recommend intestinal decolonization; (7) colonized lung transplant recipients could benefit from prophylactic inhaled antibiotics, specially for *Pseudomonas aeruginosa*; (8) colonized SOT recipients should receive an empirical treatment which includes active antibiotics, and directed therapy should be adjusted according to susceptibility study results and the severity of the infection.

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1. Introduction

1.1. The need and justification for these recommendations

The expectancy and quality of life among patients undergoing solid organ transplantation (SOT) have significantly improved over the previous decades. These advances have stemmed from the development of more potent and safer immunosuppressive drugs and the implementation of clinical guidelines that have made possible to optimize prophylaxis strategies against the main opportunistic microorganisms. However, a major threat to this improvement has emerged from the progressive increase in the incidence of post-transplant infectious complications due to multidrug resistant (MDR) Gram-negative bacilli (GNB) [1]. These include non-fermenting GNB such as *Pseudomonas aeruginosa*, *Burkholderia* spp., *Stenotrophomonas* spp. or carbapenem-resistant *Acinetobacter baumannii* (CRAB), as well as extended-spectrum β -lactamases (ESBL) and carbapenem-resistant *Enterobacteriaceae* (CRE), with a special role played by carbapenem-resistant *Klebsiella pneumoniae* (CRKP) [2,3]. SOT recipients are particularly vulnerable to developing infections by MDR GNB as they usually face prolonged exposure to the healthcare environment, have frequent requirements for invasive diagnostic and therapeutic procedures, and are commonly exposed to broad-spectrum antibiotics [2,4,5]. Long-term post-transplant immunosuppression not only plays a relevant role in enhancing susceptibility to infection, but also in determining the prognosis of such complication through its deleterious effect on the host immune response. On the other hand, the limited therapeutic armamentarium available against these microorganisms often entail the use of potentially nephrotoxic agents, which represents an additional risk for kidney transplant (KT) recipients and other transplant populations with preexisting renal impairment or other concomitant nephrotoxic therapies (i.e., calcineurin inhibitors). Therefore, the therapeutic approach to infections due to MDR GNB in SOT recipients turns out to be particularly challenging as compared to other groups of patients.

1.2. Definition of the microorganisms constituting the focus of the present recommendation

In recent years there has been an increase in the simultaneous resistance to multiple antimicrobials in a number of Gram-positive and Gram-negative microorganisms, thus notably limiting the

therapeutic alternatives for the infections produced by these pathogens. Although infections produced by Gram-positive microorganisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) and glycopeptide-resistant *Enterococcus* spp. (VRE) are frequent in some healthcare settings, newer anti-Gram-positive bacterial agents with excellent in vitro activity and favorable pharmacokinetics and safety profiles are becoming increasingly available [6–8]. However, the problem with MDR GNB is more worrisome, since some of them have developed mechanisms of resistance against most of, if not virtually all, available antimicrobials. Moreover, it is foreseeable a relative paucity of promising anti-Gram-negative bacterial agents in the pipeline over the next years. *Enterobacteriaceae*, *P. aeruginosa* and *A. baumannii* constitute the GNB in which such therapeutic challenges are more often observed in daily clinical practice and, therefore, the present recommendations will be exclusively focused on them.

Although the resistance of these microorganisms to different antimicrobials may be explained by the selection of chromosomal mutations, the most commonly involved mechanism is by far the acquisition of exogenous genes located in mobile genetic elements (plasmids, transposons). Among these genes, the pivotal role is played by those that code for the production of ESBL, AmpC β -lactamases and carbapenemases [9].

- ESBL. These enzymes can hydrolyze and, therefore, provide resistance to penicillins, aztreonam and all generations of cephalosporins, except for cephamycins (i.e., cefoxitin, cefotetan or cefmetazole). Besides cephamycins, ESBL do not hydrolyze carbapenems, and are inhibited by β -lactamase inhibitors such as clavulanic acid, tazobactam, sulbactam and avibactam. The ESBL-encoding genes can be located in plasmids, thus facilitating horizontal spread from one bacterium to another. There are multiple types of ESBL with agent-specific hydrolysis capacities. In addition to *Enterobacteriaceae*, ESBL can also be produced by *P. aeruginosa* and *Acinetobacter* spp. [10].
- AmpC-type β -lactamases. These enzymes are cephalosporinases encoded on the chromosome of many *Enterobacteriaceae* and other GNB such as *P. aeruginosa* and *Acinetobacter* spp. which confer resistance to first- and second-generation cephalosporins and cefoxitin, as well as to most penicillins and β -lactam/ β -lactamase inhibitor combinations (BLBLI). In many *Enterobacteriaceae* (including *Citrobacter freundii*, *Enterobacter cloacae* and *Serratia*

marcescens) and *P. aeruginosa*, AmpC-type β -lactamases are constitutively expressed at low level, but may be induced under exposure to β -lactams through mutations in regulator genes. The resulting AmpC overproduction may confer additional resistance to third- and fifth-generation cephalosporins, while remaining susceptible to fourth-generation cephalosporins. Genes coding for these enzymes can be also located in mobile plasmids, with the potential for dissemination to other bacteria. Nevertheless, in overall terms AmpC-type β -lactamases are less frequently found in plasmids than ESBL [11].

- Carbapenemases. These enzymes constitute a diverse group characterized by their disparate ability to hydrolyze carbapenems (ertapenem, imipenem, meropenem, doripenem) and confer, in most cases, in vitro resistance to this class of antimicrobials. Carbapenemases fundamentally belong to three different classes according to Ambler's molecular classification: i) class A, mainly KPC-type enzymes; ii) class B or metallo- β -lactamases (MBLs), mainly VIM-, IMP- and NDM-type enzymes; and iii) class D, mainly OXA-48 group. Although most of the carbapenemases also hydrolyze the remaining classes of β -lactams, some of them exerts no significant activity against broad-spectrum cephalosporins (such as cefotaxime and ceftazidime) and aztreonam (i.e., OXA-48-group carbapenemases) while others do not hydrolyze aztreonam (i.e., MBLs). Horizontal transfer via plasmids is the most common mode of dissemination. Carbapenemase producers are mainly identified among *K. pneumoniae* and *Escherichia coli* isolates, with a relatively lower contribution to the resistance mechanisms in *P. aeruginosa* and *A. baumannii* [12].

1.3. How are MDR, XDR and PDR bacteria defined?

Although the term “MDR” literally stands for resistance to more than one antimicrobial, there are currently multiple well-established definitions for MDR, extensive drug-resistant (XDR) and pandrug-resistant (PDR) bacteria, which describe the different patterns of acquired resistance observed in drug-resistant bacteria involved in healthcare-related infections. The present recommendations will use the consensus definitions jointly proposed by the European Center for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC). This document establishes standardized international terminology to describe acquired resistance profiles in *Enterobacteriaceae* (excluding *Salmonella* and *Shigella*), *P. aeruginosa* and *Acinetobacter* spp. Of note, such epidemiologically significant antimicrobial categories do not take into account the intrinsic resistance patterns shown by the different microorganisms (Table 1) [13].

In these consensus definitions for MDR, XDR and PDR bacteria, the different antimicrobial classes are distributed into categories depending on whether they are prescribed against *Enterobacteriaceae*, *P. aeruginosa* or *Acinetobacter* spp. (Table 2) [13].

- MDR. Taking into account the antimicrobial categories specifically established for *Enterobacteriaceae*, *P. aeruginosa* and *Acinetobacter* spp., a microorganism is considered MDR when it shows acquired

non-susceptibility (intermediate or resistant) to at least one agent in 3 or more antimicrobial categories (listed in Table 2).

- XDR. A microorganism is considered XDR when it shows acquired non-susceptibility to at least one agent in all but one or two antimicrobial categories (listed in Table 2) (i.e. bacterial isolate remains susceptible to only one or two of the indicated categories for each group of microorganisms).
- PDR. A microorganism is considered PDR when it shows acquired non-susceptibility to all agents in all antimicrobial categories (listed in Table 2).

To ensure that the above definitions are correctly applied, bacterial isolates should be tested against all or nearly all antimicrobial agents within each category. Although these definitions do not necessarily correlate with the presence of the most frequent resistance mechanisms found in *Enterobacteriaceae* (i.e., ESBL, AmpC-type β -lactamases or carbapenemases), according to these criteria, all isolates of this group harboring such mechanisms must be considered, at least, as MDR.

1.4. Particular clinical aspects of MDR GNB infection in different SOT populations (Table 3)

- Liver transplantation (LT): Infectious complications due to MDR GNB are associated to significant morbidity and mortality among LT recipients [4,14]. In this group of patients the rate of infection due to ESBL-producing *Enterobacteriaceae* ranges from 5.5% to 7%, with *K. pneumoniae* and *E. coli* as the most common species identified. The incidence of infections by CRE, particularly CRKP, ranges from 6% to 12.9% in some settings. Infection usually occurs at the early post-transplant period (mean of 12–24 days after the transplant procedure). More than half of the cases have an intra-abdominal origin, such as abscesses, infected bilomas, hematomas or biliary complications (i.e., cholangitis, recurrent cholangitis or biliary leakage). Healthcare-associated pneumonia (HCAP) or urinary tract infection (UTI) are other complications that may be caused by CRKP. Skin and soft tissue infections are less common, although cases of necrotizing infection (necrotizing fasciitis or myonecrosis) have been occasionally reported [15]. The mortality of LT recipients diagnosed with infection due to CRKP has been shown to be up to five times higher than that observed for carbapenem-susceptible isolates (CSKP) [16,17].

In certain series MDR microorganisms are involved in more than half of the cases of GNB bloodstream infection (BSI) in LT recipients (15). The prevalence of this antimicrobial phenotype, however, varies according to the species involved (62.5% for *A. baumannii*, 54.8% for *Enterobacteriaceae*, 54.2% for *S. maltophilia* and 51.5% for *Pseudomonas* spp.) [18].

On the other hand HCAP, including ventilator-associated pneumonia (VAP), is the most common complication associated with CRAB and MDR *P. aeruginosa* in LT recipients [19–21].

Finally, superinfection by MDR GNB in cases of tertiary peritonitis after LT is not uncommon.

Table 1
Infectious Diseases Society of America (IDSA) grading system for ranking recommendations.

Strength of recommendation	A	Good evidence to support a recommendation for use
	B	Moderate evidence to support a recommendation for use
	C	Poor evidence to support a recommendation
	D	Moderate evidence to support a recommendation against use
	E	Good evidence to support a recommendation against use
Quality of evidence	I	Evidence from ≥ 1 properly randomized, controlled trial
	II	Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results from uncontrolled experiments
	III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Table 2

Antimicrobial categories used to define MDR, XDR and PDR isolates according to specific Gram-negative bacilli (modified from Magiorakos et al. [13]).

Microorganism	Antimicrobial category
<i>Enterobacteriaceae</i>	Penicillins, penicillins with β -lactamase inhibitors, antipseudomonal penicillins combined with β -lactamase inhibitors, first- and second-generation cephalosporins, third- and fourth-generation cephalosporins, fifth-generation cephalosporins, cephamycins, monobactams, carbapenems, aminoglycosides, fluoroquinolones, folate pathway inhibitors, tetracyclines, glycyclines, phenicols, phosphonic acids (fosfomycin) and polymyxins
<i>Pseudomonas aeruginosa</i>	Antipseudomonal penicillins combined with β -lactamase inhibitors, antipseudomonal cephalosporins, monobactams, antipseudomonal carbapenems, aminoglycosides, fluoroquinolones, phosphonic acids (fosfomycin) and polymyxins
<i>Acinetobacter baumannii</i>	Ampicillin-sulbactam, antipseudomonal penicillins combined with β -lactamase inhibitors, third- and fourth-generation cephalosporins, antipseudomonal carbapenems, aminoglycosides, fluoroquinolones, folate pathway inhibitors, tetracyclines and polymyxins.

Risk factors include pre-transplant fecal carriage of ESBL-producing isolates, surgical reintervention, and a high MELD score (listed in Table 4). All-cause mortality is around 30% and reaches 41% in the presence of BSI [22,23].

- KT: The urinary tract is the source for most of the post-transplant infections, including BSI, among KT recipients, frequently in form of uncomplicated cystitis (although acute graft pyelonephritis comprises up to one-tenth of the cases). Recurrent UTI represents a common problem that requires ruling out the presence of structural abnormalities such as vesicoureteral reflux, ureterovesical junction stenosis or neurogenic bladder. Infection of renal cysts in KT recipients with underlying renal polycystic disease may also explain UTI recurrence.

In KT recipients, ESBL-producing *E. coli* accounts for up to 12% of infections, particularly in the presence of simultaneous pancreas transplantation, post-transplant requirement of renal replacement therapy, previous use of antibiotics, or urinary tract obstruction or instrumentation [21]. About 70% of the complications caused by ESBL-producing or AmpC-hyperproducing GNB are UTI, although other potential infection sources include the surgical site (SSI), the kidney cell or the presence of lymphocele or urinary fistulas [24].

CRKP may be responsible for UTI after KT, associated or not with BSI and recurrent episodes [25,26]. In addition, this microorganism is commonly involved in intra-abdominal infections related to the surgical procedure such as collections, abscesses or hematomas. Similarly to observe among LT recipients, attributable mortality is higher in infections caused by CRKP in comparison to susceptible counterparts.

With regards to MDR *P. aeruginosa*, the most common clinical manifestations in KT recipients are UTI and HCAP, often complicated by the development of associated BSI [21,27].

Similarly, CRAB constitutes a not uncommon cause of HCAP, particularly in form of VAP, and is responsible for up to 3% of all the episodes of BSI after KT [19,20].

Table 3

Major infectious syndromes caused by multidrug resistant Gram-negative bacilli in solid organ transplantation.

Syndrome	Risk group
Recurrent urinary tract infection	Kidney transplantation Kidney-pancreas transplantation
Renal cyst infection	Kidney transplantation in patients with polycystic disease and/or concomitant hepatic cysts
Recurrent respiratory tract infection	Lung transplantation Cardiopulmonary transplantation
Mediastinitis	Lung transplantation Heart transplantation Cardiopulmonary transplantation
Recurrent cholangitis	Liver transplantation Multivisceral transplantation
Infected biloma	Liver transplantation Multivisceral transplantation
Abdominal abscess and tertiary peritonitis	Liver transplantation Pancreas transplantation Intestinal and multivisceral transplantation

Risk factors generally associated with MDR GNB infection in KT recipients include age older than 50 years, hepatitis C virus (HCV) infection, renal replacement therapy after transplantation and surgical reintervention, kidney-pancreas transplantation and post-transplant nephrostomy [14,15,18,21,24] (listed in Table 4).

- Heart transplantation (HT): HCAP and UTI are the main forms of bacterial infection after HT. The incidence of pneumonia is highest in the first months after transplantation. The most common causative agents are MDR *P. aeruginosa*, CRAB and MDR *S. maltophilia*, and associate BSI is also frequent [28].

The incidence of mediastinitis and sternal surgical wound infection after HT is close to 2.5%. Although most episodes are due to *Staphylococcus* spp., an increasing number of cases of mediastinitis caused by ESBL-producing *E. coli* [29] or non-fermenting GNB has been reported in recent years [30].

- Lung Transplantation (LuT): Colonization of the respiratory tract by MDR *P. aeruginosa* during pre-transplant period is especially common in LuT recipients with cystic fibrosis, with a prevalence >50% that may increase up to 75% after transplantation [5]. On the other hand, *P. aeruginosa* is the leading cause of HCAP after LuT, accounting for up to 25% of cases [31]. It has been suggested that *P. aeruginosa* colonization and infection may play a role in the pathogenesis of bronchiolitis obliterans syndrome (BOS) and in the risk of developing bronchovascular fistula, complications that negatively impact medium- and long-term prognosis [32,33].

Most infections due to CRAB are associated to epidemic outbreaks. HCAP is the most common complication, but UTI, catheter-related BSI and SSI have been also reported [31]. Infectious complications caused

Table 4

Risk factors for developing infections by multidrug resistant Gram-negative bacilli in solid organ transplantation.

Microorganism	Associated risk factors
ESBL- <i>Enterobacteriaceae</i>	Previous antibiotic exposure; pre-transplant colonization; perioperative prophylaxis; prolonged tracheal intubation; long-term hospitalization; urologic manipulation; kidney-pancreas transplantation; renal replacement therapy after transplantation; post-transplant urinary obstruction; recurrent UTI
CRE	Post-transplant renal replacement therapy; HCV infection; hepatoma; kidney-pancreas transplantation; ureteral stent placement
MDR <i>P. aeruginosa</i>	Previous transplantation; hospital-acquired infection; previous admission to ICU; septic shock
MDR <i>A. baumannii</i>	Pre-transplant colonization; previous exposure to antibiotic therapy, specifically carbapenems or piperacillin-tazobactam; retransplantation; septic shock at onset; prolonged mechanical ventilation; cardiothoracic transplantation; kidney failure after transplantation; intraabdominal infection; prolonged cold ischemia time; fulminant hepatic failure as reason for transplantation; high MELD score

CRE, carbapenem-resistant *Enterobacteriaceae*; ESBL, extended-spectrum β -lactamases; HCV, hepatitis C virus; ICU, intensive care unit; MDR, multidrug resistant; UTI, urinary tract infection.

by this pathogen frequently entail a high mortality rate among LuT recipients [34].

Burkholderia spp. has been associated with various complications after LuT, such as chronic lung infections, mediastinal abscesses, pleural effusion or chest wall infection [35]. In this group of patients, mediastinitis is also a common complication.

>50% of all episodes of GNB BSI in LuT are produced by strains with a MDR phenotype, which may account for up to 100% of *B. cepacia* isolates in this setting [36].

1.5. Attributable mortality to MDR GNB infections in SOT recipients

Overall, infections caused by MDR GNB result in a significantly higher attributable mortality than those due to susceptible microorganisms. One study identified the inadequacy of empirical antibiotic treatment and the inability to identify the primary source of infection as risk factors for mortality associated with BSI due to ESBL-producing *E. coli* in non-transplanted patients [37]. Other authors have reported a higher risk of death associated with CRKP infection among LT and LuT recipients [16,38]. It has also been shown that patients with CRAB infection after SOT had a longer hospital stay and an increased risk of graft loss and death compared to patients without any infection or those with infection due to carbapenem-susceptible *A. baumannii* [19,20,39]. Infection due to MDR *P. aeruginosa* was associated with higher mortality in LT recipients, reaching 38% in case of BSI [21,40]. Such poorer outcomes are mainly driven by increased odds for inappropriateness of empirical antimicrobial therapy and clinical failure of targeted therapy, even when antimicrobial agents with in vitro activity are used [4].

2. Infections produced by ESBL-producing *Enterobacteriaceae*

2.1. What are the risk factors for developing ESBL-producing *Enterobacteriaceae* infections after SOT?

Studies performed in Spain have estimated that approximately 20% of infections in SOT recipients are caused by MDR bacteria, from which 75% are due to ESBL-producing *Enterobacteriaceae* [41]. >20% of all *E. coli* isolated in urine cultures of SOT recipients with a diagnosis of UTI are ESBL-producing *Enterobacteriaceae* [42]. KT recipients are significantly at risk [42]. Different period comparison has confirmed that the incidence of the infections produced by these microorganisms is increasing [43].

SOT has been identified as a classical risk factor for ESBL-producing *Enterobacteriaceae* infection, together with prior hospital admittance, use of antibiotics in last 3 months, cancer and admittance in long-term care facilities [23]. Other known risk factors are advanced age, intensive care unit (ICU) requirement, use of intravascular catheters or other intravascular devices, mechanical ventilation, renal replacement therapy and parenteral nutrition [44] (listed in Table 4).

ESBL-producing *Enterobacteriaceae* infections are more frequent in KT and kidney-pancreas transplant recipients than in other SOT because these patients have a higher incidence of UTI. Recurrence of UTI in KT is associated with ESBL-producing *Enterobacteriaceae*: half of recurrent UTI are caused by these microorganisms in some studies [41]. A Spanish study that enrolled >4,000 SOT recipients, including 249 episodes (4.4%) of bacterial UTI, reported that *E. coli* was the microorganism most frequently isolated (57.8%) and 25% were ESBL-producing bacteria [42]. Specific risk factors for ESBL-producing *Enterobacteriaceae* infection in KT include kidney-pancreas transplantation, prior use of antibiotics, renal replacement therapy after transplantation and post-transplant urinary obstruction [24]. The association between rectal ESBL-producing *Enterobacteriaceae* colonization and the risk of UTI by these microorganisms in KT has also been previously reported: 55% of patients with UTI by ESBL-producing *Enterobacteriaceae* had a previous history of rectal colonization; these studies have also confirmed that UTI

relapse by ESBL-producing *Enterobacteriaceae* is frequent (40%) and is associated with older age and persistent bacteriuria after appropriate treatment [45].

The epidemiology and risk factors vary according to the different ESBL-producing *Enterobacteriaceae*. Although the rate of horizontal transmission of ESBL-producing *K. pneumoniae* is high, it is lower in the case of ESBL-producing *E. coli* [46]. A Spanish study that analyzed 116 episodes of *K. pneumoniae* infection in SOT recipients reported that more than half of the isolates were ESBL-producers (53%); approximately half of them were diagnosed in the first month after transplantation and UTI were more frequently recorded (72%), especially in KT (11%), followed by LT (7%), HT (5%) and kidney-pancreas or liver-kidney (6%).

Prolonged use of broad-spectrum antibiotics during the pre-transplant period and long-term tracheal intubation (>72 h) have been reported as risk factors for ESBL-producing *Enterobacteriaceae* infections after LT [47]. LT recipients are considered specifically at risk since liver failure has been identified as an independent risk factor for ESBL-producing *Enterobacteriaceae* colonization [48].

Other risk factors in SOT recipients are prolonged hospitalization [49], urologic manipulation, use of ureteral stents and urethral catheterization, which is common in KT [5,50], duration of antibiotic treatment and perioperative prophylaxis, specifically in KT [51].

Outbreaks of ESBL-producing *K. pneumoniae* in pediatric intestinal transplantation have been associated with prior exposure to piperacillin-tazobactam, especially in children under 5 years of age and in patients who had had more than three central venous catheters before the infection [52].

2.1.1. Consensus recommendations

- SOT is a specific risk factor for developing ESBL-producing *Enterobacteriaceae* infections (AII).
- KT recipients and LT recipients are especially at risk for developing infections by these microorganisms. Previous antibiotic exposure, pre-transplant colonization, perioperative prophylaxis, prolonged tracheal intubation, long-term hospitalization, urologic manipulation, kidney-pancreas transplantation, renal replacement therapy after transplantation, post-transplant urinary obstruction and recurrent UTI are some of the identified risk factors (BII).

2.2. How can ESBL-producing *Enterobacteriaceae* be identified through an antibiogram?

Recognition of ESBL-producing *Enterobacteriaceae* is relatively easy as long as there are no other mechanisms of resistance that may mask their presence, such as other enzymes with an overlapped hydrolytic spectrum (plasmid-mediated AmpC, AmpC overexpression or carbapenemases) or permeability resistance mechanisms (porins and efflux pumps) [53].

There are different types of ESBL, which share a similar phenotypic profile. Cefotaxime, ceftriaxone, ceftazidime and cefepime are similarly hydrolyzed by TEM, SHV and OXA variants. This determines the increase of the minimum inhibitory concentration (MIC) values compared to the bacteria that lack these enzymes [53]. With a few exceptions (e.g. CTX-M-15), the majority of CTX-M type enzymes hydrolyze more efficiently cefotaxime, ceftriaxone and cefepime than ceftazidime. Generally, they are inactivated by the combination of penicillins or cephalosporins with a β -lactamase inhibitor (amoxicillin-clavulanic acid, piperacillin-tazobactam, ceftazidime-avibactam or ceftolozane-tazobactam) although this depends on the coexistence of other resistance mechanisms. Moreover, ESBL-producing *Enterobacteriaceae* are usually less susceptible to non- β -lactam antibiotics (aminoglycosides, quinolones or cotrimoxazole) than other bacteria [54].

The phenotypic profile and the type of enzymes in ESBL-producing *Enterobacteriaceae* isolated from clinical and/or surveillance samples of SOT recipients do not differ from other patients. Notwithstanding,

some variations can be observed, depending on the geographical area and epidemiological setting, such as those associated with outbreaks. CTX-M type, followed by SHV, is the most prevalent, while TEM-type is the less common [22,49,55,56]. Currently, it is not uncommon to also find ESBL in carbapenemase-producing *Enterobacteriaceae* (CPE) [57].

2.2.1. Consensus recommendations

It is important to recognize ESBL-producing *Enterobacteriaceae* isolated from clinical and/or surveillance samples of SOT recipients, as they increase the risk of inappropriate use of antibiotics and death (AIII).

2.3. Can a colonized or infected patient with ESBL-producing *Enterobacteriaceae* be accepted as an organ donor?

As mentioned, SOT recipients have a higher risk for developing infections by MDR microorganisms, including ESBL-producing *Enterobacteriaceae* [3]. Although donor-derived infections caused by MDR bacteria have been previously reported [58–63], there is no evidence to contraindicate transplantation from donors colonized with ESBL-producing *Enterobacteriaceae*.

2.3.1. Consensus recommendations

- Donor colonization with ESBL-producing *Enterobacteriaceae* does not constitute a contraindication to transplantation (AIII).

2.4. Can a patient colonized with ESBL-producing *Enterobacteriaceae* be accepted for transplantation?

ESBL-producing *Enterobacteriaceae* adversely affects the outcome, due to the higher risk of inappropriate use of antibiotics and higher mortality rate [64,65]. A case-control study with 55 ICU patients diagnosed with BSI confirmed a significant higher mortality rate in patients with ESBL-producing *Enterobacteriaceae* (68.8% vs. 35.9%) [66]. This trend in the mortality rate has also been confirmed in studies with neutropenic patients [67]. Despite the risk of inadequate treatment and increased morbidity and mortality in colonized patients, this should not contraindicate transplantation; nevertheless, measures should be taken to improve the prognosis of these patients.

2.4.1. Consensus recommendations

- Recipient colonization with ESBL-producing *Enterobacteriaceae* is associated with worse outcome, but it is not a contraindication for transplantation (BII).

2.5. Should a different surgical prophylaxis regimen be prescribed when a donor or a recipient is colonized with ESBL-producing *Enterobacteriaceae*?

There are no prospective studies evaluating the efficacy of a directed prophylaxis regimen against ESBL-producing *Enterobacteriaceae* in SOT recipients. However, indirect data can be obtained from the impact of colonization on these patients. According to the ENTHERE study, which is currently ongoing in seven Spanish centers, 20 of the first 112 enrolled SOT recipients (17.8%) proved to be colonized with MDR bacteria at the moment of transplantation: 45.5% with ESBL-producing *E. coli*, 24.9% with ESBL-producing *K. pneumoniae* and 9.5% were colonized with CPE (Fariñas C, personal communication). In this study, 5.15% of the colonized recipients developed an infection by ESBL-producing *Enterobacteriaceae* versus 2.4% of the non-colonized.

A French study with 710 LT recipients, and a pre-transplant colonization incidence with ESBL-producing *Enterobacteriaceae* of 5.5%, reported that 44.8% of the colonized recipients developed an infection by these microorganisms in the following four months. This incidence was significantly higher than in the non-colonized recipients (3.8%). Median time to infection was also shorter in the colonized recipients (9 vs. 25 days) [22]. This study also described a gradual increase in the

rates of ESBL-producing *Enterobacteriaceae* colonization, from 0% in 2001–2003 to 10.6% in 2009–2010. Finally, another study reported that 47% of KT recipients with asymptomatic bacteriuria caused by ESBL-producing *Enterobacteriaceae* eventually developed an UTI by the same microorganism [45].

Colonized patients should receive specific prophylactic regimens and, in the case of bacterial infection, an empirical treatment with active antibiotics against ESBL-producing *Enterobacteriaceae* [22]. There are too heterogeneous data to make a strong recommendation of the alternative use of β -lactamase inhibitors, quinolones, or aminoglycosides in these patients [65]. The use of ertapenem, cefoxitin, or fosfomycin-trometamol reduced the incidence of BSI after prostatic biopsy in patients colonized with ESBL-producing *Enterobacteriaceae* and/or resistant to quinolones, and it could be an acceptable alternative in some patients [68–70].

Since the use of carbapenems has been associated with an increased risk of carbapenemases [16], their use in prophylaxis regimens must be avoided whenever possible. As for the use of carbapenems in empirical treatment regimens, it must be reserved for restricted patients that are colonized or at risk of infections with ESBL-producing *Enterobacteriaceae* [22,71]. It is always important to balance the risk of infection against the risk of developing adverse effects to the antibiotics and/or carbapenem-resistance.

2.5.1. Consensus recommendations

- Patients colonized with ESBL-producing *Enterobacteriaceae* should receive a specific prophylaxis regimen and, in the case of infection, an empirical treatment which includes active antibiotics against these microorganisms. However, the use of carbapenems should be avoided whenever possible (BIII).

2.6. Should intestinal colonization by ESBL-producing *Enterobacteriaceae* be monitored in SOT recipients?

As mentioned, the risk of ESBL-producing *Enterobacteriaceae* infections is higher in colonized than in non-colonized recipients [22,72]. Besides, screening for colonized patients could help increase infection control [73].

In a German prospective study, all colonized patients with ESBL-producing *Enterobacteriaceae* who developed infection during follow-up received an adequate empirical treatment. On the contrary, adequate antibiotic treatment was only prescribed in two of the four non-colonized patients, and both died of severe sepsis [74].

Colonization and infection with ESBL-producing *K. pneumoniae* is more frequently healthcare-acquired, whereas colonization with ESBL-producing *E. coli* is usually community-acquired [44]. Moreover, environmental contamination is more frequent with ESBL-producing *K. pneumoniae* than with ESBL-producing *E. coli* [75].

All these data, based on retrospective studies, suggest the potential benefit of performing surveillance cultures in high-risk patients, including transplant recipients, although the real impact of this strategy should be confirmed in prospective, multicenter studies.

2.6.1. Consensus recommendations

- Data analysis of retrospective studies favors the screening of patients with high risk for ESBL-producing *Enterobacteriaceae* colonization, including SOT recipients (BII). Prospective studies are warrant for supporting this approach.

2.7. What are the isolation precautions and healthcare infection control measures recommended for a recipient colonized with ESBL-producing *Enterobacteriaceae*?

The human digestive tract is the main reservoir of ESBL-producing *Enterobacteriaceae* [76,77]. Preventive strategies against transmission of ESBL-producing *Enterobacteriaceae* in healthcare facilities include

basic measures such as timely detection of carriers, contact isolation precautions, hand and body hygiene (chlorhexidine washing) and the implementation of an antibiotic control policy [76,78,79]. However, not all these measures have proven to be equally effective. In fact, in most cases they have been implemented as part of a bundle of measures for infection control, making it difficult to estimate their importance separately.

Although a few studies have evaluated the direct impact of hand hygiene on the transmission of MDR GNB, this measure is a fundamental intervention for control of healthcare-associated outbreaks by these microorganisms [80]. Most clinical guidelines advocate the implementation of educational programs to improve and control hand hygiene [79–82] and this measure is especially critical in SOT wards. It is recommended to use alcohol-based products before and after touching the colonized patients and/or furniture in their potentially contaminated room [81].

In addition to other contact isolation measures, clinical guidelines now recommend single-room isolation for colonized or infected patients as a way of reducing the horizontal transmission. Several studies have shown that this measure is effective during ESBL-producing *K. pneumoniae* outbreaks [80,81,83]. However, in the case of patients colonized by ESBL-producing *E. coli*, isolation precautions are not as strongly recommended [76]. This has two explanations; the first is that in many hospitals it is an endemic problem and isolation is not feasible; the second is that the epidemiological pattern reported in ESBL-producing *Enterobacteriaceae* outbreaks is dependent of plasmid dissemination between different clones influenced by the selective pressure of antibiotics (more relevant in *K. pneumoniae* than *E. coli*). Avoiding the spread of ESBL, especially in the case of *E. coli*, is a major challenge and recommended measures should go beyond the hospital setting and into the community, where the number of carriers is bigger and the reservoirs and mechanisms of transmission are more difficult to identify and control [84].

It is important to improve the terminal cleansing of the rooms in which these patients are admitted. Most clinical guidelines do not recommend disinfection with hypochlorite, but hydrogen peroxide vapor is advisable [80].

A combined effort between clinical microbiology, preventive medicine, nursing staff, healthcare assistants and cleaning personnel is essential for handling the problem. The measures contemplated in the setting of an outbreak are the relocation of patients in special sectors or assigning exclusive clinical staff to these patients [80,81]. Finally, there is no consensus in performing surveillance cultures to detect healthcare personnel colonized by MDR GNB [80,81].

2.7.1. Consensus recommendations

- Hand washing and disinfection with alcohol-based gels are recommended before and after touching the patients (AIII).
- In the case of patients colonized by ESBL-producing *K. pneumoniae*, contact isolation precautions are also recommended, including single-room isolation (AIII). For patients colonized with ESBL-producing *E. coli* this recommendation is not so strong (BII).

2.8. Is intestinal decolonization recommended?

Intestinal decolonization was first evaluated in 1983 [85]. Since then several controlled clinical trials and meta-analysis have been published [86]. The goal is to minimize or prevent endogenous and exogenous infections, by reducing the bacterial overgrowth of the aerobic flora, while preserving the anaerobic flora. Most published studies enrolled patients admitted to the ICU. These studies have shown that intestinal decolonization significantly reduces rectal colonization by GNB [87]. However, the long-term benefit of these measures is doubtful. A controlled, double blind, placebo-group clinical trial demonstrated a transient effect on intestinal decolonization with ESBL-producing *Enterobacteriaceae* using colistin and neomycin [88].

Evidence in SOT is scarce. A prospective study that analyzed SOT recipients from 12 Spanish hospitals, showed no advantage in administering fluoroquinolones as an independent protective factor for the development of early bacterial infections due to *Enterobacteriaceae* [89].

A multicenter study conducted in the Netherlands, including 5939 patients admitted into the ICU, showed a difference in the incidence of ICU-acquired BSI when selective intestinal decolonization and oral decolonization were performed and a decrease of up to 3.5% in the mortality rate at day 28 in the intestinal decolonization group [90]. Other studies also demonstrated that intestinal decolonization had a positive impact on mortality reduction in ICU patients in whom eradication of the carrier state was achieved [91]. However, a meta-analysis with 32 intestinal decolonization studies performed in critically ill patients concluded that these studies overestimated the effect of intestinal decolonization on the mortality rate [92].

One of the main concerns over the use of intestinal decolonization is the risk of MDR bacteria selection. Brink et al. reported the emergence of colistin-resistant OXA-181-producing *K. pneumoniae* during the use of oral decolonization with colistin [93]. Other authors also reported an increase in the prevalence of ESBL-producing *K. pneumoniae* strains resistant to tobramycin and colistin, and an increase in BSI caused by these agents after the use of intestinal decolonization [94], including neonates [95].

Currently, a cohort study and a randomized, open-label, multicenter clinical trial study are being carried out (ENTHERE Study, EudraCT: 2013-004838-15). The aim of this study is to analyze the clinical relevance of intestinal colonization by MDR *Enterobacteriaceae* in LT and KT recipients, and evaluate whether treatment with colistin (50 mg 4 times/day) and neomycin (250 mg 4 times/day) orally for 14 days reduce the risk of infection by MDR bacteria.

2.8.1. Consensus recommendations

- There is no evidence so far to support decolonization of SOT recipients colonized by ESBL-producing *Enterobacteriaceae*. Retrospective studies performed in other types of patients have confirmed a transient effect but a potential risk of selecting resistant strains. Further studies are needed to clarify its benefits in SOT recipients (CIII).

2.9. Should inhaled antibiotics be prescribed to donors or recipients with respiratory tract colonization with ESBL-producing *Enterobacteriaceae*?

Inhaled antibiotics are an attractive option for the treatment of respiratory tract infections by MDR microorganisms. They allow for a maximum drug delivery to the target site of infection, as well as limited systemic exposure and toxic effects [96–98].

Most data on the use of inhaled antibiotics derive from patients with VAP or cystic fibrosis. Nevertheless, even in these groups of patients, the number of well-designed studies on the efficacy and tolerance of the treatment is very low. Although there is no available evidence on the use of inhaled antibiotics in SOT recipients with respiratory colonization by ESBL-producing *Enterobacteriaceae*, nebulized antibiotics are often used in specific situations, such as LuT [3,31].

There are several commercialized antibiotics prepared specifically for nebulization, but most data derive from the use of aminoglycosides and colistin. In a single-center, randomized, double-blind trial with critically ill patients, administration of inhaled gentamicin or amikacin every 8 h for 2 weeks was associated with a greater eradication of MDR microorganisms compared to placebo [99]. In another small sample size study, inhaled tobramycin-solution was effective and had less adverse effects than intravenous tobramycin for the treatment of VAP caused by *P. aeruginosa* or *Acinetobacter* spp. [100].

Recently, it was reported that the combination of inhaled amikacin and fosfomycin in patients with Gram-negative VAP was not associated with clinical improvement when compared to the placebo [101]. Some studies have shown that nebulized colistin can be effective and safe in the treatment of pneumonia caused by MDR GNB [102,103]. However, other studies have not confirmed these results [104,105].

Choosing the nebulized antibiotic treatment depends both on the antibiotic and the nebulization device. The antibiotic should be selected based on the susceptibility profile, taking into account that cut-off values used for systemic treatment are not applicable for nebulized therapy. Moreover, if an antibiotic without a specific commercialized preparation is prescribed, bronchodilator drugs should be previously administered to reduce the risk of associated bronchospasm. On the other hand, to improve the effectiveness of this type of treatment, appropriate nebulization devices are essential. Vibrating mesh nebulizers, which are smaller and faster than jet nebulizers, are recommended [106].

One concern about nebulized therapy is the possibility of inducing antibiotic resistance. However, studies with both cystic fibrosis and critically ill patients did not report a resistance increase when compared to conventional therapy or placebo [99,107,108].

2.9.1. Consensus recommendations

- The use of inhaled antibiotics may be considered for LuT recipients with respiratory tract colonization with ESBL-producing *Enterobacteriaceae* or that have received a colonized graft. Appropriate nebulization devices (electronic or vibrating mesh nebulizers) are recommended (BIII).

2.10. What treatment should be prescribed? Can BLBLI be used for the treatment of ESBL-producing *Enterobacteriaceae* infections in SOT recipients?

While ESBL are capable to hydrolyze β -lactam antibiotics and non-cephamycin-type cephalosporins, they do not hydrolyze carbapenems. As such, carbapenems are usually considered as first-line treatment. There are no comparative studies between the different carbapenems for the treatment of ESBL-producing *Enterobacteriaceae* infections. However, in the case of ESBL-producing *E. coli* strains exposed to carbapenems, a greater selection of strains resistant to ertapenem and meropenem, but almost none to imipenem, has been described [109].

β -Lactamase inhibitors are capable of inactivating ESBL, which is not the case with chromosomal-mediated AmpC β -lactamases. Several retrospective observational studies have been conducted to assess the efficacy of BLBLI compared to carbapenems for the treatment of ESBL-producing *Enterobacteriaceae* infections. Second-generation BLBLI, such as ceftolozane-tazobactam and ceftazidime-avibactam have acceptable activity against ESBL-producing *Enterobacteriaceae* and appear to be reasonable alternatives to carbapenems.

Amoxicillin-clavulanic acid has shown efficacy in the treatment of UTI caused by ESBL-producing *E. coli*, with a 93% cure rate with susceptible strains and 56% with intermediate or resistant strains [110]. Piperacillin-tazobactam cured 10/11 patients with ESBL-producing *E. coli* or *Klebsiella* spp. infections from sites other than the urinary tract when the MIC was $\leq 16/4$ $\mu\text{g/mL}$, but only 1/5 patients when the MIC was $>16/4$ $\mu\text{g/mL}$ [111]. Resistance during treatment with piperacillin-tazobactam was reported in a case of ESBL-producing *Klebsiella* endocarditis [112], which leads to the question of the efficacy of BLBLI in infections with high bacterial load. Mortality rates are higher when BSI caused by ESBL-producing *Enterobacteriaceae* is treated empirically with BLBLI than with a carbapenem: 38% (10/16) vs 16% (10/63) for ESBL-producing *E. coli* or *K. pneumoniae* [113] and 25% (2/8) versus 14% (8/57) for ESBL-producing *E. coli*, *K. pneumoniae* and *Proteus mirabilis*, respectively [114]. A recent study that included 331 patients with ESBL-producing *Enterobacteriaceae* BSI, 103 (48%) treated with piperacillin-tazobactam and 110 (52%) treated with carbapenem, showed that the risk of death was 1.92 times higher in the group treated empirically with piperacillin-tazobactam [115]. However, two other recent published articles showed similar mortality rates in the treatment of BSI caused by ESBL: the first included 151 patients treated empirically with either piperacillin-tazobactam (94) or carbapenem (57), with similar mortality rates (30.9% and 29.8%, respectively), and risk-adjusted mortality rate (OR 1.0, 95% CI; 0.45–2.17) [116]; the second study

differentiated between empirical treatment (365 patients), directed treatment (601 patients) and overall cohort (627 patients), finding no differences in cure/improvement or 30-day mortality rate between carbapenem and BLBLI [117].

Second-generation BLBLI, ceftolozane-tazobactam and ceftazidime-avibactam, have a better activity profile against ESBL-producing *Enterobacteriaceae*. Data extracted from two pivotal clinical trials of ceftolozane-tazobactam for the treatment of UTI [118] and intra-abdominal infections [119] included 150/1346 patients with ESBL-producing *Enterobacteriaceae* infections [120]. Clinical cure rates were 97.4% (76/78) for ceftolozane-tazobactam, 82.6% (38/46) for levofloxacin (prescribed for UTI) and 88.5% (23/26) for meropenem (prescribed for intra-abdominal infections) [120]. The in vitro activity profile of ceftazidime-avibactam against ESBL-producing *Enterobacteriaceae* and plasmid-determined AmpC is excellent, reaching almost 100% of all susceptible strains [121].

Cephamycins, such as cefoxitin, cefotetan or cefmetazole have shown in vitro activity against ESBL-producing *Enterobacteriaceae*. Although the number and quality of the clinical studies is very limited, cefoxitin has shown efficacy for the treatment of UTI caused by ESBL-producing strains [122]. A recent retrospective study with 69 patients with ESBL-producing BSI, in which 26 were treated with cefmetazole and 43 with carbapenems, showed an adequate efficacy of the cephamycin (1 death in the cefmetazole group and 5 deaths in the carbapenem group) [123].

Other active antibiotics against ESBL-producing *Enterobacteriaceae* are aminoglycosides, colistin, fosfomycin, and tigecycline. All of them should be considered second-line antibiotics due their adverse effects and the increased mortality rate when compared to β -lactams.

2.10.1. Consensus recommendations

- Carbapenems are recommended as empirical and targeted treatment of moderate or severe infections caused by ESBL-producing *Enterobacteriaceae* in SOT recipients (BII).
- The use of BLBLI seems reasonable in recipients with non-bacteremic ESBL-producing *Enterobacteriaceae* infections (especially UTI) (BII).

3. Infections produced by CPE

3.1. What are the risk factors for developing CPE infections after SOT?

Approximately 3 to 10% of all SOT recipients in areas where CPE are endemic develop an infection by these microorganisms. The infection site frequently correlates with the type of transplant performed. Mortality rates associated with CPE infections in SOT recipients are close to 40% [124]. Therefore, it is very important to know the risk factors for developing infections by these microorganisms (listed in Table 4).

Several studies have evaluated the risk factors for developing a CPE infection. Renal replacement therapy (especially >3 sessions after transplantation) has been identified as the major risk factor for developing CPE infections in LT recipients that were already colonized before transplantation (up to 82% of carriers) [125]. Kidney-pancreas transplantation and ureteral stent placement have also been identified as risk factors for CPE infections in KT. In these cases, patient's outcome is poor due to the higher incidence of recurrence and greater 30-day mortality rate (42% in KT) [126].

Other studies, showed in the univariate analysis that LT due to HCV infection and/or hepatoma were risk factors for BSI caused by CRKP, whereas SOFA and APACHE II were risk factors for mortality [127]. Previous exposure to broad-spectrum antibiotic therapy was also reported as a risk factor for CRKP infection in LT. Age, gender, diabetes and other comorbidities did not entail a greater risk. The mortality rate in patients with CRKP infections was 46% (far superior to the mortality rate in patients with CSKP infections) [25].

2.10. 应该使用什么治疗方案？BLBLI 可以用于治疗产 ESBL 的肠杆菌科感染的实体器官移植（SOT）接受者吗？

2.10.1. 共识建议

- 碳青霉烯类药物被推荐为由产 ESBL 的肠杆菌科引起的 SOT 受者中度或重度感染的经验性和目标性治疗（B-II）。
- BLBLI 在非产 ESBL 细菌的肠杆菌科感染（尤其是 UTI）的器官移植患者中的应用似乎是合理的（B-II）。

In the non-transplanted population, risk factors for CPE include previous antibiotic selective pressure (glycopeptides, cefoperazone/sulbactam, fluoroquinolones and cephalosporins) [128], advanced age, mechanical ventilation [129], prolonged central venous catheterization [130] and tracheostomy [131]. Likewise, studies carried out during healthcare-associated outbreaks have identified age, severity of the infection, ICU admittance, previous use of antibiotics (mainly carbapenems, fluoroquinolones and cephalosporins), invasive procedures (principally mechanical ventilation) and previous colonization by these agents as risk factors for CPE [132].

In a study involving 94 patients, prolonged hospital stay, mechanical ventilation, use of catheters and previous surgery were associated with a higher rate of infection by CRKP [133]. CRKP colonized patients develop more infections and, usually, more severe. In a study that enrolled non-transplanted diabetic patients diagnosed with diabetic foot, the mortality rate was much higher in the colonized group than in the control group (47% vs. 4%). Overall, 28% of the colonized patients developed a foot ulcer infection [134].

ICU admission, use of central venous catheters, antibiotic exposure, and diabetes mellitus have been identified as risk factors for colonization with CPE. Exposure to fluoroquinolones and metronidazole has been associated with subsequent infection by these microorganisms. In conclusion, antibiotic therapy, and specifically fluoroquinolones and metronidazole, should be cautiously used in CPE carriers [135].

3.1.1. Consensus recommendations

- Post-transplant renal replacement therapy, HCV infection, hepatoma and previous antibiotic exposure have been identified as risk factors for CPE in LT. Kidney-pancreas transplantation and ureteral stent placement have been reported as risk factors in KT (AII).

3.2. What microbial mechanisms cause resistance to carbapenems? How can CPE be identified through an antibiogram?

In addition to carbapenemase production, carbapenem resistance can also occur by the combination of class C enzymes expression (encoded by chromosomal or plasmid genes) or some ESBL and the loss or structural modification of porins [136,137], and, less frequently, due to changes in penicillin-binding proteins [138].

Detection of carbapenem resistance is based on EUCAST (http://www.eucast.org/clinical_breakpoints/) or CLSI breakpoints [139], and in analyzing the overall susceptibility of each microorganism, as CPE frequently contain genes that cause resistance to many other antimicrobial families [140]. Some carbapenemase-producing strains have a MIC value below the susceptible clinical breakpoint or have an inhibition halo diameter, measured by disc diffusion method, greater than the one defined as susceptible. Therefore, EUCAST recommends suspecting the presence of these enzymes considering screening cut-off values. Phenotypic methods (available at each Microbiology Unit or Department) and genotypic methods (available at each center or microbiology reference laboratories) allow for microbiologists to confirm carbapenemase production and for the enzyme characterization. EUCAST has a guide for the detection of CPE.

(http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Resistance_mechanisms/EUCAST_detection_of_resistance_mechanisms_v1.0_20131211.pdf).

3.2.1. Consensus recommendations

- Standard EUCAST clinical breakpoints should be used for detection of carbapenem resistance in *Enterobacteriaceae* (AIII).
- Carbapenemase production should be suspected when EUCAST screening cut-off values are exceeded (AII).
- Clinical Microbiology Units or Departments must have the means for the phenotypic detection of carbapenemase and for their genotypic classification or have access to reference laboratories for enzyme characterization (AIII).

3.3. Can a colonized or infected patient with CPE be accepted as an organ donor?

When assessing the risk of transmitting a CPE infection from a colonized and/or infected donor, we can only rely on the limited experience from specific centers with an endemic outbreak, mainly from colonization/infection with KPC-producing *K. pneumoniae* (KPC-Kp). The only study that systematically analyzed donor-transmission of these microorganisms included only 5 colonized or infected donors with KPC-Kp. Donor-derived infection occurred in four of eleven recipients (36%). Three of the recipients (two kidney and one liver) developed a severe SSI, with a death-related case [61]. Failure in communicating the microbiological data and, therefore, a delay of >7 days in beginning the specific antibiotic regimen were identified as risk factors for both transmission and severe infection development [61]. Case records of KPC-Kp donor-derived infections make up for the rest of the limited published data [59,60,62]. The only relevant conclusion that can be drawn out of these limited data is that grafts with high potential colonization by CPE should be avoided (KT from donors with UTI, LuT from donors with respiratory tract infections). If the donor has an undiagnosed BSI before transplantation, recipients should receive, at least, 7-days of adequate treatment.

3.3.1. Consensus recommendations

- Donation from patients with non-bacteremic, non-graft-related CPE infections is not contraindicated. Nevertheless, recipients should receive, as soon as possible, a minimum of 7-days effective antibiotic treatment after transplantation (BIII).
- Donation should be avoided if the donor has a CPE bacteremic infection. If transplantation was performed before microbiological data was available, a minimum 7-days effective antibiotic treatment should be prescribed as soon as possible (BIII).
- It is recommended to avoid kidney grafts from donors with CPE-related UTI (BIII) and lung grafts from patients with lung CPE-related infection (BIII).

3.4. Can a patient colonized with CPE be accepted for transplantation?

There are only a few studies that have focused on determining if the presence of a previous colonization in a recipient could determine the risk of developing a severe infection by CPE after transplantation. Most of the scarce available data derives from LT. A LT center with an endemic setting of KPC-Kp infection reported that 5 of the 6 previously colonized recipients subsequently developed an infection. In most cases it was a recurrence of a previous infection [17]. Although this study reported a 35% overall mortality rate associated with the KPC-Kp infection, the specific outcome of these infections was not detailed.

A different study that compared the clinical outcomes of 9 LT recipients colonized with KPC-Kp with 18 LT recipients in whom carbapenem-resistant pathogens were not detected, reported that 8 of the 9 patients developed an infection, 5 of them with BSI, with an overall mortality rate of 78%. The authors concluded that pre-transplant KPC-Kp colonization could constitute a relative contraindication to transplantation [141]. Other studies coincided in the increase of the mortality rate related to KPC-Kp infections in LT recipients [16,142,143].

In KT, the impact of the recipient previous colonization with CEP was not clearly evaluated. Nevertheless, an increase in the morbidity, mortality and risk of recurrences associated with these microorganisms has been reported [126,144]. KPC-Kp infection was also related to a higher mortality rate in LuT [38].

With the available data, it can only be concluded that CEP infected/colonized SOT recipients have a higher risk of recurrence and/or de novo infection by these microorganisms. Associated morbidity and mortality is also high. There are no studies that specifically measure whether this risk is outweighed by the negative impact of excluding these patients from transplantation. In any case, transplantation should

depend on our ability to control the infection, similar to potential recipients infected/colonized by other microorganisms.

3.4.1. Consensus recommendations

- There are no data to contraindicate the transplantation of patients colonized with CPE. Nonetheless, these recipients have an increased risk of graft infection and, probably, of death (CIII).

3.5. Should a different surgical prophylaxis regimen be prescribed when a donor or a recipient is colonized with CPE?

There are no studies that have specifically addressed the surgical prophylaxis regimens in patients colonized with CPE. As we mentioned, SOT recipients previously colonized by CPE have a higher risk of developing infections by these microorganisms [125]. However, the incidence of SSI in SOT is very variable and is directly related to the epidemiological situation of the center. A RESITRA study that included 1400 KT recipients, reported a high incidence of SSI due to GNB. Prophylaxis with cefazolin was not associated with an increased risk of infection by these microorganisms [145]. A different RESITRA study with 1222 LT recipients, observed that SSI caused by GNB was also more frequent and prophylaxis with cefazolin, in the univariate analysis, was identified as a risk factor. Nonetheless, this association was lost in the multivariate analysis, when variables, such as center or Child-Pugh score, were involved [146]. On the other hand, a Chinese study has shown that ertapenem is as effective as ceftriaxone/metronidazole for the prophylaxis of SSI in patients undergoing elective colorectal surgery [147]. In a different study, patients who underwent colorectal surgery and received ertapenem had a lower rate of SSI (4% patients with ertapenem vs. 13% with other antibiotic, $P = 0.01$) [148].

With the available data, it is not possible to issue recommendations concerning the surgical prophylaxis in patients colonized by CPE. Nevertheless, centers with a high rate of SSI caused by these bacteria, should adjust their prophylaxis regimen according to their antibiotic susceptibility patterns.

3.5.1. Consensus recommendations

- It is not recommended to use of a different surgical prophylaxis regimen in patients colonized with CPE. Nevertheless, centers that have a high incidence of SSI caused by CPE should change their prophylaxis regimen according to the microorganisms' susceptibility results (BIII).

3.6. When and how should CPE colonization screening studies be performed in SOT recipients?

Surveillance cultures for detection of colonized patients with CPE and implementation of contact precautions, among other measures, have allowed a reduction of the infection rate, both in outbreak and in endemic settings [149–151]. However, none of the studies specifically addressed the SOT population. A recent systematic review which included ten studies and a total of 1806 patients described a 16.5% risk of CEP infection in colonized patients (intestinal colonization was detected by rectal swab screening in most studies) [152]. One of the studies specifically included LT recipients [141].

Infections caused by carbapenemase-producing *K. pneumoniae* have been associated with an increase of the morbidity and the mortality rates [17,153]. In endemic areas, the incidence of CRKP after LT is approximately 5%, with a crude mortality rate between 25 and 71% [16,57,141,154]. A prospective Italian study which included LT recipients, screened for intestinal colonization with CRKP by obtaining rectal swab samples before and after transplantation. Of the 237 transplanted patients, 41 were colonized (11 at the moment of transplantation and 30 after transplantation). Twenty developed a CRKP-associated infection (BSI in 18 and pneumonia in 2 patients), mean of 41.5 days after transplantation. The incidence of infection among non-colonized

patients, colonized at the moment of transplantation and colonized after transplantation was 2%, 18.2% and 46.7% ($P < 0.001$), respectively [155]. In a German case-control study, intestinal colonization with KPC-Kp (carbapenemase type 2, KPC-2-Kp) was associated with an increased risk of infection after a LT (relative risk of 7, 95% CI; 1.8–27.1). The mortality rate was also higher (78% vs. 11% in non-colonized patients, $P = 0.001$) [141]. In another study with KT recipients, CRKP bacteriuria after transplantation was associated with pre-transplant CRKP infection or colonization (OR 18.3, 95% CI; 2.0–170.5). An increase in the mortality rate was also observed when compared to recipients with CSKP bacteriuria (30% vs. 10%, $P = 0.03$) [156].

According to these data, it seems advisable to recommend obtaining rectal swabs from SOT recipients at the moment of transplantation in order to assess intestinal colonization by CPE (especially in LT recipients). Subsequently surveillance cultures could be recommended depending on the local epidemiological pattern and the individual risk factors of each patient.

3.6.1. Consensus recommendations

- Rectal swab samples should be obtained at transplantation as a screening measure for CPE intestinal colonization, especially in LT (CII). It is recommended that subsequent surveillance cultures be obtained based on the local epidemiological setting and the individual risk factors of each recipient (CIII).

3.7. What are the isolation precautions and healthcare infection control measures recommended for a recipient colonized with CPE? Is intestinal decolonization recommended?

According to international guidelines, besides standard precautions that include good hand hygiene compliance policies as the main measure to avoid dissemination, contact precautions should be established for all infected/colonized patients with CPE [157,158]. These include disposable gloves and gowns whenever entering the patient's single isolation room and if physical contact with the patient or the patient's surrounding is assumed.

A thorough hygiene and environmental cleaning interventions are essential. Numerous studies have highlighted the important role played by the environmental reservoir, surfaces and medical equipment in the dissemination of these microorganisms [159]. Isolation rooms should be cleansed twice a day. If located in high risk departments, this procedure should be even more frequent [160].

Intestinal decolonization therapies are applied as an infection prevention strategy by using different oral antibiotic regimens, usually aminoglycosides, colistin or the combination of both. A recent meta-analysis showed good tolerance and significant reduction of colonization rates: from 37.1% (CI 95%; 27.5%–47.7%) to 57.9% (CI 95%; 43.1%–71.4%) at the end of treatment [161]. However, 4 of the 13 analyzed studies described the emergence of resistance to the antibiotics administered. A randomized, double-blind, placebo-controlled study, reported the efficacy of selective intestinal decolonization with oral gentamicin and polymyxin E for 7 days in 40 patients colonized with CRKP. At week 2, 16.1% of rectal swab cultures in the placebo group and 61.1% in the treatment group were negative (OR 0.13, 95% CI; 0.02–0.74, $P < 0.0016$). A similar difference was also reported at week 6 (33.3% vs 58.5%) [162]. In another study, 44 of 77 (57.1%) patients colonized with colistin-resistant CRKP were decolonized with oral aminoglycosides (gentamicin or neomycin/streptomycin). Patients who received aminoglycosides had a lower mortality rate. Those who received gentamicin also had fewer invasive CRKP infections and a better microbiological response at the 180-day follow-up [163].

Long-term effects and clinical impact of these decolonization therapies are unclear. More studies are necessary, since available data is still insufficient to resolve the doubts concerning the effectiveness of intestinal decolonization among carriers.

3.7.1. Consensus recommendations

- Educational programs on hand hygiene compliance reduce transmission of CPE (AII).
- Contact precaution measures are recommended for patients infected and/or colonized with CPE (AII).
- There is not sufficient data to recommend intestinal decolonization among carriers of CPE (CIII).

3.8. How is a healthcare-associated outbreak caused by CPE in a SOT ward diagnosed and controlled?

A structure that allows rapid detection of carriers and fast implementation of measures against outbreaks caused by CPE is fundamental for minimizing their dissemination. These measures are usually implemented as a bundle, and it is difficult to point out their isolated efficacy. Early detection of carriers at admission, good hand hygiene, contact precautions, assigning qualified healthcare personnel and cleaning staff to attend that specific area and group of patients, educational programs and good antibiotic stewardship programs are the measures usually included in most studies [149,164–167]. An exhaustive systematic review of the literature, with the purpose of better defining the effectiveness of these different infection controls and preventing measures, in order to reduce the incidence of colonization/infection, concluded that the most successful measures were systematic screening of carriers, contact precautions, and cohort nursing by a separate team [168].

3.8.1. Consensus recommendations

- Assigning healthcare personnel to specific areas and group of patients reduces the risk of acquiring CPE, as well as the possibility of transmission and dissemination (AII).
- Systematic screening for carriers at admission, followed by correct contact precaution measures reduces dissemination of CPE (AIII).
- Antimicrobial stewardship programs and interventional measures in the management and treatment of infections caused by CPE reduce dissemination of these bacteria (AIII).

3.9. Should inhaled antibiotics be prescribed to donors or recipients with respiratory tract colonization with CPE?

There are no data on SOT recipients with respiratory tract colonization by CPE. A pilot study that included patients with VAP caused by *P. aeruginosa* or *Acinetobacter* spp. reported that the administration of inhaled tobramycin was safe and effective when compared to intravenous tobramycin [100].

Some studies have shown that inhaled colistin may be effective and safe in patients diagnosed with HCAP due to MDR GNB [102,169]. However, these data have not been confirmed in other studies [104,170]. A recent retrospective study showed an acceptable efficacy of nebulized

colistin in patients with extremely resistant *A. baumannii* pneumonia but was not effective in patients with respiratory tract colonization [171].

In conclusion, the administration of inhaled antibiotics to LuT recipients with respiratory tract colonization by CPE could be useful. The decision on whether to prescribe aminoglycosides or colistin should be made according to the susceptibility test results of the microbiological isolates.

3.9.1. Consensus recommendations

- Inhaled antibiotics could be prescribed to LuT recipients with respiratory tract colonization with CPE (CII).

3.10. What is the first-line therapy for a patient with an infection caused by CPE? Is monotherapy or combination therapy recommended?

CPE infections are an important and worrying threat to SOT recipients [57,124,154,172]. Carbapenem monotherapy regimens could be considered in the case of mild infections, if the site of the infection is adequately controlled and the isolate is susceptible, while combination therapy is the best treatment regimen for critically ill patients [124,173–176]. Combination therapy with at least two active drugs was associated with lower mortality rate in an Italian study (OR 0.52, 95% CI; 0.35–0.77). Moreover, regimens that have included meropenem were associated with significantly higher rates of survival whenever the KPC-Kp had a MIC value ≤ 8 mg/L [176]. In a different study, which also included KPC-Kp strains, patients treated with a monotherapy regimen of colistin/polymyxin B or tigecycline had a significantly higher mortality rate (66.7%) than those treated with a therapy regimen that combined a carbapenem antibiotic with the previous antibiotics (12.5%) [177]. Daikos et al. have also described a lower mortality rate in treatment regimens that included carbapenems (19.3% vs 30.6%); carbapenem treated episodes with a MIC value ≤ 8 mg/L had a lower mortality rate than those with a MIC value > 8 mg/L (19.3% vs 35.5%) [178]. There is not enough data to support the use of carbapenems in a combination therapy regimen if the MIC value is > 8 mg/L. In this case, carbapenems are probably ineffective, especially if the MIC value is > 16 mg/L.

Ceftazidime-avibactam is active against KPC-producing carbapenemase-resistant *Enterobacteriaceae*, and has been recently approved by the FDA for the treatment of complicated intra-abdominal infections and complicated UTI. Studies on pneumonia have not yet been published [179–182]. Treatment with ceftazidime-avibactam could be considered whenever the strains show in vitro susceptibility (Table 5).

3.10.1. Consensus recommendations

- Combination therapy is recommended as first-line treatment for patients diagnosed with a severe infection caused by CPE (BII).
- Monotherapy is recommended for non-severe infections, whenever a fully active antimicrobial, with an adequate infection site

Table 5

Dose regimens of the most frequent antibiotics recommended for the treatment of multidrug resistant Gram-negative bacilli.

Antibiotic	Dose
Amoxicillin-clavulanic acid ^a	2 g amoxicillin plus 0.2 g clavulanic acid, infused over 30 min every 8 h
Piperacillin-tazobactam ^a	4 g piperacillin plus 0.5 g tazobactam, infused over 30 min every 6 h or 4 g piperacillin plus 0.5 g tazobactam, infused over 3–4 h every 8 h or 6 h in critically ill patients
Meropenem	2 g infused over 3 h every 8 h (6 g per day)
Aztreonam	6–8 g daily via an intravenous continuous infusion is recommended for strains with intermediate susceptibility
Tigecycline	200 mg loading dose followed by 100 mg/12 h should be considered for patients in septic shock, VAP or <i>Enterobacteriaceae</i> with MIC ≥ 1 mg/L
Fosfomycin ^b	4–6 g every 6 h or 8 g every 8 h
Ceftazidime-avibactam	2 g ceftazidime plus 0.5 g avibactam, administered via a 2-h intravenous infusion every 8 h
Ceftalozane-tazobactam	2 g of ceftalozane plus 1 g of tazobactam, every 8 h
Colistin ^c	Loading dose of 6–9 MU followed by 4.5 MU every 12 h

CRRT, continuous renal replacement therapy; ESBL, extended-spectrum β -lactamases; IHD, intermittent hemodialysis; MIC, minimum inhibitory concentration; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

^a Most data derives from UTI caused by ESBL-producing *E. coli*. Data on other sources of infection or other *Enterobacteriaceae* are scarce.

^b Should always be considered as part of a combination regimen which includes at least one more active agent, preferably three-drug combination treatments.

^c The dose of colistin for patients with renal replacement therapy is not well established. Nevertheless, experts recommend, for patients undergoing IHD, 0.9 MU on non-IHD days and 1.5 MU on IHD days, after HD. In the case of CRRT, a dose of 2 MU every 8 h is suggested.

penetration, can be prescribed, particularly, for non-severe UTI (in this case, fosfomycin-trometamol or aminoglycosides could be considered) (CIII).

- Carbapenem monotherapy (administered by extended-infusion) may be considered for mild infections if the isolate is susceptible and the site of the infection is adequately controlled, e.g., urinary sepsis without urinary tract obstruction, or symptoms or signs of severe sepsis or septic shock (CIII).
- Patients for whom combination therapy is recommended, a carbapenem with a MIC value ≤ 8 mg/L, administered by extended-infusion, plus one or two fully active antimicrobials (including colistin, tigecycline, an aminoglycoside or fosfomycin) could be considered. Fosfomycin is preferably used in three-drug combination treatments. The mean serum concentrations and the urinary concentrations of tigecycline are low. Therefore, tigecycline is unsuitable for the treatment of BSI and UTI. These treatment regimens are mainly recommended for patients with severe infections due to KPC-Kp (BII).
- There are not enough data to recommend the use of a carbapenem antibiotic in a combination therapy regimen if the MIC value is > 8 mg/L. In this case, carbapenems are probably ineffective, especially if the MIC value is > 16 mg/L. We recommend a combination therapy regimen that includes at least two completely active antimicrobials, according to the susceptibility study and the site of the infection (colistin, aminoglycosides, fosfomycin and tigecycline) (CIII).
- **Ceftazidime-avibactam** may be considered if the strain shows in vitro susceptibility (CIII).
- Patients with less severe invasive infections and complicated UTI could benefit of a carbapenem-free treatment regimen (colistin, aminoglycosides, fosfomycin and tigecycline –the latter not for UTI). Both monotherapy and combination treatment regimens could be considered, as previously mentioned (CIII).

4. Infections produced by MDR *P. aeruginosa*

4.1. What are the risk factors for developing MDR *P. aeruginosa* infections after SOT?

The incidence of infections produced by MDR *P. aeruginosa* strains is higher in SOT recipients than in the general population. Almost 50% of all *P. aeruginosa* BSI in SOT recipients are caused by MDR strains [18,27]. The risk of infection is higher in LuT, since more than half of the cystic fibrosis patients that are candidates for LuT are colonized by MDR strains, and up to 75% will subsequently be colonized after transplantation [32].

The risk of developing MDR *P. aeruginosa* infections depends on several factors, such as previous antibiotic therapy, renal replacement therapy, surgical reoperation, prolonged ICU stay, prolonged tracheal intubation and tracheostomy [18,41,183–186]. Most of these risk factors have been identified in critically ill or ICU patients [187–190]. Of note, in SOT, most of the studies are focused on the risk factors for developing infections due to MDR GNB and not specifically due to MDR *P. aeruginosa*.

Only two studies have analyzed the risk factors for developing infections caused by MDR *P. aeruginosa* in SOT recipients. A prospective study that included 318 LT, KT and HT recipients diagnosed with BSI identified that the risk factors for XDR *P. aeruginosa* BSI were previous transplantation, nosocomial acquisition and septic shock [21]. A different retrospective study that included 207 episodes of *P. aeruginosa* BSI in SOT and hematopoietic stem cell transplant recipients identified that previous transplantation, nosocomial acquisition and ICU admission in the previous year were risk factors for BSI caused by MDR *P. aeruginosa* [27]. Nosocomial acquisition and previous transplantation were risk factors identified in both studies (listed in Table 4).

4.1.1. Consensus recommendations

- The risk factors for developing MDR *P. aeruginosa* BSI in SOT recipients include previous transplantation, hospital-acquired infection, previous admission to ICU, and septic shock (BIII).

4.2. What are the most important mechanisms of antimicrobial resistance in MDR/XDR *P. aeruginosa*? How can MDR/XDR *P. aeruginosa* be identified through an antibiogram?

The prevalence of infections caused by MDR *P. aeruginosa* varies accordingly to the geographical area, the type of transplant performed and the definition used [3,5].

Worldwide, the prevalence of MDR *P. aeruginosa* strains already exceeds 30%. This includes Spanish hospitals; approximately half of the MDR isolates would also be XDR in this country [191]. The increasing prevalence is due to the extraordinary ability of *P. aeruginosa* to develop resistance by chromosomal mutations and the increasing production of exogenous resistance determinants [192]. The main mutational mechanisms of antibiotic resistance include constitutive hyperproduction of inducible chromosomal cephalosporinase AmpC (derepression), responsible for resistance to penicillins and antipseudomonal cephalosporins, inactivation of the OprD porin, which confers resistance to carbapenems or hyperexpression of some of the multiple efflux pumps. MDR/XDR phenotypes result from the combination of several of these mutations. Nevertheless, these strains frequently remain susceptible to the new BLBLI (ceftolozane-tazobactam and ceftazidime-avibactam). On the other hand, though proportionally lesser common, the detection of mobile genetic elements carrying carbapenemase or ESBL genes is increasingly frequent. Recent studies show that most carbapenemase-producing or ESBL-producing strains belong to the so-called high-risk clones, mainly ST235, ST111 or ST175 [193]. High risk clone ST175, whose antibiotic resistance is mainly due to mutational mechanisms, remains susceptible to ceftolozane-tazobactam and ceftazidime-avibactam [194,195].

Class B or MBL carbapenemases are particularly concerning. When compared to the strains with a mutational resistance mechanism, class B or MBL carbapenemases have a bigger ability to disseminate and are resistant to the new BLBLI.

Specific selective media, such as MacConkey agar supplemented with meropenem, are recommended for screening of colonization with MDR/XDR *P. aeruginosa* [196]. Study of LuT isolates may be hampered by the typical cystic fibrosis phenotype (eg, mucoid, slow-growing, or hypermutator strains) [197]. The definition of MDR/XDR strain is exclusively based on the resistance profile reported by the antibiogram. Nevertheless, due to its particular epidemiological relevance and resistance to new β -lactams, it is recommended to perform phenotypic, biochemical and genetic tests for detection of MBL-producing strains [196].

4.2.1. Consensus recommendations

- In order to recognize the resistance profile of the *P. aeruginosa* isolate (MDR or XDR), it is necessary to create an antibiogram that contains the appropriate antibiotics in accordance with the existing recommendations. Phenotypic, biochemical and genetic test for the detection of MBL-producing strains are recommended due to their particular epidemiological relevance and resistance to the new β -lactams (AIII).

4.3. Can a colonized or infected patient with MDR *P. aeruginosa* be accepted as an organ donor?

Data are very limited. LuT and KT are generally not recommended if the donor has respiratory or urinary tract colonization with MDR bacteria, respectively. If this is not the case, then donation is accepted. Nevertheless, all recipients should be closely monitored after transplantation, since MDR *P. aeruginosa* transmission from donors diagnosed with

2.10. 应该使用什么治疗方案？BLBLI 可以用于治疗产 ESBL 的肠杆菌科感染的实体器官移植（SOT）接受者吗？

2.10.1. 共识建议

- 碳青霉烯类药物被推荐为由产 ESBL 的肠杆菌科引起的 SOT 受者中度或重度感染的经验性和目标性治疗（B-II）。
- BLBLI 在非产 ESBL 细菌的肠杆菌科感染菌血症（尤其是 UTI）的器官移植患者中的应用似乎是合理的（B-II）。

3.10. CPE 感染患者的一线治疗是什么？是推荐单药治疗还是联合治疗？

3.10.1. 共识推荐

- 对于诊断为 CPE 引起的严重感染的患者，推荐联合治疗作为一线治疗（B-II）。
- 单药疗法推荐用于非严重感染，尤其是对于非严重的 UTI（在这种情况下，可考虑使用磷霉素-氨丁三醇或氨基糖苷类药物），只要在感染部位有足够的组织渗透性的、有完全活性的抗菌药物就可使用（CIII）。
- 如果分离菌敏感，且受感染部位的感染情况得到充分控制，例如无尿路梗阻的、或无严重脓毒症或脓毒性休克的症状或体征的尿脓毒症，则可考虑对轻度感染进行碳青霉烯单药疗法（通过延长输注进行）。（CIII）。
- 对于推荐联合治疗的患者，碳青霉烯 MIC 值 ≤ 8 mg/L，延长输注时间，再增加一到两种广谱的抗菌药物（包括粘菌素、替加环素、氨基糖苷或磷霉素）。磷霉素最好用于三种药物联合治疗。替加环素平均血药浓度和尿药浓度较低。因此，替加环素不适用于 BSI 和 UTI 的治疗。这些治疗方案主要推荐用于因 KPC-Kp 引起严重感染的患者（B-II）。
- 如果 MIC 值大于 8 mg / L，则没有足够的数据推荐在联合治疗方案中使用碳青霉烯类抗生素。在这种情况下，碳青霉烯类可能无效，特别是如果 MIC 值大于 16 mg/L。根据敏感性研究和感染部位，我们建议联合治疗方案包括至少两种广谱的抗菌药物（粘菌素，氨基糖苷类，磷霉素和替加环素）（CIII）。
- 如果该菌株显示体外敏感，可考虑使用头孢他啶/阿维巴坦（CIII）。
- 具有严重程度较轻的侵袭性感染和复杂 UTI 的患者可能受益于不含碳青霉烯的治疗方案（粘菌素，氨基糖苷类，磷霉素和替加环素-后者不适用于 UTI）。如前所述，单药治疗和联合治疗方案均可考虑使用（CIII）。

表 5，推荐用于治疗多药耐药革兰氏阴性杆菌感染的最常见抗生素的剂量方案。

抗生素	剂量
阿莫西林-克拉维酸 ^a	2g 阿莫西林加 0.2g 克拉维酸，每 8 小时输注 30 分钟以上
哌拉西林-他唑巴坦 ^a	4 g 哌拉西林加 0.5 g 他唑巴坦，每 6 小时输注 30 分钟以上 或者 4 g 哌拉西林加 0.5 g 他唑巴坦，危重病人每 8 小时或 6 小时输注 3-4 小时以上
美罗培南	每 8 小时输注 3 g 以上，每次 2g（每天 6 g）
氨曲南	对于具有中等敏感的菌株，建议每天通过静脉内连续输注 6-8 g
替加环素	考虑应用于脓毒性休克，VAP 或肠杆菌科感染者，MIC $\geq$ 1mg/L 时，使用剂量为 200 mg 负荷剂量，然后 100 mg/12 h
磷霉素 ^b	每 6 小时 4-6g 或每 8 小时 8g
头孢他啶/阿维巴坦	2g 头孢他啶加 0.5g 阿维巴坦，每 8 小时用药一次，通过 2 小时静脉内输注给药
头孢洛扎/他唑巴坦	每 8 小时用药一次，使用剂量为 2 克头孢洛扎加 1g 他唑巴坦
粘菌素 ^c	负荷剂量为 6-9 MU，然后每 12 小时用药剂量为 4.5 MU

CRRT，持续肾脏替代疗法；ESBL，超广谱 β -内酰胺酶；IHD，间歇性血液透析；MIC，最低抑菌浓度；UTI，泌尿道感染；VAP，呼吸机相关性肺炎。

a 大多数数据来源于产 ESBL 的大肠杆菌引起的 UTI。其他感染源或其他肠杆菌科的数据很少。

b 应始终将其视为组合方案的一部分，所述组合方案包括至少一种抗菌活性更强的药物，优选三种药物组合治疗。

c 对于肾替代疗法患者，粘菌素的剂量尚未确定。尽管如此，专家建议，对于接受 IHD 治疗的患者，血透后，非 IHD 日为 0.9 MU，IHD 日为 1.5 MU。在接受 CRRT 的情况下，建议每 8 小时剂量为 2 MU。

pneumonia to KT recipients has been described, with fatal outcomes due to the lack of an effective antibiotic prophylactic or directed treatment in some cases [63,198]. A case of MDR *P. aeruginosa* transmission from a donor with an infected peritoneal fluid to HT, LT and KT recipients has also been reported. All received directed antibiotic treatment from the first day after transplantation, and although 2 recipients died, mortality did not appear to be clearly associated with a donor-derived infection [199]. If we refer strictly to colonized, uninfected donors, there are no data regarding MDR *P. aeruginosa*. Nevertheless, it seems recommendable to change the surgical prophylaxis regimen according to the donor's colonization isolates. The larger experience dates from 2015; 30 recipients received an organ from 18 donors that were infected or colonized with a carbapenem-resistant GNB, and which was not known at the moment of transplantation. Donor transmission was detected in 4 cases. No donor-derived infections were diagnosed in patients who received an effective antibiotic treatment, in whom the graft was not colonized or in cases where no BSI was detected [61]. In any case, the decision to accept the organ from a colonized donor must be individualized.

4.3.1. Consensus recommendations

- In exceptional cases, organs from donors colonized with MDR *P. aeruginosa* can be accepted for transplantation, as long as the strain remains susceptible to some antibiotics (BIII).

4.4. Can a patient colonized with MDR *P. aeruginosa* be accepted for transplantation?

Up to 50% of LuT recipients diagnosed with cystic fibrosis have their respiratory tract colonized with MDR/XDR *P. aeruginosa*. It can reach up to 75% after transplantation [200]. Despite this, survival is similar regardless of colonization [201]. For this reason, it does not constitute an absolute contraindication for LuT. Notwithstanding, the development of bronchiolitis obliterans (the principal limitation for long-term survival after LuT) has been associated to this infection, and, as such, candidates should be individually evaluated [202].

As for the rest of SOT, not enough data are available for issuing strong recommendations. Prior rectal colonization with CRKP has been identified as a risk factor for developing an infection after LT transplantation [155]. It has even been associated with higher post-transplant mortality rate in the setting of an epidemic outbreak [141]. This was not confirmed in KT [126]. Therefore, at the moment and due to the absence of further data, transplantation should not be contraindicated. No specific preventive measures are recommended for SOT candidates, apart from LuT candidates colonized with MDR *P. aeruginosa*.

4.4.1. Consensus recommendations

- Previous colonization with MDR *P. aeruginosa* does not constitute a contraindication for LuT (AII) or any other type of SOT (AIII).

4.5. Should a different surgical prophylaxis regimen be prescribed when a donor or a recipient is colonized with MDR *P. aeruginosa*?

4.5.1. Consensus recommendations

- Surgical prophylaxis should be the same for all non—LuT recipients colonized with *P. aeruginosa* (CIII).
- Recipients with a septic lung disease (with cystic fibrosis or bronchiectasis) should receive antibiotics accordingly to their preoperative culture results (CIII).
- The duration of prophylactic antibiotic therapy in LuT will depend on the donor's and the recipient's bronchial aspirate (BAS) or bronchoalveolar lavage (BAL) culture results, obtained at the moment of transplantation. If cultures are informed as sterile, antimicrobials will be stopped within 3–5 days. If they are informed as positive or the receptor has a septic lung disease, then they are adjusted accordingly and maintained for 10–15 days (CIII).

4.6. What are the isolation precautions and healthcare infection control measures recommended for a recipient colonized with MDR *P. aeruginosa*?

Most of the data concerning this problem does not come from studies that have specifically focused the transplanted population. However, there is sufficient data concerning MDR *P. aeruginosa* in other group of patients to issue recommendations for the SOT population.

Patients can acquire MDR *P. aeruginosa* through contact with a contaminated environment or through the hands of healthcare workers [203–205]. Patient-to-patient transmission of MDR *P. aeruginosa* epidemic clones has also been reported in patients with cystic fibrosis [206].

Hand hygiene with soap and water or alcohol based solutions significantly reduces colonization by GN bacteria [207]. The implementation of contact isolation measures as a bundle of care has shown to significantly reduce the dissemination of these agents within the hospital setting: hand washing, surveillance cultures, single room isolation, use of gowns and gloves, together with educational courses and meetings [208]. There is no consensus concerning its duration. It is recommended to maintain contact isolation measures until two or three weekly separated sterile cultures have been obtained, and antibiotic treatment must have been stopped at least one week before [81].

Active screening through rectal, urinary, respiratory and wound swab sampling can identify colonized patients earlier. However, the false-negative rate is high [209]. Moreover, there is still a debate concerning frequency and timing, as well as the type of samples used. The existence of risk factors for colonization with MDR *P. aeruginosa* could help discriminate the population that would benefit from these measures. However, a single retrospective study failed to demonstrate differences of infection/colonization rate with carbapenem-resistant *P. aeruginosa* before and after the implementation of screening measures at the moment of admission and weekly afterwards [151].

4.6.1. Consensus recommendations

- Hand hygiene with an alcohol based solution before and after touching the patient is essential (AII).
- Contact isolation measures should be implemented: single room or cohort isolation for all infected/colonized patients, wearing gowns and gloves before entering the room and using disposable or patient-specific materials (AII). Isolation measures should be maintained until two or three weekly separated sterile cultures have been obtained. Antibiotic treatment must have been stopped at least one week before (BIII).
- Active screening of colonization with MDR *P. aeruginosa* should not be performed in the case of an endemic setting (BIII).

4.7. Should inhaled antibiotics be prescribed to donors or recipients with respiratory tract colonization with MDR *P. aeruginosa*?

Most lung recipients with septic lung disease have chronic *P. aeruginosa* infection and are treated with nebulized antibiotics. A high percentage is MDR or XDR *P. aeruginosa*. Treatment with nebulized colistin, tobramycin or aztreonam will depend on the strain's resistance pattern at the moment of transplantation [210,211].

Colonization with *P. aeruginosa* in the immediate post-transplant period may lead an infection of the bronchial anastomosis and dehiscence of the suture. Moreover, it is a risk factor for pneumonia since these patients are immunosuppressed and their lungs, in this initial moment, are denervated and poorly perfused. As such, it is a common practice to prescribe nebulized colistin if *P. aeruginosa* is isolated from respiratory secretions of a LuT recipient in the immediate post-transplant period.

Different studies have shown that LuT recipients with chronic *P. aeruginosa* infection not only have a higher risk of developing chronic rejection, but also to develop it in an earlier stage [32,212]. Treatment of chronic MDR or XDR *P. aeruginosa* infection is complicated, as the only available drugs (colistin, amikacin) have a high rate of nephrotoxicity. Chronic MDR or XDR *P. aeruginosa* infection has not been shown to

decrease the survival of these recipients [5,201,213]. Therefore, in LuT, considering the lack of guidelines and data, and using as example chronic *P. aeruginosa* infection in patients diagnosed with cystic fibrosis, it is a common practice to prescribe nebulized colistin for a prolonged period of time. Of note, cases of possible synergistic nephrotoxicity between inhaled tobramycin and calcineurin inhibitors in LuT recipients have been described [214,215].

Non-lung SOT recipients colonized with MDR/XDR *P. aeruginosa* should be treated as a non-transplanted patient, considering the risk of nephrotoxicity associated with aminoglycosides and colistin. Most of these patients will have bronchiectasis, and nebulized antibiotic prescription will be recommended.

4.7.1. Consensus recommendations

- Most LuT recipients with septic lung disease and chronic *P. aeruginosa* infection, regardless of the antimicrobial resistance pattern, should receive nebulized antibiotics (colistin, tobramycin, or aztreonam) before transplantation (AIII).
- LuT recipients should start receiving nebulized colistin immediately after transplantation if *P. aeruginosa* is isolated from respiratory secretions, in order to protect the bronchial suture (CIII).
- After transplantation, nebulized colistin treatment regimens should be prescribed to recipients with chronic *P. aeruginosa* infection, in order to reduce the risk of chronic lung allograft dysfunction (CIII).

4.8. What is the first-line therapy for a patient with an infection caused by MDR *P. aeruginosa*? Is monotherapy or combination therapy recommended? When should empirical treatment be prescribed? What are the therapeutic options?

The level of evidence for all the issued recommendations on the treatment of severe MDR *P. aeruginosa* infections is very low, because most of the available data come from single case reports, case series or retrospective studies that have compared clinical treatment outcomes.

At least two recent retrospective comparative studies that included BSI caused by *P. aeruginosa*, with susceptible and MDR strains, have not shown that combination therapy improved survival with regard to monotherapy, provided that the empirical treatment included at least one active antibiotic against the strain [216,217]. Two published meta-analysis have confirmed these results [218,219]. Patients with *P. aeruginosa* BSI could benefit from empirical combination antibiotic regimens, as they increase the probability that at least one antibiotic will be active against the strain [220,221].

There are published data on the use of ceftolozane-tazobactam for the treatment of severe infections caused by MDR *P. aeruginosa* [119,222–225]. Some published case reports and an ongoing clinical trial suggest that it may be more appropriate, from the pharmacokinetic point of view, to use a dosing regimen of 2 g of ceftolozane and 1 g of tazobactam every 8 h [223,224,226]. Aztreonam has been used for the treatment of *P. aeruginosa* susceptible to this antibiotic but resistant to other β -lactams [227,228]. For strains with intermediate susceptibility, it is recommended to administer the antibiotic by intravenous continuous infusion (Table 5).

4.8.1. Consensus recommendations

- High-dose ceftolozane-tazobactam could be prescribed to SOT recipients diagnosed with BSI and/or pneumonia caused by *P. aeruginosa* resistant to carbapenems and other β -lactams, as long as the strain shows in vitro susceptibility (AIII).
- Aztreonam is another therapeutic option for strains susceptible to this antibiotic (AIII).
- For strains with intermediate susceptibility to aztreonam, it is recommended to administer the antibiotic by intravenous continuous infusion (AIII).

- Intravenous aminoglycosides (amikacin, gentamicin, tobramycin) are recommended for SOT recipients diagnosed with complicated UTI (including pyelonephritis) caused by *P. aeruginosa* resistant to carbapenems and other β -lactam antibiotics, provided that the strain is susceptible and the risk of nephrotoxicity is acceptable (AII).
- Colistimethate sodium is the recommended treatment for SOT recipients diagnosed with severe infections caused by *P. aeruginosa* resistant to carbapenems and other β -lactams, and to whom ceftolozane-tazobactam, aztreonam or aminoglycosides cannot or should not be prescribed (AIII).
- Combination treatment is not recommended for SOT recipients with a severe infection caused by *P. aeruginosa* resistant to carbapenems and other β -lactams if the directed treatment includes an active first-line antibiotic (BIII).
- Empiric treatment against MDR *P. aeruginosa* is recommended to all SOT recipients with clinical signs of severe infection and recent history of colonization or infection by this type of strains. It should also be prescribed when infections produced MDR *P. aeruginosa* have been detected in the healthcare setting (AIII).
- Empirical combination antibiotic therapies could be recommended, with the goal of including in the treatment regimen an active antibiotic against the strain (AIII).

5. Infections produced by MDR *A. baumannii*

5.1. What are the risk factors for developing MDR *A. baumannii* infections after SOT?

A. baumannii infection in SOT recipients is above all a healthcare-associated infection. Its incidence varies widely depending on the center's epidemiological data, ranging from 8% to 50% [18,41,185,229–233]. *A. baumannii* infections are more prevalent among transplant recipients than among other non-transplanted patients admitted to the ICU after undergoing surgery [34].

Although SOT recipients frequently have infections caused by MDR microorganisms, data in this population are limited. The risk factors for MDR *A. baumannii* infection in SOT recipients are: previous antibiotic therapy, specifically carbapenems or piperacillin-tazobactam, retransplantation, septic shock at onset, prolonged mechanical ventilation, cardiothoracic transplantation, kidney failure after transplantation, intra-abdominal infection, prolonged cold ischemia time, fulminant hepatic failure as reason for transplantation, high MELD score and *A. baumannii* pre-transplant colonization [5,18,20,185] (listed in Table 4).

In a prospective study with LT recipients, infection/colonization by MDR *A. baumannii* before transplantation was associated with an increased risk of developing infection by this microorganism after transplantation. In the majority of cases, infection was caused by the same strain that had been isolated in the pre-transplant period [233]. Other authors have found similar results [234]. An ischemia time for more 400 min has been associated with a higher risk of SSI after LT [235–237].

Patients transplanted due to fulminant hepatitis usually have a higher MELD score, and longer hospital and ICU stay [231,235,238].

Post-transplant kidney failure which required renal replacement therapy has been associated with an increased risk of healthcare-associated infection by CRAB [233]. The use of invasive procedures and prolonged ICU stay may justify this trend [18,185].

Similar to immunocompetent patients, exposure to antibiotics is associated with MDR *A. baumannii* colonization in SOT recipients [18,185].

5.1.1. Consensus recommendations

- The risk factors for developing MDR *Acinetobacter baumannii* infections in SOT are: previous exposure to antibiotic therapy, specifically carbapenems or piperacillin-tazobactam, retransplantation, septic shock at onset, prolonged mechanical ventilation, cardiothoracic transplantation, kidney failure after transplantation,

intra-abdominal infection, prolonged cold ischemia time, fulminant hepatic failure as reason for transplantation, high MELD score, and *A. baumannii* pre-transplant colonization (BII).

5.2. What are the most important mechanisms of antimicrobial resistance in MDR *A. baumannii*? How can MDR *A. baumannii* be identified through an antibiogram?

The resistance mechanisms with greater clinical importance in *A. baumannii* are the ones that reduce susceptibility to carbapenems and colistin. Resistance to carbapenems is multifactorial: carbapenemases and, to a lesser extent, permeability changes and overexpression of efflux pumps of the RND family (AdeABC, AdeFGH and AdeJJK) [239–241]. The most important carbapenemases in *A. baumannii* are acquired oxacillinases (class D), which belong to 4 different groups: a) OXA-23-like, b) OXA-24-like, c) OXA-58, and OXA-143-like. The most prevalent is OXA-23 [242,243]. OXA-51 is a chromosome intrinsic oxacillinase with a small carbapenemase activity, and plays a questionable role in carbapenem resistance. MBLs (class B), and class A carbapenemase are other less frequent carbapenemase associated to *A. baumannii* [240–243]. *A. baumannii* also produces a class C chromosomal cephalosporinase with an irrelevant role in establishing resistance to carbapenems.

CRAB is easily detected in antimicrobial susceptibility testing systems, especially when the strains produce OXA-23-like or OXA-24-like oxacillinases, because of their usually high MIC values. Detection of OXA-58-producing strains may be more troublesome because they often show hetero-resistance to carbapenems and express relatively lower MIC values; for a correct identification, a high inoculum size, which is not used in automated systems, is required. Nevertheless, these strains are easily detectable if diffusion methods are used [244,245].

Acquisition of mutations in genes of the pmrAB system (pmrAB mutants), which encodes an enzyme that adds phosphoethanolamine residues to the lipid A of the lipopolysaccharide, is the most frequent mechanism of colistin resistance in *A. baumannii* [246–248]. Mutations in metabolic genes involved in lipid A biosynthesis (*lpx* mutants) have also been described. Nevertheless, they are less frequent because of the biological cost associated with the loss of the lipopolysaccharide. Both mechanisms of resistance are chromosomal, so dissemination of colistin resistance in *A. baumannii* is clonal. Detection of colistin resistance can be problematic due to factors associated to the microorganism (hetero-resistance) or to the method used. The recommended test method for determining colistin susceptibility is broth microdilution [248,249]. Disk diffusion is an unreliable method due to its lack of reproducibility, and is not recommended [250].

5.2.1. Consensus recommendations

- Carbapenem-resistance in *A. baumannii* strains is multifactorial; class D (OXA) carbapenemases are the most relevant (AIII).
- Carbapenem-resistance is easily detectable because of the high MIC values (AIII).
- The most important mechanisms of colistin resistance in *A. baumannii* are chromosomal. As such, dissemination is usually clonal (AIII).
- The detection of colistin resistance can be troublesome. Susceptibility should be determined by broth microdilution (BIII).

5.3. Can a colonized or infected patient with MDR *A. baumannii* be accepted as an organ donor?

Organ donors are usually hospitalized in the ICU, and are inevitable exposed to MDR microorganisms. However, there is very little data on the eligibility of these organs for transplantation. In 2009, the Israeli Society for Infectious Diseases and the Israel Transplant Center developed a systematic national system for the use of organs from donors colonized with MDR microorganisms, including *A. baumannii*. The working

group recommendations were based on previous data on the use of organs from donors with BSI and on their own experience.

Their recommendations were: 1. Donors with a positive rectal swab for any MDR GN microorganism: all organs could be accepted for transplantation. 2. Donors with MDR GN microorganisms isolated from airway secretions (colonized/infected), without an adequate antibiotic treatment for pneumonia: the lungs should not be accepted, but all other organs are appropriate for transplantation. If, on the other hand, there is an adequate antibiotic treatment for pneumonia, and to which the MDR GN strain is susceptible, then all organs could be accepted for transplantation. 3. Donors with a positive urine culture for MDR GN microorganisms: all organs could be accepted, except for the kidneys.

Mularoni et al. [61] in a study conducted in Italy in 2012–2013, reported that there was no donor-derived disease transmission in the case of respiratory tract colonization with *A. baumannii*.

5.3.1. Consensus recommendations

- The organs from donors with a positive rectal swab for MDR *A. baumannii* can be accepted for transplantation (AII).
- Except for the kidneys, the organs from donors diagnosed with MDR *A. baumannii* urinary colonization can be accepted for transplantation, provided that there is an effective antibiotic therapy (AII).
- The organs from donors diagnosed with respiratory tract colonization with MDR *A. baumannii* can be accepted for transplantation, except for the lungs if no effective antibiotic therapy is available in the case of developing pneumonia (AII).

5.4. Can a patient colonized with MDR *A. baumannii* be accepted for transplantation?

Numerous groups agree that infection by MDR *A. baumannii* is more frequent in SOT recipients than in non-transplanted patients and that the associated mortality is high [18,34,251–253]. Nevertheless, pre-transplant colonization or infection of a SOT candidate with *A. baumannii* has rarely been associated with morbidity after transplantation, though its true impact is not known [254]. A retrospective study reported that 32% of patients that developed an infection by *A. baumannii* had been previously colonized. Moreover, colonized patients were more likely to develop recurrent infections. Colonization rates by MDR *A. baumannii* were similar between all types of transplantation, but invasive infections were more frequent among cardiothoracic recipients [20].

5.4.1. Consensus recommendations

- Rectal, urinary or respiratory tract colonization with *A. baumannii* does not constitute an absolute contraindication for SOT (AIII).

5.5. Should a different surgical prophylaxis, with carbapenems or colistin, be prescribed to SOT recipients colonized with *A. baumannii*?

No study has specifically focused on analyzing whether the surgical prophylactic regimen should be different in a MDR *A. baumannii* colonized patient. Due to its long-lasting absence, recommendations are only issued according to the following indirect data.

Prior colonization with *A. baumannii* is a risk factor for developing an infection by this microorganism in SOT [20]. The incidence of SSI caused by *A. baumannii* after transplantation is highly variable, and is directly related to the epidemiological setting of the healthcare center. RESITRA studies with 292, 1400, and 1222 HT, KT and LT recipients, reported an incidence of SSI of 0%, 0.2% and 0.5% respectively [29,145,146]. On the other hand, the incidence of SSI reached 10% in a report that included 196 LT recipients from a center with a rate of *A. baumannii* colonization/infection of 53.6% [255].

The antibiotics usually recommended for surgical prophylaxis in SOT [233] are ineffective against *A. baumannii*. As such, carbapenems or colistin, depending on the degree of resistance, would be the antibiotics

of choice. The efficacy of these antibiotics as antimicrobial prophylaxis, for both general surgery and SOT, is not known. The only data were limited to four LT recipients, colonized with CRAB before transplantation, who received perioperative prophylaxis with colistin. Despite the use of colistin, the patients developed SSI. Moreover, there is the potential risk of developing adverse effects to each antibiotic and antibiotic resistance. Nephrotoxicity reaches up to 51% in patients with *A. baumannii* pneumonia [256], but its incidence could be higher in SOT considering the concomitant administration of other nephrotoxic drugs and the increased susceptibility to kidney failure in KT.

Previous exposure to carbapenems [257] and to colistin [258] is the main risk factor for developing resistance to these antibiotics. While five of 14 colistin-treated SOT recipients (36%) developed resistance [20], it was identified as the only independent risk factor for developing colistin-resistant *A. baumannii* infection in LT [253]. It is also a real collective risk factor, as *A. baumannii* is easily transmitted to other patients through the hands of healthcare personnel, and could lead to an outbreak situation [259].

5.5.1. Consensus recommendations

- Patients colonized with *A. baumannii* should receive the same surgical prophylaxis as non-colonized patients. This prophylaxis regimen should be active against the common pathogens of the skin, and therefore neither carbapenems nor colistin should be used (AII).

5.6. What are the isolation precautions and healthcare infection control measures recommended for a recipient colonized with MDR *A. baumannii*?

The recommended measures to prevent transmission of *A. baumannii* include standard precautions, environmental decontamination, hand hygiene compliance and education of the healthcare personnel. Surgical face mask and goggles are also mandatory whenever a diagnostic or therapeutic procedure is performed on an infected/colonized respiratory tract [260,261].

These control measures are of particular importance in the case of SOT recipients colonized with *A. baumannii*. SOT recipients receive antibiotics more frequently than non-SOT patients, and their antibiotic regimens are usually more prolonged. For this reason, they are considered as high-risk patients for developing antibiotic resistance. Since the hospitalization rate is also higher in this group of patients, they are a source of healthcare-associated infections caused by MDR bacteria, including *A. baumannii*.

Recently, the benefit of antimicrobial stewardship programs in reducing SSI in transplant recipients, combined with other infection control measures, has been described. This improvement was mainly due to a better compliance of the surgical prophylaxis protocol [261].

5.6.1. Consensus recommendations

- All *A. baumannii* infected or colonized SOT recipients require the standard universal and contact precautions. Surgical face mask and goggles are also mandatory whenever a diagnostic or therapeutic procedure is performed on an infected/colonized respiratory tract (AII).

5.7. Should inhaled antibiotics be prescribed to donors or recipients with respiratory tract colonization with MDR *A. baumannii*?

There is sufficient clinical evidence to recommend adjuvant therapy with inhaled colistin for severe respiratory tract infections caused by several colistin-susceptible microorganisms, together with an appropriate systemic antibiotic treatment. Although there is no clear evidence of its benefit in reducing the mortality rate, its use is clearly associated with an improvement in the rates of microbiological eradication at the respiratory tract [262]. Although MDR *A. baumannii* colonization of the respiratory tract in SOT recipients may increase the risk of subsequent

infections, there is no available clinical data on the usefulness of inhaled or systemic anticipated treatment for the prevention of infections caused by this microorganism.

5.7.1. Consensus recommendations

- Inhaled antimicrobials –colistin or polymyxin B– as adjuvant therapy together with a systemic antimicrobial treatment, have not yet demonstrated to improve the clinical outcome of patients with respiratory tract infections caused by MDR *A. baumannii*, though it may offer superior rates of microbiological eradication (CIII).
- Inhaled antimicrobial therapy has not demonstrated any benefit in preventing infections caused by MDR *A. baumannii* in both colonized donors and SOT recipients (CIII).

5.8. What is the first-line therapy for a SOT recipient with an infection caused by MDR *A. baumannii*?

The recommendations for the treatment of SOT recipients diagnosed with infections caused by MDR *A. baumannii* have not been issued based on randomized controlled trials (RCT). As such, they have to be obtained from published data with heterogeneous group of patients, including different types of SOT recipients.

The efficacy of various antimicrobials with in vitro activity against MDR *A. baumannii* is well demonstrated. Monotherapy with colistin or polymyxin B, has not proven to be more effective than their comparators in VAP caused by this microorganism [263–265]. The main limitation of these studies lies in the heterogeneity of the patients enrolled and in the variability of the colistin dosage. The use of colistin monotherapy can lead to hetero-resistant mutants [266] and failure in microbiological eradication can reach up to 30% [263,265].

A recent RCT reported that treatment with sulbactam (ampicillin-sulbactam 9 g every 8 h) compared to colistin for HCAP had similar adverse effects and similar clinical and microbiological outcomes [265]. Other observational studies have reported similar outcomes with different associations of sulbactam versus their comparators [267,268].

The available data on the use of tigecycline alone for the treatment of infections caused by MDR *A. baumannii* is scarce. A large observational study with 386 patients diagnosed with an infection caused by strains only susceptible to colistin or tigecycline, reported that the 266 patients treated with tigecycline (monotherapy or combination therapy) had a significantly lower rate of unfavorable outcome (30.8% vs. 50%, $p < 0.0001$). Moreover, when compared to the 120 patients treated with a combination of imipenem and sulbactam, no significant differences in the mortality rate at day 3 were described. The comparative analysis between both groups of patients suggested that those treated with tigecycline had a less severe clinical condition (lower ICU admission and lower incidence of renal impairment or sepsis) [269]. It is well established that the use of tigecycline alone can favor the appearance of resistance during treatment [270,271]. Higher doses of tigecycline (loading dose of 200 mg, followed by a maintenance dose of 100 mg every 12 h) may be associated with an improvement in the clinical response rate, without an increase of adverse affects in critically ill patients [272].

Several antibiotics, such as rifampicin or fosfomycin, have shown in vitro activity against MDR *A. baumannii* [273]. Animal models and in vitro studies have proven that these drugs have synergistic activity, especially when combined with colistin [274]. However, monotherapy use of these antimicrobials is associated with a rapid emergence of resistant strains [275]. Glycopeptides (vancomycin, teicoplanin and telavancin) are able to inhibit the synthesis of peptidoglycan of the *A. baumannii* cell wall, although they are not able to penetrate through its outer membrane and, therefore, do not have specific in vitro activity. However, disruption of the outer membrane by another active drug allows these antimicrobials to reach their therapeutic targets and show synergistic activity. Such is the case with colistin [276–278].

A retrospective observational study with 69 SOT recipients diagnosed with a MDR *A. baumannii* infection (mostly HCAP), reported that the use of colistin-carbapenem combination therapy provided an improvement in the clinical response and survival rate, although none of these patients were treated with colistin monotherapy [20].

Different observational studies have described a significant improvement in the clinical course of MDR *A. baumannii* infections treated with a combination of colistin and rifampicin [279–281]. However, two recent comparative studies failed to prove superiority of this combination, though higher rates of microbiological eradication in patients with respiratory tract infection was observed [282,283]. A systematic review has confirmed the lack of clinical efficacy of this combination and increased hepatic toxicity [284].

Combination therapy of colistin and sulbactam has not demonstrated superior hospital survival rate compared to colistin monotherapy, although a higher rate of microbiological eradication has been observed in patients who received combination therapy [285,286]. Combination of tigecycline and colistin or a carbapenem has not shown to reduce in the mortality rate [287].

The potent in vitro synergistic activity of combining colistin and a glycopeptide [288,289] has not correlated with an improvement in clinical efficacy. A retrospective series of 57 patients diagnosed with severe *A. baumannii* infection failed to prove a better outcome, while an increase in the risk of renal failure was described [290].

There is reasonable clinical evidence to recommend the use a loading dose of 6–9 MU of colimycin, as a way to improve its pharmacokinetic parameters and achieve earlier therapeutic levels, which may improve the prognosis in the case of severe infections. Although renal elimination of colistin is very limited, its prodrug sodium colistimethate is eliminated by the kidneys. Therefore, maintenance doses should be adjusted according to renal function, with proportional dosage intervals increments, or by monitoring plasma drug levels. Recommendations for patients with renal replacement therapy are not well established [291] (Table 5).

Adequate and early antimicrobial therapy is a key element for improving the prognosis of SOT recipients with severe infections caused by MDR *A. baumannii*. Several recent observational studies have shown that different factors are related to an unfavorable clinical course in this population, including mechanical ventilation, LT or liver-kidney transplantation and the late-onset of infection. Patients with high mortality risk admitted to units with an endemic MDR *A. baumannii* setting could benefit from empirical therapy with colistin or a combination of colistin and tigecycline [19,20,229].

5.8.1. Consensus recommendations

- Patients with infections caused by CRAB should receive antimicrobial therapy with intrinsic laboratory-proven activity. These include polymyxins (especially colistin), sulbactam and tigecycline (AII).
- Certain antimicrobials with in vitro activity against *A. baumannii*, such as rifampicin, glycopeptides or fosfomycin, may only be used in combination therapy with other active antibiotics, particularly colistin (AII).
- SOT recipients diagnosed with severe MDR *A. baumannii* infections, especially VAP, may benefit from combination therapy with antibiotics that have in vitro synergistic activity, especially colistin-carbapenem (meropenem or doripenem, both administered by extended infusion), rather than a monotherapy regimen with colistin (CII).
- Combination treatment of colistin and rifampicin has not demonstrated superiority to colistin alone for the treatment of severe infections caused by MDR *A. baumannii*, although it offers a higher rate of microbiological eradication (BII).
- Combination treatment of colistin and sulbactam or tigecycline has not demonstrated superiority to colistin alone for the treatment of severe infections caused by MDR *A. baumannii* (BIII).

- Combination therapy of colistin and vancomycin has not demonstrated superiority to colistin alone for the treatment of severe infections caused by MDR *A. baumannii* and increases the risk of renal toxicity (EII).
- Colistin should be administered with a loading dose of 6–9 MU, regardless of renal function, to obtain adequate plasma levels within the first 24 h. Maintenance dose should be individualized according to creatinine clearance or by monitoring plasma levels (BII).
- Previously colonized SOT recipients or with high clinical suspicion of CRAB infection, who have risk factors for poor clinical outcome (mechanical ventilation, LT or kidney-liver transplantation or late-onset of infection), may benefit from empirical therapy with colistin or colistin and tigecycline (CIII).

Transparency declaration

The authors have no conflicts of interest to disclose.

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Consensus statement

Executive summary of the consensus document of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), the Spanish Network for Research in Infectious Diseases (REIPI) and the Spanish Society of Haematology and Haemotherapy (SEHH) on the management of febrile neutropenia in patients with hematological malignancies[☆]



Download Clinical Guidelines

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ABSTRACT

Keywords:

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Targeted antibiotic therapy
Antibiotic resistance

Febrile neutropenia is a very common complication in patients with hematological malignancies receiving chemotherapy, and is associated with high morbidity and mortality. Infections caused by multidrug-resistant bacteria have become a therapeutic challenge in this high-risk patient population, since inadequate initial empirical treatment can seriously compromise prognosis. However, reducing antimicrobial exposure is one of the most significant cornerstones in the fight against resistance. The objective of these new guidelines is to update recommendations for the initial management of hematological patients who develop febrile neutropenia in this scenario of multidrug resistance. The two participating Societies (the *Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica* [Spanish Society of Infectious Diseases and Clinical Microbiology] and the *Sociedad Española de Hematología y Hemoterapia* [Spanish Society of Haematology and Haemotherapy]), designated a panel of experts in the field to provide evidence-based recommendations in response to common clinical questions. This document is primarily focused on bacterial infections. Other aspects related to opportunistic infections, such as those caused by fungi or other microorganisms, especially in hematopoietic stem cell transplantation, are also touched upon.

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[☆] The complete consensus statement is available as Appendix in supplementary material.

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Palabras clave:

Fiebre neutropénica
Neutropenia
Enfermedad hematológica
Tratamiento antibiótico empírico
Tratamiento antibiótico dirigido
Resistencia antibiótica

Resumen ejecutivo del documento de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC), la Red Española de Investigación en Patología Infecciosa (REIPI) y la Sociedad Española de Hematología y Hemoterapia (SEHH) sobre el manejo de la neutropenia febril en el paciente hematológico

R E S U M E N

La neutropenia febril es una complicación muy frecuente en los pacientes hematológicos que reciben tratamiento quimioterápico, y se asocia a una importante morbilidad. Las infecciones por bacterias multirresistentes se han convertido en un reto terapéutico en esta población de pacientes de alto riesgo, en los que un tratamiento empírico inicial inadecuado puede comprometer gravemente su pronóstico. Sin embargo, reducir la exposición a los antimicrobianos es uno de los pilares más importantes en la lucha frente a las resistencias. El objetivo de esta nueva guía es actualizar las recomendaciones sobre el manejo inicial del paciente hematológico que desarrolla neutropenia febril en el escenario actual de multirresistencia. Para la elaboración de este documento, las 2 sociedades implicadas (la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica y la Sociedad Española de Hematología y Hemoterapia) designaron expertos en este tema, quienes han realizado recomendaciones basadas en la evidencia, en respuesta a cuestiones clínicas habituales. Este documento está enfocado básicamente a la infección bacteriana. Otros aspectos relacionados con las infecciones oportunistas, como las producidas por hongos u otros microorganismos, sobre todo en el seno del trasplante de progenitores hematopoyéticos, se abordan de forma tangencial.

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Executive summary

Introduction: justification and objectives

Recent years have witnessed the re-emergence of bacterial infections with a gram-negative etiology in patients with febrile neutropenia (FN), together with a significant increase in their resistance to antimicrobials. These epidemiological changes are of particular importance in hematologic patients with FN because inadequate initial empirical antibiotic therapy can have a serious adverse effect on prognosis in high-risk patients. Likewise, the management of infections caused by multidrug-resistant bacteria is a major clinical problem in this population.

The management of hematologic patients has also changed in recent years, with a tendency towards outpatient care and new types of immunosuppressive treatment. In the era of multidrug resistance, the objective of these new guidelines is to update the recommendations for the initial management of hematologic patients who develop FN. This document focuses basically on bacterial infection. Other aspects associated with opportunistic infections, such as fungal infections or those due to other microorganisms, especially in hematopoietic stem cell transplantation (HSCT), are also touched upon. Only infections in adult patients will be discussed.

Methodology

The two participating Societies, the Spanish Society of Infectious Diseases and Clinical Microbiology (*Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica*) and the Spanish Association of Hematology and Hemotherapy (*Sociedad Española de Hematología y Hemoterapia*) nominated two coordinators, who selected the rest of the members of the panel of experts. The scientific committees of both societies approved the proposal. The questions to be considered were approved by both scientific societies involved and then distributed among the various members of the panel of experts. The present Document was written following the SEIMC guidelines for consensus documents (www.seimc.org), as well as the recommendations of the AGREE collaboration

(www.agreecollaboration.org) for evaluating the methodological quality of clinical practice guidelines. The PubMed search engine (<http://www.ncbi.nlm.nih.gov/pubmed>) was used to perform a literature search of the MEDLINE database for relevant scientific publications. The key words used for each question are also shown. Only complete articles published in English or Spanish were selected. No specific period of inclusion was defined, although authors were instructed to gather the most recent evidence from the literature to form the basis of their answers. The coordinators wrote the first draft, which was submitted for review by the panel of experts and by SEIMC members after being published on the web page of that society. The complete text has been approved by all authors. The criteria used to evaluate the strength of the recommendation and the quality of the evidence are summarized in [Table 1](#). Possible conflicts of interest associated with all members of the panel of experts are listed at the end of the document.

Recommendations

Classification of febrile neutropenia risk

1. What tools are available to determine risk in a patient with FN? When should they be applied and in what contexts?

Search terms: "Risk factors" "Risk stratification", "Febrile neutropenia", "Cancer patients".

1. Patients presenting with FN should undergo risk assessment for complications, preferably in the first hour of contact with the healthcare system (**A-II**).
2. The MASCC (Multinational Association for Supportive Care in Cancer) risk index is a prognostic scale that can be used to assess the risk of complications in patients with FN (**B-II**).
3. A patient with a MASCC risk index score of <21 is defined as high risk (**B-II**) and should be hospitalized and receive intravenous empirical antibiotic treatment (**B-II**).
4. A patient with a MASCC risk index score of ≥ 21 is defined as low risk (**B-II**). Some of these patients may be candidates for a

Table 1
Strength of recommendations.

<i>Strength of recommendation</i>	
A	Strongly supports a recommendation for use
B	Moderately supports a recommendation for use
C	Marginally supports a recommendation for use
<i>Quality of evidence</i>	
I	Evidence from at least one randomized controlled trial supports the recommendation being made
II	Evidence from at least one well-designed clinical trial without randomization, cohort study or case-controlled study
III	Evidence based on expert opinion and clinical experience or descriptive cases

regimen of oral antibiotics and can be managed as outpatients, provided that they are not receiving induction chemotherapy for acute myeloid leukemia or in the pre-engraftment phase of allogeneic hematopoietic stem cell transplantation (**B-II**).

- Clinical criteria can also be used to determine risk in patients with FN.
- Patients with an absolute neutrophil count (ANC) of $\leq 100/\text{mm}^3$, expected neutropenia duration of >7 days, and/or significant comorbidities (hypotension, pneumonia, gastrointestinal symptoms, neurological symptoms) are considered high-risk. These patients should be admitted to hospital and receive intravenous empirical therapy (**A-II**).
- Patients with ANC $< 500/\text{mm}^3$, expected neutropenia duration ≤ 7 days and having no or few comorbidities or significant evidence of renal or hepatic impairment are considered as low-risk. These patients may be candidates for oral empirical therapy and outpatient care (**A-II**).

Diagnostic management

1. What microbiology diagnostic tests should be carried out in patients with FN?

Search terms: “Febrile neutropenia” AND “Etiology”. “Febrile neutropenia” AND “Microbiological diagnosis”.

- It is recommended that at least two, and preferably three, sets of blood cultures be collected from any patient with FN, whether they are in-patients or seen in the emergency room, high-risk or low-risk. Blood should be drawn through all available catheterized venous access in the patient, paying special attention to long-term devices, as well as samples taken by venipuncture from peripheral vein sites (**A-I**).
- If an infection of extravascular origin is suspected, it is recommended to send representative samples from the possible focus of infection. Rapid microbiological tests can be performed on these samples (**A-I**).
- For patients being monitored in an outpatient setting with symptoms or radiological signs of respiratory infection, rapid urine antigen tests for the detection of *Streptococcus pneumoniae* and *Legionella pneumophila* antigens can be used (**A-II**).
- During annual flu epidemics, molecular methods should be used for early diagnosis. In the case of flu, rapid techniques on nasopharyngeal swabs are preferred (**B-II**).
- If the patient presents diarrhea, it is advisable to request a *Clostridium difficile* toxin stool test, on which rapid immunochromatographic assays or PCR can be performed (**C-III**).

2. When and how should pre-emptive screening for fungal infection be carried out?

Search terms: “Febrile neutropenia AND fungal infection diagnosis”, “Febrile neutropenia AND investigation for invasive fungal infection”.

- In patients with FN, pre-emptive screening for fungal infection should be considered when fever persists for 4–7 days after having started broad-spectrum antibiotics, expected duration of neutropenia is >7 days, and in clinically compatible cases (**A-I**).
- Blood cultures are the microbiological test of choice for the diagnosis of yeast infections (**A-I**).
- In clinically stable patients who are not receiving antifungal prophylaxis against filamentous fungi, it is recommended to screen for *Aspergillus* infection by carrying out serial testing for circulating galactomannan (GM) in serum twice a week. In the event of a positive GM test, a CT scan of the lungs is recommended (**A-I**).
- In patients receiving antifungal prophylaxis against filamentous fungi, a CT scan of the thorax is recommended if fever persists (>7 days after initiating broad-spectrum antibiotics, with no other identifiable cause of fever). In the event of findings suggestive of invasive fungal infection, bronchoscopy is recommended for galactomannan testing, and pan-fungal PCR on the bronchoalveolar lavage (BAL) fluid. If results are negative, lesion puncture is recommended (**B-II**).

3. Are biomarkers useful for infection diagnosis in FN and for determining length of antibiotic treatment?

Search terms: “Biomarkers and infection diagnosis”, “Febrile neutropenia”, “Bacteremia and biomarkers”, “Length of antibiotics in febrile neutropenia”.

- Biomarkers are not recommended as a guide to antibiotic use in FN, due to the lack of studies demonstrating the safety and usefulness of basing clinical decisions on their results (**B-III**).
- It has been demonstrated that neutropenic patients with bacteremia present significantly higher procalcitonin (PCT), C-reactive protein, IL-6, and presepsin levels than those without bacteremia. (**A-II**). The possible impact of this information on the future management of FN is yet to be clarified.
- Biomarkers are not useful for determining length of antibiotic treatment (**A-II**).
- C-reactive protein levels, especially those that are elevated ($>20\text{--}30\text{ mg/dl}$), are correlated with greater mortality. This relationship has not been demonstrated with the other biomarkers (PCT, presepsin, IL-6) (**C-III**).

Empirical antibiotic treatment

1. What empirical treatment strategies are there for patients with NF?

Search terms: “Febrile neutropenia”, “Empirical antibiotic treatment”.

- Any febrile patient with an ANC of $< 500/\text{mm}^3$ and those with ANC of $500\text{--}1000/\text{mm}^3$ and predicted to decline imminently should receive early empirical antibiotic treatment (**A-II**) with

an appropriate broad-spectrum antibiotic (**A-I**) and a bactericidal agent.

2. Surveillance programs (antimicrobial stewardship) established in the center for the appropriate use of antibiotic treatment should be taken into consideration (**B-III**).
3. A strategy of *dose-escalation* can be applied in patients with an uncomplicated clinical presentation, no previous colonization/infection with multidrug-resistant bacteria, and in centers where there is a low incidence of drug-resistant microorganisms (**B-II**). In other situations, a *de-escalation* strategy should be applied (**B-II**).

2. What is the empirical antibiotic treatment of choice when there is no obvious clinical focus of infection?

Search terms: "Febrile neutropenia", "Empirical antibiotic treatment", "Fever unknown origin".

1. It is recommended to use a beta-lactam antibiotic with antipseudomonal activity as monotherapy, or in combination with another antibiotic, depending on the risk of infection due to multidrug-resistant microorganisms and clinical presentation (**A-I**).
2. For the escalation strategy:
 - 2.1 Use of piperacillin-tazobactam (**A-I**), or cefepime (**A-I**), or ceftazidime (**B-II**) is recommended.
 - 2.2 In settings with a high prevalence of ESBs, cephalosporins and piperacillin-tazobactam in monotherapy are not recommended (**B-II**).
3. For the de-escalation strategy:
 - 3.1 Imipenem or meropenem in monotherapy are recommended for use (**B-II**), or a combination of antipseudomonal beta-lactam plus an aminoglycoside or a fluoroquinolone (if it has not been used as prophylaxis) (**B-III**). Carbapenems should be reserved for critically ill patients.
 - 3.2 The aminoglycoside should be given in a single daily dose (**A-II**). The need to continue the aminoglycoside should be reassessed at 48–72 h.
 - 3.3 If there is risk of infection due to multidrug-resistant nonfermenting gram-negative bacilli, it is recommended to combine the beta-lactam with the lowest antimicrobial resistance rate in the center + amikacin or colistin (**B-III**).
 - 3.4 The need for empirical treatments with other combinations can be considered, according to local epidemiology or in outbreak settings (**C-III**).
 - 3.5 The use of antibiotics with activity against gram-positive cocci resistant to beta-lactams (vancomycin, daptomycin, linezolid) would be indicated only in cases of hemodynamic instability and/or risk of methicillin-resistant *Staphylococcus aureus* (MRSA) infection (**B-III**).
 - 3.6 The empirical addition of vancomycin to initial antibiotic therapy is not recommended if fever persists at 3 days (**A-I**).
 - 3.7 In hemodynamically unstable patients, treatment should be started immediately with a broad-spectrum beta-lactam with antipseudomonal activity together with an antibiotic active against beta-lactam-resistant gram-negative bacilli, and a drug with activity against methicillin-resistant gram-positive cocci (**B-III**). In patients with septic shock not receiving antifungal prophylaxis, consider adding active treatment against *Candida* spp to the initial regimen (**C-III**).

3. What is the empirical treatment of choice when there is an obvious clinical source of infection?

Search terms: "Febrile neutropenia", "Empirical antibiotic treatment"

1. Oropharyngeal mucositis/esophagitis

- 1.1 In patients with mild forms of mucositis, anaerobic coverage is not essential and cefepime may be used (**B-III**).
- 1.2 In more severe forms, ensure anaerobe coverage with piperacillin-tazobactam, imipenem or meropenem (**A-III**).
- 1.3 Consider initiating antiviral and/or antifungal treatment in patients not receiving prophylaxis who have suggestive oral lesions or symptoms compatible with esophagitis (**C-III**).

2. Neutropenic enterocolitis (typhlitis)

- 2.1 Start treatment with a broad-spectrum antibiotic such as piperacillin-tazobactam, imipenem or meropenem that includes activity against gram-negatives, Gram-positives and anaerobes (**A-III**).
- 2.2 Consider adding treatment for *C. difficile* if there is a high index of suspicion (**C-III**).

3. Perianal infection

- 3.1 Performing a digital rectal examination is contraindicated in the neutropenic patient. Nevertheless a thorough examination of the perianal region is fundamental (**B-III**).
- 3.2 The treatments of choice are piperacillin-tazobactam, imipenem or meropenem (**A-III**).
- 3.3 If there is clinical suspicion of a perianal abscess, ensure active treatment against gram-negative bacilli, *Enterococcus* spp. and anaerobes (**A-III**).

4. Skin and soft tissue infection (SSTI)

- 4.1 Start treatment with a broad-spectrum, antipseudomonal beta-lactam agent with activity against Gram-positive cocci, including *S. aureus* (**A-III**).
- 4.2 Consider adding an antibiotic with activity against MRSA if there is a history of previous colonization/infection (**B-III**).
- 4.3 It is recommended to obtain a sample of tissue for microbiological and histopathologic analysis from any skin lesion suspected of being a source of infection (**B-III**).
- 4.4 The possibility of a serious necrotizing soft tissue infection should always be ruled out (**B-III**).
- 4.5 If a serious necrotizing infection is suspected, it is recommended to use agents such as clindamycin that inhibit protein synthesis, and so inhibit toxin production (**A-III**).

5. Intravascular catheter-related infection

- 5.1 Start treatment with an antipseudomonal beta-lactam together with an agent with specific activity against drug-resistant Gram-positive organisms such as vancomycin or daptomycin (**A-III**).
- 5.2 Linezolid is not recommended in this situation (**B-III**).
- 5.3 If the infection is considered serious and the catheter is the obvious source of infection, remove the catheter promptly before the microbiological results are known (**B-III**).

6. Paranasal sinuses

- 6.1 Start treatment with a broad-spectrum antipseudomonal beta-lactam with activity against Gram-positive cocci, including *S. pneumoniae* and *S. aureus* (A-III).
- 6.2 In risk patients (prolonged neutropenia, corticotherapy), consider adding treatment with activity against *Aspergillus* or Mucorales, which can give a picture of sinusitis that is initially difficult to differentiate from one with a bacterial etiology (B-III).

7. Pneumonia

- 7.1 Start with a broad-spectrum beta-lactam with activity against *S. pneumoniae* and *P. aeruginosa* (A-III).
- 7.2 In critically ill patients, nosocomial cases and patients previously colonized/infected with MDR gram-negative bacilli, it is advisable to combine with a second antibiotic, according to local epidemiology (B-III).
- 7.3 If the infection is community-acquired and an atypical pneumonia is suspected, consider combining with fluoroquinolones or macrolides (B-III).
- 7.4 In patients with MRSA colonization or epidemiological settings of high endemicity, combination with an active agent such as linezolid or vancomycin must be considered. (B-III).
- 7.5 During flu epidemics, add empirical treatment with oseltamivir (C-III). Once samples have been collected and the results are known, continuation or withdrawal of treatment can be assessed.
- 7.6 In risk patients with bilateral infiltrates, consider other possible etiologies (*Pneumocystis jirovecii*, cytomegalovirus) (B-III).

8. Urinary tract infection

- 8.1 Start with a beta-lactam with antipseudomonal activity (A-III).
- 8.2 Consider adding a second antibiotic in critically ill patients, those with indwelling urinary catheters, and/or a previous history of colonization/infection with multidrug-resistant bacteria, according to local epidemiology (aminoglycoside, glycopeptide) (B-III).

9. Central nervous system infections

- 9.1 In cases of acute meningitis, antibiotic treatment should include a beta-lactam with activity against *S. pneumoniae* and *P. aeruginosa* with good penetration into cerebrospinal fluid (CSF) (cefepime or meropenem) and ampicillin to cover *Listeria monocytogenes* (A-III).
- 9.2 In risk patients with suggestive clinical forms, or patients with space-occupying lesions, consider other etiologies (*Cryptococcus*, *Listeria*, *Nocardia*, filamentous fungi, toxoplasmosis and *Mycobacterium tuberculosis*) (B-III).

4. What is the duration of antibiotic treatment in patients with FN without clinically or microbiologically documented infection?

Search terms: "Duration OR discontinuation" AND "Neutropenia" AND "Antimicrobial OR antibiotic" AND "Therapy OR treatment".

1. Empirical antibiotic treatment can be stopped in hematologic patients with FN who do not have clinically or microbiologically documented infection, if they have been afebrile for at least 72 h, and hemodynamically stable and asymptomatic since

presentation, regardless of neutrophil count or expected duration of neutropenia (A-II).

2. After treatment is discontinued, the patient should be kept under close clinical observation for at least 24–48 h, so that antibiotic treatment can be restarted early if fever returns (B-II).
3. Centers that provide antibacterial prophylaxis should consider restarting it after stopping empirical antimicrobial therapy for as long as the neutropenia lasts (C-III).

5. Can patients with FN be treated with oral antibiotics? When? Which antibiotics?

Search terms: "Febrile neutropenia", "Oral treatment", "Hematological malignancies".

1. Patients considered to be at low risk for complications can be treated with oral antibiotics provided that they are also properly followed-up in the outpatient setting (A-II).
2. Treatment must include a fluoroquinolone with antipseudomonal activity (ciprofloxacin 750 mg/12 h/po) and an agent fully active against Gram-positive cocci, such as amoxicillin/clavulanic acid (875 mg/8 h/po), or clindamycin (300–600 mg/8 h po), if the patient has a proven allergy to all beta-lactams or a history of hypersensitivity (A-I). Another alternative is a combination of ciprofloxacin with cefixime or cefuroxime (A-II).
3. Other oral regimens including levofloxacin or ciprofloxacin in monotherapy have been studied less (B-III).
4. Fluoroquinolones should not be used as initial empirical treatment in patients who have received them as prophylaxis. (A-III).
5. Any patient, whether in the emergency room or after admission, who presents signs and symptoms of hemodynamic instability, focality, oral intolerance, new clinical signs and symptoms, or microbiological species not susceptible to initial empirical therapy are isolated, should be admitted to hospital or continue as an inpatient in order to expand the tests for fever syndrome and modify empirical treatment according to the protocol for high-risk patients (A-III).

6. When is empirical antifungal treatment indicated in a patient with NF?

Search terms: "Febrile neutropenia AND empirical antifungal treatment". "Febrile neutropenia AND pre-emptive antifungal therapy OR diagnostic-driven approach".

1. High-risk neutropenia patients not receiving prophylaxis against filamentous fungi can be given empirical antifungal treatment if fever with no other obvious cause persists after 4–5 days of broad-spectrum antibiotics and hemodynamic instability (B-II).
2. Alternative treatment strategies, such as biomarker-guided treatment using galactomannan (GM) or beta-D-glucan (BDG), reduce the use of antifungals safely and without affecting mortality in neutropenic patients (A-I).
3. Empirical antifungal treatment is not recommended in the vast majority of hematologic patients with high-grade neutropenia who receive antifungal prophylaxis covering filamentous fungi (A-II).

Targeted antibiotic treatment

1. In documented cases of microbiological isolates, can antibiotic treatment be adjusted to the susceptibility of the microorganism identified, even if neutropenia persists?

1. NF 患者有哪些经验性治疗策略？

搜索术语：“发热性中性粒细胞减少症”，“经验性抗生素治疗”。

1. 任何ANC<500/mm³和ANC为500–1000/mm³，且预计会立即下降的发热患者，都应接受早期经验性抗生素治疗（A-II），并使用合适的广谱抗生素（A-I）和抗菌药物。
2. 应考虑在中心建立的适当使用抗生素治疗的监测计划（抗菌管理）（B-III）。
3. 剂量递增策略可应用于临床表现不复杂，既往无多重耐药细菌定值/感染的患者，以及耐药微生物发生率较低的中心（B-II）。在其他条件下，降级策略也应该适当使用（B-II）

2. 当没有明显的感染临床重点时，选择哪种经验性抗生素治疗？

检索词：“发热性中性粒细胞减少症”，“经验性抗生素治疗”，“发热不明原因”。

1. 建议使用具有抗假单胞菌活性的β-内酰胺类抗生素作为单一疗法，或与其他抗生素联合使用，具体取决于多重耐药微生物感染的风险和临床表现(A-I)。
2. 升级策略
 - 2.1 推荐使用哌拉西林-他唑巴坦（A-I）、头孢吡肟（A-I）或头孢他啶（B-II）。
 - 2.2 在 ESB 患病率高的地区，不建议在单药治疗中使用头孢菌素和哌拉西林-他唑巴坦（B-II）。
3. 降级策略
 - 3.1 在单药治疗中，推荐使用亚胺培南或美罗培南（B-II），或联合使用抗假单胞菌的β-内酰胺加氨基糖苷类或氟喹诺酮（如果它尚未用作预防用药）（B-III）。碳青霉烯类药物应用于危重病人。
 - 3.2 氨基糖苷类应该按照单日剂量给药（A-II）。应在48-72小时内重新评估是否需要继续使用氨基糖苷类药物。
 - 3.3 如有感染多重耐药非发酵革兰阴性杆菌的风险，建议联合使用治疗中心最低的微生物耐药率的β-内酰胺药物+阿米卡星或粘菌素（B-III）。
 - 3.4 根据当地流行病学或爆发环境，可以考虑其他组合的经验性治疗（C-III）。
 - 3.5 只有在血流动力学不稳定和/或耐甲氧西林金黄色葡萄球菌（MRSA）感染风险的情况下，才能使用具有抗β-内酰胺类耐药革兰氏阳性球菌（万古霉素，达托霉素，利奈唑胺）活性的抗生素（B-III）。
 - 3.6 如果发热持续3天，则不推荐经常添加万古霉素进行初始抗生素治疗（A-I）。
 - 3.7 在血流动力学不稳定的患者中应立即开始治疗，使用具有抗假单胞菌活性的广谱β-内酰胺和以及对β-内酰胺耐药革兰阴性杆菌有效的抗生素，以及具有抗甲氧西林抗革兰氏阳性球菌活性的药物（B-III）。对于未接受抗真菌预防治疗的感染性休克患者，考虑在初始方案中添加对念珠菌的有效治疗药物（C-III）。

3. 当有明显的临床感染源时，选择怎样的经验性治疗方法？

搜索词：“发热性中性粒细胞减少症”，“经验性抗生素治疗”

1. 口咽粘膜炎/食管炎

- 1.1 对于轻度粘膜炎患者，厌氧菌覆盖是非必需的，可以使用头孢吡肟（B-III）。
- 1.2 在更严重的情况下，确保使用哌拉西林-他唑巴坦，亚胺培南或美罗培南进行厌氧菌覆盖（A-III）。
- 1.3 那些未接受预防性治疗且提示具有与食道炎相容的口腔病变或症状的患者，考虑进行抗病毒和/或抗真菌治疗（C-III）。

2. 中性粒细胞减少性小肠结肠炎（伤寒）

- 2.1 开始使用广谱抗生素治疗，包括对革兰氏阴性、革兰氏阳性和厌氧菌的活性的药物，如哌拉西林/他唑巴坦、亚胺培南或美罗培南（A-III）。
- 2.2 如果疑似感染指数高，考虑增加艰难梭菌的治疗（C-III）。

3. 肛周感染

- 3.1 中性粒细胞减少患者中禁忌进行直肠指检。然而，彻底检查肛周区域是基本的（B-III）。
- 3.2 选择的治疗方法是哌拉西林-他唑巴坦、亚胺培南或美罗培南（A-III）。
- 3.3 如果临床怀疑有肛周脓肿，确保对革兰氏阴性杆菌肠球菌和厌氧菌进行积极治疗（A-III）。

4. 皮肤和软组织感染（SSTI）

- 4.1 开始用广谱抗假单胞菌β-内酰胺药物治疗，该药物具有抗革兰氏阳性球菌的活性，包括金黄色葡萄球菌（A-III）。
- 4.2 如果有先前的定植/感染病史（B-III），考虑添加抗MRSA活性的抗生素。
- 4.3 建议从任何被怀疑为感染源的皮肤病变处获得用于微生物和组织病理学分析的样本（B-III）。
- 4.4 应始终排除严重坏死性软组织感染的可能性（B-III）。
- 4.5 如果怀疑有严重的坏死性感染，建议使用抑制蛋白质合成的克林霉素等药物，以抑制毒素的产生（A-III）。

5. 血管内导管相关感染

- 5.1 开始用抗假单胞菌β-内酰胺类药物和具有针对革兰氏阳性菌药物（如万古霉素或达托霉素）一起治疗（A-III）。
- 5.2 在这种情况下不建议使用利奈唑胺（B-III）。
- 5.3 在知晓微生物学结果之前，如果认为感染严重且导管是明显的感染源，请立即取出导管（B-III）。

6. 副鼻窦

- 6.1 开始用广谱抗假单胞菌β-内酰胺治疗，具有抗革兰氏阳性球菌的活性，包括肺炎链球菌和金黄色葡萄球菌（A-III）。

6.2 对于有风险的患者（长期中性粒细胞减少、皮质治疗），考虑增加对曲霉菌或粘液的治疗，因为很难区分致病细菌，因此可以提供鼻窦炎的圖片（B-III）。

7. 肺炎

7.1 从具有抗肺炎链球菌和铜绿假单胞菌（A-III）活性的广谱β-内酰胺开始用药。

7.2 建议在危重病人，院内病例和先前定植/感染MDR革兰阴性杆菌的患者中，根据当地流行病学与第二种抗生素联合使用（B-III）。

7.3 如果感染是社区获得性的并且怀疑患有非典型肺炎，可考虑联合使用氟喹诺酮类药物或大环内酯类药物（B-III）。

7.4 对于MRSA定植或流行病学高度流行的患者，必须考虑与利奈唑胺或万古霉素等活性药物联合使用（B-III）。

7.5 在流感流行期间，加用奥司他韦进行经验性治疗（C-III）。一旦收集了标本并且结果已知，就可以评估继续治疗或撤回。

7.6 在有双侧浸润风险的患者中，考虑其他可能的病因（肺孢子虫、巨细胞病毒）（B-III）。

8. 泌尿道感染

8.1 从具有抗假单胞菌活性的β-内酰胺开始用药（A-III）。

8.2 根据当地流行病学，考虑在重症患者、留置导尿管患者、和/或先前的多药耐药细菌定植/感染史的患者中添加第二种抗生素（氨基糖苷类，糖肽类）（B-III）。

9. 中枢神经系统感染

9.1 在急性脑膜炎的情况下，抗生素治疗应包括具有抗肺炎链球菌和铜绿假单胞菌的、具有良好的穿透脑脊液能力的（CSF）β-内酰胺类药物，（头孢吡肟或美罗培南）和覆盖单核细胞李斯特菌的氨苄西林（A-III）。

9.2 在提示具有临床表现的风险患者或占位性病变患者中，考虑其他病因（隐球菌、李斯特菌、诺卡氏菌、丝状真菌、弓形虫和结核分枝杆菌（B-III）。

6. NF患者何时需要进行经验性抗真菌治疗？

检索词：“发热性中性粒细胞减少症和经验性抗真菌药治疗”。“发热性中性粒细胞减少和预防性的抗真菌治疗或诊断导向的方法”

1. 如果在广谱抗生素和血流动力学不稳定4-5天后出现没有其他明显原因的发热，未接受抗丝状真菌化学预防治疗的高危中性粒细胞减少症患者则可以给予经验性抗真菌治疗（B-II）。

2. 替代治疗策略，例如使用半乳甘露聚糖（GM）或β-D-葡聚糖（BDG）的生物标志物引导治疗，可以安全地减少抗真菌药物的使用，而不会影响中性粒细胞减少患者的死亡率（A-I）。

3. 绝大多数接受抗真菌药物预防的高级别中性粒细胞减少症的血液学患者不建议进行经验性抗真菌治疗（A-II）。

Search terms: “targeted OR de-escalation” AND “therapy OR treatment” AND “febrile neutropenia” AND “antimicrobial OR antibiotic”.

1. In patients with documented microbiological isolates, treatment should be targeted at the isolate, taking into account its in vitro activity (including MIC), pharmacokinetic/pharmacodynamic properties, as well as the individual characteristics of the patient (**A-I**).
2. If the microorganism isolated is considered to be the only causative agent of the febrile episode, it is preferable to use an antimicrobial, normally a beta-lactam, with a narrower spectrum when active (**B-III**).
3. Beta-lactam monotherapy is appropriate for targeted treatment of most cases of gram-negative bacteremia (**A-I**).

2. What is the duration of antibiotic treatment in patients with FN and clinically or microbiologically documented infection?

Search terms: “duration OR discontinuation” AND “neutropenia” AND “antimicrobial OR antibiotic” AND “therapy OR treatment”.

1. In hematologic patients with FN and clinically documented infection, antibiotic treatment can be discontinued when the clinical signs and symptoms of infection have resolved and the patient has been afebrile for at least 72 h (**B-II**).
2. In hematologic patients with FN and microbiologically documented infection, treatment should be maintained until clinical and microbiological cure of infection (resolution of signs and symptoms of infection and microbiological eradication) and after at least 4 days of apyrexia and a minimum of 7 days of antibiotic treatment (**B-III**).
3. In both situations, if neutropenia persists after treatment has been discontinued the patient should be kept under close clinical observation for at least 24–48 h, so that antibiotic treatment can be restarted promptly if fever recurs (**B-II**).
4. Centers that give prophylactic antibacterial agents should consider renewing this regimen when empirical antibiotics have been discontinued for as long as the neutropenia continues (**C-III**).

3. When is removal of a central venous catheter indicated?

Search terms: “central venous catheter removal”, “catheter-related infection”, “management of central venous catheter infection” “catheter-related bloodstream infection”.

1. When CVC infection is documented, consider removal of the catheter wherever possible, weighing up the advantages of removal against the difficulty of obtaining new venous access (**A-II**).
2. It is recommended to remove the CVC when there is documented catheter-related bloodstream infection (CRBSI) and local signs at the insertion site (suppuration), along the tunnel tract (tunnel infection), or if the patient presents criteria for severe sepsis with hemodynamic instability (septic shock) (**A-II**).
3. To improve the prognosis of the patient, it is recommended to remove the CVC when there is documented CRBSI due to fungi (normally *Candida* spp), *S. aureus*, enterococci, gram-negative bacilli (especially *P. aeruginosa*) and mycobacteria (**A-II**). Removal is also recommended in infections with associated bacteremia caused by microorganisms that are difficult to eradicate (*Bacillus* spp., *Micrococcus* spp. and *Propionibacterium* spp.) (**B-II**).

4. In uncomplicated infections or where bacteremia is caused by microorganisms different from those mentioned above, systemic targeted antibiotic treatment can be applied without removing the CVC and antibiotic lock therapy should be considered (**B-II**).
5. Removal of the CVC is recommended if persistent bacteremia is detected (evidenced in positive follow-up control cultures) 48 h–72 h after starting targeted antibiotic treatment (**A-II**), if there is no other obvious clinical focus (**B-II**), if there is infective endocarditis or peripheral embolism (**A-II**) or an early relapse due to the same microorganism after completion of antibiotic treatment, or failure of conservative treatment (**B-II**).
6. If fever persists in a neutropenic patient with an indwelling catheter after other focalities have been ruled out, but catheter-related infection has not been confirmed, consider removal of the catheter if there is sepsis or local erythema in the pericatheter area (**B-II**), or if fever persists and there is no other possible cause despite the absence of sepsis or local signs of infection (**C-III**).

Treatment of infections caused by multidrug-resistant Gram-negative bacilli (MDR-GNB)

1. What is the treatment of choice for cephalosporin-resistant Enterobacteriaceae?

Search terms: “(ESBL or extended-spectrum beta-lactamase) and treatment and outcome”; “AmpC and *Enterobacter*” and treatment and outcome”.

1.1 Targeted therapy in infections caused by extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae

- 1.1.1 In stable patients, the targeted therapy of choice against extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae is a beta-lactam/beta-lactamase inhibitor (BLBLI) combination, provided that in vitro susceptibility is shown (**B-II**).
- 1.1.2 Use of carbapenems is recommended for patients with sepsis or septic shock criteria (**C-I**).
- 1.1.3 Piperacillin-tazobactam and meropenem should be administered in extended infusion, since this has been shown to improve prognosis in severe infections compared with short-term infusions (**A-I**).
- 1.1.4 Piperacillin-tazobactam should be avoided for treating high-inoculum infections caused by strains with MIC ≥ 4 mg/L (**B-II**).

1.2 Targeted therapy in infections caused by AmpC-producing Enterobacteriaceae

- 1.2.1 Cefepime and fluoroquinolones are the preferred treatment options for infections due to AmpC-producing Enterobacteriaceae susceptible to these antimicrobials (**B-II**).
- 1.2.2 Piperacillin-tazobactam is a valid therapeutic option if in vitro activity is shown (**B-II**), but should be avoided for treating high-inoculum infections caused by AmpC-producing Enterobacteriaceae with MIC ≥ 4 mg/L (**B-III**).
- 1.2.3 Use of carbapenems is recommended for patients without alternative treatment options, or with sepsis or septic shock criteria (**C-I**).
- 1.2.4 We recommend that piperacillin-tazobactam, cefepime and meropenem be administered in extended infusion, since this has been shown to improve the prognosis in severe infections when compared with short-term infusions (**A-I**).

2. What is the treatment of choice for carbapenem-resistant Gram-negative bacilli?

2.1 Targeted treatment of infections caused by carbapenem-resistant Enterobacteriaceae (CRE).

Search terms: “(carbapenemase or KPC or OXA or NDM or VIM) and treatment and outcome”.

- 2.1.1 Severe infections caused by KPC-producing Enterobacteriaceae in neutropenic patients should be treated with a combination of at least two active drugs from the options included in the antibiogram (meropenem, colistin, tigecycline, fosfomycin and aminoglycosides) (B-II). We recommend the same approach for treating severe infections caused by other carbapenemase-producing Enterobacteriaceae (CRE) (C-III).
- 2.1.2 For infections caused by strains with meropenem MICs < 16 mg/L, the combination regimen should include high-dose meropenem (2 g every 8 h) in extended infusion (over 3 h) (B-II).
- 2.1.3 Ceftazidime-avibactam may be an alternative for severe infections due to KPC-producing or OXA-48-producing Enterobacteriaceae (C-III). We do not have well-designed comparative studies available that enable this drug to be positioned against other treatment options (undecided). Nor are there data to support its use in combination therapy (undecided).
- 2.1.4 In this type of infection, it is especially important to ensure control of the source of infection and to administer high-dose antibiotics with optimized dosage regimens, monitoring plasma levels whenever possible (Table 4) (B-II).

2.2 Targeted therapy of extensively drug-resistant (XDR) and pandrug-resistant (PDR) non-fermenting gram-negative bacilli (NFGNB).

Search terms: BGN-NF XDR and PDR: (*Acinetobacter* or *Pseudomonas*) and (resistant or resistance or MDR or XDR or PDR) and treatment and outcome.

- 2.2.1 In the case of XDR NFGNB infections for which there is a fully active therapeutic alternative, single-agent treatment is recommended with optimized administration (B-I), prioritizing the use (in the following order) of beta-lactams, sulbactam (in infections due to *A. baumannii*) and colistin, provided that *in vitro* susceptibility is shown (C-II). Avoid monotherapy with aminoglycosides or tigecycline for the treatment of severe infections (A-II, A-I).
- 2.2.2 For severe infections due to XDR-NFGNB strains with borderline susceptibility to the available treatment options, optimized administration of combination therapy using two or more agents should be considered, based on the best options specified in the antibiogram (B-II).
- 2.2.3 For XDR or PDR *P. aeruginosa* infections, use of ceftolozane-tazobactam may be considered (C-II) or ceftazidime-avibactam (C-I), although there is as yet limited experience of their use in this setting.
- 2.2.4 If these options are not available or the infection is caused by pan-resistant isolates, it will be necessary to develop combination therapy regimens using two or more agents, choosing those with intermediate susceptibility, or whose MICs are closest to the susceptibility cut-off (C-III).
- 2.2.5 It is particularly important in these infections to ensure control of the source of infection and to administer high-dose

antibiotics with optimized administration regimens, monitoring plasma levels whenever possible (B-II).

3. Targeted treatment of *Stenotrophomonas maltophilia* infections.

Search terms: “*Stenotrophomonas* and treatment”.

- 3.1 The treatment of choice for infections due to *S. maltophilia* is co-trimoxazole (trimethoprim 15 mg/kg/day in 3–4 divided doses) (C-II).
- 3.2 In patients with infections with co-trimoxazole-resistant strains, or those who cannot take co-trimoxazole (because of hypersensitivity, for example), the recommended treatment is minocycline (C-II) or fluoroquinolones (C-II) if they are active. There is more limited experience of the use of ceftazidime, tigecycline and colistin in monotherapy (C-III). In the case of patients with serious or refractory infections who require second-line therapy, consider combining two drugs with *in vitro* activity categorized as susceptible.

Adjuvant measures and prevention

1. Is the use of colony-stimulating factors indicated for treatment of FN? When?

Search terms: “febrile neutropenia”, “colony stimulating factor”, “treatment”.

1. Colony-stimulating factors (CSF) are not routinely recommended in the treatment of FN (B-II).
2. They can be considered for therapeutic use in patients with increased-risk for infection-related complications or predictive factors of poor prognosis (B-II).

2. When would granulocyte transfusion be indicated?

Search terms: “febrile neutropenia”, “granulocyte transfusion”.

1. There is insufficient evidence of the efficacy of granulocyte transfusion in patients with FN and documented infection (C-III).
2. Granulocyte transfusions should be administered only in the context of prospective clinical trials (B-III).

3. Is antibacterial prophylaxis indicated? Which drugs?

Search terms: “febrile neutropenia”, “antibacterial prophylaxis”.

1. Antibacterial prophylaxis is not recommended in low-risk patients (A-I).
2. In high-risk patients (ANC < 500/mm³ > 7 days), use of antibacterial prophylaxis should be evaluated on an individual basis in accordance with the characteristics of the patient and local hospital epidemiology, owing to the lack of benefit for mortality and the increasing levels of resistance in gram-negative bacteria (B-I). If prophylaxis is used, epidemiological surveillance for MDRO detection should be implemented.

4. Is prophylaxis with colony stimulating factors indicated? When?

Search terms: “febrile neutropenia”, “colony stimulating factor”, “prophylaxis”

1. 头孢菌素耐药肠杆菌科的首选治疗方法是什么？

搜索术语：“（ESBL 或超广谱 β -内酰胺酶）和治疗及结果”；“AmpC 和肠杆菌*和治疗和结果”。

1.1 产ESBL大肠杆菌科细菌感染的靶向治疗

1.1.1 在病情稳定的患者中，针对产超广谱 β -内酰胺酶（ESBL）的肠杆菌科的目标性治疗是 β -内酰胺/ β -内酰胺酶抑制剂（BLBLI）联合，如果显示体外敏感（B-II）。

1.1.2 对于符合患有脓毒症或败血症性休克标准的患者，建议使用碳青霉烯类药物（C-I）。

1.1.3 哌拉西林-他唑巴坦和美罗培南应延长输注给药，因为与短期输注相比，可改善严重感染的预后（A-I）。

1.1.4 应避免使用哌拉西林-他唑巴坦治疗MIC $\geq$ 4 mg/L菌株引起的高接种率感染（b-ii）。

1.2 产AmpC肠杆菌科感染的目标性治疗

1.2.1 对由于产AmpC肠杆菌科（B-II）敏感的抗菌药物如：头孢吡肟和氟喹诺酮类药物是感染的首选治疗选择。

1.2.2 如果显示体外活性，哌拉西林-他唑巴坦是一种有效的治疗选择（B-II），但应避免用于治疗由产AmpC-的肠杆菌科且MIC $>$ 4 mg / L引起的高接种感染（B-III）。

1.2.3 对于没有替代治疗方案或符合脓毒症或败血症性休克标准的患者，建议使用碳青霉烯类药物（C-I）。

1.2.4 我们建议给予延长输注哌拉西林/他唑巴坦，头孢吡肟和美罗培南，因为与短期输注相比，这可以改善严重感染的预后（A-I）。

2. 对碳青霉烯类耐药的革兰阴性杆菌有哪些治疗选择？

2.1 针对碳青霉烯类耐药肠杆菌科（CRE）引起的感染的目标性治疗。

搜索术语：“（碳青霉烯酶或 KPC 或 OXA 或 NDM 或 VIM）和治疗及结果”。

2.1.1 在中性粒细胞减少患者中由产 KPC 肠杆菌科引起的严重感染应该用抗菌谱中包括的至少两种活性药物（美罗培南，粘菌素，替加环素，磷霉素和氨基糖苷类）联合治疗（B-II）。我们建议采用相同的方法治疗由其他产生碳青霉烯酶的肠杆菌（CRE）引起的严重感染（C-III）。

2.1.2 对于由美罗培南MIC $<$ 16 mg/L的菌株引起的感染，联合方案应包括延长输注（超过3小时）的高剂量美罗培南（每8小时2g）（B-II）。

2.1.3 对于由于产 KPC 或产 OXA-48 的肠杆菌科感染，头孢他啶/阿维巴坦可能是严重感染的替代药物（C-III）。我们没有精心设计的比较研究，可以使这种药物与其他治疗方案（未定）相对应。也没有数据支持其在联合治疗中的应用（未定）。

2.1.4 在这种类型的感染中，特别重要的是确保控制感染源并使用优化剂量方案的高剂量抗生素，尽可能监测血浆水平（表4）（B-II）。

2.2 靶向治疗广泛耐药 (XDR) 和全耐药 (PDR) 非发酵革兰氏阴性杆菌 (NFGNB)。搜索术语: BGN-NF XDR 和 PDR : (不动杆菌或假单胞菌) 和 (耐药或耐药或 MDR 或 XDR 或 PDR) 和治疗和结果。

2.2.1 对于 XDR-NFGNB 感染, 其中有一种完全有效的治疗方案, 建议采用单药治疗, 优化给药 (B-I), 优先使用 (按以下顺序) β -内酰胺类, 舒巴坦 (感染后) 和粘菌素, 只要显示体外敏感性 (C-II)。避免使用氨基糖苷类或替加环素单独治疗严重感染 (A-II, A-I)。

2.2.2 对于由 XDR-NFGNB 菌株引起的严重感染, 对现有治疗方案具有硼酸盐敏感性, 应根据抗菌谱中规定的最佳方案, 考虑使用两种或两种以上药物进行优化的联合治疗 (B-II)。

2.2.3 对于广泛耐药或 PDR 铜绿假单胞菌感染, 可考虑使用头孢洛扎/他唑巴坦 (C-II) 或头孢他啶/阿维巴坦 (C-I), 尽管目前在这方面的使用经验有限。

2.2.4 如果无法获得这些可选择的药物或感染是由泛抗性分离株引起的, 则有必要开发使用两种或更多种药物的联合治疗方案, 选择中度易感性的药物, 或其 MIC 最接近易感性折点 (C-III)。

2.2.5 在这些感染中, 确保感染源的控制和优化给药方案给予高剂量抗生素, 尽可能监测血浆水平 (B-II) 尤为重要。

3. 目标性治疗嗜麦芽寡养单胞菌感染。

搜索术语: “嗜麦芽寡养单胞菌和治疗”。

3.1 用于治疗感染的治疗剂量为马来丝氨酸-三甲氧嘧啶 (甲氧苄啶 15mg/kg/天, 3-4 次分剂量) (C-II)。

3.2 在感染复方新诺明耐药菌株的患者或不能服用复方新诺明的患者 (例如因超敏反应), 推荐的治疗方法是米诺环素 (C-II) 或氟喹诺酮类药物 (C-II)。在单一疗法 (C-III) 中使用头孢他啶, 替加环素和粘菌素的经验较为有限。对于需要二线治疗的严重或难治性感染患者, 考虑将两种药物与体外活性相结合归类为易感的药物。

1. The decision to use colony-stimulating factor prophylaxis for the prevention of FN should be based on the relative myelotoxicity of the chemotherapy regimen and the presence of potential risk factors, which should be evaluated before each cycle of chemotherapy is administered.
2. In situations where chemotherapy dose intensity or dose density strategies confer a survival benefit, prophylaxis with G-CSF should be used as supportive treatment (**A-I**).
3. Primary prophylaxis is recommended from the first chemotherapy cycle for patients whose overall risk of FN is $\geq 20\%$, based on patient-related, disease-related and regimen-related risk factors (**A-I**).
4. When the overall risk of FN is 10%–20%, attention should be focused on additional risk factors (such as comorbidities or advanced age), which increase the risk of FN and support an indication of prophylaxis with G-CSF (**A-I**).
5. Prophylaxis with G-CSF is not recommended if chemotherapy has an FN risk of $<10\%$ (**A-I**).
6. Secondary prophylaxis is recommended for patients who experienced neutropenic complications in a previous cycle of chemotherapy and in whom a dose reduction or delay in treatment could compromise progression-free or overall survival, or treatment outcome (**A-I**).
7. Prophylaxis can be given with any of the following factors (filgrastim, lenograstim and pegfilgrastim) or any of their available biosimilars (**A-I**), preferably subcutaneously.

Conflicts of interest

Carlota Gudiol has served as speaker at scientific meetings sponsored by Pfizer, MSD, Astellas and Gilead. Rafael de la Cámara has participated as speaker at scientific meetings sponsored by MSD, GSK, Novartis, Astellas, Pfizer and Gilead; and in consultancy and advisory activities for Novartis, MSD, Janssen, Clinigen and Astellas. Manuel Lizasoain has participated as speaker at scientific meetings sponsored by Pfizer, MSD and Gilead. Jordi Carratalà has participated as speaker at scientific meetings sponsored by Pfizer, MSD, Gilead and Angelini. Rafael Cantón has participated as speaker at scientific meetings sponsored by Angelini, ERN Laboratorios, MSD, Pfizer and Zambon and has received funding for research projects from AstraZeneca and MSD. Manuela Aguilar-Guisado has

participated as speaker at scientific meetings sponsored by Pfizer and MSD. Manuela Aguilar-Guisado has participated as speaker at scientific meetings sponsored by Pfizer and MSD. José Molina Gil-Bermejo has received lecturing fees in activities financed by Merck Sharp & Dohme, and has received grants to attend conferences organized by Astellas Pharma. Carlos Solano has participated as speaker at scientific meetings sponsored by Pfizer, MSD, Astellas and Gilead. He has received grants for clinical and preclinical research from Pfizer and Astellas. Carolina García-Vidal has received fees for speaking at events sponsored by Gilead Science, Merck Sharp and Dohme, Pfizer, Janssen and Novartis, and has received a subsidy from Gilead Science. María Lourdes Vázquez López has participated as speaker at scientific meetings sponsored by Pfizer, MSD, Gilead, Astellas, Amgen. José Ramón Azanza has participated as speaker at scientific meetings sponsored by Pfizer, MSD, Gilead, Janssen, AstraZeneca, Roche. José Ramón Azanza has participated as speaker at scientific meetings sponsored by Pfizer, MSD, Gilead, Janssen, AstraZeneca, Roche. Francisco Javier Candel has participated as speaker at scientific meetings sponsored by Pfizer, MSD, Gilead, Angelini, Astellas, and ERN. Isabel Ruiz-Camps has participated as speaker at scientific meetings sponsored by Astellas, Celgene, Gilead, MSD, Pfizer and in scientific consultancy for Astellas, Gilead, and Pfizer. María Suárez-Lledó has participated as speaker at scientific meetings and has collaborated in scientific studies sponsored by Pfizer and MSD. Isidro Jarque has participated as speaker at scientific meetings sponsored by Gilead, MSD, and Pfizer. Isabel Sánchez-Ortega has no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.eimc.2019.01.013](https://doi.org/10.1016/j.eimc.2019.01.013).