Neonatal bacterial diseases

黃新純

2010-6-2
Definition

- **Bacteremia**: bacteria in blood, confirmed by culture (may be transient)

- **Sepsis**: clinical evidence of infection + evidence of a systemic response to the infection. The systemic response manifested by $\geq 2$ of following:
  1. BT: $> 38$ or $< 36$
  2. HR > 90 beats/ min
  3. RR > 20 breaths/ min or PaCO2 $< 32$ mmHg
  4. WBC $> 12000$, $< 4000$ or $> 10\%$ immature (band) forms

- **Septic syndrome**: sepsis + evidence of altered organ perfusion with at least one of the following: hypoxemia, elevated lactate, oliguria, altered mentation
Sepsis neonatorum

- A bacterial disease of infants ≤ 28 d/o
- Bloodstream+, no obvious focus of infection
- Clinical evidence of infection + evidence systemic response to inf (T/P/R/WBC)
- Clin & lab findings: Ddx with transient bacteremia in healthy NB
Epidemiology

• **Inc:** 1~8/1000 live births

  Approximately 10% of all neonates admitted to NICU are treated with antibiotics for suspected sepsis.
  → A bacterial cause is found in < 10%

• **Mortality:** 50%

• **Morbidity:** *Meningitis* in 1/3 of sepsis
More facts about Neonatal Sepsis

Neonatal Sepsis affects approximately 2 infants per 1000 births with a higher incidence in premature & low birth weight infants [2].

There are two types of Neonatal Sepsis:

- Early Onset
- Late Onset

* This tutorial will focus primarily on Early Onset Sepsis
Causes of Neonatal Sepsis

The primary causes of Neonatal Sepsis are bacteria, such as Staphylococcus and Group Beta Strep (GBS).

Bacteria may be the cause of neonatal sepsis, but neonates are more susceptible to these bacteria for two reasons [3&6]:

- Immature immune response
- Genetic predisposition
What makes a neonate’s immune system immature?

Normally an immune system responds to a pathogen in a specific manner, but if there are problems with any element the immune system is unable to function properly [3&6].

1. Pathogen enters body
2. Neutrophils move in
3. Chemotaxis occurs
4. Opsonization causes phagocytosis
5. Monocytes kill pathogen
Pathogens can enter through the prenatal, perinatal, and postnatal periods [6].

<table>
<thead>
<tr>
<th>Prenatal</th>
<th>Maternal Substance Abuse</th>
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<tr>
<td></td>
<td>Premature Rupture of Membranes (&gt;18 Hours)</td>
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<td>Maternal Infection</td>
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<td>Perinatal</td>
<td>Microbial Colonization at Birth</td>
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<td>Maternal Infection</td>
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<td>Vaginal Exam of Mother</td>
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<td>Postnatal</td>
<td>Invasive Catheters</td>
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<td>Endotracheal Intubation</td>
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<td></td>
<td>Exposure to Nosocomial Microorganisms</td>
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</table>
Neutrophils: An Important Cell in Immunity Against Pathogens

Neonatal neutrophils are deficient in their ability to adhere to vessel walls at site of infection [2&6].

Further release of neutrophils depletes a neonatal storage pool because the bone marrow storage of a neonate is only 20-30% of the pool in an adult [2&6].

Neonatal neutrophils have a decreased ability to “deform” & migrate into tissues [2&6].

Image provided with permission from http://en.wikipedia.org/wiki/Image:Segmented_neutrophils.jpg
Imagine: Being in a dark tunnel without any direction or a way out. Finally you see light. You move towards the light and get out of the tunnel. Well this is like chemotaxis. The sun is the chemoattractant attracting you out to the world!!

Neonatal neutrophils have decreased chemotaxis due to decreased chemoattractant production [2&6]. Chemoattractants attract neutrophils to the site of infection [2&6].

Neonatal neutrophils therefore cannot reach the site of infection because of the chemotaxis deficiency caused by decreased chemoattractant production.
Opsonization is the coating of a pathogen with antibodies that makes it susceptible to phagocytosis [2&6].

Phagocytosis is the process of cells (phagocytes) engulfing, ingesting, & destroying pathogens [2&6].

Neonates have a decreased amount of opsonins (antibodies that promote opsonization) [2&6].
Monocytes are a type of White Blood Cell that ingests pathogens.

Neonates have a sufficient amount of monocytes and full capability to kill organisms [2], but because of a neonates deficiencies previously discussed very few monocytes get to the site of infection.
Genetic Predisposition to Sepsis

Multiple factors play into a neonate's response to infection and the possible development of sepsis. One of these factors is genetics. As science has moved into recognizing the human genome there have also been advances with finding genetic contributions to sepsis.

The body's first response to infection requires recognition of the presence of a pathogen. After recognition has occurred the body responds appropriately to resolve the problem [3&14]. Many polymorphisms have been recognized within both of these phases and they have been implicated in influencing the susceptibility to and/or outcome from sepsis [3&14].

Let's look further into these two phases to see the effect polymorphisms have on neonatal sepsis:
Symptoms and signs

- Non-specific !!!
- Acute deterioration !
- Especially in premature and ill infants !
Clinical presentation

- Temperature irregularity (high or low)
- Change in behavior
  - Lethargy, irritability, changes in tone
- Skin changes
  - Poor perfusion, mottling, cyanosis, pallor, petechiae, rashes, jaundice
- Feeding problems
  - Intolerance, vomiting, diarrhea, abdominal distension
- Cardiopulmonary
  - Tachypnea, grunting, flaring, retractions, apnea, tachycardia, hypotension
- Metabolic
  - Hypo or hyperglycemia, metabolic acidosis
Clinical manifestations

- Major signs and symptoms of sepsis:
  - Disturbances in thermoregulation
  - Respiration
  - Gastrointestinal function
Thermoregulation

- Hypothermia: 40% of cases
- Hyperthermia: less common
- Non infectious fever:
  - dehydration, elevation in ambient temperature, hematomas
  - from central origins secondary to neonatal conditions: anoxia, CNS hemorrhage, kernicterus
Respiration

- Tachypnea, grunting respirations, cyanosis, intercostal and substernal retractions, and apnea
  - Tachycardia: a sensitive indicator of early-onset neonatal sepsis
Gastrointestinal function

- poor feeding
- regurgitation
- vomiting
- weak sucking
- abdominal distention
- diarrhea
Cutaneous findings

- Cellulitis, impetiginous lesions, furunculosis, papular lesions (i.e., listeriosis), vascular lesions (i.e., *Pseudomonas*), and exfoliative dermatitis (i.e., phage group II staphylococcal disease)

- Jaundice
In utero infection

• Signs of fetal distress:
  - First indication of inf: fetal tachycardia in the 2nd stage of labor as a sign of intrauterine infection
Differential diagnosis

- RDS
- Metabolic disease
- Hematologic disease
- CNS disease
- Cardiac disease
- Other infectious processes (i.e. TORCH)
Symptoms

Symptom variability occurs because of the metabolic and inflammatory processes that occur in neonatal sepsis.

A neonate’s symptoms are rooted in these two processes.

Let’s look more into these areas:

- Metabolism
- Inflammation
Sepsis can alter a neonate’s metabolism [11].

Ebb Flow

This is the initial phase and last only 1-3 days. This is how a neonate's body initially tries to compensate for losses that occur during sepsis. The body slows things down in order to let the body recover.

The Ebb Phase consists of several clinical manifestations [11]:

- Hypometabolism
- Decreased energy expenditure
- Decreased cardiac output
- Lowered oxygen consumption
- Vasoconstriction
Flow Phase

This is the phase that occurs after the initial Ebb Phase. If the body doesn’t recover it goes into hyperdrive. This is partly due to the exaggerated inflammatory response (further discussion in inflammatory process section). This phase leads to much of the mortality and morbidity related to neonatal sepsis [11].

The Flow Phase consists of several clinical manifestations [11]:

- Hypermetabolism
- Increased energy expenditure
- Increased cardiac output
- High oxygen consumption
Inflammation in Neonatal Sepsis

It is widely known that sepsis occurs because of an exaggerated systemic inflammatory response (SIR) [12].

Let's find out how this is true‡
Inflammatory Process

- Pathogen enters body
- Inflammatory mediators released (cytokines)
- Injury to endothelium
- Tissue factors released
- Production of thrombin
- Coagulation promotes clot formation
- Increased activity of fibrinolysis inhibitors
- Decreased fibrinolysis

[12]
Inflammation

Overall, the imbalance among inflammation, over coagulation, and decreased fibrinolysis are the cause for the majority of deaths in sepsis [12].
How is Neonatal Sepsis Diagnosed?

There is no definite marker in neonatal sepsis, but there are determinants of infection.

When a neonate presents with sepsis symptoms a septic work-up is completed [2]. What is included in a septic work up?

* Complete Blood Count (CBC)
* Blood & Urine cultures
* Lumbar Puncture (LP)
* Chest X-Ray
* Line cultures
Diagnosis

• Cultures
  
  n Blood
  • Confirms sepsis
  • 94% grow by 48 hours of age
  
  n Urine
  • Don’t need in infants < 24 hrs because UTI rare in this age
  
  n CSF
  • Controversial
  • May be useful in clinically ill newborns or those with positive blood cultures
Adjunctive lab tests

- White blood cell count and differential
  - Neutropenia can be an ominous sign, but also associated with birth asphyxia, PIH
  - I:T ratio > 0.2 is of good negative predictive value
  - Serial values can establish a trend

- Platelet count
  - Late sign and very nonspecific

- Acute phase reactants
  - CRP rises early, monitor serial values
  - ESR rises late

- Other tests: bilirubin, glucose, sodium
Answer

• (a) absolute neutrophil count
  \[ 5000 \times (S_{26} + B_{22} + \text{meta}_{1} + \text{myelo}_{1} ) = 2500 \]

• (b) absolute immature neutrophil count
  \[ 5000 \times (B_{22} + \text{meta}_{1} + \text{myelo}_{1} ) = 1200 \]

• (c) immature to total neutrophil ratio
  \( \text{I:T ratio} = 0.48 \)
<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
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<tbody>
<tr>
<td><strong>Initial CBC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manroe</td>
<td>68</td>
<td>45</td>
<td>43</td>
<td>70</td>
</tr>
<tr>
<td>Rodwell</td>
<td>63</td>
<td>55</td>
<td>46</td>
<td>71</td>
</tr>
<tr>
<td>Spector</td>
<td>31</td>
<td>90</td>
<td>67</td>
<td>68</td>
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<tr>
<td><strong>CBC 12-24hr</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manroe</td>
<td>100</td>
<td>50</td>
<td>56</td>
<td>100</td>
</tr>
<tr>
<td>Rodwell</td>
<td>100</td>
<td>73</td>
<td>73</td>
<td>100</td>
</tr>
<tr>
<td>Spector</td>
<td>53</td>
<td>83</td>
<td>67</td>
<td>73</td>
</tr>
</tbody>
</table>
# Other serum markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Sepsis</th>
<th>Possible infection</th>
<th>Health</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD11b  (RFU)</td>
<td>288</td>
<td>138</td>
<td>112</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-8   (pg/ml)</td>
<td>94</td>
<td>24</td>
<td>17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP    (mg/L)</td>
<td>48</td>
<td>11</td>
<td>6</td>
<td>0.002</td>
</tr>
</tbody>
</table>
The preferred site: peripheral vein

The theoretical minimal amount of blood needed for detecting bacteremia: 0.5-1 ml

Bacterial growth is evidence in most blood cultures in 48 hrs

Blood, CSF and urine culture before initiating antibiotic therapy

Blood, urine, CSF for detection of bacterial antigens by immuno-electrophoresis, latex particle agglutination

- False positive: perineal contamination
- False negative: occult infection, partial treatment by intrapartum antibiotic therapy
Platelet

- Severe thrombocytopenia < 50,000 cells/mL, within 72 hrs of birth: perinatal asphyxia or early bacterial infection
- Late-onset thrombocytopenia: bacterial sepsis or NEC
- Platelets fall rapidly, with a nadir at 24 to 48 hours, tend to persist until the infection is controlled
- Slow recovery of platelet counts over a period of 1 to 2 weeks is common
• **elevated in 50-90% of septic infants**
  - usually rises within 24 hrs of infection, peaks within 2-3 days, and remains elevated until the inflammation is resolved
  - *It's not a sole indicator of neonatal sepsis, but used as part of a sepsis workup or serial study*
• **CXR**
  
  - Obtain in infants with respiratory symptoms
  - Difficult to distinguish GBS or *Listeria* pneumonia from uncomplicated RDS

• Renal ultrasound and/or VCUG in infants with accompanying UTI
**GBS** vs. **RDS**

**GBS**
- Non homogeneous pulmonary opacities, may have pleural fluid, lung volume is usually normal.

**RDS**
- Uniform distribution of pulmonary opacities, never has pleural effusions, has a decreased lung volume.
Epidemiology

- The risk of infection
  - <2500gm: 7-8x than >2500gm

- Death from sepsis
  - >2500gm: 0%
  - <2500gm: 11%
Route of infection

• Incidence of clinical sepsis in PROM
  - < 23 hours 2%
  - 24-47 hours 7%
  - 48-71 hours 11%

• Chorioamnionitis associated with sepsis
  - > 2500gm 4%
  - < 2500gm 16%
Group B Beta-Hemolytic Streptococcal infection

- Maternal intrapartum colonization: major risk for early-onset disease
  - Vertical transmission: occurs after the onset of labor or rupture of membranes.
- Intrauterine infection of fetus: ascending spread of GBS from colonized vagina, fetal aspiration of infected amniotic fluid
- Infants: during passage through the birth canal
- The most important risk factors of GBS early-onset disease:
  - Colonization
  - GA < 37 wks
  - PROM ≥ 18 hrs
  - Chorioamnionitis (intrapartum fever ≥ 38.0°C)
  - Young maternal age, black race, Hispanic ethnicity, and low maternal levels of anticapsular antibody.
Group B Beta-Hemolytic Streptococcal infection

- **Early-onset form:** serotype Ia, II, III, V
  - High incidence of maternal complications
  - Rapid progression
  - Pneumonia, sepsis

- **Late-onset form:** serotype III
  - Insidious onset, lack of maternal complications
  - Meningitis is higher
  - Most: 2~4 weeks of age (up to 12 weeks)
  - The mode of acquisition of B III: horizontal transmission

- Resistance among group B streptococci has been limited to certain agents, such as macrolides and clindamycin, but **not to penicillin**
Infection Rate

- GBS infection (0.6/1000)
  - Maternal colonization rate 35%
  - Vertical transmission 50-70%
  - Neonatal colonization rates 8-25%

- Type III strains of GBS, the most common pathogen, adhere better to vaginal and neonatal buccal epithelial cell

- Protective conc. of Ab to GBS type III
  - 73% of women whose NB infants were well
  - 17% of women whose neonates developed sepsis or meningitis
Diagnosis

- **Urine GBS**
  - absence of antigen does not rule out infection
- **Blood culture**
  - 96% of NB B/C were positive by 48 hrs
  - 98% of NB B/C were positive by 72 hrs
  - Antibiotic can be discontinued if the CBC and clinical S/S are unremarkable
- An infant with meningitis may present with normal CSF cytology and chemistries, particularly early in the evolution of meningitis
GBS Prophylaxis

- 10-30% of women are colonized in the vaginal and rectal areas
- Most mothers are screened at 35-37 weeks gestation
Management of the infant whose mother has received GBS chemoprophylaxis
Ill-appearing

- CBC/DC
- B/C
- Lumbar puncture
- Empiric antibiotic: ampicillin + gentamicin until laboratory culture results
- CXR: if respiratory symptoms are present
Healthy-appearing <35 weeks gestation

- IAP with penicillin, ampicillin, or cefazolin was administered to the mother at least 4 hours prior to delivery
  
- CBC/DC and blood culture without antibiotic treatment
  Observation for at least 48 hours
• IAP with penicillin, ampicillin, or cefazolin was administered to the mother < 4 hours prior to delivery

É Antibiotic treatment

• Infant delivered by Caesarean section

È CBC/DC and blood culture without antibiotic treatment
Healthy-appearing >35 weeks gestation

- IAP with penicillin, ampicillin, or cefazolin was administered to the mother at least 4 hours prior to delivery
- Observation in hospital for at least 48 hours.
• IAP with penicillin, ampicillin, or cefazolin was administered to the mother < 4 hours prior to delivery

 CBC/DC and blood culture **without** antibiotic treatment
 Observation for at least 48 hours
NEJM 2000;342
The Future

- GBS type III polysaccharide conjugate vaccine
Staphylococcal infection

• In the mid-1950s, phage group I S. aureus was the most common bacterial agent causing serious bacterial disease in newborn infants "decreased colonization and disease rate.

• Clinical: mastitis, furunculosis, suppurative arthritis, osteomyelitis, septicemia, and meningitis, omphalitis, otitis externa.

• bullous impetigo, toxic epidermal necrolysis (i.e., Ritter disease), and nonstreptococcal scarlatina

  - Ritter disease/Staphylococcal scalded skin syndrome (4S): painful erythema; bullae formation; desquamation of large epidermal sheets occurs approximately 3 to 5 days after onset of the disease. Fine desquamation is observed commonly in the perioral region.
Staphylococcal infection

- premature infants at the risk:
  - poorly developed host defense mechanisms
  - presence of central venous, UGI tract, endotracheal catheters
  - procedures causing interruption in skin integrity
  - prolonged TPN
  - steroids

- By the 3rd d/o, S. aureus and coagulase(-) staphylococci colonize the nasopharyngeal compartment of nearly all premature BBW < 1750 g
Staphylococcal infection

- 1980s, MRSA emerged as a nosocomial pathogen
  - MRSA bacteremia were reported to be less likely to have bone or joint infection
- Late 1990s, community-acquired MRSA: more frequently with skin & soft tissue inf
- Coagulase(+) staphylococcal disease (phage gr. II):
  - Most common organism associated with late-onset sepsis
  - Significant: grow in aerobic and anaerobic blood culture bottles, when growth occurs within 72 hours, or when isolated from two or more sites or from the same site at different times.
- Staphylococcus epidermidis: late-onset
Staphylococcal infection

- Infected patients usually are not very ill and respond well to antimicrobial therapy.

- Frequently the central venous catheters must be removed to prevent further seeding of the bloodstream.
Escherichia coli infection

- Most common gram(-) bacteria that cause septicemia in neonates.
- 40 percent of E. coli strains causing septicemia possess K1 capsular antigen.
- In early-onset sepsis, E. coli isolates have shown an increase in resistance to ampicillin (>80%), women with ampicillin-resistant E. coli infections were more likely to have received intrapartum ampicillin than were those with susceptible strains.
**Klebsiella pneumoniae Infection**

- Major pathogen responsible for neonatal sepsis in many developing countries.
- Inc: 4.1~ 6.3/1000 live births, fatality rate 16~68%
- Early-onset disease
- Through normal flora in GI and vaginal sites, isolation of resistant strains is more likely related to hospital acquisition in heavily contaminated environmental reservoirs
Listeria monocytogenes infection

- The most common foci: lung and gut
- Transmission:
  - from mothers with occult sepsis developing and resulting in chorioamnionitis (transplacental, blood-borne route)
  - from mothers carrying *Listeria* in the gastrointestinal or perianal regions that contaminates the skin and respiratory tract of their babies during birth (aspiration).
- “Early-onset” listeriosis: serotypes Ia, Ib, IVb
  - abortion, stillbirth, or premature delivery of a severely infected infant
  - pustular skin lesions (granulomatosis infantisepticum) and granulomatous hepatitis
  - Mortality rate: ~20%
  - hypothermia, lethargic, poor feeding, rash (small, salmon-colored papules scattered primarily on the trunk)
  - Premature infants with early passage meconium
  - CXR: parenchymal infiltrates suggest aspiration pneumonitis
Listeria monocytogenes infection

- “Late-onset” listeriosis: serotype IVb
  - During 2nd~8th wks of life
  - Involves the meninges in almost all cases

- The bacteriology laboratory should be forewarned of the clinical suspicion of listerial meningitis because these microorganisms frequently are discarded as contaminants because of their tinctorial and morphologic similarities with diphtheroids

- The peripheral WBC count usually shows leukocytosis with a predominance of polymorphonuclear leukocytes. A significant elevation in the number of monocytes to 7 to 21 percent of the total WBC count.
Pseudomonas aeruginosa infection

- Characteristic violaceous papular lesions, in which central necrosis developed several days (ecthyma gangrenosum), noma (gangrenous lesions of nose, lips and mouth)
- Suppurative vasculitis, and deep-seated abscess formation
- Treated with broad-spectrum antimicrobial agents, environment potentially contaminated by “water bugs” (respirators, moist oxygen)
- Usually late-onset
Treatments for Neonatal Sepsis

It is of vital importance that treatment is initiated as soon as sepsis is suspected, especially for those infants at risk.

Broad Spectrum Antibiotics (Ampicillin & Gentamicin) are the first line of defense against neonatal sepsis [2].

Why????

What are other recommendations/options?
Why is it so important to start antibiotic treatment?

If not treated as soon as sepsis is suspected a neonate is more likely to die from sepsis and it’s complications.

For this reason it is of vital importance that healthcare workers (nurses and physicians) notice and act upon even the most subtle changes in a neonate's assessment, particularly those infants at risk (GBS+).
Management

• Antibiotics
  
  • Primary sepsis: ampicillin + gentamicin
    • Ampicillin: against GBS, Listeria, Proteus, most enterococci, and 15~30% of current E. coli strains
    • Aminoglycosides: against many Enterobacteriaceae, including most E. coli, Klebsiella-Enterobacter, and Proteus strains, and P. aeruginosa. Amikacin or cefotaxime, ceftazidime if resistant
  
  • Nosocomial sepsis: vancomycin + gentamicin or cefotaxime
  
  • Change based on culture sensitivities
  
  • Don’t forget to check levels
Antibiotics treatment

- Ampicillin + amikacin + clindamycin for suspected NEC
- Vancomycin + an aminoglycoside or cefotaxime for central vascular lines
- Nafcillin + an aminoglycoside for skin inf
- Avoiding empiric vancomycin therapy seems to be a reasonable approach for treating late-onset sepsis because coagulase(-) staphylococci are common contaminants of blood cultures and are associated with a very low frequency of fulminant infection.
Treatment

- Ampicillin alone: for enterococcal and Listeria
- Ampicillin or penicillin: for GBS † combination of ampicillin and an aminoglycoside for the first 3 to 5 days, followed by ampicillin for the balance of 7 to 10 days.
- S. epidermidis infection: vancomycin
- Add rifampin to vancomycin therapy: for persistent coagulase(-) staphylococci bacteremia
Treatment

- Gram(-) enteric susceptible to ampicillin and aminoglycosides: prefer treat with both drugs for at least a portion of the treatment period.
- For Pseudomonas infections, combined therapy with ticarcillin, piperacillin, or ceftazidime and an aminoglycoside should be used for the duration of therapy.
Treatments

- For infants who fail antimicrobial therapy or have superficial cultures positive for Candida albicans, empiric use of amphotericin/fluconazole should be considered.
- Ceftazidime and cefotaxime should not be used routinely in neonatal units because of the potential for emergence of resistant Enterobacter and Serratia spp.
Treatment

• Septic premature infant who prolong hospitalization, previous antibiotic therapy, possible prolong tracheal intubation, placement of a central or peripheral intravascular catheter

  Major pathogens: coagulase-negative and coagulase-positive staphylococci (including MRSA), aminoglycoside-resistant coliforms, highly resistant opportunistic organisms (e.g., Pseudomonas, Serratia), fungi, and possibly enterococci.
Treatment

- Duration: 7~10 days
- Delayed clinical improvement or persistently positive blood cultures during therapy: inappropriate antibiotics or occult sites of infection (e.g., endocarditis, abscesses, infected foreign bodies).
- For infants whose initial bacterial cultures are sterile after 48 to 72 hours of incubation, a negative CRP at 72 hours ends discontinued A/B
Supportive therapy

- Respiratory
  - $O_2$ and ventilation as necessary

- Cardiovascular
  - Support BP with volume expanders and/or pressors

- Hematologic
  - Treat DIC with FFP and/or cryo

- CNS
  - Treat seizures with phenobarbital
  - Watch for signs of SIADH (decreased UOP, hyponatremia) and treat with fluid restriction

- Metabolic
  - Treat hypo/hyperglycemia and metabolic acidosis
Immunotherapy

- Granulocyte transfusion
  - neutrophil depletion
- IVIG
  - provide type-specific antibodies, but of transient effect
- Recombinant human cytokine administration
  - GM-CSF, G-CSF stimulate granulocyte progenitor cells
Immunotherapy

- rhGM-CSF (5 μg/kg/day) sc. for 7 days
  - Increase in ANC, eosinophil, monocytes, lymphocytes, and platelet count
  - Decreased mortality in critically ill septic neutropenic neonate

- Pediatrics Jan 2001 36-41
Immunotherapy

• rG-CSF (10μg/kg/day) iv. for 3 days
  • Did not improve mortality in critically ill septic neutropenic neonate
  • Associated with acquiring fewer nosocomial infections over the subsequent 2 weeks

• Pediatrics Jan 2001 30-35
Others

- Intravenous nutrition
- NG feeding
- Encourage breast milk (provide immunologic protection)
- Encourage parental contact to ease the stress
Gram(-) bacilli inf in NICU

- Several NICU outbreaks caused by Enterobacter, Klebsiella, and Serratia recently

- Dose prevention of early-onset GBS infection by prophylactic intrapartum antibiotics increase the incidence of GNB neonatal sepsis?

A:

Early –onset neonatal sepsis:
Gram-negative organisms were the most frequent cause between 1998-2000

Late onset neonatal sepsis:
Coagulase-negative Staphylococcus
• GNB infections are becoming more resistant to commonly used parenteral antibiotics!!
• Maternal antibiotics exposure during labor may be shifting the susceptibility pattern of Gram-negative bacilli infecting the offspring.
• Molecular method analyze bacterial DNA
-
The outbreak clone has been identified from numerous environmental sources, including rectal thermometers, incubator doors, pulse oxymeter probes, re-used suction catheters, handwashing disinfectants, cockroaches, nutritional source (parenteral nutrition solutions and formula)
- ESR, CRP, haptoglobin, prealbumin, transferrin, fibronectin, interleukin-6

- Procalcitonin:
  - A sensitive and specific marker of bacterial infection
  - Viral infection, bacterial colonization, and sterile inflammatory stress: normal or slightly raised concentrations
  - Respiratory distress syndrome, acute lung and inhalation injuries, hemodynamic failure, and severe trauma: very high serum concentrations
  - Cut off values: a concentration of 2 ng/mL - reliable in distinguishing between viral and bacterial infection
Treatment (1)

- The choice of antibiotics:
  - the infectious history of the nursery,
  - the antimicrobial susceptibilities of bacteria
  - the probable etiologic agent,
  - CSF penetration of antibiotics,
  - the infant's hepatic and renal function.

- Factors that determine the probable infecting organism:
  - patient age and birth weight;
  - environment (home versus hospital);
  - previous antibiotic therapy;
  - perinatal or nosocomial exposure to pathogens (e.g., MRSA);
  - presence of central lines, drains, or endotracheal tube;
  - identification of specific infections, such as meningitis, necrotizing enterocolitis, peritonitis, thrombophlebitis, pneumonia, and soft tissue infections.
# Treatment

**TABLE 78-5**  -- Recommended Empiric Antimicrobial Treatment of Several Neonatal Bacterial Infections on the Basis of Probable Etiologic Microorganisms

<table>
<thead>
<tr>
<th>Bacterial Infection</th>
<th>Recommendation</th>
<th>Alternatives</th>
<th>Observations</th>
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<tbody>
<tr>
<td>Sepsis</td>
<td>AMPI + GENTA</td>
<td>AMPI + CEFO</td>
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</tr>
<tr>
<td>Early onset (&lt;5 days)</td>
<td>AMPI + GENTA</td>
<td>AMPI + CEFO</td>
<td>Readmission of the neonate at term</td>
</tr>
<tr>
<td>Late onset</td>
<td>AMPI + GENTA</td>
<td>AMPI + CEFO</td>
<td></td>
</tr>
<tr>
<td>Nosocomial</td>
<td>VAN ± OXA/NAF + GENTA or AMIK</td>
<td>VAN + CEFTA</td>
<td>Consider AMPHO</td>
</tr>
<tr>
<td>Meningitis</td>
<td>AMPI + CEFO</td>
<td>AMPI + GENTA</td>
<td></td>
</tr>
<tr>
<td>Otitis media</td>
<td>AMOX/CLAV</td>
<td>CEFUROXIME</td>
<td>Given orally unless systemic signs present</td>
</tr>
<tr>
<td>Urinary infection</td>
<td>AMPI + GENTA</td>
<td>AMPI + CEFO</td>
<td></td>
</tr>
<tr>
<td>Osteoarticular infection</td>
<td>VAN ± OXA/NAF + CEFO</td>
<td>VAN + CEFO</td>
<td>Consider AMPHO</td>
</tr>
<tr>
<td>Cellulitis/fasciitis/funisitis/omphalitis</td>
<td>VAN ± OXA/NAF or CLIN + GENTA or AMIK</td>
<td>VAN + CEFTA</td>
<td>Surgery</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>AMPI + GENTA</td>
<td>AMPI + CEFO</td>
<td></td>
</tr>
<tr>
<td>Early onset (&lt;5 days)</td>
<td>AMPI + GENTA</td>
<td>AMPI + CEFO</td>
<td></td>
</tr>
<tr>
<td>Nosocomial</td>
<td>VAN ± OXA/NAF + GENTA or AMIK</td>
<td>VAN + CEFTA</td>
<td>Consider macrolide</td>
</tr>
</tbody>
</table>
• **Infusion of intravenous immunoglobulin**: Potential therapeutic benefits include enhanced chemotaxis and opsonophagocytosis and improved bactericidal activity.

• The efficacy of **granulocyte transfusions** in reducing mortality from severe neonatal sepsis.
  - Only benefit for infants with granulocyte-depleted storage pools.
  - Bone marrow aspiration is required

• The use of recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF):()