Neonatal Infection and Antibiotic Use, 2019

Michael Speer, MD
Professor of Pediatrics & Medical Ethics
Baylor College of Medicine
Disclosures: Michael E. Speer, MD

• I have no relevant financial relationships to disclose or conflicts of interest to resolve.

• I will not discuss any unapproved or off-label, experimental or investigational use of a product, drug or device.
Necrotizing Enterocolitis

Pneumatosis intestinalis

Resected portion of necrotic bowel
Incidence of Septicemia & Meningitis
USA

- Septicemia: 0.3-0.5/1000 live births
- Meningitis: 0.3/1000 live births

- 1000 – 1500 grams: 10%
- < 1000 grams: 35%
- < 500 grams: 40 - 50%

http://pediatrics.aappublications.org/content/110/2/285.full
Incidence of Neonatal Meningitis

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4332563/
### Incidence of Infection: VLBW

<table>
<thead>
<tr>
<th>Category</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>Early Onset (&lt;72 h)</td>
<td>1.5% to 2%</td>
</tr>
<tr>
<td>22-28 weeks’ gestation</td>
<td>2.05 to 2.44%</td>
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<tr>
<td>Late Onset</td>
<td>21%</td>
</tr>
<tr>
<td>&lt; 25 weeks’ GA</td>
<td>45%</td>
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<tr>
<td>&lt; 1500 grams BW</td>
<td>20% with ≥2 sepsis</td>
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http://pediatrics.aappublications.org/content/110/2/285.short
Mortality

- Overall – Variable Depending Upon the Organism
  
  - Average Gram Negative = 36%
    - Pseudomonas, 74%; E. coli, 34%
  
  - Average Gram Positive = 11.2%
    - CONS, 9.1%; GBS, 21.9%; Staph a., 17.2%

- Day of Life 1 – Up to 50%

- 50% of neonatal deaths after 2 weeks of life
Mortality

- Evidence of viral, fungal or bacterial infection present at autopsy frequently

- ELBW: 61% of infections diagnosed at autopsy, not diagnosed prior to death
  - Histologic diagnoses
Routes of Acquisition

- Prepartum – Maternal Infection
- Intrapartum – Maternal Vaginal Flora
- Postpartum – Hospital Acquired (Nosocomial)
Prepartum

- Salmonella species
- *Mycobacterium tuberculosis*
- *Listeria monocytogenes*
- *Streptococcus pneumoniae*
- *Neisseria meningitidis*
- *Staphylococcus aureus*
- *Escherichia coli*
Intrapartum

- Streptococcal species – Group B, Gamma hemolytic, Group A
- *Escherichia coli*
- *Listeria monocytogenes*
- *Streptococcus pneumoniae*
- *Neisseria gonorrhoeae*
- *Heamophilus influenzae*
Post Partum – HAC (Nosocomial)

- *Staphylococcus aureus*
- Coagulase Negative Staphylococcus
- Pseudomonas species
- Enterobacter species
- Klebsiella species
- *Escherichia coli*
- Salmonella species
- Candida sp.
Host Defenses of the Neonate

- ↓ Humoral antibodies: IgG, IgM, IgA
- ↓ Polymorphonuclear phagocytes
- ↓ Phagocytosis
- ↓ White cell killing
- ↓ Complement, opsonins, lysozymes
- ↓ Specific enzyme production
Postnatal IgG Levels

Systemic Inflammatory Response

- **Bacterial infection**
- **Pro-Inflammatory Cytokines**
  - TNF, IL-1 (α,β), IL-6, IL-8, IL-12, IFN-γ
  - ?Uncontrolled Inflammation
- **Anti-Inflammatory Cytokines**
  - IL-10, IL-4, IL-13
  - IL-1RA, IL-1RII
- **Immune Balance**
- **Cytokine Gene Polymorphisms**
- ?Immunosuppressive State
Bacteria & the Innate Immune System

1. Subversion of detection & modification of inflammation: Adenosine monophosphate to adenosine, an immunosuppressant to leukocyte receptors
2. Inhibition of phagocytosis
3. Resistance to intracellular killing
4. Resistance to or escape from innate effectors
Bactericidal vs. Bacteriostatic Antibiotics

Bactericidal antibiotics kill bacteria; bacteriostatic antibiotics slow their growth or reproduction.

**Bactericidal**
- Inhibit cell wall synthesis & cell membrane function,
- DNA fragmentation, and
- Protein synthesis inhibitors

**Bacteriostatic**
- Interfere with bacterial protein production, DNA replication, or other aspects of bacterial cellular metabolism
# Bactericidal vs. Bacteriostatic Antibiotics

<table>
<thead>
<tr>
<th>Bactericidal</th>
<th>Bacteriostatic</th>
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<tbody>
<tr>
<td><strong>Beta-lactam antibiotics</strong></td>
<td><strong>Tetracyclines</strong></td>
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<tr>
<td>Penicillin derivatives, Cephalosporins, Carbapenems, Vancomycin,</td>
<td>Sulfonamides</td>
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<tr>
<td><strong>Aminoglycosides</strong></td>
<td>Spectinomycin</td>
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<tr>
<td>Kanamycin, Gentamicin, Amikacin, Tobramycin</td>
<td>Trimethoprim</td>
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<tr>
<td><strong>Fluoroquinolones</strong></td>
<td>Chloramphenicol</td>
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<td>Macrolides</td>
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<td>Clindamycin</td>
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Pharmacokinetics/Pharmacodynamics

- Pharmacokinetics: Time course of antimicrobial concentrations
- Pharmacodynamics: Relationship between antibiotic concentrations and effect.
Bacterial Killing

- Time dependent or concentration dependent
  - Concentration dependent killing antibiotics
    - Aminoglycosides, fluoroquinolones
    - Maximize concentration
  - Time dependent killing antibiotics
    - Penicillin, cephalosporins
    - Maximize duration of exposure
  - Time dependent with moderate persistent killing
    - Vacomycin, azithromycin
    - Maximize amount of drug received
Treatment: Antibiotics

- Early Onset Infection
  - Ampicillin
  - Gentamicin

- Late Onset Infection (>72 hours)
  - Vancomycin
  - Gentamicin

  • If Gram negative meningitis suspected add cephalosporin
Gentamicin

- Serum Levels:
  - If renal function normal, and treatment anticipated to ≤ 48 h, no levels needed
    - If gentamicin given > 2 doses, trough and peak levels at 3rd dose
Gentamicin

- Serum levels
  - Peak: 5-10 mcg/mL
  - Trough: < 1.5 mcg/mL

- For Synergy: e.g. staphylococcal or enterococcal infections
  - All ages: 1-1.5 mg/kg/dose q 24 h
Vancomycin

- Serum levels
  - Peak: 20-40 mcg/mL
  - Trough: 10-20 mcg/mL

- Vancomycin is **not** usually nephrotoxic;

- If trough levels less than optimal either interval or dose needs to be adjusted to achieve higher levels
Cephalosporins & broad spectrum antibiotics

- Use of broad spectrum antibiotics (third generation cephalosporins) and others associated with:
  - Rapid occurrence of bacterial resistance
  - Increase risk of fungal infection

- Limit usage to patients with gram negative meningitis

Infection Prevention

- Hand washing
- Care bundles to prevent CLABSI & VAP
- Cohorting
- Avoid Crowding
- Avoid Overuse of Antibiotics
- Prevention of Prematurity
Handwashing/Hand Hygiene

- Most effective methods to reduce transmission
  - Alcohol based vs. soap/water
  - If hands visibly soiled, soap + scrub
Central Line Care Bundles

- The whole is better than its parts
  - Equipment
  - Pre-insertion
  - Maintenance

- Line maintenance should be performed with aseptic technique and a conducive environment

Diagnosis of Central Line Non-Pathogen Infections

• Red Book Criteria suggesting infection
  - Peripheral blood culture & central line: 2 cultures with at least 1 mL of blood obtained
  - Growth of the same organism in each culture (similar or identical genotypes among all isolates)
  - Growth within 15 hours
  - Intravascular catheter in place for ≥3 days
Cohortting

- The principle of confining an infant to a location within a nursery until discharged from hospital or moved to another nursery
Overuse of Antibiotics

- Use narrow spectrum antibiotics
- Treat only for clear symptoms
- If culture (-) and ongoing symptoms not compatible with infection: Stop Antibiotics
  - i.e., use $\leq$ 48 hours