




Neonatal Infection and Antibiotic Use, 2019

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Disclosures: Michael E. Speer, MD

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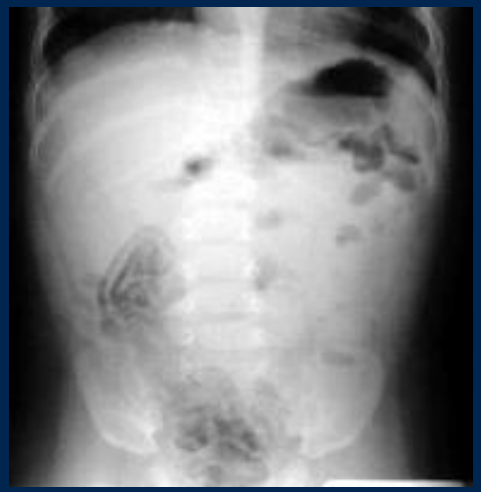
Necrotizing Enterocolitis



Pneumatosis intestinalis

Resected portion of necrotic bowel.

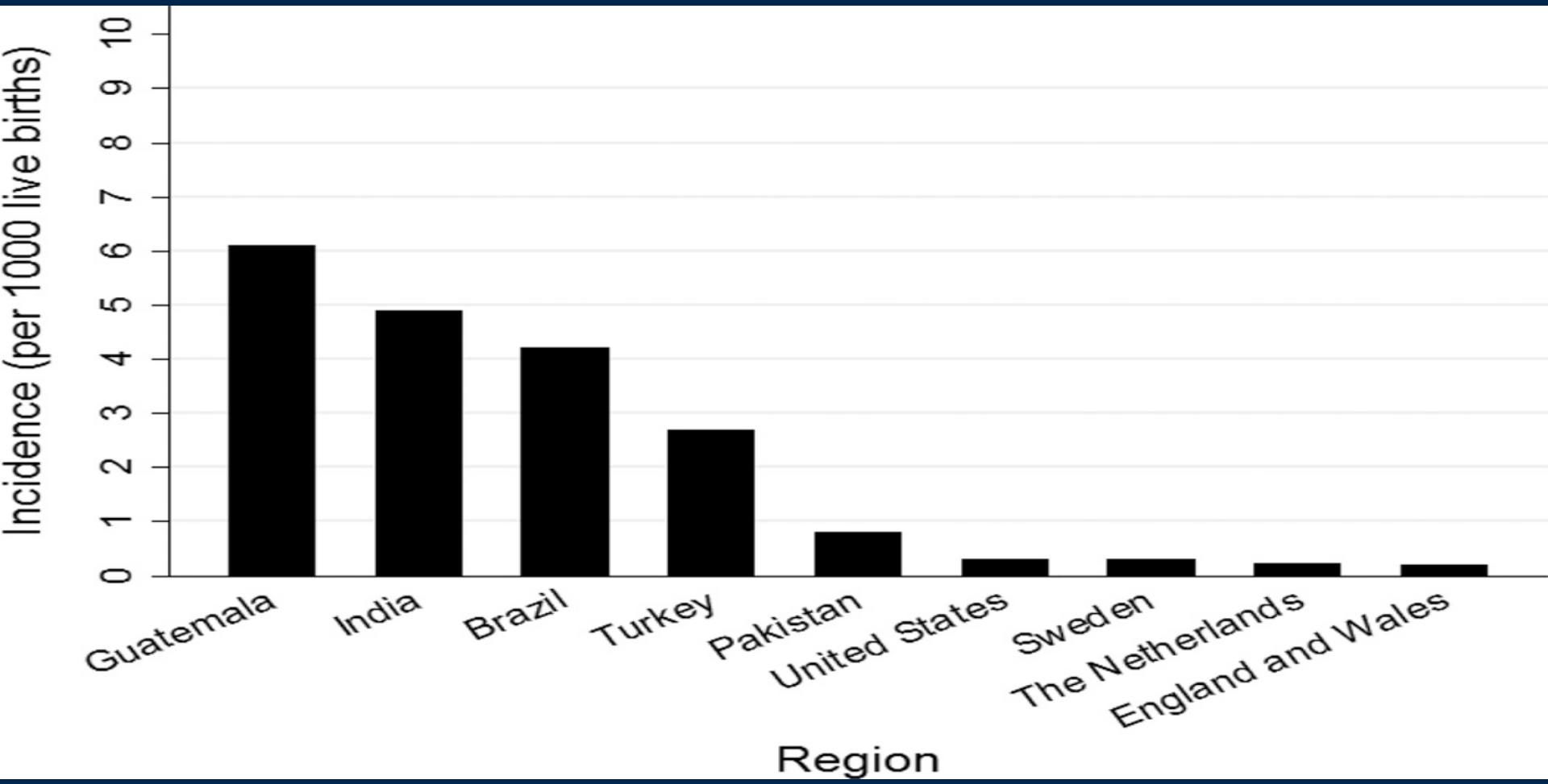
Incidence of Septicemia & Meningitis USA

- 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

Early Onset (<72 h)	1.5% to 2%
22-28 weeks' gestation	2.05 to 2.44 %
Late Onset	21%
• < 25 weeks' GA	45%
• <1500 grams BW	20% with ≥2 sepsis

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)

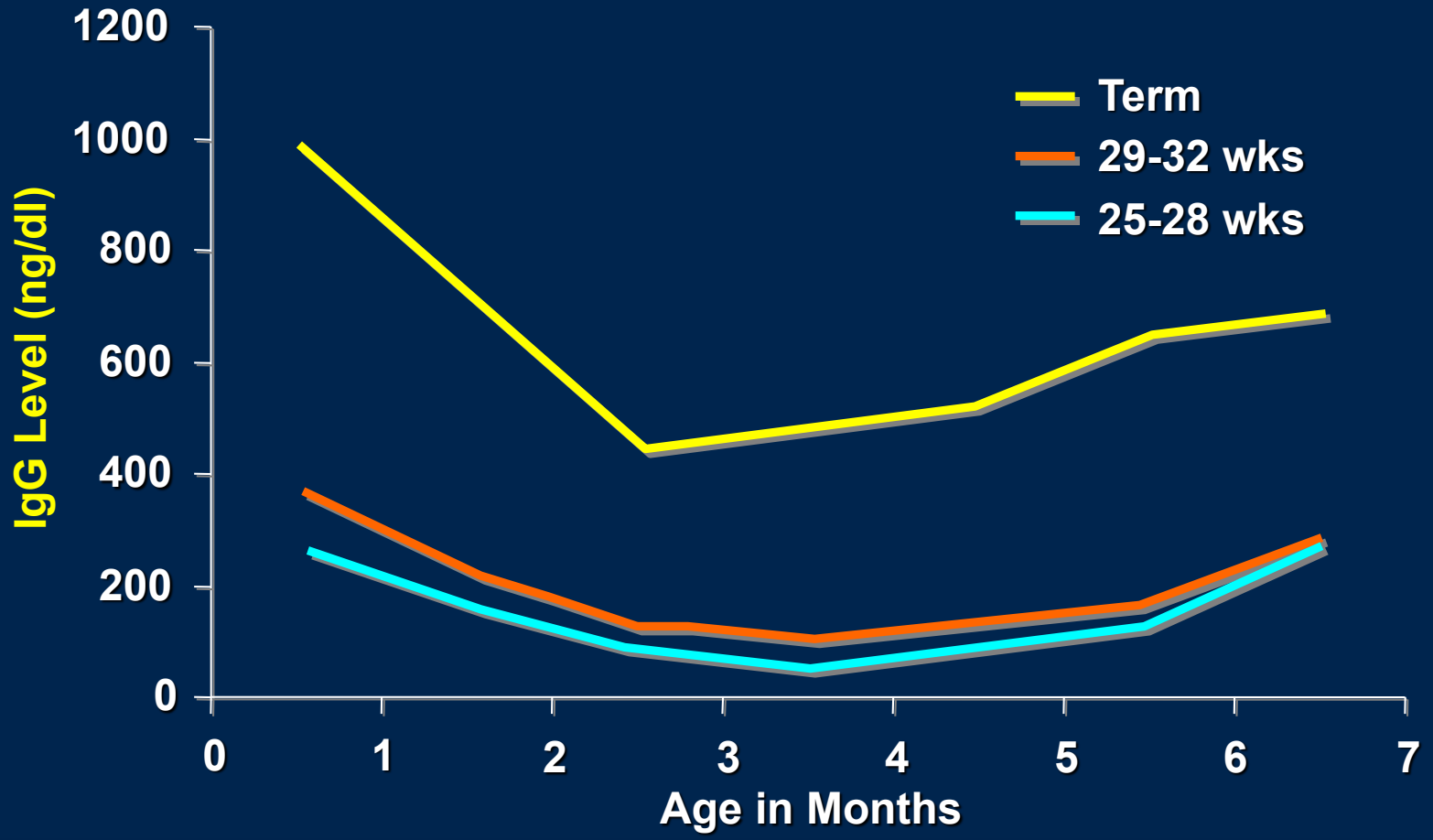
- *Staphylococcus aureus*
- Coagulase Negative Staphylococcus
- Pseudomonas species
- Enterobacter species
- Klebsiella species
- *Escherichia coli*
- Salmonella species
- Candida sp.

Host Defenses of the Neonate

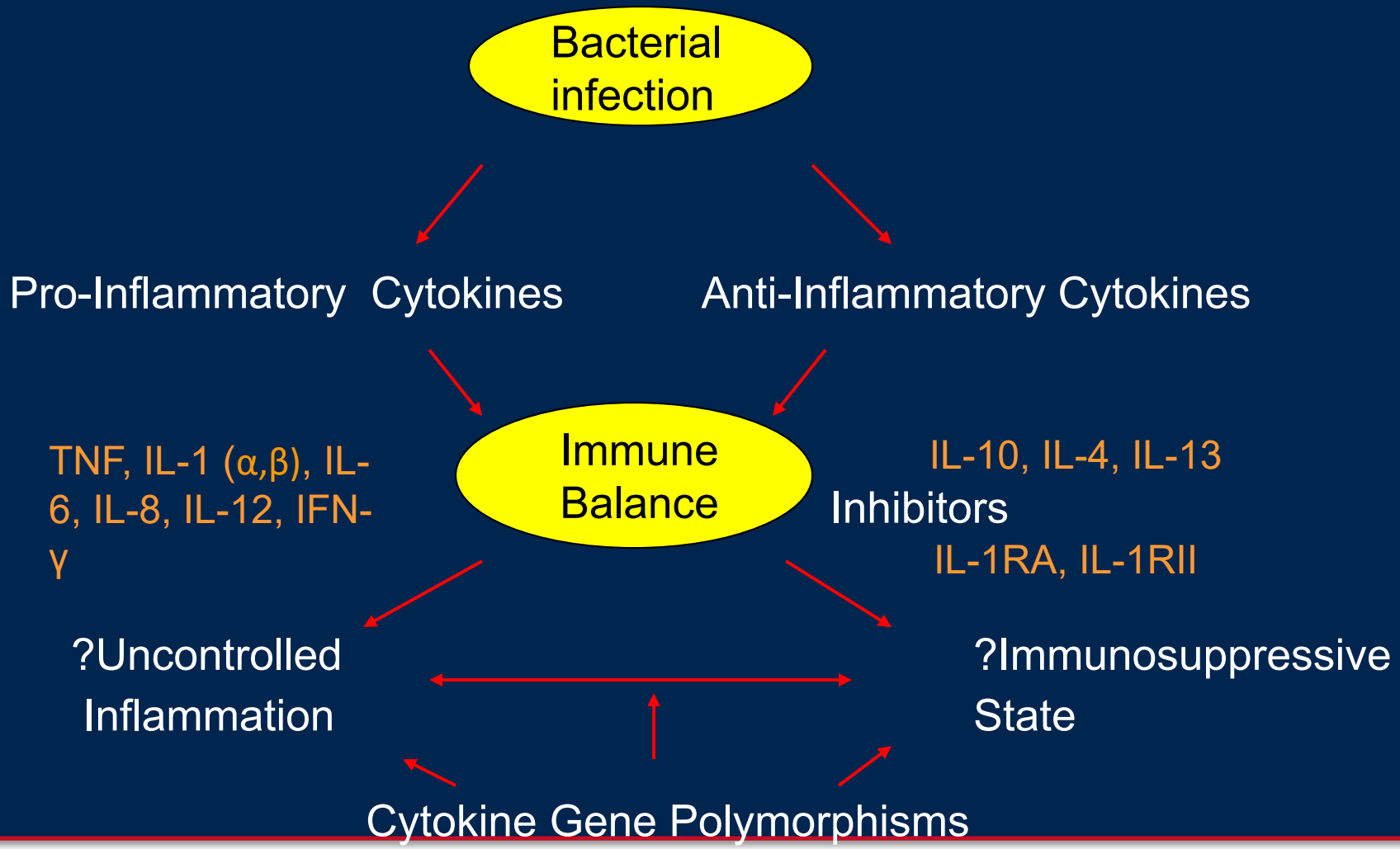
- ↓ Humoral antibodies: IgG, IgM, IgA
- ↓ Polymorphonuclear phagocytes
- ↓ Phagocytosis
- ↓ White cell killing
- ↓ Complement, opsonins, lysozymes
- ↓ Specific enzyme production

Postnatal IgG Levels

Ballow M, Cates KL, Rowe JC, et al. *Pediatr Res*. 1986;20(9):899-904.



Systemic Inflammatory Response



Bacteria & the Innate Immune System

1. Subversion of detection & modification of inflammation: Adenosine monophosphate to adenosine, an immunosupressant 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

Bateriostatic

- Interfere with bacterial protein production, DNA replication, or other aspects of bacterial cellular metabolism

Bactericidal vs. Bacteriostatic Antibiotics

Bactericidal

Beta-lactam antibiotics

Penicillin derivatives, Cephalosporins, Carbapenems, Vancomycin,

Aminoglycosides

Kanamycin, Gentamicin, Amikacin, Tobramycin

Fluoroquinolones

Bacteriostatic

Tetracyclines

Sulfonamides

Spectinomycin

Trimethoprim

Chloramphenicol

Macrolides

Clindamycin

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 specrum antibiotics (third generation cephalosporins) and others associated with:
  - Rapid occurrence of bacterial resistance
  - Increase risk of fungal infection
- Limit usage to patient with gram negative meningitis

*Pediatrics. 2010 Oct;126(4):e865-73; ^Pediatrics. 2009 Jan;123(1):58-66.

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

Pediatrics. 2011 Mar;127(3):436-44.

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

Cohorting

- 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 ≤ 48 hours