Chorioamnionitis, Neonatal Sepsis and Antibiotic Stewardship

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Disclosure Statements:

- I have no relevant financial relationships to disclose or conflicts of interest to resolve.
- The off-label use of any drug will be identified, discussed and strongly discouraged.

What are we trying to fix?

- Do all infants born to mothers’ with a diagnosis of chorioamnionitis need antibiotics?
- What about all mothers with GBS colonization?
- How long do we need to treat an asymptomatic infant who is culture negative?
“Current intrapartum and neonatal prevention strategies result in:
• significant levels of obstetric and neonatal antibiotic exposure
• with largely undefined impacts on healthcare utilization, maternal/infant social development
• as well as on long-term health outcomes”

Problems

• Chorioamnionitis is hard to diagnosis and the term is not consistently used
• There is no laboratory test that performs well at identifying ever infant with sepsis (no false negatives) and most test have high false positive rates which leads to prolonged therapy.
• Prolonged antibiotics are not benign and between 20-30% of infants admitted for suspected sepsis are treated for more than 3 days
• “When we administer surfactant or caffeine to infant A, there is no potential risk to infant B located in the same nursery. Antibiotics are different. Every time we provide prolonged antibiotics to 1 infant, we expose every infant in the nursery to a small increased risk of resistant infection.” (Cotten CM et al. Pediatrics 2012;130(4):e1052-e1053)

In January 2015, the Eunice Kennedy Shriver National Institute of Child Health and Human Development invited an expert panel to a workshop to address numerous knowledge gaps and to provide evidence-based guidelines for the diagnosis and management of pregnant women with what had been commonly called chorioamnionitis and the neonates born to these women.

The panel noted that the term chorioamnionitis has been used to label a heterogeneous array of conditions characterized by infection and inflammation or both with a consequent great variation in clinical practice for mothers and their newborns. Therefore, the panel proposed to replace the term chorioamnionitis with a more general, descriptive term: “Intraterine inflammation or infection or both,” abbreviated as “Triple I.”
Prevention of Early-onset GBS Disease

**Intrapartum antibiotics (IAP)**
- Highly effective at preventing early-onset disease in women at risk of transmitting GBS to their newborns
- Efficacy in clinical trials: 100%
- Effectiveness in observational studies: 86-89%

**Challenge: How best to identify women who should receive IAP?**

http://www.cdc.gov/groupbstrep/guidelines/guidelines.html

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Key Prevention Strategies Remain Unchanged in 2010

http://www.cdc.gov/groupbstrep/guidelines/guidelines.html

- Universal screening of pregnant women for GBS at 35-37 weeks gestational age
- **Intrapartum antibiotic prophylaxis for:**
  - Positive screening test
  - Colonization status unknown with
    - Delivery <37 weeks
    - Temperature during labor >100.4°F (≥38.0°C)
    - Rupture of membranes >18 hours
  - Previous infant with GBS disease
  - GBS in the mother's urine during current pregnancy
- Penicillin preferred drug for IAP
  - Ampicillin acceptable alternative
  - Cefazolin preferred for penicillin-allergic at low risk of anaphylaxis

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- Most recent recommendation from North America are for universal culture based screening
- UK uses a risk-based approach.
- Neither will prevent all cases of EOGBS and factors such as the practicalities and cost-effectiveness need to be considered.
- Screening has to be carried out at the right time (35–37 weeks) with the correct technique (vaginal and anorectal swab), reach the laboratory where selective media and enrichment broth are required, and the results need to be available and acted upon.


- 10% of women with negative screening turn positive for GBS when in labour
- 50% of women with a positive screen result are negative for GBS when in labour.
- Screening approach is more expensive and exposes more women to antibiotics than the risk-based approach.


- The risk-based approach recommends that all women with one or more of the following factors be offered intrapartum antibiotic prophylaxis (IAP):
  - A previous GBS-infected baby
  - GBS bacteriuria of any count during the current pregnancy
  - Preterm (<37 weeks) labor and imminent birth
  - Intrapartum fever > 38°C
  - Membrane rupture > 18 hours


Articles that should challenge our approach to antibiotic use in the NICU

- Thomas Jefferson University, Philadelphia, Penn
- EGA>35 weeks born between November 2006 and September 2012.
- NICU patients only but “all neonates born to a mother with a clinical diagnosis of chorioamnionitis were admitted to the NICU”
- Blood culture on admission.
- Empiric antibiotic therapy - ampicillin and gentamicin.
- CBC with differential and CRP are on admission and at 12 hours of age


- Before guidance, 20.9% babies stayed >5 days, which increased to 27.7% following NICE recommendations.
- A 6.8% INCREASE FOR A COMMON PROBLEM MEANS LOTS MORE PATIENT DAYS AND ANTIBIOTIC DOSES - PROBABLY A BAD THING
- Repeat CRP measurements increased from 45% to 97%. In 58% of these babies, repeat CRPs influenced management and hospital stay.
- An increase in LPs performed from 14% to 23% was noted.
- There were no positive blood cultures or LP results.
“CONCLUSIONS:
.... repeat CRP led to further investigations, increased LPs and longer durations of treatment and stay.
This, in turn, impacted on workload and cost, and influenced parental experience in the first few days of life.”

Magnitude of the problem

- Total Patients 1997 to 2013 n=974,699
  - 633,056 (65%) were treated empirically with ampicillin on the day of birth or day 1 or 2 of life for a total of 2,162,555 days (>4 million doses)
  - 302,271 (48%) of treated infants were 36 weeks of more estimated gestational age and in these infants the duration of hospital stay is directly correlated to the duration of antibiotics
  - There were 12,181/633,056 (2%) of the ampicillin treated infants who had a positive blood culture if CONS is include.

Event Rates/All Admits

Treated with Ampicillin on Day of Birth or Day 1 or 2 after birth (Early Empiric Treatment)/All Admits
INBORN CARED FOR AT A SINGLE SITE WITHOUT ANOMALIES AND HAD A CULTURE REPORTED
RELATIVE RISK FOR ANY POSITIVE CULTURE
(n=640,147, 9303 positive culture including CONS)

Summary

- More than 95% of the patients we treat with antibiotics have negative cultures and this is true even in “high risk patients”
- We use lots of antibiotics for lots of days and lots of doses.
- With every extra day and every extra dose there is the potential for error.
- Accumulating evidence from several different sources suggest prolonged exposure to antibiotics is associated with NEC, mortality, and a higher likelihood of subsequent development of infections with resistant organisms.

Are we (NICUs) consistent with how we use antibiotics?
Antibiotic utilization rates (AUR) is the total number of patient days that infants were exposed to 1 or more antibacterial or antifungal agents administered intravenously or intramuscularly per 100 patient-days in the reporting NICU, expressed as a percentage.

Overall antibiotic use varied 40-fold, from 2.4% to 97.1% of patient-days; median = 24.5%.

At all levels of care, it was independent of proven infection, NEC, surgical volume, or mortality.

Fifty percent of intermediate level NICUs were in the highest antibiotic use quartile, yet most of these units reported infection rates of zero.

Regional NICUs in the highest antibiotic quartile reported inborn admission rate 218% higher (0.24 vs 0.11, P = .03), and length of stay 35% longer (90.2 days vs 66.9 days, P = .03) than regional NICUs in the lowest quartile.
Is there a better way to think about neonatal sepsis?


- "It is possible to combine objective maternal data with evolving objective neonatal clinical findings to define more efficient strategies for the evaluation and treatment of EOS in term and late preterm infants.
- Judicious application of our scheme could result in decreased antibiotic treatment in 80,000 to 240,000 US newborns each year”


- Probability of Neonatal Early-Onset Sepsis Based on Maternal Risk Factors and the Infant’s Clinical Presentation
- The tool is intended for the use of clinicians trained and experienced in the care of newborn infants.
- Using this tool, the risk of early-onset sepsis can be calculated in an infant born \( > \) 34 weeks gestation.
- The interactive calculator produces the probability of early onset sepsis per 1000 babies by entering values for the specified maternal risk factors along with the infant’s clinical presentation.
Summary

- More than 98% of the patients we treat with antibiotics have negative cultures and this is true even in "high risk patients."
- If we exclude CONS and other contaminants, less than 1% of infants admitted for NICU care will have a positive culture.
- We use lots of antibiotics for lots of days and lots of doses.
- With every extra day and every extra dose there is the potential for error.
- Accumulating evidence from several different sources suggest prolonged exposure to antibiotics is associated with NEC, mortality, and a higher likelihood of subsequent development of infections with resistant organisms.

What are the consequences of antimicrobial over use?
Potential Unintended Consequences of GBS Prevention Guidelines
http://www.cdc.gov/groupbstrep/guidelines/guidelines.html

- Adverse drug reactions
  - Anaphylaxis among women receiving GBS IAP very rare
  - Two studies reviewing >12,000 births found one non-fatal case
  - Four published case reports in U.S. since 1996

- Impact on non-GBS sepsis
  - Stable or decreasing rates in most studies
  - E.coli sepsis may be increasing among pre-term infants, but trends not consistent across studies

- Health services utilization for neonates
  - Studies conducted during 1996-2002 reported increased, stable, or decreased use of health services for neonates whose mothers received IAP

- No studies on the impact of the 2002 guidelines

Antimicrobial Exposure and NEC
Yale cohort replicates association reported by Cottent


AGE AT DISCHARGE BY EARLY AMPICILLIN DURATION GROUP
(NEONATES, CARED FOR AT ONE HOSPITAL, NO ANOMALIES, EGA=36 WEEKS, 2010 TO 2013)
Unfortunately, overuse and misuse of antibiotics have resulted in increasing resistance, creating the real and growing threat of new "super-bugs" that are increasingly difficult to treat.

- 30-50 percent of antibiotics prescribed in hospitals are unnecessary or inappropriate.
- **Misuse**
  - use of antibiotics when not needed,
  - continued treatment when no longer necessary, wrong dose,
  - use of broad-spectrum agents to treat very susceptible bacteria, and
  - wrong antibiotic to treat an infection.

Unlike other medications, the potential for spread of resistant organisms means that the misuse of antibiotics can adversely impact the health of patients who are not even exposed to them.

- The Centers for Disease Control and Prevention (CDC) estimates more than two million people are infected with antibiotic-resistant organisms, resulting in approximately 23,000 deaths annually.
Mechanisms of Antibiotic Resistance

Bacteria resist the effects of antibiotics by using the following genetic strategies, with thousands of variations:

• producing destructive enzymes to neutralize antibiotics;
• modifying antimicrobial targets, by mutation, so that drugs cannot recognize them;
• removing antimicrobial agents by pumping them out (efflux);
• preventing antibiotics from entering by creating a "biofilm" or otherwise reducing permeability; and
• creating bypasses that allow bacteria to function without the enzymes targeted by antibiotics.
Percentage of extended-spectrum beta-lactamase producing Escherichia coli*, by country (most recent year, 2011–2014)
Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming

What can we do to make things better?

Antibiotic Stewardship
Antimicrobial stewardship, as defined by the Infectious Diseases Society of America (IDSA), includes interventions targeted toward the improvement and monitoring of appropriate antimicrobial use by selecting the most optimal drug regimen, including the type of drug used, the dose, duration of therapy, and route of administration.
Prevention Of Antimicrobial Resistance

Prevention depends on appropriate clinical practices that should be incorporated into all routine patient care. These include:

- Optimal management of vascular and urinary catheters
- Prevention of lower respiratory tract infection in intubated patients
- Accurate diagnosis of infectious etiologies
- And judicious antimicrobial selection and utilization.

Guidance for these preventive practices include the Campaign to Reduce Antimicrobial Resistance in Healthcare Settings. This is a multifaceted, evidence-based approach with four parallel strategies:

- Infection prevention
- Accurate and prompt diagnosis and treatment
- Prudent use of antimicrobials
- And prevention of transmission.

Standard Precautions, as described in the Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings 2007, should control the spread of MRSA in most instances.

Summary of Core Elements of Hospital Antibiotic Stewardship Programs

- Leadership Commitment: Dedicating necessary human, financial and information technology resources.
- Accountability: Appointing a single leader responsible for program outcomes. Experience with successful programs show that a physician leader is effective.
- Drug Expertise: Appointing a single pharmacist leader responsible for working to improve antibiotic use.
- Action: Implementing at least one recommended action, such as system evaluation of ongoing treatment need after a set period of initial treatment (i.e. “antibiotic time out” after 48 hours).
- Tracking: Monitoring antibiotic prescribing and resistance patterns.
- Reporting: Regular reporting information on antibiotic use and resistance to doctors, nurses and relevant staff.
- Education: Educating clinicians about resistance and optimal prescribing.
Revised Neonatal Management Algorithm

- Applies to all newborns
  - Regardless of whether mother received IAP
- Management based on clinical appearance, risk factors (maternal chorioamnionitis, prolonged rupture of membranes, preterm), and adequacy of IAP if indicated for mother
- Adequate IAP clarified
  - ≥4 hours of IV penicillin, ampicillin, or cefazolin before delivery
  - All other agents or durations are considered inadequate for purposes of neonatal management
- Aims to reduce unnecessary evaluations and antibiotics in newborns at relatively low risk for early-onset GBS disease

Even with selective treatment strategies, most treated infants will not have bacterial infection.

In treated infants, serial normal diagnostic tests, such as blood counts or C-reactive protein levels, are highly predictive of the absence of infection and should be relied upon (in addition to culture results) to minimize the duration antibiotic exposure.

However, isolated abnormal hematological or acute-phase-reactant measurements should not justify continuation of empiric antibiotics for more than 48 hours in well-appearing infants with negative culture results.
Are we making progress?

Reports Of a Positive Culture >3 Days Inborn VLBW Infants


- 50% decrease in central line-associated bloodstream infections between 2008 and 2014
- No change in overall catheter-associated urinary tract infections between 2009 and 2014
- 17% decrease in surgical site infections (SSI) related to the 10 select procedures tracked in previous reports
- 8% decrease in hospital-onset Clostridium difficile (C. difficile) infections between 2011 and 2014
- 13 percent decrease in hospital-onset methicillin-resistant Staphylococcus aureus (MRSA) bacteremia (bloodstream infections) between 2011 and 2014