Therapeutic Illusions – ‘Antibiotics are Perfectly Safe’

Reese H. Clark, MD

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 is a “Therapeutic Illusion”

• “In medicine, it may be called the “therapeutic illusion” (a label first applied in 1978 to “the unjustified enthusiasm for treatment on the part of both patients and doctors”2).
• When physicians believe that their actions or tools are more effective than they actually are, the results can be unnecessary and costly care. Therefore, I think that efforts to promote more rational decision making will need to address this illusion directly.”

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

Antimicrobial Exposure and NEC
Yale cohort replicates association reported by Cotten


- Overuse of antibiotics can facilitate antibiotic resistance and is associated with adverse neonatal outcomes.
- We studied the association between duration of antibiotic therapy and short-term outcomes of very low birth weight (VLBW) (<1500 g) infants without culture-proven sepsis.
- Included VLBW infants admitted to NICUs in the Canadian Neonatal Network between 2010-2016 who were exposed to antibiotics but did not have culture-proven sepsis in the first week of life.
- Antibiotic exposure was calculated as the number of days an infant received antibiotics in the first week of life.
- Composite primary outcome was defined as mortality or any major morbidity (severe neurologic injury, retinopathy of prematurity, necrotizing enterocolitis, chronic lung disease, or hospital-acquired infection).

• Of the 14,207 included infants, 21% (n = 2,950), 38% (n = 5,401), and 41% (n = 5,856) received 0, 1 to 3, and 4 to 7 days of antibiotics, respectively.

• Antibiotic exposure for 4 to 7 days was associated with higher odds of the composite outcome (adjusted odds ratio 1.24; 95% confidence interval [CI] 1.09-1.41).

• Each additional day of antibiotic use was associated with 4.7% (95% CI 2.6%-6.8%) increased odds of composite outcome and 7.3% (95% CI 3.3%-11.4%) increased odds in VLBW infants at low risk of early-onset sepsis (born via cesarean delivery, without labor and without chorioamnionitis).

Joseph Y. Ting et al. Pediatrics 2019;143:e20182286

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Antibiotic Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None (N = 1512), n (%)</td>
</tr>
<tr>
<td>Composite outcome^d</td>
<td>364 (24)</td>
</tr>
<tr>
<td>Composite outcome II^a</td>
<td>356 (24)</td>
</tr>
<tr>
<td>Mortality after 7 d of life</td>
<td>18 (1)</td>
</tr>
<tr>
<td>Severe neurologic injury^f</td>
<td>28 (2)</td>
</tr>
<tr>
<td>PDA requiring treatment</td>
<td>140 (9)</td>
</tr>
<tr>
<td>Greater than or equal to stage 2 NEC</td>
<td>43 (3)</td>
</tr>
<tr>
<td>HAI</td>
<td>125 (8)</td>
</tr>
<tr>
<td>CLD</td>
<td>251 (18)</td>
</tr>
<tr>
<td>Greater than or equal to stage 3 ROP or ROP treated</td>
<td>21 (3)</td>
</tr>
<tr>
<td>PVL</td>
<td>17 (1)</td>
</tr>
</tbody>
</table>

• Identified 9 RCTs and 38 observational studies. The quality of the majority of studies was poor to moderate. There was a significant association between prolonged antibiotic exposure and an increased risk of NEC in five observational studies (5003 participants) and/or risk of death in five observational studies (13 534 participants).

• Eleven of 15 studies with data on broad- versus narrow-spectrum regimens reported an increased risk of invasive fungal infections after broad-spectrum antibiotic exposure, in particular with third-generation cephalosporins and carbapenems.

• Prolonged antibiotic exposure in uninfected preterm infants is associated with an increased risk of NEC and/or death, and broad-spectrum antibiotic exposure is associated with an increased risk of invasive fungal infections.


• We assembled a cohort of inborn neonates, from our deidentified administrative database, who had documented exposure to ampicillin during the first 3 days after birth. Infants treated concurrently with cefotaxime or gentamicin were evaluated, to identify the factors that were associated independently with death before discharge, with both univariate and multivariate analyses.

• There were 128914 neonates selected as the study cohort; 24111 were treated concurrently with ampicillin and cefotaxime and 104803 were treated concurrently with ampicillin and gentamicin.

• Logistic modeling showed that neonates treated with ampicillin/cefotaxime were more likely to die (adjusted odds ratio: 1.5; 95% confidence interval: 1.4-1.7) and were less likely to be discharged to home or foster care than were neonates treated with ampicillin/gentamicin. This observation was true across all estimated gestational ages.
Adjusted OR (based on final model) within gestational-age groups (logistic regression [odds of death] adjusted for need for assisted ventilation, anomalies, birth depression, and estimated gestational age [EGA] within each estimated gestational-age group).


**Neonatal Antibiotics and wheeze and asthma risk: systematic review and meta-analysis – Slide from Mike Cotten**

- 18 studies eligible for meta-analysis
  - pooled OR 1.27 (95% CI 1.12-1.43)
- 9 Studies *without design bias*
  - pooled OR 1.12 (95% CI 0.98-1.26)
- 3 studies focused on wheeze/asthma beyond 5-6 yrs of age
  - pooled OR 1.08, 95% CI 0.93-1.23; dominated by one study


**Alternative:** “A *robust and dose-dependent association was found between antibiotic use in the first 2 yr of life and asthma at age 7.5 yr but did not appear to be mediated through an association with atopy.”

Early Antibiotics Impact Microbial Diversity - Slide From Mike Cotten

• 3 sites; Serial samples, < 32 weeks GA; n = 74, serial samples, days 0 – 23, 16S ribosomal DNA (or 16S rDNA)
• > 7 day survivors, w/o NEC or infection first postnatal week,
• Treatment groups: 0 days, 1-4 days, 5 – 7 days (amp/gent)

Longer ABX: More Enterobacter vs Staph

Longer ABX: less diversity over time

Simpson Diversity Index: species richness (number of species present) and evenness of abundance


Problems/Adverse Impact

• 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.”4 (Cotten CM et al. Pediatrics 2012;130(4):e1052‐e1053)
Carina B. Ramirez, Joseph B. Cantey. Antibiotic Resistance in the Neonatal Intensive Care Unit
NeoReviews Vol. 20 No. 3 March 01, 2019 pp. e135-e144.

• Antibiotic-resistant bacteria in the NICU are an increasing threat to the well-being of our smallest and most vulnerable infants.
• Resistant bacteria can be introduced from the community or created de novo by selective antibiotic pressure.
• Agents such as MRSA, VRE, and ESBL-producing gram-negative organisms have been joined more recently by vancomycin-resistant S. aureus, carbapenem-resistant gramnegatives, and other organisms for which we have limited treatment options.
• Targeted decolonization has some efficacy against MRSA colonization, but *fecal carriage of VRE and ESBL producers is difficult to mitigate.*
• Routine surveillance cultures, effective antibiotic stewardship, and meticulous hand hygiene remain the best weapons we have to combat antibiotic resistance in the NICU.

New Challenge: Emergence of Resistance: Percent Of All Positive Blood and CSF Cultures By Year

![Graph showing emergence of resistance in positive blood and CSF cultures by year.](http://example.com/graph.png)

Year MEDNAX started collecting resistance data

<table>
<thead>
<tr>
<th>Year</th>
<th>E Coli</th>
<th>E Coli, Ampicillin Resistant</th>
<th>E Coli, Extended Spectrum beta-lactamase producing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>6.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>7.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>8.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>8.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>8.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>8.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>8.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>8.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>8.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>8.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>8.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>8.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>8.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>8.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>8.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>8.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>8.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>8.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>8.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>8.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td>8.2%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What are we trying to fix?

- Who do we need to treat?
- Do all infants born to mothers’ with a diagnosis of chorioamnionitis need antibiotics?
- How long do we need to treat asymptomatic infants whose cultures are negative and what are the most important confounding variables?
- What antibiotics should we use to treat infants with suspected early onset sepsis?
- What adverse events are associated with use of antibiotics?
Treated with Ampicillin on Day of Birth or Day 1 or 2 after birth (Early Empiric Treatment/All Admits)

Likelihood of ever having a positive blood or CSF culture by age in all inborn infants. No Filters – Includes transfers, and infants with anomalies. Data from 1997 to 2017
Likelihood of ever having a positive blood in all inborn infants.
No Filters – Includes transfers, and infants with anomalies. Data from 1997 to 2017

Infections are most likely among the most vulnerable babies of lowest GA
Likelihood of EVER having a positive blood or CSF culture BY EGA in all inborn infants.
No Filters – Includes transfers, and infants with anomalies. Data from 1997 to 2017
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.


- **Setting, and Participants:** This retrospective cohort study used a comprehensive administrative database of inpatient encounters from 297 academic and community hospitals across the United States to examine data concerning very low-birth-weight (VLBW) infants (<1500 g), including extremely low-birth-weight (ELBW) infants (<1000 g), who were admitted to the neonatal intensive care unit and survived for at least 1 day.
- **Data collection took place in November 2015 and analysis took place from February 2016 to November 2016.**
- **Exposures:** Antibiotic initiation within the first 3 days of age and subsequent antibiotic administration for more than 5 days.
- **Results:** We identified 40364 VLBW infants (20447 female [50.7%]) who survived for at least 1 day, including 12947 ELBW infants, from 297 centers. The majority of premature infants had early antibiotic initiation (31715 VLBW infants [78.6%] and 11264 ELBW infants [87.0%]), and no differences were observed over time in temporal trend analyses.
• We also observed variation in early antibiotic exposures across centers.
• Sixty-nine of 113 centers (61.1%) started antibiotic therapy for more than 75% of VLBW infants, and 56 of 66 centers (84.8%) started antibiotic therapy for more than 75% of ELBW infants.
• The proportion of VLBW and ELBW infants administered prolonged antibiotics ranged from 0% to 80.4% and 0% to 92.0% across centers, respectively.
• Conclusions and Relevance: Most premature infants in this study received empirical early antibiotic therapy with little change over a recent 7-year period. The variability in exposure rates across centers, however, suggests that neonatal antimicrobial stewardship efforts are warranted to optimize antibiotic use for VLBW and ELBW infants.
Variation in the proportion of neonates who received antibiotics >3 days by NICU. The denominator is all VLBW infants (N = 20,741).

Joseph Y. Ting et al. Pediatrics 2019;143:e20182286

Most Important Measures of Antibiotic Stewardship.

• Percent of infants who have a blood culture drawn/all births (or NICU admissions)
• Percent of infants with a positive culture/all births (or NICU admissions)
• Percent of infants treated/all births (or NICU admissions)
• Duration of initial course of antibiotics (remember this drive hospital days in late preterm and term infants). From this you can derive categorical values.
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”

- **Tool to assess the risk of early-onset sepsis** in an infants 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.
• 204,485 infants born at 35 weeks' gestation or later at a Kaiser Permanente Northern California hospital from January 1, 2010, through December 31, 2015.

• The study compared 3 periods when EOS management was based on
  1. National recommended guidelines (baseline period [January 1, 2010, through November 31, 2012]),
  2. Multivariable estimates of sepsis risk at birth (learning period [December 1, 2012, through June 30, 2014]), and
  3. The multivariable risk estimate combined with the infant's clinical condition in the first 24 hours after birth (EOS calculator period [July 1, 2014, through December 31, 2015]).
The study cohort included **204,485 infants born at 35 weeks’ gestation or later**:
95,343 in the baseline period, 52,881 in the learning period, and 56,261 in the EOS calculator period.

In a comparison of the baseline period with the EOS calculator period, **blood culture use decreased from 14.5% to 4.9%** (adjusted difference, -7.7%; 95% CI, -13.1% to -2.4%).

**Empirical antibiotic administration in the first 24 hours decreased from 5.0% to 2.6%** (adjusted difference, -1.8; 95% CI, -2.4% to -1.3%).

No increase in antibiotic use occurred between 24 and 72 hours after birth; use decreased from 0.5% to 0.4% (adjusted difference, 0.0%; 95% CI, -0.1% to 0.2%).

The **incidence of culture-confirmed EOS was similar during the 3 periods** (0.3% baseline and learning period, and 0.2% in the EOS calculator period).

**Readmissions for EOS (within 7 days of birth) were rare in all periods (5.2 per 100,000 births in the baseline period, 1.9 per 100,000 births in the learning period, and 5.3 per 100,000 births in the EOS calculator period) and did not differ statistically (P = .70).**

**Incidence of adverse clinical outcomes, including need for inotropes, mechanical ventilation, meningitis, and death, was unchanged after introduction of the EOS calculator.**

Table 2. Comparison of Sepsis Evaluation and Antibiotic Use in the Baseline and EOS Calculator Periods

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study Period</th>
<th>Absolute Difference, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (n = 95 543)</td>
<td>EOS Calculator (n = 56 261)</td>
</tr>
<tr>
<td>Blood culture in first 24 h</td>
<td>13 797 (14.5)</td>
<td>274 (4.9)</td>
</tr>
<tr>
<td>Antibiotic use in first 24 h</td>
<td>4741 (5.0)</td>
<td>1482 (2.6)</td>
</tr>
<tr>
<td>Antibiotic use at &gt;24 to 72 h</td>
<td>485 (0.5)</td>
<td>216 (0.4)</td>
</tr>
<tr>
<td>Antibiotic use days per 100 infants</td>
<td>16.0</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Remember fewer cultures were done during the EOS calculator period

Table 3. Clinical Characteristics and Outcomes of Infants With EOS by Study Period

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%) of Infants by Study Perioda</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (n = 24)</td>
<td>Learning Period (n = 15)</td>
<td>EOS Calculator (n = 12)</td>
</tr>
<tr>
<td><strong>Organism</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GBS</td>
<td>11 (45.8)</td>
<td>6 (40.0)</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>5 (20.8)</td>
<td>6 (40.0)</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (33.3)</td>
<td>3 (20.0)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td><strong>Symptomatic at birth</strong></td>
<td>12 (50.0)</td>
<td>8 (53.3)</td>
<td>6 (50.0)</td>
</tr>
<tr>
<td>Developed symptoms before discharge</td>
<td>4 (16.7)</td>
<td>4 (26.7)</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>Never symptomatic</td>
<td>8 (33.3)</td>
<td>3 (20.0)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>0</td>
<td>2 (13.3)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Inotropic agents</td>
<td>2 (8.3)</td>
<td>1 (6.7)c</td>
<td>1 (8.3)c</td>
</tr>
<tr>
<td>CSF culture positive</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Elevated CSF WBC count</td>
<td>1 (4.2)</td>
<td>2 (13.3)</td>
<td>2 (16.7)d</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>1 (6.7)c</td>
<td>1 (8.3)d</td>
</tr>
</tbody>
</table>
• The infant who died during the learning period had pulmonary hypertension and respiratory failure and underwent immediate treatment with antibiotics, mechanical ventilation, and ECMO.

• The infant who died during the EOS calculator period was born with severe hypoxic-ischemic encephalopathy and underwent immediate treatment with antibiotics, mechanical ventilation, inotropic agents, therapeutic hypothermia, and ECMO.


Is there a better way to think about Chorioamnionitis?

- Study aimed to reduce maternal-infant separation while continuing to use a clinical examination-based approach to identify early-onset sepsis (EOS) in CE infants.
- Using a quality improvement framework, well-appearing CE infants ≥/35 weeks' gestation were monitored clinically while in couplet care in the postpartum unit without laboratory testing or empirical antibiotics. Clinical monitoring included physician examination at birth and nurse examinations every 30 minutes for 2 hours and then every 4 hours until 24 hours of life.
- Infants who developed clinical signs of illness were further evaluated and/or treated with antibiotics. Antibiotic use, laboratory testing, and clinical outcomes were collected.
- Among 319 initially well-appearing CE infants, 15 (4.7%) received antibiotics, 23 (7.2%) underwent laboratory testing, and 295 (92.5%) remained with their mothers in couplet care throughout the birth hospitalization.
- One infant had group B Streptococcus EOS identified and treated at 24 hours of age based on new-onset tachypnea and had an uncomplicated course.
- A framework for repeated clinical assessments is an essential component of identifying infants with EOS

Flow diagram of infants born during the quality improvement phase II study period.

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 and injury.
- 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
- There is evidence we can do better.
Puopolo KM, Benitz WE, Zaoutis TE. Management of Neonates Born at $\geq 35$ 0/7 Weeks' Gestation With Suspected or Proven Early-Onset Bacterial Sepsis. Pediatrics 2018;142(6).

- The incidence of neonatal early-onset sepsis (EOS) has declined substantially over the last 2 decades, primarily because of the implementation of evidence-based intrapartum antimicrobial therapy.
- However, EOS remains a serious and potentially fatal illness.
- *Laboratory tests alone are neither sensitive nor specific enough to guide EOS management decisions.*
- The incidence of EOS, the prevalence and implications of established risk factors, the predictive value of commonly used laboratory tests, and the uncertainties in the risk/benefit balance of antibiotic exposures all vary significantly with gestational age at birth.
Puopolo KM, Benitz WE, Zaoutis TE. Management of Neonates Born at \( \geq 35 \) 0/7 Weeks' Gestation With Suspected or Proven Early-Onset Bacterial Sepsis (EOS). Pediatrics 2018;142(6).

- **GBS is the most common bacteria isolated in EOS cases among term and late-preterm infants, accounting for approximately 40% to 45% of all cases.**
- **E coli infections represent approximately 10% to 15% of cases.**
- **The remaining cases are caused primarily by other Gram-positive organisms (predominantly viridans group streptococci and enterococci), and approximately 5% are caused by other Gram-negative organisms.**
- **S aureus (approximately 3%–4%) and L monocytogenes (approximately 1%–2%) are less common causes of EOS among term infants.**

Puopolo KM, Benitz WE, Zaoutis TE. Management of Neonates Born at \( \geq 35 \) 0/7 Weeks' Gestation With Suspected or Proven Early-Onset Bacterial Sepsis (EOS). Pediatrics 2018;142(6).

- **Ampicillin and gentamicin, in combination, is the first choice for empirical therapy for EOS.**
- **This combination will be effective against GBS, most other streptococcal and enterococcal species, and L monocytogenes.**
- **Although two-thirds of E coli EOS isolates and most other Gram-negative EOS isolates are resistant to ampicillin, the majority remain sensitive to gentamicin.**
- **Extended-spectrum \( \beta \)-lactamase–producing organisms are rarely reported among EOS cases in the United States.**
- **The routine empirical use of broader-spectrum antibiotic agents is typically not justified and may be harmful.**
- **Approximately 7% of E coli cases (1.7% of all EOS cases) were resistant to both ampicillin and gentamicin in recent CDC surveillance studies.**
- **Among term newborn infants who are critically ill, the empirical addition of broader-spectrum therapy should be considered until culture results are available.**
Puopolo KM, Benitz WE, Zaoutis TE. Management of Neonates Born at ≤34 6/7 Weeks’ Gestation With Suspected or Proven Early-Onset Bacterial Sepsis. Pediatrics 2018;142(6).

• Early-onset sepsis (EOS) remains a serious and often fatal illness among infants born preterm, particularly among newborn infants of the lowest gestational age.

• Currently, most preterm infants with very low birth weight are treated empirically with antibiotics for risk of EOS, often for prolonged periods, in the absence of a culture-confirmed infection.

• Retrospective studies have revealed that antibiotic exposures after birth are associated with multiple subsequent poor outcomes among preterm infants, making the risk/benefit balance of these antibiotic treatments uncertain.

• Gestational age is the strongest single predictor of EOS, and the majority of preterm births occur in the setting of other factors associated with risk of EOS, making it difficult to apply risk stratification strategies to preterm infants.

• Laboratory tests alone have a poor predictive value in preterm EOS.

• Delivery characteristics of extremely preterm infants present an opportunity to identify those with a lower risk of EOS and may inform decisions to initiate or extend antibiotic therapies.

Puopolo KM, Benitz WE, Zaoutis TE. Management of Neonates Born at ≤34 6/7 Weeks’ Gestation With Suspected or Proven Early-Onset Bacterial Sepsis. Pediatrics 2018;142(6).

• E coli is the most common bacteria isolated in EOS cases that occur among preterm infants

• Overall, E coli is isolated in approximately 50%, and GBS is isolated in approximately 20% of all EOS cases occurring among infants born at <34 weeks’ gestation.

• Fungal organisms are isolated in <1% of cases.

• Approximately 10% of cases are caused by other Gram-positive organisms (predominantly viridans group streptococci and enterococci), and approximately 20% of cases are caused by other Gram-negative organisms.

• S aureus (approximately 1%–2%) and L monocytogenes (approximately 1%) are uncommon causes of preterm EOS.

• If an anaerobic culture is routinely performed, strict anaerobic bacteria are isolated in up to 15% of EOS cases among preterm infants with VLBW, with B fragilis being the predominant anaerobic species isolated.
Puopolo KM, Benitz WE, Zaoutis TE. Management of Neonates Born at $\leq$34 6/7 Weeks' Gestation With Suspected or Proven Early-Onset Bacterial Sepsis. Pediatrics 2018;142(6).

- The combination of **ampicillin and gentamicin is the most appropriate empirical antibiotic regimen** for infants at risk for EOS. Empirical administration of additional broad-spectrum antibiotics may be indicated in preterm infants who are severely ill and at a high risk for EOS, particularly after prolonged antepartum maternal antibiotic treatment.

- When blood cultures are sterile, antibiotic therapy should be discontinued by 36 to 48 hours of incubation, unless there is clear evidence of site-specific infection.

- **Persistent cardiorespiratory instability is common among preterm infants with VLBW and is not alone an indication for prolonged empirical antibiotic administration.**

- **Laboratory test abnormalities alone rarely justify prolonged empirical antibiotic administration, particularly among preterm infants at a lower risk for EOS.**

Algorithm of recommendations on when to perform a lumbar puncture in neonates being evaluated for sepsis.

Samia Aleem, and Rachel G. Greenberg Neoreviews 2019;20:e124-e134