Antimicrobial Stewardship in the NICU at Levine Children’s Hospital

9th Annual Quality and Patient Experience Sharing Day
July 25th, 2018

James Jones, D.O., Neonatologist, LCH NICU Director of Quality Improvement
Risk of Antibiotics in Neonates

• Necrotizing enterocolitis and Mortality
• Late-onset infection
• Obesity
• Asthma
• Allergic diseases
• Inflammatory bowel disease
• Multi-drug resistant pathogens
• Fungal infections
• Adverse drug reactions

Risk of Antibiotics in Neonates

• Multicenter, retrospective cohort of 4039 extremely low birth weight infants (<1000 g)
  • Infants who received >4 days of therapy had a higher risk of necrotizing enterocolitis
  • Higher mortality

• Retrospective cohort of 365 very low birth weight infants (<1500 g)
  • Infants who received >4 days of therapy had a higher risk of late-onset sepsis
  • Higher composite risk of late-onset sepsis, necrotizing enterocolitis and mortality

Nicu Antibiotic Use

- Retrospective cohort study of 127 NICUs in California in 2013
- Overall antibiotic use varied 40-fold (2% to 97% of patient days; median 25%)
  - WIDEST known scale of antibiotic prescribing practice variation published
- Variation independent of proven infection, NEC, surgical volume or mortality
- Most NICU antibiotic use is empirical
- 28% of all antibiotic courses in one NICU study deemed to be inappropriate
  - 42% of antibiotics continued past 72 hours inappropriate

Our Objective

The purpose of the LCH NICU antibiotic stewardship project is to **decrease** unnecessary antibiotic use while **optimizing** appropriate use in the newborns.

**SMART AIM:** Reduce antibiotic use in the LCH NICU by 20% by December 2017
Our Multifaceted Approach

- National and state collaboration
  - Vermont Oxford Network (VON)- joined January 2016
  - Perinatal Quality Collaborative of North Carolina (PQCNC)
- Kaiser calculator: risk stratification for early onset sepsis
- Guidelines
  - Early onset sepsis (EOS)
  - Late onset sepsis (LOS)
  - Necrotizing enterocolitis (NEC)
  - Antibiotics for surgical prophylaxis
- Automatic antibiotic stops for EOS
- Antibiotic “Time Out” during rounds
- Patient education
The Improvement Process

• **EDUCATION**: Initial PDSA cycles: assessing antibiotic prescribing practices, providing educational webinars courtesy of VON, and education and discussion through best practice and evidence-based medicine review

• Engaged a large multidisciplinary team

• Involved clinicians from almost every Atrium Health NICU and the newborn nursery at LCH to encourage spread to the other facilities

• Committee discussions to develop protocols with expert opinions

• Performed multiple PDSA cycles to assure each of the interventions were successful prior to adoption
**Global Aim**
Reduce antibiotic resistance, health care costs in the NICU, and risk of mortality and morbidities such as necrotizing enterocolitis, late-onset infection, or other conditions potentially affected by alterations in the microbiome.

**SMART Aim**
Reduce antibiotic usage in the NICU at Levine Children’s Hospital by 20% from a mean of 422 days of antibiotic therapy per 1000 patient days to 337 days of antibiotic therapy per 1000 patient days by December 2017.

**Population**
All infants admitted to the NICU at Levine Children’s Hospital with spread to other nurseries in the Atrium System.

**Key Drivers**
- Achieve buy-in from various disciplines who care for infants in the NICU and nurseries in the system
- Reduce antibiotic overuse for early-onset sepsis evaluations (1st 48 hrs)
- Appropriate prescribing of antibiotics with respect to choice, indication, dose, duration, safety monitoring, and de-escalation
- Mechanisms for ongoing data collection re: antibiotic use in the NICU and other nursery units
- Have standardized approach for antibiotic selection for late-onset sepsis antibiotic selection and duration
- Have standardized approach for necrotizing enterocolitis and abdominal surgical antibiotics including duration
- Spread newborn antibiotic stewardship and encourage development of similar protocols in other system NICUs and nurseries

**Interventions**
- Join VON and PQCN collaboratives, form multidisciplinary committee, and give education via meetings and webinars
- Introduce and implement the Kaiser Early-onset calculator for infants >34 wks and develop algorithm using CDC and AAP COFN guidelines for infants <34 wks. Have link to calculator available on Cerner tab and smartphone app.
- Implement stop on antibiotic ordering in Cerner via ordering # of doses as opposed to duration to provide 48 hrs coverage if culture remains negative at 36 hrs
- Implement prospective audit and feedback via the antibiotic stewardship team to recommend appropriate prescribing
- Micro lab implement rapid blood culture ID system via PCR to assist in de-escalation of broad spectrum antibiotics and appropriate antibiotic choice
- Data collection for EOS via data sheets filled out by providers and enter into internal and PQCN data base. Utilize pharmacy Theradoc for AUR and specific antibiotic utilization data
- Develop and educate late-onset sepsis antibiotic algorithm. Engage experts and develop surgical antibiotic guideline. Utilize NEC protocol
- Engage other system NICU and nursery providers in educational and protocol decision process (encourage enrollment in PQCN and VON)
Determining Risk of EOS

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Prevention of Perinatal Group B Streptococcal Disease: Revised Guidelines from CDC, 2010
## EOS Kaiser Calculator

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of Early-Onset Sepsis</td>
<td></td>
</tr>
<tr>
<td>Gestational age</td>
<td>weeks, days</td>
</tr>
<tr>
<td>Highest maternal antepartum temperature</td>
<td>Fahrenheit</td>
</tr>
<tr>
<td>ROM (Hours)</td>
<td></td>
</tr>
<tr>
<td>Maternal GBS status</td>
<td>Negative, Positive, Unknown</td>
</tr>
<tr>
<td>Type of intrapartum antibiotics</td>
<td>Broad spectrum antibiotics &gt; 4 hrs prior to birth, Broad spectrum antibiotics 2-3.9 hrs prior to birth, GBS specific antibiotics &gt; 2 hrs prior to birth, No antibiotics or any antibiotics &lt; 2 hrs prior to birth</td>
</tr>
</tbody>
</table>

### Risk per 1000/births

- **EOS Risk @ Birth**

<table>
<thead>
<tr>
<th>EOS Risk after Clinical Exam</th>
<th>Risk per 1000/births</th>
<th>Clinical Recommendation</th>
<th>Vitals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well Appearing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equivocal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Illness</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Classification of Infant's Clinical Presentation: Clinical Illness, Equivocal, Well Appearing

[https://neonatalsepsiscalculator.kaiserpermanente.org/](https://neonatalsepsiscalculator.kaiserpermanente.org/)
# EOS Kaiser Calculator

<table>
<thead>
<tr>
<th>Clinical Exam</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Clinical Illness</strong></td>
<td>1. Persistent need for NCPAP / HFNC / mechanical ventilation (outside of the delivery room)</td>
</tr>
<tr>
<td></td>
<td>2. Hemodynamic instability requiring vasoactive drugs</td>
</tr>
<tr>
<td></td>
<td>3. Neonatal encephalopathy /Perinatal depression</td>
</tr>
<tr>
<td></td>
<td>- Seizure</td>
</tr>
<tr>
<td></td>
<td>- Apgar Score @ 5 minutes &lt; 5</td>
</tr>
<tr>
<td></td>
<td>4. Need for supplemental O₂ ≥ 2 hours to maintain oxygen saturations &gt; 90% (outside of the delivery room)</td>
</tr>
<tr>
<td><strong>Equivocal</strong></td>
<td>1. Persistent physiologic abnormality ≥ 4 hrs</td>
</tr>
<tr>
<td></td>
<td>- Tachycardia (HR ≥ 160)</td>
</tr>
<tr>
<td></td>
<td>- Tachypnea (RR ≥ 60)</td>
</tr>
<tr>
<td></td>
<td>- Temperature instability (≥ 100.4°F or &lt; 97.5°F)</td>
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<tr>
<td></td>
<td>- Respiratory distress (grunting, flaring, or retracting) not requiring supplemental O₂</td>
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<td></td>
<td>2. Two or more physiologic abnormalities lasting for ≥ 2 hrs</td>
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<tr>
<td></td>
<td>Note: abnormality can be intermittent</td>
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<tr>
<td><strong>Well Appearing</strong></td>
<td>No persistent physiologic abnormalities</td>
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### EOS Kaiser Calculator

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<td>Incidence of Early-Onset Sepsis</td>
<td>0.5/1000 live births (CDC national)</td>
</tr>
<tr>
<td>Gestational age</td>
<td>34 weeks</td>
</tr>
<tr>
<td></td>
<td>1 days</td>
</tr>
<tr>
<td>Highest maternal antepartum temperature</td>
<td>101 Fahrenheit</td>
</tr>
<tr>
<td>ROM (Hours)</td>
<td>6</td>
</tr>
<tr>
<td>Maternal GBS status</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative</td>
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### Risk per 1000/births

| EOS Risk @ Birth | 7.11 |

### EOS Risk after Clinical Exam

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<tr>
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<th>Clinical Recommendation</th>
<th>Vitals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well Appearing</td>
<td>2.93</td>
<td>Blood culture</td>
<td>Vitals every 4 hours for 24 hours</td>
</tr>
<tr>
<td>Equivocal</td>
<td>34.57</td>
<td>Empiric antibiotics</td>
<td>Vitals per NICU</td>
</tr>
<tr>
<td>Clinical Illness</td>
<td>131.80</td>
<td>Empiric antibiotics</td>
<td>Vitals per NICU</td>
</tr>
</tbody>
</table>
EOS Kaiser Calculator: Implementation

- PDSAs on guidelines in November 2016
- Successfully adopted February 2017 based on provider satisfaction
- Link tab available in Cerner® to ensure availability for provider use in real time
EOS ( < 34 Weeks Gestation)

- Signs of Sepsis or clinically ill?
  - Yes: Full diagnostic evaluation and empiric antibiotic therapy
  - No: OB suspicion or known diagnosis of maternal chorioamnionitis

- OB suspicion or known diagnosis of maternal chorioamnionitis
  - Yes: Full diagnostic evaluation and empiric antibiotic therapy
  - No: GBS prophylaxis indicated for mother including GBS unknown

- GBS prophylaxis indicated for mother including GBS unknown
  - Yes: Adequate prophylaxis ≥ 4 hrs of penicillin, ampicillin, or cefoxitin
  - No: PPROM ≥ 18 hrs

- PPROM ≥ 18 hrs
  - Yes: Observe and CBC w/diff + CRP on admission
  - No: labs are abnormal

- Labs are abnormal
  - Well-appearing neonate
    - Blood culture, CBC w/diff + CRP, and empiric antibiotics if PPROM ≥ 18 hrs, inadequate IAP, and/or abnormal labs
  - Infant no longer well or blood culture positive, or no improvement on antibiotics then start, continue, or adjust antibiotics

- Ongoing management
  - If remains well or stable and blood culture negative, d/c antibiotics at 36 hrs (i.e., ampicillin x 3 doses and gentamicin x 1 dose according to Neofax dosing)
90% of bacterial pathogens isolated within 72 hours have a time to positivity prior to 36 hours.

Negative predictive value for isolation of any organism: 97% at 36 hours.

**Note:** If empiric antibiotics are ordered and blood culture(s) remains negative at 36 hrs and suspicion of sepsis remains low, consider discontinuation of antibiotics. It is encouraged to order empiric antibiotics according to doses as below so that unnecessary additional doses of antibiotics are not given.

- For infants ≥35 weeks gestation recommended to order ampicillin x 3 doses and gentamicin x 2 doses
- For infants <35 weeks gestation recommended to order ampicillin x 3 doses and gentamicin x 1 dose

The dosing recommendations should be according to Neofax and the above number of doses ordered will allow antibiotic coverage through at least 36 hrs.

Late Onset Sepsis (≥72 hours of life)

- **MRSA Colonized**
  - Vancomycin + Gentamicin
  - Clinically deteriorating despite antibiotic therapy or not improving despite therapy**
    - Vancomycin + Cefepime

- **No MRSA colonization**
  - No NEC or intraabdominal infection
    - Nafcillin + Gentamicin
  - Suspected or confirmed NEC or intraabdominal infection
    - Ampicillin + gentamicin and follow NEC pathway. Add metronidazole if intestinal perforation or at high risk for perforation.
    - Severe intraabdominal infection with shock or clinical deterioration and not improving on current therapy**
      - Vancomycin + piperacillin tazobactam

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*Note:* Treatment options marked with an asterisk (*) are based on available evidence and expert consensus. Additional options may be considered based on institutional protocols and patient-specific factors. **Indicates high-risk conditions requiring immediate attention and potential escalation of care.**
## Antibiotics for Surgical Prophylaxis

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Antibiotic Regimen</th>
<th>Duration of Prophylaxis or Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEC surgery (with, or at high risk for perforation)</td>
<td>ampicillin + gentamicin + metronidazole</td>
<td>7 days</td>
</tr>
<tr>
<td>NEC surgery (with shock or clinical deterioration(^1))</td>
<td>piperacillin/tazobactam ± vancomycin(^2)</td>
<td>10 days</td>
</tr>
<tr>
<td>Small bowel atresia repair (without evidence of contamination)</td>
<td>cefazolin(^3)</td>
<td>Up to 24h post-op</td>
</tr>
<tr>
<td>Gastrochisis</td>
<td>ampicillin + gentamicin</td>
<td>Until abdominal closure</td>
</tr>
<tr>
<td>TEF repair</td>
<td>cefazolin(^4)</td>
<td>Single dose pre-op</td>
</tr>
<tr>
<td>Hirschsprung without enterocolitis, esophageal atresia, imperforate anus, and other closed, noncontaminated surgeries</td>
<td>cefazolin</td>
<td>Single dose pre-op</td>
</tr>
</tbody>
</table>
Prospective Audit and Feedback

• The pediatric ASN: pediatric infectious diseases trained pharmacists and physicians

• Utilized computer decision support software (Theradoc®) to alert them of any patient in the NICU on an antimicrobial or with any positive cultures

• Recommendations to optimize appropriate antibiotic selection, dosage, monitoring, duration, and de-escalation made in real-time during working hours

• Initiated December 2016
Prospective Audit and Feedback

• Rapid blood culture identification detection system via PCR technology went live January 2017

• Monitored in real time by ASN and allowed for:
  • Timely treatment of serious blood stream infections
  • Avoidance of antibiotic treatment for contaminants
  • Use of targeted narrow spectrum antibiotics for select organisms
  • Escalation of antibiotics with identification of resistant pathogens
Antibiotic Time Out

5 Rights for Using Antibiotics Responsibly

“Antibiotic Timeout” discussed during rounds to reassess the continuing need and optimization of antibiotics

1. **Right Indication** (Does the patient have an infection that will respond to antibiotics?)

2. **Right Antibiotic** (Can a more targeted antibiotic be used to treat the infection?)

3. **Right Route** (IV/IM/PO) (May not apply to most NICU patients)

4. **Right Dose** (mg/kg and interval) (including drug levels and pharmacy consult when appropriate)

5. **Right Duration** (How long should the patient receive antibiotics?)
Family/Caregiver Involvement

• Approved by the Parent Advisory Council by the parent advocate on the committee

**5 Questions to Ask Your Baby’s Doctor Before Your Baby is Given Antibiotics**

1. Why does my baby need antibiotics?
2. What are the risks?
3. Are there simpler, safer options?
4. How will I know if my baby still needs antibiotics?
5. When can the antibiotics be stopped?

**Use these 5 questions to talk to your baby’s doctor about when your baby needs antibiotics—and when your baby does not.**

Antibiotics can help prevent or treat some infections
But if they are used for the wrong reason, they may cause unnecessary harm.

Talk to your baby’s doctor to make sure your baby is only given antibiotics for the right reasons—and at the right time.
NICU admissions receiving antibiotics during 1st 48 hrs of life

• In conjunction with Vermont Oxford Network Choosing Antibiotics Wisely and the Perinatal Quality Collaborative of North Carolina (PQCNC) Antibiotic Stewardship Newborn Sepsis projects

• Early-onset sepsis antibiotic monitored use via the NICU database (Neodata©) and chart audits.

• Tracking sheets completed by neonatologists and NNPs

• Data collection sheets entered in our internal Excel© database and the PQCNC database (Delphi©)
NICU antibiotic usage in first 48 hrs of life

- 7.5% reduction in NICU admissions receiving antibiotics in the 1st 48 hours of life

**Percent NICU Admissions Receiving Antibiotics in 1st 48 hrs of Life**

- 1/20/16 Abx stewardship…
- Joined PQCNC collaborative, piloted EOS calculator, & hard…
- Implemented EOS calculator and EOS protocol with PQCNC data tracking.
Overall Antibiotic Use Reduction

37% reduction in overall antibiotic use (2015 baseline compared to 2017)

*All systemic antibiotics reported to NHSN
40% reduction in anti-Pseudomonals* (2015 baseline compared to 2017)

*cefepime, meropenem, zosyn
Vancomycin Reduction

58% reduction in vancomycin (2015 baseline compared to 2017)

LCH NICU and NPCN Vancomycin Usage Rate

- Joined PQCNC collaborative, piloted EOS calculator, & hard stops when ordering antibiotics
- Prospective audit and feedback
- Implemented EOS calculator and EOS protocol with PQCNC data tracking. Rapid BCID.
- NICU antibiotic stewardship committee formed and joined VON collaborative
- Joined PQCNC collaborative, piloted EOS calculator, & hard stops when ordering antibiotics
- Antibiotic timeouts
- LOS protocol
- Surgical antibiotic protocol

Days of antibiotic therapy/1000 patient days

Date (Month/Year)

- Monthly DOT/1000 patient days
- Average Monthly DOT/1000 patient days
- Control Limits
• ASN: 92% acceptance rate (total 191 interventions Dec 2016-Mar 2017)

- Discontinued: 20%
- Narrowed: 18%
- Broadened: 13%
- Alternative abx: 10%
- ID consultation: 3%
- Duration optimization: 6%
- Drug info question or culture review: 4%
- Micro optimization: 13%
- Labs optimization: 6%
- Other: 2%
Other Outcomes

• Drug acquisition costs: $2000 savings
  • Does not include pharmacy/nursing labor
  • Does not consider the cost of avoiding MDRO/fungal infections or avoiding a case of antibiotic induced nephrotoxicity

• Assisting other Atrium Health facilities
  • LCH nursery:
    • Dramatic reduction of infants exposed to antibiotics (2.1% → 0.2%)
    • 83% reduction antibiotic days of therapy
  • Union nursery: 69% reduction in antibiotic days of therapy

• NO cases of confirmed sepsis/bacteremia missed by the Kaiser calculator
Continuous Quality Improvement

- Continual engagement of providers
- Implementation of hard stops in PowerPlans
- Revision of existing neonatal PowerPlans with antibiotics
- Addressing variability in duration of therapy
- Potential improved integration of Kaiser sepsis calculator into Cerner
- Continual update of best practices based on new evidence
- Improve engagement of patient’s families in antibiotic decision making
- Encouraging expansion to all Atrium newborn nurseries and NICUs
Team Members: It Takes a Village

- **Project leader and physician champion**: Jamie Jones, D.O., Neonatologist
- **Project application authors**: Jamie Jones, D.O., Rupal Patel, Pharm D, Jeanne, Forrester, Pharm D, and Jennifer Barnes, Pharm D
- **Neonatology clinical advisors**: Michelle Chiu, MD and David Fisher, MD
- **Newborn Nursery advisor and newborn nursery project leader**: Usha Ramkumar, MD
- **Infectious Disease and antibiotic stewardship expert advisors**: Lee Morris, MD, Lisa Davidson, MD, Rupal Patel, Pharm D, Jeanne Forrester, Pharm D
- **Pharmacy advisor**: Jennifer Barnes, Pharm D
- **Other Atrium Health System NICU clinician advisors**: Rob Silver, MD, Lydia Nunn, NNP, and Norene Newman, NNP (JGCH and University nurseries), Siew-Jyu Wong, MD (Union nurseries), Christopher Young, MD (Pineville and Union nurseries)
- **Administration and NICU leadership support**: David Fisher, MD, Alisa Dent, MSN, Drew Herman, MD, CMO, and Meghan Elliot RN, Gail Harris, DNP, PNP
- **Nurse management and bedside nursing leaders including data collection and entry**: Michelle Suggs, RN, ANM and Melissa Tyo, RN
- **Nursing education support**: Della Wrightson, MSN and Jenna Anderson, RN
- **Patient family advisor**: Adam Blake
- **Data collection and project feedback thanks to the neonatologist and neonatal nurse practitioners of Levine Children’s Hospital**