



# Antibiotic Use in Newborns

## When Less is More

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## Objectives

- Characterize current practices in antibiotic prescribing in newborns.
- Describe the adverse effects associated with the overuse of antibiotics in newborns.
- Develop antimicrobial stewardship measures to optimize antibiotic therapy in newborns.



“

*When antibiotics were first developed and deployed, the overwhelming consideration was control of pathogens. We now realize that their widespread application has considerable collateral effect on the microbiome, which may be of special importance in developing children*



Aversa J. Mayo Clin Proc. 53:54-94, 1990. :

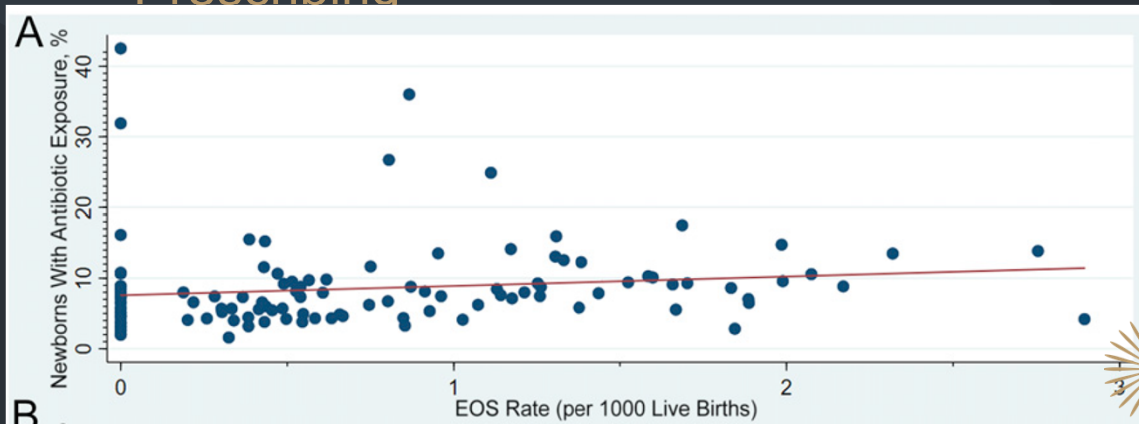


## Traditional Antibiotic Use

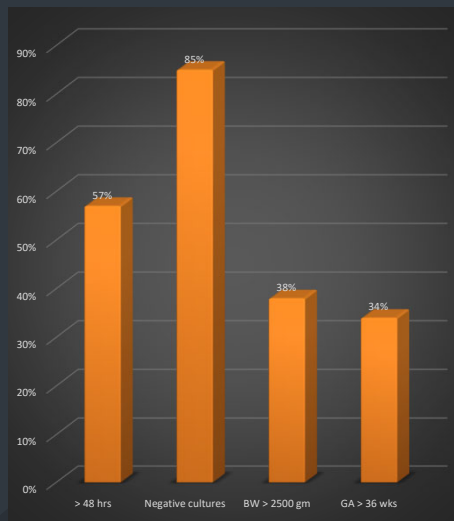
- Preterm labor & premature rupture of membranes
  - 4/3 result of maternal infection
  - < 0.8% of premature infants receive antibiotics in first 3 days of life
- Risk of early onset infections (EOS),
  - 35-53% mortality risk in extremely premature infants
  - X% mortality risk in term infants



## Wide Variations in Antibiotic Prescribing



Schulman J. Pediatrics 534:444-5, 2019:1105



## Antibiotic Utilization

### Audit of antibiotic use in 158 VON centers

- 55 of 445: 12%, infants received antibiotics
  - No differences in use by level of unit
  - 44% EOS
- 445 of 55: 80%, received antibiotics for > 48 hrs
  - 59% had a positive culture
  - 4% had no culture obtained



Ho T. Pediatrics 534:445-9, 2019:4355

“

*“Culture size is too small to grow bacteria.”*

*“Mom got antibiotics so you cannot rely on the cultures to grow.”*

*“The baby is clinically septic despite negative cultures.”*



## Short Term Risks Associated with Antibiotic Use

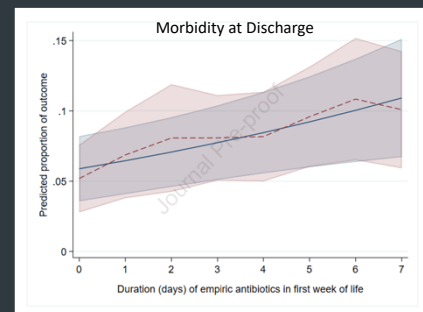
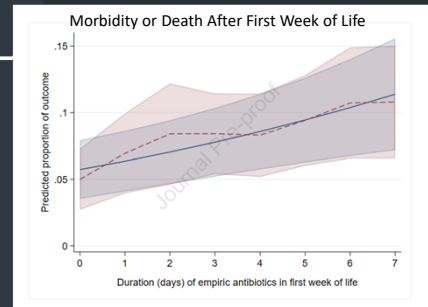
- NICU admission for antibiotics
  - Separation from mother
  - Exposure to nosocomial infections/  
multidrug resistant organism
- Alter microbiome
  - Gut flora
  - Respiratory microbiome





## Outcomes of Early Empiric Antibiotic Exposure in Preterm

- Population cohort study of 55<9 preterm infants < 35 wks GA
- Antibiotic exposure in the first week of life increased
  - Severe BPD  $\Delta$ OR 5.4,
  - Severe morbidity  $\Delta$ OR 4.88,
  - Death  $\Delta$ OR < .33,
- Each additional day of antibiotic exposure in the first week of life associated with 44% higher  $\Delta$ OR of death or severe BPD/morbidity



Vatne A. J Pediatr. 2015;155(3):e35-40. doi:10.1016/j.jpeds.2015.03.035. Epub 2015 Apr 15.



## Broad Spectrum Antibiotic Use

Numerous trials have shown increased risks to preterm infant exposed to prolonged, broad spectrum antibiotics

- Late onset sepsis
- NEC
- BPD
- Cholestasis
- Mortality
- ○ Alterations in microbiome



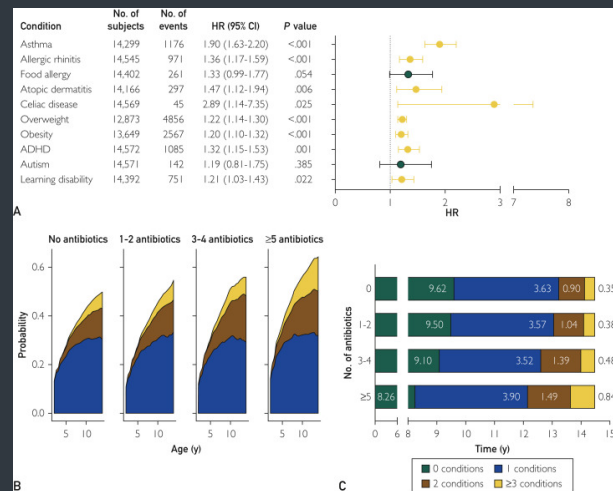
## Health Outcomes - Antibiotic Exposure in the First 2 Years

Evaluation of health outcomes in 44,515 children

3% received antibiotics in first 5 years of life

Early antibiotic exposure associated with

- Asthma
- Allergic rhinitis
- Atopic dermatitis
- Celiac disease
- Obesity
- ADHD



Aversa J. Mayo Clin Proc. 53:54-94; 1990: .

“

*In the United States, an estimated 400,000 uninfected term infants receive empirical antibiotics at birth every year, and upwards of 90% of extremely preterm infants receive antibiotics “*



## Optimizing antibiotic use

### Prevent infections from occurring

- Effective infection prevention practices
- Minimize prosthetic devices

### Optimize diagnostics

- Obtain appropriate cultures before starting antibiotics
- Avoid culturing non-viable sites; interpret results cautiously
- Use supplemental laboratory tests with good NPV

### Use narrow but effective empiric therapy

- Use local epidemiology, including active surveillance
- Avoid empiric vancomycin or third-generation cephalosporins

### Re-evaluate therapy with new information

- Decontaminate after 36-48 hours of sterile cultures
- Use identification, susceptibility to streamline therapy

### Only treat infections

- Avoid treating "culture-negative" sepsis
- Minimize duration for suspected pneumonia
- Do not treat colonization (bacterial cultures, skin flora) or colonization (single CONS isolates)

### Optimize administration

- Standard protocols for empiric therapy
- Monitor drug levels and adjust accordingly
- Integrate pharmacokinetics to ensure proper administration

### Be accountable

- Work with antibiotic stewardship program
- Prospective audit and feedback and education
- Nominate a "champion" to represent neonatology

Optimal antibiotic use

## What Can We Do?

- Prevention of infection
- Improve evaluation and empiric therapy
- Shorten duration and/or narrow antibiotic spectrum

Cantey JB. Pediatr Drugs 53:49-53 < 455 > DOI 10.1007/s43550-019-00404-4

## Early Onset Sepsis (EOS) Risk

Multivariate risk assessment tool

- Synthesizes risk factors and neonatal condition to estimate risk of EOS
- Validated for infants  $\geq 34$  3/4 wks
- Improves consistency of practice
- Requires close observation of infants off antibiotics to avoid missing cases of EOS

Neonatal Early-Onset Sepsis Calculator

Home Classification References General FAQ FAQ for EOS Implementation Kaiser Permanente Research

Probability of Neonatal Early-Onset Sepsis Based on Maternal Risk Factors and the Infant's Clinical Presentation

The tool below 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  $\geq 34$  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.

Please enter details below.

Predictor: Incidence of Early-Onset Sepsis

Gestational age: weeks, days

Highest maternal antepartum temperature: Fahrenheit

ROM (hours):

Maternal GBS status: ☐ Negative ☐ Positive ☐ Unknown

Type of intrapartum antibiotics: ☐ Broad spectrum antibiotics  $\geq 4$  hrs prior to birth ☐ Broad spectrum antibiotics 2-3 hrs prior to birth ☐ GBS specific antibiotics  $\geq 2$  hrs prior to birth ☐ No antibiotics or any antibiotics  $< 2$  hrs prior to birth

Calculate + Clear

Risk per 1000 births

EOS Risk @ Birth

| EOS Risk after Clinical Exam | Risk per 1000 births | Clinical Recommendation | Visual |
|------------------------------|----------------------|-------------------------|--------|
| Well Appearing               |                      |                         |        |
| Equivocal                    |                      |                         |        |
| Clinical Illness             |                      |                         |        |

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

<https://neonatalespsiscalculator.kaiserpermanente.org/>

Please enter details below.

| Predictor                               | Scenario                                                                                                                                                                                                                                                                                                                   |
|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Incidence of Early-Onset Sepsis         | 0.5/1000 live births (CDC ratio)                                                                                                                                                                                                                                                                                           |
| Gestational age                         | 38 weeks<br>2 days                                                                                                                                                                                                                                                                                                         |
| Highest maternal antepartum temperature | 37.1 Celsius                                                                                                                                                                                                                                                                                                               |
| ROM (Hours)                             | 24                                                                                                                                                                                                                                                                                                                         |
| Maternal GBS status                     | <input type="radio"/> Negative<br><input checked="" type="radio"/> Positive<br><input type="radio"/> Unknown                                                                                                                                                                                                               |
| Type of intrapartum antibiotics         | <input type="radio"/> Broad spectrum antibiotics > 4 hrs prior to birth<br><input type="radio"/> Broad spectrum antibiotics 2-3.9 hrs prior to birth<br><input type="radio"/> GBS specific antibiotics > 2 hrs prior to birth<br><input checked="" type="radio"/> No antibiotics or any antibiotics < 2 hrs prior to birth |

**Calculate** **Clear**

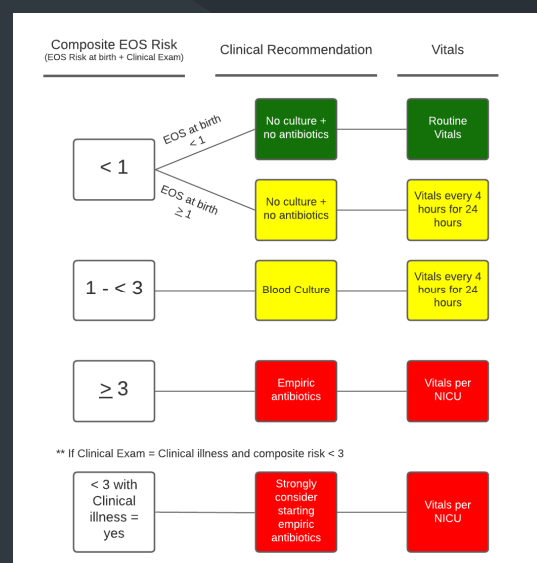
| Risk per 1000/births         |                      |                            |                                   |
|------------------------------|----------------------|----------------------------|-----------------------------------|
| EOS Risk @ Birth             | 0.47                 |                            |                                   |
| EOS Risk after Clinical Exam | Risk per 1000/births | Clinical Recommendation    | Vitals                            |
| Well Appearing               | 0.19                 | No culture, no antibiotics | Routine Vitals                    |
| Equivocal                    | 2.33                 | Blood culture              | Vitals every 4 hours for 24 hours |
| Clinical Illness             | 9.82                 | Empiric antibiotics        | Vitals per NICU                   |

Classification of Infant's Clinical Presentation: [Clinical Illness](#) [Equivocal](#) [Well Appearing](#)

| Classification of Infant's Clinical Presentation (Hide) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|---------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Clinical Exam                                           | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Clinical Illness                                        | <ol style="list-style-type: none"> <li>Persistent need for NCPAP / HFNC / mechanical ventilation (outside of the delivery room)</li> <li>Hemodynamic instability requiring vasoactive drugs</li> <li>Neonatal encephalopathy / Perinatal depression <ul style="list-style-type: none"> <li>Seizure</li> <li>Apgar Score @ 5 minutes &lt; 5</li> </ul> </li> <li>Need for supplemental O<sub>2</sub> &gt; 2 hours to maintain oxygen saturations &gt; 90% (outside of the delivery room)</li> </ol>                                                                                                                                                                                                                                                                     |
| Equivocal                                               | <ol style="list-style-type: none"> <li>Persistent physiologic abnormality ≥ 4 hrs <ul style="list-style-type: none"> <li>Tachycardia (HR ≥ 160)</li> <li>Tachypnea (RR ≥ 60)</li> <li>Temperature instability (≥ 100.4°F or &lt; 97.5°F)</li> <li>Respiratory distress (grunting, flaring, or retracting) not requiring supplemental O<sub>2</sub></li> </ul> </li> <li>Two or more physiologic abnormalities lasting for ≥ 2 hrs <ul style="list-style-type: none"> <li>Tachycardia (HR ≥ 160)</li> <li>Tachypnea (RR ≥ 60)</li> <li>Temperature instability (≥ 100.4°F or &lt; 97.5°F)</li> <li>Respiratory distress (grunting, flaring, or retracting) not requiring supplemental O<sub>2</sub></li> </ul> </li> </ol> <p>Note: abnormality can be intermittent</p> |
| Well Appearing                                          | No persistent physiologic abnormalities                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

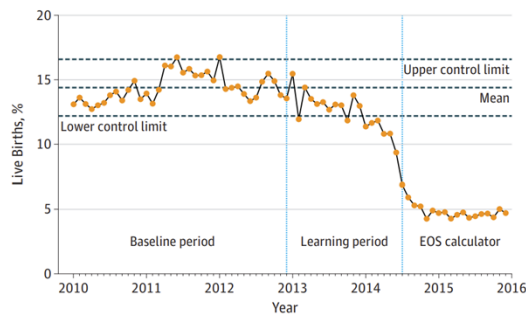


# EOS Risk Calculator



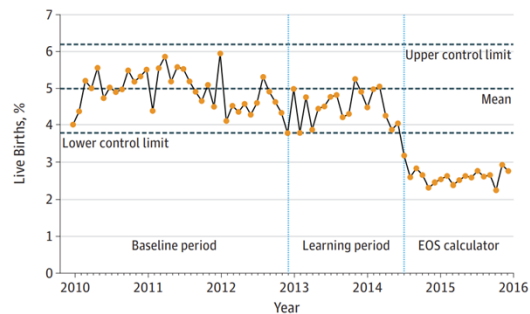
# Impact of the Use of EOS Risk Calculator

Figure 1. Monthly Early-Onset Sepsis (EOS) Evaluation Rate



Monthly percentage of infants born at 35 weeks' gestation or later undergoing EOS evaluation with a blood culture performed in the first 24 hours of life.

Figure 2. Monthly Antibiotic Treatment Rate



Monthly percentage of infants born at 35 weeks' gestation or later receiving intravenous antibiotic therapy in the first 24 hours of life. EOS indicates early-onset sepsis.

Kuzniec M W JAMA Pediatr. 534: 4: 44, 395-3: 4.



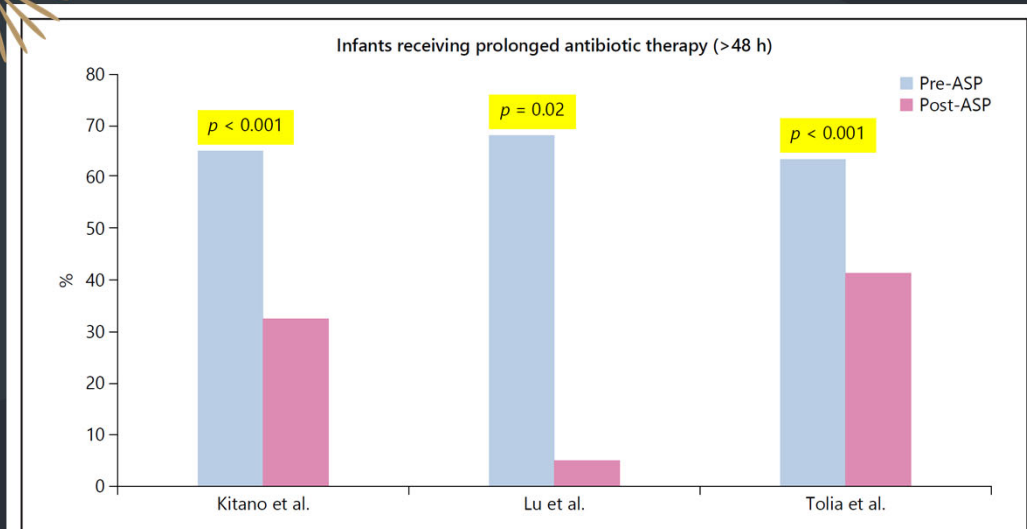
## Antimicrobial Stewardship Measures to Shorten Duration

- Automatic stop orders at 39 04 8 hrs
- Start & stop order criteria
- Improve process of report culture results
- Limit duration of treatment for culture negative sepsis
- Educational programs





## ASP Impact on Antibiotic Duration of Therapy



Rajar P. Neonatology 53:53-59: 3-989



## Measures to the Narrow Spectrum of Antibiotics

- Standardize empiric antibiotic regimens
- Limit cephalosporin use for empiric EOS
- Enhanced laboratory measures (PCR,
- Surveillance programs
  - indications for broad spectrum antibiotic use
  - antibiotic resistance patterns
- Education programs





## Summary

- While variations in current antibiotic prescribing practices exist
- Prolonged exposure  $>48$  hrs, in absence of positive culture results
- Antibiotic exposure in infancy associated with increased short and long term risks
- Efforts should focus on limiting antibiotic exposure in newborns



Questions?

Thank You

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