

*An Evidenced-Based Approach to Early-Onset Sepsis:  
Finding a Needle in a Haystack*

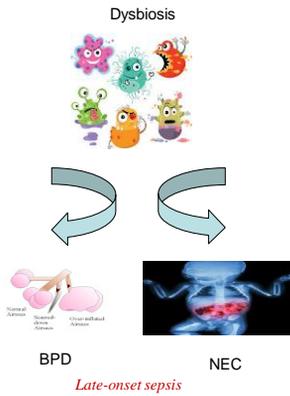
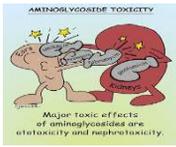


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*Our Nursing and Physician Staff*





*Consequences of Indiscriminate Use of Antibiotics*

- \* Prolonged hospitalizations and increased expenses
- \* Separation of mothers and infants (delayed breast feeding and bonding)
- \* Unnecessary procedures and testing (risk of IV infiltration)

*Economic Consequences of Sepsis Work-ups*

- Malloy analyzed data from the National Center of Health Statistics for the year 2008 (including data on chorioamnionitis) on infants 37-42 weeks (n = 2,281,396)
- He estimated that the cost to prevent one neonatal death by admitting and treating every infant exposed to chorioamnionitis for 48 hours would be \$10,424,400 (at a per diem rate of \$2,920)

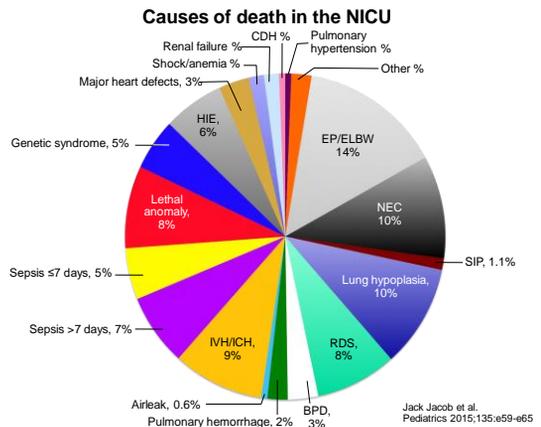
Malloy MH J Perinatology 2014

*Neonatal Sepsis by the Numbers (I)*

|             | Sepsis Incidence (per 1,000) | Sepsis Mortality |
|-------------|------------------------------|------------------|
| ≥ 37 weeks  | 0.5                          | 1.6%             |
| 34-36 weeks | 1.0                          | 1.3%             |
| 25-28 weeks | 6.0                          | 30%              |
| 22-24 weeks | 32.0                         | 50%              |

*Neonatal Sepsis by the Numbers (II)*

- \* Neonatal sepsis is an uncommon disease (0.5-1.0/1,000 live births)
- \* In well appearing term and late preterm infants the incidence of early-onset sepsis (EOS) may be as low as 1/25,000
- \* Sepsis work-ups are far more common (30-200x) than infants with proven sepsis.
- \* Half of all sepsis workups are for clinical symptoms, but most infants have non-infectious diseases



## Corollary

- \* How do we identify the infant with clinical signs or risk factors who is actually infected? i.e., *finding a needle in the haystack*
- \* Can we *safely* decrease antibiotic exposure in newborn infants at “lower” risk for sepsis?

### Opportunities to Decrease Antibiotic Exposure

- \* Healthy appearing late preterm and term infants ( $\geq 35$  weeks gestation) *with any risk factor* for infection
- \* Symptomatic preterm infants with non-infectious diseases (RDS) born to women *without evidence of maternal infection (who are not critically ill)*.
- \* Preterm infants with *no risk factors for infection* (e.g., elective cesarean section for maternal indications with either artificial rupture of membranes or rupture of membranes at delivery)

### Potential Strategies to Decrease the Use of Antibiotics in Well – Appearing Term and Late Preterm Infants with Risk Factors for Sepsis

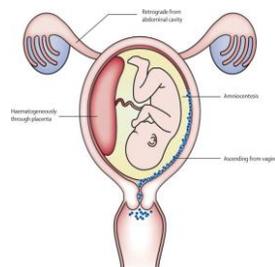
- \* Sepsis calculator (or similar scoring system) with observations.
- \* *Serial observations without laboratory testing.*
- \* Physical examination *and* screening laboratory studies (WBC and differential count or acute phase reactants – CRP or Procalcitonin)

### Disclosures About Evidence

- \* Absence of evidence is not evidence of absence
- \* Evidence is not all it's cracked up to be!



### Pathways of Neonatal Sepsis



*Chorioamnionitis is a key step in the pathway of early-onset neonatal sepsis.*

*Chorioamnionitis as a Risk Factor*

- \* The risk of sepsis in infants born to women with chorioamnionitis is strongly *dependent on gestational age*
- \* In 3 recent studies the incidence of EOS in infants ≥ 35 weeks gestation born to women with clinical chorioamnionitis ranged from 0.40% to 1.24 %

Jackson\* et al 2004 & 2012, Kiser et al 2014\*, Soraisham \*\* 2009, Garcia Munoz Rodrigo \*\* 2014, Yates et al 2017

*Intraamniotic infection and the Risk of EOS in Preterm Infants*

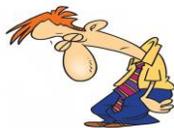
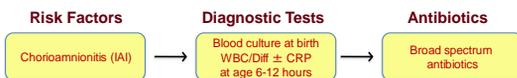
|                             | 22 wk | 23 wk | 24 wk | 25 wk | 26 wk | 27 wk | 28 wk |
|-----------------------------|-------|-------|-------|-------|-------|-------|-------|
| Histologic chorioamnionitis | 70%   | 61%   | 59%   | 51%   | 48%   | 41%   | 34%   |
| Clinical chorioamnionitis   | 28%   | 26%   | 20%   | 19%   | 19%   | 15%   | 14%   |
| Early-onset sepsis          | 6%    | 4%    | 4%    | 2%    | 2%    | 2%    | 1%    |

Stoll et al Pediatrics 126: 443-456, 2010

- \* In 2017, ACOG replaced the term *chorioamnionitis* with *intraamniotic infection* to signify infection of the fetus, fetal membranes amniotic fluid or decidua.

- \* The definition of intraamniotic infection is important because it determines subsequent management of the infant.

*Evaluation of Asymptomatic Infants Risk Factor - Chorioamnionitis*



*Consequences of CDC/AAP/NICE Guidelines*

- \* Increased workups for neonatal sepsis in well appearing infants.
- \* Prolonged antibiotic therapy based solely on abnormal laboratory values
- \* Increased length of stay and unnecessary invasive procedures (e.g., LP)

Mukhopadhyay et al Pediatrics 2014; Mukherjee et al AD-FNN 2014; Kiser et Pediatrics 2014

*Intraamniotic Infection: ACOG Committee Opinion 2017*

*Can we Diagnose Intraamniotic Infections with Better Precision?*

- \* *Isolated maternal fever*: a maternal temperature of 38-39° C \*
- \* Diagnosis of *suspected IAI* includes a maternal fever (> 39° C) or 38° - 39° C with one additional clinical risk factor: maternal leukocytosis, purulent cervical drainage or fetal tachycardia.
- \* Diagnosis of *confirmed IAI* is based on a positive amniotic fluid test consistent with infection or evidence of placental infection or inflammation

\* persists > 30 minutes

*Case*

*Intraamniotic Infection: ACOG Committee Opinion 2017*

- \* When IAI is *suspected or confirmed*, administer intrapartum antibiotics.
- \* Antibiotics should be considered in women with *isolated maternal fever*, unless a source other than IAI is identified and documented.

- \* Baby Kim was delivered at 37<sup>2/7</sup> weeks gestation following rupture of membranes for 26 hours. The mother was culture positive for GBS and received intrapartum antibiotics (ampicillin and gentamicin) 2.5 hours before delivery for a temperature of 38° C. The baby was suctioned and dried by the nurse and placed on NPCPAP with 21% O<sub>2</sub>. Apgar scores were 6 & 8 and the respiratory distress quickly resolved. The CPAP was discontinued.



*“Early-onset Sepsis and Risk Factors”*

*How would you manage this infant?*

- \* Supportive care and no antibiotics, testing or cultures
- \* Blood Culture and broad spectrum antibiotics
- \* Screening WBC/CRP and blood culture

| <i>Condition</i>                                       | <i>Incidence of Proven Sepsis</i> |
|--|-----------------------------------|
| <i>PROM &gt; 18 hours</i>                              | 1%                                |
| <i>Maternal + GBS (pre-prophylaxis era)</i>            | 0.5-1.0%                          |
| <i>Maternal + GBS (prophylaxis era)</i>                | 0.1-0.2%                          |
| <i>Maternal + GBS + other risk factors e.g., PROM)</i> | 4-7%                              |
| <i>Chorioamnionitis</i>                                | 3-8%                              |
| <i>GBS + and Chorioamnionitis</i>                      | 6-20%                             |
| <i>PROM &amp; Preterm</i>                              | 4-6%                              |
| <i>PROM &amp; low Apgar score</i>                      | 3-4%                              |

*Risk Factors are additive!*

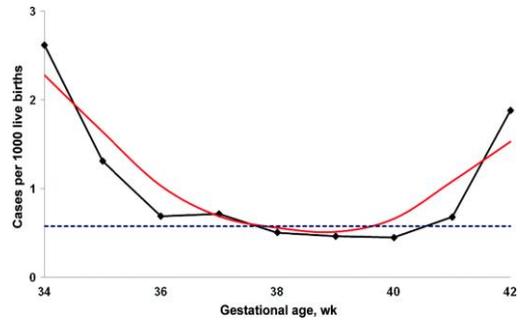
*Estimating the Probability of Neonatal Early-Onset Infection on the Basis of Maternal Risk Factors*

- \* Nested case control study of infants  $\geq 34$  weeks gestation
- \* Cases had early-onset sepsis ( $\leq 72$  hours) n = 350 (1,063 controls)
- \* Rather than using cutoff values, risk factors were treated as continuous variables.
- \* The two best predictive values were the highest maternal temperature and gestational age.

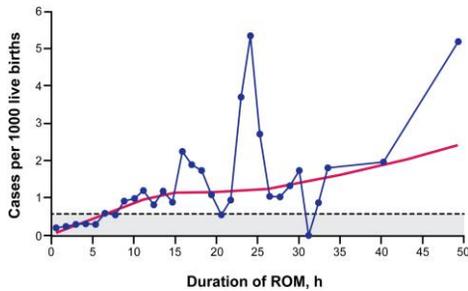
\* Nearly 1/3 of infants with positive cultures were asymptomatic in the first 12 hours of life

Puopolo et al Pediatrics 128: e1155, 2011

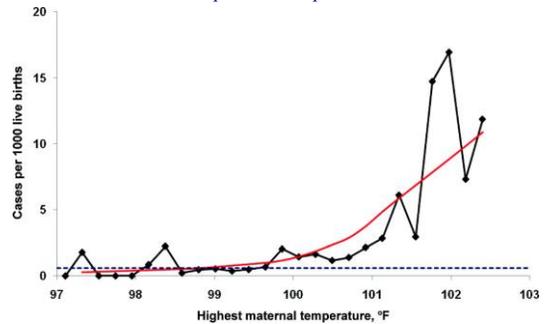
*Rate of sepsis according to gestational age*



*Rate of sepsis according to duration of rupture of membranes*



*Rate of sepsis according to highest maternal intrapartum temperature*



*Probability of Neonatal Early-Onset Infection Based on Maternal Risk Factors for Infants > 34 weeks gestation*

- \* Gestational age (weeks/days)
- \* Temperature
- \* ROM (Hours)
- \* GBS status (positive, negative, uncertain)
- \* Maternal intrapartum treatment (GBS specific or broad spectrum)
- \* Was IAP given  $\geq 4$  hours prior to delivery

Predicted probability/(1,000 live births) =

Puopolo et al 2011

*Probability of Neonatal Early-Onset Infection Based on Maternal Risk Factors for Infants  $\geq 35$  weeks gestation*

- \* Gestational age (weeks/days) 37 weeks 2 days
- \* Temperature 38.0° C
- \* ROM (Hours) 26 hours
- \* GBS status (positive, negative, uncertain) Positive
- \* Maternal intrapartum treatment Broad spectrum
- \* Was IAP given 2.0-3.9 hours prior to delivery Yes

Predicted probability/(1,000 live births) =

Puopolo et al Pediatrics 128: e 1155, 2011

### Stratification of Risk Early-Onset Sepsis in Newborns > 34 weeks

- \* Retrospective nested case (n = 350) control (n = 1063) study of infants  $\geq 34$  weeks gestation
- \* Probability of sepsis based on the risk estimation at birth (historical data – *pretest probability*) and the infant's clinical presentation (clinical illness, equivocal presentation or well appearing) during the first 6-12 hours of life (*post-test probability*). *Bayesian analysis*



Escobar et al Pediatrics 133: 30-36, 2014

### Sepsis is much less likely in a well-appearing infant With identical risk factors

|                             |   |       |
|-----------------------------|---|-------|
| <i>Well</i>                 | Predicted probability(/1,000 live births) = | 0.66  |
| <i>Equivocal</i>            | Predicted probability(/1,000 live births) = | 7.98  |
| <i>Clinical<br/>Illness</i> | Predicted probability(/1,000 live births) = | 32.97 |

<http://www.dor.kaiser.org/external/DORExternal/research/InfectionProbabilityCalculator.aspx>

Escobar et al Pediatrics 133: 30-36, 2014

### Management Controversies

- \* Does early-onset sepsis occur in infants who appear completely well at birth?
- \* Does suspected IAI in the mother mandate treatment of all newborn infants?
- \* How effective are serial observations alone without the sepsis calculator?

- \* *What is the risk of Sepsis in the Asymptomatic Infant?*

‡ In the well appearing term and late preterm infant at birth (with risk factors), the risk of sepsis is reduced by 60-70%, but it is not zero!

### Are Infants born to Women with an Intraamniotic infection Symptomatic or Asymptomatic?

- \* Retrospective observational study of 232 symptomatic and asymptomatic infants with EOS (+ blood or CSF) born to women with chorioamnionitis (229 records were reviewed)
- \* 48% had clinical and histologic chorioamnionitis; 18% had clinical chorioamnionitis alone; 34% had histologic chorioamnionitis alone
- \* 96% of preterm infants were symptomatic and 72% of term infants were symptomatic at birth (5 term infants developed symptoms within 72 hours of birth)
- \* All infants who died were symptomatic within 6 hours of birth.

Wortham et al Pediatrics 2016

### Risk of sepsis in the Asymptomatic Infant born to a Woman with an Intraamniotic Infection?

- \* Assuming complete implementation of current guidelines, the authors estimated that 60-1400 newborns would be evaluated and treated to identify one infected asymptomatic newborn with sepsis.
- \* How can we improve the precision of which infants get evaluated and treated?

Wortham et al Pediatrics 2016

### 2018 Recommendations from the AAP Committee on the Fetus and Newborn for Infants $\geq 35$ weeks gestation

- \* *No method* can be used to identify all infants with Early-onset sepsis with precision
- \* Each strategy has merits and limitations
- \* Each strategy must include measures to monitor the infant and minimize the duration of antibiotic therapy
- \* Birth centers should choose a strategy that is best suited to their local resources.

#### Limitations: Sepsis Calculator

- \* The sepsis calculator misses a substantial proportion of infants with early-onset sepsis (~ 40%) and recommends treatment of > 200 infants for each case of confirmed sepsis.
- \* Infants with an equivocal presentation and a calculator score  $\geq 1$  but < 3 require a blood culture an assessment every 4 hours for 24 hours.
- \* Blood cultures have poor sensitivity in that setting.
- \* Definition for an equivocal presentation is likely to overlap with that of well appearing depending on when assessments are made.

### 2018 Recommendations: Multivariate Risk Assessment

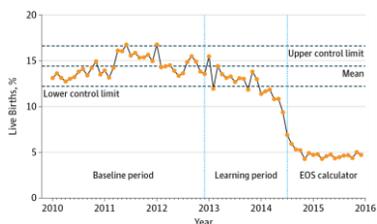
- \* “Sepsis calculator” based on a cohort of 608,000 newborn infants
- \* Uses objective data at birth and the evolving newborn condition at 6-12 hours of life.
- \* Blood culture and enhanced clinical observations are recommended for an EOS risk  $\geq 1$  per 1,000 but < 3/1000 live births
- \* Antibiotics are recommended for an EOS risk  $\geq 3$  per 1,000 live births

#### Validation Study for the Sepsis Calculator

- \* This retrospective cohort study (n ~ 200,000  $\geq 35$  weeks gestation) compared sepsis management in 3 time periods:
  - \* 2010-2012: when national guidelines were followed
  - \* 2012-2014: a learning/transitional period in which clinical signs were not included in the calculator
  - \* July 2014- December 2015: complete sepsis calculator was used

Kuzniewicz et al JAMA Pediatrics 2017

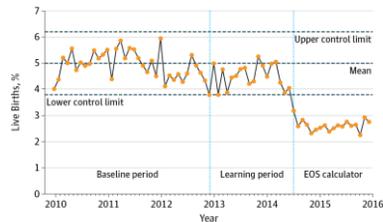
#### Monthly Sepsis Evaluation Rates



Blood cultures decreased from 14.5% to 4.9%

Kuzniewicz et al JAMA Pediatrics 2017

#### Monthly Antibiotic Treatment Rates



Empiric antibiotics decreased from 5.0% to 2.6%

Kuzniewicz et al JAMA Pediatrics 2017

### Validation of the Sepsis Calculator

- Of the 12 infants with positive blood cultures during period 3:
- 6 were *symptomatic* at birth with risk factors and were treated;
- 5 became *symptomatic well after birth* and were then cultured and treated; none of them would have been identified by the calculator.
- 1 infant had a predicted sepsis incidence of 2.3/1,000 live births and had a blood culture at birth, but was not treated. The initial blood culture was positive for GBS, but a follow-up blood culture was negative (transient bacteremia?).

Kuzniewicz et al JAMA Pediatrics 2017

### Retrospective Application of the Sepsis Calculator in Newborns with Suspected Infection\*

| Study  | Number of infants | Gestational age | Number of <i>true</i> positive blood cultures | Number of missed <i>true</i> positives |
|--------|-------------------|-----------------|---|--|
| Kerste | 108               | ≥ 34 weeks      | 2   | 2                                      |
| Carola | 896               | ≥ 35 weeks      | 2   | 2                                      |
| Money  | 362               | term            | 1   | 1                                      |
| Goel   | 3593              | > 34 weeks      | 5   | 2                                      |

\* In every study, antibiotic use was significantly reduced

### 2018 Recommendations: Serial Observations

- Relies on clinical signs of illness to identify infants with EOS
- Using this approach, regardless of any risk factors for EOS, infants who appear ill at birth and those who develop signs of illness up to 48 hours are either treated or evaluated by laboratory screening.

### Limitations: Serial Observations

- Limited data.
- This approach requires hospitals to develop systems for serial observations and documentation of findings.
- Adds to the cost of well newborn care.
- Who will do the assessments and in what setting will the serial assessments take place?

Are Frequent Observations without Laboratory Determinations an alternative to the sepsis calculator in well appearing infants ≥35 weeks' gestation ?

### "Watchful waiting" in well appearing infants born to women with an intraamniotic infection

| Study             | Total No. at risk infants (chorioamnionitis, fever or other risk factors identified by the CDC) | Cases of suspected sepsis | Culture proven sepsis in infants who were well appearing at birth | Number of infants harmed |
|-------------------|---|---------------------------|---|--------------------------|
| Jan (2017)        | 240 infants ≥ 35 weeks gestation  | 78                        | 12 (only 2 were symptomatic*)<br>* 10/12 abnormal labs            | 0                        |
| Berardi (2015)    | 3003 infants (≥ 35 weeks)   | 44                        | 4 (3 with severe symptoms and 1 with mild symptoms)               | 3                        |
| Ottolini (2003)   | 1665 infants (≥ 35 weeks)   | 17                        | 8   | 0                        |
| Cantoni (2013)    | 764 infants (≥ 37 weeks)  | 38                        | 0   | 0                        |
| Joshi (2017/2019) | 563 infants (≥ 34 weeks)  | 33                        | 1   | 0                        |

*Watchful waiting "in well appearing infants born to women with chorioamnionitis*

- \* Among 6235 infants, severe symptoms developed in 3 infants and might have been harmed by the "watchful waiting approach with risk factors for sepsis. NNH = 2078
- \* IV infiltration NNH = 9.1 when a risk factor based strategy is employed
- \* Delayed breast feeding (in first 2 hours of life) NNH = 2.1

*Conclusions and Recommendations*

- \* Late preterm and term babies with clinical signs of EOS should receive empiric antibiotic therapy.
- \* Asymptomatic late preterm infants and term infants, with risk factors for sepsis (including IAI) can be **closely observed** without empiric therapy **or** evaluated by using the **sepsis calculator** **plus** frequent observations.

*"A Successful Outcome to our case "*

- § The blood culture was negative and because of the unremarkable laboratory values, the infant was only treated for 48 hours. As 'baby Kim' grew up he decided to style and color his hair differently and eventually became President of the United States (defeating a well known celebrity).

