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

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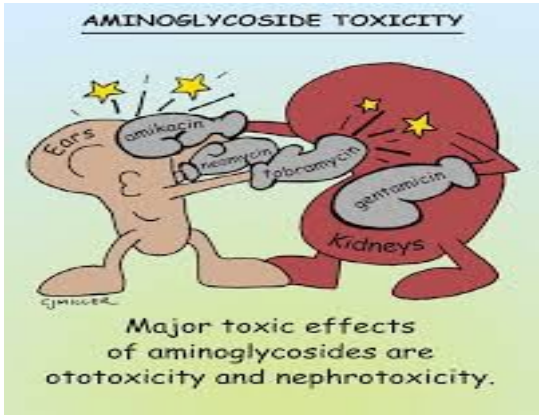
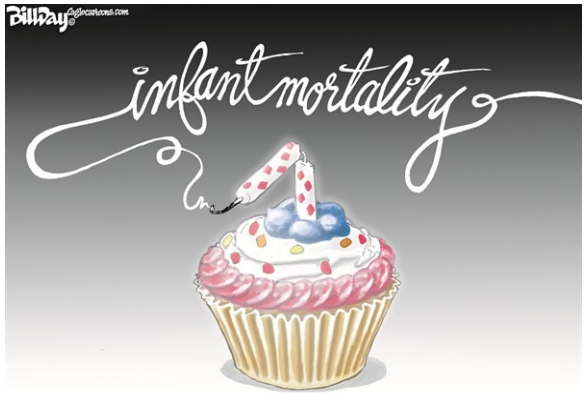
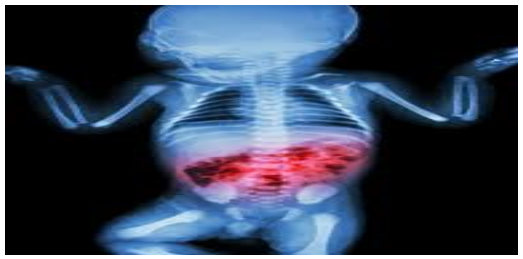




Dysbiosis

BPD



NEC

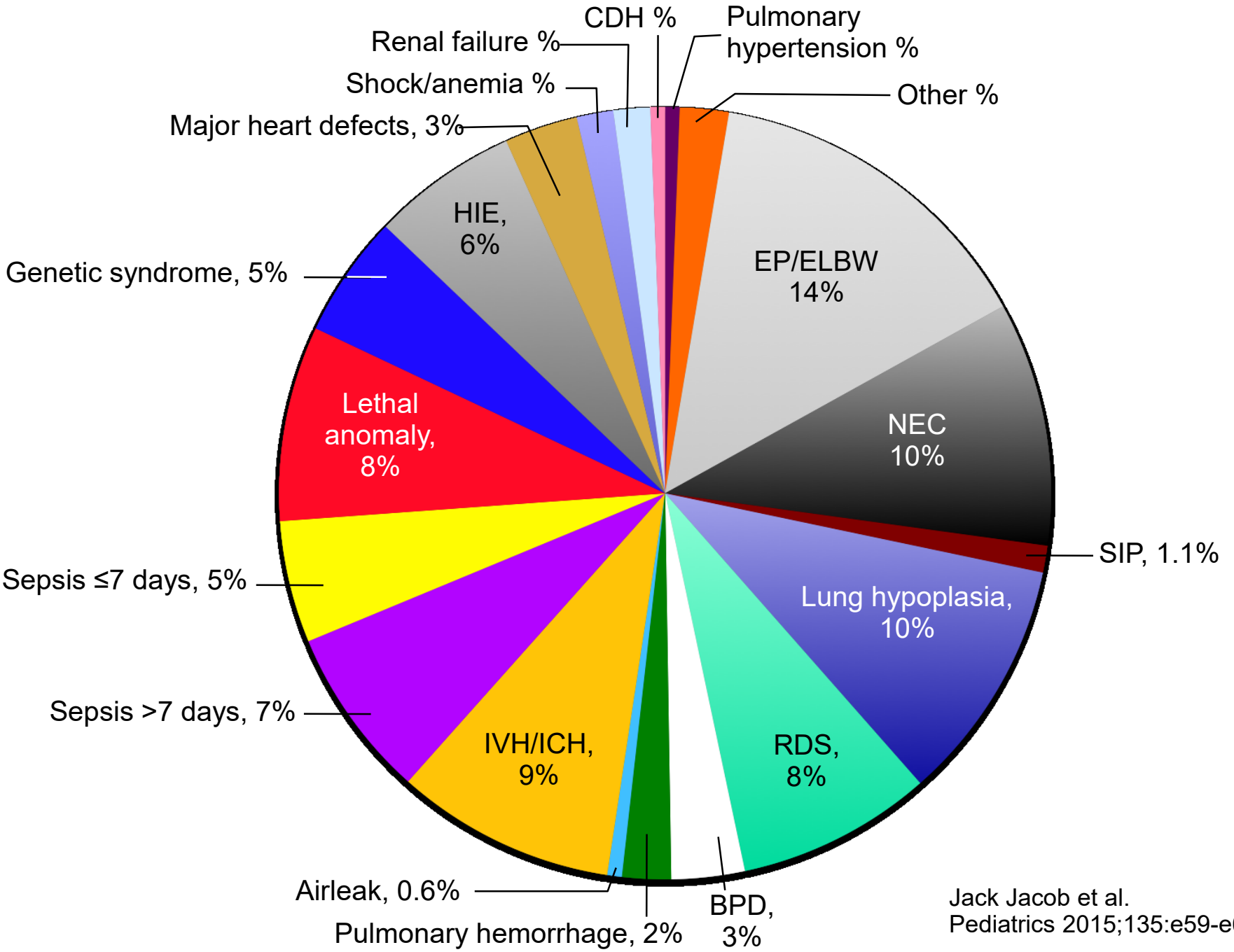
Consequences of Indiscriminate Use of Antibiotics

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

Neonatal Sepsis by the Numbers

- 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
- ★ In VLBW infants the incidence of sepsis is 20 times that of infants born at term.
- ★ 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

Causes of death in the NICU



Jack Jacob et al.
Pediatrics 2015;135:e59-e65

- How do we identify the infant with clinical signs or risk factors who is actually infected? i.e., *finding a needle in the haystack*

Key Question

- Can we *safely* decrease antibiotic exposure in newborn infants at "lower" risk for sepsis?

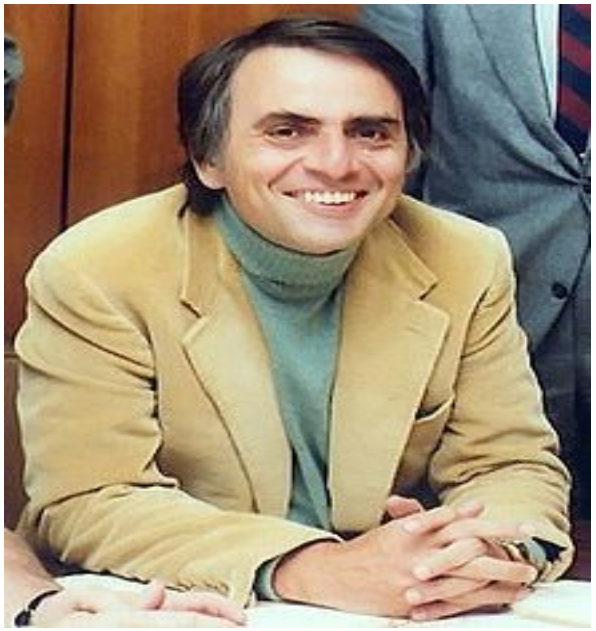
Term & Late Preterm Infants with Clinical Signs or Risk factors for EOS who may not require antibiotics

- Healthy appearing infants (≥ 35 weeks gestation) *with risk factors* for sepsis (including chorioamnionitis).
- Symptomatic term or late preterm infants with non-infectious diseases (RDS or TTN) and *no risk factors* for sepsis (who are not critically ill).

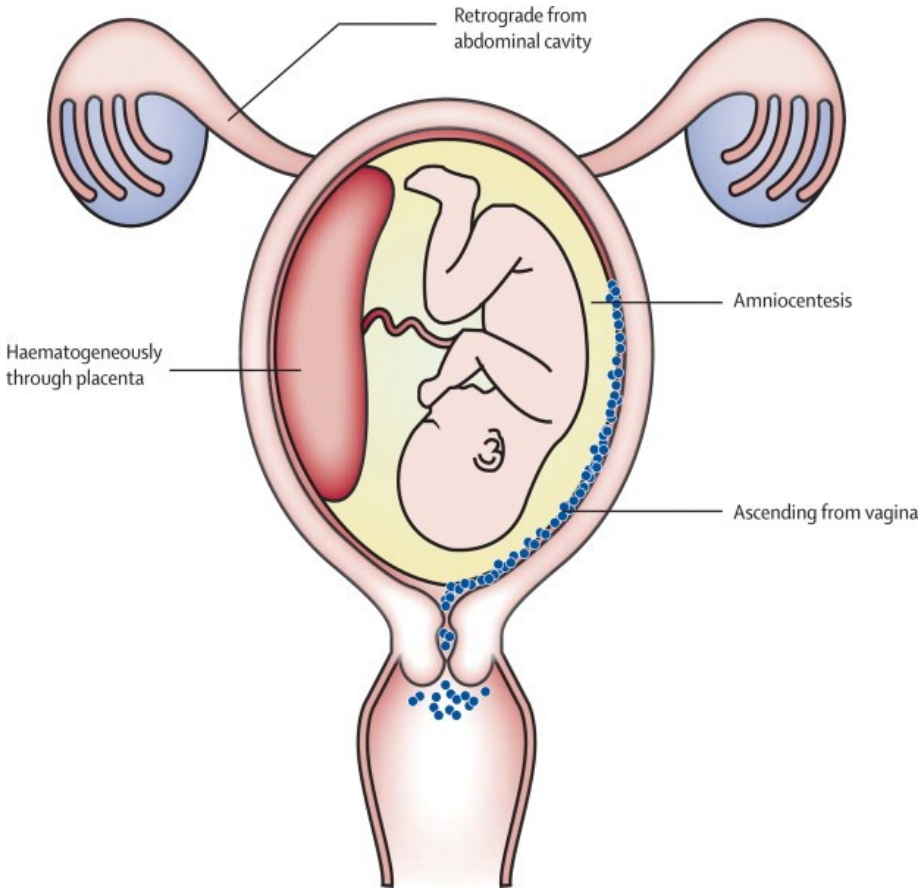
Disclosures About Evidence

- 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*

Chorioamnionitis 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

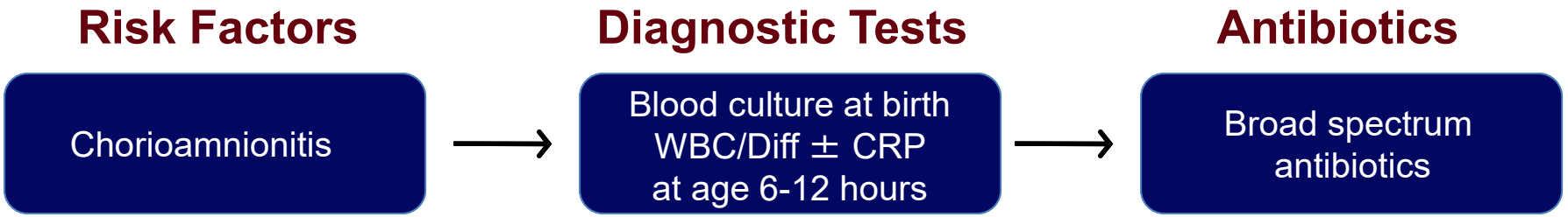
- *The definition of chorioamnionitis is important because it determines subsequent management of the infant.*

Guidelines

mea culpa

AAP Recommendation 2012

Evaluation of Asymptomatic Infants Risk Factor - Chorioamnionitis



★ *National Institute for Health and Clinical Excellence (NICE guideline 2012)*

★ Begin antibiotics in any neonate born to a mother who received antibiotics for a confirmed or suspected bacterial infection

Risk Factors		Diagnostic Tests		Antibiotics
Chorioamnionitis	→	Blood culture at birth CRP before starting antibiotic	→	Benzyl penicillin and gentamicin

★ In the most recent NICE guidelines, suspected chorioamnionitis is not considered a major risk factor for neonatal sepsis. Treatment of the neonate depends on clinical signs and "red flags"

★ *National Institute for Health and Clinical Excellence (NICE guideline 2016)*

Quality standards

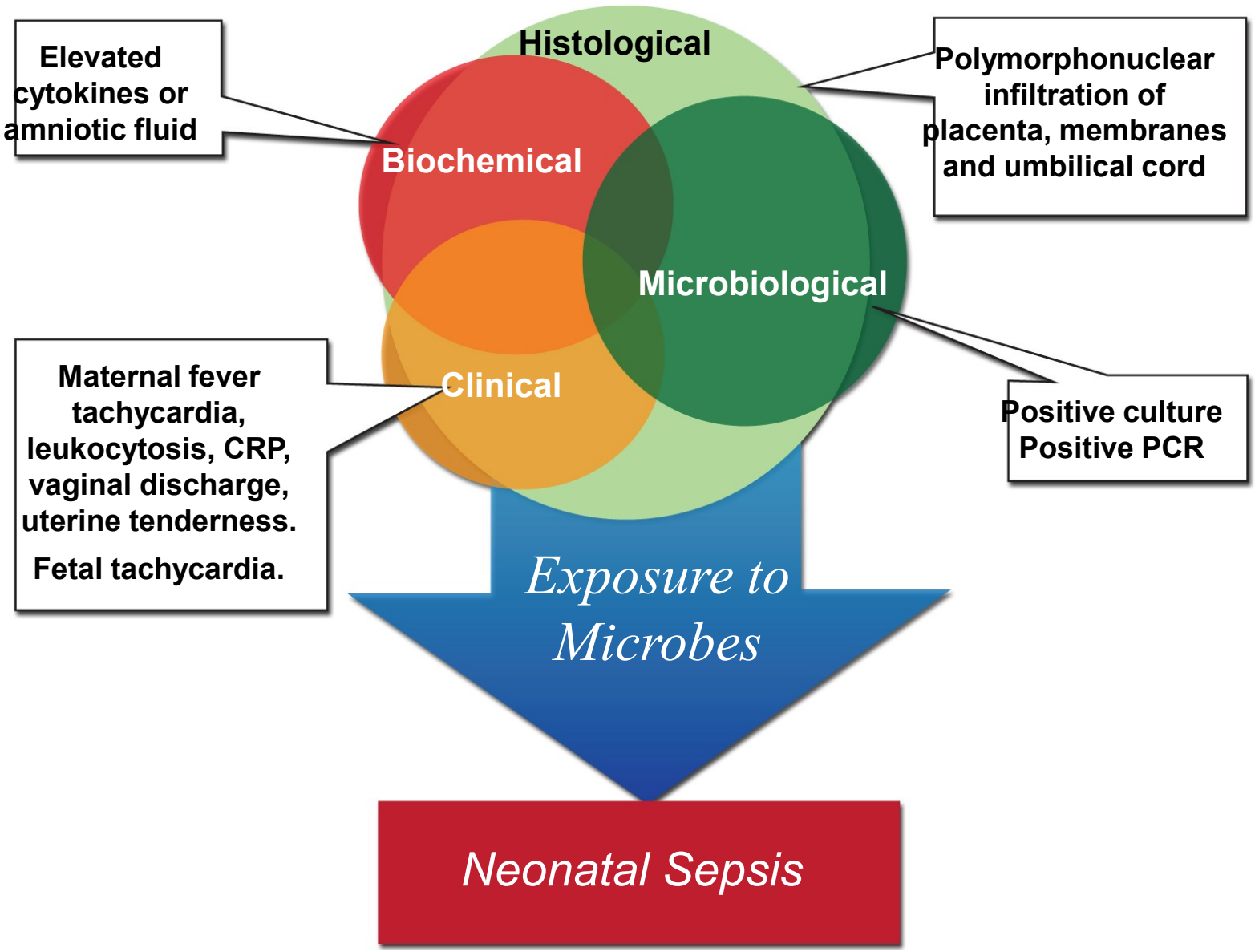
Risk Factor	*Red Flag*
Parenteral antibiotic treatment given to the woman for confirmed or suspected invasive bacterial infection (such as septicemia) at any time during labor, or in the 24-hour periods before and after the birth [This does not refer to intrapartum antibiotic prophylaxis.	Yes
Suspected or confirmed infection in another baby in the case of a multiple pregnancy	Yes

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 at al AD-FNN 2014; Kiser et Pediatrics 2014

Can we Diagnose Clinical Chorioamnionitis with Better Precision?


Elevated cytokines or amniotic fluid
Histological
Biochemical
Polymorphonuclear infiltration of placenta, membranes and umbilical cord
Microbiological
Clinical
Maternal fever tachycardia, leukocytosis, CRP, vaginal discharge, uterine tenderness.
Fetal tachycardia.
Positive culture
Positive PCR
Exposure to Microbes
Neonatal Sepsis

Intraamniotic Infection: ACOG Committee Opinion 2017

- The term chorioamnionitis was replaced by *intraamniotic infection* to signify infection of the amniotic fluid, placenta, fetus, fetal membranes or decidua.
- 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

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.

Problems with the New ACOG Definition of Intraamniotic Infection

- Fever will still be used as the sole criteria for intraamniotic infection by obstetricians.
- The source of fever may be extrauterine or environmental
- The diagnosis generally represents a "guess" on the part of the obstetrical provider, before laboratory data are available (lacks precision).

Case

- An infant is delivered at $37^{2/7}$ weeks gestation following rupture of membranes for 26 hours. Intrapartum antibiotics (ampicillin and gentamicin) were given to the mother 2 hours before delivery. He was suctioned and dried by the nurse and placed on NPCPAP with 21% O_2 . Apgar scores were 6 & 8 and the respiratory distress quickly resolved. The CPAP was discontinued.

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

- *Symptomatic or Asymptomatic*
- *Presence or Absence of Risk Factors*

Achieving a Treatment Threshold for Early-Onset Sepsis

Critically Ill
Symptomatic

Treatment
Abnormal

Observe

Diagnostic testing

No risk factors
(not critically ill)

Asymptomatic and Risk Factors

Treatment

Diagnostic testing

Observation

Normal
No treatment

"Early-onset Sepsis and Risk Factors"

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

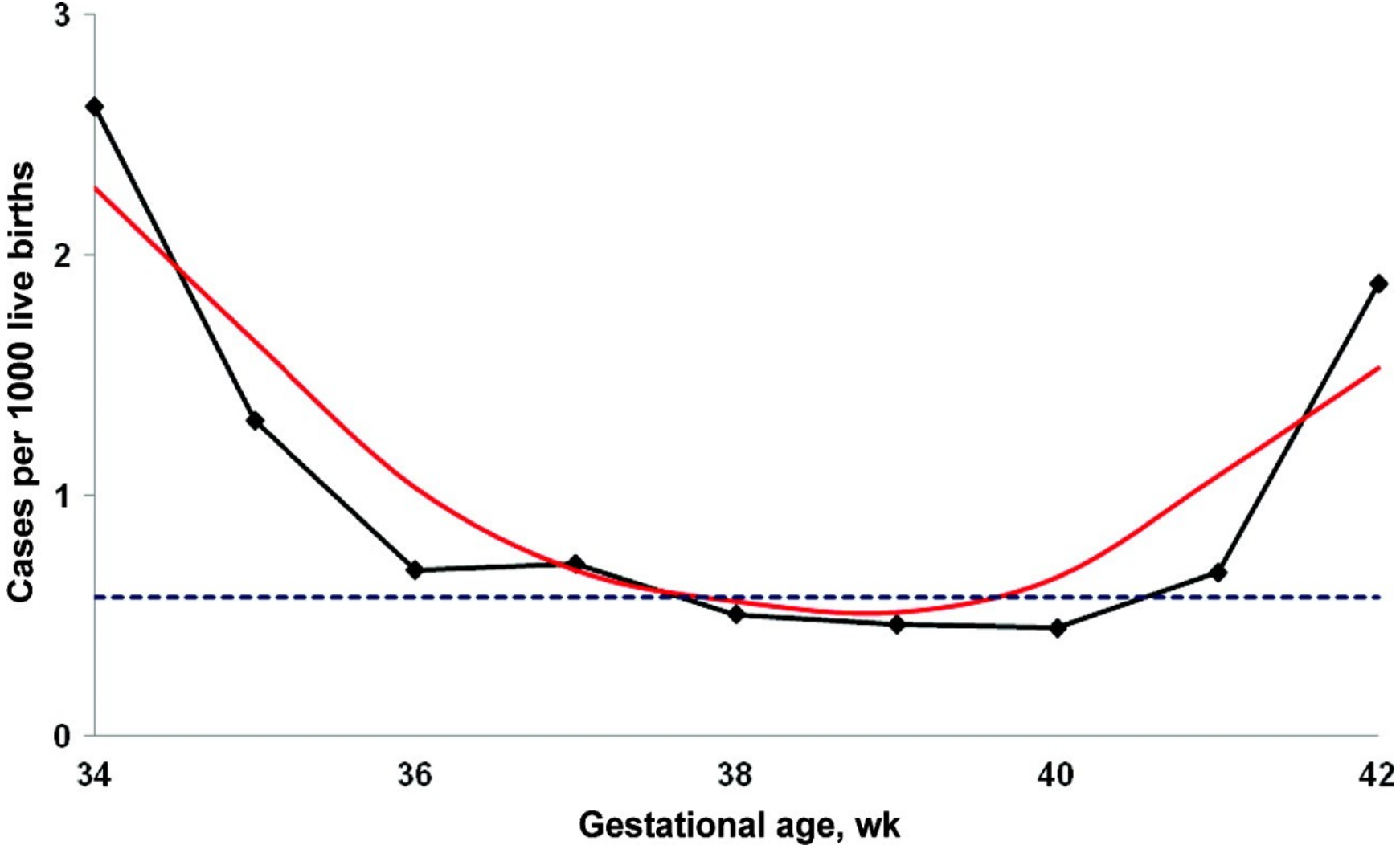
Risk Factors are additive!

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

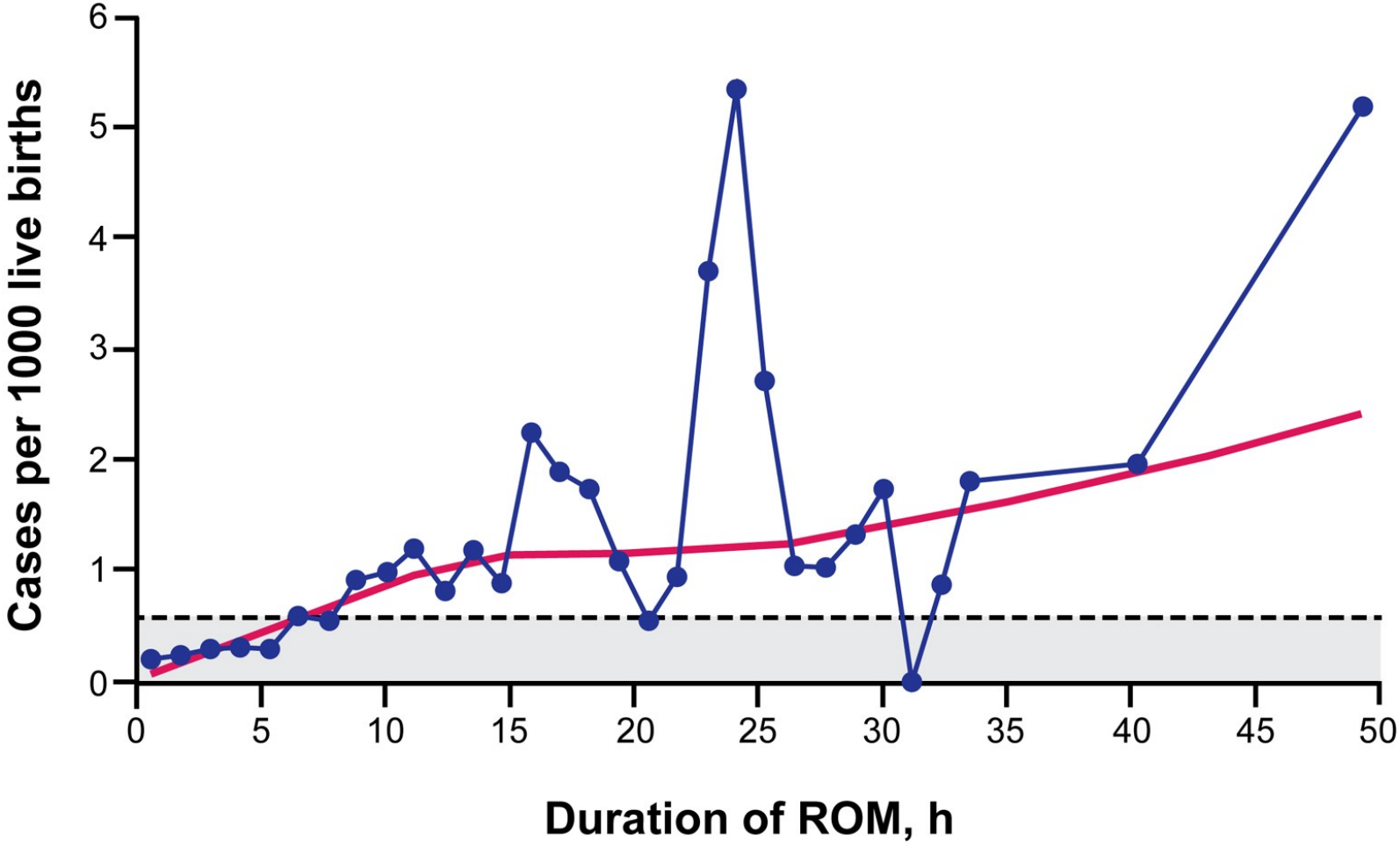
- Nested case control study of infants ≥ 34 weeks gestation
- Cases had early-onset sepsis (≤ 72 hours) n = 350 (1,063 controls)
- Rather than using cutoff values, risk factors were treated as continuous variables.
- The two best predictive values were the highest maternal temperature and gestational age, which accounted for 58% and 17% of the predictive model.

Puopolo et al Pediatrics 128: e1155, 2011

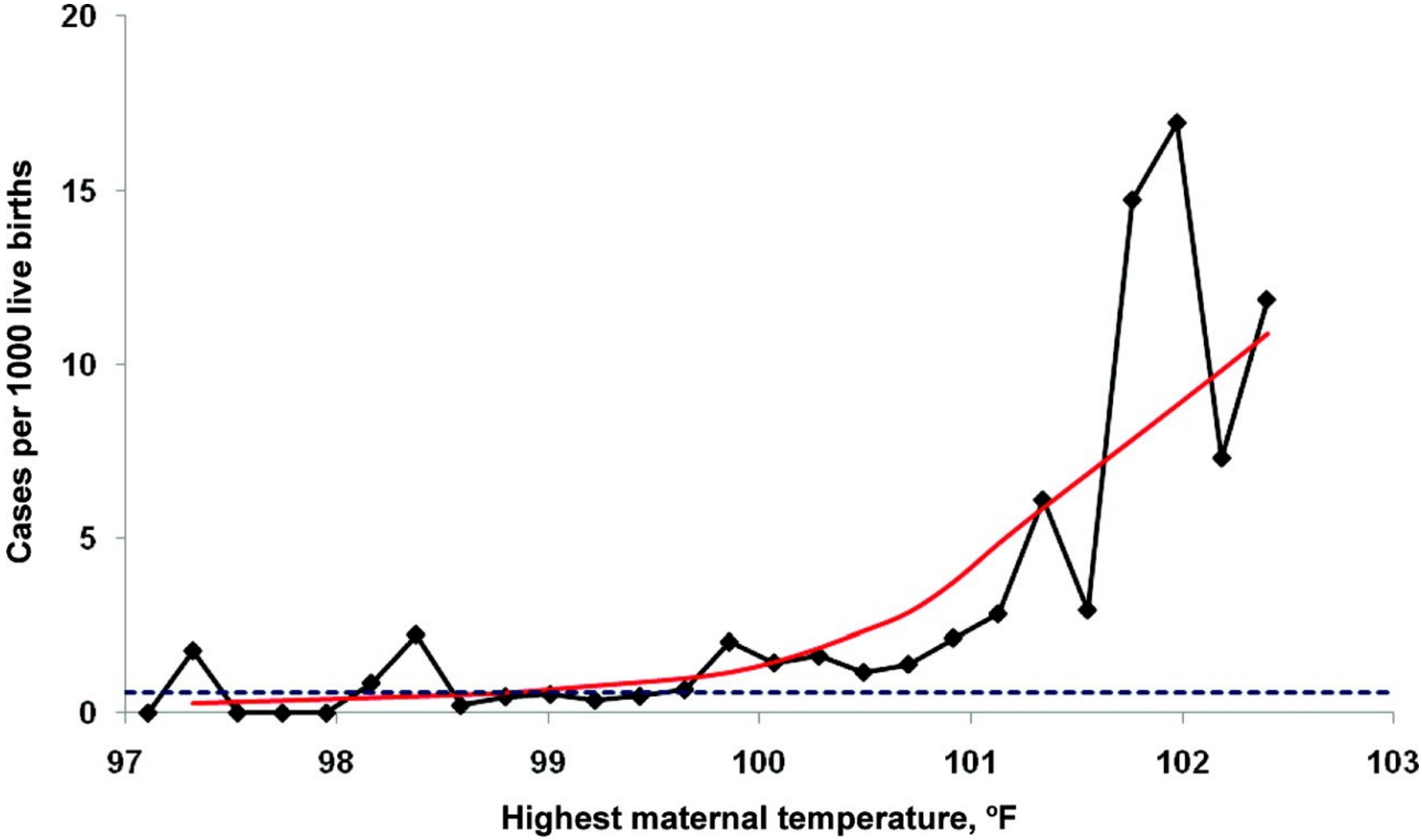
Rate of sepsis according to gestational age



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 ≥ 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 ≥ 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) = *1.61*

Puopolo et al Pediatrics 128: e 1155, 2011

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

- Retrospective nested case (n = 350) control (n = 1063) study of infants ≥ 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*

Pretest Probability
Risk of sepsis based on historical data

Escobar et al Pediatrics 133: 30-36, 2014

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

Well	Predicted probability(/1,000 live births) =	*0.66*
Equivocal	Predicted probability(/1,000 live births) =	*7.98*
Clinical Illness	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 of Neonates with Suspected Sepsis

Management of Symptomatic Infants

- When sepsis is suspected because of abnormal signs, broad spectrum antibiotics should be given.
- However, some infants will become asymptomatic within 6 hours of birth as they undergo the transition to postnatal life; those infants can be observed (especially if there are no risk factors for sepsis)

Current Controversies

- Does early-onset sepsis occur in infants who appear completely well at birth?
- What is the value of the sepsis calculator vs. close observation?

Risk of sepsis in the asymptomatic Infant born to a woman with chorioamnionitis?

- 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*

Wortham et al Pediatrics 2016

Risk of sepsis in the asymptomatic Infant born to a woman with chorioamnionitis?

- All infants who died were symptomatic within 6 hours of birth.
- Assuming complete implementation of current guidelines and a chorioamnionitis prevalence of 0.5%, 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

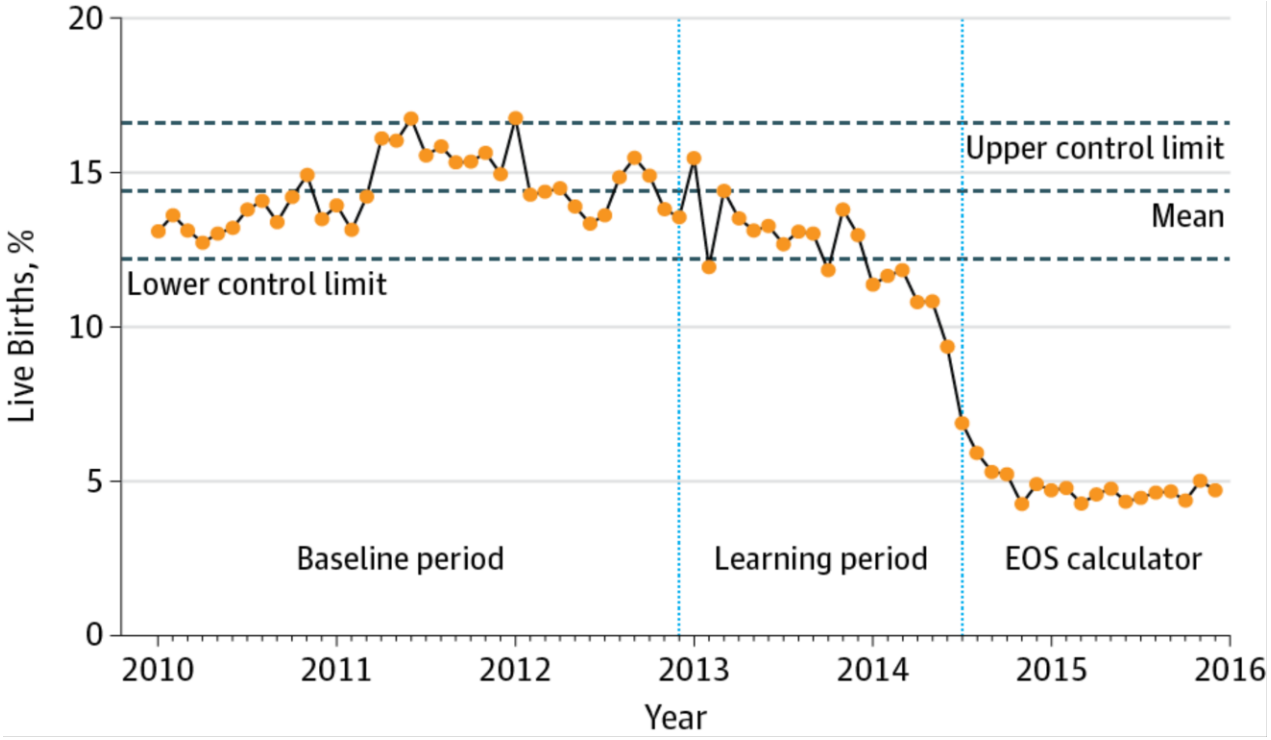
What is the Value of the Sepsis Calculator?

Validation Study for the Sepsis Calculator

- This retrospective cohort study (n ~ 200,000 ≥ 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

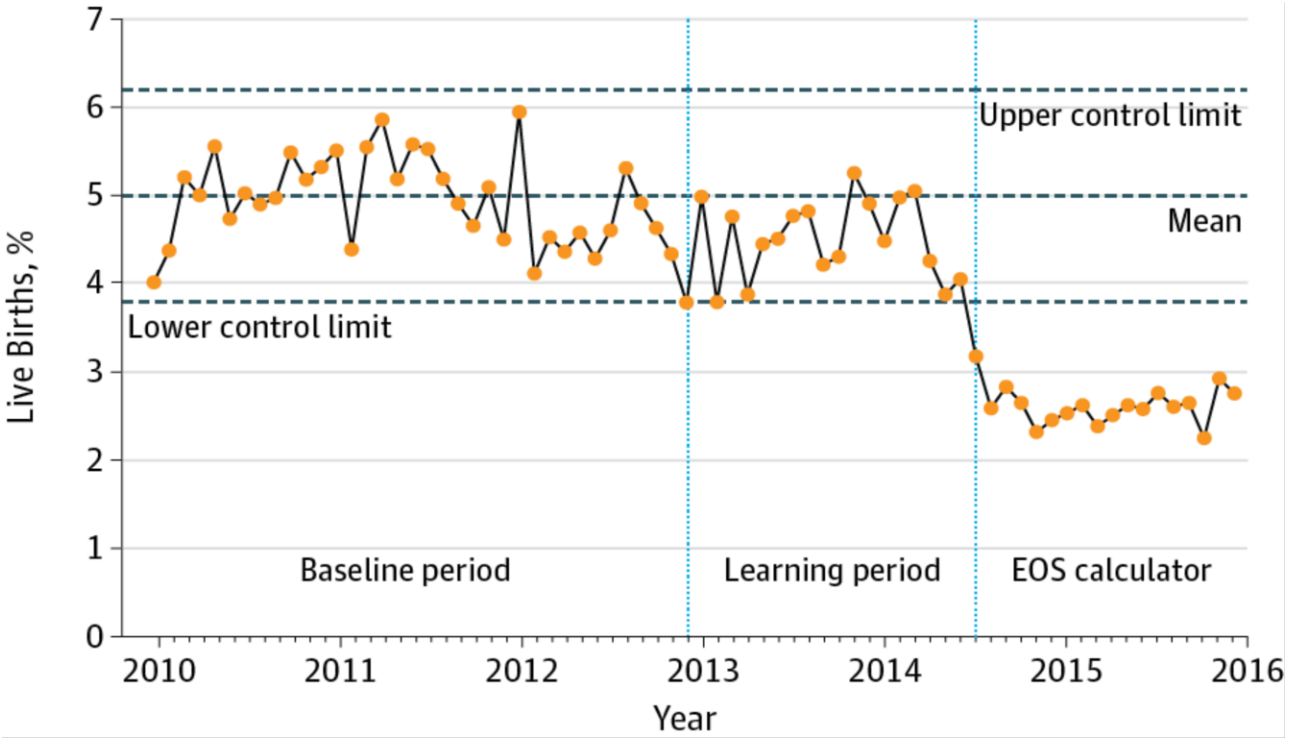
Monthly Sepsis Evaluation Rates



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

Does the Sepsis Calculator Improve Upon a Careful Physical Examination?

- 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

The Sepsis Calculator – Remaining Controversies

- Definition for an equivocal presentation is likely to overlap with that of well appearing depending on when assessments are made.
- When using the calculator, what should the thresholds be for choosing observations without testing, only drawing a blood culture or administering empiric antibiotics?

Are Frequent Observations an alternative to the sepsis calculator in well appearing infants $\geq$ 35 weeks' gestation ?

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

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*) * 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)	277 infants (≥ 34 weeks)	32	0	0

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

- Among 5,949 infants, severe symptoms developed in 3 infants and might have been harmed by the "watchful waiting approach with risk factors for sepsis. NNH = 1611
- 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

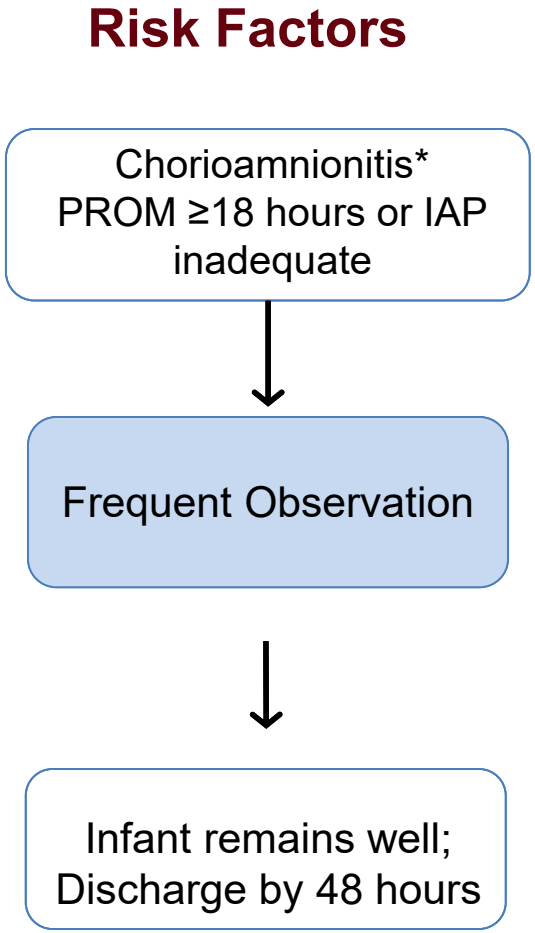
Controversies surrounding Physical Examination

- Data are limited.
- Which groups of infants can be safely observed
- What is the ideal frequency of observations and who will do them?
- How will serial physical examinations be documented?
- When should interventions take place?

Conclusions and Recommendations

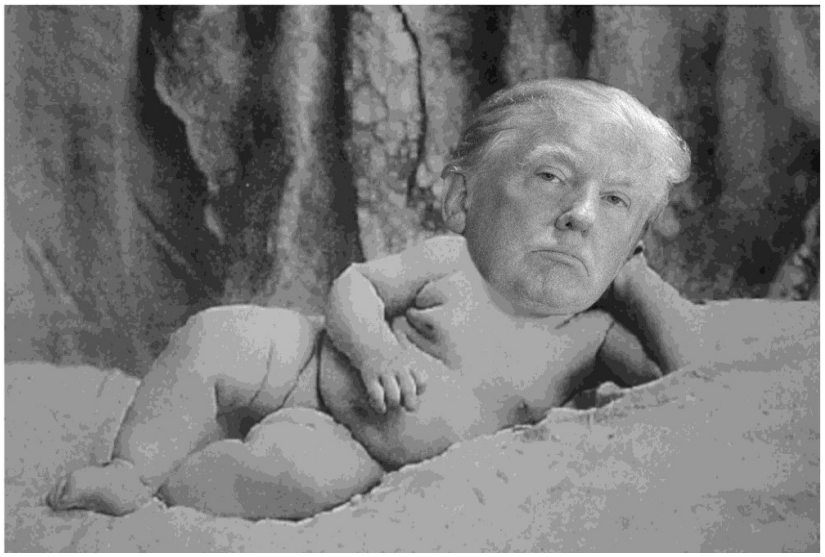
- Routine laboratory testing may not be of much value in the the modern era (controversial).
- Babies with clinical signs of EOS should receive empiric antibiotic therapy.
- Asymptomatic late preterm infants and term infants, with risk factors for sepsis (including chorioamnionitis) can be closely observed without empiric therapy or evaluated by using the sepsis calculator.
- More data are needed before antibiotics can be excluded in symptomatic preterm infants without risk factors

Evaluation of Asymptomatic Infants ≥ 35 Weeks Gestation with Risk Factors for Sepsis (including chorioamnionitis):



"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 the infant grew up he became a billionaire (selling toupees) and eventually became President of the United States.



"Trump Hair piece"