PEDIATRIC INFECTIOUS DISEASES WEEKEND 2014

Symposium:

INFECTION IN NEONATES AND INFANTS (Part I)

Diselenggarakan atas kerjasama:

IDAI Cabang Jawa Timur (Perwakilan Jatim I, II, III),
Kelompok Studi Penyakit Infeksi dan Tropik Anak Surabaya
dan Departemen Ilmu Kesehatan Anak FK Unair/
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INFECTION IN NEONATES AND INFANTS: EPIDEMIOLOGY ASPECTS

(INFEKSI PADA NEONATUS DAN BAYI: ASPEK EPIDEMIOLOGI)

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ABSTRACT

Neonatal infection is a one of the major cause of death and morbidity, especially in the first week of their life. So it is important to know about epidemiology aspects of neonatal infection and prevent neonatal sepsis by early diagnosis of Early Onset Sepsis (EOS) and managed this condition, as the first golden hours in neonatal infection.

The challenges for clinicians are three fold: (1) identifying neonates with a high likelihood of sepsis promptly and initiating antimicrobial therapy; (2) distinguishing "high risk" healthy-appearing infants or infants with clinical signs who do not require treatment; and (3) discontinuing antimicrobial therapy once sepsis is deemed unlikely.

The optimal treatment of infants with suspected EOS is broad-spectrum antimicrobial agents (ampicillin and aminoglycoside). Once the pathogen is identified, antimicrobial therapy should be narrowed (unless synergism is needed). Antimicrobial therapy should be discontinued at 48 hours in clinical situations in which the probability of sepsis is low.

Keyword: *Infection in neonates and infants, epidemiology aspects.*

INTRODUCTION

Infection is a major cause of death in newborn infants. "Suspected sepsis" is one of the most common diagnoses made in the NICU. However, the signs of sepsis are non specific, and inflammatory syndromes of non infectious origin mimic those of neonatal sepsis. EOS in neonates continues to be a serious and feared complication.[1,2]

Early Onset Sepsis (EOS) from group β-Streptococcus (GBS) has decreased with the widespread use of Intrapartum Antibiotic Prophylaxis (IAP), which has led to declines in the overall incidence of EOS among term and late preterm infants. The Centers for Disease Control and Prevention (CDC) 2002 (and revised 2010) Guidelines for the prevention of neonatal GBS disease provide algorithms for the evaluation of infants at risk for EOS. Estimating the probability of neonatal EOS on the basis of maternal risk factors better than algorithms based on risk-factor threshold values. This model establishes a prior probability for newborn sepsis, which could be combined with neonatal physical examination and laboratory values to establish a prior probability to guide treatment decisions.[1,2,3]

The challenges for clinicians are three fold: (1) identifying neonates with a high likelihood of sepsis promptly and initiating antimicrobial therapy; (2) distinguishing "high risk" healthy-appearing infants or infants with clinical signs who do not require treatment; and (3) discontinuing antimicrobial therapy once sepsis is deemed unlikely.[1,2,3]

The purpose of this paper is encourage all of us to know about epidemiology aspects of neonatal infection and aware to this three fold: (1) identifying neonates with a high likelihood of sepsis promptly and initiating antimicrobial therapy; (2) distinguishing "high risk" healthy-appearing infants or infants with clinical signs who do not require treatment; and (3) discontinuing antimicrobial therapy once sepsis is deemed unlikely.

EPIDEMIOLOGY ASPECTS

The incidence rate of neonatal infection in several refferral hospitals in Indonesia is approximately 8.76-30.29%, with the mortality rate is 11,56-49,9%. Cipto Mangunkusumo Hospital reported at January-September 2005, the incidence of sepsis was 13.68% with the mortality rate 14.18%. Dr Soetomo Hospital reported that 49 from 2416 patients showed bacterial positive blood culture (proven bacteremia sepsis).[4]

The overall incidence of EOS in the United States in the past 10 years is 1 to 2 cases per 1,000 live births; the incidence is 10 fold higher in VLBW infants.[5]

Mikrobiology EOS

Table 1. Organisms Causing Neonatal Early-onset Sepsis

Organism	Centers for Disease Control and Prevention (n=408)	%	Brigham and Women's Hospital (n=307)	%
GBS	166	40.7	130	42.3
Escherichia coli	70	17.2	64	20.8
Other streptococci*	93	22.7	37	12.1
Enterococcus	16	3.9	13	4.2
Staphylococcus aureus	15	3.7	12	3.9
CONS	–	–	14	4.6
Listeria	6	1.5	2	0.7
Bacteroides	5	1.2	14	4.6
Klebsiella	9	2.2	4	1.3
Haemophilus influenzae	9	2.2	6	2.0
Other gram-negative†	18	3.9	5	1.6
Other‡	3	0.7	6	2.0
Total gram-positive	299	73.3	211	68.7
Total gram-negative	109	26.7	96	31.3

CONS=coagulase-negative *Staphylococcus*, GBS=group B *Streptococcus*.
*Other streptococci include *S pneumoniae*, *S bovis*, *S mitis*, *Peptostreptococcus*, and viridans streptococci.
†Other gram-negative organisms include *Pseudomonas*, *Proteus*, *Morganella*, and *Torulopsis*.
‡Other organisms include *Bacillus* and *Clostridium*.
Adapted from Hyde et al. *Pediatrics* 2002;110:690–695.

Epidemiology EOS, Neo Reviews 2008;9;e571 (Puopolo, 2008).[5]

Mikrobiology EOS

Table 2. Organisms Causing Early-onset Sepsis in Very Low-birthweight Infants

Organism	National Institute of Child Health and Development (n=102)	%	Brigham and Women's Hospital (n=95)	%
GBS	12	11.8	20	21.1
Escherichia coli	42	41.2	31	32.6
Other streptococci[a]	9	8.8	12	12.6
CONS	15	14.7	5	5.3
Listeria	2	2.0	1	1.1
Other gram-positive[b]	8	7.8	5	5.3
Bacteroides	N/A	-	9	9.5
Haemophilus influenzae	2	2.0	3	3.2
Enterobacter	4	3.9	1	1.1
Citrobacter	3	2.9	2	2.1
Other gram-negative[c]	3	2.9	4	4.2
Fungal	2	2.0	2	2.1
Total gram-positive	48	45.1	43	45.3
Total gram-negative	54	52.9	50	52.6

CONS=coagulase-negative *Staphylococcus*; GBS=group B *Streptococcus*.
[a]Other streptococci include *S pneumoniae*, *S mitis*, viridans streptococci, and group A *Streptococcus*.
[b]Other gram-positive organisms include *Bacillus*, *Corynebacterium*, *Staphylococcus aureus*.
[c]Other gram-negative organisms include *Klebsiella*, *Pseudomonas*, *Acinetobacter*, *Proteus*, *Morganella*, and *Pasteurella*.
Adapted from Stoll et al. *Pediatr Infect Dis J*. 2005;24:635–639.

Epidemiology EOS, Neo Reviews 2008;9;e571 (Puopolo, 2008).[5]

Mikrobiology EOS & LOS

Tabel 4. Jenis mikroorganisme penyebab sepsis neonatorum (n=102)

Jenis mikroorganisme	Awitan sepsis		Jumlah	%
	dini	lambat		
Acinetobacter calcoaceticus	15	0	15	14,7
Staphylococcus epidermidis	5	2	7	6,9
Enterobacter aerogenes	5	0	5	4,9
Pseudomonas sp	4	0	4	3,9
Eschericia coli	2	2	4	3,9
Klebsiella pneumoniae	2	0	2	2
Klebsiella sp	1	0	1	1
Proteus mirabilis	0	1	1	1
Streptococcus viridans	1	0	1	1
Streptococcus anhemolyticus	1	0	1	1
Candida tropicalis	0	1	1	1
Sel ragi	0	1	1	1
Steril	53	6	59	57,8
Total	89	13	102	100

Microorganism profile as the cause of neonatal sepsis in Childhealth Dept. Cipto M Hospital Jakarta, Sari Pediatri, Vol 10, 2008 (Aminullah A, 2008).[6]

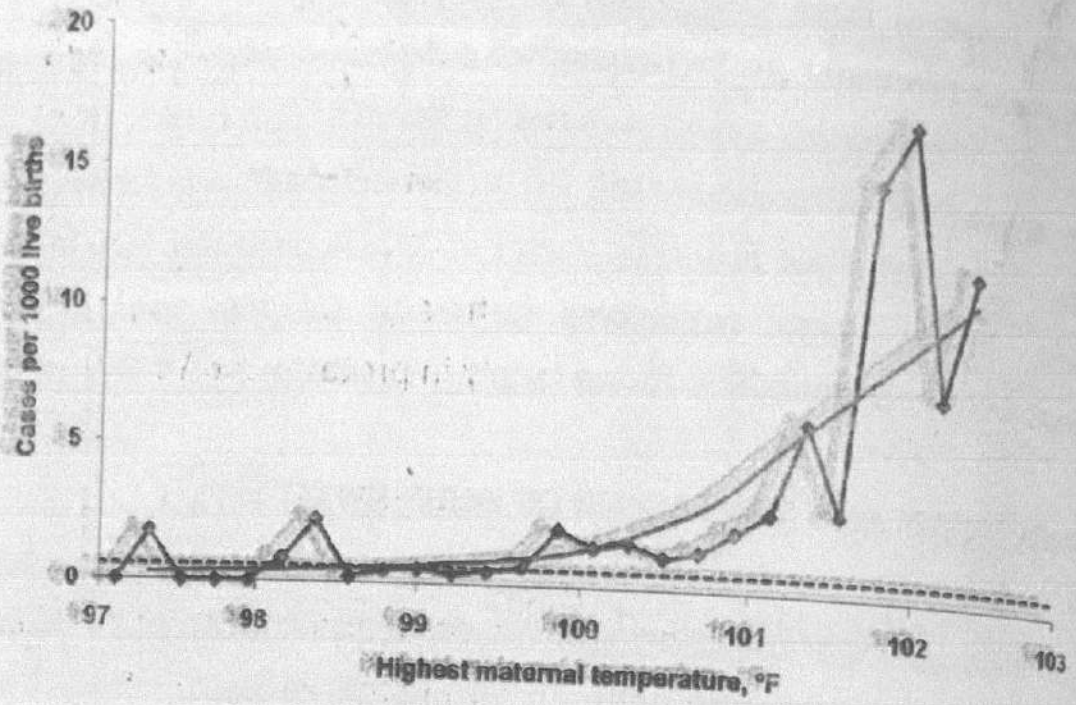
OTHER ORGANISMS RESPONSIBLE FOR EOS

Although both methicillin-sensitive and methicillin-resistant *S aureus* (MRSA) cause a large proportion of hospital acquired infection in VLBW infants and represent an increasing issue in community-acquired pediatric infections, they remain a rare cause of neonatal EOS. A recent study of 5,732 pregnant women documented a 3.5% incidence of MRSA in GBS rectovaginal screening cultures but found no cases of MRSA neonatal EOS in delivered infants. Finally, fungal organisms (primarily Candida spp) rarely cause neonatal EOS. Fungal EOS is found largely in preterm and VLBW infants.[5]

PATHOGENESIS AND RISK FACTOR OF EARLY ONSET SEPSIS

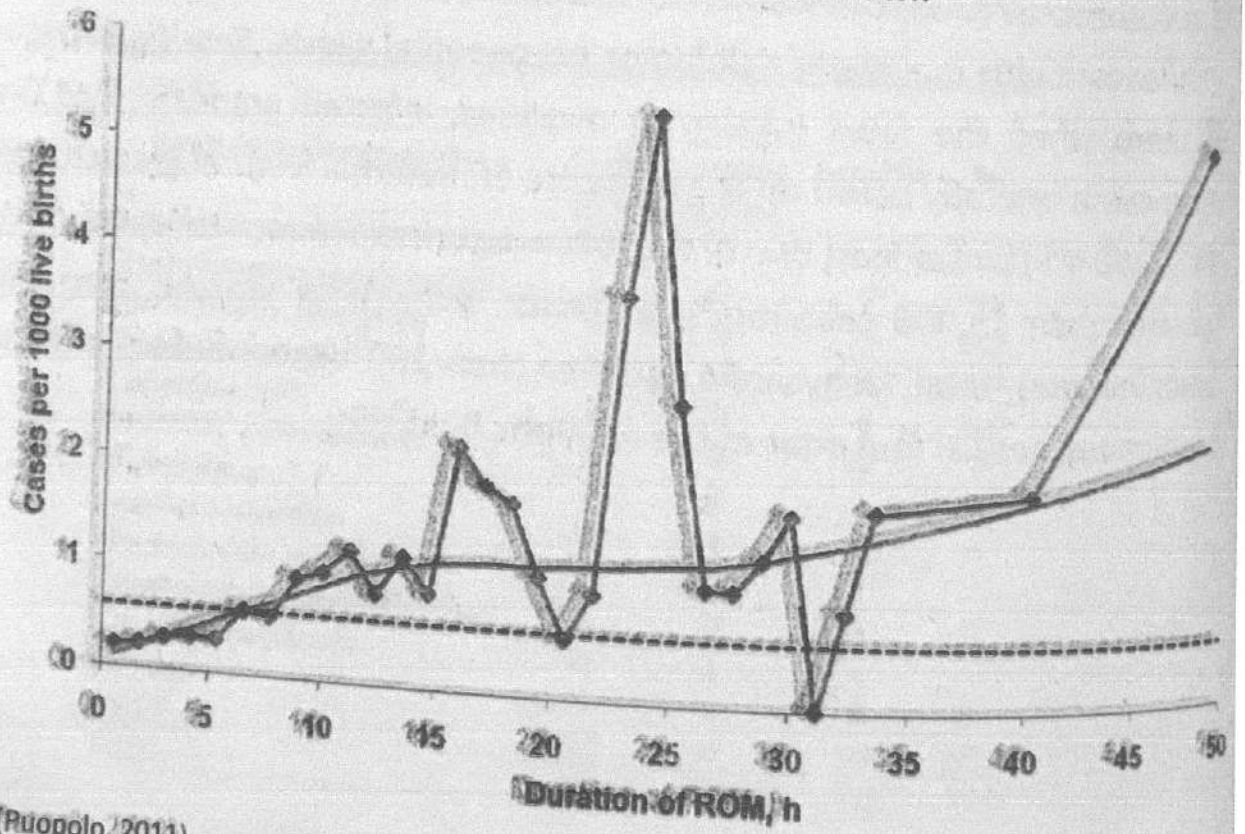
Before birth, the fetus optimally is maintained in a sterile environment. Organisms causing EOS ascend from the birth canal either when the amniotic membranes rupture or leak before or during the course of labor, resulting in intra-amniotic infection. Chorioamnionitis as intra-amniotic infection indicates infection of the amniotic fluid, membranes, placenta, and/or decidua. Group β streptococcus (GBS) can also enter the amniotic fluid through occult tears. Chorioamnionitis is a major risk factor for neonatal sepsis. Sepsis can begin in utero when the fetus inhales or swallows infected amniotic fluid.The diagnosis is typically based on the presence of maternal fever of greater than 38°C (100.4°F) and at least two of the following criteria: maternal leukocytosis (greater than 15,000 cells/mm^3), maternal tachycardia (greater than 100 beats/minute), fetal tachycardia (greater than 160 beats/minute), uterine tenderness, and/or foul odor of the amniotic fluid.[1,2,3]

Figure 1. Rate of sepsis according to highest maternal intra-partum temperature.[2]



(Puopolo, 2011)

Figure 2. Rate of sepsis according to duration of ROM.[2]



(Puopolo, 2011)

The major risk factors for EOS are preterm birth, maternal colonization with GBS, rupture of membranes (ROM) >18 hours, and maternal signs or symptoms of intra-amniotic infection.[1,2,3]

The major perinatal risk factors for neonatal sepsis are listed in Table 1. 4

Table 1
Risk factors for neonatal sepsis

Conditions	Incidence of proven sepsis
PROM >18 hours	1%
Maternal + GBS (preprophylaxis era)	0.5%–1%
Maternal + GBS (in prophylaxis era)	0.2%–0.4%
Maternal + GBS and PROM, fever or preterm	4%–7%
Chorioamnionitis	3%–8%
+GBS and chorioamnionitis	6%–20%
PROM + preterm	4%–6%
PROM + low Apgar score	3%–4%

(Gerdes, 2004)

DIAGNOSTIC TESTING FOR EARLY ONSET SEPSIS

Blood Culture

A single blood culture in a sufficient volume is required for all neonates with suspected sepsis. Although 0.5 mL of blood has previously been considered acceptable, in vitro data from Schelonka et al demonstrated that 0.5 mL would not reliably detect low-level bacteremia (4 colony-forming units [CFU]/mL or less). Blood cultures with an adequate volume were twice as likely to yield a positive result. A blood culture obtained through an umbilical artery catheter shortly after placement for other clinical indications is an acceptable alternative to a culture drawn from a peripheral vein. The problem with the blood culture in neonates is that the sensitivity for identifying sepsis is only 50% to 80% at best. A positive blood culture with a pathogenic organism is diagnostic of neonatal sepsis; however, a negative blood culture in noway rules out the disease.[7,8,9]

Urine Culture

A urine culture should not be part of the sepsis workup in an infant with suspected EOS. Sterilely acquired bladder tap or catheterized specimens minimize false-positive cultures, but they are difficult to obtain in the low-urine state of the newborn infant, and there is a very low yield in the first 72 hours of life. Unlike urinary tract infections in older infants (which are usually ascending infections), urinary tract infections in newborn infants are attributable to seeding of the kidney during an episode of bacteremia.[7,8,9]

Tracheal Aspirates

Cultures and Gram stains of tracheal aspirate specimens may be of value if obtained immediately after endotracheal tube placement. Once an infant has been intubated for several days, tracheal aspirates are of no value in the evaluation of sepsis.[7,8,9]

Lumbar Puncture

The decision to perform a lumbar puncture in a neonate with suspected EOS remains controversial. The lumbar puncture should be performed in any infant with a positive blood culture, infants whose clinical course or laboratory data strongly suggest bacterial sepsis, and infants who initially worsen with antimicrobial therapy. The median number of white blood cells in infants who were born at greater than 34 weeks' gestation and had bacterial meningitis was 477/mm^3. With a delay in analysis (>2 hours), white blood cell counts and glucose concentrations decrease significantly.[7,8,9]

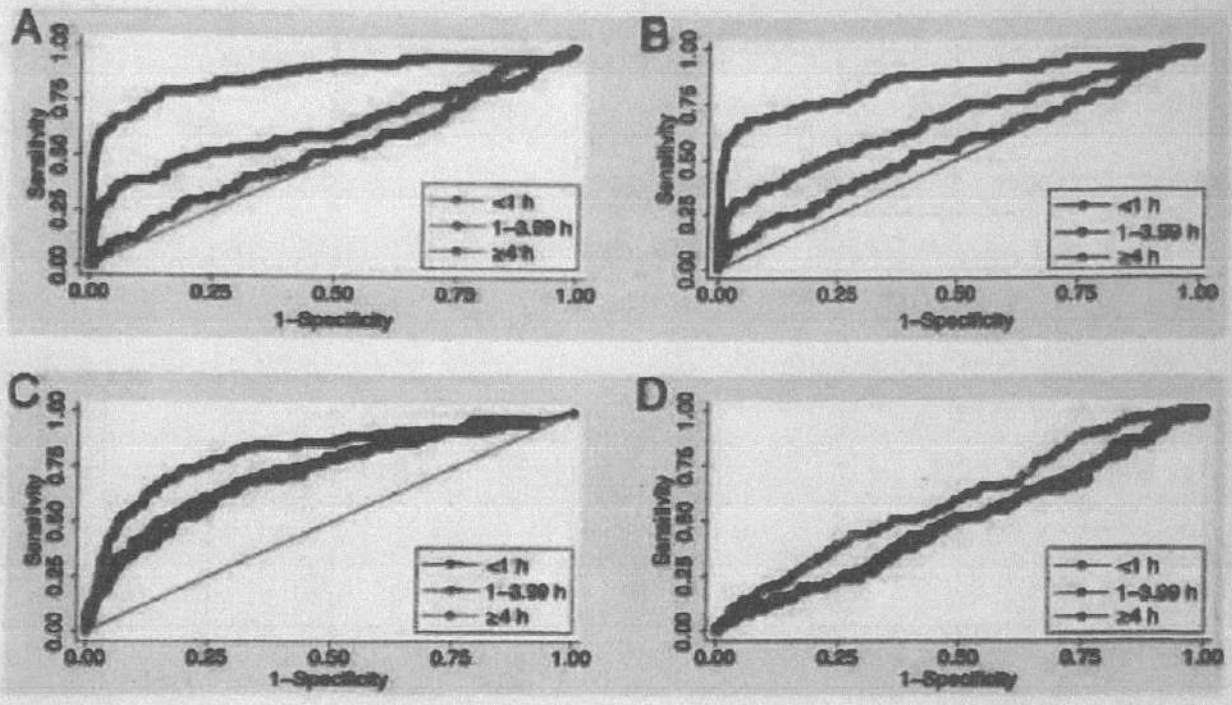
Peripheral White Blood Cell Count and Differential Count

Total white blood cell counts have little value in the diagnosis of EOS and have a poor positive predictive accuracy. The normal range for the total white blood count is broad and not usefully clinically, unless it is low (< 5,000/mm^3). Absolute Neutrophil Count (ANC), absolute band count, and Immature to Total neutrophil (I/T) ratio to identify infected infants. Neutropenia may be a better marker for neonatal sepsis and has better specificity than an elevated neutrophil count, because few conditions besides sepsis (maternal

pregnancy-induced hypertension, asphyxia, and hemolytic disease) depress the neutrophil count of neonates. ANC obtained immediately after birth are frequently normal.

Therefore if sepsis is suspected, a count obtained 6-12 hours following birth is more informative.[7,8,9]

Figure 3. Interpreting Complete Blood Counts Shortly After Birth.[4]



(Gerdes, 2004)

The lower limits of normal for neutrophil values at birth were 3,500/mm^3 in infants born at >36 weeks' gestation, 1,000/mm^3 in infants born at 28 through 36 weeks' gestation, and 500/mm^3 in infants born at <28 weeks' gestation. Peak values occurred at 6 to 8 hours after birth; the lower limits ofnormal at that time were 7,500/mm^3, 3,500/mm^3, and 1,500/mm^3 for infants born at >36 weeks' gestation, 28 to 36 weeks' gestation, and <28 weeks' gestation, respectively.[7,8,9]

The I/T ratio has the best sensitivity of any of the neutrophil indices. A single determination of the I/T ratio has a poor positive predictive accuracy (approximately 25%) but a very high negative predictive accuracy (99%). The

I/T ratio may be elevated in 25% to 50% of uninfected infants. The I/T ratio is <0.22 in 96% of healthy preterm infants born at <32 weeks' gestational age. In healthy term infants, the 90th percentile for the I/T ratio is 0.27.[7,8,9]

Platelet Counts

Despite the frequency of low platelet counts in infected infants, they are a nonspecific, insensitive, and late indicator of sepsis. Moreover, platelet counts are not useful to follow clinical response to antimicrobial agents, because they often remain depressed for days to weeks after a sepsis episode.[7,8,9]

C-reactive protein (Acute-Phase Reactants)

CRP is an acute-phase reactant protein synthesized by the liver in response to, and as part of, the inflammatory response. Interleukin-6 is the major stimulus to production of CRP, along with interleukin-1 and Tumor Necrosis Factor alpha (TNFα). CRP is released 6-8 hours of an infective process with a half-life of 24-48 hours and then diminishes over time as the inflammation resolves. Sensitivity improves (> 90%) if the first determination is obtained 8-12 hours following birth. A variety of non-infectious/stress conditions can elevate the CRP. CRP levels may be slow to normalize, limiting their value in following the response to antibiotics.[7,8,9,10,11]

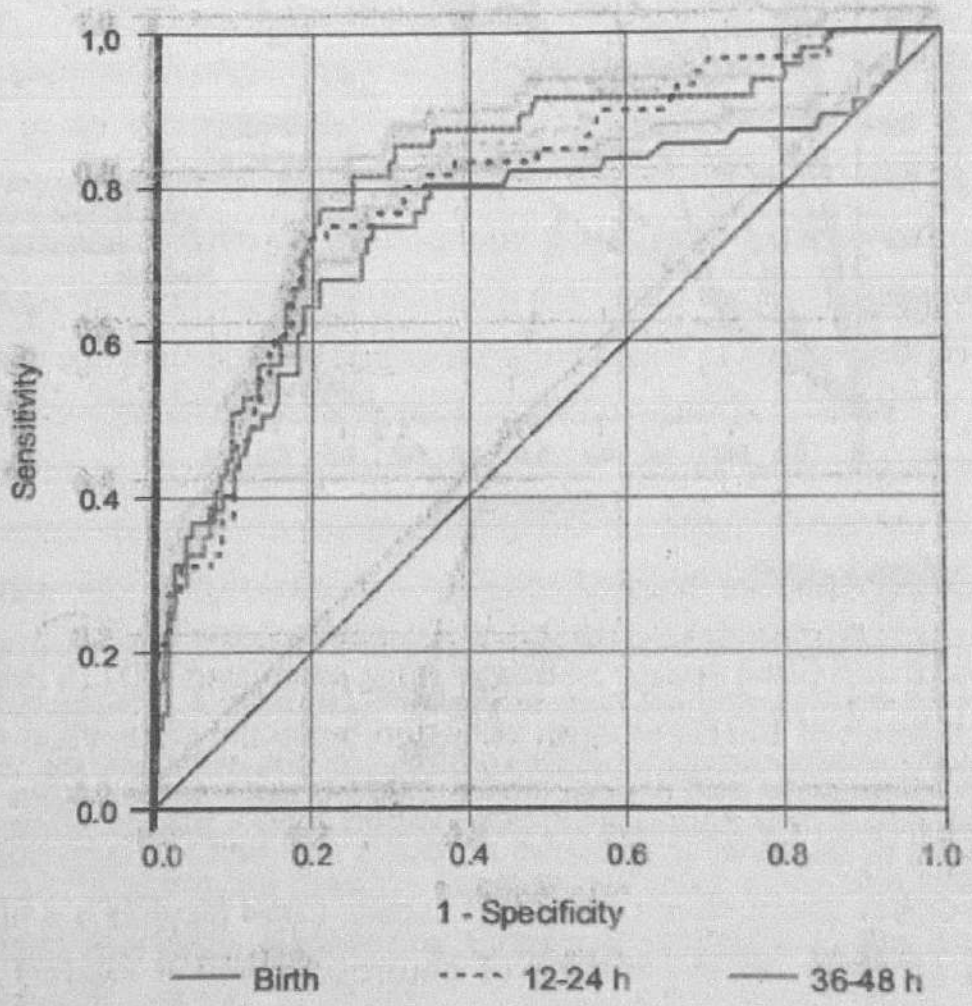
Serum Procalcitonin (PCT)

Procalcitonin (a precursor of calcitonin) produced by the liver and monocytes. There is a physiologic rise in the first 24 hours of life & non-infectious conditions elevate levels (mean PCT in healthy infants 1.5-2.5 ng/ml vs. 3-4 ng/ml in infants with RDS). Serum levels rise within 2 hours of an infectious episode (peak at 12 hours) and normalize within 2-3 days (better prognostic indicator than CRP).[7,8,9,12,13]

Serum PCT concentration showed a moderate diagnostic value for the detection of sepsis of vertical transmission, with better results after 12 h of birth. The reliability of PCT as a maker of bacterial infection requires specific

cut-off values for each evaluation time point beyond the first 48 h of life. PCT sensitivity and specificity were greater than those of CRP or interleukin 6 (IL-6) if different cut-off points at birth and at 24 h and 48 h of life were used. Some studies have shown that PCT is more reliable than CRP as a test for the diagnosis of Early-Onset neonatal Sepsis, but other studies have not found any advantage of PCT over CRP. The sensitivity and specificity values according to specific cut-off points for each evaluation point over the first 48 h of life are within the range of 57–100% sensitivity and 50–100% specificity previously reported for thresholds ranging between 0.5 and 100 ng/ mL.[7,8,9,12,13]

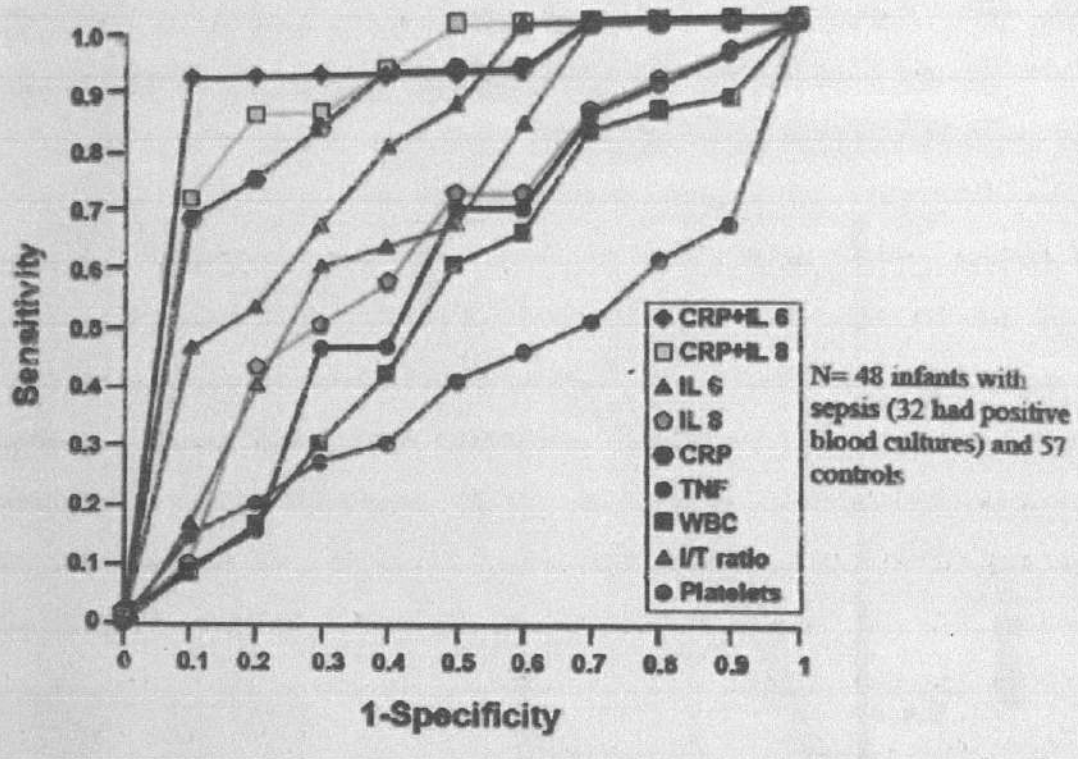
Figure 4. ROC curves. ROC curves of PCT at birth, and at 12–24 hand 36–48 h of life for the diagnosis of neonatal sepsis of vertical transmission (Sastre, 2010)



CYTOKINES AND CHEMOKINES

'Early warning' markers e.g., IL-6, IL-8, TNF-α that rise in infants with early and Late-Onset Sepsis. Levels can be elevated in non-infectious conditions (e.g. asphyxia, RDS & TTN). Interleukin-6 has high sensitivity (87-100%) and negative predictive value (93-100%) with early-onset sepsis but non-infectious conditions can elevate values. Interleukin-8 is more sensitive, but less specific marker than CRP (rises earlier than CRP).[7,8,9,11]

Figure 5. Diagnostic value of cytokines and C-reactive protein in the first 24 hours of neonatal sepsis.[13]



(Laborada, 2003)

CD11b and CD64 appear to be the most promising. CD11b (Mac-1, CR3) is the α subunit of the β2-integrin adhesion molecule involved in neutrophil adhesion, diapedesis and phagocytosis. CD11 is detectable within 5 minutes of exposure to bacteria or bacterial products and better diagnostic accuracy for Early-Onset Sepsis than Late-Onset Sepsis. CD64 (FcγR1) is a high affinity antibody receptor on the surface of neutrophils which interacts with the

Fc portion of the immunoglobulin molecule. CD64 is a sensitive diagnostic marker for early and late onset neonatal sepsis, but processing time for CD64 is long.[7,8,9]

TREATMENT OF NEONATES WITH SUSPECTED EARLY ONSET SEPSIS

Rational choice of antibiotics for the infant with presumed infection requires review of antibiotic susceptibility of the predominant organisms that cause disease at the local level. Treatment of the infected infant must be based on antibiotic susceptibility of the infecting organism and clinical outcome. Ampicillin and gentamicin continue to be the recommended empiric antibiotics for the infant at riskfor EOS. All GBS isolates tested were sensitive to ampicillin and 96% of *E coli* isolates tested were sensitive to gentamicin. [10,12,14,15,16]

Third-generation cephalosporins (e.g. cefotaxime) represent a reasonable alternative to an aminoglycoside. However, several studies have reported rapid development of resistance when cefotaxime has been used routinely for the treatment of Early-Onset neonatal Sepsis, and extensive/prolonged use of third-generation cephalosporins is a risk factor for invasive candidiasis. Ceftriaxone is contraindicated in neonates because it is highly protein bound and may displace bilirubin, leading to a risk of kernicterus.[10, 12,14,15,16]

The duration of antimicrobial therapy in infants with negative blood cultures is controversial. When considering the duration of therapy in infants with negative blood cultures, the decision should include consideration of the clinical course as well as the risks associated with longer courses of antimicrobial agents. Antibiotics therapy should be stopped by 48 hours if the cultures are negative and the infant remains asymptomatic. Antibiotics should be continued for 7 days in any critically ill infant. Prolonged empirical therapy with antibiotics (≥5 days) in the first few days of life was associated with increased mortality, Necrotizing Enterocolitis (NEC) or the combined outcome of death and NEC.[10,12,14,15,16]

PREVENTION STRATEGIES FOR EARLY ONSET SEPSIS

The only intervention proven to decrease the incidence of Early-Onset neonatal Sepsis is maternal treatment with intrapartum intravenous antimicrobial agents for the prevention of GBS infections. Intrapartum antimicrobial agents are indicated for the following situations:

1. Positive antenatal cultures or molecular test at admission for GBS (except for women who have a cesarean delivery without labor or membrane rupture);
2. Unknown maternal colonization status with gestation <37 weeks, rupture of membranes >18 hours, or temperature >100.4°F (>38°C);
3. GBS bacteriuria during the current pregnancy;
4. Previous infant with invasive GBS disease.[10,12,14,15,16]

ALGORITHMS FOR DIAGNOSIS AND MANAGEMENT OF EARLY ONSET SEPSIS

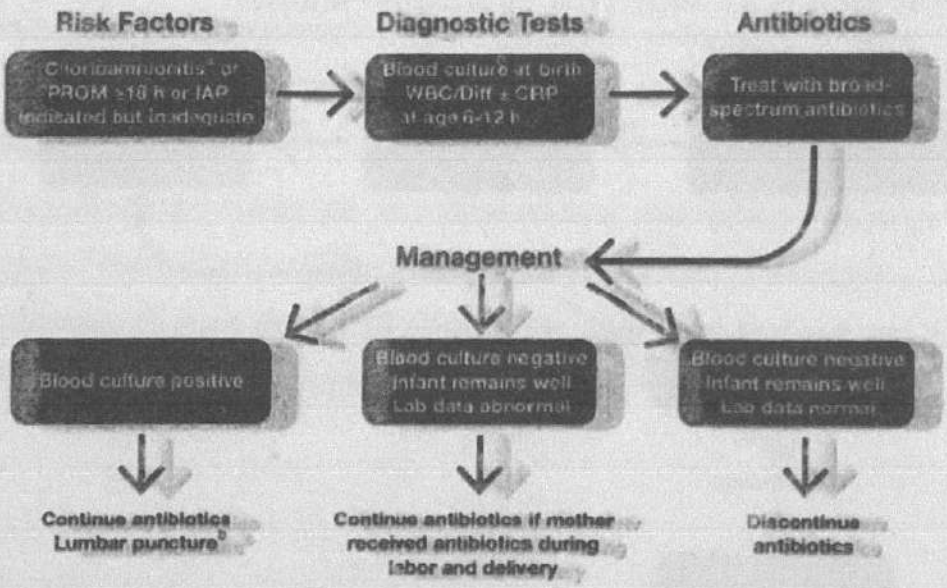
1. **Identifying Neonates With Clinical Signs of Sepsis With a "High Likelihood" of Early Onset Sepsis Who Require Antimicrobial Agents Soon After Birth.**

   Most infants with Early-Onset Sepsis exhibit abnormal signs in the first 24 hours of life. Approximately 1% of infants will appear healthy at birth and then develop signs of infection after a variable time period. Every critically ill infant should be evaluated and receive empirical broad-spectrum antimicrobial therapy after cultures, even when there are no obvious risk factors for sepsis. The 6-hour window should not be considered absolute; however, most infants without infection demonstrate some improvement over that time period. Any worsening of the infant's condition should prompt starting antimicrobial agents after cultures have been obtained.[10,12,14,15,16]

2. **Identifying Healthy-Appearing Neonates With a "High Likelihood" of Early-Onset Sepsis Who Require Antimicrobial Agents Soon After Birth.**

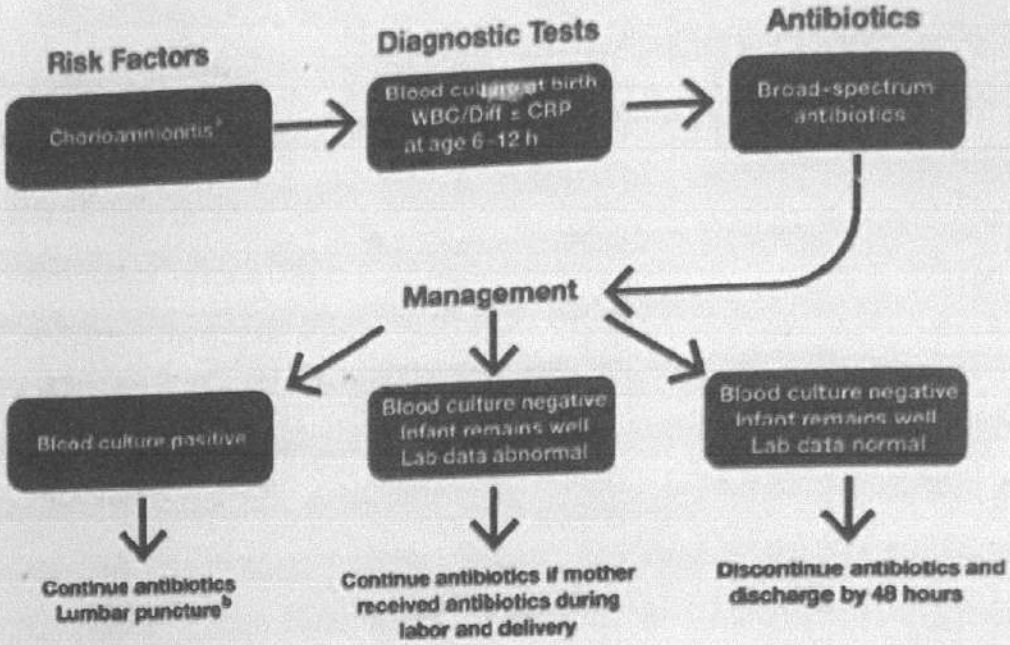
This category includes infants with 1 of the risk factors for sepsis noted previously (colonization with GBS, prolonged rupture of membranes >18 hours, or maternal chorioamnionitis). GBS is not a risk factor if the mother has received adequate intrapartum therapy (penicillin, ampicillin, or cefazolin for at least 4 hours before delivery) or has a cesarean delivery with intact membranes in the absence of labor. The decision of whether to treat a high-risk infant depends on the risk factors present, the frequency of observations, and gestational age. The threshold for initiating antimicrobial treatment generally decreases with increasing numbers of risk factors for infection and greater degrees of prematurity.[10,12,14,15,16]

Figure 6. Evaluation of asymptomatic infants < 37 weeks' gestation with risk factors for sepsis.[1]



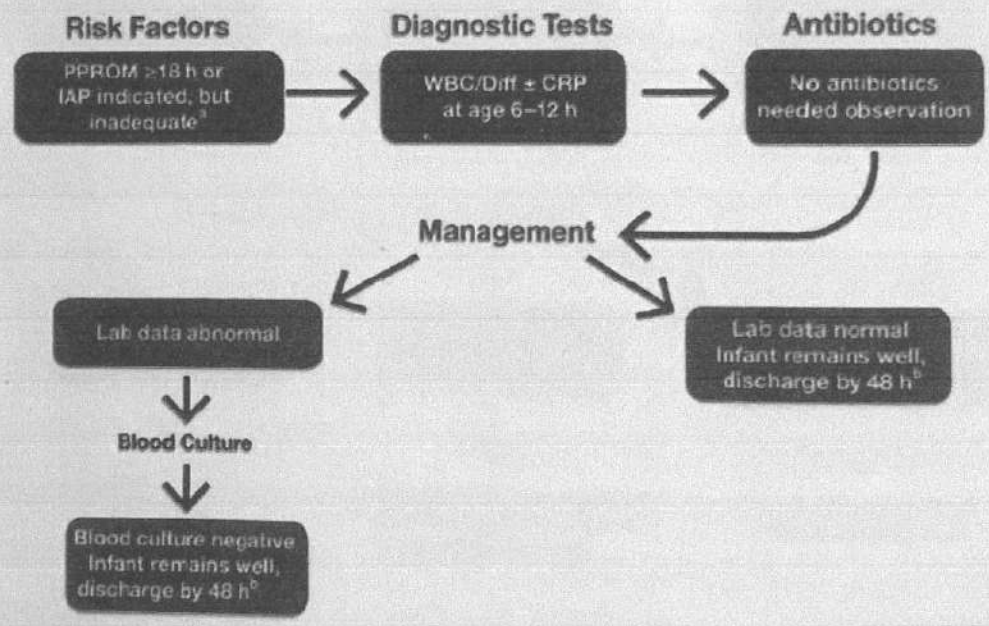
(Polin, 2012)

Figure 7. Evaluation of asymptomatic infants ≥ 37 weeks' gestation with risk factors for sepsis.[1]



(Polin, 2012)

Figure 8. Evaluation of asymptomatic infants ≥37 weeks' gestation with risk factors for sepsis (no chorioamnionitis).[1]



(Polin, 2012)

CDC 2010 revises the algorithm for secondary prevention of early-onset group β streptococcus (GBS) disease among newborns. Diagnostic evaluation including (+/-empiric antibiotics) for symptomatic infants, maternal chorioamnionitis and in adequate IAP combined with other risk factors. The following are key components of the neonatal management algorithm:

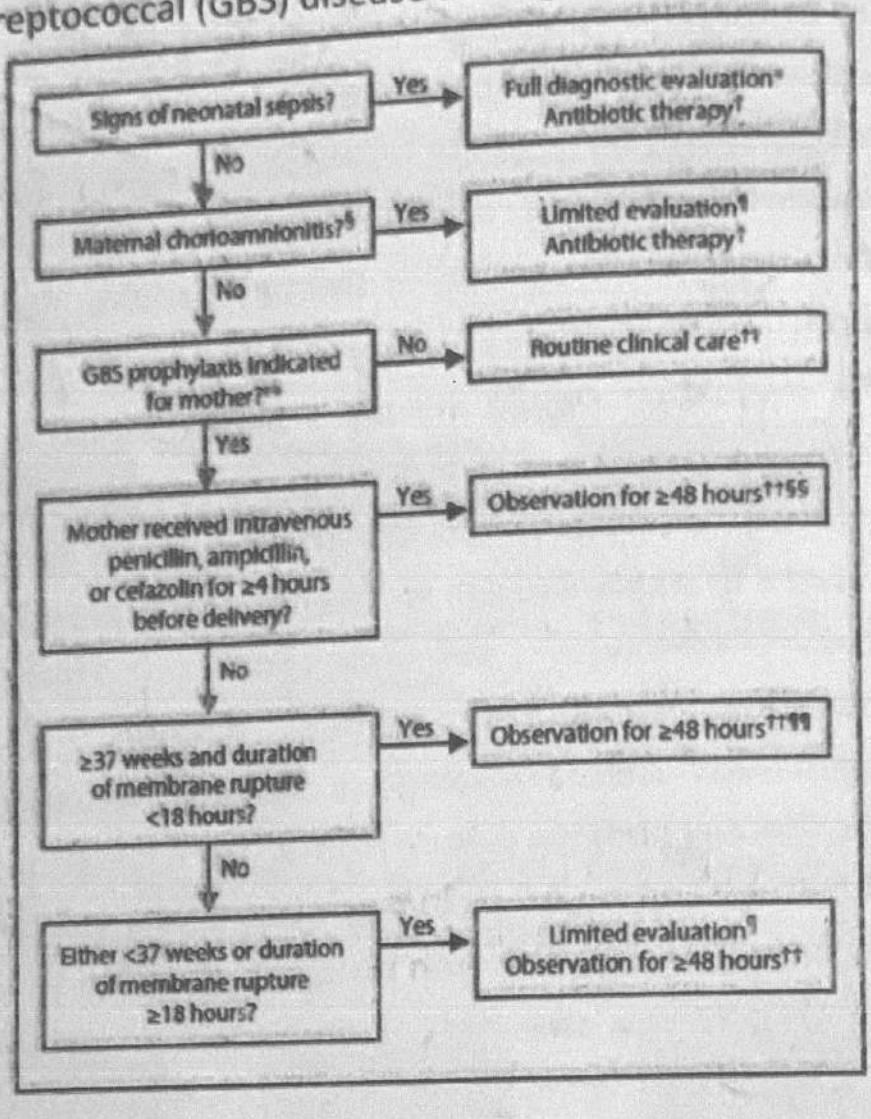
1. Any newborn with signs of sepsis should receive a full diagnostic evaluation and receive antibiotic therapy pending the results of the evaluation.

   The evaluation should include a blood culture; a CBC including white blood cell differential and platelet count; a chest radiograph if any abnormal respiratory signs are present; and a lumbar puncture if the newborn is stable enough to tolerate the procedure and sepsis is suspected.[10,12,14,15,16]

2. Well-appearing newborns whose mothers had suspected chorioamnionitis should undergo a limited evaluation and receive antibiotic therapy pending culture results. The evaluation should include a blood culture and a CBC including white blood cell dif¬ferential and platelet count. Consultation with obstetric providers to assess whether chorioamnionitis was suspected is important to determine neonatal management.[10,12,14,15,16]

3. Well-appearing infants of any gestational age whose mother received adequate intrapartum GBS prophylaxis (≥4 hours of penicillin, ampicillin, or cefazolin before delivery) should be observed for ≥48 hours, and no routine diagnostic testing is recommended.[10,12,14,15,16]

Figure 9. Algorithm for secondary prevention of early-onset group B streptococcal (GBS) disease among newborns.[5]



(Schrag, 2010)

SUMMARY

Early Onset Sepsis (EOS) remains life-threatening but increasingly rare disease of newborns. Microbiology among term infants still dominated by GBS and other gram-positive pathogens. Gestational age, maternal fever, duration of ROM and use of intrapartum antibiotics remain strong predictors as risk factors of EOS among both term and preterm infants.

There are no ideal tests for the diagnosis of early or late-onset neonatal sepsis. Physical examination has an important role in identifying infants at low risk for sepsis who are asymptomatic. There are no sepsis marker can

diagnose close to 100% of infected cases. Some studies have shown that PCT is more reliable than CRP as a test for the diagnosis of EOS, but other studies have not found any advantage of PCT over CRP. Cytokine and chemokine determinations are expensive tests and are not routinely automated. Current sepsis markers (neutrophil indices, CRP) are useful adjunct tests in identifying infants with a low probability of infection.

The optimal treatment of infants with suspected EOS is broad-spectrum antimicrobial agents (ampicillin and an aminoglycoside). Once the pathogen is identified, antimicrobial therapy should be narrowed (unless synergism is needed). Antimicrobial therapy should be discontinued at 48 hours in clinical situations in which the probability of sepsis is low.

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