Neonatal Sepsis

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Definitions

- Non-specific and varied presentation
- Aimed to find current definitions of "neonatal sepsis"

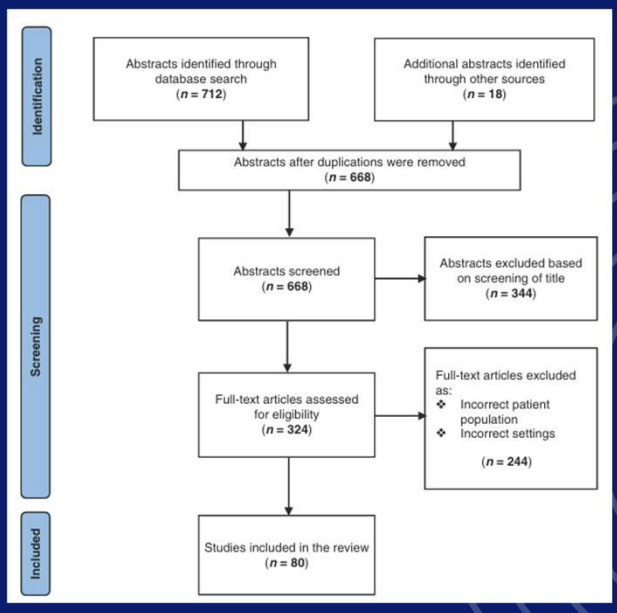

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Table 1. Definitions of neonatal sepsis by primary criteria.

Combination of primary criteria	*N*
Culture alone	35
Culture + signs	29
Signs + laboratory	25
Culture + signs + laboratory	12
Signs alone	7
Culture + labs	6
Signs + radiology	6
Laboratory alone	4
Signs + risk factors	2
Culture + laboratory + radiology	1
Radiology alone	1

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Table 2. Definitions mentioning specific culture source.

Culture source	*N*
Blood	71
Cerebrospinal fluid	29
Urine	10
Skin/surface	4
Pus [unspecified]	3
Tracheal aspirate	2
Synovial fluid	1
Peritoneal fluid	1
Intravascular catheter	1
Any sterile site	1

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Constitutional		Respiratory	
Symptom	***N***	**Symptom**	***N***
Lethargy	27	Apnoea	22
Temperature instability	27	Respiratory distress	12
Feeding intolerance	17	Tachypnoea	10
Glucose intolerance	9	Ventilatory support	6
Irritability	5	Supplemental O_2	6
Hypothermia	4	Desaturations	4
Hyperthermia	3		
Fever	3	Grunting	4
Poor feeding	3	Cyanosis	3
Excessive crying	1	Gagging	1
Poor cry	1	Apnoea	22
Colour	1	Respiratory distress	12
		Tachypnoea	10

Cardiovascular	
Symptom	***N***
Haemodynamic instability	8
Hypotension	7
Poor perfusion	7
Tachycardia	6
Bradycardia	6
Inotropic/fluid support	5
CRT > 3 s	5
Pallor	3
Rate > 2 SD above normal	2
Shock	2
Cardiovascular collapse	2
BP < 2 SD below normal	2
Rate instability	1
Cold extremities	1

Neurological	
Symptom	***N***
Altered consciousness	7
Seizure	6
Hypotonia	4
Reduced reflexes	2
Bulging fontanelle	1
Gastrointestinal	
Symptom	***N***
Abdominal distension	11
Vomiting	5
Hepatomegaly	5
Splenome	
Jaundice/	
Increased	

Miscellaneous	
Symptom	***N***
Disseminated haemorrhage	2
Unexplained bleeding	2
Petechiae	1
Purpura	1
Pyoderma	1
Sclerema	1
Conjunctivitis	1
Organ dysfunction [unspecified]	3
Staff concern	1

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Table 4. Frequency of laboratory signs in the RCT definitions reviewed.

Laboratory signs	*N*
C-reactive protein	30
Not specified	9
>5 mg/L	1
>9 mg/L	1
>10 mg/L	13
>12 mg/L	1
>20 mg/L	4
>60 mg/L	1
White cell count (WCC)	16
I:T ratio	15
Neutrophil count	13
Platelet count	10
Micro-ESR	8
Band cell count	7
Full blood count (FBC)	3
IL-6	3
Glucose	3
Toxic granules in peripheral smear	2
Bacterial antigen	2
TNF-alpha	1
Procalcitonin	1
Lactate	1
pH	1
Histologic diagnosis of pneumonia	1
Cerebrospinal WCC	1
Viral polymerase chain reaction (PCR)	1
CSF Gram stain	1

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- Definitions of neonatal sepsis - considerable variability
- Microbiological culture persists in most RCTs
- Any sepsis definition that includes organ dysfunction → first requires definition of normal organ function in the vulnerable preterm population

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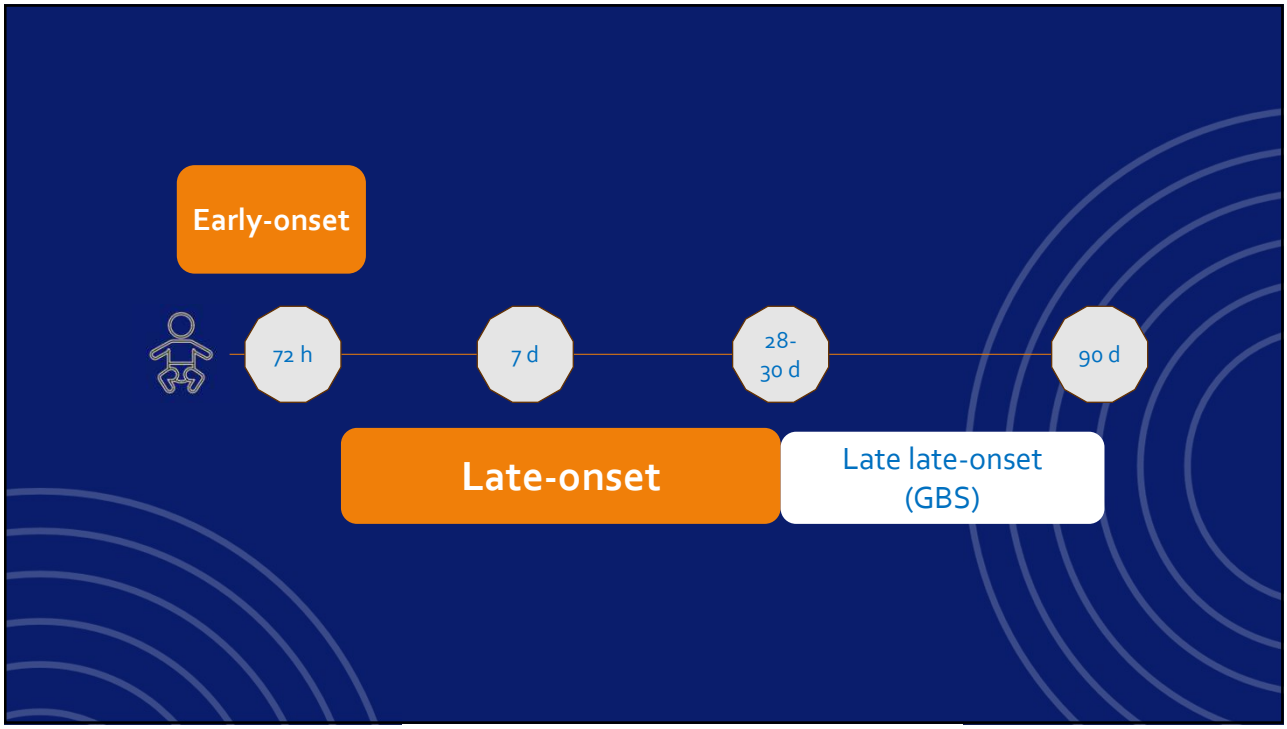

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Early-onset sepsis (EOS)

Incidence

- 0.77 – 1.08 per 1000 live births (USA)
- Higher in preterm

Pathogens

- Group B Streptococcus (GBS), *E. coli*
- *E. coli* – most common in VLBW infants
- *Haemophilus* spp., *Staph aureus* – *3rd & 4th in VLBW*
- Listeria monocytogenes
- Others: *Klebsiella, Enterobacter, Citrobacter, Acinetobacter, and Pseudomonas*

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Early-onset sepsis (EOS)

Transmission

- Amniotic fluid
- Intrapartum: bacterial flora from mothers' GU tract
- After rupture of membranes
- Cross placenta

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Risk factors of EOS

Maternal factors
- GBS colonization, bacteriuria, or a previous child with invasive GBS infection
- Intra-amniotic infection (IAI)
- Prolonged ROM
- Inadequate IAP

Neonatal factors
- Prematurity, LBW
- Congenital anomalies
- Complicated delivery

IAI: maternal T >39◦C or T 38-39◦C PLUS one of -leukocytosis, purulent cervical drainage, or fetal tachycardia

IAI=intra-amniotic infection; IAP=intrapartum antibiotics prophylaxis; ROM=upture of membranes

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Indications of IAP for GBS

Risk of EOS
- Preterm labor
- Preterm premature ROM
- Prolonged ROM ≥18 h
- Maternal fever >38◦C
- Bacteriuria in current pregnancy
- Hx of GBS colonization
- Hx of previous child with GBS

Adequate IAP:
- IV
- Penicillin G or Ampicillin or Cefazolin
- At least 1 dose, ≥4 h prior to delivery

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Late-onset sepsis (LOS)

- Incidence varies
- Pathogens
  - Coagulase-negative staphylococci (CoNS), *S. aureus*
  - GBS, *E. coli*
  - Fungal infection, other organisms in individual unit
  - Environment (hospital, community) -> infant colonization of pathogenic bacteria, esp in GI tract
- Risk factors
  - Prematurity -> longer hospital stay
  - Indwelling vascular catheters
  - Unit congestion
  - Use of H_2 blockers, proton pump inhibitors, GI pathology -> gram-negative bacilli

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Clinical presentation of sepsis

- Tachycardia, respiratory distress
- Temperature instability: hypothermia, fever
- Lethargy, irritability
- Apnea/bradycardia
- Hypotonia
- Poor feeding, abdominal distention
- Poor perfusion, bleeding problems
- Etc.

Meningitis: Lethargy, hypotonia, hypertonia, seizures

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Clinical presentation of sepsis

- Nonspecific
- Can mimic noninfectious causes
- Complete physical examination (look for source of infection)

HIGH INDEX of SUSPICIOUS

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Diagnosis of sepsis

Isolation of pathogens from normally sterile sites (blood, CSF, urine)

Hemoculture: at least 1 ml of blood (recommended)

Lumbar puncture should be considered EXCEPT respiratory or hemodynamic instability
- Isolated meningitis 1-2 per 100,000 live births
- Higher in VLBW infants (17-fold >term infants)

Urine collection – suprapubic aspiration or sterile catheterization
- Not recommended in EOS (seeding from bacteremia)
- Recommended for LOS (possible ascending infection)

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CBC with differential

At 6-12 h after birth (EOS, if possible)

- Leukopenia or leukocytosis
- Low or high ANC
- High I:T ratio (peripheral blood smear)
- Thrombocytopenia

*No individual value is predictive or safely excludes sepsis

Leukopenia & thrombocytopenia – DDx: maternal pre-eclampsia, chronic abruption, and PROM

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Acute phase reactants

- C-reactive protein (CRP) and procalcitonin
- **Healthy neonates:** increase physiologically after birth, peaking at 24 hours of age
- Inversely proportional to birth weight and GA but not to sex

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C-reactive protein

Limitations

- **Infection**: Increases within 6-8 h and peaks after 24 h
- Sensitivity: lowest during early infection → increases over the next 10-12 h
- **Preterm** infants: lower CRP values and response

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Procalcitonin

- **Infection**: peak in 6-8 h
- Also increases in RDS
- Better sensitivity but less specificity than CRP

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Metabolic changes in sepsis

Acidosis - common

Hyperglycemia or hypoglycemia

Hyperbilirubinemia

Electrolytes imbalance

- Meningitis -> SIADH
- Enteral / parenteral nutrition

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Evaluation of infants ≥35 wk for risk of EOS

1. Multivariate risk assessment (neonatal EOS calculator)
2. Categorical risk assessment
3. Risk assessment based on enhanced observation

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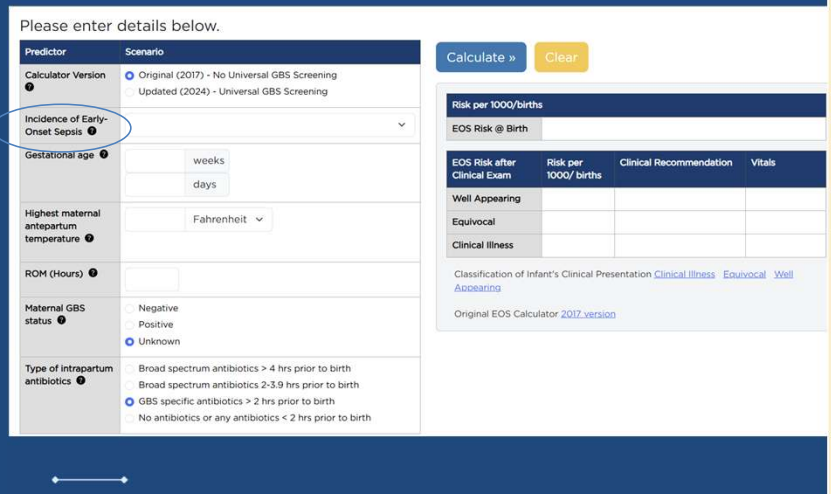
Nonatal EOS calculator

https://neonatalsepsiscalculator.kaiserpermanente.org/



Clinical Exam	Description

Clinical illness	• Persistent need for NCPAP/ HFNC/mechanical ventilation (outside of the delivery room)
	• Hemodynamic instability requiring vasoactive drugs
	• Neonatal encephalopathy/ perinatal depression
	  • Seizure
	  • Apgar score <5 at 5 min
	• Need for supplemental O_2 ≥2 h to maintain oxygen saturations >90% (outside of the delivery room)

Equivocal	• Persistent physiologic abnormality ≥4 h
	  • Tachycardia (HR ≥160)
	  • Tachypnea (RR ≥60)
	  • Temperature instability (≥100.4°F or <97.5°F)
	  • Respiratory distress (grunting, flaring, or retracting) not requiring supplemental O_2
	• Two or more physiologic abnormalities lasting for ≥2 h
	  • Tachycardia (HR ≥160)
	  • Tachypnea (RR ≥60)
	  • Temperature instability (≥100.4°F or <97.5°F)
	  • Respiratory distress (grunting, flaring, or retracting) not requiring supplemental O_2
	Note: Abnormality can be intermittent.

Well appearing	No persistent physiologic abnormalities

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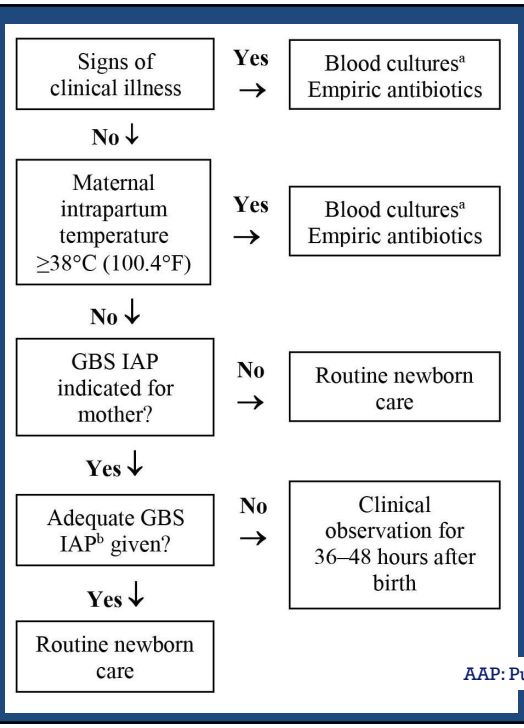
Categorical risk assessment



[a] include CSF culture

AAP: Puopolo KM, et al. *Pediatrics* 2019

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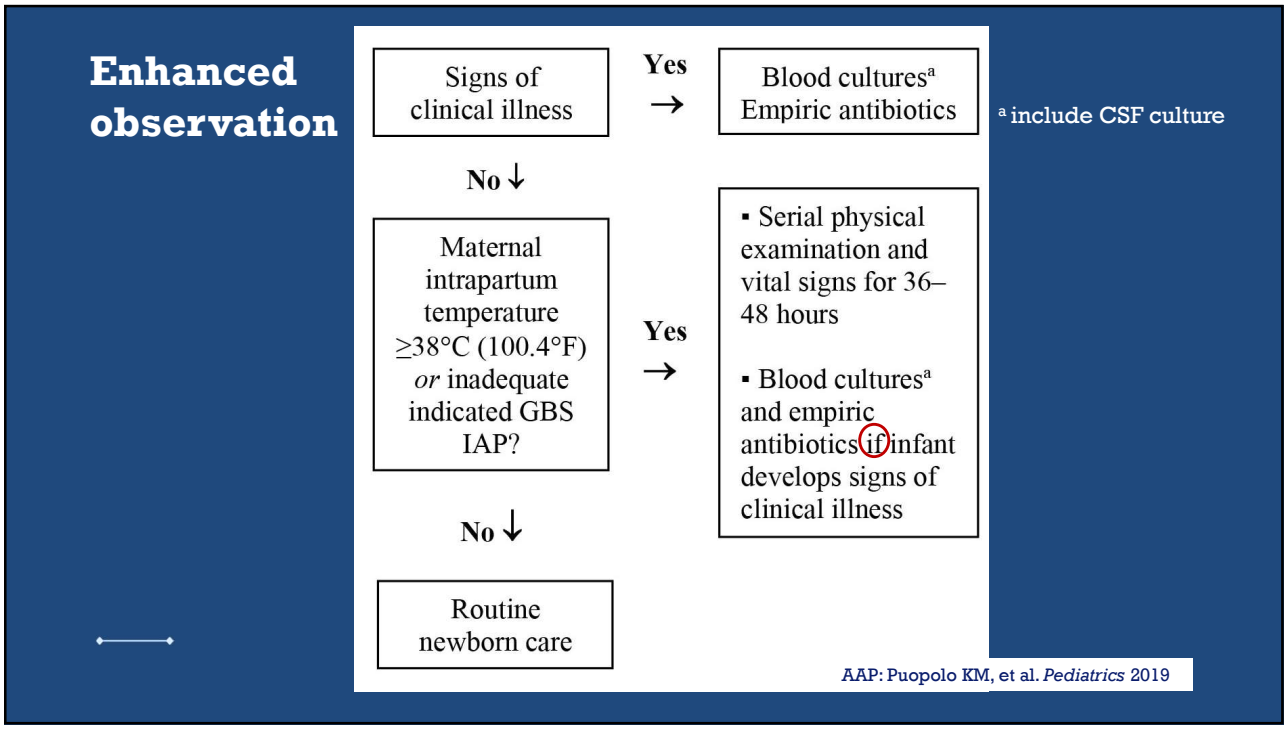
Enhanced observation
Signs of clinical illness
Yes
Blood cultures[a] Empiric antibiotics
[a] include CSF culture
No
Maternal intrapartum temperature ≥38°C (100.4°F) or inadequate indicated GBS IAP?
Yes
▪ Serial physical examination and vital signs for 36–48 hours
▪ Blood cultures[a] and empiric antibiotics if infant develops signs of clinical illness
No
Routine newborn care
AAP: Puopolo KM, et al. Pediatrics 2019

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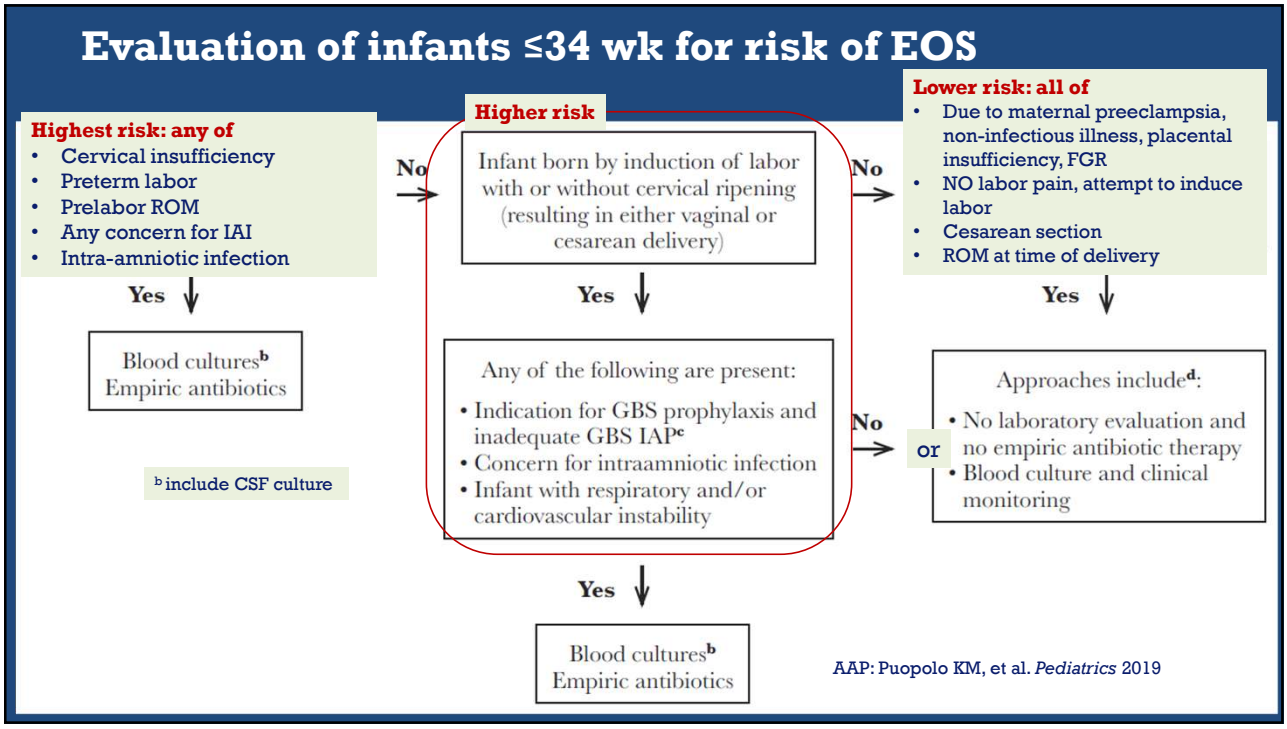
Evaluation of infants ≤34 wk for risk of EOS
Highest risk: any of
• Cervical insufficiency
• Preterm labor
• Prelabor ROM
• Any concern for IAI
• Intra-amniotic infection
Yes
Blood cultures[b] Empiric antibiotics
[b] include CSF culture
Higher risk
No
Infant born by induction of labor with or without cervical ripening (resulting in either vaginal or cesarean delivery)
Yes
Any of the following are present:
• Indication for GBS prophylaxis and inadequate GBS IAP[c]
• Concern for intraamniotic infection
• Infant with respiratory and/or cardiovascular instability
Yes
Blood cultures[b] Empiric antibiotics
No
Lower risk: all of
• Due to maternal preeclampsia, non-infectious illness, placental insufficiency, FGR
• NO labor pain, attempt to induce labor
• Cesarean section
• ROM at time of delivery
Yes
or
Approaches include[d]:
• No laboratory evaluation and no empiric antibiotic therapy
• Blood culture and clinical monitoring
AAP: Puopolo KM, et al. Pediatrics 2019

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Empiric antibiotics: early-onset

Ampicillin & aminoglycoside	• *3rd gen cephalosporins – not recommended for empiric use*
Add **cefotaxime** or ceftazidime for suspected - gram-negative meningitis - non-GBS ampicillin resistant	• Up to 80% of *E. coli* – ampicillin resistant • 8% of EOS pathogens - both ampicillin & gentamicin resistant (more common in VLBW)

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Empirical treatment in well-appearing infants

- Discontinue after 36-48 h. if hemoculture is negative (blood volume for culture is important)
- Cautions
  - Hematologic test results –> false positive, negative
  - Blood volume for culture
  - Empiric antibiotics >5 d – increases risk of NEC, candidemia, and mortality in preterm infants
  - Antibiotic exposure -> microbiome alteration

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Empiric antibiotics: late-onset

*Nafcillin & aminoglycoside or 3rd generation cephalosporin	• CoNS, *S. aureus*, and gram-negative organisms • GBS
*Vancomycin & 3rd gen cephalosporin	➢ Preterm with complex medical problems ➢ Central venous catheterization ➢ Hx of MRSA ➢ High local MRSA rate
Ampicillin & gentamicin or cephalosporins (cefotaxime, ceftazidime, cefepime)	• Community-acquired + not critically ill, and no meningitis • If meningitis is suspected – cephalosporin is preferred

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Treatment per susceptibility test

Organism	Antibiotic	Duration	Note
GBS Bacteremia	Ampicillin or Penicillin	10 d	GA <32 wk: 10-14 d
GBS meningitis (uncomplicated)	-Ampicillin or PGS & gentamicin initially -Monotherapy when clinical improve and CSF culture-negative	14[2]-21[1] d or 2 wk after first negative culture	2nd LP 24-48 h after Rx
Gram-negative bacteremia		10-14 d	
Gram-negative meningitis	Plus aminoglycoside until CSF culture-negative	21 d or 2 wk after first negative CSF culture (whichever is longer)	2nd LP 24-48 h after Rx

[1]Neonatal-Perinatal Medicine 12th Ed.
[2]Redbook 2024-2027

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Penicillins

Drug	Route	GA ≤34 wk 6 d		GA ≥35 wk 0 d	
		PNA ≤7 d	PNA >7 d	PNA ≤7 d	PNA >7 d
Bacteremia					
Ampicillin	IV, IM	50 mg/kg every 12 h	75 mg/kg every 12 h	50 mg/kg every 8 h	50 mg/kg every 8 h
Penicillin G aqueous	IV, IM	50 000 U/kg every 12 h	50 000 U/kg every 8 h	50 000 U/kg every 12 h	50 000 U/kg every 8 h
Meningitis					
Ampicillin	IV, IM	100 mg/kg every 8 h	75 mg/kg every 6 h	100 mg/kg every 8 h	75 mg/kg every 6 h
Penicillin G aqueous	IV, IM	150 000 U/kg every 8 h	125 000 U/kg every 6 h	150 000 U/kg every 8 h	125 000 U/kg every 6 h

Drug	Route	GA ≤34 wk 6 d		GA ≥35 wk 0 d	
		PNA ≤7 days	PNA >7 days	PNA ≤7 days	PNA >7 days
Nafcillin, oxacillin[b]	IV, IM	25 mg/kg every 12 h	25 mg/kg every 8 h	25 mg/kg every 8 h	25 mg/kg every 6 h

Table 4.2, Redbook 2024-2027

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Cephalosporins

Drug	Route	GA ≤31 wk 6 d		GA ≥32 wk 0 d	
		PNA <7 days	PNA ≥7 days	PNA ≤7 days	PNA >7 days
Cefazolin[c]	IV, IM	25 mg/kg every 12 h	25 mg/kg every 12 h	25 mg/kg every 8 h	25 mg/kg every 8 h
Cefotaxime[d]	IV, IM	50 mg/kg every 12 h	50 mg/kg every 8 h	50 mg/kg every 12 h	50 mg/kg every 8 h
Ceftazidime	IV, IM	50 mg/kg every 12 h	50 mg/kg every 8 h	50 mg/kg every 12 h	50 mg/kg every 8 h
Cefuroxime	IV, IM	50 mg/kg every 12 h	50 mg/kg every 8 h	50 mg/kg every 12 h	50 mg/kg every 8 h

Drug	Route	GA ≤31 wk 6 d		GA ≥32 wk 0 d
		PNA ≤7 days	PNA >7 days	
Cefoxitin	IV, IM	35 mg/kg every 12 h	35 mg/kg every 8 h	35 mg/kg every 8 h
Ceftolozane/tazobactam	IV	--	--	20 mg ceftolozane/kg every q8h

Drug	Route	All neonates
Ceftriaxone[e]	IV, IM	50 mg/kg every 24 h

Drug	Route	GA ≤35 wk 6 d	GA ≥36 wk 0 d
Cefepime	IV	30 mg/kg every 12 h	50 mg/kg every 12 h[f]

Table 4.2, Redbook 2024-2027

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Aminoglycosides

Drug	Route	GA ≤29 wk 6 d		GA 30 wk 0 d – 34 wk 6 d		GA ≥35 wk 0 d	
		PNA ≤14 days	>14 days	≤10 days	>10 days	≤7 days	>7 days
Amikacin[k]	IV, IM	15 mg/kg every 48 h	15 mg/kg every 36 h	15 mg/kg every 36 h	15 mg/kg every 24 h	15 mg/kg every 24 h	18 mg/kg every 24 h
Gentamicin[l]	IV, IM	5 mg/kg every 48 h	5 mg/kg every 36 h	5 mg/kg every 36 h	5 mg/kg every 24 h	4 mg/kg every 24 h	5 mg/kg every 24 h
Tobramycin[l]	IV, IM	5 mg/kg every 48 h	5 mg/kg every 36 h	5 mg/kg every 36 h	5 mg/kg every 24 h	4 mg/kg every 24 h	5 mg/kg every 24 h

Vancomycin[m]

Begin with a 20-mg/kg loading dose followed by a maintenance dose, according to the table

GA ≤28 wk 6 d		GA ≥29 wk 0 d	
Creatinine (mg/dL)	Dosage	Creatinine (mg/dL)	Dosage
<0.5	15 mg/kg every 12 h	<0.7	15 mg/kg every 12 h
0.5–0.7	20 mg/kg every 24 h	0.7–0.9	20 mg/kg every 24 h
0.8–1	15 mg/kg every 24 h	1–1.2	15 mg/kg every 24 h
1.1–1.4	10 mg/kg every 24 h	1.3–1.6	10 mg/kg every 24 h
>1.4	15 mg/kg every 48 h	>1.6	15 mg/kg every 48 h

Check drug levels

Table 4.2, Redbook 2024-2027

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Prevention of late-onset sepsis

Send the baby home ASAP

Infection control: hand hygiene, central lines care, VAP bundle, etc.

Antibiotics stewardship

Nutrition: use of breast milk**,** feeding protocol

Limited use: H2 blockers, PPI

Etc.

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