Early Onset Neonatal Sepsis

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DEVELOPMENT COOPERATION

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1. introduction

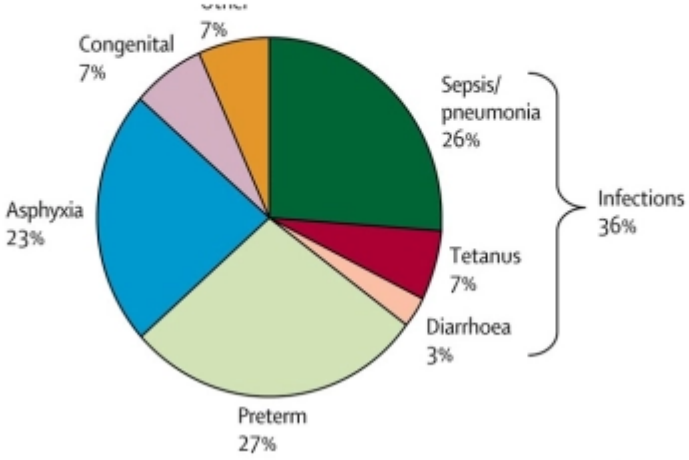
Important cause of morbidity and mortality

Incidence–low

Potential for serious adverse outcomes

Low threshold for evaluation and treatment

Causes of neonatal death



WHO

2. definitions

Neonatal Sepsis - Clinical syndrome in an infant 28 days of life or younger manifested by systemic signs of infection and isolation of a bacterial pathogen from the blood stream

- Early-onset

- Before 7 days of life
- Birth hospitalization
- Vertical transmission
- Ascending infection from maternal GI/GU tract bacteria
- Bacteremia or sepsis

3. epidemiology

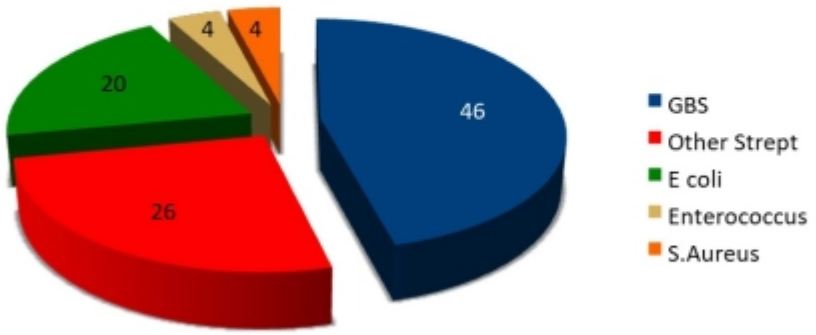
Overall world incidence of early-onset sepsis is 1 to 5/1000 live births (WHO)

- Incidence has decreased due to a reduction in GBS sepsis, due to the use of intrapartum antibiotic prophylaxis (IAP)
- Late-onset sepsis has remained stable (CDC

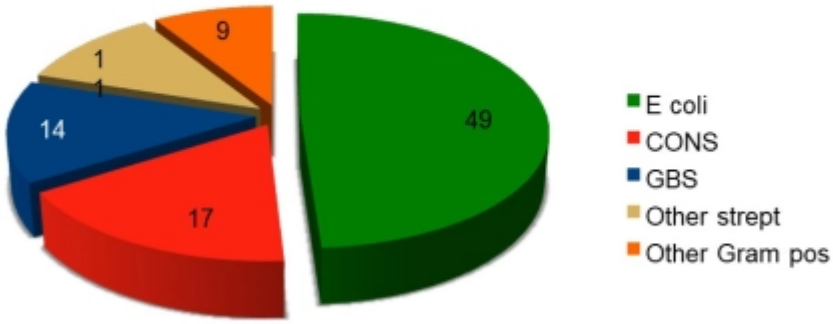
4. microbiology

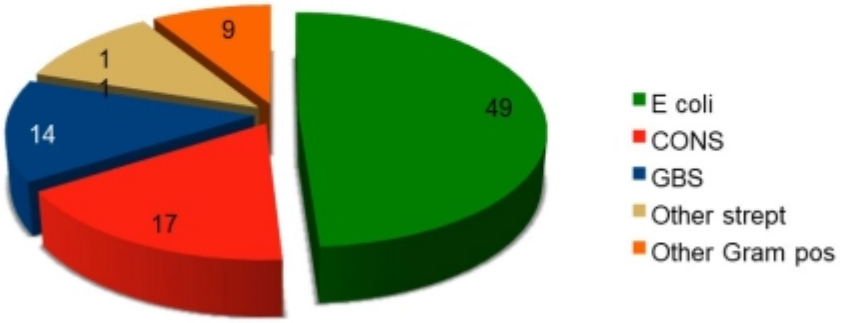
- GBS and E.coli are the most common causes: 2/3 of early-onset
- Listeria monocytogenes: rare
- Staphylococcus aureus: emerging pathogen, skin involvement
- Enterococcus: preterm infants

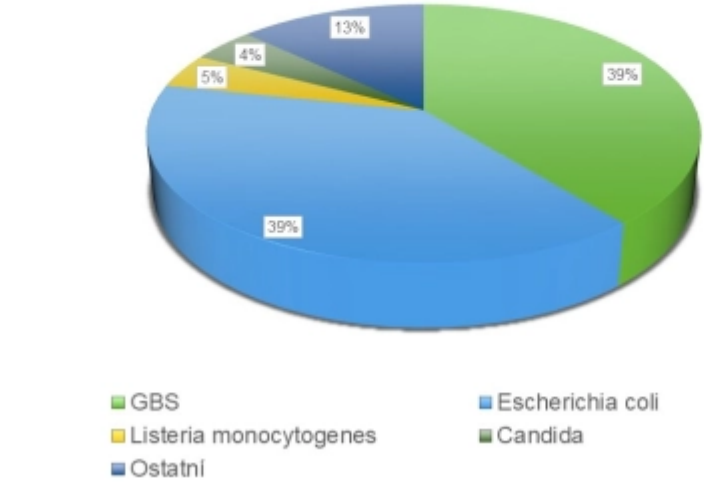
Early Onset Sepsis in Full Term



Early Onset Sepsis in WLBW



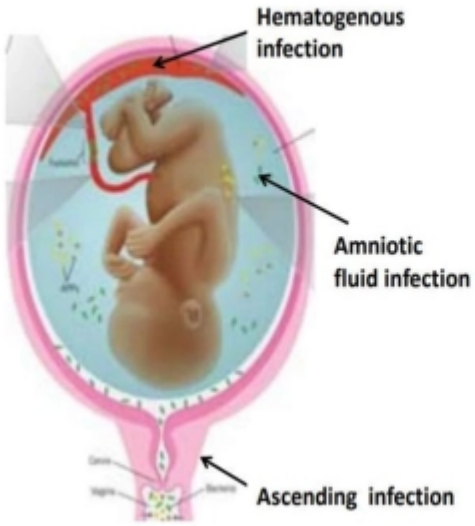




Impact of GBS Intrapartum Antibiotic Prophylaxis

- Center for Disease Control and Prevention's Active Bacterial Core Surveillance Report, 2015
- Early-onset GBS infection rate in the US declined by 80%-from 0.6/1000 live births in 2000 to 0.25/1000 live births in 2013
- Late-onset GBS infection rates remained stable at 0.29/1000 live births

EOS pathogenesis

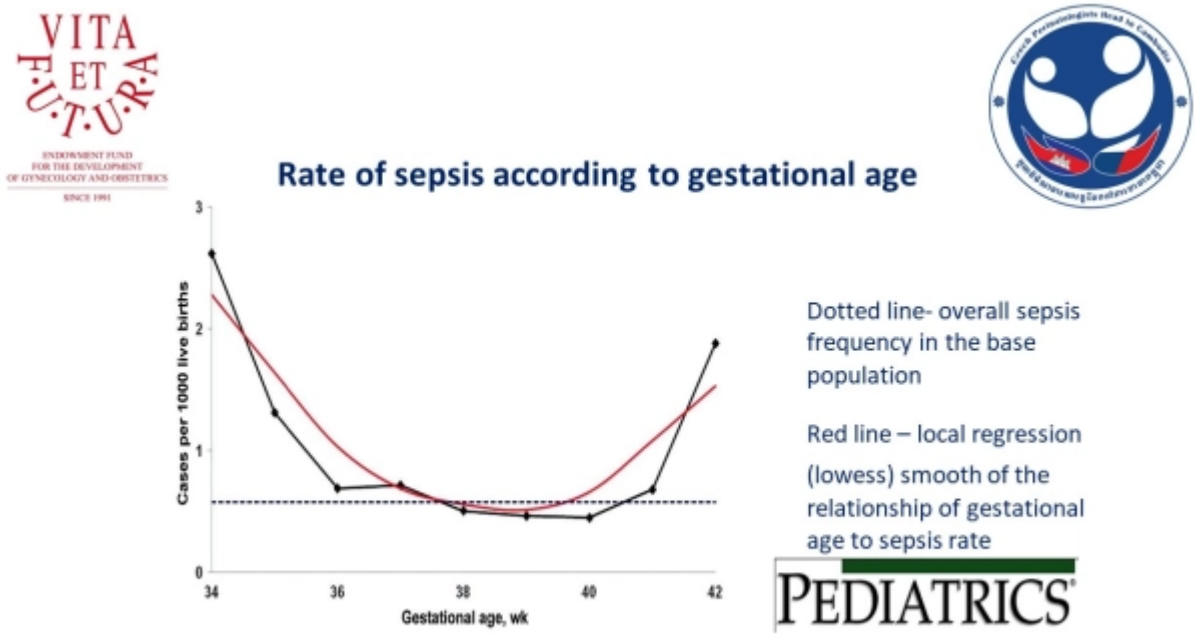


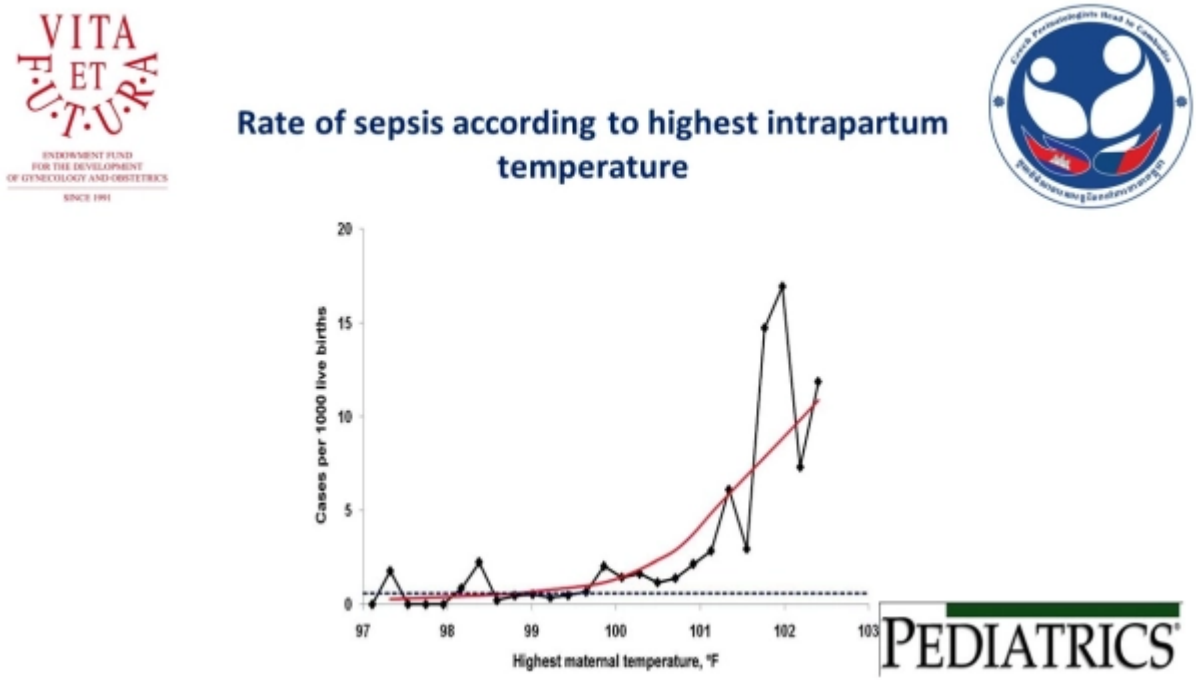
- Bacterial (unlike viral) neonatal sepsis has an *in utero* pathogenesis
- EOS due to ascending colonization and subsequent infection of uterine compartment, (amniotic fluid, placenta, umbilical cord and fetus) with maternal GI/GU flora
- *Listeria* is notable exception

Benirschke (1960) *Am J Dis Child*; Blanc (1961) *J Pediatr*; Wynn and Levy (2010) *Clin Perinatol*

5. rsk factors

- There have been successful attempts to devise a sepsis risk calculator based on a multivariate model nested case control study





Risk factors

- Prompt initiation of antibiotic therapy is essential to prevent both maternal and fetal complications in the setting of clinical chorioamnionitis
- Risk factors for early-onset neonatal infection: Parenteral antibiotic treatment given to the woman for confirmed or suspected invasive bacterial infection at any time during labour, or in the 24-hour periods before and after the birth.

- AAP Management of Neonates With Suspected or Proven Early-Onset Bacterial Sepsis

6. Clinical presentation

Wide range from subtle to shock.

Can occur in infants with an initially reassuring status.

Temperature instability and respiratory distress are the most common.

Term newborns without risk factors with symptoms that improve over the first 6 hours usually do not have sepsis

7. evaluation

- Blood culture – Gold Standard
- Sepsis screen
- Radiology
- Lumbar Puncture
- Urine R/M, Culture
- RBS, Arterial blood gases, PT/Aptt
- Advanced Diagnostic Methods

Bloodculture

- **Gold standard**
- A positive blood culture with sensitivity of the isolated organism is the best guide to antimicrobial therapy
- Cultures should be collected only from a fresh venepuncture site

Sepsis-screen

Consists of 5 items:

- C-reactive protein (CRP)
- Total leukocyte count
- Absolute neutrophil count (ANC)
- Immature to total neutrophil ratio (ITR)
- Micro-erythrocyte sedimentation rate (μ-ESR)**i**

CRP

- Nonspecific marker of inflammation and tissue necrosis
- Normal concentrations in neonates – variable
- Detectable increased CRP value-within 6 to 18 hours
- Peak CRP - 8 to 60 hours after onset
- Half-life is 5 to 7hours.
- Decreases promptly in the presence of appropriate therapy

Limitations

- Infants with on set of infection in the first 12 hours of life and with GBS infection may not have an elevated CRP
- Noninfectious processes, including meconium aspiration pneumonitis, asphyxia can have an elevated CRP up to 10 times the normal concentration
- CRP has alow positive predictive value and should not be used alone to diagnose sepsis

IT Ratio

- Immature neutrophils (band forms, metamyelocytes, myelocytes)
- Mature + immature neutrophils early predictor of sepsis
- N value= 0.16 in first 24 hours, decreasing to 0.12 by 60 hours
- Upper limit >0.2
- Limitation-many noninfectious processes, including prolonged induction with oxytocin, stressful labor, and even prolonged crying, are associated with Iincreased I:T ratios

Micro-ESR

Positive Value (mm in first hour)- 3+ age in days (in the first week)

Limitations:

- increased in noninfectious (anemia, hyperglobulinemia)
- superficial infections and noninfectious processes, including asphyxia, aspiration pneumonia, and respiratory distress syndrome
- Values vary inversely with the haematocrit

Presence of two abnormal parameters in a screen is associated with sensitivity of 93-100%, specificity of 83%, positive and negative predictive values of 27% and 100% respectively in detecting sepsis

Advanced Diagnostic Methods

Cytokine measurement – IL-6, IL-8, IL-10, IL-1b, G-CSF, TNF- alfa

- IgM
- Polymerase chain reaction (PCR)
- DNA micro array technology

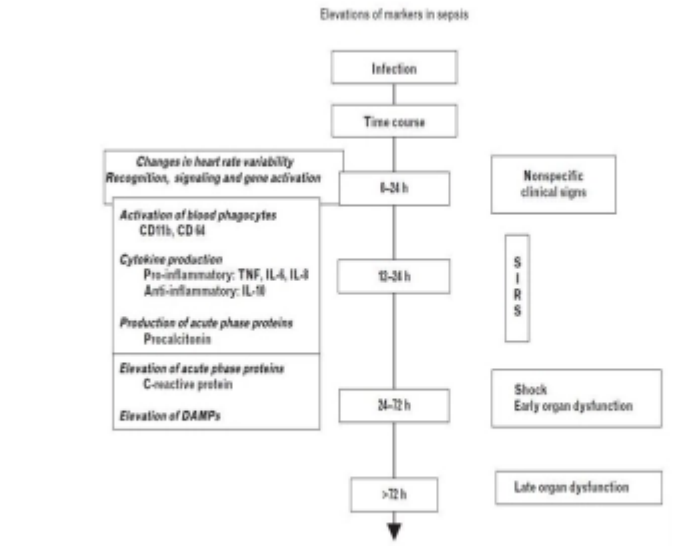


FIGURE 1. Elevations of markers in sepsis. CD, cluster of differentiation; DAMPs, damage-associated molecular patterns; IL, interleukin; SIRS, Systemic inflammatory response syndrome; TNF, tumor necrosis factor.

Role of procalcitonine

- PCT becomes detectable within 2 to 4 hours after a triggering event and peaks by 12 to 24hours.
- PCT secretion parallels -closely the severity of the inflammatory insult, with higher levels associated with more severe disease and declining levels with resolution of illness
- In the absence of an ongoing stimulus, ProCT is eliminated with a half-life of 24 to 35 hours, making it suitable for serial monitoring.

ProCT level of >2.0 ng/mL --- predicts sepsis and
>10 ng/mL --- septic shock
>20 ng/mL --- guarded prognosis
higher the PCT level --- worse the prognosis.
When sepsis has been successfully treated, PCT levels should fall with a half-life of

24 to 35 hours.

Polymerase Chain Reaction (PCR)

Under investigation for bacterial and fungal infection

- amplification of 16S rRNA a gene universally present in bacteria but absent in humans

Sensitivity	96%
Specificity	99,4%
Positive predictive value	88,9%
Negative predictive value	99,8%

Lumbar puncture

Indication: In EOS - a positive blood culture or clinical picture consistent with septicaemia.

Tests in CSF	Term	Preterm
Cells	7(0-32)	9(0-29)
Polymorphonuclear cells	61%	57%
Protein(mg/dl)	90(20-170)	115(65-150)
Glucose (mg/dl)	52(34-119)	50(24-63)
Protein:glucose	81(44-288)	74(55-105)

Diagnosis

- Diagnosis of neonatal sepsis - established only by a positive blood culture
- Ongoing research - validated risk stratification strategies - predictive ability to detect neonatal sepsis

Diagnosis

- **Culture-proven sepsis** – Blood culture- diagnostic of sepsis when a bacterial pathogen is isolated
- **Probable sepsis** — Clinical course (e.g.-ongoing temperature instability; ongoing respiratory, cardiocirculatory, or neurologic symptoms not explained by other conditions; or ongoing laboratory abnormalities suggestive of sepsis [cerebrospinal fluid (CSF) pleocytosis, elevated ratio of immature to total neutrophil counts, or elevated C-reactive protein])

Diagnosis

- Infection unlikely — Infants with mild and/or transient symptoms (ie. fever alone or other symptoms that quickly resolve) who remain well-appearing with normal laboratory values and negative cultures at 48 hours are unlikely to have sepsis.
- Empiric antibiotic therapy should be discontinued after 48 hours in these neonates

8. management

- Aggressive supportive care
- Antimicrobial therapy
- Adjuvant therapies

Supportive care

1.Thermo-neutral environment- prevention of hypo or hyperthermia

2.Maintenance of normoglycemic status

3.Maintenance of Oxygen saturation (91 to 94%)

4.Maintenance of tissue perfusion and blood pressure using colloids and inotropes

5.Maintenance of adequate nutrition by enteral feeding if not feasible by parenteral nutrition

6.Blood products to normalize the coagulation abnormalities, correction of anemia and thrombocytopenia

Antimicrobial Therapy

- Choice of antimicrobial drug- based on predominant pathogen and antibiotic sensitivity pattern.

Indications for Starting Antibiotics:

- presence of >3 risk factors for early onset sepsis
- presence of foul smelling amniotic liquor
- presence of 2 antenatal risk factor and
- a positive septic screen and strong clinical suspicion of sepsis

Antimicrobial Therapy

Choice of antimicrobial drug- based on predominant pathogen and antibiotic sensitivity pattern.

Indications for Starting Antibiotics:

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a positive septic screen and strong clinical suspicion of sepsis

Duration of Antibiotic Therapy

1.Clinical sepsis (Based on clinical suspicion and/or sepsis screen positivity): 7-10 days

2.Culture positive sepsis (not meningitis), UTI -14 days

3.Meningitis-2 weeks after sterilization of CSF culture or for a minimum of 2 weeks for gram positive meningitis and 3 weeks for gram negative meningitis, whichever is longer

4.Bone and joint infection 4-6 weeks

Evidence for intrapartum antibiotics in GBS colonization

The incidence of early GBS infection was reduced with IAP

compared to no treatment (risk ratio (RR) 0.17, 95%

confidence interval (CI) 0.04 to 0.74, three trials, 488 infants; risk difference -0.04, 95% CI -0.07 to -0.01; number needed to treat to benefit 25, 95% CI.

Evidence for intrapartum antibiotics in pprom

Erythromycin in pPROM – reduction in childhood disability prolongation of pregnancy, reductions in neonatal treatment with surfactant, decreases in oxygen dependence at 28 days of age and older, fewer major cerebral abnormalities on ultrasonography before discharge, and fewer positive blood cultures.

Evidence for intrapartum antibiotics in pprom – childhood follow up

Neither antibiotic had a significant effect on the overall level of behavioural difficulties experienced, on specific medical conditions, or on the proportions of children achieving each level in reading, writing, or mathematics at key stage one

The prescription of antibiotics for women with preterm rupture of the membranes seems to have little effect on the health of children at 7 years of age

Evidence for intrapartum antibiotics in spl

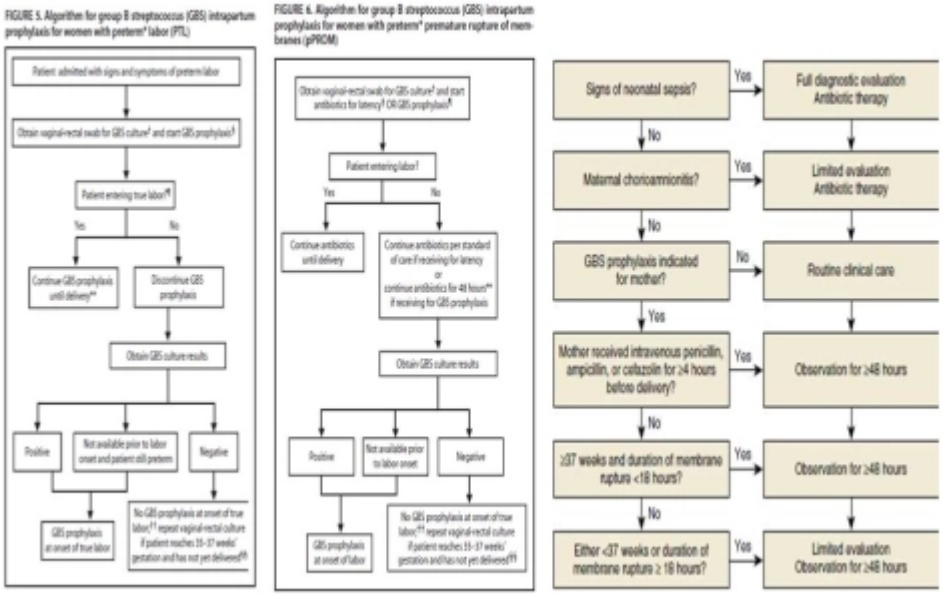
None of the trial antibiotics was associated with a lower rate of the composite primary outcome than placebo (erythromycin 90 [5·6%], co-amoxiclav 76 [5·0%], both antibiotics 91 [5·9%], vs placebo 78 [5·0%]). However, antibiotic prescription was associated with a lower occurrence of maternal infection.

Antibiotics should not be routinely prescribed for women in spontaneous preterm labour without evidence of clinical infection.

Evidence for intrapartum antibiotics in spl – childhood follow up

More children whose mothers had received erythromycin or co-amoxiclav developed cerebral palsy than did those born to mothers who received no erythromycin or no co-amoxiclav, respectively (erythromycin: 53 [3·3%] of 1611 vs 27 [1·7%] of 1562, 1·93, 1·21–3·09; co-amoxiclav: 50 [3·2%] of 1587 vs 30 [1·9%] of 1586, 1·69, 1·07–2·67). The number needed to harm with erythromycin was 64 (95% CI 37–209) and with co-amoxiclav 79 (42–591).

The prescription of erythromycin for women in spontaneous preterm labour with intact membranes was associated with an increase in functional impairment among their children at 7 years of age



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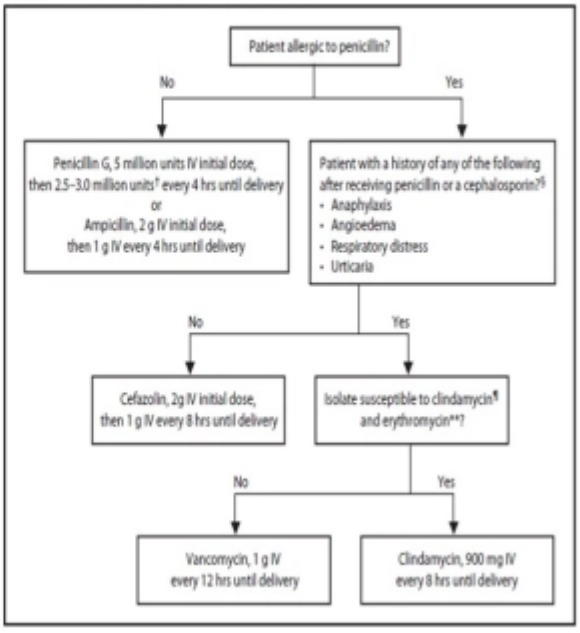
SINCE 1991

2010 GBS Guidelines: Algorithm for Selecting IAP Regimens

FIGURE 8. Recommended regimens for intrapartum antibiotic prophylaxis for prevention of early-onset group B streptococcal (GBS) disease*



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GBS Epidemiology

TABLE 3. Indications and nonindications for intrapartum antibiotic prophylaxis to prevent early-onset group B streptococcal (GBS) disease

Intrapartum GBS prophylaxis indicated	Intrapartum GBS prophylaxis not indicated
• Previous infant with invasive GBS disease	• Colonization with GBS during a previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)
• GBS bacteriuria during any trimester of the current pregnancy*	• GBS bacteriuria during previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)
• Positive GBS vaginal-rectal screening culture in late gestation† during current pregnancy*	• Negative vaginal and rectal GBS screening culture in late gestation† during the current pregnancy, regardless of intrapartum risk factors
• Unknown GBS status at the onset of labor (culture not done, incomplete, or results unknown) and any of the following: – Delivery at <37 weeks' gestation§ – Amniotic membrane rupture ≥18 hours – Intrapartum temperature ≥100.4°F (≥38.0°C)¶ – Intrapartum NAAT** positive for GBS	• Cesarean delivery performed before onset of labor on a woman with intact amniotic membranes, regardless of GBS colonization status or gestational age

Abbreviation: NAAT = Nucleic acid amplification tests

* Intrapartum antibiotic prophylaxis is not indicated in this circumstance if a cesarean delivery is performed before onset of labor on a woman with intact amniotic membranes.

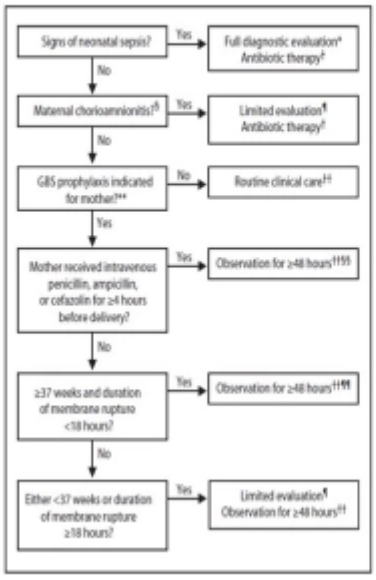
† Optimal timing for prenatal GBS screening is at 35–37 weeks' gestation.

§ Recommendations for the use of intrapartum antibiotics for prevention of early-onset GBS disease in the setting of threatened preterm delivery are presented in Figures 5 and 6.

¶ If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis.

** NAAT testing for GBS is optional and might not be available in all settings. If intrapartum NAAT is negative for GBS but any other intrapartum risk factor (delivery at <37 weeks' gestation, amniotic membrane rupture at ≥18 hours, or temperature ≥100.4°F [≥38.0°C]) is present, then intrapartum antibiotic prophylaxis is indicated.

FIGURE 9. Algorithm for secondary prevention of early-onset group B streptococcal (GBS) disease among newborns



* Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and lumbar puncture (if patient is stable enough to tolerate procedure and sepsis is suspected).

† Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other gram-negative pathogens) and should take into account local antibiotic resistance patterns.

§ Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific.

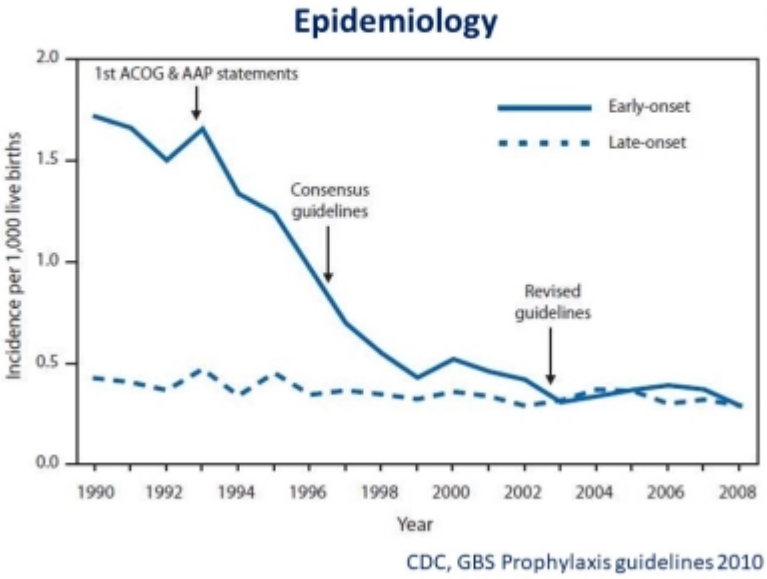
¶ Limited evaluation includes blood culture (at birth) and CBC with differential and platelets (at birth and/or at 6–12 hours of life).

** See table 3 for indications for intrapartum GBS prophylaxis.

†† If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated.

§§ If ≥37 weeks' gestation, observation may occur at home after 24 hours if other discharge criteria have been met, access to medical care is readily available, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved.

¶¶ Some experts recommend a CBC with differential and platelets at age 6–12 hours.



CDC, GBS Prophylaxis guidelines 2010

Intrapartum Antibiotics Prophylaxis (IAP)

- **Penicillin or ampicillin**
- Cefazolin
- Clindamycin
- Erythromycin
- Vancomycin