

# Neontal Sepsis

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# Incidence and Mortality

- Neonatal sepsis: Term used to describe any systemic bacterial infection documented by a positive blood culture in the first month of life
- Two relatively distinct illnesses based on postnatal age
  - Early Onset
  - Late Onset
  - Very Late Onset

	<b>Early &lt; 7 days</b>	<b>Late &gt; 7days-3 Months</b>	<b>Very Late &gt; 3 Months</b>
<b>Intrapartum complications</b>	Often Present	Usually absent	Varies
<b>Transmission</b>	Vertical, often acquired from maternal GU tract	Vertical/ Postnatal environment	Usually postnatal environment
<b>Manifestations</b>	Fulminant, multisystem, Pneumonia common	Insidious or acute, Focal infection, Meningitis common	Insidious
<b>Case-Fatality</b>	5-20 %	5%	Low

# Microbiology

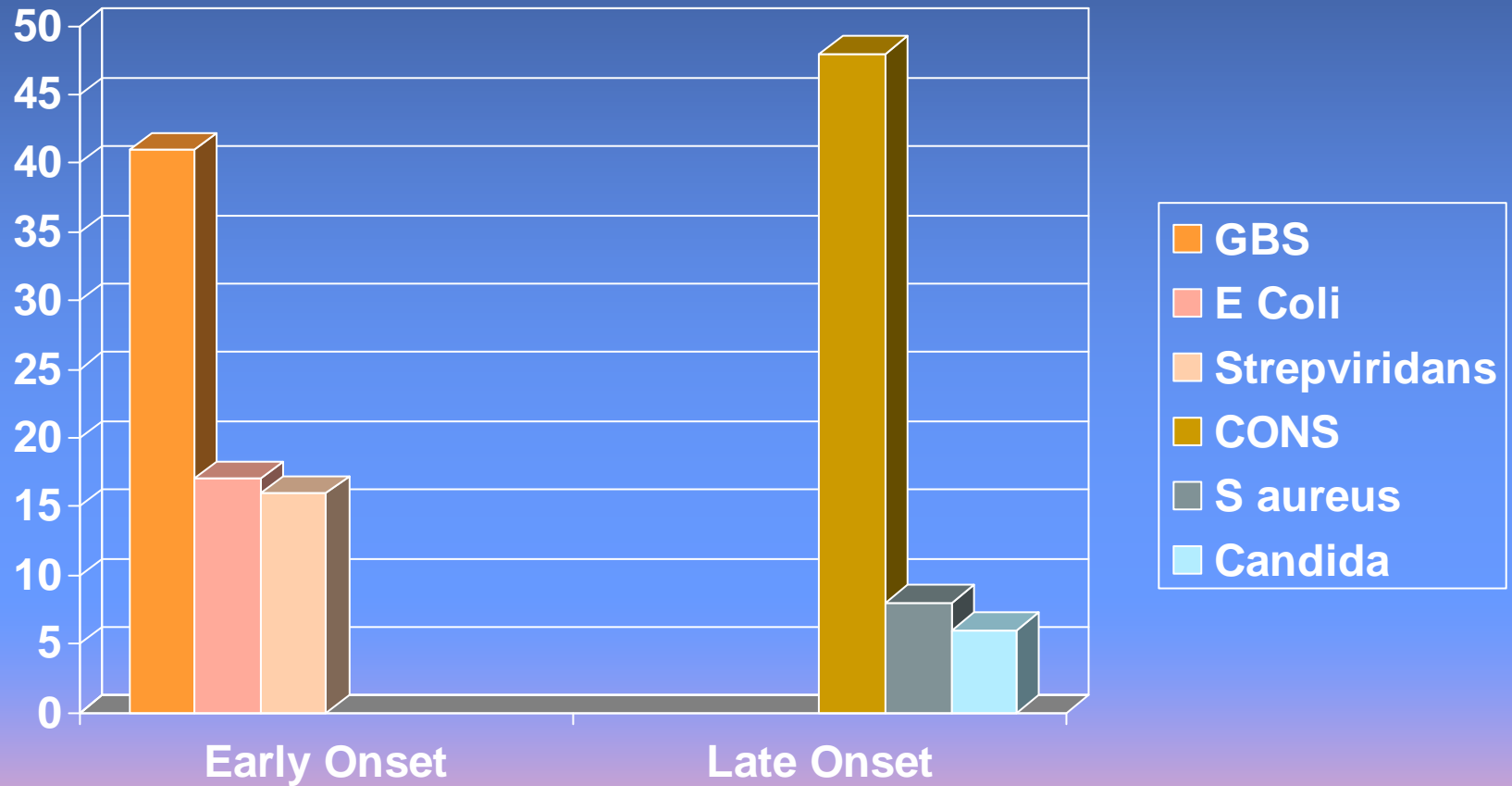
- Tend to change over time
- Since 1960's GBS (*S agalactiae*) emerged
- In Neonates of VLBW with early-onset sepsis, GBS is the most frequent pathogen
- An Increase in the incidence of E Coli and a decrease in GBS has been recently reported



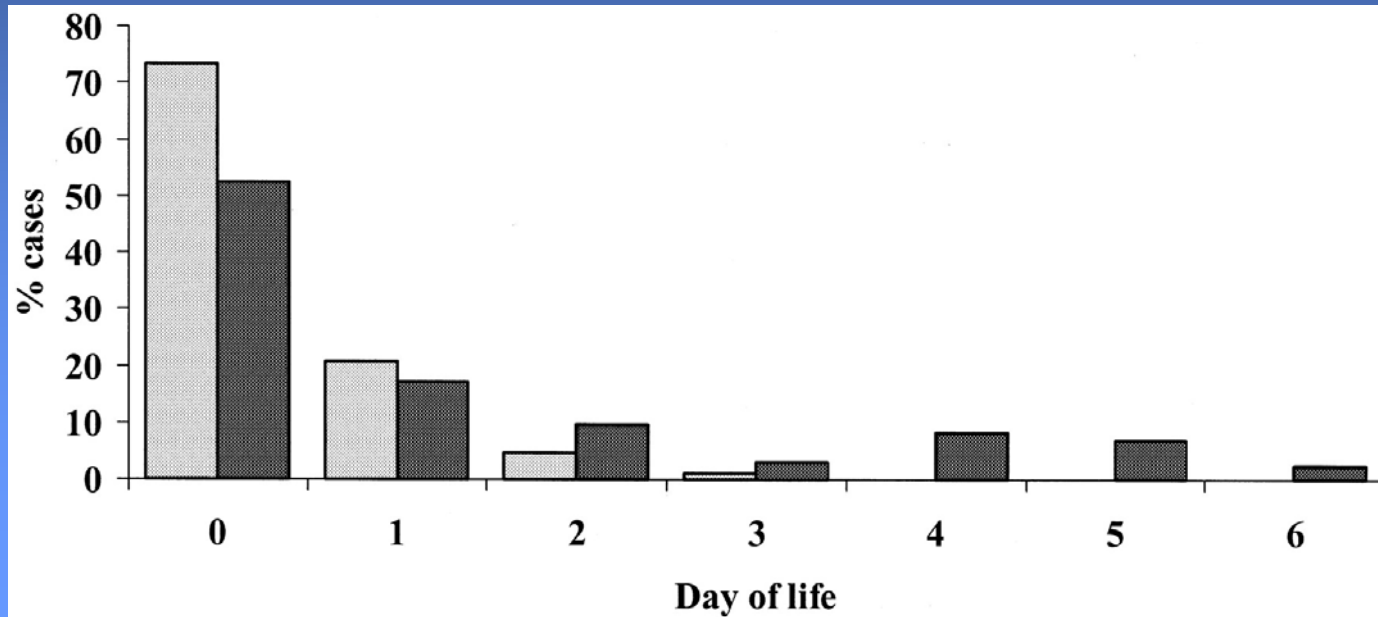
# Etiologic Agent

Stoll et al: Late onset sepsis in VLBW neonates: NICDH, Pediatrics 2002

Hyde et al: Trends in incidence and antimicrobial resistance of early-onset sepsis, Pediatrics 2002



**Fig 1. Day of onset of infection in infants <7 days of age caused by GBS and by all other bacterial pathogens**




**Hyde, T. B. et al. Pediatrics 2002;110:690-695**

# Transmission

- Early Onset: ascending amniotic fluid infection or colonized birth canal
- Late Onset: Acquired vertically in the peripartum period or horizontally from fomites in the environment or from colonized caregivers after delivery



# Risk Factors - Maternal

- AA
  - Malnutrition
  - Recent STD
  - GBS Colonization
  - Low SES: Inversely related prematurity and LBW
  - Maternal Fever, PROM
  - Asymptomatic Bacteriuria
  - Colonization with Mycoplasma associated with IBW
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# Risk factor- Peripartum

- Untreated or incompletely treated focal infections ( UTI, Vaginitis, Cervicitis )
- Systemic infection, Maternal FUO
- Risk of Infection X 4 with Maternal Chorioamnionitis and PROM > 24 hrs
- Fetal Scalp electrodes( 4% scalp Abscess)
- Cephalhematoma ( rare )
- Perinatal asphyxia with PROM

# Risk factor- Neonatal

- Male Infants have higher incidence ( possibly related to X- linked immunoregulatory genes)
- Metabolic Disorders
- VLBW with late onset : mechanical ventilation, umbilical vessel catheterization, central vessel access, HAL, duration of hospitalization

# Risk factor- Others

- Bottle feeding
- Prior antibiotic use
- High infant-nurse ratio in NICU
- Contaminated parenteral fluids

# Symptoms and Signs

- Non-specific
- Temp instability
- Respiratory symptoms: tachypnea, cyanosis, apneas
- Feeding difficulties
- Lethargy
- Keep high index of suspicion



# Leukocyte count

- Based on GA and postnatal age reference range
- I:T Ratio
- CRP: serial levels at 12 hrs interval increases sensitivity, GBS and < 12hr onset of disease may not have high CRP



# Tests

- Blood culture: minimum 0.5 ml per bottle
- Cath urine sample: Bag, clean catch not acceptable
- Others:
  - CSF
  - Tracheal
  - Skin lesions
  - Stool cultures

# Empiric Antibiotic

- Based on timing and setting of disease
- Microorganisms most frequently encountered
- Susceptibility profiles of organisms
- Site of infection
- Penetration of specific antibiotic
- Safety profile of antibiotic
- Nonbacterial infectious agents



# Early Onset

- Ampicillin + aminoglycoside:
- Listeria and GBS are uniformly susceptible to ampicillin but E coli is less reliable
- Gentamicin added for gram negative and acts synergistically with ampicillin for GBS and Listeria
- If meningitis suspected: cefotaxime instead aminoglycoside

# Late- onset

- Ampicillin + third generation Cephalosporin
- Health care associated late onset
  - Vancomycin: active against all staph, strep, most enterococcus, MRSA
  - Cefotaxime: meningitis, not active against listeria, enterococcus and pseudomonas
  - Ceftazidime + Aminoglycoside: Pseudomonas

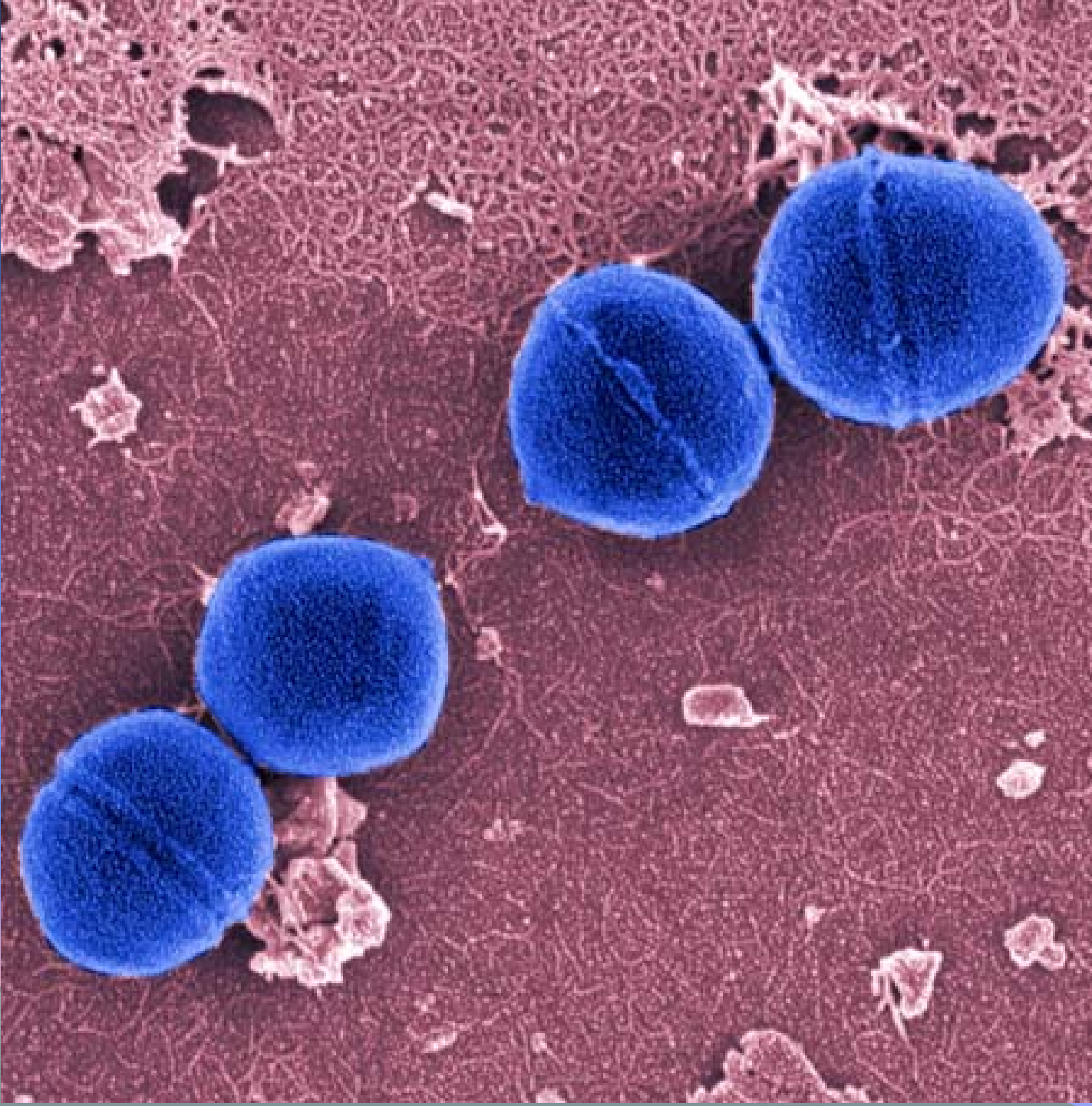


# IVIG

- Meta-analysis of studies of IVIG for the treatment of neonates with sepsis showed a significant decrease in mortality rate compared with standard therapies

# *Streptococcus agalactiae*

- Gram-positive coccus
- When cultured on sheep blood agar, forms glistening gray-white colonies with a narrow zone of beta hemolysis
- Colonize the vaginal and gastrointestinal tract in healthy women
- Carriage rates in women: 5-40%
- Causes asymptomatic bacteriuria, UTI, amnionitis, endometritis, wound infection

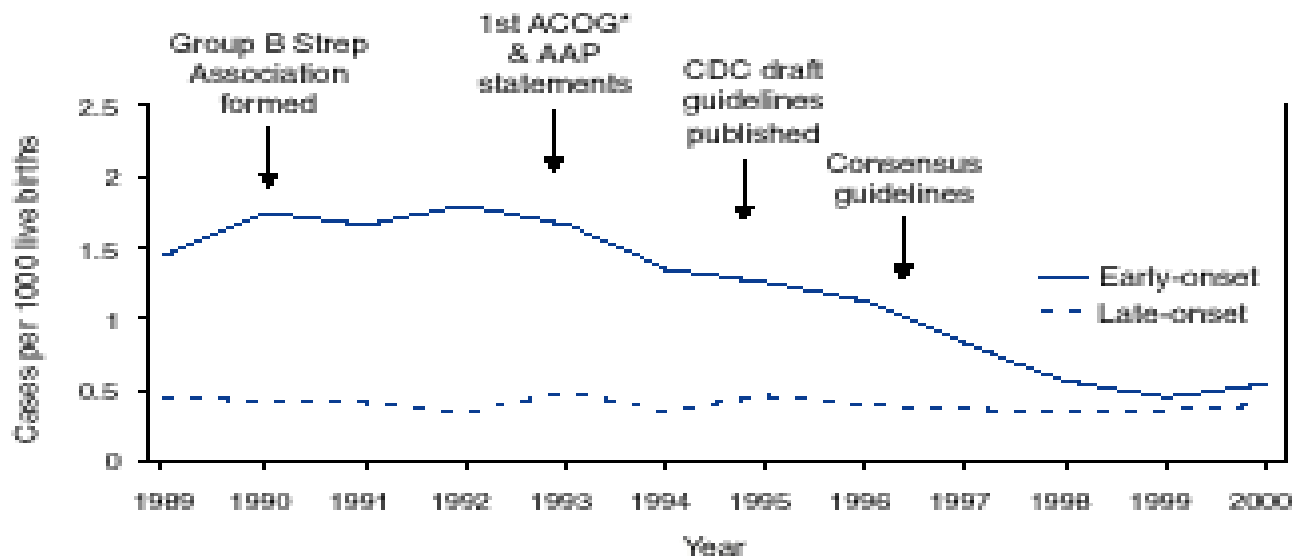


# GBS disease – Risk Factors

- < 37 weeks of gestation
- Rupture of membranes 18 hours before delivery
- Intrapartum fever
- women with heavy GBS colonization
- African-American, Hispanic
- <20 years of age
- GBS bacteriuria during pregnancy
- Low concentrations of anti-GBS capsular antibody in their sera

# Impact and Implementation of the 1996 Guidelines

**FIGURE 1. Incidence of early- and late-onset invasive group B streptococcal disease—selected Active Bacterial Core surveillance areas, 1989–2000, and activities for prevention of group B streptococcal disease**



\* ACOG, American College of Obstetricians and Gynecologists; AAP, American Academy of Pediatrics. **Source:** Adapted from CDC. Early-onset group B streptococcal disease, United States, 1998–1999. *MMWR* 2000;49:793–6; and Schrag SJ, Zywicki S, Farley MM, et al. Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. *N Engl J Med* 2000;342:15–20.

**FIGURE 2. Indications for intrapartum antibiotic prophylaxis to prevent perinatal GBS disease under a universal prenatal screening strategy based on combined vaginal and rectal cultures collected at 35–37 weeks' gestation from all pregnant women**

Vaginal and rectal GBS screening cultures at 35–37 weeks' gestation for **ALL** pregnant women (unless patient had GBS bacteriuria during the current pregnancy or a previous infant with invasive GBS disease)

### **Intrapartum prophylaxis indicated**

- Previous infant with invasive GBS disease
- GBS bacteriuria during current pregnancy
- Positive GBS screening culture during current pregnancy (unless a planned cesarean delivery, in the absence of labor or amniotic membrane rupture, is performed)
- Unknown GBS status (culture not done, incomplete, or results unknown) and any of the following:
  - Delivery at <37 weeks' gestation\*
  - Amniotic membrane rupture  $\geq$ 18 hours
  - Intrapartum temperature  $\geq$ 100.4°F ( $\geq$ 38.0°C)<sup>†</sup>

### **Intrapartum prophylaxis not indicated**

- Previous pregnancy with a positive GBS screening culture (unless a culture was also positive during the current pregnancy)
- Planned cesarean delivery performed in the absence of labor or membrane rupture (regardless of maternal GBS culture status)
- Negative vaginal and rectal GBS screening culture in late gestation during the current pregnancy, regardless of intrapartum risk factors

\* If onset of labor or rupture of amniotic membranes occurs at <37 weeks' gestation and there is a significant risk for preterm delivery (as assessed by the clinician), a suggested algorithm for GBS prophylaxis management is provided (Figure 3).

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

**BOX 2. Recommended regimens for intrapartum antimicrobial prophylaxis for perinatal GBS disease prevention\***

<b>Recommended</b>	Penicillin G, 5 million units IV initial dose, then 2.5 million units IV every 4 hours until delivery
<b>Alternative</b>	Ampicillin, 2 g IV initial dose, then 1 g IV every 4 hours until delivery
<b>If penicillin allergic<sup>†</sup></b> Patients not at high risk for anaphylaxis	Cefazolin, 2 g IV initial dose, then 1 g IV every 8 hours until delivery
Patients at high risk for anaphylaxis <sup>§</sup> GBS susceptible to clindamycin and erythromycin <sup>¶</sup>	Clindamycin, 900 mg IV every 8 hours until delivery
	<b>OR</b>
	Erythromycin, 500 mg IV every 6 hours until delivery
GBS resistant to clindamycin or erythromycin or susceptibility unknown	Vancomycin,** 1 g IV every 12 hours until delivery

\* Broader-spectrum agents, including an agent active against GBS, may be necessary for treatment of chorioamnionitis.

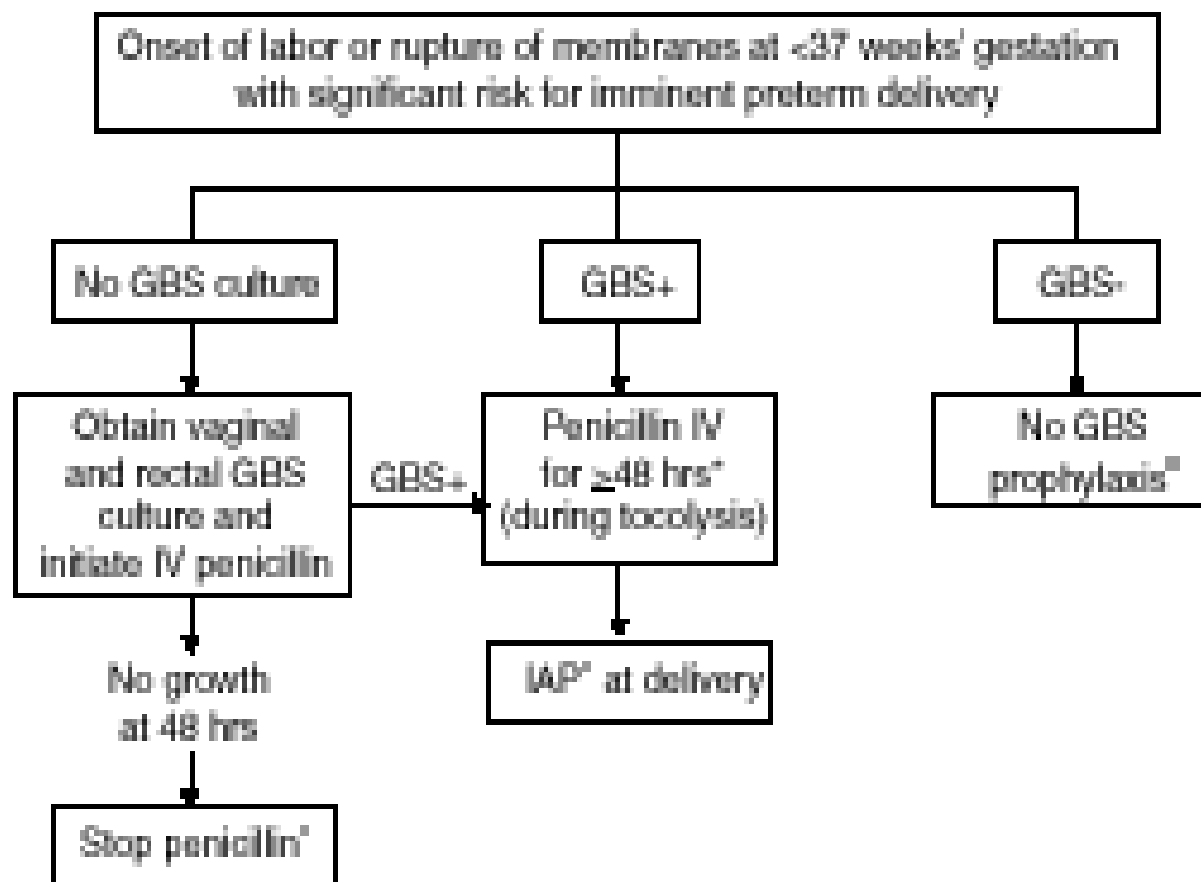
† History of penicillin allergy should be assessed to determine whether a high risk for anaphylaxis is present. Penicillin-allergic patients at high risk for anaphylaxis are those who have experienced immediate hypersensitivity to penicillin including a history of penicillin-related anaphylaxis; other high-risk patients are those with asthma or other diseases that would make anaphylaxis more dangerous or difficult to treat, such as persons being treated with beta-adrenergic-blocking agents.

§ If laboratory facilities are adequate, clindamycin and erythromycin susceptibility testing (Box 1) should be performed on prenatal GBS isolates from penicillin-allergic women at high risk for anaphylaxis.

¶ Resistance to erythromycin is often but not always associated with clindamycin resistance. If a strain is resistant to erythromycin but appears susceptible to clindamycin, it may still have inducible resistance to clindamycin.

\*\* Cefazolin is preferred over vancomycin for women with a history of penicillin allergy other than immediate hypersensitivity reactions, and

**FIGURE 3. Sample algorithm for GBS prophylaxis for women with threatened preterm delivery. This algorithm is not an exclusive course of management. Variations that incorporate individual circumstances or institutional preferences may be appropriate.**

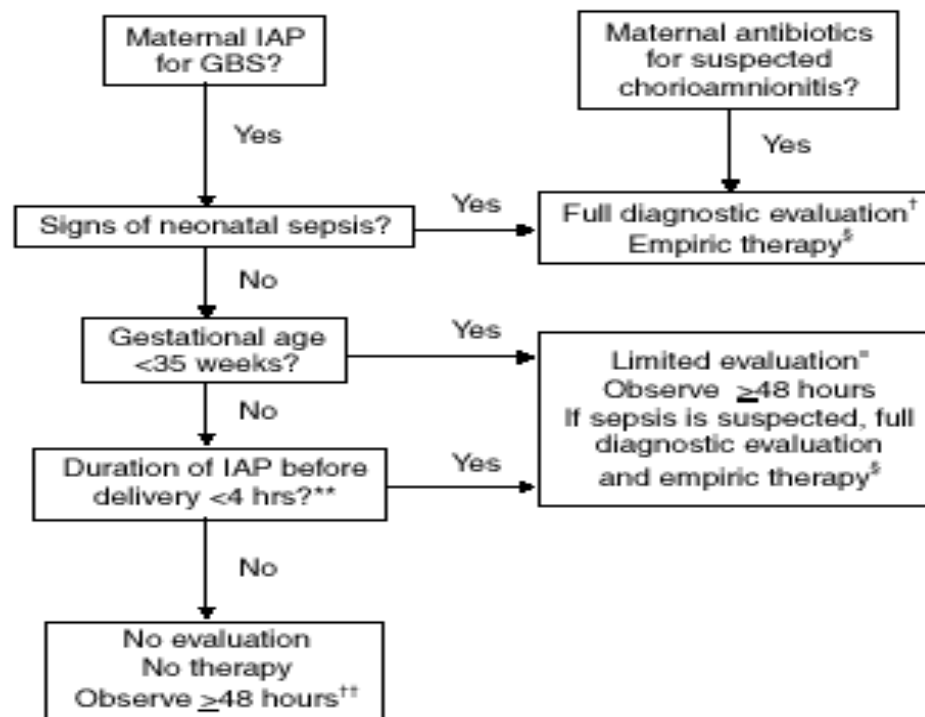


\* Penicillin should be continued for a total of at least 48 hours, unless delivery occurs sooner. At the physician's discretion, antibiotic prophylaxis may be continued beyond 48 hours in a GBS-culture-positive woman if delivery has not yet occurred. For women who are GBS culture positive, antibiotic prophylaxis should be reinitiated when labor likely to proceed to delivery occurs or recurs.

\*\* If delivery has not occurred within 4 weeks, a vaginal and rectal GBS screening culture should be repeated and the patient should be managed as described, based on the result of the repeat culture.

† Intrapartum antibiotic prophylaxis.

**FIGURE 4.** Sample algorithm for management of a newborn whose mother received intrapartum antimicrobial agents for prevention of early-onset group B streptococcal disease\* or suspected chorioamnionitis. This algorithm is not an exclusive course of management. Variations that incorporate individual circumstances or institutional preferences may be appropriate.



\* If no maternal intrapartum prophylaxis for GBS was administered despite an indication being present, data are insufficient on which to recommend a single management strategy.

† Includes complete blood cell count and differential, blood culture, and chest radiograph if respiratory abnormalities are present. When signs of sepsis are present, a lumbar puncture, if feasible, should be performed.

§ Duration of therapy varies depending on results of blood culture, cerebrospinal fluid findings, if obtained, and the clinical course of the infant. If laboratory results and clinical course do not indicate bacterial infection, duration may be as short as 48 hours.

¶ CBC with differential and blood culture.

\*\* Applies only to penicillin, ampicillin, or cefazolin and assumes recommended dosing regimens (Box 2)

†† A healthy-appearing infant who was ≥38 weeks' gestation at delivery and whose mother received ≥4 hours of intrapartum prophylaxis before delivery may be discharged home after 24 hours if other discharge criteria are met.

# Future Prevention Technology

- Rapid Tests to Detect GBS Colonization Status
- Vaccines To Prevent GBS Disease



# Reference

- Clinical Outcome of Neonates With GBS Positive Culture-12 Year Retrospective Study *Study ID Numbers: SHEBA-06-4132-TS-CTIL*
- [WWW.CDC.gov/guidelines](http://WWW.CDC.gov/guidelines)
- AMERICAN ACADEMY OF PEDIATRICS:  
Revised Guidelines for Prevention of Early-onset Group B Streptococcal (GBS) Infection , *PEDIATRICS Vol. 99 No. 3 March 1997*
- *Larsen JW, Dooley SL Group B streptococcal infections: an obstetrical viewpoint. Pediatrics. 1993;*
- American College of Obstetricians and Gynecologists Group B streptococcal infections in pregnancy: ACOG's recommendations. *ACOG Newsletter. 1993*

# Questions

- Describe the classification of Neonatal Bacterial sepsis and some major features of each.
- What are the three bacteria implicated in early and three that are implicated in late-onset neonatal sepsis?
- What are the maternal and fetal risk factors for GBS sepsis?
- What are the signs and symptoms suggestive of neonatal sepsis? Are they specific for any particular bacteria?
- What are the choices for empiric antibiotic treatment for suspected neonatal sepsis? What work-up is indicated?
- What are the indications for Intra-partum prophylaxis for GBS disease? Has the routine screening and IAP for GBS impacted the neonatal GBS disease?