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Key Inforbits

- Overview of preeclampsia
- Risk factors for preeclampsia
- Treatment for preeclampsia
- Overview of Group B *Streptococcus* (GBS) in pregnancy
- Screening for GBS
- Intrapartum GBS prophylaxis recommendations

ABOUT PREECLAMPSIA

May was preeclampsia awareness month. Preeclampsia is hypertension in pregnancy defined as a systolic blood pressure greater than 140 mmHg or a diastolic blood pressure greater than 90 mmHg based on at least 2 measurements obtained 4 hours apart. In addition, to diagnose preeclampsia the patient must have proteinuria (≥ 300 mg per 24 hours), protein/creatinine ratio of at least 0.3, or urine dipstick of 1+. If proteinuria is not present, but the following are present with hypertension, it is indicative of preeclampsia.[1,2]

- Thrombocytopenia (platelet count < 100,000/microliter)
- Serum creatinine > 1.1 mg/dL or doubling of the serum creatinine
- Elevated liver transaminases
- Pulmonary edema
- Cerebral or visual symptoms

Other hypertensive disorders in pregnancy are defined as follows[1,2]

- Gestational hypertension – blood pressure elevation after 20 weeks of gestation without proteinuria or the above systemic findings
- Chronic hypertension – hypertension that predates pregnancy
- Superimposed preeclampsia – chronic hypertension in association with preeclampsia

Severe signs of preeclampsia are persistent severe headache/vomiting, hyperreflexia, chest pain or dyspnea, or HELLP (hemolysis, elevated liver enzymes, low platelets). It usually occurs after the first 20 weeks of gestation, and it is a progressive multisystem complication that

occurs in about 2% to 8% of pregnancies. Preeclampsia can cause renal failure, maternal morbidity and mortality, preterm delivery, and intrauterine growth restriction. It can quickly progress to eclampsia, which is the occurrence of seizures and is considered a medical emergency.[1,2]

RISK FACTORS AND PREVENTION

Risk factors include: history of preeclampsia, intrauterine growth restriction (IUGR), preterm birth, placental abruption and fetal death, maternal comorbid conditions (type 1 or 2 pre-gestational diabetes, chronic hypertension, renal disease, and autoimmune disorders), or multi-fetal gestation. In pregnant women at high risk for preeclampsia (1 or more risk factors), low dose aspirin 81 mg after 12 weeks of gestation is recommended.[3]

Table 1: Preeclampsia Risk Assessment

Risk Level	Risk Factors	Recommendation
High	History of preeclampsia, especially when accompanied by an adverse outcome Multifetal gestation Chronic hypertension Diabetes Renal disease Autoimmune disease	Low dose aspirin if the patient has 1 or more high risk factors
Moderate	Nulliparity Obesity (BMI > 30 kg/m^2) Family history of preeclampsia (mother or sister) Sociodemographic characteristics (African American race, low socioeconomic status) Age of 35 years or greater Personal history factors (low birthweight or small for gestational age, previous adverse pregnancy outcome, > 10 y pregnancy interval)	Consider low dose aspirin if patient has several of these moderate risk factors
Low	Previous uncomplicated full term delivery	Do not recommend aspirin

Lefevre ML. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161(11):819-26.

Preeclampsia begins in the placenta, due to poor trophoblast invasion and remodeling of spiral arteries. This causes decreased utero-placental arterial flow and episodes of hypoxia. The abnormalities in perfusion to the placenta generates reactive oxygen species resulting in the release of cytokines, lipid peroxides, and microfragments from the placenta into the maternal circulation. Aspirin is an NSAID, which works in preeclampsia through its anti-inflammatory effects. The majority of studies found no association between low dose aspirin and congenital anomalies, neonatal intraventricular hemorrhage, premature closure of the ductus arteriosus, maternal post partum bleeding, or placental abruption.[4] Table 1 above summarizes risk factor assessment and aspirin recommendations.

TREATMENT

Table 2: Signs/symptoms of gestational hypertension, mild and severe preeclampsia			
Symptom	**Gestational hypertension**	**Mild preeclampsia**	**Severe preeclampsia**
Systolic blood pressure	140 mmHg	140 mmHg	160 mmHg
Diastolic blood pressure	90 mmHg	90 mmHg	110 mmHg
Proteinuria	None	300 mg/24 hour or 1+ proteinuria on dipstick or Protein/creatinine ratio ≥ 0.3 mg/dL	≥ 2 g/24 hour or 3+ proteinuria on dipstick
Thrombocytopenia	Normal	Normal	< 100,000
Liver function tests	Normal	Normal	2x normal
Creatinine	Normal	Normal	1.1 mg/dL
Pulmonary edema	No	No	Yes
Cerebral disturbances	No	No	Yes
Visual disturbances	No	No	Yes

Dhariwal NK, Lynde GC. Update in the Management of Patients with Preeclampsia. Anesthesiol Clin. 2017;35(1):95-106.

Table 2 above differentiates mild and severe preeclampsia, which will guide treatment. The only definitive treatment is delivery of the fetus. The current guidelines recommend delivering if the patient presents with severe preeclampsia or at or after 37 0/7 weeks of gestation. If between weeks 34 0/7 and 37 0/7 with certain complications, delivery may also be required. For other patients with non-severe preeclampsia close monitoring it recommended. The mother should perform daily checks for fetal movement.[5] Also, mothers should report any severe headaches, visual changes, epigastric pain, and shortness of breath. Blood pressure checks and urine protein analysis should be monitored twice weekly, along with weekly liver enzymes and serum creatinine levels. Ultrasound measurements for amniotic fluid volume should be performed. Antihypertensive therapy is indicated if systolic blood pressure is 150 mmHg or greater OR diastolic blood pressure is 100 mmHg or greater.[5] In pregnancy, labetalol, nifedipine, or methyldopa may be used.[5,6] See tables 3 & 4 for dosing and other information for urgent control and non-urgent control.

Table 3: Antihypertensive Agents for Urgent BP control in Pregnancy

Drug	Dose	Comments
Labetalol	10-20 mg IV, then 20 to 80 mg every 20-30 min to a max dose of 300 mg or Constant infusion 1-2 mg/min IV	Considered a first line agent Tachycardia is less common and fewer adverse effects Contraindicated in patients with asthma, heart disease, or congestive heart failure
Hydralazine	5 mg IV or IM, then 5-10 mg IV every 20-40 min or Constant infusion 0.5-10 mg/h	Higher or frequent dosage associated with maternal hypotension, headaches, and fetal distress.
Nifedipine	10-20 mg orally, repeat in 30 minutes if needed; then 10-20 mg every 2-6 hours	May observe reflex tachycardia and headaches

Task Force on Hypertension in Pregnancy. Hypertension in Pregnancy. American College of Obstetricians and Gynecologists Women's Health Care Physicians; 2013. Available from: http://www.acog.org/Resources-And-Publications/Task-Force-and-Work-Group-Reports/Hypertension-in-Pregnancy

Table 4: Oral Antihypertensive Agents in Pregnancy

Drug	Dosage	Comments
Labetalol	200-2,400 mg daily in 2-3 divided doses	Well tolerated Potentially bronchoconstrictive Avoid in patients with asthma and congestive heart failure
Nifedipine	30-120 mg daily of a slow release preparation	Do not use sublingual form
Methyldopa	0.5-3 grams daily in 2-3 divided doses	Childhood safety data up to 7 years of age May not be as effective in control of severe hypertension
Thiazide diuretics	Depends on agent	Second line agent
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers	Depends on agent	Associated with fetal anomalies Contraindicated in pregnancy and preconception period

Task Force on Hypertension in Pregnancy. Hypertension in Pregnancy. American College of Obstetricians and Gynecologists Women's Health Care Physicians; 2013. Available from: http://www.acog.org/Resources-And-Publications/Task-Force-and-Work-Group-Reports/Hypertension-in-Pregnancy

Parenteral magnesium sulfate is used for patients with eclampsia (have had seizures), those with severe preeclampsia during the intrapartum-postpartum period to prevent eclampsia, and for women undergoing a cesarean delivery who have preeclampsia.[5,6]

There have been no new treatments discovered for preeclampsia. One recent randomized, double blind, placebo controlled trial studied the use of antithrombin III in patients with non-severe preeclampsia occurring before 30 weeks of gestation.[7] The study was stopped early due to low enrollment. Although they found antithrombin III to be safe, there was no difference in fetal/neonatal outcomes and no prolongation of pregnancy.[7] Close monitoring, anti-hypertensives, magnesium sulfate, and delivery remain the mainstays of preeclampsia/eclampsia treatment.

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Introduction to Group B Strep (GBS)

Group B streptococci, or *Streptococcus agalactiae*, is a gram-positive bacterial organism that is commonly found in the gastrointestinal tract or lower reproductive tracts of men and women. Pregnant women are often colonized with GBS, and current statistics show 10% to 30% will test positive for GBS in the vagina or rectum during pregnancy.[1,2] The main concern regarding GBS in pregnancy is transmission from mother to baby, which can occur prior to labor (prenatal-onset), during labor or within the first week of life (early-onset), or after the first week of life (late-onset). GBS infection can manifest as maternal urinary tract infections, amnionitis, endometriosis, sepsis, or meningitis. In newborns, invasive GBS typically presents as sepsis, pneumonia, or meningitis.[1,2,3] Reported mortality due to neonatal GBS infection is variable, but ranges from 11% to 50%.[3]

Guidelines for the prevention of early-onset GBS have been published since the early 1990s and the incidence has decreased dramatically since that time. Important aspects that have led to this decline are understanding of risk factors for early-onset GBS, increased identification of GBS during prenatal care, and improved intrapartum antibiotic prophylaxis recommendations.

Risk Factors for GBS

Several risk factors for GBS are discussed in the guidelines, but one specifically has been shown to be the most predictive of early-onset GBS—maternal GBS colonization. Women who are colonized with GBS during pregnancy are at an extremely high risk of having infants who develop early-onset GBS (> 25x women without GBS colonization). Other risk factors for early-onset GBS include gestational age < 37 weeks, longer duration of membrane rupture, intra-amniotic infection, young maternal age, black race, previous delivery of an infant with invasive GBS disease, and intrapartum temperature > 99.5 F.[1,2]

Screening for GBS

Women should be routinely screened for GBS in the urine during pregnancy, and treatment for symptomatic or asymptomatic GBS urinary tract infection (UTI) should be initiated if positive at any point during any trimester. In addition, positive GBS UTI is an automatic indication for GBS prophylaxis. Guidelines also recommend all women should have vaginal/rectal cultures collected at 35-37 weeks of gestation to test for GBS. If the culture is positive for GBS, intrapartum antibiotic prophylaxis is required unless a cesarean delivery is performed and amniotic membranes are intact. No antimicrobials should be given for GBS colonization prior to delivery following a positive culture at 35-57 weeks as it is only needed to prevent transmission from mother to baby.[1,2] The full list of indications for GBS prophylaxis is found in **Table 5** below.

Table 5: Indications for GBS Intrapartum Antibiotic Prophylaxis

Intrapartum GBS Prophylaxis Indicated	Intrapartum GBS Prophylaxis NOT Indicated
• Positive GBS vaginal-rectal screening culture at 35-37 weeks *(unless C-section is performed prior to rupture of amniotic membranes*	• Colonization with GBS during a previous pregnancy*
• Previous infant with invasive GBS disease	• GBS bacteriuria during a previous pregnancy*
• GBS bacteriuria during any trimester of the current pregnancy *(unless C-section is performed prior to rupture of amniotic membranes)*	• Negative vaginal and rectal GBS screening at 35-37 weeks during current pregnancy
• Unknown GBS status at onset of labor AND any of the following: o Delivery < 37 weeks gestation o Amniotic membrane rupture ≥ 18 h o Intrapartum temperature ≥ 100.4°F o Intrapartum nucleic acid amplification tests (NAAT) positive for GBS	• Cesarean delivery performed prior to rupture of amniotic membranes **These recommendations against GBS prophylaxis are negated if the woman meets any criteria in the left column.*

Adapted from CDC and ACOG Guidelines[1,2]

Rapid diagnostics, such as polymerase chain reaction (PCR) assays, are used to quickly identify organisms and provide susceptibility data. Numerous studies have shown rapid diagnostics provide improved patient outcomes for a variety of infections, and current CDC and ACOG GBS guidelines briefly discuss the use of rapid techniques in specimen processing. The guidelines were published in 2010 and 2011, and data available at the time did not support replacing the cultures performed at 35-37 weeks with rapid diagnostic testing.[1,2] Since that time, further studies have been published assessing these rapid diagnostics for GBS in labor, and future guidelines may provide additional guidance on the use of these new technologies to reduce antimicrobial usage and provide cost savings.

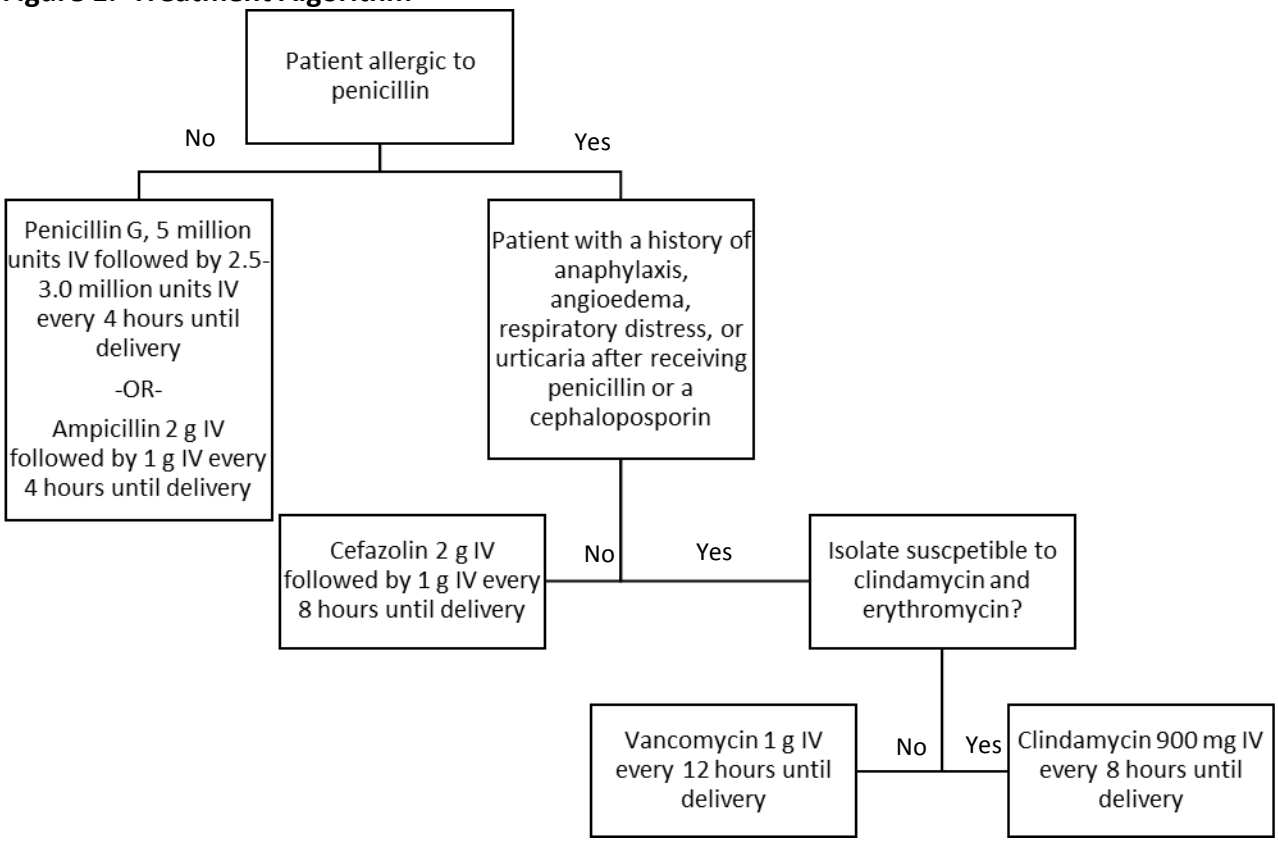
Poncelet-Jasserand and colleagues evaluated the use of PCR at delivery compared to traditional cultures at 34-38 weeks. There were 225 women included, and each patient acted as her own control. Results showed higher sensitivity (66.7 vs. 55.6) and specificity (94.9 vs. 84.5) for PCR vs. traditional cultures. A lower percentage of patients were inadequately treated with prophylactic antimicrobial treatment (4.5% vs. 13.6 ($p < 0.001$)) and more patients were not administered unnecessary antibiotics (83.5% vs. 74.2% ($p<0.05$)) with PCR vs. traditional cultures, respectively. This study also demonstrated that culture results can change from 34-38 weeks to delivery. Of the women with an available culture at 34-38 weeks, 5.9% changed from negative to positive and 6.4% changed from positive to negative at delivery, which is a total discrepancy of 12.3%.[4] Additional studies need to be conducted to demonstrate the full benefits and the cost effectiveness associated with conducting of rapid diagnostic tests for GBS at the time of delivery.

Treatment Recommendations

Despite growing concern for resistant organisms, GBS is remains susceptible to first-line treatment options, including intravenous (IV) penicillin, ampicillin, and cefazolin. IV clindamycin and erythromycin are second-line options in patients with penicillin allergy at high risk for anaphylaxis, but these antimicrobials have documented resistance to GBS and must be tested for susceptibilities if clindamycin is planned for intrapartum prophylaxis. If the organism is resistant to clindamycin or susceptibilities are unknown at the time of labor, IV vancomycin is recommended.[1,2,5] No oral agents are recommended at this time due to concerns regarding absorption and adequate antimicrobial concentrations reaching the fetus.[1,2]

The treatment algorithm in **Figure 1** is used by the CDC and ACOG guidelines.[1,2] This algorithm outlines the antibiotic recommendations for women who have an indication to receive intrapartum GBS prophylaxis, and treatment is based on patient's allergies and culture and sensitivity data. This algorithm should not be utilized in patients who present with chorioamnionitis in whom broad spectrum antimicrobials are required.[1,2] Initiate the appropriate antimicrobial at admission and continue at the recommended interval (eg, every 4 hours until delivery for penicillin and ampicillin) to ensure interruption of vertical transmission.[6]

Figure 1: Treatment Algorithm



Secondary prevention of early-onset GBS for newborns is also discussed in the guidelines. Newborns should be closely evaluated for signs and symptoms of infection in the days following birth. Any signs of neonatal sepsis warrants a full diagnostic evaluation, including cultures, complete blood count (CBC), and possibly a chest radiograph and/or lumbar puncture. In addition, antibiotics should be initiated that cover GBS and gram-negative organisms, such as E.

coli. If GBS prophylaxis was used during delivery, newborns should be observed for ≥ 48 hours either at the hospital or at home and treated for infection if signs and symptoms occur. For newborns < 37 weeks gestation or duration of membrane rupture ≥ 18 hours, a limited evaluation, including blood culture and CBC, should be performed and the baby will be closely monitored for ≥ 48 hours as described above.[1,2]

The prevention and treatment early-onset GBS has improved over the past two decades, but research into a GBS vaccine and rapid diagnostics may hold the key to further advances in care. In addition, research into prevention of late-onset GBS and pre-natal-onset GBS need to be conducted to lower the burden of these diseases. Public awareness of the risks associated with GBS can make a major impact in women asking the right questions during pregnancy. Help us spread the word about International GBS Awareness Month to improve the care of pregnant women across the world!

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The last "dose" …

Birth is not only about making babies. Birth is about making mothers—strong, competent, capable mothers who trust themselves and know their inner strength.
–Barbara Katz Rothman, PhD [American author, 1948 -]

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