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Asymptomatic GBS bacteriuria during antenatal visits: To treat or not to treat?

Abstract: Inconsistencies persist regarding the efficacy of treating asymptomatic group B Streptococcus bacteriuria in pregnant individuals with colony counts below 10^5 (100,000) CFU/mL. Despite these discrepancies, treatment still occurs. This article examines the role of screening and treatment, evidence-based guidelines, and practice patterns to provide clarification and resolve local practice disparities.

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Streptococcus agalactiae, known as group B Streptococcus (GBS), is a Gram-positive coccus commonly found to colonize the human genital and gastrointestinal tracts, and the upper respiratory tract of infants.¹ GBS was identified as a significant cause of perinatal morbidity and mortality in the 1970s.^{2,3}

Since that time, implementation of clinical practice guidelines for intrapartum antibiotic prophylaxis has reduced the incidence of neonatal sepsis due to GBS by approximately 80% in the US.^{1,4} In pregnant individuals, GBS is a known source of asymptomatic bacteriuria, urinary tract infection (UTI), pyelonephritis, upper

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genital tract infection, postpartum endometritis, pneumonia, sepsis, and bacteremia.⁵ In neonates/infants, the rate of early-onset invasive GBS infection in 2016 was 0.22 cases per 1,000 live births, in the CDC surveillance study.⁴

Colonization of pregnant individuals with high colony counts of GBS continues to be a major risk factor for both maternal and neonatal infections.¹ High colony counts are defined as at least 10^5 (100,000) colony-forming units per milliliter (CFU/mL) in the urine. Low colony counts are less than 10^5 (100,000) CFU/mL.⁶ A urine culture obtained using a mid-stream, clean-catch urine sample at 12 to 16 weeks gestational age is the standard of care and the established method for diagnosing asymptomatic bacteriuria (ASB).⁶ A confirmatory culture of a second sample to control for contamination or transient ASB is recommended, although not typically implemented.⁶ A culture result of at least 10^5 (100,000) CFU/mL of GBS is considered positive, and lower counts indicate anogenital colonization.⁶ Historically, at least 10^4 (10,000) CFU/mL was used as a threshold for treatment of GBS ASB during pregnancy.^{4,6} However, the efficacy of treating ASB with low colony counts is controversial, and the data appear limited or contradictory.

The authors conducted an internal case review in a cohort of 459 individuals seeking prenatal care in a family practice clinic using an interprofessional team including: physicians, residents, NPs, nurse midwives, and pharmacists. The purpose was to analyze the prevalence and local practice patterns related to GBS ASB, and define best evidence-based practice for management of GBS ASB. To examine the associations between the role of screening and treating GBS ASB during pregnancy, the authors searched MEDLINE, CINAHL, PubMed, Embase, and the Cochrane Database of Systematic Reviews. Criteria in the review included: written in English; published between 2015 and 2020; randomized controlled trials, systematic reviews with or without meta-analyses; clinical practice guidelines and studies that addressed relationships between GBS bacteriuria, morbidity and mortality, and antibiotic resistance. The search terms used were: Group B strep* infection, bacteriuria, pregnancy, urinary tract infection, antibiotic resistance, maternal and neonatal morbidity and mortality.

■ Risks of UTIs, pyelonephritis, chorioamnionitis, and preterm birth

UTIs are among the most common complications experienced during pregnancy.⁷ The literature reveals 2% to 10% of all pregnancies are complicated by ASB, defined as bacteriuria in the absence of acute UTI symptoms.⁶⁻⁸ If left untreated, as many as 20% to 35% of pregnant individuals with ASB will develop UTI that may lead to pyelonephritis.^{7,8} While *E. coli* is the predominant organism found in symptomatic and asymptomatic UTIs, GBS has been isolated in 2.1% to 30% of ASB cases in pregnant individuals.^{7,9}

During pregnancy, individuals with bacteriuria have an increased risk of developing pyelonephritis.

During pregnancy, individuals with bacteriuria have an increased risk of developing pyelonephritis.¹⁰ In the clinical setting, pyelonephritis is diagnosed by a positive urine culture in the presence of fever, urinary symptoms, nausea/vomiting, flank pain, and/or costovertebral angle tenderness.¹¹

Maternal GBS bacteriuria is a marker for anogenital tract colonization, which poses a risk for an infection of the amniotic fluid, membranes, placenta and/or decidua, known as chorioamnionitis, or intra-amniotic infection.¹¹ Clinical signs include fever, uterine tenderness, maternal and fetal tachycardia, purulent amniotic fluid, and maternal leukocytosis.¹¹ GBS is among the most common bacterial organisms implicated as a cause of chorioamnionitis.¹² Although the final diagnosis of chorioamnionitis can only be confirmed after birth by culture and histologic examination of the placenta and membranes, in clinical practice, antibiotic treatment is initiated with the onset of maternal fever during labor with any of the other clinical signs noted above.^{11,12}

In the 1960s, Kass reported asymptomatic GBS bacteriuria was associated with preterm birth (prior to 37 weeks gestation).¹³ In 1984, Møller and colleagues noted premature rupture of fetal membranes and preterm labor were more common in the GBS bacteriuria group.¹⁴ A prospective cohort study in 1995 found bacteriuria was associated with preterm birth in the initial analysis, but after further adjustment for medical, demographic, and social factors, association of

Summary of GBS bacteriuria studies^{9,21-31}

Author and year	Design and sample	Outcomes	OR, RR, and/or prevalence
Smaill and Vazquez, 2015 ²¹ Updated in 2019 ³¹	Systematic review of 15 randomized controlled trials N = 2,000	Low-quality evidence found for antibiotic treatment of ASB during pregnancy in reducing the risk of pyelonephritis, preterm birth, and low birth weight.	2015: RR, 0.23 (95% CI 0.13-0.41) for pyelonephritis 2019: RR, 0.24 (95% CI 0.13-0.41; 12 studies, 2,017 women; low-certainty evidence) for pyelonephritis 2015: RR, 0.27 (95% CI 0.11-0.62) for preterm birth 2019: RR, 0.34 (95% CI 0.13-0.88; 3 studies, 327 women; low-certainty evidence) for preterm birth 2015: RR, 0.64 (95% CI 0.45-0.93) for low birthweight babies 2019: RR, 0.64 (95% CI 0.45-0.93; 6 studies, 1,437 babies; low-certainty evidence) for low birthweight babies
Ahmad, 2015 ⁹	Prospective cohort study in Saudi Arabia n = 3,863	To prevent ASB complications all pregnant women should be screened at the first antenatal visit with a urine culture.	2.1% had GBS ASB Among the women with GBS ASB, 84.2% had cystitis and 15.8% had pyelonephritis.
Eastwood et al., 2015 ²²	Retrospective observational study in Northern Ireland n = 574	Guideline adherence for intrapartum antibiotic prophylaxis to prevent GBS neonatal infection needs improvement to reduce the incidence of early-onset GBS disease of 0.57/1,000 live births.	Of the total cases identified with GBS, 43 neonates had early-onset GBS disease and 22 had late-onset GBS disease. Of the total cases, only 25.5% received intrapartum antibiotic prophylaxis.
Kazemier et al., 2015 ²³	Prospective cohort study with embedded RCT n = 4,283 RCT = 85	In uncomplicated singleton pregnancy, ASB was not associated with preterm birth. RCT: untreated ASB is associated with pyelonephritis with a low absolute risk.	OR, 1.5 (95% CI 0.6-3.5) RCT: OR, 3.9 (95% CI 1.4-11.4)
Kram et al., 2016 ²⁴	Retrospective study with multi-variable analysis in Eastern Wisconsin n = 99,305	Geographic and demographic characteristics were associated with maternal GBS colonization and infant death. Further studies are needed to determine if increased treatment of mothers colonized with GBS decreases the risk of fetal demise at birth.	Prevalence was 22.3% overall Highest in Black Americans at 34.1%; White Americans at 20.1% Rate of infant death was 5.7/1,000 births
Bianchi-Jassir et al., 2017 ²⁵	Systematic review and meta-analysis of 45 studies worldwide N = 269,191	Preterm birth was associated with maternal GBS colonization worldwide, especially where there was evidence of GBS bacteriuria. However, results may be due to confounding, which was not addressed in most studies.	RR, 1.21 (95% CI 0.99-1.48) in cohort and cross-sectional studies OR, 1.85 (95% CI 1.24-2.77) in case control studies RR, 1.98 (95% CI 1.45-2.69) in cohort studies
Perez-Moreno et al., 2017 ²⁶	Prospective cohort study n = 608	GBS bacteriuria was found to be a risk factor for intrapartum GBS colonization regardless of the colony count. GBS bacteriuria was significantly associated with intrapartum maternal GBS colonization and also found in women with negative rectovaginal screening cultures.	Sensitivity (41%), specificity (94.7%), positive (59.3%), and negative (89.5%) predictive values of urine culture predicting GBS colonization. Sensitivity (76.9%), specificity (95.4%), positive (76.9%), and negative (95.4%) predictive values of rectovaginal screening cultures predicting GBS colonization.

(Continues)

Summary of GBS bacteriuria studies^{9,21-31} (Continued)

Author and year	Design and sample	Outcomes	OR, RR, and/or prevalence
Köves et al., 2017 ²⁷	Systematic review and meta-analysis of 50 studies N = 7,088 all studies Low birth weight n = 1,689 Preterm birth n = 854	Antibiotic treatment of ASB during pregnancy was associated with lower risk of preterm birth and low birth weight. Authors noted low quality of evidence for these studies.	Low birth weight RR, 0.58 (95% CI 0.36-0.94) Preterm birth RR, 0.34 (95% CI 0.18-0.66)
Khalil et al., 2019 ²⁸	Population-based retrospective cohort study N = 34,285 divided into 3 groups Group I (n = 249) included women whose urine culture was positive for GBS. Group II (n = 5,765) included women whose urine was negative for GBS. Group III (n = 28,271) included women whose urine had not been cultured during pregnancy.	No association between preterm delivery and GBS bacteriuria was found in the cultured groups. After controlling for potential confounders, preterm delivery remained not associated with GBS bacteriuria. Previous suggestions of such association may have been compromised by a selection problem for testing due to a high-risk profile for complications in pregnant women selected for urine culture. The cultured group differed considerably from the group without urine cultures on a majority of variables examined.	OR, 0.89 (95% CI 0.5-1.4) Adjusted OR, 0.99 (95% CI 0.6-1.6)
Khalil et al., 2018 ²⁹	Prospective observational study n = 902	GBS bacteriuria is strongly associated with a high load of vaginal GBS colonization intrapartum, but it may not perform satisfactorily as a standalone-screening marker for risk of early-onset GBS disease.	Positive predictive values for colony counts of GBS bacteriuria at 35-37 weeks' gestation: 35% for <10 ⁴ (10,000) CFU/mL, 70% for =10 ⁴ (10,000) CFU/mL, 67% for >10 ⁴ (10,000) CFU/mL.
Edwards et al., 2019 ³⁰	Retrospective cohort study N = 60,029	Adjusted comparisons of GBS-positive and -negative women noted a decreased risk of chorioamnionitis, short cervix, wound infection, preterm birth, and operative delivery rates in the GBS positive group. No significant differences noted in preterm labor, endometritis, pyelonephritis, or sepsis.	21.6% prevalence for GBS colonization Chorioamnionitis RR, 0.76 (95% CI 0.66-0.87) Preterm RR, 0.49 (95% CI 0.45-0.53)
Abbreviations: OR, odds ratio; RR, relative risk			

bacteriuria and spontaneous preterm birth was no longer statistically significant.^{15,16} A small trial of 69 individuals by Thomsen and colleagues reported a reduction in rates of preterm labor and preterm rupture of the membranes in those treated with penicillin for GBS ASB at any colony count compared with those who received a placebo.¹⁷ Historically, these early studies contributed to the practice of treating GBS ASB at low colony counts and informed the practices of most senior obstetricians in the US.¹⁸

■ Internal case review

After approval by the institutional review board, an internal electronic medical record review was conducted. The prevalence of GBS bacteriuria at any colony count was 7.2% among the 459 pregnant individuals initially included and 6.6% among the 458 individuals with complete outcomes data. The authors noted a local practice pattern for treating asymptomatic GBS bacteriuria with colony counts ranging from 10^2 (100) to over 10^5 (100,000) CFU/mL.

Among the 31 individuals with GBS bacteriuria with complete data regarding the gestational age at the time of birth, two cases of preterm birth were found with a prevalence of 6.5%, one of which also had low birth weight. Both individuals were treated with antibiotics at the time of GBS bacteriuria identification during pregnancy and again with intrapartum prophylaxis. In the two cases of preterm birth, the infants were admitted to the neonatal ICU and monitored closely. One of these infants was diagnosed with respiratory distress syndrome due to suspected neonatal GBS disease. Both infants received prophylactic antibiotics and had negative blood cultures for GBS disease.

Newer retrospective and prospective studies have not demonstrated a higher risk of preterm birth in individuals with GBS bacteriuria.

Among the 30 individuals with GBS bacteriuria with complete data regarding maternal and neonatal complications, there were 25 cases of GBS ASB that were treated with antibiotics at the time of identification and again during labor. One of these 30 cases went on to develop chorioamnionitis, with a prevalence of 3.3%. Interestingly, this individual was

treated with cephalexin for GBS bacteriuria in early pregnancy based on $\geq 10^4$ (10,000) CFU/mL culture results and again with penicillin after test of cure noted $\geq 10^5$ (100,000) CFU/mL on urine culture. Of note, one patient moved away immediately after delivery; thus, was lost for follow-up of maternal or neonatal complications beyond discharge from the hospital.

None of these 31 cases of GBS bacteriuria developed pyelonephritis during pregnancy. Twenty-five of the 31 individuals with GBS bacteriuria were treated with antibiotics at the time of identification during pregnancy. The six individuals not treated at the time of GBS identification in the urine had low colony counts ranging from 10^2 (100) to 25×10^3 (25,000) CFU/mL, and none of those six experienced maternal or neonatal complications. The authors also noted five local cases of clindamycin-resistant GBS bacteriuria, one of which was an individual who was allergic to penicillin.

■ Literature review

A literature review was conducted to provide clarification regarding treatment of GBS bacteriuria during pregnancy and resolve local practice discrepancies. Early studies revealed most individuals receiving antibiotics to treat or eliminate GBS colonization during pregnancy were recolonized within 3 weeks after the antibiotic was discontinued.¹⁹ A search of clinical practice guideline collections among the national and international specialty societies found the threshold for diagnosis and treatment of GBS ASB varied in the literature.^{4,20} (See *Summary of GBS bacteriuria studies*.) Variable statistical reporting of prevalence, incidence, relative risk, significance, and/or odds ratios was noted and provided when available.

The early studies supported antibiotic treatment of asymptomatic GBS bacteriuria to reduce the incidence of maternal and neonatal morbidity and mortality.^{13,14,17} Newer retrospective and prospective studies have not demonstrated a higher risk of preterm birth in individuals with GBS bacteriuria.^{23,24,28,30} In more recent studies that controlled for potential confounders, GBS bacteriuria was not associated with preterm delivery or significant differences in the rates of endometritis, pyelonephritis, or maternal sepsis.^{28,30} Newer evidence

shows a significantly lower risk of pyelonephritis than found in earlier reviews.³⁰ Additionally, newer concerns regarding antibiotic use have surfaced, including antibiotic resistance and changes to the microbiome, potentially increasing the magnitude of harm.⁶ Recent information regarding the human microbiome suggests asymptomatic bacterial colonization may play a protective role for both pregnant individuals and neonates.⁶

The 2010 CDC Prevention of Perinatal Group B Streptococcal Disease guidelines recommend against the use of antimicrobials prior to the intrapartum period.⁴ The guidelines received formal endorsements from the American Academy of Family Physicians (AAFP), the American Academy of Pediatrics (AAP), the American College of Nurse-Midwives (ACNM), the American College of Obstetricians and Gynecologists (ACOG), and the American Society for Microbiology (ASM).⁴

The CDC transitioned the 2010 guidelines to ACOG and AAP, and those organizations published updated guidelines in 2019.^{4,32} ACOG and the Infectious Diseases Society of America both published separate updated guidelines in 2019 in support of treating asymptomatic GBS bacteriuria at the time of identification in pregnant individuals at a threshold of at least 10^5 (100,000) CFU/mL.^{32,33} Both note that fewer than 10^5 (100,000) CFU/mL GBS bacteriuria indicates maternal anogenital colonization and does not require treatment at the time of identification in asymptomatic individuals, but that individuals with GBS bacteriuria at any colony count during pregnancy should receive intrapartum antibiotic prophylaxis.³² Penicillin is the antibiotic of choice for GBS in nonallergic individuals, and antibiotic sensitivities should be determined for those allergic to penicillin.³² ACOG guidelines now recommend performing universal vaginal-rectal swab GBS screening between 36 0/7 and 37 6/7 weeks of gestation, if not previously detected in the urine with positive vaginal-rectal culture as an indication for an individual to receive intrapartum antibiotics.³²

In 2016 and 2018, the World Health Organization (WHO) issued recommendations for a 7-day antibiotic regimen for all pregnant individuals with ASB to prevent persistent bacteriuria, preterm birth, and low birth weight.³⁴ The WHO's recommendation

Antibiotics for treatment of GBS bacteriuria in pregnancy^{21,34-36}

Antibiotic	Dose
Amoxicillin	500 mg POTID for 5-7 days
Penicillin VK	500 mg PO QID for 5-7 days
Cephalexin	500 mg PO QID for 5-7 days
Clindamycin	150-300 mg PO Q6-12 hours for 5-7 days
Nitrofurantoin	100 mg PO BID for 5-7 days Use only in 2nd and early 3rd trimesters; avoid <12 weeks and ≥36 weeks

Note: WHO recommends a full 7-day course of antibiotic treatment for ASB. Updated FDA Risks for all above: Pregnancy Clinical Summary—may use during pregnancy; possible risk of teratogenicity based on conflicting human data; no known risk of fetal harm based on animal data at 10x recommended human dose (replaces categories).

was based on the evidence from the Cochrane Review that included 14 trials involving more than 2,000 individuals.²¹ In these trials, bacteriuria was defined as at least one clean-catch, midstream or catheterized urine specimen with more than 10^5 (100,000) CFU/mL on culture, but some of the included studies defined ASB with lower colony counts.^{21,31,35} The 2015 and 2019

Penicillin is the antibiotic of choice for GBS in nonallergic individuals, and antibiotic sensitivities should be determined for those allergic to penicillin.

Cochrane Reviews were limited by the quality of the studies due to numerous different designs, lack of information about randomization methods, different definitions of ASB based on varying colony counts, low statistical power, and bias.^{21,31,35}

GBS remains susceptible to the beta-lactams, but individuals with a penicillin allergy should have antibiotic sensitivities determined.³² The preferred antibiotic should be selected based on drug safety considerations and local resistance patterns. (See *Antibiotics for treatment of GBS bacteriuria in pregnancy*.) With antibiotic resistance to erythromycin, clindamycin, and cefazolin on the rise, definitive antibiotic therapy should be based on culture and guided by the sensitivity pattern.³⁷⁻³⁹ Although nitrofurantoin typically has been avoided in the first trimester due to potential risk of birth defects, it may

be prescribed in the second and early third trimesters.^{35,37} Nitrofurantoin and trimethoprim/sulfamethoxazole should be avoided after 36 weeks gestational age when they may increase neonatal jaundice and predisposition to kernicterus if taken in the last week before delivery.³⁵ Additionally, nitrofurantoin has been associated with a low risk of fetal or neonatal hemolytic anemia if the mother has glucose-6-phosphate deficiency. Thus, the drug should be prescribed with caution.³⁷

The CDC considers antibiotic resistance a global threat with no new antibiotics having been produced since the 1980s and has advised that alternative and/or innovative therapies need to be considered.⁴ New studies are investigating maternal and perinatal outcomes to explore the efficacy, risks, and benefits of potential maternal GBS vaccination.^{30,40}

Conclusion

The authors reviewed the literature to provide evidence-based recommendations regarding the management of GBS bacteriuria in pregnant individuals and found contradictory or inconclusive results with substantial biases. Caution is advised when drawing conclusions for treating GBS ASB at low colony counts. The review clearly noted that treatment at the time of identification of GBS ASB with colony counts lower than 10^5 (100,000) CFU/mL is not recommended, as this reflects maternal anogenital colonization and may lead to antibiotic resistance. Antimicrobial stewardship is a must. Nontreatment of GBS bacteriuria at colony counts lower than 10^5 (100,000) CFU/mL in asymptomatic individuals offers an important opportunity to decrease inappropriate antimicrobial use.

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