PENICILLIN TOLERANCE IN GROUP B STREPTOCOCCUS

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Group B Streptococcus (Streptococcus agalactiae, GBS) is a gram-positive β-hemolytic bacterium that is the most common cause of neonatal blood infections and meningitis, and a frequent cause of pneumonia. Under the 2002 Centers for Disease Control (CDC) guidelines, pregnant women are screened for GBS at 35-37 weeks of gestation. Treatment recommendations for women who test positive for GBS are β-lactam antibiotics such as penicillin G, given at 4 hours prior to delivery. Following the implementation of the CDC GBS screening guidelines, neonatal GBS disease declined from 1.7 per 1,000 live births in 1993 to 0.34 per 1,000 live births in 2005. Despite a dramatic drop in the incidence of infection in the United States, GBS remains a leading cause of newborn morbidity and mortality, resulting in an estimated 1,425 early onset cases and 63 deaths annually.

To date, no cases of penicillin resistance have been reported in GBS in the scientific literature. Our laboratory, however, has identified a phenotype of penicillin tolerance in which the microorganism is inhibited for growth in the presence of the drug, but remains viable for an extended period of time as compared to susceptible strains. These strains can then start propagating once the drug concentration decreases below the effective levels. The proposed bactericidal mechanism of penicillin on GBS and other gram-positive bacteria is initiated by the inhibition of penicillin binding proteins (PBPs). PBPs are enzymes that synthesize the bacterial peptidoglycan cell wall. The inhibition of the PBPs by penicillin triggers the up-regulation and secretion of large amounts of bacterial autolytic enzymes, resulting in cell wall degradation and cell lysis. Our hypothesis is that penicillin tolerant (PT) strains are more resistant to autolysin digestion due to differences in the construction of the cell wall or differences in the level of secreted autolysins. This phenomenon has been identified and reported in a number of other organisms, including Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes, Enterococcus faecalis, and Mycobacterium tuberculosis.

We examined clinical isolates of GBS, of which approximately 15.7% were found to be tolerant to penicillin and other β-lactam antibiotics, such as ampicillin and cefazolin. Whereas, non-β-lactams, such as erythromycin, clindamycin, or vancomycin were still effective. We have identified two novel amino acid polymorphisms in a PBP found within approximately 50% of the penicillin tolerant GBS strains and are virtually absent in the penicillin susceptible GBS strains. These GBS tolerant strains, as well as a susceptible strain expressing the PBP tolerant gene, were found to be significantly more resistant to cell wall digestive enzymes and found to have evidence of structural changes in the peptidoglycan cell wall. This supports our hypothesis that penicillin tolerant strains are more resistant to autolysin digestion due to differences in the construction of the cell wall. These data have been submitted to a peer-reviewed journal for publication.

Currently, the mechanism(s) of the other 50% of the PT strains are under investigation. Here, tolerance may be due to differences in cell wall synthesis rate, wall thickness, autolysin secretion, or disruption in the penicillin-induced autolysin upregulation via a signal transduction mechanism. Additionally, investigating the incidence of PT GBS infections by collecting clinical isolates from mothers and their infected neonates is underway. Although increasing the duration of penicillin treatment will eventually kill PT GBS strains, this is not a practical option when dealing with labor and delivery. However, we hypothesize that by alerting physicians to the phenomena of penicillin tolerance we can directly affect patient care by prompting the prescription of alternative non-β-lactam antibiotics, such as erythromycin, clindamycin, or vancomycin, and further decrease the incidence of illnesses and deaths associated with newborns infected with GBS.

Because for most labs, the test requisition serves as the test order, we do not believe that the new rule will change CMS’s historical position that requisitions sent to the lab do not need to be signed. However, this latest word from CMS seems to emphasize that the physician has an independent duty, regardless of whether he or she signs the requisition, to include his or her signature either in the text of the patient’s medical record or by a signed order attached to the medical record.

Moreover, physicians should take note of the fact that their failure to sign test requisitions could lead to an audit of the physicians medical records by Medicare, Medicaid or commercial insurers.

Some experts say that just because CMS may not require a signature on the physician order for laboratory tests does not mean that laboratories should not obtain physician signatures on the test requisitions. For example, some state Medicaid plans, including New Jersey and other payors require physician signatures for patients covered under such plans or policies.

Therefore, MDL will continue to encourage its physician clients to sign all test requisitions, in addition to including signed orders in the patient’s medical record that a test was ordered and the clinical justification for ordering the test.

3. See letter April 1, 2008 Terrence L. Kay Hospital and Ambulatory Policy Group www.clinical-labs.org/.../ACLAPhysicianSignatureLettertoTerryKay.pdf

The authors investigated 189 Group B Streptococcal clinical isolates from Japanese patients with invasive infections. Early (10.8%) and late (70.8%) onset GBS infections in children occur primarily through vertical transfer from mother to neonate. Whereas GBS infections in adults, which manifest as sepsis (75%), cellulitis, arthritis, necrotizing fasciitis, meningitis, and bacterial endocarditis, occurred primarily in people greater than 50 years of age with underlying health issues (88.7%) such as diabetes, liver dysfunction, or immune compromise. These GBS strains were characterized based on capsular type by PCR, for antimicrobial susceptibility, and for the presence of resistance genes. They found that predominantly capsular type III (67.7%) were isolated from children, whereas types Ib (31.5%) and V (18.5%) were predominant among adults. 9.2% and 28.2% of the strains isolated from children and adults were resistant to the fluoroquinolone, levofloxacin, respectively. Interestingly, the levofloxacin resistant isolates were predominantly capsular type Ib in both the children (100%) and adults (91.4%). PFGC molecular typing data suggests that these type Ib, levofloxacin resistant strains are closely related and may represent a single clone that acquired fluoroquinolone resistance and has spread rapidly throughout Japan.


This study investigates the antimicrobial susceptibility of 3,813 Group B Streptococcus clinical isolates obtained during 1996-2003 from invasive GBS disease from four participating institutions in GA, MN, NY, and OR of the Centers for Disease Control and Prevention’s Active Bacterial Core surveillance (ABcs) system of the Emerging Infections. All 3,813 were sensitive to penicillin, ampicillin, cefazolin, cefotaxime, and vancomycin. Clindamycin and erythromycin resistance was 12.7% and 25.6%, respectively, and associated with serotype V (P < .001). Clindamycin resistance increased from 10.5% to 15.0% and erythromycin resistance increased from 15.8% to 32.8%. These data support the need for GBS erythromycin and clindamycin susceptibility testing and surveillance for those patients who are penicillin allergic and at high risk for anaphylaxis.


This study attempted to estimate the frequency of genital tract colonization by methicillin-resistant Staphylococcus aureus (MRSA) among pregnant women and evaluate the association of such colonization with infant outcome. Between July 2003 and July 2006, anovaginal screening cultures for Group B Streptococcus (GBS) were prospectively obtained in the third trimester (35 to less than 37 weeks of gestation) and were also processed for identification of Staphylococcus aureus including methicillin-resistant strains. Maternal colonization by MRSA was linked to a computerized database of invasive neonatal infections that occurred at the study center during the study period. Among 5,732 mothers (who delivered 5,804 infants) with GBS screening cultures and infant infection data available, 22.9% were GBS-positive and 14.5% were positive for Staphylococcus aureus. A total of 24.3% of the Staphylococcus aureus isolates were MRSA. The overall MRSA colonization rate was 3.5%. Colonization by any Staphylococcus aureus (relative risk 1.6, 95% confidence interval 1.4-1.9) as well as MRSA (relative risk 2.2, 95% confidence interval 1.6-2.8) was significantly more common among GBS-positive than among GBS-negative women. No cases of early-onset invasive neonatal infection by MRSA occurred among infants in the study. Genital tract colonization with MRSA affected 3.5% of pregnant women. Such MRSA colonization is associated with colonization by GBS but does not predispose to a high risk of early-onset neonatal MRSA infection.


Group B Streptococcus (GBS), traditionally considered to be a neonatal pathogen, is an important cause of morbidity and mortality among older adults and among those with underlying medical conditions. This study used population-based surveillance to examine trends in adult GBS disease during the period 1990-2007 and to describe the epidemiology of adult GBS disease to guide prevention efforts. Active Bacterial Core surveillance was conducted in selected counties in ten US states. A case was defined as isolation of GBS from a normally sterile site in a nonpregnant resident of a surveillance area who was 18 years of age. Rates were calculated using US Census data. Demographic and clinical information was abstracted from medical records. Serotyping and susceptibility testing were performed on isolates collected from a subset of case patients. A total of 19,512 GBS cases were identified in nonpregnant adults during 1990-2007 (median patient age, 63 years); the incidence of adult GBS disease doubled from 3.6 cases per 100,000 persons during 1990 to 7.3 cases per 100,000 persons during 2007 (P < .001). The mean difference in incidence between black and white persons was 4.6 cases per 100,000 persons (range, 3.1 cases per 100,000 persons during 1991 to 5.8 cases per 100,000 persons during 1999). Common clinical syndromes in 2007 included bacteremia without focus (39.3%), skin and/or soft-tissue infection (25.6%), and pneumonia (12.6%). Most (88.0%) GBS cases in adults had 1 underlying condition; diabetes was present in 44.4% of cases. Serotypes V, Ia, II, and III accounted for 80.8% of infections during 1998-1999 and 78.5% of infections during 2005-2006. Invasive GBS disease in nonpregnant adults represents a substantial and increasing burden, particularly among older persons, black persons, and adults with diabetes. Prevention strategies are needed.


In newborns with infections, it is necessary to detect various pathogens rapidly and accurately, because the infections are often fatal when diagnosis is delayed. However, no diagnostic tools that rapidly detect pathogens causing neonatal infectious diseases are available. The objective of this study was to establish a rapid diagnostic tool using multiplex polymerase chain reaction (PCR) to detect 8 major pathogens that often cause neonatal infections, including Group B Streptococcus, Escherichia coli, Pseudomonas aeruginosa, methicillin-resistant Staphylococcus aureus, Ureaplasma urealyticum, herpes simplex virus, Cytomegalovirus, and Candida albicans, and to validate this tool in the neonatal intensive care unit (NICU). One hundred and thirty clinical samples were obtained from newborns with any infectious signs or histories. DNA was extracted from these samples and multiplex PCR was performed with a mixture of 8 primer pairs, all designed to amplify pathogenic DNA and produce different sizes of amplicons. Seventy-seven samples with suspicion of bacterial infections were also examined by bacterial culture to evaluate the accuracy of the multiplex PCR results. Six of the eight pathogens could be rapidly detected by their multiplex PCR method, within 3.5-4.5 h. These positive results led them to immediately diagnose and select proper drugs against each pathogen. In comparison with culture results, their test characteristics were as follows: specificity: 93%, negative predictive value: 96%, and concordance rate: 90%. They established and validated a rapid diagnostic tool for detecting pathogens using multiplex PCR, which may be useful for the confirmed diagnosis of neonatal infections in the NICU.
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1. Group B Streptococcus (GBS) infections in the newborn can manifest as…
   a. Sepsis  b. Meningitis  c. Pneumonia  d. All of the above

2. True or false. If a newborn does not develop symptoms of GBS infection within one week of birth, they will not develop it at all.

3. True or false. The incidence of group B streptococcal disease in babies less than a week old declined by over 70% in the 1990s, coinciding with increased use of intrapartum antibiotic prophylaxis
   a. HLA-A  b. HLA-DR  c. HLA-C  d. HLA-G

4. The Centers for Disease Control and Prevention (CDC) recommends universal prenatal screening for vaginal and rectal group B strep colonization of all pregnant women at ______ weeks’ gestation.

5. In the United States, GBS remains a leading cause of newborn morbidity and mortality, resulting in an estimated 1,425 early onset cases and _____ deaths annually.
   a. 7  b. 27  c. 63  d. 93

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