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Optimal Duration of Intrapartum Antibiotic Prophylaxis for Group B Streptococcus And Effects on Practice Patterns

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OPTIMAL DURATION OF INTRAPARTUM ANTIBIOTIC PROPHYLAXIS FOR GROUP B STREPTOCOCCUS AND EFFECTS ON PRACTICE PATTERNS.

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The 2002 CDC guidelines recommend a minimum of four hours of intrapartum penicillin G prophylaxis to assure a neonate is adequately prophylaxed against group B streptococcus (GBS). We examined the validity of this duration through the relationship between duration of prophylaxis and fetal serum penicillin G levels among fetuses exposed to less than 4 hours of prophylaxis compared to longer durations. We also investigated if clinicians were altering management to achieve four hours of prophylaxis.

Ninety-eight laboring GBS positive women carrying singleton gestations >37 weeks received penicillin G according to the CDC protocol. Umbilical cord blood samples were collected at delivery and penicillin G levels measured by high-performance liquid chromatography. Intra and inter-assay coefficient of variation were <3%. Seventy of 96 eligible clinicians (72.9%) completed our survey.

Fetuses exposed to less than 4 hours prophylaxis had higher penicillin G levels than those exposed to greater than 4 hours ($p=0.003$). In multivariable linear regression analysis, fetal penicillin G levels were determined by time of exposure, time since last dose, dosage, and number of doses, but not maternal BMI. Penicillin G levels increased linearly until 1 hour ($R^2=.40$) and then decreased rapidly according to a power-decay model ($R^2=.67$). All sub-groups analyzed were above the minimum inhibitory concentration (MIC) for GBS (0.1µg/mL)($p<0.002$). Individual samples were 10-179 fold above the MIC. In our survey, only 22.9% of clinicians reported ***not*** altering their management of labor in GBS positive pregnancies that achieved less than 4 hours of prophylaxis. These alterations included “laboring down” or delaying pushing; turning off or decrease an oxytocin infusion; or delaying or avoiding artificial rupture of membranes.

Short durations of prophylaxis achieved levels significantly above the MIC, suggesting a benefit even in precipitous labors. The designation of infants exposed to less than 4 hours of prophylaxis as particularly at risk for GBS sepsis may be pharmacokinetically inaccurate. However, clinicians report delaying labor to achieve four hours. The 2002 CDC guidelines are being interpreted differently in the clinical setting than the authors may have intended. The effects and consequences of this interpretation are unknown.

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INTRODUCTION

Group B Streptococcus: the organism and its pathology

Group B streptococcus also known as streptococcus agalactiae, is a gram-positive beta-hemolytic diplococcus that occurs in both pairs and chains. The name agalactiae means "without milk" as group B streptococcus was originally isolated from the breast of a cow and was thought to be a pathogen that only affected domesticated cattle causing mastitis.

The main virulence factor of group B streptococcus is its polysaccharide capsule. The capsule prevents the deposition of complement on the surface of the organism unless a specific antibody is present. These polysaccharides are made up of approximately 150 repeating oligosaccharide subunits.[1] The organism is further classified into 9 different serotypes based upon the different immunologic reactivity of its various capsules. The nine capsular serotypes differ in the arrangements of monosaccharides within the oligosaccharide-repeating units. Each of the oligosaccharide-repeating units ends in a sialic moiety. The sialic acid moiety, made up of N-acetylneuraminic acid, is the crucial portion of the capsule, which prevents the complement deposition. Through molecular mimicry, the sialic acid moiety prevents the human immune system from recognizing the organism. Presence of an antibody specific to the capsular polysaccharide has been shown to be sufficient to prevent invasive disease.[2]

Additional virulence factors of group B streptococcus allow it to invade into the host tissues and cells. For example, the invasion-associated gene (iagA) encodes a glycosyltransferase.[3] This glycosyltransferase produces a cell membrane anchor for

lipoteichoic acid and allows the bacteria to invade into the blood-brain barrier. A second virulence factor is alpha protein C. It is a protein on the surface of group B streptococcus, which binds to the host glycosaminoglycans and also promotes invasion.[4] Additionally, pilins present in group B streptococcus function as adhesins, which promote entry of group B streptococcus into the central nervous system.[5] A fourth factor is a C5a peptidase enzyme which cleaves the complement protein C5a when it is deposited on the organism's surface. This prevents formation of the membrane-associated complex that is necessary for host immune system mediated killing of the organism.[6]

Group B streptococcus was originally described by Rebecca Lancefield in 1933 and carries the designation "group B" as it carries the B Lancefield antigen. In 1935, Lancefield described the first association of group B streptococcus in humans when she recorded the asymptomatic carriage of group B streptococcus in the vagina. Since that time, the organism has been found to be present in an asymptomatic carrier state in the vagina, urethra, rectum and other areas of the gastrointestinal tract. It can also cause symptomatic infection in non-pregnant adults in the form or urinary tract infections or in immunocompromised patients or patients with chronic disease, it can cause sepsis, cellulitis and pneumonia. The case fatality rate for these adult group B streptococcal infections is 15-32%.[7, 8] In pregnant patients, group B streptococcus causes urinary tract infection, amnionitis, endometritis, wound infection, and more rarely, maternal sepsis or meningitis.[9-13] Urinary tract infections with group B streptococcus are present in 2-4% of all pregnancies.[14, 15]

Although the organism can cause morbidity and mortality in adult populations it has been most noted for its pathogenic effects in neonates. Eickhoff described the first case of neonatal group B streptococcal sepsis in 1964 and since that time, group B streptococcus has been recognized as the leading cause of neonatal sepsis.[16-18] It is also a major cause of neonatal pneumonia, and meningitis.[19] Neonatal group B streptococcal sepsis has been divided into two categories, early-onset disease and late-onset disease. Early-onset disease is responsible for 80% of the total of neonatal group B streptococcal infections. Early-onset disease, by definition, occurs in the first 7 days of life. Furthermore, in 90% of cases, symptoms and disease presentation occur in the first 24 hours of life. Early-onset disease presents as pneumonia or respiratory symptoms in 54% of neonates; as sepsis without focus in 27% of neonates; and as meningitis in 15% of neonates.[20] In contrast, late onset disease is defined as disease that occurs at greater than 1 week of life and before 3 months of life. Late onset disease presents as sepsis in 46% of neonates and as meningitis in 37% of neonates.

In various studies, group B streptococcus has been found to colonize the vagina and rectum in anywhere from 1.2% to 35% of pregnant women;[20] a range of 10-30% is the figure most often quoted in the literature.[9, 16, 21-24] Data from colonization studies is present dating back to 1980. These studies have been performed in many geographic areas, including Africa, Asia, Europe, the Americas and the Middle East. Colonization rates vary in different cultural contexts, communities, and across national boundaries. Previously, the rates of group B streptococcus colonization were less in developing countries, but there is new evidence that rates of colonization in the developing world are catching up to rates in the developed world.[25] The reasons for this increase are hypothesized to do with increasing contact of individuals in a

population with one another and the increased propensity for spread of bacteria that results from such contact.

Maternal colonization with group B streptococcus is identified by using swabs to sample the maternal rectum, vagina, and perineum. These swabs are placed in culture media and the isolates present are allowed to grow to determine if group B streptococcus is present. Rapid antigen testing is an alternative method of detection, but, is limited by a lower sensitivity.[26] Recently, the use of polymerase chain reaction (PCR) and optical immunoassay have been proposed as alternative "rapid" techniques which could be used to evaluate women while they are in labor rather than using cultures which must be taken during prenatal visits in the weeks before labor.[27, 28] The ability to detect organism at the time of delivery is especially important as women may be colonized transiently and may be culture negative in the weeks before delivery, but culture positive at the crucial time of birth.

As mentioned previously, the presence of group B streptococcus in the mother is most often as an asymptomatic carrier state; however, transmission to the child can cause significant neonatal morbidity and mortality. The mechanism of this transmission is either: (1) transmission to the fetus *in utero;* or (2) transmission to the fetus during descent through a birth canal infected with group B streptococcus. In the first mechanism, intrauterine infection of the fetus occurs as a result of the organism ascending into the amniotic fluid compartment, often in the setting of ruptured membranes, and proliferating there. Fetal aspiration of group B streptococcus infected amniotic fluid can result in pneumonia and sepsis. The fetus can also be exposed to the organism during passage through the vaginal canal. Passage through a group B streptococcus infected

vaginal canal causes the infant to be colonized by the organism on the skin and mucous membranes; however, the transmission of group B streptococcus from a colonized mother to her neonate is not universal. Once the organism is present on the neonatal mucous membranes or neonatal respiratory epithelium, it must invade these structures. Proteins on the surface of the organism such as alpha-C proteins, the Rib protein, fibrinogen binding protein A and a C5a peptidase are crucial for the attachment of the organism to the epithelium and extracellular matrix and the organism's intracellular invasion of host cells.[29]

Data on the rates of neonatal colonization after birth varies in different studies from 35% to 69% and the figure is often reported to be approximately 50%.[30, 31] However, only 1-2% of infants born to mothers with group B streptococcal colonization develop early onset group B streptococcal disease.[32] Once the neonate has group B streptococcal disease, the case fatality rate is estimated to be 4% for all neonates[22] and 6% among premature neonates.[33] Data from the 1970s suggested a higher case fatality rate of 15-50%, but due to improved neonatal care the case fatality rate has been steadily decreasing.[16] Neonatal infection also has neurologic sequelae in 10-20% of cases.[9, 22] Sequelae can include long term hearing loss, blindness and developmental delay.[22]

There are numerous risk factors associated with early-onset invasive neonatal group B streptococcal disease. They include: maternal bacteriuria during pregnancy[9], maternal urinary tract infection[34], maternal fever[34], preterm delivery (less than 37 weeks),[35] post-date delivery (greater than 42 weeks)[36], rupture of membranes greater than 12 hours before delivery[37],

previous miscarriage[38], previous infant born with invasive group B streptococcal disease[9], black race[38], teenage mother[38], and gestational diabetes[39].

As discussed previously, the first case of group B streptococcal neonatal sepsis was identified in 1964.[40] In the 1970s, there were 2-3 cases of group B streptococcal sepsis per 1,000 live births.[41] These rates were higher than the rates of congenital syphilis, rubella and herpes, all diseases for which routine screening and treatment strategies had been designed and implemented. As a result, various strategies were pursued to attempt to decrease the transmission of group B streptococcus to neonates and decrease the disease incidence. Initially, attempts were made to treat mothers with antibiotics in an attempt to eradicate group B streptococcus from the maternal reservoir. In one study, pregnant women colonized with group B streptococcus were given oral antibiotics for 1 week during the third trimester. Upon presentation to the labor floor, 30% were colonized at the time of delivery and there was no difference in colonization rates between the group treated with antibiotics and those women who were not treated.[42] A second study treated pregnant women with a 14-day long course of antibiotic treatment in the third trimester and also treated their sexual partners to eliminate a possible source of re-infection. Seventy percent of those women were colonized three weeks following this treatment.[43] From these two studies it was concluded that it was not possible to eradicate group B streptococcus in the maternal gastrointestinal tract and vagina through use of intermittent antibiotic treatment and focus shifted to other methods of treatment, namely, intrapartum antibiotic prophylaxis.

History of Public Policy and Research Surrounding Intrapartum Prophylaxis

The idea of intrapartum antibiotic prophylaxis to treat group B streptococcus was first suggested in 1976 by Ablow.[44] The aims of intrapartum prophylaxis are: (1) to decrease colony counts throughout the birth canal at the time of delivery; (2) to prevent the organism from ascending and proliferating in the amniotic fluid compartment; and (3) to achieve adequate levels of effective antibiotic in the fetal bloodstream during labor.[45] Two non-randomized studies conducted in the late 1970s and early 1980s offered support for intrapartum prophylaxis by showing that neonatal colonization with group B streptococcus was decreased through the use of intravenous ampicillin given to the mother at the time of delivery. Although these studies were underpowered to show statistical significance, they did report a reduction in early-onset invasive group B streptococcal disease in those neonates born to mothers treated with ampicillin.[46, 47]

The first randomized trial to examine the question of intrapartum prophylaxis as a preventative measure for group B streptococcal disease was Boyer et al performed in 1986.[48] They studied a group of women whom they considered to be at a higher risk for having a child with group B streptococcal disease. Enrollment in the study required the patient to have a positive group B streptococcus culture recorded during prenatal care and to have the presence of a risk factor. Risk factors were either preterm labor (< 37 weeks gestation) or prolonged rupture of membranes (> 12 hours prior to presentation to the labor floor). Women with fever (>37.5 degrees Celsius) were excluded from the study as they could not be randomized to the control treatment (no drug) and all were given ampicillin. The rationale behind selection of this higher risk population was that the incidence of early-onset group B streptococcal disease among infants born to these mothers was 41 per 1,000 births as compared with the 2-3 cases per 1,000 births among mothers

in the general population. Additionally, neonates born to mothers with these risk factors represented 62% of cases of early onset disease and 94% of all case fatalities at the authors' institution. These women with risk factors and positive cultures were randomized to received intrapartum ampicillin or no antibiotic treatment. Of note, the neonates in the intrapartum ampicillin group also received 4 doses of intramuscular ampicillin at 12 hours intervals following delivery. The outcomes evaluated by the study were neonatal colonization as measured by cultures taken at birth from 5 external sites on the neonate (external auditory canal, stomach contents obtained by nasogastric aspiration, throat, umbilicus and rectum) and neonatal bacteremia. The results showed that neonatal colonization was statistically significantly lower ($p<0.001$) in the ampicillin group (8/85 neonates, 9%) compared with the control group (40/79 neonates, 51%). Colonization at multiple sites (defined as 3 or greater sites) was also lower in the ampicillin group (3/85, 4% vs. 24/79, 30%; $p<0.001$). Bacteremia was present in 0/85 (0%) of the ampicillin treated infants and 5/79 (6%) of the control group infants ($p=0.024$). The paper concluded that "intrapartum ampicillin prophylaxis in women with positive prenatal cultures for group B streptococcus who have certain perinatal risk factors can prevent early-onset neonatal group B streptococcal disease".[48] This paper was the seminal work on intrapartum prophylaxis for prevention of group B streptococcal disease and became the foundation for future clinical recommendations.

Certain aspects of Boyer et al warrant mention. First, in a study in which carriage of an organism known to cause infection in the fetus via amniotic fluid infection, the authors elected to exclude women with fever. Fever is one of the risk factors for group B streptococcal disease and in analysis has been shown to be the risk factor with the largest relative risk for developing early

onset disease.[49] These women with fever represented 13 women in the study. Second, the authors stopped enrollment in the study once their results had achieved statistical significance, they did not use predetermined power calculations. Third, the Boyer protocol differs in key respects from the protocol used today for intrapartum prophylaxis. The "at risk" neonates in the study were treated with intramuscular ampicillin following birth (neonatal cultures were taken prior to administration of intramuscular ampicillin); the intrapartum antibiotic was ampicillin instead of penicillin; and neonates were identified for receipt of intrapartum antibiotics according to different criteria than we use today. These are not limitations of the study itself, but it does prevent us from making inferences about the current CDC recommended protocol based on the results of Boyer et al.

Another study published in 1987 concurred with the results of the Boyer study. Teres et al[50] performed a study in which they randomized pregnant women to receive ampicillin or no treatment. The colonization rate in neonates born to mothers treated with ampicillin (n=57) was 3.3% vs. 42.9% of those not treated with ampicillin (n=64). This data was reported to be statistically significant although an exact p-value was not reported. The study also showed a significant difference between the neonates in regard to neonatal group B streptococcal sepsis; 1.8% of infants born to mothers treated with ampicillin had group B streptococcal septicemia whereas 13% of neonates born to untreated women had group B streptococcal septicemia ($p=0.04$).[50] The rates of septicemia in this study were incredibly high when considered against the background rate of neonatal group B streptococcal sepsis at the hospital at which the study was performed (1 case per 1,000 live births). The high rates of septicemia observed are

concerning and raise concern that the population may not be representative due to some form of selection bias.

In 1990, a group of concerned parents formed the Group B Strep Association. The organization's mission was to advocate for prevention of neonatal disease. Broad media coverage ensued and based on this pressure and the data from the Boyer and Teres studies, the first formal recommendations about intrapartum prophylaxis for group B streptococcal disease were made by the American Association of Pediatrics (AAP)[41] and the American College of Obstetricians and Gynecologists (ACOG)[51] in 1992. The ACOG Guidelines were not as far-reaching and not as specific as the AAP guidelines. The Boyer and Teres studies are the only studies that were cited by the AAP in support of the efficacy of intrapartum prophylaxis. The AAP guidelines recommended that all pregnant women should be screened for group B streptococcus by culture performed at 26-28 weeks of gestation. Women with a positive group B streptococcal culture and one or more of the defined risk factors were recommended to receive intrapartum ampicillin. The risk factors were (1) preterm labor (gestational age less than 37 weeks), (2) premature rupture of membranes at less than 37 weeks gestation, (3) fever during labor, (4) multiple births, and (5) rupture of membranes greater than or equal to 18 hours prior to delivery at any gestational age. They also recommended that any woman who had previously delivered an infant with invasive group B streptococcal disease should receive intrapartum prophylaxis in each of her subsequent pregnancies.

The ACOG recommendations differed from the AAP recommendations in a few ways. First, they did not recommend a specific gestational age at which prenatal cultures should be

performed. Second, they recommended that either penicillin or ampicillin could be used for prophylaxis instead of a preference for ampicillin as recommended by AAP. Third, they made no recommendation about the duration of prophylaxis (AAP recommended 4 hours of prophylaxis before delivery). Fourth, the risk factors were the same with the exception of multiple births, which are not included in the ACOG recommendations and the addition of a previous sibling born with invasive group B streptococcal disease as a risk factor. The approaches put forward by both ACOG and AAP to administering intrapartum prophylaxis were later deemed a "risk factor based approach" as only women with risk factors *and* positive group B streptococcal culture were treated. Although these recommendations were based on few studies which had some methodological flaws as described above these recommendations began slowly to be adopted nation-wide.

The next update to recommendations regarding neonatal group B streptococcal disease were made by the Centers for Disease Control (CDC) in 1996.[16] These recommendations were supported by both the AAP and ACOG, but the CDC felt that widespread adoption of the guidelines in the obstetric community had not taken place and wished to issue guidelines with a more powerful government backing.[52, 53] These recommendations differed from the 1992 recommendations in a number of ways. The most significant was that the CDC now recommended two alternative approaches to prevention of early onset group B streptococcal disease: the "screening-based approach" and the "risk-factor based approach".

In the screening-based approach, all pregnant women would be screened by culture at 35-37 weeks (change in timing from 1992 recommendations) for group B streptococcus. All women

who tested positive were recommended to be offered the option of intrapartum antibiotic prophylaxis and, after being informed of the risks and benefits, should make an informed decision. Alternatively women could be evaluated using the risk-factor approach. The risk-factor approach had also changed from the 1992 AAP recommendations. It now consisted of risk factors *alone* with no group B streptococcus culture performed. The risk factors had also changed and now included: (1) gestational age less than 37 weeks, (2) duration of membrane rupture greater than or equal to 18 hours, (3) maternal temperature greater than or equal to 100.4 degrees Fahrenheit or 38.0 degrees Celsius, (4) group B streptococcal bacteriuria and (5) prior infant with invasive group B streptococcal disease. The presence of one or more risk factors indicated the need for intrapartum prophylaxis. There were now two viable options recommended, but the screening approach was presented first in the document and the risk factor based approach was deemed "an acceptable alternative". Interestingly, in the flow chart for decision making which accompanied the recommendations stated that treatment for patients who had risk factors was to "give intrapartum penicillin" whereas the treatment for those with positive group B streptococcal cultures was to "offer intrapartum penicillin".

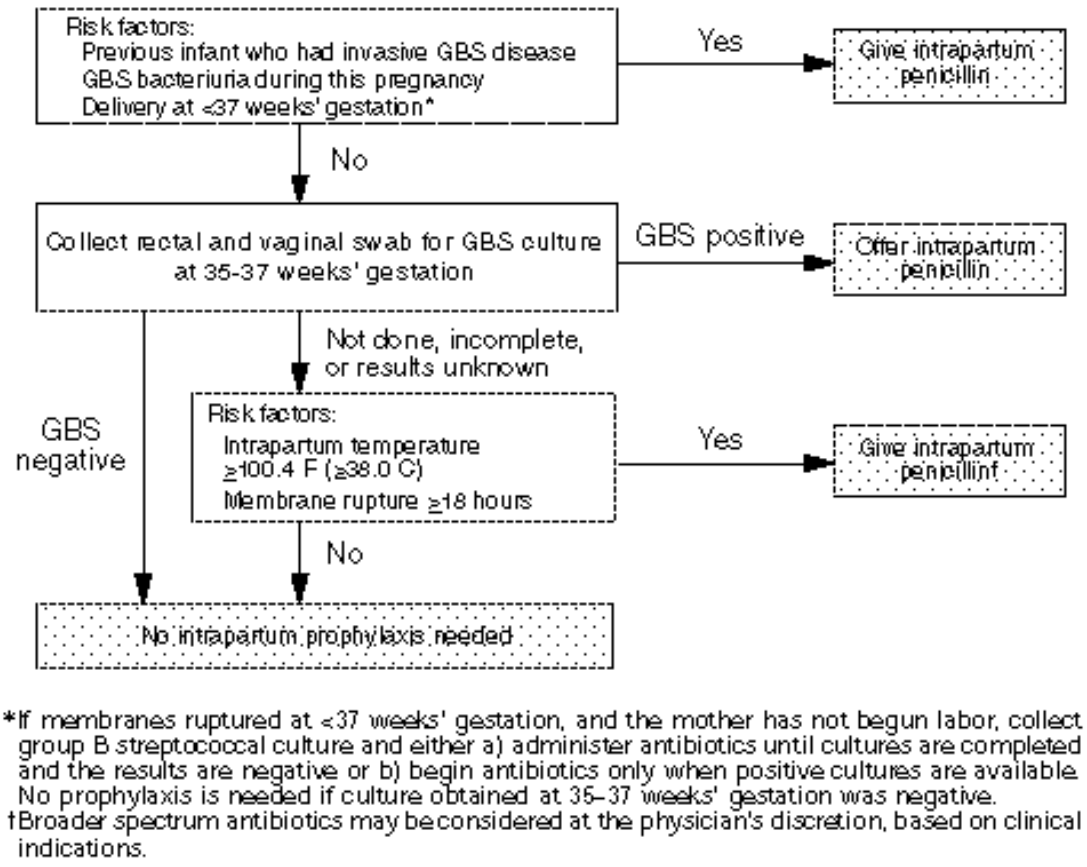

Figure 1: Management flow chart from 1996 CDC guidelines instructing clinicians on how to assess need for intrapartum prophylaxis.[16]

The CDC also made recommendations about two populations of patients regardless of which screening strategy was pursued. Pregnant women with group B streptococcal bacteriuria (whether symptomatic or asymptomatic) should be immediately treated with antibiotics to treat the bacteriuria. Furthermore, because bacteriuria represented such a high burden of bacterial colonization, those women would receive intrapartum antibiotics at delivery independent of the time of diagnosis of bacteriuria and even if it was successfully treated. The other population, women who had previously delivered an infant with invasive group B streptococcal disease, was recommended to universally be treated with intrapartum prophylaxis.

One of the major changes in the 1996 CDC recommendations from the 1992 AAP and ACOG recommendations was for culture to be performed at 35-37 weeks gestation instead of 26-28 weeks gestation. Screening at 35-37 weeks had not been validated in large clinical trials, but an early study, Yow et al published in 1979[47] recommended screening at 34-36 weeks based on the results of their own colonization studies in pregnancy[54] as well as data from longitudinal colonization studies done in 1978 which showed that women could be culture negative in the weeks before birth, but become culture positive at the time of birth[55]. The authors of that paper speculated that the closer to labor the cultures could be performed the more accurate they were likely to be. Analysis of data from the Boyer study did show that the closer to delivery screening cultures were collected, the higher the predictive value of the cultures.[56] A large clinical study in Australia had also used cultures at 32 weeks gestation to evaluate for group B streptococcal carriage.[37] There were also changes in the definition of risk factors. First, the temperature that defined fever was adjusted upwards from 37.5 to 38.0 degrees Celsius. The reasons for this change are not elucidated or addressed in the recommendations. The second change was the exclusion of multiple gestations as a risk factor. This was based on evidence from large studies which suggested that multiple gestations was not a significant independent risk factor and was likely a risk factor due to its association with prematurity.[38, 57]

The 1996 CDC recommendations represented a shift from the 1992 recommendations of ACOG and the AAP. Whereas in 1992 patients needed to have both a positive group B streptococcal culture ***and*** the presence of a risk factor to be considered "at risk" of having a neonate develop early-onset invasive group B streptococcal disease; now, the presence of either a risk factor ***or*** a positive culture was sufficient. Studies available in 1996 indicated that treating women

identified with the risk factor based approach that represents 4.6% - 8.9% of the obstetric population.[48, 58] Data on colonization of pregnant women quoted in the 1996 CDC recommendation stated that 10-30% of women were colonized with group B streptococcus, representing a much larger group of individuals.[16] What new evidence had come to light in those four years that caused this shift that represented treating many more women? All of the 6 studies quoted in the 1996 recommendations which supported the use of intrapartum antibiotic prophylaxis for "unselected women colonized with group B streptococcus"[16] were done between 1979-1991.[37, 46, 47, 59-62] It was not any new information or data that caused the introduction of universal screening, but rather a reassessment of previously collected information. The reinterpretation of these studies or rationale for this shift in thinking are not explained or addressed in the guidelines. The authors state that the incidence of group B streptococcal disease has not decreased although data from these six studies show that intrapartum prophylaxis can be effective at preventing transmission of the organism. They state that the reason the incidence has not declined is that not enough patients are being exposed to intrapartum prophylaxis. The reassessment of the guidelines performed in 1996 seemed to have been designed to encompass a larger group of women.

Following the introduction of the guidelines in 1996 there was a shift towards increased utilization of chemoprophylaxis across the country. A national survey of ACOG members in 2000 showed that 98% had a policy regarding group B streptococcus and that 75% were using the universal screening approach.[63] As a result of this increased chemoprophylaxis, the rates of early onset invasive neonatal group B streptococcal disease dropped. The incidence was 2-3 cases per 1,000 live births before the guidelines were instituted, but by 1999, the incidence had

decreased to 0.5 cases per 1,000 live births, a reduction in incidence of 70%.[22] The incidence of group B streptococcal infection among pregnant women, such an endometritis and amnionitis, also declined from 0.29 per 1,000 births in 1993 to 0.23 in 1998, representing a reduction of 21%.[22]

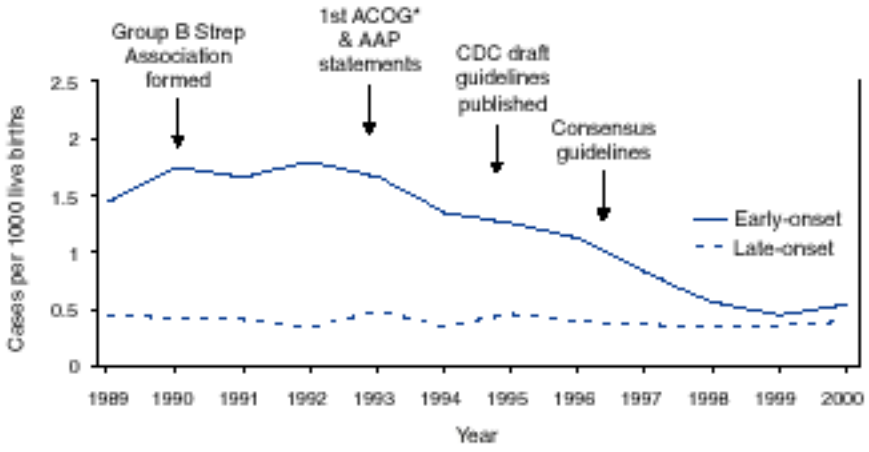

FIGURE 2: Trends in incidence of invasive neonatal group B streptococcal disease over time with superimposed dates of implementation of guidelines and recommendations. Figure taken from 2002 CDC Guidelines.[9]

In 1996, there had not been any studies which compared the risk factor based approach and the universal screening approach. Furthermore, it was thought that the universal screening approach would be much more difficult to implement and so both options were deemed appropriate until further evidence was available. That further evidence came in 2002 with the publication of a large CDC-sponsored multi-center retrospective cohort study published in the New England Journal of Medicine that directly compared the two approaches: Schrag et al.[49] The study examined a sample of 5,144 births representing a population of over 629,912 live births in eight distinct geographical areas. They found that the relative risk of early-onset group B streptococcal disease was significantly lower among the neonates born to mothers in the universal screening group as compared with the risk-based group (RR=0.46, CI – 0.36-0.60).

The screening approach was 50% more effective that the risk factor based approach. This difference between the two approaches persisted even after controlling for increased presence of known risk factors for group B streptococcal disease present in the risk factor cohort. Based on this study and the results of smaller individual hospital based studies that also showed a benefit of the universal screening approach,[64-67] the CDC again revised the guidelines in 2002. It now recommended that all pregnant women are screened at 35-37 weeks gestation for group B streptococcus and, if positive, be treated with intrapartum antibiotic prophylaxis. The risk factor approach was no longer considered an adequate alternative.

Other benefits to the universal screening approach were noted in the 2002 CDC recommendations. First, the authors expressed that the universal screening approach was more straightforward to implement and as a result more women in the universal screening groups received antibiotics (40-80% in the risk factor groups[64, 68-70] and 90% in the universal screening groups[64, 66, 71-76]). Second, an assumption based on the data available in the 1996 recommendations was that universal screening would expose a larger cohort of women to intrapartum antibiotics (see data provided in above section on 1996 recommendations). However, data cited in the 2002 recommendations now stated that perfect implementation of both the risk factor and universal screening strategies would result in intrapartum antibiotic prophylaxis rates of 24%, because women who are culture negative for group B streptococcus, but do have risk factors were not to be treated with antibiotics.[22, 49] Therefore, the two strategies could no longer be differentiated on the basis of how many women and their neonates would be exposed to antibiotic prophylaxis. Third, although the culture and follow-up documentation of

cultures do represent a cost, in regards to cost efficacy, the 2002 recommendations expressed that the strategies did not differ by overall cost savings due to disease prevention.[77, 78]

The 2002 guidelines were also the first guidelines that made recommendations about how to manage neonates exposed to intrapartum prophylaxis. The 1996 recommendations stated that there was not enough experience or evidence to offer suggestions on management of infants who had received prophylaxis.[16] But, in the 2002 recommendations a flow chart was provided [Figure 3] that divided infants into two groups depending on whether or not they had received four hours of intrapartum prophylaxis.

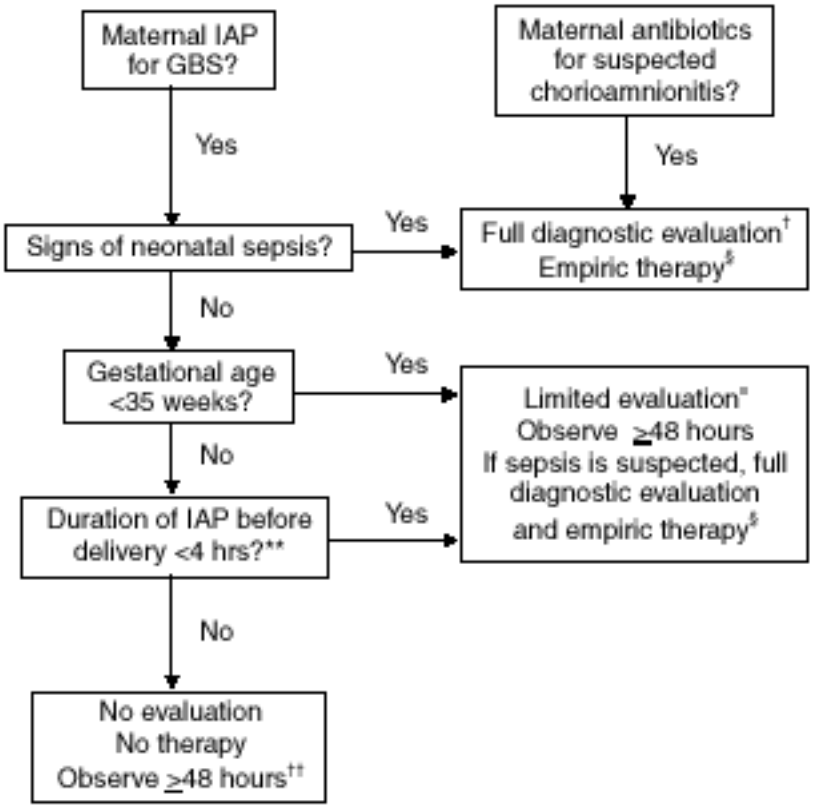

FIGURE 3: Sample algorithm for management of newborns exposed to intrapartum prophylaxis presented in CDC 2002 Guidelines. A clear division of management is made based following the "duration of IAP before delivery <4hrs?" box.[9]

If a woman had received less than four hour of prophylaxis it was recommended that her child be observed for greater than 48 hours (as most cases of early onset disease present in the first 24 hours) in the hospital to watch for signs of sepsis and a "limited evaluation" should be performed. It was also recommended that if an infant is born at a gestational age greater than 38 weeks and has a mother who received greater than four hours of intrapartum prophylaxis, that infant may be discharged to home as early as 24 hours after delivery. The recommendations created two distinct groups of infants to be managed differently based on whether or not they had received adequate prophylaxis according to what has become known as the "four hour rule" on labor floors across the country.

As discussed previously, following the introduction of the 1996 recommendations and the adoption of intrapartum prophylaxis the rate of invasive group B streptococcal disease decreased. From 2000 until 2003 the incidence further decreased from 0.52 to 0.31 cases per 1,000 live births. Unfortunately, from 2003-2006 the incidence increased, from 0.31 to 0.40. Interestingly, this increase in the incidence was driven by an increase in disease among African-American term infants. The incidence among African-American infants was 2.8 times higher than the incidence among Caucasian infants. A higher incidence among black infants has been demonstrated since rates of group B streptococcal disease have been monitored. The reasons for the racial discrepancy are unknown. It is also unclear why the rates of early onset sepsis have decreased in a higher proportion among Caucasian infants in response to intrapartum prophylaxis compared with African-American infants.

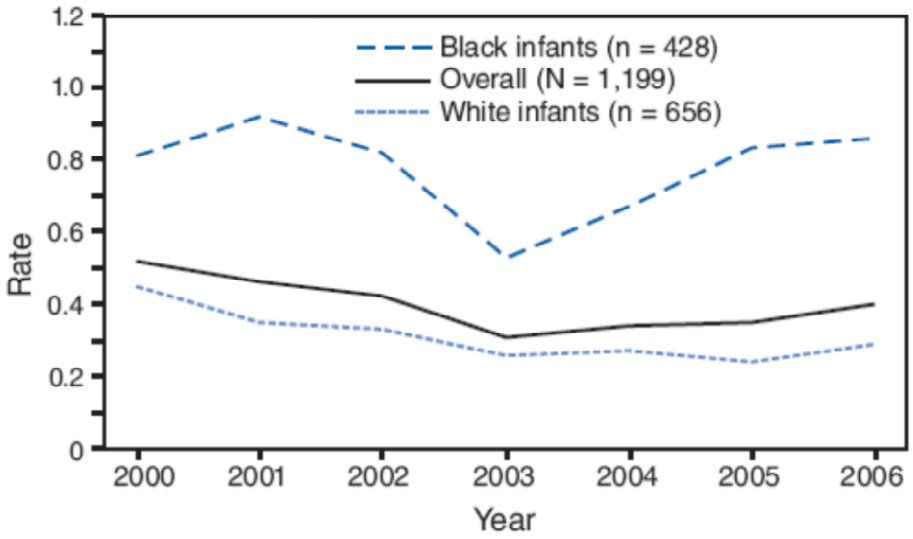

Figure 4: Rate per 1,000 live births of early-onset group B streptococcal disease from 2000-2006 according to CDC.[18]

The majority of the evidence-base for the recommendations of the CDC come from studies of the Active Bacterial Core (ABC) surveillance system data. This is a ten-state database operated and managed by the CDC, which conducts active population-based surveillance for invasive group B streptococcal disease. All information about incidence in the United States population is collected from this database. Because the incidence of group B streptococcal disease is so low, performing randomized controlled trials to investigate the role of intrapartum prophylaxis to prevent group B streptococcal disease or the question of the risk factor based approach vs. universal screening approach is impractical. As a result, the studies that examine the ABC data, the only data set large enough to explore the outcome of group B streptococcal disease, are retrospective cohort studies. There have been two studies based on the CDC ABC data that explore issues surrounding the receipt of intrapartum antibiotics: Schrag et al 2002[9], and VanDyke et al 2009[23]. The only other papers published using the ABC data include papers examining incidence of neonatal disease, disease burden in adults, and antimicrobial resistance.

Schrag et al[49] estimated the relative risk of group B streptococcal disease associated with various variables. They found that universal screening for group B streptococcus was associated with a decreased relative risk of development of neonatal group B streptococcal disease. Medicaid payment, group B streptococcal bacteriuria, preterm delivery, prolonged rupture of membranes, inadequate prenatal care, black race, maternal age less than 20 years, previous infant with group B streptococcal disease and intrapartum fever were the other variables for which a relative risk was calculated.[49] Missing from this list of variables is receipt of intrapartum antibiotics. The absence is very curious. Although, 89% of women in the universal screening group received antibiotics and only 61% in the risk factor group received antibiotics, only the two approaches of universal screening vs. risk factor are compared. The relative risk of receipt of intrapartum antibiotics vs. no antibiotics is not compared, although it is clear that the authors did collect data on receipt of antibiotics. Without comparing these two groups head to head, it is not clear that the success of the universal screening approach relies on intrapartum antibiotics. Instead, it may be that clinicians treat women with a positive group B streptococcus culture differently than a woman with unknown colonization status. They may treat them more aggressively, perhaps admitting them earlier in the labor process or performing Cesarean section rather than allow a longer duration of ruptured membranes. Without calculating the relative risk of receipt of antibiotics specifically we cannot assume that the success of the universal screening approach relies on intrapartum antibiotics. The fact that the authors reported the relative risk for so many different variables, but not intrapartum antibiotics, even though they had the data to do so, is puzzling.

A more recent paper using the ABC data examined the implementation of the 2002 guidelines to examine missed opportunities for disease prevention and to characterize the remaining burden of group B streptococcal disease in the era of intrapartum prophylaxis. Similar to Schrag et al 2002, this paper did not address the issue of clinical efficacy of intrapartum prophylaxis although the data to do so was available. The paper reported that there had been broad uptake of the guidelines. In 1998-1999 the percentage of women who were screened for group B streptococcus was 48.1%, this rose to 85.0% in 2003-2004. The percentage of women with an indication for intrapartum antibiotics who received antibiotics also increased from 73.8% to 85.1%. They identified groups of women who were less likely to receive intrapartum prophylaxis when indicated. These included women who deliver preterm with unknown colonization status, women who are allergic to penicillin, and women with false negative screening results (61.4% of the mothers of infants with group B streptococcal disease were culture negative). They also addressed the issue of racial disparity in incidence of disease. There was no difference between races in screening rates or in rates of receipt of intrapartum antibiotics. The reasons for the racial disparity in rates of early onset GBS disease remained elusive. Again, as in the other ABC data based paper, Schrag 2002, receipt of IAP was also not one of the factors analyzed.

As mentioned above, the ABC data is the only data set that is large enough and currently available to perform an outcome-based assessment of the clinical efficacy of intrapartum antibiotics and optimal duration of antibiotic treatment. This analysis has not been done for unclear reasons. However, a recent Cochrane review attempted to answer this question.[20] The primary aim of the review was to assess the effect of intrapartum prophylaxis in reducing

mortality from group B streptococcal disease. Secondary objectives included assessing the effect of intrapartum prophylaxis on vaginal colony counts and maternal outcomes such as chorioamnionitis, sepsis, urinary tract infections, etc. The review was only able to identify three randomized controlled trials that fit inclusion criteria. They noted that these trials were all performed 20 years ago and had serious concerns for bias. Based on these trials they found that there was not sufficient evidence to support a decrease in neonatal mortality as a result of intrapartum prophylaxis. They did note a reduction in the incidence of group B streptococcal sepsis in neonates treated with intrapartum prophylaxis. The issue of antibiotic selection was also evaluated and the conclusion was reached that there is no conclusive data to support the use of penicillin over ampicillin or ampicillin over penicillin as the antibiotic of choice. The Cochrane review concludes that the use of intrapartum antibiotics to prevent group B streptococcal disease is not supported by conclusive evidence. Given that guidelines have already been put into place with regards to intrapartum prophylaxis for group B streptococcal disease it may not be feasible to perform randomized controlled trials making the ABC cohort data all the more important in addressing this question. In fact, the 2002 guidelines rest almost exclusively on the evidence provided by Schrag et al 2002 based on ABC data.

Optimal Duration of Antibiotic Prophylaxis

In order to be effective, it is hypothesized that intrapartum prophylaxis requires the antibiotic to cross into the fetal circulation as well as enter the amniotic fluid via fetal micturition. The antibiotic is also hypothesized to function by attaining sufficient maternal serum concentrations to decrease colony counts in the vaginal canal; therefore, decreasing transmission of the organism to the neonatal mucous membranes. Throughout the history of policy and guidelines

for intrapartum prophylaxis, the appropriate duration of prophylaxis to achieve the previously mentioned goals has remained a question.

A separate arm of the Boyer study, a prospective cohort, published in 1983, was the first to address the question of appropriate duration of prophylaxis.[59] The study found neonatal colonization rates were 28% when the mothers received less than one hour of ampicillin prophylaxis and were only 4% when mothers received greater than one hour of prophylaxis. The one-hour time point was the duration of prophylaxis that made a difference in rates of neonatal colonization. However, that data is not cited in the 1992 AAP recommendations about duration of prophylaxis. Instead, the authors chose to use another mechanism to evaluate the appropriate duration of prophylaxis: the presence of antibiotic in appropriate concentrations in the amniotic fluid and fetal circulation. They stated the "chemoprophylaxis ideally should be administered at least 4 hours before delivery. This allows sufficient time to achieve optimal concentrations of ampicillin or penicillin G in the amniotic fluid as well as in the placental circulation."[41] The data cited to support this recommendation were from a pharmacokinetic study, Bray et al, performed in 1966[79] However, the AAP authors misinterpreted the 1966 study setting off a chain of citations leading to the modern day recommendations.

The Bray study was performed when ampicillin was first synthesized and introduced as a new microbial option. The primary aim of the study was to evaluate the concentration of ampicillin in maternal blood, fetal cord blood and the amniotic fluid to evaluate the possibility of using ampicillin as a treatment for chorioamnionitis, endometritis and intrauterine infection of the fetus. As can be seen from Figure 1, levels of ampicillin in the fetal bloodstream reached a peak

of 6.2 μg/mL one hour after administration. The amniotic fluid levels took longer to rise and rose in an arc. The peak concentration of 5.20 μg/mL occurred at the 8-hour time point. Levels at 2 hours were 1.0 μg/mL and at 4 hours were 3.5 μg/mL. The minimum inhibitory concentration for group B streptococcus is 0.04-0.1 μg/mL.[40, 56, 80] All ampicillin levels measured between 0-4 hours in the amniotic fluid, maternal serum and fetal serum were above the minimum inhibitory concentration. Why the authors of the AAP recommendations chose the four hour time point as significant to achieve amniotic fluid levels which were sufficient to treat group B streptococcus is entirely unclear. The four-hour time point did not represent a peak concentration, nor do the authors of Bray et al mention the four hour time point as significant.[79] The 1992 AAP guidelines cite Bray et al to support that "chemoprophylaxis ideally should be administered at least 4 hours before delivery. This allows sufficient time to achieve optimal concentrations of ampicillin in the amniotic fluid and placental circulation". As can be seen from Figure 5, the data from Bray et al do not support this conclusion.

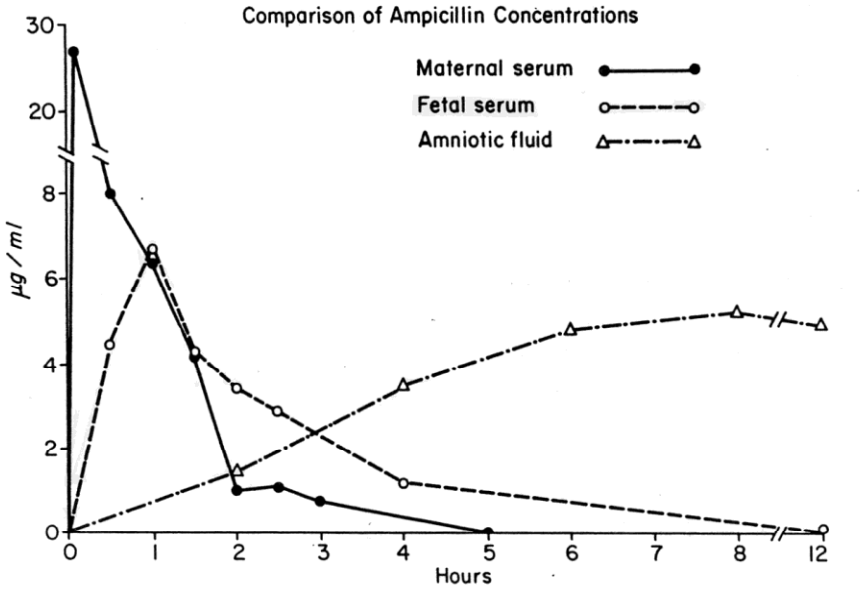

Figure 5: Ampicillin concentrations in maternal serum, fetal serum and amniotic fluid over time. Measurements taken after administration of 500mg of ampicillin.[79]

In fact, when Eickhoff first described the problem of neonatal group B streptococcal disease in 1964, he noted that the minimum inhibitory concentration of ampicillin against group B streptococcus was 0.04 μg/mL (range 0.02-0.1).[40] The minimum inhibitory concentration is the concentration of antibiotic that is required to eliminate visible growth of the organism. This would suggest that ampicillin levels (25-fold the minimum inhibitory concentration) are achieved at the one-hour time point and calling into question the recommendation for four hours of antibiotic prophylaxis. Furthermore, the authors of the 1992 AAP recommendations chose to use antibiotic levels instead of the data on colonization rates from the Boyer study. Both antibiotic levels and colonization rates are proxies for the outcome of interest: early-onset invasive neonatal group B streptococcal disease. Why the authors chose one proxy from 1966 data on drug concentration over the more recent 1986 proxy of neonatal colonization data is unclear. Furthermore, the Bray study is cited repetitively over the years as evidence for a duration of four hours of intrapartum prophylaxis against group B streptococcus despite the fact that it did not show the four hours of prophylaxis was necessary nor address group B streptococcus as an organism of interest.

Based on the Bray data, ampicillin persisted as the drug of choice for intrapartum prophylaxis until the 1996 recommendations, which recommended penicillin G as the antibiotic of choice in place of ampicillin. A short paragraph is devoted to this change and argues that ampicillin and penicillin have the same activity against group B streptococcus; however, penicillin has a narrower spectrum of activity and therefore decreases the chance of selecting for resistant organisms through the use of intrapartum prophylaxis. It is also noted that both ampicillin and

penicillin cross the placenta and achieve bactericidal levels in fetal tissues. The only reference for this entire idea of changing antibiotics is a short article published in 1994 by Amstey.[81] The article is an argument/opinion piece and makes a case for the use of penicillin G over ampicillin. Amstey states that the strongest reason for use of penicillin over ampicillin is the narrower antimicrobial spectrum. He also notes that the minimum inhibitory concentration of penicillin G (as it was calculated at the time) for group B streptococcus (0.02 μg/mL, range 0.01-0.04) is slightly smaller than the minimum inhibitory concentration of ampicillin for group B streptococcus (0.04μg/mL, range 0.02-0.1). Furthermore, he argues that both ampicillin and penicillin G have been evaluated pharmacokinetically and are known to cross the placenta readily.[82] No references to studies that document the rate of crossing the placenta are made. He concludes that, "Future clinical trials should compare penicillin to ampicillin prophylaxis for group B streptococcal infection of the neonate".[81]

In the 1996 recommendations, only two of the six studies cited to support intrapartum prophylaxis to prevent neonatal group B streptococcal disease studies used penicillin instead of ampicillin. One study done in Australia used penicillin (1 million units intravenously, every six hours) and found a significant reduction in mortality from invasive group B streptococcal disease in neonates of treated women (untreated n = 26,915, treated n = 30,197).[37] Another study used benzyl penicillin (600 mg intramuscularly at 8 hour intervals) and found neonatal colonization of 3% in the antibiotic group (n=38) and 45% in the untreated group (n=49) ($p<0.001$).[60] The other four studies used to support intrapartum prophylaxis all used ampicillin. At the time there was one other study that used a penicillin G dosing regimen. The study used fast latex agglutination testing to identify women with heavy vaginal colonization. 199 women were identified using

this approach and randomized to receive penicillin or antibiotic. The neonates of penicillin treated mothers had a lower incidence of early-onset group B streptococcal disease (1.1%) when compared with the controls (9.0%) ($p<0.01$).[83] However, the study population only included heavily colonized women and so was not included as support for use of intrapartum antibiotics in the culture positive population.

Based on this argument set forward by Amstey, the antibiotic recommendations were changed to penicillin G. The dosing regimen proposed was a 5 million-unit infusion of penicillin G intravenously upon presentation to the labor floor, followed by 2.5 million units every 4 hours until delivery. Ampicillin was considered an alternative antibiotic, but an inferior one due to its wider spectrum. The ampicillin-dosing regimen recommended was 2 grams intravenously upon arrival to the labor floor, followed by 1 gram every 4 hours until delivery. It has previously been discussed that the origin of a four hour interval dosing regimen for ampicillin was based on little data; however, this four hour dosing regimen using ampicillin had been used and tested in the seminal Boyer et al New England Journal of Medicine paper which showed it was effective in reducing neonatal colonization. Why a four-hour interval for penicillin was chosen as well is not clear. The studies up to this time point using penicillins had not used four hour dosing intervals nor had penicillin G been used in most of the studies. Furthermore, although both penicillin and ampicillin belong to the same drug family, penicillin differs pharmacokinetically in that it is bound to protein at a different rate than ampicillin. It seems that the assumption was made that penicillin G behaved enough like ampicillin to use a four-hour dosing regimen as well. The assumption is not made explicitly and the rationale for that assumption is not addressed in the recommendations; nor are any sources cited which address the question of dosing regimen and/or

appropriate duration of prophylaxis with regards to the penicillin family or penicillin G specifically.

The 2002 CDC recommendations continued to advocate a dosing regimen of a 5 million-unit infusion of penicillin G, followed by 2.5 million units every 4 hours until delivery. The recommendations cited "new evidence that 4 or more hours of intrapartum ampicillin or penicillin prophylaxis administered according to recommended dosing intervals significantly reduces vertical transmission of group B streptococcus and the risk of early onset group B streptococcal disease".[9] The authors of the recommendations favored using a minimum of four hours of prophylaxis in contrast to a minimum of two doses of prophylaxis (i.e. the loading dose and the first dose of 2.5 million units at the four-hour time point) advocated by the AAP in their 1997 recommendation. The papers cited to give support to a duration of four hours were Pylipow et al 1994[84] Lin et al, 2001[85] and DeCueto et al, 1998[86].

In 2006, a systematic review on the topic of appropriate duration of prophylaxis only identified four studies which addressed duration of prophylaxis (the three cited above and an additional one).[45] All four studies included a patient population of women with risk factors for group B streptococcal disease, not a universal screening population.[59, 84-86] Three of the studies used ampicillin antibiotic regimens exclusively[59, 84, 86] and one study examined patients who had received either ampicillin or pencillin.[85] One study showed that greater than 1 hour of prophylaxis was effective in reducing neonatal colonization,[59] while two studies showed that greater than 2 hours of prophylaxis were effective.[85, 86] One study was inconclusive. The

conclusion of this review was that an evidence base for an optimal duration of four hours as compared with any other duration is lacking.

Pylipow was a retrospective cohort study that examined a population of patients who were group B streptococcus culture positive ***and*** had obstetric risk factors. Furthermore, the antibiotic regimen used was ampicillin. The study showed that neonates of pregnant women who received two doses of ampicillin (4 hours apart) had lower rates of group B streptococcal colonization. However, the study was inconclusive about the optimal duration of prophylaxis.

The Lin study was a retrospective case-control study that compared neonatal cases of group B streptococcal disease with controls. These patients received both ampicillin and penicillin dosing regimens as well as alternate antibiotics (patients treated with antibiotics for chorioamnionitis such as clindamycin were also included in the intrapartum prophylaxis group) and patients were treated according to the risk factor based protocol, not the universal screening protocol. The conclusions of this study were that in order to achieve maximum protective effect, the first dose of antibiotic should be administered at least **two hours** before delivery.

The DeCueto study is a colony count study which measured neonatal colonization with group B streptococcus and showed that 46% of neonates were colonized at birth when exposed to 1 hour of prophylaxis, 28% at 2 hours of prophylaxis and only 1-3% were colonized at the 3 and 4 hour time points.[86] The antibiotic regimen was ampicillin, however, the cultures were not taken prenatally, rather they were taken at the time of admission to the hospital. This means that all women in the study had to wait for culture results before being treated. Culture results were

available 12 hours after admission in 65% of the patients and at 18 hours after admission in 95% of the patients. Therefore, all women in this study had labors that were longer than 12 hours and given that rupture of membranes for an extended duration is a risk factor, this is an unrepresentative patient population.

None of these studies was performed in the population of interest: women with no obstetric risk factors, but positive group B streptococcal cultures (the universal screening population). Two used ampicillin and one suggested that two hours of penicillin prophylaxis was sufficient. The cited studies do not support the concept that a minimum of four hours of penicillin G prophylaxis is necessary to ensure adequate treatment among patients identified by the universal screening approach.

As described above, there has been little evidence cited to support the selection of duration of 4 hours as optimal for intrapartum prophylaxis. Additional evidence regarding duration of intrapartum prophylaxis has been cited from the pharmacokinetic literature. These studies rely on the premise that intrapartum prophylaxis functions through three mechanisms: 1) decreasing vaginal colony counts 2) achieving sufficient antibiotic concentration in the amniotic fluid and 3) achieving sufficient antibiotic concentration in the fetal circulation. Of note, we do not know which of these mechanisms is most important; all three are hypothesized mechanisms of action of intrapartum prophylaxis. Data on colony counts and fetal colonization studies have been the most commonly used proxy to study invasive group B streptococcal disease; however few studies have examined colony counts in relation to duration of prophylaxis. The most recent study examined vaginal colony counts during delivery in patients undergoing the recommended

CDC dosing regimen of penicillin G. Vaginal colony counts declined 5-fold after 2 hours of prophylaxis and by 4 hours of prophylaxis, colony counts had decreased 50-fold.[87] It is not known what the critical colony count below which the risk of fetal infection decreases. Does the colony count needs to be zero, or is there some amount of organism that the neonate can tolerate. The authors of this study concluded, "this has potential clinical significance in that women commonly deliver less than 4 hours after the penicillin G loading dose, given that babies born to these women may be kept for prolonged observation unnecessarily."

Data from the pharmacokinetic literature attempts to demonstrate that intrapartum prophylaxis is effective by documenting sufficient concentrations of antibiotic in amniotic fluid and fetal circulation (mechanisms 2 and 3). The most often cited publication on this topic by Bray et al. in 1966 demonstrated bactericidal ampicillin levels above the minimum inhibitory concentration in amniotic fluid at the first time point measured which was 2 hours after a 500mg maternal intravenous ampicillin infusion. Ampicillin concentration in the amniotic fluid continued to rise until 8 hours after the initial infusion.[79] In 1974, a similar study found that ampicillin levels greater than 1.5 μg/ml were detected in the amniotic fluid one hour following an infusion of 1-2 grams of ampicillin in women in labor, which the authors depict as exceeding the minimum inhibitory concentration for group B streptococcus.[88]

More recent work, using high-performance liquid chromatography on sera collected at elective cesarean section after a 2g maternal infusion of ampicillin, demonstrated ampicillin levels in maternal and fetal sera exceeding the minimum inhibitory concentration for group B streptococcus within 3 minutes of infusion.[89] Likewise, bactericidal concentrations of ampicillin

were found in amniotic fluid as early as 5 minutes after infusion. The only study to date on the pharmacokinetics of penicillin G in pregnancy examined maternal serum levels only and was published in 2001. This study demonstrated that maternal levels of penicillin G exceeded the minimum inhibitory concentration for group B streptococcus 5 minutes after a 1 million-unit infusion of penicillin G. After 4 hours, the average maternal serum concentration was still 120-fold greater than the minimum inhibitory concentration.[80]

To date, there has been no study that examines penicillin G levels in either amniotic fluid or fetal circulation nor have there been studies that examine the pharmacokinetics of the recommended CDC penicillin G dosing regimen. In the first portion of this study, we sought to examine the amount of time required after maternal infusion of penicillin G to achieve the minimum inhibitory concentration for group B streptococcus in fetal serum and to examine the fetal pharmacokinetic profile of this maternal penicillin G dosing regimen over time, in order to partially address the question of the validity of the recommended optimal duration of four hours of antibiotic prophylaxis.

As discussed previously, based on the 2002 CDC guidelines, a maternal-infant dyad is considered adequately treated if the mother has received four or more hours of prophylaxis before delivery (the "four hour rule"). However, there are no stated recommendations to attempt to prolong the course of labor to achieve this duration. If the mother has received less than four hours of prophylaxis, infants are recommended to undergo a limited evaluation, which may include blood cultures at some institutions, and to be observed for 48 hours in the hospital. As many as 25-50% of group B streptococcus

positive women in labor fail to achieve the recommended four hours of antibiotics due the rapidity of their labors.[23, 75] Due to the implicit assumption that four hours of intrapartum prophylaxis is beneficial and less than four hours is "inadequate", as well as institutional protocols being applied to newborns born prior to four hours of therapy, it is possible that the guidelines have created an incentive for clinicians to deliver neonates who have received greater than four hours of prophylaxis. In the second portion of this study, we sought to investigate how clinicians are responding to this created incentive: to examine if clinicians were altering their care of group B streptococcus positive women in labor in order to achieve greater than four hours of prophylaxis. We developed a survey to query clinicians about their interpretation and clinical application of the 2002 CDC guidelines on prevention of neonatal group B streptococcal disease.

MATERIALS AND METHODS

Patient Recruitment

Laboring group B streptococcus culture positive women who were administered penicillin G by their medical provider according to the 2002 CDC protocol, as standard of care, were eligible for the study. Yale University Institutional Review Board approval was obtained, and patients were enrolled after obtaining informed consent. Inclusion criteria included: pregnancy ≥37 weeks; singleton gestation; group B streptococcus carrier status by rectovaginal or urine culture; and receipt of intravenous intrapartum penicillin G prophylaxis in standard CDC dosing regime doses. The exclusion criteria included hypertensive or renal disease, multiple gestation, penicillin allergy, and current other antibiotic usage. Following consent, duration and timing of antibiotic infusions, maternal height, weight, and demographic information were all recorded

from patient charts. Based on estimated means and variances from Johnson et al[80], we estimated that we required 10 patients in each time interval (<1 hr, 1 to <2 hrs, 2 to <3 hrs, 3 to <4 hrs, ≥4 hrs), to achieve >80% power to detect penicillin G concentration statistically greater than the minimum inhibitory concentration (0.1 μg/ml), alpha=0.05.

Umbilical cord blood samples were obtained from the Yale New Haven Hospital blood bank, which stores samples for blood typing of all infants. The blood was stored in glass tubes labeled with patient name and medical record number at 4ºC for one week until a research team member collected them. The blood was then centrifuged at 3000g for 15 minutes and stored in 0.5mL aliquots at -80ºC until high-performance liquid chromatography (HPLC) analysis. This approach was validated by comparing penicillin G levels in fresh cord blood collected at delivery to blood bank samples in 18 subjects.

High-performance liquid chromatography

The penicillin G concentration was measured by high-performance liquid chromatography and ultraviolet detection (HPLC-UV). The ESA reverse-phased HPLC system (Chelmsford, MA) was equipped with two dual piston pumps (Model 582), a refrigerated autosampler (model 542), high-pressure mixer and an ESA Model 528 UV-VIS detector. It was controlled and data acquired using ESA CoulArray for Windows software. An Intersil ODS-3 C_{18} column (150 x 4.6 I.D.), 5 μm particle size (GL Science Inc, Japan) was protected with a Platinum C_{18} (7.5 x 4.6 mm I.D.) 5 μm particle size guard column (AllTech GmbH, USA). The mobile phase was prepared using 0.05 dihydrogen phosphate (99.99% purity, pH 5.0; VWR International, West Chester, PA) and acetonitrile (90:10 vol/vol; Fisher Scientific, Fair Lawn, NJ). Serum samples

were analyzed at a gradient condition with mobile phase A of 0.05M sodium dihydrogen phosphate in 10% acetonitrile (PH=5) and B of 100% acetonitrile. The internal standard (IS) was prepared by dissolving 2.5 mg of ampicillin sodium salt (potency 98%; Sigma Chemical Company, St. Louis, MO) in 5 mL of HPLC grade water (Fisher Scientific, Fair Lawn, NJ) to a final stock concentration of 0.5 mg/mL. Penicillin sodium salt (5 mg, potency 99%; Sigma Chemical Company, St. Louis, MO) was dissolved in 5mL of HPLC grade water to a final stock concentration of 1 mg/mL. Serum standards for penicillin G were prepared in blank serum at 2.5, 5, 10, 20, and 40 μg/mL to create a standard curve for quantification (r=.9997). Both patient serum samples and serum standard curve samples were deproteinated by adding 100 μL of sample to 108 μL acetonitrile/ampicillin(IS) solution for a final concentration of 40 μg/mL of IS for each sample. Samples were vortexed for 15 seconds, placed at 4ºC for 10 minutes, and then centrifuged at 3000g for 10 minutes. 100 μL of aqueous phase from each serum sample was transferred to a clean autosampler vial. A 25 μL sample was injected onto the column at a flow rate of 1.0 mL/min. Both penicillin G and ampicillin (IS) were detected at 200 nm. Ampicillin and penicillin G had elution times of 2.28 and 13.2 min respectively. The CV was calculated by running three samples in three separate runs (CV = 2.9637; accuracy range: ± 3%). Additionally, every single run contained a serum standard curve point of known concentration. The calculated CV for those samples was 2.12%, verifying accuracy for all samples on each run. The lower limit of detection of penicillin G sodium was 0.192 μg/mL. A blank serum sample was also run and showed no evidence of a penicillin G peak ruling out the possibility of carry over from run to run. The concentration of penicillin G sodium salt was quantified by comparing peak height ratio (penicillin G/IS) from the unknown cord serum samples and those obtained from the penicillin G standard curve.

Statistical analysis was performed using Student's t-test, analysis of variance, and multivariable linear regression using SAS 9.1 software.

Clinician Survey

We designed a survey to query clinicians about their interpretation of the 2002 CDC guidelines. The Human Investigation Committee at Yale University approved the survey. The focus of the survey addressed whether or not clinicians alter their management of labor in response to the 2002 protocol by asking a series of questions using clinical scenarios. We also addressed clinician perceptions of the protocol and any perceived patient or provider stress they had observed.

This survey was offered to all midwives, resident physicians and attending physicians who have privileges on the labor and birth unit of Yale-New Haven Hospital, which has approximately 4,700 deliveries annually, of which about 20% occur in the setting of maternal group B streptococcus colonization. Surveys were distributed in three ways: providers were given surveys at Grand Rounds for the Department of Obstetrics and Gynecology at Yale University; surveys were made available on the labor and delivery floor of Yale-New Haven Hospital; and surveys were distributed by e-mail. All surveys were confidential and collected in a sealed box to preserve anonymity. When surveys were collected, respondents' names were checked off a list to ensure that a single individual did not return multiple surveys.

RESULTS

Stability of Penicillin G in cord blood

The primary aim of the pharmacokinetic portion of this study was to evaluate women who delivered quickly (less than 4 hours) and thus did not receive the duration of prophylaxis recommended by the 2002 CDC Guidelines. Obtaining cord blood samples on the labor floor for these rapidly progressing deliveries is logistically difficult, while obtaining blood bank samples after delivery is more straightforward. After obtaining and processing 18 labor floor obtained cord blood samples and the blood bank obtained cord blood samples from the same patients, penicillin levels were determined by HPLC and compared. For all 18 samples, the levels of penicillin G were very close to one another. The penicillin level was consistently slightly lower in the blood bank samples when compared with the delivery floor samples. The percent lost ranged from .40% to 16.40% with a mean of 9.54 ± 4.76%.

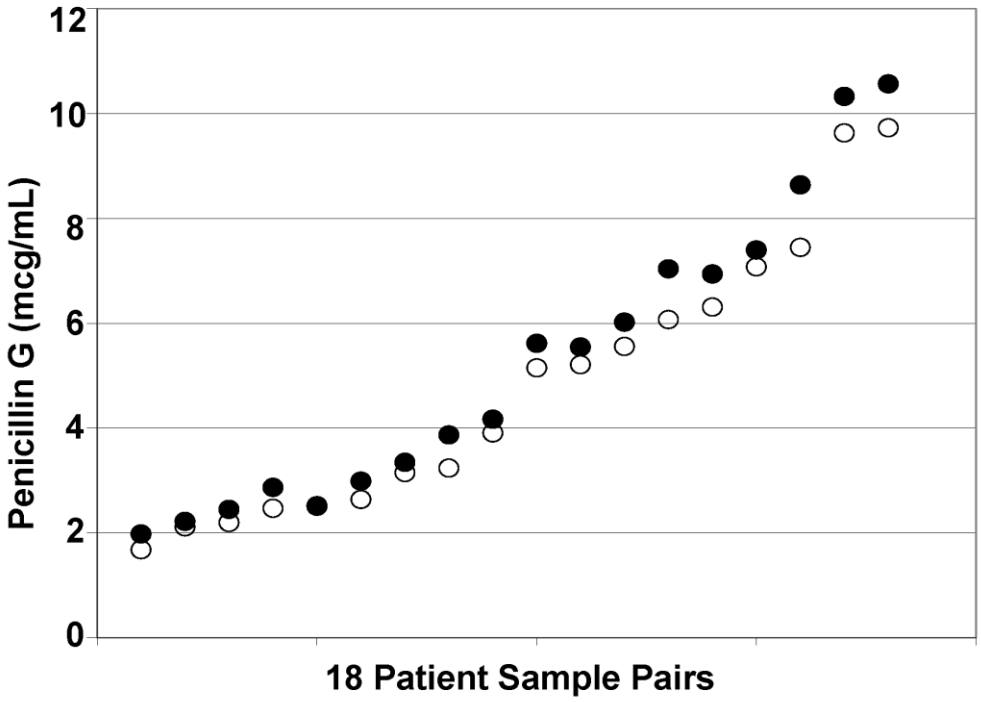

Figure 6: Blood bank and labor floor umbilical cord serum sample penicillin G concentration measured for 18 patients. Each patient has one of each sample and patients are organized in order of increasing penicillin G concentration, from left to right. The solid circles represent the samples obtained on the labor floor and the outlined circles represent the samples taken from the blood bank after one week of storage.

We performed mathematical modeling to calculate the predicted labor floor concentration based upon the concentration found in the blood bank sample as well as the percent lost. We then calculated the predicted labor floor concentration based on the blood bank concentration for each of the samples. However, the mathematical modeling introduced an inherent component of variability, as we were no longer working with HPLC data, but rather calculated predicted concentrations. The primary aim of the study is to determine if cord blood levels *above* the minimum inhibitory concentration are achieved when women receive less than 4 hours of prophylaxis. By analyzing the blood bank values, our data and conclusions contain a degree of underestimation. We used this conservative approach because if the underestimated values from

the blood bank were significant, than by extension, values at the time of delivery would also be significant.

Dosing Regimen

After confirmation of the feasibility of using blood bank samples to measure penicillin G levels in cord blood, an additional 80 maternal-infant dyads were included in the study. Consent was obtained consistent with standards of the IRB at our institution. One-hundred-ten eligible patients were approached at Yale-New Haven Hospital from June 6th, 2007 until August 14th, 2007. Ninety-eight patients consented to participate, yielding a participation rate of 89%. Reasons for non-participation included lack of time or desire to discuss the study or to read and sign the consent form. The cohort was representative of the population served by our urban, academic medical center; demographic and clinical characteristics of the patients enrolled are listed in Table 1.

Table 1. Demographics. Characteristics of 98 patients who gave informed consent and were enrolled in the study.

Maternal Age	**28.5 ± 6.5 yrs**
Maternal BMI at Delivery	**31.6 ± 5.9**
Gestational Age	**39.3 ± 1.2 wks**
Neonatal Weight	**3338.4 ± 450.9 g**
Gravidity	**2 (1, 3: 2)**
Parity	**1 (0, 2: 2)**
Race	
White	**49 (50%)**
Black	**20 (20.4%)**
Latina	**22 (22.5%)**
Asian	**5 (5.1%)**
Other	**2 (2%)**
Provider Type at Delivery	
Physician	**65 (66.3%)**
Midwife	**33 (33.7%)**
Site of Prenatal Care	
Private	**60 (61.2%)**
Hospital Clinic	**38 (38.8%)**
Type of Birth	
NSVD	**76 (77.6%)**
Caesarean Section	**22 (22.4%)**

*Data for continuous variables is presented as Mean ± Standard Deviation or median (1^{st} quartile, third quartile: interquartile range).
*Data for categorical variables are presented at Number of Patients (Percent of Total Patients).

For all patients in the study, the number of minutes from first dose administration until delivery ranged from 32 to 1473 min with a mean of 352.7±363.5 min. The penicillin G concentrations for all patients ranged from 1.02 to 17.93 μg/mL with a mean of 6.25±4.15 μg/mL. Patients were divided into 7 groups for analysis [Table 2].

Table 2. Duration of prophylaxis and fetal serum concentration of penicillin G for all patients grouped by duration of prophylaxis (minimum inhibitory concentration for GBS = 0.01μg/ml).

Group (#)	Duration Prophylaxis (hours)	N	Penicillin G Concentration [mean±SD] (μg/ml)
1	Less than 1 h	10	11.60 ± 4.49
2	1-2 h	15	9.74 ± 3.42
3	2-3 h	15	6.62 ± 3.75
4	3-4 h	17	3.64 ± 1.80
5	More than 4 h, no 2nd dose	6	2.28 ± 0.89
6	4-8	11	6.88 ± 3.67
7	More than 8 h	24	4.10 ± 2.60

Grouping based upon hour time blocks are presented throughout the literature on this topic, as time cutoffs are used clinically to determine adequate duration of prophylaxis and assess neonates at risk for group B streptococcal disease.[48, 84, 85, 90] Each of the 7 groups of patients was compared to the minimum inhibitory concentration for group B streptococcus (0.1 μg/mL)[21, 90] using Student's t-test. All groups were statistically significantly above the minimum inhibitory concentration, $p<0.002$. Furthermore, penicillin G levels observed in each individual cord blood sample were 10-179 fold above the minimum inhibitory concentration.

Each of the seven groups was also compared with one another using analysis of variance. Penicillin G levels for those patients receiving less than 1 hour of prophylaxis (group 1) were

statistically significantly greater ($p<0.05$) than all other groups of patients receiving greater than 2 hours of prophylaxis (groups 3,4,5,6,7). Rather than requiring four hours to reach levels of penicillin G above the minimum inhibitory concentration in the fetal bloodstream, we found statistically significantly higher levels during the 0-2 hour time points when compared with longer durations, even after subsequent re-dosing with 2.5 million units at four-hour intervals.

For graphical pharmacokinetic analysis, the data for those patients who received only one dose of 5 million units of penicillin G [Figure 7] were analyzed by using time elapsed since most recent dose. As can be seen in Figure 7, the relationship between penicillin G concentration and time elapsed since dose of 5 million units of penicillin G was not strictly linear. The concentration rose linearly ($R^2 = .40$) [Equation: [Con. penicillin] = 0.255(min) + 1.2718], as the penicillin G made its way across the placenta and into the fetal circulation, until the one-hour time point. After one hour, the penicillin G concentration decreased according to a power-decay model ($R^2 = .67$) determined by optimizing the r^2 [Equation: [Con. penicillin] = 2745.5(min)^(-1.2503)]. This period represents the combined efforts of both maternal and fetal clearance, as well as maternal and fetal metabolism. In order to accommodate the non-linearity of penicillin G levels over time, the time variable was transformed according to the power-decay model equation above for values greater than one hour. Multiple linear regression analysis performed on the cohort of all patients showed that fetal penicillin G levels were associated with duration of exposure to penicillin, time since last dose, dosage, and number of doses, but not maternal BMI. Assuming maternal BMI is an adequate, though imperfect, marker for maternal size and maternal volume of distribution, the maternal volume of distribution did not appreciably alter the fetal cord blood concentrations of penicillin.

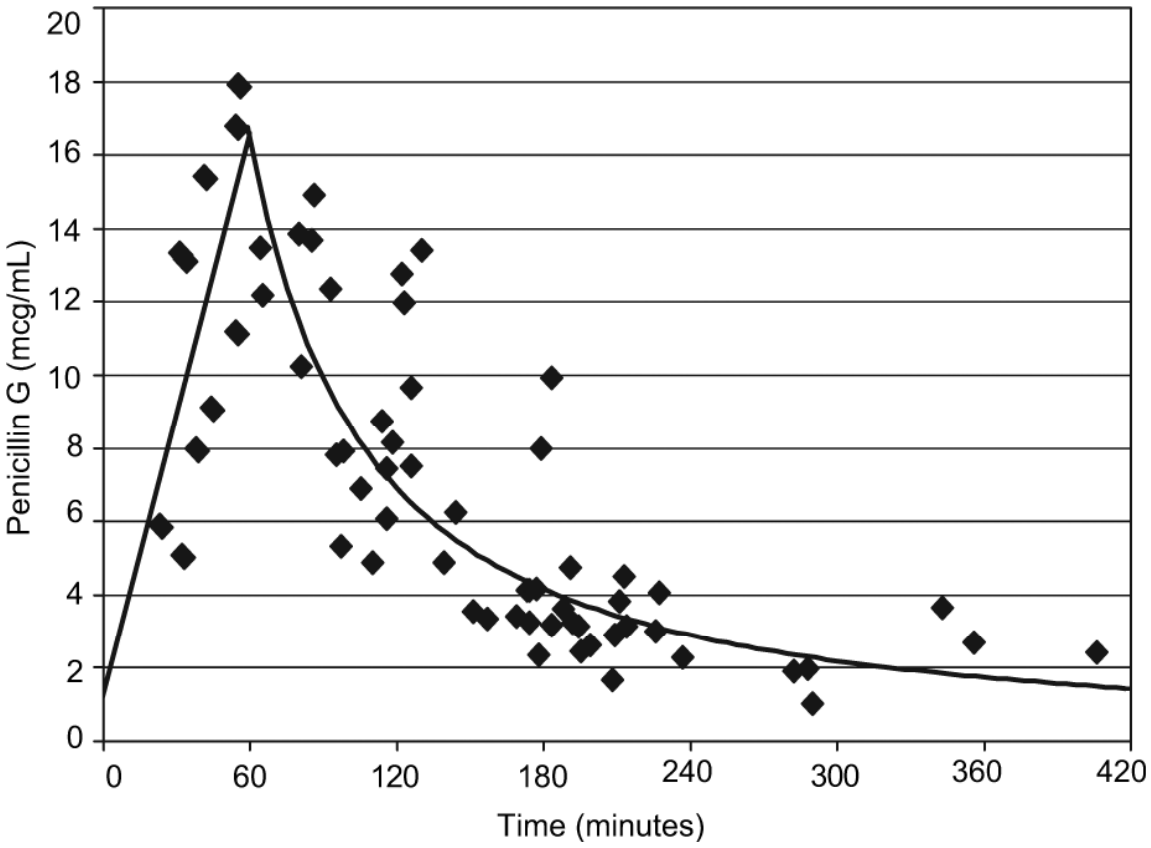

Figure 7. Time After Infusion of Penicillin G vs. Concentration in Umbilical Cord Serum at Delivery. Relation between time elapsed since initial dose of 5 million units of penicillin G and concentration of penicillin G in umbilical cord serum at the time of delivery.

As seen in figure 7, the highest value of penicillin G concentration in the cord blood was observed at around 1 hour after administration of the loading dose of 5 million units. The lowest value observed for all patients was 1.02 μg/ml seen in a patient who delivered 5 hours and 34 minutes after receiving her initial dose. Additionally, the group with the lowest mean (2.28 ±0.89 μg/ml) was represented by six patients who failed to receive their additional 2.5 million units at the four-hour time point. For patients receiving maintenance doses of 2.5 million units every four hours, levels remained consistently above the minimum inhibitory concentration and decayed in the same fashion as the loading dose. Of note, fetal serum penicillin G levels did not accumulate with repeated maintenance dosing.

Clinician Survey

All clinicians surveyed had active privileges on the labor and birth unit of Yale-New Haven Hospital during the period of survey collection, July 12th, 2007 – September 15th, 2007. A total of 96 clinicians met the criteria to receive the survey, and 70 completed it, yielding a participation rate of 72.9%. All 70 survey respondents answered all of the survey questions. Demographics for all respondents are reported in Table 3.

Table 3: Demographics for all 70 clinicians who completed our survey.

Gender	
Male	26 (37.1%)
Female	44 (62.9%)
Provider Type	
Midwives	17 (24.3%)
Physicians	38 (54.3%)
Residents	15 (21.4%)
Provider Practice Type	
Private Practice	36 (51.4%)
Hospital staff/faculty	34 (48.6%)
Patient Insurance Status	
> 80% private insurance	39 (55.7%)
< 80% private insurance	31 (44.3%)
Date Completed Training	
Before 1990	38 (54.3%)
After 1990	32 (45.7%)
Attended CME on GBS	19 (27.1%)

We asked clinicians how, if at all, they changed their management of group B streptococcus positive multiparous women compared with group B streptococcus negative multiparous women. Only 21.4% responded they did not change their management at all; 35.7% encouraged group B streptococcus positive women to come to the hospital at the first signs of labor; 11.4% reported that they admitted group B streptococcus positive women to the hospital before they were in active labor; and 57.1% said that they admitted group B streptococcus positive women earlier in the course of

labor than they would normally admit group B streptococcus negative women. We also specifically addressed the labor course itself and asked clinicians if they recommended any interventions if a group B streptococcus positive woman had not yet received four hours of prophylaxis. Only 22.9% of clinicians responded that they would not alter their management of labor; 21.4% recommended "laboring down"/delay pushing; 27.1% would turn off or decrease an oxytocin infusion; 74.3% reported that they delay or avoid artificial rupture of membranes. This data is reported in Table 4.

Table 4: Survey responses from clinicians in response to questions about labor management of group B streptococcus positive pregnancies in the setting of the 2002 CDC protocol.

Given that the CDC recommends a minimum of 4 hours of prophylaxis, do you change your management of GBS+ *multiparous* women in any of the following ways (check all that apply):	Encourage admission at the first signs of labor (35.7%) Admit GBS+ women earlier than GBS- women (57.1%) Admit women before they are in active labor (11.4%) Make no changes in management (21.4%)
When a GBS+ woman has received <4hrs prophylaxis, would you recommend any of the following to prolong the labor (check all that apply):	"Labor down" or delay pushing (21.4%) Delay/Avoid artificial rupture of membranes (74.3%) Turn off or decrease oxytocin infusion (27.1%) Make no changes to prolong labor (22.9%)

The majority (71.4%) of providers said that they would consider a woman who received 4.5 hours of prophylaxis as adequately treated even if she never received a second dose of penicillin G at the 4 hour time point (Table 4). This is in accordance with the 2002 CDC guidelines and differentiates from the 1996 protocol[16], which required a 2nd dose of antibiotic even if the woman was in the act of delivering at the 4 hour time point.

We also solicited their opinions about the 2002 CDC protocol (Table 5). The majority (55.7%) of clinicians responded that the protocol was "excessive", while 46.3% described it as "optimal". They also responded that trying to achieve four hours of intrapartum prophylaxis created significant stress for themselves as providers (35.7%), the patient (54.3%), the labor and delivery floor staff (42.9%), and the patient's family (30%).

Table 5: **Clinicians' opinions and interpretations.** Survey responses from clinicians in response to questions about clinician's opinions and interpretations of the 2002 CDC protocol.

Does the 4 hour prophylaxis protocol cause additional stress or anxiety to (check all that apply):	Me, the provider (35.7%) Patient (54.3%) Delivery floor staff (42.9%) Patient's family (30%)
Do you believe that the duration of 4 hours of intrapartum prophylaxis to prevent GBS transmission to the neonate is (select one):	Excessive (55.7%) Optimal (46.3%) Inadequate (0%)
Would you consider a woman who received intrapartum prophylaxis of 4.5 hours adequately treated if she never received her second dose of 2.5 million units?	Yes (71.4%) No (28.6%)

DISCUSSION

The data presented here demonstrates that shorter durations of exposure to intrapartum antibiotic prophylaxis are effective in attaining levels of penicillin G in the neonatal bloodstream significantly above the minimum inhibitory concentration for group B streptococcus. Up until this point, little has been documented regarding the pharmacokinetic properties of penicillin G in the pregnant woman and her fetus. Similar studies on ampicillin have shown that ampicillin levels rise rapidly in the fetal serum following maternal intravenous administration.[91] To date, studies on penicillin G pharmacokinetics have generally been performed on non-pregnant women or men or neonates themselves (dose given to the neonate after delivery).[92-94] One recent

study examined serum concentrations of penicillin G in pregnancy, but examined only the maternal circulation and not the fetal.[80] Another study gave one IM dose of penicillin G benzathine and then measured the maternal penicillin G levels at 30 days and fetal levels at the time of delivery. This study showed levels above the minimum inhibitory concentration at 30 days after injection.[95] Our current investigation documents penicillin G levels in the fetus using the current CDC dosing regimen.

Intrapartum antibiotic prophylaxis likely works to prevent transmission from mother to child by decreasing colony counts in the vaginal tract at the time of delivery; preventing organism ascension into amniotic fluid; and achieving effective antibiotic levels in the fetal bloodstream during labor. All three mechanisms attempt, ultimately, to decrease rates of neonatal sepsis, pneumonia, and meningitis. This study examines the protective mechanism of achieving effective antibiotic levels in the fetal bloodstream during labor by measuring fetal serum levels of penicillin G. Due to natural variability in duration of labor, we cannot control duration of prophylaxis in relation to the timing of umbilical cord blood sampling. This investigation is therefore limited to observational study and cannot assess the impact of duration of prophylaxis on rates of early onset group B streptococcal sepsis of the newborn. Furthermore, as was discussed previously, this investigation used blood bank samples due to the difficulty of obtaining consent during the rapidly progressing, less than four hour deliveries we were interested in studying. The blood bank samples represent an underestimation of the penicillin G levels contained in the cord blood at the time of delivery and not the actual levels at the time of delivery.

This study also did not evaluate the levels of penicillin G in the amniotic fluid, only in the neonatal cord blood. Evaluating the amniotic fluid would have required performing an invasive procedure, amniocentesis, in the setting of rapidly progressing deliveries or would have required limiting our cohort to women undergoing Caesarian sections, which would have limited the generalisability of our findings. As we did not examine the levels in the amniotic fluid, we are unable to ascertain whether sufficiently high levels of penicillin G were obtained in the amniotic fluid to prevent transmission via that route. However, in studies of ampicillin and cefazolin when adequate concentrations were achieved in the cord blood, they were also reported in the amniotic fluid.[89, 96]

The 4-hour time threshold recommended by the CDC is present throughout the literature on intrapartum penicillin G chemoprophylaxis for group B streptococcus, but its origins are unclear. A systematic review of published evidence suggests at best, that in women *with established risk factors* for early-onset group B streptococcus disease of the newborn, greater than 1 or 2 hours of intrapartum antibiotic prophylaxis is effective in reducing neonatal group B streptococcal colonization or disease.[48, 84, 97-99] Studies evaluating the current recommended penicillin G dosing regimen in a cohort of maternal-fetal dyads have not been performed. We examined the duration of maternal chemoprophylaxis necessary to achieve and maintain concentrations of penicillin G above the minimum inhibitory concentration for group B streptococcus in fetal serum. As can been seen from the demographic table [Table 1], our patient population is racially diverse, represents both private and hospital clinic patients and patients cared for by both midwives and physicians. Maternal age and gestational age were also varied. This patient population is representative of a reproductive aged cohort of women at a large urban academic medical center.

Even with the most valiant of efforts, there will frequently be group B streptococcus positive mothers who arrive at the labor floor and deliver in less than four hours. Obstetric providers have little control over the time patients arrive at the hospital to begin prophylaxis and likewise little control over the progression of labor and the ultimate timing of delivery. Providers may believe that four hours of prophylaxis are necessary to achieve adequate levels in the fetal bloodstream to prevent group B streptococcus transmission and therefore, may choose *not* to begin penicillin G dosing during precipitous labor. Our data indicates that fetal serum levels far exceed the minimum inhibitory concentration at durations well under one hour, suggesting that antibiotic prophylaxis should be pursued even in the most precipitous of deliveries.

The declining levels of penicillin G levels in the six patients who failed to receive the protocol recommended 2.5 million units at the four-hour time point supports the four-hour dosing interval recommended by the CDC. Additionally, patients who received 6 additional doses of 2.5 million units had similar levels to those who received two additional doses. Fetal serum penicillin G levels do not build with time, rather they return very close to baseline at the end of each four-hour interval. Therefore, adherence to dosing every four hours, independent of the duration of the intrapartum prophylaxis should be a priority.

Knowledge about the dosing regimen has implications beyond the labor and delivery floor. Preliminary studies as well as data from a large health maintenance organization demonstrated that 40-50% of group B streptococcus colonized women do not receive antibiotics at least 4 hours prior to delivery due the rapidity of their labors.[23, 100] More recent data from this year from

the Active Bacterial Core Surveillance, a 10-state population based system which monitors group B streptococcal disease, reported that in their group of patients 25% did not receive antibiotics four hours prior to delivery.[23] This effect is especially notable for multiparous women. According to the 2002 CDC guidelines, the newborns of all group B streptococcus positive women who present to labor units and deliver prior to 4 hours of intrapartum antibiotic prophylaxis are deemed as 'at risk' and recommended to undergo blood cultures, complete blood count, and 48 hours of observation.[9] At some institutions, these infants have been placed in designated observation units for up to 6 hours after delivery to monitor for signs of sepsis, often causing great angst for parents and care providers. These interventions have not been proven to reduce or detect more cases of group B streptococcal sepsis.[101] Knowledge that fetal serum penicillin G levels are far above the minimum inhibitory concentration within one hour raise the possibility that these interventions and testing may be at best, superfluous, and at worst, expensive and deleterious.

This study shows that fetal serum penicillin G levels far exceed the minimum inhibitory concentration even for short durations of maternal intrapartum prophylaxis. However, studies which correlate duration of prophylaxis with the clinical outcomes of early onset group B streptococcal sepsis are needed before clinical practice can change. Much of the current literature has examined neonatal group B streptococcal colonization, but the utility of using this as a surrogate for risk of early onset group B streptococcal sepsis does not have much, if any, supporting evidence. Therefore, studies investigating the duration of prophylaxis in relation to incidence of early onset group B streptococcal sepsis are necessary. If those studies are in line with the evidence presented here, the results may

alter group B streptococcal sepsis protocols, so that in appropriate circumstances, shorter durations of intrapartum prophylaxis may be considered adequate.

National agencies of health are charged with promoting the public health and welfare and therefore have enormous responsibility to create guidelines and recommendations for hospitals and health care providers to reduce the disease burden within our population. Early-onset neonatal group B streptococcal disease has become largely preventable with antenatal group B streptococcus screening among pregnant women and the use of intrapartum antibiotic prophylaxis.[102] Therefore, it is very appropriate that the CDC has issued guidelines on this topic. The variations in the interpretation and application of guidelines are often hard to anticipate. The recommendation to perform additional testing and prolonged observation of newborns who have been exposed to less than four hours of intrapartum prophylaxis has led many maternity care providers to attempt to either prolong the duration of labor or avoid common interventions to hasten labor, in the belief that four hours of intrapartum antibiotic exposure is preferable to a shorter labor and a shorter duration of fetal exposure to the maternal organism. This is not an irrational conclusion, especially if we assume that the evidence to support special attention to infants born to group B streptococcus positive mothers after short labors is well justified. However, if this evidence is not compelling or of high quality, prolonging labor and fetal exposure to the organism may be neither in the best interest of the neonate nor the mother.

In the past several years, we have learned that the evidence supporting the four hour threshold is weak, especially for low risk group B streptococcus positive women.[45] These would include those who are delivering at term, are afebrile, have no history of group B streptococcus bacteriuria, have intact chorioamniotic membranes upon arrival, and have no prior history of a group B streptococcus septic infant.[16] Studies regarding the duration of prophylaxis among these women and their newborns are lacking; however, low risk women make up more than 90% of parturients exposed to the intrapartum prophylaxis protocol.[49] Among group B streptococcus positive women ***with risk factors***, the existing evidence supports at least one or two hours of intrapartum prophylaxis to significantly reduce neonatal group B streptococcal colonization or disease.[45] Maternal rectovaginal group B streptococcal colonization declines rapidly within two to four hours of initiating intrapartum prophylaxis[87], while pharmacokinetic data shows that fetal penicillin G levels peak within the first hour after maternal intravenous administration and remain 10-79-fold greater than the minimum inhibitory concentration throughout the remainder of the four hour interval.[103] We are not aware of evidence to support attempts to prolong labor in group B streptococcus positive women in order to reduce the risk of early onset neonatal group B streptococcal sepsis. It is quite possible that efforts to prolong labor in such women would actually increase the risk of sepsis in newborns. Indeed, the CDC guidelines outline management for newborns that happen to deliver before four hours have passed; the guidelines do not recommend altering the course of labor to achieve a four-hour threshold. However, the confusion is understandable if providers assume that an intrapartum antibiotic duration of four hours is strongly evidence-based.

Our survey documents that on the labor floor at our academic medical center, the 2002 CDC guidelines on prevention of perinatal group B streptococcal disease had altering effects on management of labor. The 2002 CDC document[9] provides a flowchart approach to the management of neonates born to mothers with group B streptococcal colonization which indicates that maternal–infant dyads exposed to greater than four hours of intrapartum antibiotic prophylaxis are considered adequately treated. In our survey, respondent clinicians placed great emphasis on duration of prophylaxis and attainment of four hours. Only 21.4% of clinicians stated that there would be no difference in their instruction about time of admission between the group B streptococcus positive and negative women. Once in labor, a majority of clinicians also indicated that they would manage the labor course of group B streptococcus positive women differently if they had not yet received four hours of prophylaxis with only 22.9% of clinicians replying that they would make no changes to prolong the course of labor for these women. Interventions included delaying rupture of membranes, stopping oxytocin infusions, or instructing women to delay pushing or "labor down". These alterations may or may not negatively impact labor. Delaying rupture of membranes could have theoretical benefit if the clinician is concerned about exposure of the fetus to the colonized birth canal or ascending group B streptococcus infection in a slowly progressing labor. However, stopping oxytocin infusions and "laboring down" carry the risk that the fetus may spend a longer duration in the birth canal, increasing exposure to the organism. Clinicians also reported increased stress resulting from the protocol for patients, providers, hospital staff and patient families.

According to data published in 2009, women who were positive for group B streptococcus were less likely to receive any intrapartum antibiotics when they presented to the labor floor less than four hours before delivery when compared with those women who presented greater than four hours before delivery.[23] Anecdotally, we have heard many staff on labor floors who believe that if a woman does not receive four hours of antibiotics she is untreated and so there is no purpose in beginning antibiotic prophylaxis if delivery is imminent. Under this interpretation of the 2002 guidelines, no antibiotic is equal to 2 hours which is equal to 3 hours. From the data reviewed in this paper, this is clearly not a valid interpretation of the literature. The institution of a four hour cutoff may have the unintended impact of preventing women who would benefit from a short duration of antibiotics from receiving any antibiotics at all.

Using a survey-based instrument to study provider practice patterns clearly has limitations, because it depends on clinician report, which may not always mirror actual practice. Documenting and comparing durations of labor and obstetric interventions among group B streptococcus positive and negative women would be another means to investigate provider practice patterns; however, it would not yield information about how providers are interpreting the CDC guidelines and how they are applying the information to different clinical scenarios. Our goal was to elucidate the latter, and therefore we chose a survey-based approach. Another potential limitation of this study is that Yale respondents may not necessarily be representative of clinicians at other medical centers, because this center has a particular interest in this topic. Other medical center surveys would be of interest.

The 2002 Prevention of Perinatal Group B Streptococcal Disease guidelines from the CDC provide an interesting case study on how guidelines can be interpreted differently in the clinical setting than how might have been intended by the authors. This hospital-based survey reveals that a majority of clinicians have altered their management of labor among group B streptococcus positive women based on guidelines about managing newborns after delivery exposed to different durations of intrapartum prophylaxis. Further studies will be needed to enhance the evidence around optimal duration of intrapartum prophylaxis, so that we can determine if prolonging labor to achieve this threshold is actually more beneficial than delivering the infant in an expedited or naturally timed fashion. Furthermore, additional testing and prolonged observation of infants born to group B streptococcus positive mothers without other risk factors should be more evidence-based given the unexpected repercussions that it has had on clinical practice and patient and provider anxiety.

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