Prevention of early-onset invasive neonatal group B streptococcal disease in a private hospital setting: The superiority of culture-based protocols

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OBJECTIVE: In a large private tertiary care hospital we compared the two different approaches to group B streptococcal screening and intrapartum chemoprophylaxis suggested by The American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, and the Centers for Disease Control and Prevention: risk factor–based protocol and culture-based protocol.

STUDY DESIGN: A 2-year baseline period was followed by sequential prospective observational studies of the impacts of two different group B streptococcal management protocols, 3 years with the risk-based approach and 2 years with the culture-based approach of universal screening at 35 to 37 weeks' gestation.

RESULTS: During the baseline period the rate of early-onset group B streptococcal infection was 1.1 cases per 1000 births (n = 8 cases per 6829 births). With the risk-based strategy the rate was also 1.1 cases per 1000 births (15 cases/13,270 births). After we switched to the culture-based protocol for 2 years, there were no cases of early-onset group B streptococcal infections among 9304 births (P = .001; χ^2 = 10.9). There were no increases in other early-onset infections or in antibiotic resistance.

CONCLUSIONS: In our setting, which included good prenatal care and good communication between laboratories and the hospital, the approach based on maternal culture at 35 to 37 weeks' gestation and treatment during labor of all patients with positive results significantly reduced early-onset group B streptococcal infections without increasing infections from resistant organisms. (Am J Obstet Gynecol 2000;182:1344-54.)

Key words: Antibiotics during labor, group B streptococci, perinatal infection

For the last 20 years group B streptococcal infection has been the leading cause of early onset sepsis, meningitis, and pneumonia among neonates.[1] Fifteen years ago it was established that intrapartum administration of appropriate antibiotics could interrupt the transmission of group B streptococci from mother to infant and thus eliminate a large portion of early-onset (within the first 7 days after birth) group B streptococcal disease.[2] Recommendations for the prevention of early-onset group B streptococcal disease have been issued by the Centers for Disease Control and Prevention (CDC), The American College of Obstetricians and Gynecologists (ACOG), and the American Academy of Pediatrics.[1-3] Implementation of these recommendations has been controversial, with concerns centered around the extensive use of antibiotics, efficacy in environments other than research hospitals, impact on other microorganisms, and cost.[4] These protocols potentially affect the care of all obstetric patients in the United States. Despite this there are few large-scale studies with which to make the judgment regarding which protocol is optimal for which clinical care setting.

The fact that early-onset group B streptococcal disease has a low frequency (1-2 cases/1000 births) has made analysis even more difficult. Identifying differences in protocols at this level of incidence is beyond the ability of most delivery units of average size. In this article we present the results of serial application of the risk-based and the culture-based CDC and ACOG protocols in a large private hospital setting for 7 years, comprising >25,000 births. We examined not only the efficacy of the protocols in preventing early-onset group B streptococcal infections but also the effects on other early-onset serious neonatal infections, the usefulness of risk factors in our population, and the use of cultures and antibiotics during the culture-based protocol study period.

Material and methods

California Pacific Medical Center (CPMC) has a large delivery service (4890 births in 1998) in San Francisco that both serves as a primary obstetric practice site for 70 obstetricians and is a tertiary perinatal referral center for a network of hospitals in northern California. This prac-

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Presented at the Sixty-sixth Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society, Cancun, Mexico, October 20-24, 1999.

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0002-9378/2000 $12.00 + 0 ***6/6/106245***

doi:10.1067/mob.2000.106245

tice pattern results in a population that both is rich in normal obstetric cases and has a high preterm birth rate. CPMC has an active 30-bed neonatal intensive care unit. Perinatal outcomes have been a major focus of the obstetrics and neonatal divisions during the last decade, with the implementation of a combined mother-baby comprehensive perinatal database (Perinatal Data Center; Site of Care Systems, San Francisco, Calif). The system is made up of nearly 20 workstations throughout the perinatal units. The Perinatal Data Center is used to summarize with detail the care of each labor and birth; to create discharge summaries, diagnosis summary sheets, and birth certificates; and to serve as the on-line medical record and coding system for all ill neonates. In addition the system generates all obstetric and neonatal statistics and billing information for the intensive care nursery unit. To serve all these needs there are multiple data validation steps throughout the medical record process. This computerized clinical database and medical record system was the source of most of the information for our study. Data examining office culture results and the confirmation of use of antibiotics during labor were substantiated by review of 1000 sequential obstetric paper medical records. This study was performed with the guidance and approval of the CPMC perinatal quality improvement committee and the CPMC institutional review board.

The first period, January 1, 1992, through December 31, 1993, represents data from the former Children's Hospital of San Francisco (24 months) and the former Pacific Presbyterian Hospital (6 months), which merged obstetric units in July 1993 to form CPMC. During this period a variety of less organized approaches were used for group B streptococcal prophylaxis, with an emphasis on antibiotic treatment of preterm labor and intrapartum fevers. Earlier audits indicate that antibiotics were used in <50% of cases meeting these criteria.

After publication of the first ACOG bulletin on the subject in 1992[5] we had a series of interdepartmental discussions regarding risk-based and culture-based approaches. A protocol that was based on cultures at 28 weeks' gestation appeared unsound because of the long period from culture to delivery, so we chose to establish a risk-based approach. This was formally begun in January 1994, which marked the beginning of the second period (January 1, 1994–December 31, 1996). The risk-based protocol followed the guidelines presented by the CDC and ACOG.[1-3] Patients were treated with antibiotics at the labor and delivery unit if they had any of the following risk factors: preterm labor, preterm rupture of membranes, prolonged rupture of membranes (>18 hours) at term, fever (temperature >38°C) during labor, previous infant with early-onset group B streptococcal infection, or maternal urinary infection with group B streptococci during the index pregnancy. The antibiotic used was 2 g ampicillin administered intravenously as a loading dose, followed by 1 g intravenously every 4 hours. If the patient reported a history of penicillin allergy, an alternative regimen of 900 mg clindamycin every 8 hours administered intravenously was used. If there was a fever or suspected chorioamnionitis, gentamicin 1.5 mg/kg every 8 hours administered intravenously was recommended to be added to the previously described antibiotic regimens. Frequent department meetings, nursing in-service training sessions, mailings, and quality improvement activities focused on group B streptococcal infection and the new protocol were held during this period.

In the fall of 1996 the final CDC and ACOG recommendations were issued.[1, 3] At that point it also became clear that we were not getting the drop in the early-onset group B streptococcal infection rate for which we had hoped. After several joint department meetings between obstetrics and pediatrics we decided to switch to the protocol calling for universal group B streptococcal culture at 35 to 37 weeks' gestation as of January 1, 1997. The third study period, January 1, 1997, through December 31, 1998, represents the culture-based approach. The protocol followed was as outlined by the CDC. Group B streptococcal swabs were collected from all women from the distal vagina and anus between 35 and 37 weeks' gestation and cultured in selective media. Key local laboratories were contacted regarding group B streptococcal culturing techniques and the importance of reporting the results both to the office and to the CPMC labor and delivery unit. In addition, patients were educated regarding early-onset group B streptococcal infection and were given their culture results to bring to the hospital during labor as an additional backup to the laboratory system. The protocol was to treat all patients with a positive prenatal group B streptococcal culture result once they were admitted to the hospital. All patients admitted to the hospital with preterm labor were to be treated while cultures were pending. Likewise, term patients with fevers >38°C and patients with a previous affected infant were to receive antibiotics. The antibiotic regimen was unchanged from the previous study period. Mothers for whom group B streptococcal culture results were not available were managed according to the risk-based protocol.

An additional analysis was performed of the 15 mothers whose infants acquired early-onset group B streptococcal infections during the risk-based protocol period. Each chart was examined for the presence of risk factors as defined previously. Furthermore, the duration of antibiotic therapy before delivery was noted, and an assessment was made regarding whether it was likely that earlier treatment would have had an impact.

Early-onset group B streptococcal disease was defined as blood or cerebrospinal fluid culture positive for group B streptococci within the first 7 days after birth. A similar requirement for positive blood culture result was used for

Table I. Obstetric and demographic characteristics of study populations

	Baseline period (1992-1993)		*Risk-based period (1994-1996)*		*Culture-based period (1997-1998)*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Births						
Total	6829		13,270		9304	
<37 wk	704	10.3	1,289	9.7	951	10.2
Mothers delivered	6719		12,960		9078	
Race						
White	2964	44.1	7,102	54.8	5047	55.6
Asian	3053	45.4	5,108	40.6	3651	40.2
African American	450	6.7	536	4.1	318	3.5
Other	262	3.9	56	0.5	62	0.7
Parity						
0	3336	49.6	6,942	53.6	4843	53.3
>0	3383	50.4	6,018	46.4	4235	46.7
Age						
<20 y	169	2.5	197	1.5	120	1.3
20-35 y	5024	74.8	9,555	73.7	6563	72.3
>35 y	1526	22.7	3,208	24.8	2395	26.4
Prenatal care initiation ≤14 wk	6524	97.1	13,044	98.3	8978	96.5

the diagnosis of early-onset infection with organisms other than group B streptococci. *Early-onset pneumonia* was defined as clinical pneumonia with a positive aspirate culture result within the first 7 days after birth.

The major outcome measured was the rate of early-onset group B streptococcal disease. Additional neonatal end points were rates of early-onset infection with organisms other than group B streptococci, early-onset group B streptococcal pneumonia, and early-onset pneumonia not related to group B streptococci. In evaluation of the risk-based strategy we analyzed the proportion of mothers of infants with early-onset group B streptococcal infection who had recognizable risk factors and whether they had received sufficient antibiotic prophylaxis. In analysis of the culture-based strategy we examined the frequencies of maternal cultures being done and the results being available in the labor and delivery unit, the proportion of patients who either had a positive culture result or were preterm who received antibiotics, and the number of patients who had an unknown culture result who were appropriately treated on the basis of risk factors. Finally, we examined the rate of antibiotic use in the obstetric service during the period of culture-based screening.

Comparison of categoric variables (such as presence of sepsis) was done with χ^2 analysis. The Yates correction for continuity was used for all 2×2 contingency tables. The rate of early-onset infections was calculated for each treatment strategy and presented as the incidence per 1000 births. Statistical calculations were done with StatView Statistics Package (SAS Institute, Inc, Cary, NC). Odds ratios were not calculated because of the 0 rates for some periods.

Results

Demographic and obstetric characteristics of our hospital during the 7 years of the study are presented in Table I. The three study periods (baseline, risk-based protocol, and culture-based protocol) were 2, 3, and 2 years in duration and represented 6829, 13,270, and 9304 births, respectively. The rate of preterm births was high (approximately 10%), reflecting our tertiary referral center status. The racial composition was almost exclusively white and Asian American, with only a small minority of African Americans. This patient composition changed somewhat at the time of the hospital merger in 1993 (more whites and fewer African Americans) and reflects the patient compositions of the two hospitals. Also of note are the increasing rates of nulliparity and maternal age >35 years (26.4%). All these changes were significant ($P < .001$). However, they were clinically modest and occurred between the first and second periods only. There were no significant changes in these measures between the risk-based protocol (second) and the culture-based protocol (third) periods. The rates of initiation of prenatal care within the first 14 weeks of gestation were >95% and changed little during the study periods.

Fig 1 shows the numbers of early-onset group B streptococcal sepsis cases and the rates per 1000 births for each year studied. Of note is the year-to-year fluctuation in rate seen after the start of the risk-based protocol in 1994. The fall noted in 1995 was considered encouraging but did not reach statistical significance. This trend did not continue in 1996. No cases of early-onset group B streptococcal sepsis were noted in either year of the culture-based protocol beginning in 1997. Fig 2 combines all the data for each period and displays the statistical analy-

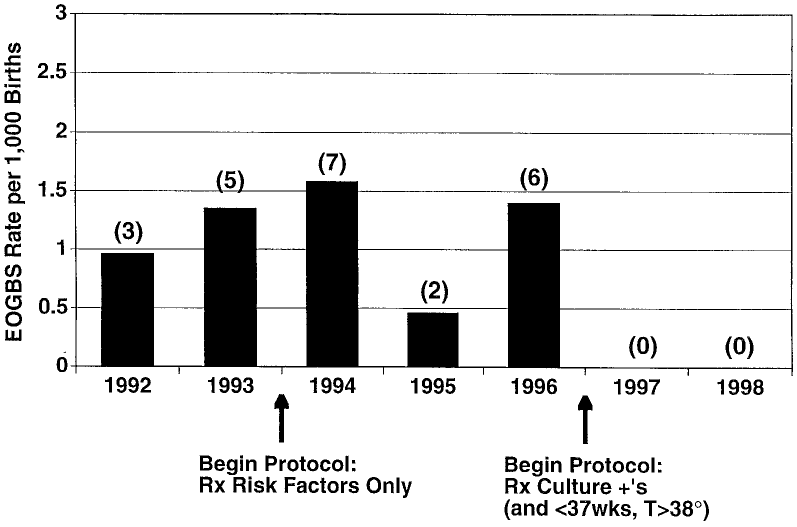

Fig 1. Rates *(bars)* and actual case numbers *(numbers in parentheses)* of early-onset group B streptococcal *(EOGBS)* invasive disease (sepsis and meningitis) displayed for each year. *Rx*, Prescribe according to; *plus signs*, positive results; *T*, temperature.

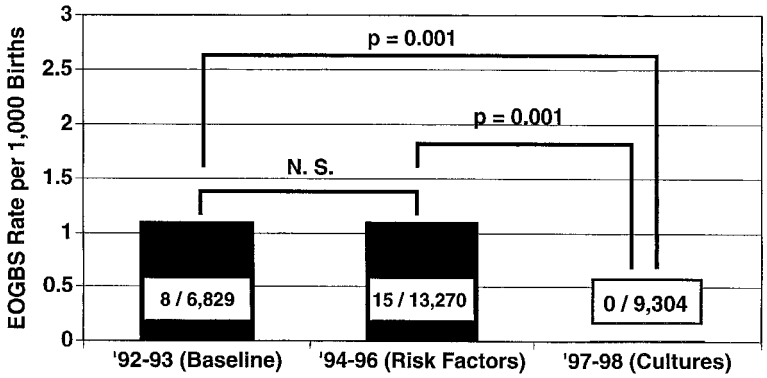

Fig 2. Rates *(bars)* and actual case numbers *(numbers in bars)* of early-onset group B streptococcal *(EOGBS)* invasive disease (sepsis and meningitis) displayed for each study period. *N.S.*, Not statistically significant.

sis comparing the periods. There was no difference between the rates in the baseline and risk-based protocol periods (both 1.1 cases / 1000 births). The rate during the culture-based protocol period (0 cases / 1000 births) was significantly better than both earlier periods (P = .001; χ^2 = 10.9).

Table II presents the outcomes of all serious early-onset infections in our neonatal population. In this table early-onset group B streptococcal sepsis and pneumonia were combined for analysis, as were early-onset sepsis and pneumonia caused by organisms other than group B streptococci. There was no evidence of any increase in infections caused by organisms other than group B streptococci during either of the CDC and ACOG protocol periods. In fact, a statistically nonsignificant downward trend in infections caused by organisms other than group B streptococci was seen (Fig 3). The overall rate of early-onset infection (caused by both group B streptococci and organisms other than group B streptococci) fell during the culture-based protocol period to 0.8 cases per 1000 births from the baseline rate of 3.2 cases per 1000 births and the risk-based protocol rate of 2.7 cases per 1000 births (P = .001).

The clinical characteristics of the 15 mothers whose infants acquired early-onset group B streptococcal infections during the risk-based protocol period are reviewed in Table III. Of note, 13 of the 15 (87%) were term pregnancies (≥37 weeks' gestation). In examining the term group for risk factors it was found that 6 of these 13 (46%) had no identifiable risk factors. We then assessed whether earlier antibiotics could have been helpful. One woman was delivered shortly after spiking a fever, 1 woman received no antibiotics because the prolonged

Table II. Rates of serious early-onset (<7 days after birth) infections among neonates during three study periods

Infection	*No.*	*Rate per 1000 births*
Baseline, 1992-1993 (n = 6829 births)		
Group B streptococcal early-onset sepsis	8	
Group B streptococcal early-onset pneumonia	3	
All early-onset group B streptococcal infections	11	1.6
Other early-onset sepsis	8	
Other early-onset pneumonia	3	
All other early-onset infections	11	1.6
All early-onset infections	22	3.2
Risk-based, 1994-1996 (n = 13,270 births)		
Group B streptococcal early-onset sepsis	15	
Group B streptococcal early-onset pneumonia	7	
All early-onset group B streptococcal infections	22	1.7
Other early-onset sepsis	4	
Other early-onset pneumonia	10	
All other early-onset infections	14	1.1
All early-onset infections	36	2.7
Culture-based, 1997-1998 (n = 9302 births)		
Group B streptococcal early-onset sepsis	0	
Group B streptococcal early-onset pneumonia	0	
All early-onset group B streptococcal infections	0	0.0*
Other early-onset sepsis	5	
Other early-onset pneumonia	2	
All other early-onset infections	7	0.8
All early-onset infections	7	0.8*

*P = .001 by χ^2 analysis for 1997 and 1998 versus other periods; all other comparisons not significant.

rupture of membranes was not recognized, and 3 women received <2 hours of antibiotic therapy because of fevers close to delivery. In addition it was considered that in 4 cases of "adequate" antibiotic prophylaxis (>4 hours) in the setting of prolonged rupture of membranes an earlier start of prophylaxis might have led to an improved outcome. Waiting until 18 hours after rupture of membranes in a woman with group B streptococcal colonization may allow ascension of the bacteria to the uterine cavity and fetus and may not allow sufficient time for antibiotics to be effective. In summary, among 15 cases of early-onset group B streptococcal disease, 6 showed no risk factors and at least 5, and perhaps 8, would have benefited from an earlier onset of antibiotic prophylaxis, such as would be offered by a culture-based program.

A culture-based protocol involves a different set of activities: performance of cultures, communication and recognition of results, and timely initiation of antibiotic prophylaxis. We reviewed 1000 consecutive parturients beginning in September 1998 to determine our progress in this area. The results are presented in Table IV. Among the 899 term patients 807 had culture results available at the labor and delivery unit (89.8%). Among those with culture results available 699 had negative results and 108 had positive results. This positivity rate of 13.4% is similar to the rate found in an earlier sample in 1992 at CPMC (13.1%) and to the rates reported in periodic CDC surveys of the San Francisco Bay Area (14%).[6, 7]

Table V describes the use of antibiotics during the culture-based protocol period according to chart review. Among 108 mothers with positive group B streptococcal results 102 (94.4%) received antibiotics during labor but 17 had <4 hours of treatment before delivery and 3 had <2 hours. The primary reason for both the six failures to treat and the three cases in which <2 hours of treatment was provided was precipitate labor, a factor that will limit any of the current approaches to this problem. The second largest indication for antibiotic prophylaxis during labor was preterm labor or preterm rupture of membranes. Among 101 preterm mothers 92 (91%) received antibiotics during labor. The reasons for not being treated included precipitate delivery in 2 cases and obstetrician judgment that antibiotics were not needed in 7 cases (2 patients with cesarean birth without labor or rupture of membranes and 5 patients who had known, recently negative group B streptococcal vaginal culture results and were at 35-37 weeks' gestation). Fever was treated aggressively with ampicillin and gentamicin during this period. Of note, fever or chorioamnionitis was present during labor in 51 of the 699 patients with negative group B streptococcal culture results (7.3%) and only 2 of the 108 mothers with positive group B streptococcal results (1.8%; P = .03).

Of interest are the outcomes among the 92 patients who had no culture results available at the labor and delivery unit and were therefore managed according to the risk-based protocol. Fifteen received antibiotics for fever or prolonged rupture of membranes (>18 hours). Six patients without a culture result and with >18 hours of rupture of membranes did not receive antibiotics, illustrat-

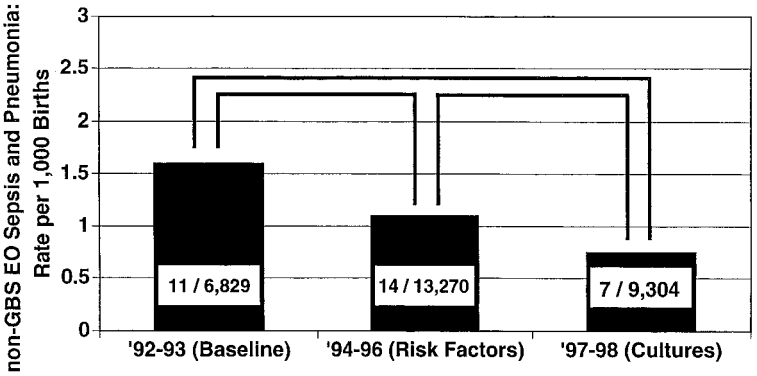

Fig 3. Rates *(bars)* and actual case numbers *(numbers in bars)* of early-onset serious severe infections caused by organisms other than group B streptococci *(non-GBS EO)* displayed for each study period. All comparisons were not statistically significant.

ing the problem of missing risk factors during labor. In contrast, 6 women with known negative group B streptococcal results and with rupture of membranes >24 hours were overtreated according to the culture-based protocol. A final 11 patients received ampicillin and gentamicin for cardiac prophylaxis. The total of mothers treated during labor was 26.3%.

Comment

The optimal approach to group B streptococcal chemoprophylaxis has not been established and indeed may vary from site to site according to the local frequency of early-onset group B streptococcal infection, frequencies of other early-onset bacterial infections, the organization of medical care, and the patient population.[3, 4] The obstetric staff were initially hesitant to embrace universal in-office group B streptococcal screening of all gravid women because of concerns regarding the complexity of obtaining the cultures and reliably getting the information to the labor and delivery unit in time to be available for clinical care. The secondary concern was that the large amount of antibiotics that would be used in our unit would increase the frequency of multi-drug–resistant bacteria. Therefore in 1994 we began the risk-based protocol for group B streptococcal prevention. This new protocol was preceded and followed by a rigorous program of education for the nursing and physician staffs. We followed outcomes closely each year. After 3 years and 13,270 births without a change in the early-onset group B streptococcal infection rate, we reevaluated our position. The pediatric staff were also dissatisfied with the risk-based approach because they had no culture results to help them evaluate babies whose mothers were treated because of risk factors. In 1996 the CDC published new protocols that called for vaginal and anal cultures at 35 to 37 weeks' gestation.[1, 3] This approach made more sense in our environment and was therefore embraced. After a new educational campaign for physicians, staff, and patients a culture-based protocol was initiated on January 1, 1997. Two years and 9304 births later, we have not had any cases of early-onset group B streptococcal infection. Ten cases would have been expected with this number of births according to rates in the baseline and risk-based protocol periods.

The experiences of others attempting to eliminate group B streptococcal disease have been mixed. Recently Lieu et al[8] from Northern California Kaiser Permanente looked at the risk-based protocol and found a modest reduction in early-onset group B streptococcal disease (not statistically significant). They also noted difficulties with protocol adherence. Factor et al[9] studied women at Jackson Memorial Medical Center in Miami during 1992 through 1995 and noted a highly significant fall in early-onset group B streptococcal rates (from 1.7 to 0.2 cases/1000 births) after implementation of a risk-based approach. This was a remarkable achievement, because barely 50% of women with risk factors actually received antibiotics. Locksmith et al,[10] also in Florida, compared the risk-based and culture-based protocols in a sequential manner. They could not find a difference in early-onset group B streptococcal infection rates but noted significantly fewer cases of chorioamnionitis with a culture-based approach. Hafner et al[11] in Vienna noted a modest decline with a risk-based approach but a much larger and significant benefit from a culture-based protocol. The Australian Neonatal Collaborative Study[12] noted a reduction in the national rate of early-onset group B streptococcal disease in reporting units from a baseline of 2.0 cases per 1000 births (1991-1993) to a level of 0.5 cases per 1000 births (1995-1997). They attributed most of this decline to the intrapartum use of antibiotics. However, a mix of culture-based and risk-based protocols similar to those of the CDC was used, and it was not possible to compare the two protocols.

Could the decline seen in this study and in the previously cited investigations be the result of a natural cyclic lull in

Table III. Analysis of risk factors for the 15 infants who contracted early-onset group B streptococcal sepsis during the 1994-1996 study period (treatment based on risk factors)

Gestational age (wk)	*Duration of membrane rupture (h)*	*Fever (temperature >38°C)*	*Risk factors present**	*Treatment*	*Likelihood of benefit of earlier treatment†*
Group A: No risk factors, no treatment					
39	12	No	No	None	Possible
38	4	No	No	None	Possible
39	8	No	No	None	Possible
40	3	No	No	None	Possible
38	8	No	No	None	Possible
38	2	No	No	None	Possible
Group B: Risk factors, inadequate treatment protocol					
27	3	Yes	Yes	Antibiotics <2 h	Strong
36	6	Yes	Yes	Antibiotics <2 h	Strong
38	27	No	Yes	None	Strong
41	16	Yes	Yes	Immediate delivery	Strong
42	8	Yes	Yes	Antibiotics <2 h	Strong
Group C: Risk factors, adequate treatment per protocol					
40	35	Yes	Yes	Antibiotics >4 h	Some
41	37	No	Yes	Antibiotics >4 h	Some
41	21	Yes	Yes	Antibiotics >4 h	Some
40	10	Yes	Yes	Antibiotics >4 h	Some

*Total with no risk factors, 6 of 15 overall and 6 of 13 at term.
†Total with strong likelihood, 5; total with some likelihood, 4.

Table IV. Group B streptococcal screening culture results: Review of 1000 consecutive parturients, September-November 1998 (during period of culture-based protocol)

Gestational age	*Culture results*	*No.*	*Comments*
Term (≥37 wk)	Negative	699	89.8% of patients at term had cultures done and results available at labor and delivery unit
	Positive	108	13.4% of patients at term with a result had a positive result
	Unknown	92	10.2% of term patients did not have results available at labor and delivery unit
Preterm (<37 wk)	—	101	10.1% of all infants were born at <37 wk
TOTAL	—	1000	

group B streptococcal activity? Group B streptococcal infection rates have been noted to demonstrate regional or even national fluctuations that remain unexplained.[13] Evidence against this hypothesis is that other bacterial infection rates fell concomitantly with group B streptococcal infection rates in our study and in the Australian study. This suggests that a general antibacterial agent (an antibiotic) was active. Furthermore, we have noted no change in the frequency of positive group B streptococcal genital tract carriage rates in our population during the last 6 years (13%-14%). The CDC has reported declines in early-onset group B streptococcal disease rates in some areas of the country (including the Bay Area) but no change in several others.[7] The areas with declining early-onset group B streptococcal disease rates are also areas with high intrapartum antibiotic use. In any case, there is a continued need to carefully follow local rates of early-onset group B streptococcal infection during the next years.

A major limitation with the risk-based approach is the low frequency of antecedent risk factors present among mothers of infants who go on to acquire early-onset group B streptococcal disease. In our study 46% of term infants with early-onset group B streptococcal infection had no maternal risk factors. Recent studies from the CDC[14] and Kaiser Permanente[8] substantiate this concern, with 46% and 40%, respectively, of mothers of infected infants lacking risk factors. McLaren et al[15] in Illinois reported an even higher rate of absence of risk factors at term (90%). An additional problem now being recognized is that waiting until a risk factor at term (such as 18-hour rupture of membranes or fever) becomes apparent may not leave enough time to adequately treat the fetus before birth. This was a problem in the Kaiser Permanente study,[8] and in our analysis 8 of 15 patients with risk-based treatment failures might have benefited from earlier antibiotic administration. Others have also noted that delayed decision for antibiotic prophylaxis could have played a role in early-onset group B streptococcal disease.[10] In our unit a decision to wait for 18 hours of rupture of membranes before starting antibiotics often led to missing the timeline by multiple hours (or in a few cases even altogether). The “cleanest” time for decision making regarding antibiotics is at admission. We have had high compliance with simple antibiotic treatment decisions made at that time (on the basis of preterm labor or rupture of membranes or of positive group B strepto-

Table V. Antibiotic use during labor: Review of 1000 consecutive parturients, September-November 1998 (during period of culture-based protocol)

Indication	*No.*	*Comments*
Positive result of group B streptococcal screening culture	102	102/108 (94.4%) patients with positive group B streptococcal culture result received antibiotics; 6 precipitate births; 17 patients had <4 h of treatment (only 3 <2 h)
Fever >38°C or chorioamnionitis (patients with negative group B streptococcal culture result)	51	51/699 (7.3%) patients with negative group B streptococcal culture results had fever or chorioamnionitis, vs 2/108 (1.8%) patients with positive group B streptococcal culture results (nearly all treated with antibiotics); $P = .03$
Preterm labor or preterm premature rupture of membranes	92	83/92 (91%) preterm patients received antibiotics; 9 preterm patients not treated because of precipitate delivery (n = 2), cesarean delivery without labor (n = 2), known recent negative group B streptococcal culture result and gestation >35 wk (n = 5)
Pending or unknown culture result with risk factor	15	7 patients with fever or chorioamnionitis; 8 with rupture of membranes >18 h (there were 6 with rupture of membranes >18 h not treated, contrary to protocol)
Overtreatment	6	Known negative group B streptococcal culture result, but treated for prolonged rupture of membranes (>24 h)
Cardiac prophylaxis	11	
TOTAL	263	26.3% of all parturients received antibiotics

coccal culture status) and much less satisfactory compliance with decisions made later on the basis of ongoing labor risks (prolonged rupture of membranes at term). Others have emphasized that group B streptococcal protocol compliance is a major problem and that compliance is directly related to the protocol's simplicity or lack thereof.[15, 16]

Another type of risk factor is the patient population. Whitney at al[17] and others have noted that African American women and women with no prenatal care have significantly higher attack rates and suggest that this be taken into account when outcomes are compared. Indeed, our hospital has very low numbers of African American patients, and <4% of patients have not received prenatal care during the first trimester. Although these patient characteristics may affect our group B streptococcal colonization rate and our early-onset group B streptococcal disease rate, they do not explain our improved outcomes with a culture-based protocol.

An additional advantage of treating mothers with positive group B streptococcal culture results during labor was the reduction in the rate of chorioamnionitis. We did note a significant decline in the rate of fever and chorioamnionitis in the group of women with positive group B streptococcal culture results who received chemoprophylaxis. This also suggests that many of the fever-inducing cervicovaginal bacteria in our patient population are sensitive to ampicillin.

In this study the total proportion of the population treated with antibiotics during labor was 26.3%. This number was driven upward by our high rate of preterm labor or rupture of membranes (10.1%), the high rate of treatment of women with positive group B streptococcal culture results (13%), and the inclusion of cardiac prophylaxis in the total. Even so the total is not dissimilar to that predicted by the decision analysis model of Rouse et al.[4] In an earlier study of our population in 1995 we found that a risk-based approach would yield a similar rate of antibiotic use if all patients with risk factors were treated: preterm, 9.5%; term with fever, 7%; term with >18 hours of rupture of membranes (and no fever), 8% (unpublished observations). In many of the risk-based protocols compliance with treatment is considerably lower because of overlooked risk factors, which partially accounts for the lower use of antibiotics. Have we seen any downside to the use of ampicillin in 25% of our parturients? In our facility we have not noted increased rates of infection from penicillin-resistant bacteria, nor have group B streptococci lost their sensitivity to penicillins. The cost of ampicillin or penicillin is quite low. Nursing familiarity with ampicillin is high, and the antibiotic is stocked premixed in our labor unit, which reduces the potential for drug errors. As with other aspects of group B streptococcal infection, the answer to this question will require continued scrutiny.

This study illustrates the strengths and weaknesses of our current strategies for control of early-onset group B streptococcal disease. In our private hospital with excellent prenatal care and an organized care system we were able to report a rate of early-onset group B streptococcal infection of 0 of 9304 births with a culture-based strategy. Others with different patient populations and care organizations might do better with a risk-based approach. However, in light of the complexities of the strategies, the low incidence of early-onset group B streptococcal disease, and the possible natural variation in group B streptococcal

virulence, the universal requirement of all group B streptococcal prevention programs is constant surveillance.

Addendum

Continued surveillance through 1999 with the culture-based protocol identified 1 case of early-onset group B streptococcal sepsis (in a preterm pregnancy in which ampicillin was stopped after a week) among 4793 births. The rate of early-onset group B streptococcal sepsis over the last 3 years is now 0.07 per 1000 (1/14,095).

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Editors' note: This manuscript was revised after these discussions were presented.

Discussion

DR WILLIAM H. CLEWELL, Phoenix, Arizona. Early-onset group B streptococcal disease has long been recognized as an important cause of neonatal morbidity and mortality. The importance of maternal genital tract colonization in this process has only been acknowledged for the past 20 yeas. In the mid-1970s, when we asked the microbiology laboratories to look for group B streptococci in maternal genital cultures, we were told that they were not pathogens in that site. Because 10% to 30% of pregnant women are colonized with this organism and for the most part have no symptoms, that statement was correct as far as it went. Such maternal colonization, however, is the usual precursor of early-onset group B streptococcal disease in the neonate.

Main and Slagle compared the two strategies proposed to prevent transmission of group B streptococcal infection to the baby. From January 1, 1994, to December 31, 1996, they followed the risk-based protocol, and from January 1, 1997, to December 31, 1998, they used the culture-based protocol. Previous publications had estimated that a risk-based protocol would result in 18.3% of women receiving antibiotics during labor and a 68.3% reduction in early-onset group B streptococcal disease. In this study the risk-based protocol resulted in 24% of the patients being candidates for antibiotics during labor but no reduction in the incidence of early onset group B streptococcal disease. Among the 15 infected babies 6 had no risk factors identified and 8 had prolonged rupture of membranes (>18 hours), fever, or both. Main and Slagle speculated that in these latter cases earlier use of antibiotics might have prevented neonatal infection.

I was somewhat surprised that there were no cases of early-onset group B streptococcal infection during the culture-based protocol period. Cultures are estimated to have a false-negative rate of 5%. With a prevalence of maternal colonization of 13% one would expect about 60 undiagnosed carriers in a population of 9000 women. The estimated transmission rate among low-risk patients is 0.5%; among high-risk patients the rate is 4%. One would thus expect between 0.3 and 2.4 cases among 9000 births. This is probably not statistically different from their observation of no cases.

It is clear from Main and Slagle's article that in their institution the culture-based protocol was far superior to the risk-based protocol. Although the culture-based approach may not work as well in all practice situations, the

failures during their risk-based protocol experience illustrate the weakness of that approach and have implications for all institutions. It would seem that the best approach to this problem would be to implement the culture-based protocol and to use the risk-based protocol for those situations in which a culture result is not available and for patients with no prenatal care. This strategy could be applied in virtually any clinical situation.

Dr Main, in this era of cost containment and managed care we must at least ask how much the culture-based protocol costs compared with the risk-based protocol. I suspect that this cost is much more than offset by the reduction in neonatal costs associated with early onset group B streptococcal disease. Could you comment?

Dr R. Glen F. Steinke, Fresno, California. I have three questions. It is interesting to note the same amount of antibiotic use in the culture-based group as in the risk-based group despite significant differences between the two groups in fetal group B streptococcal infection. How can you account for this difference? Twenty-six percent of your patients were receiving antibiotics. According to my calculations 750 to 1000 patients per year in your institution receive antibiotics. What is the incidence of antibiotic reactions, including anaphylactic rashes? How would you change the CDC protocols if given the opportunity?

Dr Patricia A. Robertson, San Francisco, California. I have a contrasting experience with a culture-based protocol in the community-based hospitals that I visit in northern California. One of my jobs as a perinatologist is to attend morbidity and mortality conferences at these outreach hospitals. At least six times per year, there has been a case of group B streptococcal sepsis in the nursery in a hospital that uses culture-based protocols, often as a result of a false-negative group B streptococcal culture result from the mother a few weeks before or because of confusion of communication between the office and the hospital about the culture results. At the University of California–San Francisco we have used a risk-based protocol for the past 3 years, with no cases of neonatal group B streptococcal sepsis. It is interesting that for 8 of the 9 infants who did acquire the disease at Main and Slagle's hospital during the risk-based protocol period there were risk factors that were not treated, such as >18 hours of ruptured membranes. It could be that in a tertiary care hospital with an active maternal-fetal medicine service with clear directives to physicians there is a different population than in the hospitals that more frequently deliver community-based patients. Can you apply your findings to community-based hospitals?

Dr James C. Caillouette, Pasadena, California. Dr Main, you stated that logic would tell us that antibiotics are not needed by patients with a positive culture and unruptured membranes undergoing cesarean delivery. Dr Kurt Benirschke, an honorary member of this Society, has written a book entitled *Pathology of the Human Placenta*. In his chapter on chorioamnionitis he makes it clear and has substantiated that bacteria can ascend the cervical canal and pass through the intact membranes to create chorioamnionitis. I am having trouble understanding your logic in light of Dr Benirschke's data.

Dr Main (Closing). With respect to costs we did not do a formal cost analysis of the obstetric portion of the care. However, our study's parameters (rates of antibiotic use and the rates of positivity) fit well within those that Rouse et al[1] used in a cost-benefit analysis of some 19 different protocols for group B streptococcal prophylaxis. The culture-based approach was one of the most cost-effective. Having said that, though, the real costs are hidden in the neonatal care, not in the obstetric care. Indeed, that is a study that I am doing with Dr Slagle, my neonatal counterpart. We will be looking at the neonatal length of stay in detail, because that is the cost driver. Concern regarding neonatal length of stay was indeed one of the reasons that we changed protocols 2½ years ago, moving to the culture-based approach. Pediatricians were continually keeping babies in the nursery who had risk factors and whose mothers had been treated prophylactically because they did not know the maternal group B streptococcal culture status. It was difficult to send those babies home in a timely manner. Because the pediatricians now know the group B streptococcal culture status, they are much more ready and able to send the babies home with their mothers at 36 or 48 hours after birth.

Dr Steinke asked about the incidences of rashes and other adverse effects. We have not had any cases of anaphylactic reaction. Because most patients only receive one to three doses of ampicillin during labor, we have not had significant rashes during labor. Those would appear during the next day or two, but that has not been a significant issue. We did choose ampicillin rather than penicillin because of a number of reactions, particularly local irritation, that people have had to penicillin during labor. Our nursing staff are more familiar with ampicillin, and it is particularly easy to administer. They just hang the premixed bag that is available in our unit and it is done.

Dr Steinke also asked why we got such different results when about the same percentages of women received antibiotics during each protocol period. This I believe is a key to the group B streptococcal prophylaxis controversy. When treating risk factors 80% or more of women treated will not be group B streptococcal carriers and therefore will be overtreated. We are treating the wrong women. If we want to reduce group B streptococcal transmission, it only makes sense to concentrate our efforts on women who are group B streptococcal carriers.

How would I change CDC protocols? In the risk-based protocol I might begin treatment at 12 hours of rupture of membranes, rather than 18 hours, but that would significantly increase the number of women treated. I do think that for now the culture-based approach is better, provided that you have a system in place to make it work. I think it is important that we should all view the group B streptococcal protocols as a holding process until we have a better solution, such as vaccination.

Dr Robertson asked about other community-based hospitals and their experiences. We have worked with several other community-based hospitals that have culture-based group B streptococcal protocols, and these protocols have been successful as long as there is leadership and recognition by the staff of the need to follow the pro-

tocol. I think that the process that we went through, first going through the risk-based approach and identifying the issues and drawbacks to the risk-based approach in our own population, allowed us to transition to the culture-based approach with good acceptance and good compliance by both the physician and nursing staffs. As I said earlier, the nursing staff drive the process by making certain that the culture results are there when the patient comes to the labor and delivery unit. They will call the laboratory, call the office, whatever it takes. Indeed, they are as attentive to group B streptococcal status in our unit as they are to blood type and Rh factor. That is critical to make the process work; you cannot just put a protocol out there and say, "Well, treat some; just read the protocol." Second, you have to have a clear and simple protocol. I think that simplicity of the protocol is critical. You cannot have an algorithm that has too many branch points. At each branch the chance of successfully following the protocol falls dramatically. I think the culture approach is better because it is simple. If a woman has a positive culture result, if she has a fever, if she is preterm, she gets treated, and those are about all the decisions you have to make. Most of those are clear-cut and can be decided on arrival at the labor and delivery unit. You want to minimize decisions that need to be made as care evolves during labor. If something is unfolding during the labor process, there are many more opportunities to miss a risk factor, such as overlooking whether it has been 18 hours since rupture of membranes.

Finally, with respect to treatment of risk factors during the risk factor protocol period, all but one of the mothers whose infants acquired group B streptococcal infections and had risk factors received antibiotics. The 8 cases that we described represent what I considered to be opportunities to prevent group B streptococcal transmission if the antibiotics had been administered earlier (which could have happened if the culture status had been known), rather than waiting for the risk factor to blossom (fever, 18-hour rupture of membranes) and then hurrying to try to treat before delivery.

Dr Caillouette, I certainly would not want to be in opposition to Dr Benirschke. What I was referring to were a few cases in which a cesarean delivery was done for breech presentation or previous cesarean in early labor or with no labor before 37 weeks' gestation. Is it better to wait 3 to 4 hours to give antibiotics or to perform the cesarean delivery immediately? That issue is unresolved. Also unresolved is the treatment of women at 35 to 37 weeks' gestation with a recent negative culture result. Do they still need prophylaxis because they are at <37 weeks' gestation? We do not have data to guide us in these areas.

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