

CHANGES IN PATHOGENS CAUSING EARLY-ONSET SEPSIS IN VERY-LOW-BIRTH-WEIGHT INFANTS

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ABSTRACT

Background It is uncertain whether the rates and causes of early-onset sepsis (that occurring within 72 hours after birth) among very-low-birth-weight infants have changed in recent years, since antibiotics have begun to be used more widely during labor and delivery.

Methods We studied 5447 very-low-birth-weight infants (those weighing between 401 and 1500 g) born at centers of the Neonatal Research Network of the National Institute of Child Health and Human Development between 1998 and 2000 who had at least one blood culture in the first three days of life and compared them with 7606 very-low-birth-weight infants born at centers in the network between 1991 and 1993.

Results Early-onset sepsis (as confirmed by positive blood cultures) was present in 84 infants in the more recent birth cohort (1.5 percent). As compared with the earlier birth cohort, there was a marked reduction in group B streptococcal sepsis (from 5.9 to 1.7 per 1000 live births of infants weighing 401 to 1500 g, $P < 0.001$) and an increase in *Escherichia coli* sepsis (from 3.2 to 6.8 per 1000 live births, $P = 0.004$); the overall rate of early-onset sepsis was not significantly changed. Most *E. coli* isolates from the recent birth cohort (85 percent) were resistant to ampicillin, and mothers of infants with ampicillin-resistant *E. coli* infections were more likely to have received intrapartum ampicillin than were those with ampicillin-sensitive strains (26 of 28 with sensitivity data vs. 1 of 5, $P = 0.01$). Infants with early-onset sepsis were more likely to die than uninfected infants (37 percent vs. 13 percent, $P < 0.001$), especially if they were infected with gram-negative organisms.

Conclusions Early-onset sepsis remains an uncommon but potentially lethal problem among very-low-birth-weight infants. The change in pathogens over time from predominantly gram-positive to predominantly gram-negative requires confirmation by ongoing surveillance. (N Engl J Med 2002;347:240-7.)

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EARLY-ONSET sepsis is an important cause of illness and death among infants with very low birth weights (less than 1500 g).¹⁻⁵ Antibiotics are used increasingly during labor to decrease the risk of neonatal group B streptococcal infection and to reduce the risk of neonatal illness after preterm rupture of the membranes.⁶⁻¹² However, there is concern that increased use of antibiotics might result in a change in the spectrum of organisms, their susceptibility to antibiotics, or both.¹³⁻¹⁶ We conducted a study to assess the rates and sequelae of early-onset sepsis, the types of pathogens involved, and their possible association with maternal antibiotic use in a large cohort of very-low-birth-weight neonates born between 1998 and 2000. We also compared the distribution of pathogens with that documented among very-low-birth-weight infants in an earlier birth cohort (1991 to 1993).¹

METHODS

Population Data Base

We studied infants who were born at the 15 neonatal centers that belong to the Neonatal Research Network of the National Institute of Child Health and Human Development (NICHD). The network maintains a registry of all very-low-birth-weight infants (those weighing between 401 and 1500 g) who are born or cared

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for at participating centers.¹⁷ Information on infants weighing between 401 and 500 g began to be included in the data base in 1993.¹ Trained research nurses collect data on mothers at the time of delivery and on infants from birth to 120 days, hospital discharge, or death, whichever comes first. The registry includes information on early-onset sepsis as documented by positive blood cultures, the type of infecting organism, the mother's age and marital status, any complications of the pregnancy, characteristics of the labor and delivery, characteristics of the infant, other medical conditions in the infant, and the infant's final status. In September 1998, surveillance for infection was expanded to include information on maternal antibiotic use during the hospitalization for delivery, the dates and results of all blood and cerebrospinal fluid cultures in the infant, C-reactive protein levels, any indwelling lines, use of antibiotics in the newborn, and the susceptibility patterns of the pathogens causing cases of early-onset sepsis. During the hospitalization for delivery, all antibiotic use in the mother within seven days before delivery was recorded. We have no information on the use of antibiotics by the mother before admission.

Outcomes

Early-onset sepsis was defined by a positive culture of blood drawn within 72 hours after birth. Cultures that were positive for organisms that are generally considered to be contaminants — including corynebacterium, propionibacterium, and diphtheroids — were excluded from analysis. Cultures that tested positive for coagulase-negative staphylococci were reviewed to distinguish definite or possible coagulase-negative staphylococcal infections from the effects of contaminants. Definite infection was defined by two positive cultures of blood specimens drawn within two days of each other or one positive culture and a blood C-reactive protein level greater than 1 mg per deciliter¹⁸ within two days after the blood culture; possible infection was defined by one positive culture and treatment for at least five days with vancomycin, oxacillin, a semisynthetic antistaphylococcal agent, or another drug to which the organism was susceptible. Contamination was considered probable if there was one positive culture without an elevated C-reactive protein level or antibiotic therapy as outlined above. Infants with definite or possible coagulase-negative staphylococcal sepsis were included in the analysis. For all other pathogens, sepsis was defined by the presence of the organism in cultured blood. To identify possible changes in the distribution of pathogens over time, we compared the pathogen-specific infection rates among infants enrolled in the very-low-birth-weight registry of the NICHD Neonatal Research Network between 1991 and 1993¹ with those in the recent birth cohort.

Gestational age was either determined by obstetrical methods including dating from the last menstrual period and the use of prenatal ultrasonography or estimated by a neonatologist on the basis of physical and neurologic criteria. Intraventricular hemorrhage was graded according to the method of Papile et al.¹⁹ Necrotizing enterocolitis was classified according to the system of Bell et al.²⁰ For this analysis, respiratory distress syndrome was defined by the following: the need for supplementary oxygen at 6 to 24 hours of life; clinical features of respiratory distress (including grunting, nasal flaring, and chest retractions) within the first 24 hours; the need for respiratory support (continuous positive airway pressure or ventilation) during the first 24 hours; and an abnormal chest radiograph within the first 24 hours. Chronic lung disease or bronchopulmonary dysplasia was defined by the need for supplementary oxygen at 36 weeks of postmenstrual age. The study was approved by the institutional review board at each study site, and informed-consent procedures were followed as required at each site.

Statistical Analysis

Early-onset sepsis was treated as a binary variable. We assessed associations between early-onset sepsis and maternal and neonatal variables, characteristics of the hospital course, and death. Chi-

TABLE 1. CHARACTERISTICS OF THE INFANTS BORN BETWEEN 1991 AND 1993 AND BETWEEN 1998 AND 2000.*

CHARACTERISTIC	1991–1993	1998–2000
	(N=7606)	(N=5447)
	no. (%)	
Race or ethnic group†		
Non-Hispanic black	3940 (52)	2273 (42)
Non-Hispanic white	2576 (34)	2188 (40)
Hispanic	887 (12)	803 (15)
Other	197 (3)	165 (3)
Sex		
Female	3813 (50)	2753 (51)
Male	3793 (50)	2694 (49)
Gestational age		
<25 wk	905 (12)	670 (12)
25–28 wk	3354 (44)	2383 (44)
≥29 wk	3347 (44)	2394 (44)
Birth weight		
401–500 g‡	24 (<1)	121 (2)
501–750 g	1445 (19)	1040 (19)
751–1000 g	1769 (23)	1306 (24)
1001–1250 g	2052 (27)	1380 (25)
1251–1500 g	2316 (30)	1600 (29)

*Differences between the birth cohorts were significant for race or ethnic group (P<0.001) and birth weight (P=0.001).

†Data were missing on race for 6 infants born between 1991 and 1993 and 18 infants born between 1998 and 2000.

‡Information on infants weighing 401 to 500 g began to be included in the data base in 1993.

square tests or Fisher's exact tests were used to compare the rates of early-onset sepsis among centers, to evaluate changes between the two birth cohorts, and to assess the relations between maternal ampicillin use and *Escherichia coli* sepsis and between the type of pathogen and the risk of death. Logistic-regression models were used to assess associations between early-onset sepsis and maternal variables, neonatal characteristics, complications, and the risk of death. Linear regression models were used to compare infants with and without early-onset sepsis in terms of the duration of umbilical catheter use, mechanical ventilation, and the hospital stay. Gestational age was included as a variable in all models.

Infants from both single and multiple gestations were included. Because of the possible correlation of findings between twins or among higher-order multiples, the association between maternal variables and early-onset sepsis was explored in two ways by logistic regression. First, a model was used in which all observations among infants were assumed to be independent. Next, infants were clustered according to the mother in models that used the generalized-estimating-equation method to account for the correlation between siblings. Robust estimators of variance were used, with the working correlation structure first specified as independent and in the second model as exchangeable. Analysis of clustered data was performed with the software package SUDAAN.²¹ All other analyses were completed with SAS software.²²

RESULTS

Rates of Early-Onset Sepsis

Between September 1, 1998, and August 31, 2000, 6204 very-low-birth-weight neonates were born at network centers; 757 of these infants (12 percent) did not have an early blood culture performed and were

excluded. Over half (51 percent) of the neonates without blood cultures had extremely low birth weights (401 to 750 g) and received no or limited care. We studied the 5447 infants who had one or more blood cultures during the first three days of life. Eighty-four infants had early-onset sepsis — a rate of 15.4 per 1000 live births of infants weighing 401 to 1500 g. The incidence of early-onset sepsis in a given center ranged from 4 to 27 per 1000 live births (differences were not significant). On the basis of the findings in an earlier published study involving network centers,¹ we determined that there was a nonsignificant decline in the rate of early-onset sepsis between 1991 to 1993 and 1998 to 2000 (from 19.3 per 1000 very-low-birth-weight infants to 15.4 per 1000 very-low-birth-weight infants). Fewer infants in the earlier cohort (255 of 7861 [3 percent]) were excluded from the analysis because they had not been evaluated for early sepsis.¹ Demographic characteristics of the infants in the two cohorts are presented in Table 1.

Distribution of Pathogens

The majority of early-onset infections in the recent cohort (60.7 percent) were caused by gram-negative organisms (Table 2). *E. coli* was the single most common pathogen (accounting for 44.0 percent of all infections). Gram-positive pathogens accounted for 36.9 percent of infections. Fungal infections were rare.

The distribution of organisms causing early-onset sepsis among infants receiving care between 1991 and 1993¹ and in the recent cohort is shown in Table 3. Whereas gram-positive organisms were responsible for the majority of infections between 1991 and 1993,¹ gram-negative organisms were the most frequent cause of early-onset sepsis between 1998 and 2000. From the first birth period to the second, the rate of infections with group B streptococci declined from 5.9 to 1.7 per 1000 live births of infants weighing 401 to 1500 g ($P < 0.001$), whereas the rate of *E. coli* infections increased from 3.2 to 6.8 per 1000 live births of such infants ($P = 0.004$). The gestational age at birth was similar in the two periods, but there were more infants with birth weights between 401 and 500 g during the later period (0.3 percent vs. 2.2 percent, $P < 0.001$). However, almost all cases of early-onset sepsis (98 percent) occurred in infants with birth weights over 500 g, and there were no infections with either *E. coli* or group B streptococci in infants weighing less than 500 g. We could not compare the rates of sepsis with coagulase-negative staphylococci in the two cohorts, because different definitions of true infection were used in the two periods.

Sensitivity to Antibiotics

Information on sensitivity to antibiotics was available for 33 of the 37 isolates of *E. coli* from infants in

TABLE 2. DISTRIBUTION OF PATHOGENS AMONG 84 CASES OF EARLY-ONSET SEPSIS OCCURRING IN 5447 INFANTS BORN BETWEEN SEPTEMBER 1, 1998, AND AUGUST 31, 2000.*

ORGANISM	No. WITH SEPSIS (%)
Gram-negative organisms	51 (60.7)
<i>Escherichia coli</i>	37 (44.0)
<i>Haemophilus influenzae</i>	7 (8.3)
Citrobacter	2 (2.4)
Other†	5 (6.0)
Gram-positive organisms	31 (36.9)
Group B streptococcus	9 (10.7)
Viridans streptococcus	3 (3.6)
Other streptococci‡	4 (4.8)
<i>Listeria monocytogenes</i>	2 (2.4)
Coagulase-negative staphylococcus§	9 (10.7)
Other¶	4 (4.8)
Fungi	2 (2.4)
<i>Candida albicans</i>	2 (2.4)
Total	84 (100)

*Seven of the 84 infants had two positive blood cultures for the same organism.

†Other gram-negative organisms included klebsiella (in one infant), bacteroides (in two infants), *Eikenella corrodens* (in one infant), and *Stenotrophomonas maltophilia* (in one infant).

‡Other streptococci included group A streptococcus (in one infant) and three cases in which the species was unknown.

§Of 18 positive blood cultures for coagulase-negative staphylococci, 1 met the criteria for definite infection and 8 for possible infection; in the other 9 cases, the organism was considered to be a contaminant (see the Methods section).

¶Other gram-positive organisms included *Staphylococcus aureus* (in one infant), bacillus (in two infants), and peptostreptococcus (in one infant).

the recent birth cohort: 28 of the 33 isolates (85 percent) were resistant to ampicillin and 1 of the 33 (3 percent) was resistant to gentamicin. All 26 *E. coli* isolates tested for sensitivity to selected third-generation cephalosporins were sensitive to these agents. Although the numbers were small, the mothers of infants with ampicillin-resistant strains of *E. coli* were significantly more likely to have received intrapartum ampicillin than were those with ampicillin-sensitive strains (26 of 28 [93 percent] vs. 1 of 5 [20 percent], $P = 0.01$). Sensitivity data were not collected between 1991 and 1993, so it is not possible to compare the two cohorts.

Maternal Antibiotic Use

Twenty percent of the infants born in 1998 to 2000 were the products of multiple gestations, and a total of 4887 mothers were included in the analysis. A total of 65 percent of these women (3186 of 4887) received antibiotics during the hospitalization for delivery; 26 percent of these received only one dose of antibiotics, and 74 percent received two or more doses. Mothers who did not receive antibiotics were significantly more

TABLE 3. RATES OF EARLY-ONSET SEPSIS AND ASSOCIATED PATHOGENS IN 1991–1993 AND 1998–2000.*

EARLY-ONSET SEPSIS	1991–1993		1998–2000	
	NO. INFECTED/ TOTAL NO.	RATE/ 1000 LIVE-BORN VLBW INFANTS	NO. INFECTED/ TOTAL NO.	RATE/ 1000 LIVE-BORN VLBW INFANTS
Any	147/7606	19.3	84/5447	15.4
Gram-positive	83/7606	10.9	31/5447	5.7†
Group B streptococci	45/7606	5.9	9/5447	1.7‡
Gram-negative	63/7606	8.3	51/5447	9.4
<i>Escherichia coli</i>	24/7606	3.2	37/5447	6.8§
Fungus	1/7606	0.1	2/5447	0.4

*Data from the period from 1991 to 1993 are from Stoll et al.¹ P=0.007 for the change in the distribution of pathogens between the two periods; there was no significant change in the overall rate of sepsis. Very-low-birth-weight (VLBW) infants are defined as infants weighing between 401 and 1500 g. When the three centers that were not included in the earlier birth cohort are excluded from the analysis, the rates of group B streptococci and *E. coli* in the recent birth cohort are 2.1 per 1000 live-born very-low-birth-weight infants and 7.3 per 1000 live-born very-low-birth-weight infants, respectively, and the changes remain significant (P=0.003).

†P=0.002 for the comparison with the earlier period.

‡P<0.001 for the comparison with the earlier period.

§P=0.004 for the comparison with the earlier period.

likely to have delivered within two hours after hospital admission than were those who received antibiotics (25 percent vs. 4 percent, P<0.001).

During the 72 hours before delivery, 63 percent of mothers received antibiotics; 41 percent of these women were treated less than 6 hours before delivery, 24 percent were treated 6 to 24 hours before delivery, 15 percent were treated 25 to 48 hours before delivery, and 20 percent were treated more than 48 hours before delivery. The most frequently prescribed antibiotics were ampicillin (given to 49 percent of mothers), penicillin (14 percent), and erythromycin (13 percent). Most mothers (68 percent) received only one antibiotic, 25 percent received two antibiotics, and 7 percent received three to five antibiotics during the 72 hours before delivery. There were no significant differences in the rates of early-onset sepsis between infants whose mothers received antibiotics during their hospitalization or during the 72 hours before delivery and those whose mothers did not receive antibiotics (Table 4). No association was found between any maternal antibiotic use during the hospitalization for delivery and either the risk of *E. coli* or group B streptococcal sepsis or the risk of death due to either of these infections (data not shown). The proportion of infants with *E. coli* sepsis was higher among those whose mothers received ampicillin within 72 hours before delivery than among those whose mothers did not (25 of 2348 [1.1 percent] vs. 12 of 3099 [0.4 percent], unadjusted P=0.004). However, the

difference was not significant after the analysis was adjusted for gestational age and the interval between membrane rupture and delivery.

Base-Line Characteristics of the Mothers and Infants

Selected characteristics of the mothers and the infants are summarized in Table 4. A longer interval between the rupture of the membranes and delivery was a strong risk factor for early-onset sepsis. However, 41 percent of infected infants were born within six hours after membrane rupture. Mothers with a longer interval between membrane rupture and delivery were more likely to have received antibiotics, but the association between this interval and the risk of early-onset sepsis did not differ between women who received antibiotics and those who did not (data not shown).

Gestational age and birth weight were inversely associated with the risk of early-onset sepsis, but the presence of intrauterine growth restriction was associated with a reduced risk. The race and sex of the infant were not associated with the risk of early-onset sepsis (Table 4).

Neonatal Morbidity and Mortality

After adjustment for gestational age, infants with early-onset sepsis had a significantly higher risk of respiratory distress syndrome (63 percent vs. 43 percent; odds ratio, 1.8 [95 percent confidence interval, 1.1 to 2.9]; P=0.02), severe intraventricular hemorrhage or periventricular leukomalacia (32 percent vs. 12 per-

TABLE 4. CHARACTERISTICS OF THE MOTHERS AND INFANTS AND THE RISK OF EARLY-ONSET SEPSIS AMONG INFANTS IN THE 1998–2000 BIRTH COHORT.*

CHARACTERISTIC	TOTAL No.	INFANTS WITH EARLY-ONSET SEPSIS no. (%)	ADJUSTED ODDS RATIO FOR EARLY-ONSET SEPSIS (95% CI)	P VALUE
Maternal				
Interval between rupture of membranes and delivery†				<0.001
>48 hr	1106	38 (3.4)	3.4 (2.1–5.6)	
25–48 hr	212	5 (2.4)	2.3 (0.9–6.0)	
6–24 hr	539	5 (0.9)	1.0 (0.4–2.6)	
<6 hr‡	3502	33 (0.9)	1.0	
Maternal antibiotic use				
Any time during hospitalization for delivery				
Yes	3554	63 (1.8)	1.1 (0.6–1.8)	
No‡	1893	21 (1.1)	1.0	
Within 72 hr before delivery				
Yes	3399	58 (1.7)	1.0 (0.6–1.6)	
No‡	2048	26 (1.3)	1.0	
Infant				
Race or ethnic group§				
Non-Hispanic black	2273	33 (1.5)	0.8 (0.5–1.2)	
Hispanic	803	11 (1.4)	0.7 (0.4–1.4)	
Other	165	1 (0.6)	0.4 (0.1–2.6)	
Non-Hispanic white‡	2188	39 (1.8)	1.0	
Sex				
Female	2753	41 (1.5)	0.9 (0.6–1.4)	
Male‡	2694	43 (1.6)	1.0	
Gestational age				<0.001
<25 wk	670	16 (2.4)	2.1 (1.1–4.1)	
25–28 wk	2383	48 (2.0)	1.8 (1.1–3.1)	
≥29 wk‡	2394	20 (0.8)	1.0	
Birth weight				0.05
401–500 g	121	2 (1.7)	1.0 (0.2–5.3)	
501–750 g	1040	23 (2.2)	1.4 (0.6–3.5)	
751–1000 g	1306	25 (1.9)	1.4 (0.6–3.2)	
1001–1250 g	1380	21 (1.5)	1.4 (0.7–3.0)	
1251–1500 g‡	1600	13 (0.8)	1.0	
Intrauterine growth restriction				0.02
Yes	1179	4 (0.3)	0.2 (0.1–0.7)	
No‡	4268	80 (1.9)	1.0	

*Odds ratios for maternal characteristics were adjusted for gestational age, timing of rupture of membranes, and maternal antibiotic use. Odds ratios for characteristics of the infant were adjusted for gestational age, the presence or absence of intrauterine growth restriction, birth weight, race or ethnic group, and sex. Gestational age and birth weight were included in models as categorical variables for estimating odds ratios and as continuous variables for determining P values. If infants weighing 401 to 500 g are excluded, P=0.07 for the effect of birth weight. There were no significant associations between early-onset sepsis and maternal age, marital status, prenatal care, hypertension or preeclampsia, delivery with or without labor, type of delivery, or antenatal steroid use (data not shown). Results were similar when analyses were repeated with the possible correlation between siblings in cases of multiple births taken into account (data not shown). CI denotes confidence interval.

†Data were missing for 88 infants, including 3 with early-onset sepsis.

‡Infants in this category served as the reference group.

§Data were missing for 18 infants.

cent; odds ratio, 3.2 [95 percent confidence interval, 1.9 to 5.5]; P<0.001), and bronchopulmonary dysplasia (62 percent vs. 35 percent; odds ratio, 2.4 [95 percent confidence interval, 1.2 to 4.7]; P=0.01). Although the proportion of infants with these conditions was higher among infants infected with gram-

negative organisms than those infected with gram-positive organisms, the differences were not significant (data not shown). There were no significant differences in the duration of use of an umbilical catheter, the duration of mechanical ventilation, or the length of the hospital stay between infants with early-onset sepsis

TABLE 5. RISK OF DEATH ASSOCIATED WITH EARLY-ONSET SEPSIS.*

VARIABLE	DEATHS		ODDS RATIO FOR DEATH (95% CI)	P VALUE
	no./total no.	%		
Death				
Early-onset sepsis	31/84	37	3.5 (2.1–5.7)	<0.001
No early-onset sepsis	703/5363	13	1.0	
Gram-negative sepsis	21/51	41	2.0 (0.8–5.4)	
Gram-positive sepsis	8/31	26	1.0	
Death ≤12 hr after birth				
Early-onset sepsis	9/84	11	7.0 (3.2–15.2)	<0.001
No early-onset sepsis	76/5363	1	1.0	
Gram-negative sepsis	9/51	18	—	0.01
Gram-positive sepsis	0/31			
Death ≤72 hr after birth				
Early-onset sepsis	17/84	20	4.6 (2.5–8.4)	<0.001
No early-onset sepsis	247/5363	5	1.0	
Gram-negative sepsis	15/51	29	12.5 (1.6–100.2)	0.004
Gram-positive sepsis	1/31	3	1.0	
Death >72 hr after birth				
Early-onset sepsis	14/84	17	1.6 (0.9–3.0)	
No early-onset sepsis	456/5363	9	1.0	
Gram-negative sepsis	6/51	12	0.5 (0.1–1.5)	
Gram-positive sepsis	7/31	23	1.0	

*The odds ratio for early-onset sepsis as compared with no early-onset sepsis was adjusted for gestational age, and the odds ratio for gram-negative sepsis as compared with gram-positive sepsis is unadjusted. The odds ratio for death within 12 hours in infants with gram-negative sepsis as compared with those with gram-positive sepsis cannot be calculated because there were no deaths among infants with gram-positive sepsis. CI denotes confidence interval.

who survived to 120 days or to discharge and those without early-onset sepsis who survived that long (data not shown). Among all infants and among those who survived to 120 days or to discharge, a history of early-onset sepsis was not associated with an increased risk of late-onset sepsis or necrotizing enterocolitis (data not shown).

During follow-up to 120 days, 734 of the 5447 infants (13 percent) died. Death was more common among infants with a lower birth weight and a lower gestational age (data not shown). Infants with early-onset sepsis were significantly more likely to die within 120 days, and in particular to die within 3 days after birth, than were those without early-onset sepsis (Table 5). These differences persisted even after adjustment for gestational age. The proportion of infants who died was higher among those infected with gram-negative organisms (21 of 51 [41 percent]) than among those infected with gram-positive organisms (8 of 31 [26 percent]), but the difference was not significant. Infants with gram-negative sepsis were more likely than infants infected with other agents to die within three days after birth (15 of 51 [29 percent] vs. 2 of 33 [6 percent], $P=0.01$).

DISCUSSION

Early-onset sepsis remains a potentially lethal but uncommon problem among very-low-birth-weight in-

fant. Although only 1.5 percent of the 5447 very-low-birth-weight neonates in this cohort had early-onset sepsis, 37 percent of those with sepsis died. Extreme prematurity was the greatest risk factor for early-onset sepsis. Although the risk of early-onset sepsis was increased when the membranes ruptured more than 24 hours before delivery, 41 percent of infants with early-onset sepsis were born less than 6 hours after membrane rupture — an interval that many clinicians would not find worrisome. It has been suggested that as many as 85 percent of early preterm births are associated with intrauterine infection before membrane rupture.²³ Moreover, there are increased risks of histologic chorioamnionitis, infected amniotic fluid, and a fetal inflammatory response associated with lower gestational age at birth.^{24,25} Early-onset sepsis is associated with an increased risk of several complications of prematurity, including respiratory distress syndrome, bronchopulmonary dysplasia, and severe intraventricular hemorrhage or periventricular leukomalacia. Further study is required to assess the effect of early-onset sepsis and the cytokine response to infection on these adverse outcomes of prematurity and on long-term neurodevelopmental outcome.

There has been a marked increase in recent years in the intrapartum use of antibiotics. This increase is due in part to national programs designed to reduce the vertical transmission of group B streptococcal infec-

tion, but it also reflects an effort to reduce the risk of neonatal illness when there is preterm rupture of the membranes. For the prevention of neonatal group B streptococcal infections, antibiotics are recommended during labor when there has been a positive rectovaginal culture for group B streptococcus before labor or when there are risk factors for neonatal infection (including labor at less than 37 weeks of gestation).⁶ All mothers of infants in the recent birth cohort we studied had at least one risk factor for neonatal group B streptococcal infection, but in only 65 percent of cases did they receive antibiotics. We have no data on the reasons why antibiotics were or were not given. The observation that some women gave birth soon after hospital admission may partially explain their not receiving antibiotics during labor and delivery.

Recent reports suggest that the intrapartum use of antibiotics has reduced the prevalence of early-onset group B streptococcal infections.^{6,9,10} We noted a reduction in the incidence of early-onset group B streptococcal sepsis between the period from 1991 to 1993 and the period from 1998 to 2000. However, there was also a significant increase in the incidence of *E. coli* infections during the same interval. Although more infants weighing between 401 and 500 g were included in the later cohort, this difference did not explain our findings, since no infant weighing less than 500 g was infected with either group B streptococci or *E. coli*. Historically, the predominant organisms associated with neonatal sepsis have changed over time. Gram-negative organisms, especially *E. coli*, were the most common causes of cases of neonatal sepsis reported at Yale University from the late 1940s to the mid-1960s.²⁶ Gram-negative organisms remain the most frequently reported cause of neonatal sepsis in developing countries.²⁷

Antibiotic resistance is a major public health threat.²⁸⁻³⁰ Gram-negative organisms have both innate resistance to antibiotics and the ability to acquire resistance through new mechanisms that may be transferred from other pathogens.³¹ In our study, 85 percent of *E. coli* isolates were resistant to ampicillin.^{32,33} We do not have data to assess whether the high rate of resistance reflects antibiotic-resistance patterns in the neonatal intensive care units involved in the study or resistance patterns of genital flora in the mothers in our study or in ambulatory populations more generally. Furthermore, we have no data on antibiotic use during pregnancy but before the hospitalization for delivery.

Early-onset sepsis is an important cause of neonatal death. Gram-negative sepsis is particularly lethal. Further surveillance is warranted to determine whether the observed reduction in the incidence of early-onset gram-positive infections will be mirrored by a continued increase in the risk of infection with more virulent gram-negative organisms.

Supported by grants (U10 HD27851, U01 HD36790, U10 HD21364, U10 HD34216, U10 HD27871, U10 HD27856, U10 HD27853, U10 HD34167, U10 HD21373, U10 HD27904, U10 HD21397, U10 HD21415, U10 HD21385, U10 HD40689, U10 HD27880, and U10 HD27881) from the National Institutes of Health.

We are indebted to Mazie Tinsley for assistance in the preparation of the manuscript.

APPENDIX

The following centers belonged to the Neonatal Research Network of the NICHD between 1996 and 2000, with the principal investigator and study coordinator (and the number of patients studied, in parentheses): Brown University (396): W. Oh and A. Hensman; Case Western Reserve University (298): A.A. Fanaroff and N. Newman; Emory University (312): B.J. Stoll and E. Hale; Harvard University (429): A.R. Stark and K. Fournier; Indiana University (547): J.A. Lemons and D. Appel; Stanford University (279): D.K. Stevenson and B. Ball; University of Alabama (476): W.A. Carlo and M. Collins; University of Cincinnati (509): E.F. Donovan and M. Mersmann; University of Miami (381): C.R. Bauer and A.M. Worth; University of New Mexico (262); L.-A. Papile and C. Backstrom; University of Tennessee (372): S.B. Korones and T. Hudson; University of Texas–Dallas (337): A.R. Laptook and S. Madison; University of Texas–Houston (305): J.E. Tyson and G. McDavid; Wayne State University (316): S. Shankaran and G. Muran; Yale University (228): R.A. Ehrenkranz and P. Gettner; NICHD: L.L. Wright and B.B. McClure; Research Triangle Institute: W.K. Poole and B. Hastings. The Steering Committee chairman was A.H. Jobe.

REFERENCES

1. Stoll BJ, Gordon T, Korones SB, et al. Early-onset sepsis in very low birth weight neonates: a report from the National Institute of Child Health and Human Development Neonatal Research Network. *J Pediatr* 1996; 129:72-80.
2. Klein JO. Bacterial sepsis and meningitis. In: Remington JS, Klein JO, eds. Infectious diseases of the fetus and newborn infant. 5th ed. Philadelphia: W.B. Saunders, 2001:943-98.
3. Philip AG. The changing face of neonatal infection: experience at a regional medical center. *Pediatr Infect Dis J* 1994;13:1098-102.
4. Isaacs D, Barfield CP, Grimwood K, McPhee AJ, Minutillo C, Tudehope DI. Systemic bacterial and fungal infections in infants in Australian neonatal units. *Med J Aust* 1995;162:198-201.
5. Berger A, Salzer HR, Weninger M, Sageder B, Aspöck C. Septicaemia in an Austrian neonatal intensive care unit: a 7-year analysis. *Acta Paediatr* 1998;87:1066-9.
6. Prevention of perinatal group B streptococcal disease: a public health perspective. *MMWR Morb Mortal Wkly Rep* 1996;45(RR-7):1-24. [Erratum, *MMWR Morb Mortal Wkly Rep* 1996;45:679.]
7. Schrag SJ, Zywicki S, Farley MM, et al. Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. *N Engl J Med* 2000;342:15-20.
8. Hager WD, Schuchat A, Gibbs R, Sweet R, Mead P, Larsen JW. Prevention of perinatal group B streptococcal infection: current controversies. *Obstet Gynecol* 2000;96:141-5.
9. Schuchat A, Zywicki SS, Dinsmoor MJ, et al. Risk factors and opportunities for prevention of early-onset neonatal sepsis: a multicenter case-control study. *Pediatrics* 2000;105:21-6.
10. Benitz WE, Gould JB, Druzin ML. Antimicrobial prevention of early-onset group B streptococcal sepsis: estimates of risk reduction based on a critical literature review. *Pediatrics* 1999;103:1275. abstract.
11. Mercer BM, Miodovnik M, Thurnau GR, et al. Antibiotic therapy for reduction of infant morbidity after preterm premature rupture of the membranes: a randomized controlled trial. *JAMA* 1997;278:989-95.
12. Premature rupture of membranes: clinical management guidelines for obstetrician-gynecologists. *Int J Gynaecol Obstet* 1998;63:75-84.
13. Isaacs D, Royle JA. Intrapartum antibiotics and early onset neonatal sepsis caused by group B streptococcus and by other organisms in Australia. *Pediatr Infect Dis J* 1999;18:524-8.
14. Mercer BM, Carr TL, Beazley DD, Crouse DT, Sibai BM. Antibiotic use in pregnancy and drug-resistant infant sepsis. *Am J Obstet Gynecol* 1999;181:816-21.
15. Terrone DA, Rinehart BK, Einstein MH, Britt LB, Martin JN Jr, Perry KG. Neonatal sepsis and death caused by resistant *Escherichia coli*: possible consequences of extended maternal ampicillin administration. *Am J Obstet Gynecol* 1999;180:1345-8.

16. Towers CV, Carr MH, Padilla G, Asrat T. Potential consequences of widespread antepartal use of ampicillin. *Am J Obstet Gynecol* 1998;179:879-83.
17. Hack M, Horbar JD, Malloy MH, Tyson JE, Wright E, Wright L. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Network. *Pediatrics* 1991;87:587-97.
18. Pourcyrous M, Bada HS, Korones SB, Baselski V, Wong SP. Significance of serial C-reactive protein responses in neonatal infection and other disorders. *Pediatrics* 1993;92:431-5.
19. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr* 1978;92:529-34.
20. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis: therapeutic decisions based on clinical staging. *Ann Surg* 1978;187:1-7.
21. SUDAAN user's manual, release 8.0. Research Triangle Park, N.C.: Research Triangle Institute, 2001.
22. SAS/STAT user's guide, version 8. Cary, N.C.: SAS Institute, 1999.
23. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. *N Engl J Med* 2000;342:1500-7.
24. Gibbs RS, Romero R, Hillier SL, Eschenbach DA, Sweet RL. A review of premature birth and subclinical infection. *Am J Obstet Gynecol* 1992;166:1515-28.
25. Romero R, Sirtori M, Oyarzun E, et al. Infection and labor. V. Prevalence, microbiology, and clinical significance of intraamniotic infection in women with preterm labor and intact membranes. *Am J Obstet Gynecol* 1989;161:817-24.
26. Freedman RM, Ingram DL, Gross I, Ehrenkranz RA, Warshaw JB, Baltimore RS. A half century of neonatal sepsis at Yale: 1928 to 1978. *Am J Dis Child* 1981;135:140-4.
27. Stoll BJ. Neonatal infections: a global perspective. In: Remington JS, Klein JO, eds. *Infectious diseases of the fetus and newborn infant*. 5th ed. Philadelphia: W.B. Saunders, 2001:139-68.
28. Goldmann DA, Weinstein RA, Wenzel RP, et al. Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals: a challenge to hospital leadership. *JAMA* 1996;275:234-40.
29. Goldmann DA, Huskins WC. Control of nosocomial antimicrobial-resistant bacteria: a strategic priority for hospitals worldwide. *Clin Infect Dis* 1997;24:Suppl 1:S139-S145.
30. Weinstein RA. Controlling antimicrobial resistance in hospitals: infection control and use of antibiotics. *Emerg Infect Dis* 2001;7:188-92.
31. Waterer GW, Wunderink RG. Increasing threat of Gram-negative bacteria. *Crit Care Med* 2001;29:Suppl:N75-N81.
32. Joseph TA, Pyati SP, Jacobs N. Neonatal early-onset *Escherichia coli* disease: the effect of intrapartum ampicillin. *Arch Pediatr Adolesc Med* 1998;152:35-40.
33. Friedman S, Shah V, Ohlsson A, Matlow AG. Neonatal *Escherichia coli* infections: concerns regarding resistance to current therapy. *Acta Paediatr* 2000;89:686-9.

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