

Are the "Good Old" Antibiotics Still Appropriate for Early-Onset Neonatal Sepsis? A 10 Year Survey

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ABSTRACT: **Background:** Early-onset neonatal sepsis is a major cause of morbidity and mortality among newborn infants.

Objectives: To determine the incidence, type of pathogens and resistance to antibiotics among newborns with early-onset neonatal sepsis, and to identify the risk factors predisposing infants to resistant pathogens in order to reevaluate antibiotic regimens appropriate for resistant bacteria in these high risk neonates.

Methods: We retrospectively studied maternal and neonatal variables of 73 term and near-term infants and 30 preterm infants, born over a period of 10.5 years and exhibiting early-onset neonatal sepsis (positive blood cultures in the first 72 hours of life).

Results: Predominant pathogens in term and near-term infants were gram-positive compared with gram-negative organisms (mostly *Escherichia coli*) in preterm infants. Mothers of infants with antibiotic-resistant organisms were more likely to have prolonged rupture of membranes and prolonged hospitalization before delivery and to be treated with antibiotics. No trends towards more resistant strains of pathogens were recorded over the 10.5 years of the study period.

Conclusions: Early-onset neonatal sepsis in term infants differs in bacterial species from that in preterm infants, with predominantly gram-positive organisms in term and near-term infants and gram-negative organisms in preterms. Rates of bacterial resistance to the combination of ampicillin and gentamicin, though higher among infants born to mothers with prolonged hospitalization who had been treated with antibiotics, still remained very low in our department. Thus, it seems that our classic antibiotic regimen is still appropriate for both term and preterm newborns. *IMAJ* 2009;11:138–143

KEY WORDS: early-onset neonatal sepsis, preterm infants

Early-onset neonatal sepsis, defined as proven culture-positive sepsis in the first 3 days of life, accounts for severe morbidity and mortality among newborn infants [1-7]. Term and preterm newborns who are suspected of having EONS are treated, according to recommendations [8], with ampicillin and gentamicin, which cover common pathogens such as group B Streptococcus, gram-negative bacteria (mostly *Escherichia coli*) and Listeria. These recommendations are based upon antibiotic sensitivity to non-hospital-acquired pathogens. However, these recommendations may not take into consideration variables such as maternal hospitalization before delivery (sometimes for many weeks), prolonged premature rupture of membranes, maternal prenatal antibiotic treatment, prematurity, or suspected clinical as well as sub-clinical amnionitis.

Recent studies have shown gradual changes in the relative incidence of bacterial type causing early-onset neonatal sepsis, mainly attributed to GBS prophylaxis policy for pregnant woman, mostly GBS carriers. While the neonatal incidence of GBS infection has decreased, increased rates of *E. coli* have been recorded [1,9-11]. In addition, these changes can lead to the growth of resistant bacteria, mostly those resistant to ampicillin [1,9-11] but also some resistant to gentamicin [2].

So far, no recommendations are available for different antibiotic regimens in newborns that take into account the risk for early-onset neonatal sepsis caused by probable resistant pathogens. Thus, the purposes of the present study were twofold: to determine the incidence, type of pathogen and change in antibiotic resistance over the years among term and preterm newborns with early-onset neonatal sepsis, and to identify risk factors predisposing infants to resistant pathogens for the purpose of reevaluating antibiotic regimens appropriate for resistant bacteria in these high risk neonates.

PATIENTS AND METHODS

The study included all newborn (term and preterm) infants born at the Sheba Medical Center (a large tertiary medical center in Israel) over a period of 10.5 years (1 January 1997 to 31 July 2007) and diagnosed with EONS. EONS was defined as positive blood and/or cerebrospinal fluid culture for bacterial growth taken within the first 72 hours of life.

A pediatric infectious diseases specialist determined which pathogens were considered "true" infection and which were considered a probable sample contamination (coagulase-

EONS = early-onset neonatal sepsis

GBS = group B Streptococcus

negative staphylococci, *Streptococcus viridans* and others). The latter were excluded from the study.

We retrospectively recorded data from the medical charts of the mothers and infants. In the mothers' medical charts, the data included maternal age, parity and gravida, diseases and medications during pregnancy, duration of membrane rupture, length of hospital stay before delivery, and clinical signs of amnionitis such as fever, amniotic fluid odor, and delivery mode. In the infants' medical charts, the data included gestational age and birth weight, gender, Apgar score, mortality, clinical manifestations and neonatal complications, bacterial growth including antibiotic sensitivity and resistance, antibiotic treatment and laboratory results.

Our department policy regarding antibiotic treatment for early sepsis in high risk infants uses ampicillin and gentamicin as a first line of treatment for term as well as preterm infants. Risk factors for EONS are: a) maternal fever or other signs of amnionitis, b) any neonatal clinical signs suggesting infection (such as fever or hypothermia, respiratory distress, poor perfusion, abdominal distension, apneas, etc.), c) previous sibling with proven neonatal GBS infection, and d) a combination of two or more of the following: prematurity, maternal GBS carrier and PROM of 18 hours or more.

Screening for GBS carriers among pregnant women in our population has not yet been established, though it is gradually increasing. Thus, most of the mothers who give birth to full-term infants are not screened and as a result are not exposed to antibiotic prophylaxis. The institutional ethics committee approved this study.

RESULTS

During the 10.5 year period of the study, 90,977 infants were born at the Sheba Medical Center. Of those who were term and near term (GA ≥ 35 weeks), 73 were diagnosed with EONS, and of those who were preterm (GA ≤ 34 weeks), 30 were diagnosed with EONS, giving an overall incidence of 1:1000 live births. Of the 1296 very low birth weight infants (birth weight ≤ 1500 g) born during the study period in our institution, 17 (1.31%) had EONS.

EONS IN PRETERM INFANTS (GA ≤ 34 WEEKS)

The characteristics of the preterms with EONS are shown in Table 1. Most of the mothers were hospitalized at least 2 days before delivery and more than half had prolonged PROM (24 hours or more). Amnionitis was suspected (maternal fever, leukocytosis or foul odor of amniotic fluid) in 43.3% of the mothers on delivery. Most preterm infants were dyspneic at birth. About a quarter were asymptomatic, and bacteremia

Table 1. Characteristics of newborns with EONS

	Term or near-term (GA 35 wks) N=73	Preterm (GA 34 wks) N = 30
Gestational age (wks), mean (range)	39.3 (35–42)	30.4 (25–34)
Birth weight (g), mean (range)	3200 (1505–4580)	1520 (895–2500)
VLBW infants, N (%)		17 (56.6)
Male sex, N (%)	38 (52)	17 (56.6)
Maternal data		
Age (yrs), mean (range)	30.4 (19–41)	32.4 (21–46)
Parity number, mean (range)	2 (1–8)	2.5 (1–12)
Time of PROM (hrs), mean (range)	13 (0–432)	68.8 (0–410)
PROM > 24 hrs, N (%)	7 (9.5)	17 (56.6)
Fever > 38°C, N (%)	14 (19.1)	6 (20)
Hospitalization before delivery ≤ 2 days, N (%)	8 (10.9)	23 (76.6)
Suspected amnionitis, N (%)	1 (1.3)	13 (43.3)
Antibiotic treatment	9 (12.3)	24 (80)
Infant data, N (%)		
C/S delivery	11 (15)	19 (63.3)
Multiple	2 (2.7)	8 (26.6)
Clinical manifestations	54 (73.9)	22 (73.3)
Respiratory distress	29 (39.7)	19 (63.3)
Hypotension	8 (10.9)	12 (40)
Fever	11 (15)	1 (3.3)
Mortality*	1 (1.3)	5 (16.6)

*All cases of mortality occurred within the first 5 days of life

GA = gestational age, VLBW = very low birth weight, PROM = premature rupture of membranes, C/S = cesarean section

was detected by routine blood culture taken on admission.

The mortality rate was 16.6% (5 infants), with death occurring at the age of a few hours to 5 days of life. Four infants had extremely low birth weight (≤ 1000 g), and four mothers had suspected amnionitis. The pathogens included four cases of *E. coli* and one of *Pseudomonas aeruginosa*. All strains were resistant to ampicillin, and one case of *E. coli* was also resistant to gentamicin. All the infants who died had severe respiratory distress from birth, accompanied by hypotension requiring medical intervention.

The majority of preterm infants with EONS (23 of 30 infants, 76.6%) exhibited growth of gram-negative bacteria that included *E. coli* in 19 cases and one case each of *Klebsiella pneumoniae*, *Citrobacter*, *Pseudomonas aeruginosa* and *Haemophilus influenzae*. The other seven infants had gram-positive bacteria that included GBS in three cases, *Listeria monocytogenes* in two, and one case each of *Staphylococcus aureus* and *Enterococcus fecalis*. The characteristics of preterm infants with *E. coli* according to

PROM = premature rupture of membranes
GA = gestational age

Table 2. Characteristics of preterm infants according to resistance of *E. coli* strains

	<i>E. coli</i> (N = 19)		
	Ampicillin and gentamicin-sensitive N=6	Ampicillin-resistant N=9	*Ampicillin and gentamicin-resistant N=4
Gestational age (wks), mean (range)	30.6 ± 2.4 (27–34)	30.3 ± 3.9 (25–34)	29.2 ± 3.8 (25–33)
Birth weight (g), mean (range)	1530 ± 523 (1121–2500)	1510 ± 617 (632–2335)	1429 ± 669 (827–2300)
Male sex, N (%)	4 (66.6)	6 (66.6)	1 (25)
Maternal data			
PROM > 24 hrs, N (%)	3 (50)	8 (88.8)	3 (75)
Fever > 38°C, N (%)	3 (50)	1 (11.1)	1 (25)
Hospitalization before delivery ≤ 2 days, N (%)	4 (66.6)	9 (100)	4 (100)
Suspected amnionitis, N (%)	3 (50)	5 (55.5)	2 (50)
Antibiotic treatment	4(100)		
Infant data			
C/S delivery, N (%)	2 (33.3)	7 (77.7)	2 (50)
Multiple pregnancies, N (%)	1 (16.6)	4 (44.4)	1 (25)
Clinical manifestations, N (%)	6 (100)	7 (77.7)	2 (50)
Respiratory distress	5 (83.3)	5 (55.5)	1 (25)
Hypotension	2 (33.3)	4 (44.4)	2 (50)
Mortality	0	3 (33.3)	1 (25)

* All ampicillin and gentamicin-resistant *E. coli* were sensitive to amikacin

antibiotic sensitivity are shown in Table 2. Ampicillin-resistant *E. coli* was present in 13 of 19 preterms with *E. coli* bacteremia. All mothers had been hospitalized for at least 2 days prior to delivery and had received prenatal antibiotics. More than half of them had PROM for more than 2 days.

Four premature infants had both ampicillin and gentamicin-resistant *E. coli* with maternal hospitalization before delivery of more than 2 days. Two of them had amnionitis, and all had been administered prenatal antibiotics [Table 2]. Among those four infants, one (GA 25 weeks, birth weight 877 g) died on the fifth day of life, one had neonatal fever on admission and the other two were asymptomatic. These four infants were born in four different years (from 1998 to 2006), and their bacterial strains were sensitive to amikacin.

EONS IN TERM AND NEAR-TERM NEWBORNS (GA ≤ 35 WEEKS)

The characteristics of the term and near-term infants with EONS are shown in Table 1. Only 10.9% of the mothers were hospitalized for more than 2 days before delivery, and fewer had PROM of 24 hours or more. Fever was present in one-fifth of the mothers. More than half of the infants were symptomatic, and only one-third exhibited respiratory dis-

stress. Other neonatal clinical manifestations included bloody stool, low perfusion, hypothermia and "septic" appearance. In the others, blood cultures were obtained due to maternal fever (11 infants), known maternal GBS carrier (n=3), and PROM for more than 18 hours (n=3). One baby died – a 38 week appropriate-for-gestational age newborn whose mother had been hospitalized 11 days before delivery due to hypertension, without any known risk factors for perinatal infection. The pathogen in this patient was ampicillin-resistant and gentamicin-sensitive *Klebsiella oxytoca*.

Among the 73 term and near-term newborns with EONS, gram-positive bacteria constituted the predominant pathogens (57 infants, 78%). Forty infants (54.7%) had GBS, distributed evenly over the 10.5 years of the study. The rest of the gram-positive bacteria included *Staph. aureus* in six infants (4.1%), three cases of *E. fecalis* and three cases of other *Enterococcus*, and one case each of *Listeria monocytogenes*, *Propionibacterium*, *Moraxella catarrhalis*, *Streptococcus pyogenes* and group F *Streptococcus*. Sixteen infants (22%) had gram-negative bacteria, including 6 with *Klebsiella (pneumoniae)* in five cases and *oxytoca* in one), five with *E. coli*, three with *Enterobacter* and two infants with *Citrobacter koseri*.

Among the infants with gram-positive bacteria, all but six, who had *Staph. aureus* bacteremia, were sensitive to ampicillin. In all six, maternal hospitalization was less than one day before delivery, and duration of membrane rupture was 0–14 hours. Two mothers had fever and received prenatal antibiotics. These six infants had only mild clinical symptoms (short dyspnea in three), and all were discharged with no significant complications after antibiotics were adjusted accordingly.

Among the gram-negative bacteria, two *E. coli* strains were sensitive to ampicillin and three were resistant, though all five were sensitive to gentamicin. Of the five patients with *K. pneumoniae* infection, two had fever, one of whom was diagnosed with meningitis. Three (with *Klebsiella*) had no significant clinical manifestations. Gentamicin-resistant *Klebsiella* was found in only one patient, who had no maternal risk factors for perinatal infection. All *Klebsiella* strains were resistant to ampicillin, and one was also resistant to gentamicin.

DISCUSSION

The results of the study indicate that for preterm infants with EONS, the predominant pathogens are gram-negative bacteria, mostly *E. coli* and its strains that were commonly resistant to ampicillin. A few cases were resistant to gentamicin as well (only four infants, including one death over the 10.5 years). The mortality rate in preterm infants with EONS was 16.6%, with all deaths due to ampicillin-resistant bacteria. In term and near-term infants with EONS, the common pathogens were gram-positive bacteria, predominantly GBS. One infant died, making the mortality rate 1.3%.

The study did not detect any trend toward changes in pathogen strains and resistance along the 10.5 year study period. Such a trend has been found and described in several studies that showed decreased rates of GBS early-onset neonatal sepsis simultaneous to increased gram-negative bacterial growth as a result of antibiotic prophylaxis in maternal GBS carriers [3,5,7,11-16]. This variation in findings may be explained by diverse GBS-screening policies in different populations, as well as the type of prophylactic antibiotic given. In our population, only a minority of pregnant women were screened and treated for GBS during the study period. Indeed, for most of the infants with GBS early-onset neonatal sepsis described in the present study, the mothers were not screened during pregnancy and therefore not identified as carriers and not treated with antibiotics.

EONS with resistant bacteria strains can be related to maternal hospitalization and antibiotic treatment before delivery. Many studies describe ampicillin-resistant pathogens (mostly *E. coli*) derived from prophylactic antibiotic treatment given to GBS carriers [1-3,5,6,8,11-13,15-20], and even gentamicin-resistant strains have been documented [18]. It is difficult to differentiate these two risk factors, since most cases of preterm maternal hospitalization and suspected impending labor involve antibiotic administration. Indeed in the present study, the mothers received antibiotics in all cases of preterms with *E. coli* EONS, and all except two were hospitalized 2 days or more prior to delivery. Furthermore, in all cases of EONS with resistant *E. coli* strains, the mothers were hospitalized for long periods and all received antibiotic treatment.

In our institution, about 6% of term and near-term newborns are treated with antibiotics in the first 2 days of life, due either to maternal risk factors or to neonatal clinical manifestations suggesting sepsis. Among preterm infants, the rates of antibiotic treatment in the first days of life are much higher leading to a change of the oral flora [21]. To cope with ampicillin-resistant *E. coli*, a different combination of antibiotics should probably have been considered, specifically third-generation cephalosporins. Based on the present study, this might have saved the life of one extremely premature infant over the 10 years of the study, but would also have led to treating several hundred infants every year whose blood cultures turned out to be negative, surely causing many more resistant organisms. Thus, it seems that the antibiotic regimen given (ampicillin and gentamicin) is appropriate, even in the presence of risk factors such as prolonged maternal hospitalization, PROM and antibiotic prophylaxis.

The rates of clinical manifestations were similar in term and preterm infants. A quarter of each group was asymptomatic, and blood cultures were obtained only because of maternal risk factors (fever, and combination of PROM and GBS carrier). In preterm infants, clinical manifestations

mostly included respiratory distress (probably related to prematurity) and hypotension; and in term and near-term infants other clinical manifestations were common, such as temperature instability, apneic events, bloody stool and non-specific sick-looking infants. In these cases, the infants usually responded well to antibiotic treatment with no unfavorable events until discharge.

The mortality rates of 16.6% in preterms and 1.3% in term and near-term infants were similar to those found in a previous study [1], although among very low birth weight infants the mortality rates (23.5%) were lower than previously reported [2,3,6].

In summary, EONS in term infants differs in the bacterial species from that in preterm infants, with gram-positive organisms predominant in term and near-term infants and gram-negative organisms common in preterms. Over the last 10 years we have not seen any dramatic change in bacterial resistance. Thus, it seems that the "good old" antibiotics (ampicillin and gentamicin) are appropriate for EONS both in term and in preterm infants.

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