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Early and Late Onset Sepsis in Very-Low-Birth-Weight Infants from a Large Group of Neonatal Intensive Care Units

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Abstract

Background—Very-low-birth-weight (VLBW, <1500 g birth weight) infants are at high risk for both early- and late-onset sepsis. Prior studies have observed a predominance of gram-negative organisms as a cause of early-onset sepsis and gram-positive organisms as a cause of late-onset sepsis. These reports are limited to large, academic neonatal intensive care units (NICUs) and may not reflect findings in other units. The purpose of this study was to determine the risk factors for sepsis, the causative organisms, and mortality following infection in a large and diverse sample of NICUs.

Methods—We analyzed the results of all cultures obtained from VLBW infants admitted to 313 NICUs from 1997 to 2010.

Results—Over 108,000 VLBW infants were admitted during the study period. Early-onset sepsis occurred in 1032 infants, and late-onset sepsis occurred in 12,204 infants. Gram-negative organisms were the most commonly isolated pathogens in early-onset sepsis, and gram-positive organisms were most commonly isolated in late-onset sepsis. Early- and late-onset sepsis were associated with increased risk of death controlling for other confounders (odds ratio 1.45 [95% confidence interval 1.21, 1.73], and OR 1.30 [95% CI 1.21, 1.40], respectively).

Conclusions—This is the largest report of sepsis in VLBW infants to date. Incidence for early-onset sepsis and late-onset sepsis has changed little over this 14-year period, and overall mortality in VLBW infants with early- and late-onset sepsis is higher than in infants with negative cultures.

Keywords

early-onset sepsis; late-onset sepsis; very-low-birth-weight infants

1. Introduction

Although advances in medical technology have improved the survival of very-low-birth-weight (VLBW, <1500 g birth weight) infants [1–4], they remain at a high risk for sepsis [5, 6]. Up to 20% of all VLBW infant deaths are caused by sepsis, and infants with sepsis are nearly 3 times as likely to die as those without sepsis, even after adjusting for gestational

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Conflict of interest statement

The remaining authors have no potential conflicts to disclose.

age, sex, and other comorbidities [6,7]. Surviving VLBW infants are at increased risk for developing morbidities, including bronchopulmonary dysplasia, prolonged hospital stay, and neurodevelopmental impairment [7–11].

Early-onset sepsis (EOS)—sepsis occurring in the first 3 days of life—is typically caused by organisms transmitted vertically from the mother to the infant before or at the time of birth. A previous multicenter report found an increase in gram-negative pathogens and reduction in gram-positive pathogens among VLBW infants that was subsequently confirmed in a later cohort (Table 1) [6, 12].

Late-onset sepsis (LOS)—sepsis occurring between day of life 4 and 120—may be caused by pathogens acquired at delivery or during the course of hospital care required by preterm infants. VLBW infants are at increased risk of LOS because of their underdeveloped immune systems, need for central venous access, and prolonged hospitalizations [13]. LOS is most often caused by gram-positive organisms [7, 13].

Although previous reports of sepsis in VLBW infants represent relatively large, multicenter cohorts (Table 1), the centers providing data are all large, academic neonatal intensive care units (NICUs). Here we report on risk factors for sepsis and outcomes following sepsis from a cohort of VLBW infants admitted to 313 NICUs managed by a large private group of neonatologists.

2. Methods

2.1. Study sites and patients

We evaluated prospectively collected data from all VLBW infants admitted to 313 NICUs in North America managed by the Pediatrix Medical Group from 1997 to 2010. The database was created using a computer-assisted tool that generates clinical progress notes. We collected both maternal and infant demographic data including: gestational age, birth weight, Apgar score, sex, race, ventilation status on day of life 1, exposure to antenatal antibiotics, exposure to antenatal steroids, and inborn status. We gathered information on all cultures drawn for infants during the first 120 days of life.

2.2. Definitions

We defined EOS as a positive culture (blood, urine obtained by suprapubic tap or in-and-out catheterization, or cerebrospinal fluid) occurring on day of life 1, 2, or 3 and LOS as a positive culture occurring between day of life 4 and 120. Multiple positive cultures for the same organism within a 21-day period were considered a single episode of sepsis.

We defined definite coagulase-negative *Staphylococcus* (CoNS) sepsis as 2 positive cultures on the same day [15]; probable CoNS sepsis as 2 positive cultures for CoNS within a 4-day period, 3 positive cultures for CoNS within a 7-day period, or 4 positive cultures for CoNS within a 10-day period [16]; and possible sepsis as a culture positive for CoNS that did not meet criteria for definite or probable CoNS sepsis [7]. We included definite and probable CoNS sepsis in the analysis.

We excluded infants who died in the first 24 hours of life and who did not have a culture obtained, and sepsis episodes for organisms considered contaminants including non-specified streptococci, *Bacillus* sp., *Corynebacterium* sp., diphtheroids sp., gram-positive rods (not including *Listeria* sp.), *Lactobacillus* sp., *Micrococcus* sp., *Stomatococcus* sp., and *Bacteroides* sp. We grouped pathogenic organisms into 3 clinically relevant categories: gram-negative rods, gram-positive cocci, and *Candida*. We determined mortality for each

organism. For infants with more than 1 episode of sepsis, we used the organism identified closest to death or discharge.

2.3. Statistical analysis

The unit of observation for this analysis was the infant. Chi-square tests were used to examine demographic differences between infants with positive cultures and negative cultures for both EOS and LOS. We evaluated causative agents and cumulative incidence for EOS and LOS among VLBW infants. We used multivariable logistic regression with backward selection (p-value for removal >0.1) to identify factors associated with an increased risk of EOS and LOS. Confounders included in the analysis included gestational age, race, sex, 5-minute Apgar score, exposure to antenatal steroids, exposure to antenatal antibiotics, method of delivery, need for mechanical ventilation on day of life 1, and inborn status. We used a similar approach to examine the relationship between EOS and LOS and risk of death controlling for: gestational age, birth weight, race, sex, maternal age, 5-minute Apgar score, exposure to antenatal steroids, exposure to antenatal antibiotics, delivery method, need for mechanical ventilation on day of life 1, and inborn status.

Significance for all tests was established at a $p < 0.05$. STATA 10 (College Station, TX) was used to perform the statistical analysis. Permission to conduct this analysis without written informed consent was provided by the Duke University Institutional Review Board because the analysis was performed on de-identified data.

3. Results

3.1. Clinical characteristics

Between 1997 and 2010, 104,676 VLBW infants were admitted to Pediatrix Medical Group NICUs during the first 3 days of life, and 1032 (1.0%) developed 1037 episodes of EOS. The majority of those infants (81.9%) had at least 1 culture obtained during the first 3 days of life. The mean gestational age for infants with and without EOS was 26.8 weeks (95% confidence interval [CI] 26.6, 26.9) and 28.3 weeks (95% CI 28.2, 28.3), respectively (Table 2). Mortality for infants with EOS was 25.9% compared to 11.3% for infants with negative cultures ($p < 0.001$).

Between 1997 and 2010, 99,796 VLBW infants were admitted to Pediatrix Medical Group NICUs between day of life 4 to 120, and 12,190 (12.21%) developed 14,628 episodes of LOS. Fifty percent of VLBW infants had at least 1 culture obtained between day of life 4 and day of life 120. The mean gestational age for infants with and without LOS was 26.6 weeks (95% CI 26.6, 26.7) and 27.6 weeks (95% CI 27.6, 27.7), respectively (Table 2). Mortality for infants with LOS was 15.1% compared to 8.5% for infants with negative cultures ($p < 0.001$).

3.2. Microbiologic etiology and associated mortality

Gram-negative, gram-positive, and *Candida* sp. caused 58.2%, 34.3%, and 2.7% of EOS episodes, respectively (Table 3). *Escherichia coli*, group B *Streptococcus* (GBS), and other gram-positive cocci species were the most commonly isolated pathogens in this population. During the study period, the number of GBS EOS episodes among VLBW infants increased from 1.46/1000 admissions during the period of 1997–2001 to 1.81/1000 admissions from 2002–2010. EOS caused by *Escherichia coli* also increased slightly during this same time period (3.17 to 3.20 episodes per 1000 NICU admissions). Overall gram-negative infections decreased slightly from 5.69/1000 admissions to 5.56/1000 admissions from 1997–2001 to 2002–2010. Gram-positive infections increased from 2.97/1000 admissions to 3.36/1000

admissions from 1997–2001 to 2002–2010. EOS mortality was similar for gram-positive, gram-negative, and *Candida* sp.: 24.7%, 28.0%, and 28.0%, respectively.

The majority of LOS episodes were caused by gram-positive organisms (61.4%, 8984/14,628), followed by gram-negative organisms (26.2%, 3829/14,628) and *Candida* (10.5%, 1528/14,628) (Table 3). The most commonly observed LOS pathogens included CoNS, *Staphylococcus aureus*, *Candida* sp., and other gram-positive cocci sp. Of 4133 episodes of CoNS LOS, 35.4% were classified as definite. The mortality of definite and probable CoNS sepsis was 11.5% and 8.2%, respectively. Mortality for LOS varied by organism (Table 3) and was highest for *Listeria* species (100%), other gram-negative rods (66.6%), and *Pseudomonas* sp. (35.0%). We observed little change in mortality associated with LOS. During the years 1997–2001, overall mortality was 13.6% (248/1823); it was 15.4% (1387/8992) from 2002–2010.

3.3. Risk factors for sepsis

Risk factors for EOS among VLBW infants who had a culture obtained in the first 3 days of life on multivariable analysis included: lower gestational age, female sex, lower Apgar score, exposure to antenatal antibiotics, need for mechanical ventilation on day of life 1, and outborn status (Table 4). Risk factors for LOS among VLBW infants who had a culture obtained between day of life 4 and 120 included: lower gestational age and exposure to antenatal antibiotics (Table 4).

3.4. Risk factors for death

EOS was associated with an increased risk of death on multivariable analysis (OR = 1.45 [95% CI 1.21, 1.73]) (Table 5). LOS was associated with an increased risk of death on multivariable analysis (OR = 1.30 [95% CI 1.21, 1.40]) (Table 5).

4. Discussion

VLBW infants suffer from high rates of mortality and morbidities, and these rates are higher for infants with sepsis [7, 17]. This report identified risk factors for sepsis and outcomes following sepsis from a cohort of over 108,000 VLBW infants over a 14-year period. The incidence of EOS (9.6/1000 admissions) we observed in this cohort is lower than the most recent report from the National Institute of Child Health and Human Development Neonatal Research Network (17.0/1000 births) [12]. Gram-negative organisms were the most common cause of EOS in our report. The predominance of gram-negative organisms as a cause of EOS was first observed in 1998 with the increased use of antepartum antibiotics for prevention of vertical GBS transmission and from efforts to prolong pregnancies threatened with premature delivery [6, 18]. Prior to this, gram-positive organisms (e.g., GBS) predominated in EOS in both term and preterm infants [14].

The incidence of EOS caused by *Escherichia coli* in our cohort (3.2/1000 admissions) is less than previously reported (7.0/1000 admissions), and the rate of EOS caused by GBS (1.7/1000 admissions) is similar to prior reports (1.8/1000 admissions) [12]. The proportion of mothers receiving antenatal antibiotics in our cohort (44%) is lower than previous reports (65–69%) [12].

For LOS, we found that gram-positive organisms were the most commonly isolated pathogens, but only 28.3% of cases were caused by CoNS. However, CoNS has been reported as the cause of nearly 50% of all cases of LOS [7]. These differences may be due to various definitions used to define CoNS sepsis. Some investigators' definitions include whether an appropriate antimicrobial was used to treat the CoNS infection [7]. We did not have access to infant empirical antimicrobial exposures and only included frequency of

positive cultures in our definition. As a result, we excluded a large number of CoNS infections defined as possible infections from the analysis.

Our observed overall mortality associated with EOS (26.0%) is somewhat lower than the mortality observed in the most recently reported cohorts (36–37%) (Table 1) [6, 12]. The mortality associated with LOS in our cohort was lower (15.1%) than in previous cohorts (Table 1) [7, 13]. This is despite the fact that we observed fewer episodes of LOS caused by CoNS, a pathogen typically associated with little to no mortality [17]. Mortality with other gram-positive organisms in our cohort was also associated with relatively low mortality including *Staphylococcus aureus* (10.8%), *Enterococcus* sp. (7.1%), and GBS (7.7%).

Gestational age was a predictor of both EOS and LOS. Intrauterine infection is a risk factor for preterm birth and EOS. Less mature infants also require longer periods of mechanical ventilation, central venous access, and hospitalizations, placing them at higher risk for nosocomial infections and LOS.

Using multivariable regression to control for potential confounders, EOS and LOS were associated with increased risk of mortality (OR = 1.45 [95% CI 1.21, 1.73], and OR = 1.30 [95% CI 1.21, 1.40], respectively) in this cohort of infants. In addition to increased mortality, VLBW infants who survive episodes of sepsis are at increased risk for developing morbidities, including bronchopulmonary dysplasia, patent ductus arteriosus, prolonged hospital stay, and neurodevelopmental impairment [7–11].

The present study is the largest evaluation of sepsis in VLBW infants. Strengths of this report include a large sample size; population diversity from a large number of NICUs; quantification of every culture (blood, urine, cerebrospinal fluid) obtained for all VLBW infants during the study period; and the contemporary nature of the study period. This study is limited by lack of documentation of clinical signs or laboratory findings supportive of sepsis, and lack of information on presence and duration of central catheters and congenital anomalies requiring surgery.

We observed the following associated with EOS and LOS among VLBW infants: 1) most VLBW infants evaluated with a culture during the first 3 days of life did not have culture-proven sepsis; 2) the majority of EOS episodes were caused by gram-negative organisms; 3) the majority of LOS episodes were caused by gram-positive organisms; and 4) overall mortality in VLBW infants with EOS and LOS is higher than in infants with negative cultures.

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Table 1

Recent studies of early- and late-onset sepsis in very-low-birth-weight infants

	Total N	N (%) with sepsis	Years	Number of centers	Overall mortality (%)	Mortality of infants with sepsis (%)
Early-onset sepsis						
1996 ^{1,4}	7606	147 (1.9)	1991–1993	12	18	26
2002 ⁶	5447	84 (1.5)	1998–2000	15	13	37
2005 ¹²	5999	102 (1.7)	2002–2003	16	11	35
Late-onset sepsis						
1996 ¹³	6911	1696 (24.5)	1991–1993	12	9	17
2002 ⁷	6215	1313 (21.1)	1998–2000	15	10	18

Table 2

Demographics^a

	EOS – positive cultures, N=1037	EOS – negative cultures, N=88,243	P	LOS – positive cultures, N=14,628	LOS – negative cultures, N=150,116	P
Gestational age (weeks)			<0.001			<0.001
<25	23.7	10.6		21.1	10.4	
25–28	49.0	41.8		57.7	53.3	
>28	27.2	47.6		21.2	36.3	
Birth weight (g)			<0.001			<0.001
<500	3.0	2.2		3.9	2.1	
501–750	28.8	16.8		33.4	19.9	
751–1000	25.6	22.9		31.4	29.2	
1001–1250	19.2	25.9		19.4	26.6	
1251–1500	23.5	32.2		11.9	22.2	
Race/ethnicity			0.05			<0.001
White	43.5	47.5		44.6	47.5	
African American	30.5	27.1		28.4	26.3	
Hispanic	21.4	20.6		22.6	21.4	
Other	4.6	4.8		4.4	4.8	
Male sex	48.7	50.7	0.21	53.9	53.2	0.17
Maternal age (years)			0.02			<0.001
<20	11.6	13.2		14.1	13.2	
20–29	46.2	49.3		50.9	49.6	
30–39	38.0	33.9		32.0	33.5	
40	4.2	3.6		3.1	3.7	
5-minute Apgar score			<0.001			<0.001
0–3	13.7	4.5		6.3	4.4	
4–6	30.2	16.8		23.0	18.3	
7–10	56.2	78.7		70.7	77.3	
Antenatal steroids	70.5	73.1	0.06	73.7	74.8	0.016
Antenatal antibiotics	56.6	42.0	<0.001	44.7	42.7	<0.001
Cesarean section	63.9	71.7	<0.001	67.9	72.0	<0.001

	EOS – positive cultures, N=1037	EOS – negative cultures, N=88,243	P	LOS – positive cultures, N=14,628	LOS – negative cultures, N=150,116	P
Ventilator on day of life 1	85.7	64.8	<0.001	83.4	73.1	<0.001
Inborn	84.4	89.2	<0.001	84.8	85.9	0.001

^aData presented as percentages.

EOS, early-onset sepsis; LOS, late-onset sepsis.

Table 3

Microbiology of early- and late-onset sepsis

	EOS, N (%)	Mortality (%)	LOS, N (%)	Mortality (%)
Gram-positive organisms	356 (34.3)	24.7	8984 (61.4)	10.6
CoNS	24 (2.3)	0	4133 (28.3)	9.4
<i>Enterococcus</i> sp.	17 (1.6)	20.0	1001 (6.8)	7.1
Group B <i>Streptococcus</i>	189 (18.2)	27.1	448 (3.1)	7.7
<i>Listeria monocytogenes</i>	13 (1.3)	25.0	1 (0.01)	100.0
<i>Staphylococcus aureus</i>	22 (2.1)	15.0	2258 (15.4)	10.8
Gram-negative organisms	604 (58.2)	28.0	3829 (26.2)	21.3
<i>Enterobacter</i> sp.	5 (0.5)	20.0	720 (4.9)	12.4
<i>Escherichia coli</i>	346 (33.4)	23.4	900 (6.2)	17.9
<i>Haemophilus influenza</i>	96 (9.3)	19.1	7 (0.1)	33.3
<i>Klebsiella</i> sp.	16 (1.5)	11.1	990 (6.8)	12.7
<i>Pseudomonas</i> sp.	12 (1.2)	30.0	300 (2.1)	35.0
<i>Serratia</i> sp.	7 (0.7)	42.9	363 (2.5)	14.8
<i>Candida</i> sp.	28 (2.7)	28.0	1528 (10.5)	28.8
Other	49 (4.7)	10.6	287 (2.0)	14.2
Total	1037 (100)	26.0	14,628 (100)	15.1

CoNS, coagulase-negative *Staphylococcus*; EOS, early-onset sepsis; LOS, late-onset sepsis.

Table 4

Risk factors for early- and late-onset sepsis, odds ratio (95% confidence interval)

	Early-onset sepsis	Late-onset sepsis
Gestational age (weeks)	0.92 (0.89, 0.94)	0.89 (0.86, 0.93)
Race/ethnicity		
<i>White</i>	1.00 (reference)	1.00 (reference)
<i>African American</i>	NS	NS
<i>Hispanic</i>	NS	NS
<i>Other</i>	NS	NS
Male sex	0.85 (0.75, 0.98)	NS
5-minute Apgar score	0.83 (0.81, 0.86)	NS
Antenatal antibiotics	1.87 (1.63, 2.15)	1.33 (1.07,1.66)
Antenatal steroids	NS	NS
Cesarean section	NS	NS
Ventilator on day of life 1	1.76 (1.42, 2.18)	NS
Inborn	0.79 (0.65, 0.96)	NS

Table 5

Risk factors for mortality, odds ratio (95% confidence interval)

	Early-onset sepsis	Late-onset sepsis
Sepsis	1.45 (1.21, 1.73)	1.30 (1.21, 1.40)
Gestational age (weeks)	0.65 (0.64, 0.65)	0.69 (.67, 0.70)
Race		
<i>White</i>	1.00 (reference)	1.00 (reference)
<i>African American</i>	NS	1.28 (1.18, 1.39)
<i>Hispanic</i>	1.45 (1.21, 1.73)	1.35 (1.24, 1.48)
<i>Other</i>	NS	1.22 (1.3, 1.44)
Male sex	1.23 (1.16, 1.30)	1.21 (1.13, 1.30)
5-minute Apgar score	0.81 (0.80, 0.82)	0.91 (.89, 0.93)
Antenatal steroids	0.62 (.58, 0.66)	0.78 (0.71, 0.84)
Antenatal antibiotics	0.80 (.75, .85)	0.82 (.77, .89)
Cesarean section	NS	NS
Ventilator on day of life 1	2.47 (2.20, 2.76)	1.34 (1.18, 1.52)