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Late-Onset Bloodstream Infections in Hospitalized Term Infants

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Abstract

Background—The epidemiology and incidence of late-onset bloodstream infections (BSIs) in premature infants has been described, but studies describing late-onset BSI in term infants are sparse. We sought to describe the pathogens, incidence, risk factors, and mortality of late-onset BSI in hospitalized term infants.

Methods—A cohort study was conducted of infants 37 weeks gestational age and 120 days old discharged from Pediatric Medical Group neonatal intensive care units from 1997–2010. We examined all cultures obtained from day of life (DOL) 4–120 and used multivariable regression to assess risk factors for late-onset BSI.

Results—We found a total of 206,019 infants cared for between DOL 4 and 120, and the incidence of late-onset BSI was 2.7/1000 admissions. We identified Gram-positive organisms in 64% of the cultures and Gram-negative organisms in 26%. We found a decreased risk of late-onset BSI in infants with the following characteristics: small for gestational age, delivery by Cesarean section, antenatal antibiotic use, and discharged in the later years of the study. Late-onset BSI increased the risk of death after controlling for confounders (odds ratio 8.43 [95% confidence interval 4.42, 16.07]).

Conclusion—Our data highlight the importance of late-onset BSI in hospitalized term infants. We identified Gram-positive organisms as the most common pathogen, and late-onset BSI was an independent risk factor for death.

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Conflicts of Interest

The remaining authors have no potential conflicts to disclose.

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Keywords

sepsis; infant; term birth; infection

Although the incidence of blood stream infections (BSI) in term infants is relatively low, BSI-related mortality and morbidity are high.^{1,2} The epidemiology and incidence of late-onset BSIs in premature infants has been described, but studies describing late-onset BSI in term infants are sparse.^{3,4} Late-onset BSIs in premature infants are most often caused by coagulase-negative staphylococci (CoNS).^{5–7} Group B *Streptococcus* (GBS) is the leading cause of early-onset BSI in term infants despite the implementation of intrapartum antibiotic prophylaxis.⁵

Considering that a high proportion of infants admitted to the neonatal intensive care unit (NICU) are term infants, the need for recent data describing the epidemiology of late-onset BSI in this population is dire.⁸ We evaluated pathogen distribution, incidence, risk factors, and mortality of late-onset BSIs in term infants using contemporary data from a large cohort of hospitalized infants.

METHODS

Study Design and Setting

We identified all infants born 37 weeks gestational age (GA), admitted 120 days of life to 315 NICUs managed by the Pediatrix Medical Group in the United States, and discharged from 1997–2010. We used an administrative database that prospectively captures information from daily progress notes, laboratory results, admission and discharge notes, and maternal information. Clinicians generated notes using a computer-assisted tool on all infants cared for by the Pediatrix Medical Group. We excluded infants: 1) discharged prior to day of life (DOL) 4; 2) with major congenital anomalies; and 3) who had surgery prior to DOL 120. We collected information on neonatal and maternal demographics, discharge data, and all blood cultures drawn for each patient.

Definitions

We defined late-onset BSIs as a positive blood culture for an identified pathogen if the culture was obtained between 4 and 120 days of life; early-onset BSIs were defined as a positive blood culture in the first 3 days of life. Multiple positive blood cultures for the same organism within 21 days were considered a single episode of sepsis, and we excluded organisms considered contaminants, including non-speciated streptococci, *Bacillus* sp., *Corynebacterium* sp., diphtheroids, Gram-positive rods other than *Listeria* sp., *Lactobacillus* sp., *Micrococcus* sp., *Stomatococcus* sp., and *Bacteroides* sp. We included CoNS in the analysis if there were: 1) 2 positive blood cultures for CoNS in a 4-day period, or 2) 3 positive blood cultures for CoNS in a 7-day period, or 3) 4 positive blood cultures in a 10-day period.

We excluded infants with major congenital anomaly, which was defined as an anomaly presenting at birth with 1 of the following characteristics: 1) lethal; 2) life-shortening; 3)

life-threatening; 4) requiring major surgery; or 5) affecting the infant's quality of life in a significant way.^{9,10} The neonatologist recorded maternal antibiotic use on admission of the infant to the NICU. We classified infants as small for gestational age if birth weight was <10th percentile for age and sex.¹¹ Mortality was calculated for each organism, considering the organism identified closest to death as the cause of death for infants with >1 organism identified. If >1 organism was identified at the same day, for the culture closest to death, we considered both organisms as the cause of death.

Statistical Methods

We examined the distribution of positive blood cultures and calculated the incidence of sepsis per 1000 NICU admissions. We used time-to-event analysis with Cox model hazard ratio to assess the risk factors for late-onset BSIs among hospitalized infants and allowed for multiple failures in the Cox model. Risk of late-onset BSIs was the dependent variable, and the covariates included were GA, sex, ethnicity, small-for-gestational-age status, Apgar score at 5 minutes, mode of delivery, use of antenatal antibiotics, history of early-onset BSIs, and discharge year. To examine the relationship between late-onset BSIs and risk of death, we used multivariable logistic regression controlling for the same covariates.

STATA 12.1 (College Station, TX) was used to perform the statistical analyses. All statistical tests were 2-sided with significance defined as a *P*value <0.05. Permission to conduct this analysis was provided by the Duke University Institutional Review Board.

RESULTS

We included in the analysis a total of 206,019 infants cared for between DOL 4 and 120 (Figure 1). Of 15,480 (8%) infants who had at least 1 culture done, 3% (534) met our definition for late-onset BSI. We identified 552 episodes of late-onset BSI (18 infants had 2 episodes). The overall incidence of late-onset BSI was 2.7 episodes per 1000 NICU admissions. The mean age at late-onset BSI diagnosis was 11 days (5th, 95th percentiles: 8, 34).

For both infected and non-infected infants, the mean GA was 39 weeks (37, 41), and the mean birth weight was 3275 g (2085, 4332) and 3313 g (2343, 4285), respectively. Both infected and non-infected groups were mostly male, but a higher number of infants in the non-infected group received antenatal antibiotics (24% vs. 16%) (Table 1). The mean length of stay for infected infants was 20 days (4, 48) and for non-infected infants was 8 days (3, 17). Most infants (96%) were admitted on or before DOL 3. The mean day of admission was 4 (0, 21) for infected and 1 (0, 3) for non-infected infants.

Gram-positive organisms were the most frequent pathogens (64%) (Table 2). Gram-negative organisms represented 26% of the positive cultures, and *E. coli* (14%) was the most predominant organism in this group. We identified yeast in 5% of infants with late-onset BSI. Although the overall incidence of late-onset BSI decreased slightly over time, the incidence in 1997 was not statistically lower than that in 2010—3.3 vs. 2.5/1000 admissions; *p*=0.63 (Figure 2).

On multivariable regression, infants with the following characteristics had a reduced risk of late-onset BSI: small for gestational age, delivered via Cesarean section, exposed to antenatal antibiotics, and discharged later (Table 3). Black race was associated with higher risk of late-onset BSI.

Overall mortality was 0.3% (529/197,984). Among infants with late-onset BSI, 4% (20/480) died, compared with 0.3% (509/197,504) of non-infected infants. Mortality by organism group was highest for yeast (13% [3/23]), followed by Gram-negative organisms (4% [5/128]) and Gram-positive organisms (4% [12/319]). The organisms with highest mortality were *Pseudomonas* sp. (17% [1/6]) in the Gram-negative group and group B *Streptococcus* (7% [2/30]) among Gram-positives (Table 2). On multivariable regression, late-onset BSI was associated with increased risk of mortality (odds ratio 8.43 [95% confidence interval 4.42, 16.07]).

DISCUSSION

This is one of the largest studies to date examining late-onset BSI in hospitalized term infants. Previous studies of neonatal sepsis often included both term and premature infants.^{3,4,12–19} We examined changes in the incidence and pathogen distribution of late-onset BSI in term infants only.

The incidence of late-onset BSIs in our cohort was 2.7/1000 admissions, lower than the incidence of late-onset BSIs in hospitalized late preterm infants (6.3/1000 admissions).³ As previously reported for premature infants, Gram-positive cocci were the most prevalent organism for late-onset BSIs in term infants, and CoNS the most prevalent organism among these.⁶ Late-onset BSI pathogen distribution in our population was similar to previous reports from very-low-birth-weight (VLBW, <1500 g birth weight) and late preterm infants.^{3,7,18}

Risk factors for late-onset BSIs in premature infants include birth weight, GA, antenatal use of antibiotics, major congenital anomaly, presence of central line, and parenteral nutrition.^{6,20–22} In our proportional hazard model, small for gestational age, delivery by Cesarean section, and antenatal antibiotic use were associated with lower risk of late-onset BSI. More recent discharge year was also associated with decreased risk of late-onset BSI and may be related to improvement of infection control practices during the study period. We included year in the model to minimize the effect of confounders related to changes in infection control practices. The effect of site was tested but was not included in the results because it did not affect our results. Black race was associated with increased risk of late-onset BSI. This finding is consistent with previously reported racial disparity in late-onset GBS disease.^{23, 24}

The lower risk of late-onset BSI in small-for-gestational-age infants may be explained by the fact that they are often hospitalized simply because of their size rather than acuity of illness. Antenatal antibiotic exposure decreased risk of late-onset BSI as previously published.²⁵ However, there is a concern that antenatal antibiotic exposure may increase bacterial resistance.²⁶ However, we did not have access to antibiotic resistance patterns.

There are few recent data on mortality for hospitalized term infants with late-onset BSIs. In VLBW infants, the mortality associated with late-onset BSI is 4% vs. 0.3% among infants with late-onset BSI in our cohort.⁷ We do not have the cause of mortality for each infant, but there was a significant difference in mortality among infants with and without late-onset BSIs, and late-onset BSI was associated with increased risk of death after controlling for clinical and demographic characteristics in our multivariable regression.

Strengths of our study include the large sample size and the large number of NICUs represented. The measurement of incidence of sepsis is comprehensive, as the data source is derived from electronic medical records and has the advantage of capturing the results of every culture (positive or negative) from admission through discharge. Some variables likely related to the incidence of sepsis (antibiotic resistance, presence of maternal fever, presence of a central catheter or chorioamnionitis) were not available in our data. In addition, we were unable to identify the species for all positive cultures, and source of the blood culture (peripheral vs. line) was not available in the data.

Our results highlight the importance of late-onset BSIs in term infants without major congenital anomalies. Late-onset BSI was an independent risk factor for death. Large databases can be used to identify pathogen distribution and changes over time for specific populations, helping to guide strategies to reduce the incidence of late-onset BSI and target the use of appropriate empirical antimicrobial regimens.

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Figure 1.
Study population. DOL indicates day of life; GA, gestational age.

Figure 2.

Incidence of late-onset sepsis bloodstream infection by year. CoNS indicates coagulase-negative staphylococci; GBS, group B *Streptococcus*.

TABLE 1

Demographics, N (%)

	No Late-onset BSI (n=205,485)	Late-onset BSI (n=534)
Gestational age (weeks)		
37	42,953 (21)	110 (21)
38	51,415 (25)	155 (29)
39	50,857 (25)	120 (23)
40	44,441 (22)	117 (22)
41	13,789 (7)	22 (4)
42	2030 (1)	10 (2)
Male	120,521 (59)	331 (62)
Race/ethnicity		
White	96,029 (49)	187 (38)
Black	29,265 (15)	80 (16)
Hispanic	57,407 (30)	200 (40)
Other	11,413 (6)	29 (6)
Small for gestational age	22,539 (11)	74 (14)
Apgar score at 5 minutes		
0–3	2817 (1)	19 (4)
4–6	10,878 (5)	36 (8)
7–10	185,436 (93)	414 (88)
Cesarean delivery	90,937 (45)	215 (42)
Antenatal antibiotics	49,699 (24)	83 (16)
Early-onset BSI	2055 (1)	11 (2)

BSI indicates bloodstream infection.

TABLE 2

Incidence and Mortality of Late-onset Bloodstream Infection

Organism	Episodes, n (%)	Episodes/1000 NICU Admissions	Mortality (%)
Gram-positive organisms	353 (64)	1.7	3.7
GPC (unspecified)	153 (28)	0.7	3.0
Coagulase-negative staphylococci	71 (13)	0.3	4.6
<i>Staphylococcus aureus</i>	70 (13)	0.3	4.6
Group B <i>Streptococcus</i>	31 (6)	0.2	6.7
<i>Enterococcus</i> sp.	27 (5)	0.1	0
Gram-negative organisms	146 (26)	0.7	3.9
<i>Escherichia coli</i>	76 (14)	0.4	2.8
<i>Klebsiella</i> sp.	17 (3)	0.1	0
GNR (unspecified)	16 (3)	0.1	9.1
<i>Enterobacter</i> sp.	14 (3)	0.1	0
<i>Pseudomonas</i> sp.	6 (1)	0.03	16.7
<i>Serratia</i> sp.	5 (1)	0.02	0
Yeast	28 (5)	0.1	13.0
Other	25 (5)	0.1	0
Total	552	2.7	4.2

GPC indicates gram-positive cocci; GNR, gram-negative rods.

TABLE 3**Risk Factors Associated with Late-onset Bloodstream Infection**

	Adjusted HR (95% CI)	P
Gestational age (weeks)		
37	Reference	-
38	1.25 (0.96, 1.62)	0.10
39	1.10 (0.83, 1.46)	0.50
40	1.18 (0.88, 1.57)	0.27
41	0.60 (0.36, 1.02)	0.06
42	0.59 (0.22, 1.62)	0.31
Male	1.02 (0.85, 1.23)	0.82
Race/ethnicity		
White	Reference	-
Black	1.40 (1.07, 1.83)	0.01
Hispanic	1.15 (0.93, 1.42)	0.19
Other	0.95 (0.62, 1.46)	0.82
Small for gestational age	0.66 (0.50, 0.86)	0.002
Apgar score at 5 minutes		
7–10	Reference	-
4–6	0.86 (0.61, 1.21)	0.39
1–3	0.72 (0.46, 1.14)	0.17
Cesarean delivery	0.77 (0.64, 0.93)	0.007
Antenatal antibiotics	0.71 (0.55, 0.92)	0.009
Early-onset BSI	0.64 (0.36, 1.14)	0.13
Discharge year	0.96 (0.93, 0.98)	<0.001

HR indicates hazard ratio; CI, confidence interval; BSI, bloodstream infection.