Late-Onset Sepsis Among Very Preterm Infants

Dustin D. Flannery, DO, MSCE,[a,b,c] Erika M. Edwards, PhD, MPH,[d,e,f] Sarah A. Coggins, MD,[a,c] Jeffrey D. Horbar, MD,[d,f] Karen M. Puopolo, MD, PhD[a,b,c]

abstract

OBJECTIVES: To determine the epidemiology, microbiology, and associated outcomes of late-onset sepsis among very preterm infants using a large and nationally representative cohort of NICUs across the United States.

METHODS: Prospective observational study of very preterm infants born 401 to 1500 g and/or 22 to 29 weeks' gestational age (GA) from January 1, 2018, to December 31, 2020, who survived >3 days in 774 participating Vermont Oxford Network centers. Late-onset sepsis was defined as isolation of a pathogenic bacteria from blood and/or cerebrospinal fluid, or fungi from blood, obtained >3 days after birth. Demographics, clinical characteristics, and outcomes were compared between infants with and without late-onset sepsis.

RESULTS: Of 118 650 infants, 10 501 (8.9%) had late-onset sepsis for an incidence rate of 88.5 per 1000 (99% confidence interval [CI] [86.4–90.7]). Incidence was highest for infants born ≤23 weeks GA (322.0 per 1000, 99% CI [306.3–338.1]). The most common pathogens were coagulase negative staphylococci (29.3%) and *Staphylococcus aureus* (23.0%), but 34 different pathogens were identified. Infected infants had lower survival (adjusted risk ratio [aRR] 0.89, 95% CI [0.87–0.90]) and increased risks of home oxygen (aRR 1.32, 95% CI [1.26–1.38]), tracheostomy (aRR 2.88, 95% CI [2.47–3.37]), and gastrostomy (aRR 2.09, 95% CI [1.93–2.57]) among survivors.

CONCLUSIONS: A substantial proportion of very preterm infants continue to suffer late-onset sepsis, particularly those born at the lowest GAs. Infected infants had higher mortality, and survivors had increased risks of technology-dependent chronic morbidities. The persistent burden and diverse microbiology of late-onset sepsis among very preterm infants underscore the need for innovative and potentially organism-specific prevention strategies.

[a]*Division of Neonatology, and* [b]*Clinical Futures, Children's Hospital of Philadelphia; Philadelphia, Pennsylvania;* [c]*Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania;* [d]*Larner College of Medicine, and* [e]*College of Engineering and Mathematical Sciences at the University of Vermont, Burlington, Vermont; and* [f]*Vermont Oxford Network, Burlington, Vermont*

Dr Flannery conceptualized and designed the study, and drafted the initial manuscript; Dr Edwards contributed to the study design, and conducted the initial analyses; Drs Puopolo and Coggins conceptualized and designed the study; Dr Horbar contributed to the study design, and coordinated and supervised data collection; and all authors reviewed and revised the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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Address correspondence to Dustin D. Flannery, DO, MSCE, Division of Neonatology, Children's Hospital of Philadelphia Newborn Care at Pennsylvania Hospital, 800 Spruce St, Philadelphia, PA 19107. E-mail: flanneryd@chop.edu

WHAT'S KNOWN ON THE SUBJECT: Late-onset sepsis is a significant cause of morbidity and mortality among very preterm infants, leading to high rates of empirical antibiotic administration for suspected infection. Substantial infection prevention efforts have been implemented over the last 3 decades.

WHAT THIS STUDY ADDS: Late-onset sepsis incidence rates in 2018 to 2020 have plateaued, and remained alarmingly high among infants born at the lowest gestational ages. Infected very preterm infants had lower survival, and survivors had increased adjusted risks of technology-dependent chronic morbidities.

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Late-onset sepsis is a significant cause of morbidity and mortality among very preterm infants. Infants who develop late-onset sepsis are at higher risk of in-hospital morbidities, death, and poor neurodevelopmental outcomes among survivors.[1–4] Accordingly, substantial late-onset sepsis prevention efforts have been implemented over the last 3 decades.[5] Despite these efforts, antibiotic administration for suspected or confirmed late-onset sepsis drives as much as one-third of antibiotic use in NICUs.[6]

Contemporary data informing late-onset sepsis epidemiology among preterm infants in the United States are crucial to understand the impact of prevention efforts and to continually refine risk assessment and prognostication for infected infants. Pathogen surveillance among preterm infants with late-onset sepsis also informs empirical antibiotic decisions when late-onset sepsis is suspected, and allows for detection of changing microbiological trends. Reports that focus solely on extremely low birth weight (BW) and low gestational age (GA) infants do not address the incidence and outcomes of pathogen-specific infections across the GA spectrum. In this study, we sought to determine the epidemiology, microbiology, and associated outcomes of late-onset sepsis among very preterm infants born 2018 to 2020 using a large and nationally representative cohort from NICUs across the United States.

METHODS

Data Source and Study Population

Vermont Oxford Network (VON) is a worldwide community of practice dedicated to improving the quality, safety, and value of newborn care through a coordinated program of quality improvement, education, and research. This prospective observational study included infants born 401 to 1500 g and/or 22 to 29 weeks' GA at the reporting hospital, or transferred to the reporting hospital within 28 days after birth, from January 1, 2018, to December 31, 2020, at 774 participating centers from 49 US states. Infants who died in the delivery room or who had length of stay of <4 days were excluded. Data were collected from birth until hospital discharge, death, or first birthday (whichever came first). Transferred infants were tracked to determine their ultimate disposition and LOS. The institutional review board at the University of Vermont determined that use of the VON database for this analysis was not human subjects research.

Study Definitions

Late-onset sepsis was defined as isolation of a bacterial or fungal pathogen from blood and/or bacterial pathogen from cerebrospinal fluid cultures obtained >3 days after birth. Pathogenic species were specified in the VON manual of operations (Supplemental Information).[7] Coagulase-negative staphylococci (CONS) from blood or cerebrospinal fluid culture was considered a true case of late-onset sepsis if there were signs of generalized infection and ≥5 days of antibiotics. For *Staphylococcus aureus*, data collection did not distinguish between methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) isolates. For fungi, pathogen was not recorded. For infants with >1 pathogen identified, we could not distinguish between polymicrobial infection in a single episode and multiple episodes.

The primary outcome was survival to hospital discharge. Secondary outcomes among survivors included home oxygen, tracheostomy, and gastrostomy (or jejunostomy). Infants who had tracheostomy or gastrostomy at transfer were assumed to have these at discharge; infants on supplemental oxygen at the time of transfer were not assumed to have this at discharge. Maternal race/ethnicity, maternal hypertensive disorders, maternal diabetes, chorioamnionitis, antenatal steroids, congenital anomalies, pneumothorax, periventricular leukomalacia, early-onset sepsis, and necrotizing enterocolitis (NEC) were defined per the VON manual of operations.[7] Small for GA was defined as BW <10th percentile.[8] Length of stay was calculated as days from birth to discharge or death. Chronic lung disease was defined for infants born <33 weeks' GA as supplemental oxygen at 36 weeks' corrected GA or as oxygen dependence at transfer if transferred at 34 or 35 weeks' GA. Severe intraventricular hemorrhage was defined as grade 3 or 4 on the basis of radiographic imaging before day 28 after birth. Severe retinopathy of prematurity was defined as stage 3 to 5 disease.[9] All morbidities occurred before discharge or death; late-onset sepsis, retinopathy, NEC, pneumothorax, and leukomalacia were not associated with a specific timing relative to birth. NICU level of care was defined using the VON membership survey.

Statistical Analysis

Demographics, clinical characteristics, and unadjusted outcomes were compared between infants with and without late-onset sepsis using standard descriptive statistics. The incidence rate of late-onset sepsis was determined per 1000 eligible infants overall, by study year, by GA category, and by pathogen type (CONS, Group B

Streptococcus [GBS], other gram-positive, gram-negative, and fungal). Incidence analyses among the same cohort were repeated using the composite outcome of late-onset sepsis or death, as these are competing outcomes. The proportion of deaths for infants with and without late-onset sepsis was determined overall, by GA category, and by pathogen type. Outcomes were evaluated using generalized estimating equation regressions, adjusting for GA, small for GA, multiple birth, mode of delivery (vaginal or cesarean), inborn/outborn status, and accounting for clustering of infants within centers. Statistical analyses were performed using SAS 9.4 (Cary, N.C.).

RESULTS

Characteristics of the Study Participants and Centers

During the study period, 124 497 infants born 401 to 1500 g and/or 22–29 weeks' GA were admitted to participating NICUs, of which 118 650 infants survived >3 days and were included in the analysis (Table 1). Median BW was 1110 g (interquartile range [IQR] 834–1340) and median GA was 28 weeks (IQR 26–30). Half of cohort infants were male and the median length of stay among survivors was 66 days (IQR 45–96). Of the infants admitted to centers with NICU-level designation available (N = 118 192), 29 325 (24.8%) were at NICU Type A, 52 706 (44.6%) were at NICU Type B, and 36 161 (30.6%) were at NICU Type C centers. Regarding US geographic region designation, 17 722 (14.9%) infants were admitted to centers in the Northeast, 26 196 (22.1%) in the Midwest, 23 359 (19.7%) in the Pacific, and 51 373 (43.3%) in the South.

Incidence

Overall, 10 501 (8.9%) infants had late-onset sepsis for an overall incidence rate of 88.5 per 1000 eligible very preterm infants (99% confidence interval [CI] [86.4–90.7]). Incidence was highest for infants born ≤23 completed weeks' GA (322.0 per 1000; 99% CI [306.3–338.1]) (Table 2). Pathogen-specific incidence rates were similar across the 3 study years, and proportions of infants with all pathogen-specific types of late-onset sepsis increased with decreasing GA (Table 2). Incidence of composite late-onset sepsis or death was 135.1 per 1000 infants (99% CI [132.5–137.6]), and was highest for infants born ≤23 weeks' GA (549.7 per 1000; 99% CI [532.7–566.6]) (Supplemental Table 6).

Microbiology

From the 10 501 infants with late-onset sepsis, 12 117 isolates and 34 pathogens were identified. Gram-positive bacteria accounted for 62.9% of isolates and gram-negatives accounted for 32.0% (Table 3). CONS (3549 of 12 117; 29.3%) and *Staphylococcus aureus* (2784 of 12 117; 23.0%) were the most-common pathogens. *Escherichia coli* (1479 of 12 117; 12.2%) and *Klebsiella* spp. (1005/12 117; 8.3%) were the third and fourth most common pathogens, respectively. *Enterococcus* spp. accounted for 5.3% (642 of 12 117) and fungi accounted for 5.1% (620/12 117); all other pathogens accounted for <5% (Table 3). Distribution of pathogen types by GA demonstrated higher proportions of gram-negative and fungal infections, and lower proportions of GBS and other gram-positive infections, among infants at lower GAs compared with those at higher GAs (Supplemental Table 7). Proportions of CONS infections were similar across GA categories (Supplemental Table 7).

Comparison of Infants With and Without Late-Onset Sepsis

Multiple maternal and infant characteristics differed between infected and uninfected infants (Table 1). Infants with late-onset sepsis were more often born vaginally (33.0% vs 24.5%), to mothers with chorioamnionitis (17.8% vs 12.2%) and without hypertension (30.2% vs 40.3%). Infected infants had lower BWs (median 760 g vs 1140 g) and GAs (median 25 weeks versus 29 weeks) compared with uninfected infants. Infected infants had longer length of stay compared with uninfected infants (median 102 vs 62 days); length of stay was also longer among surviving infants with late-onset sepsis compared with uninfected surviving infants (median 114 vs 64 days). Median length of stay for infants with late-onset sepsis who died was 21 days (IQR 11–46).

Outcomes

Infected infants had lower overall survival (78.2% vs 94.9%; adjusted risk ratio [aRR] 0.89, 95% CI [0.87–0.90]) and lower survival in each GA category (Table 4). Survival among infected infants by pathogen type, overall and by GA category, is shown in Supplemental Table 8. Length of stay among infants who did not survive to hospital discharge, by pathogen type, is shown in Supplemental Table 9. Notably, uninfected infants born ≤23 weeks' GA had 66.4% survival, compared with 75.1% for CONS and 69.1% for GBS (Supplemental Table 8), though median length of stay for uninfected infants born ≤23 weeks' GA was only 10 days (Supplemental Table 9). Infants with late-onset sepsis who survived to discharge had significantly increased adjusted risks for home oxygen (aRR 1.32, 95% CI [1.26–1.38]), tracheostomy (aRR 2.88, 95% CI [2.47–3.37]), and gastrostomy (aRR 2.09, 95% CI [1.93–2.57]) when

TABLE 1 Demographics and Clinical Characteristics of Infants With and Without Late-Onset Sepsis (N = 118 650)

	Overall			Late-Onset Sepsis			No Late-Onset Sepsis		
	N	No.	% or Median (IQR)	*N*	No.	% or Median (IQR)	*N*	No.	% or Median (IQR)
Maternal characteristics									
Race/ethnicity									
Black/Non-Hispanic	117 346	36 873	31.4	10 379	3580	34.5	106 967	33 293	31.1
Hispanic	117 346	22 881	19.5	10 379	2141	20.6	106 967	20 740	19.4
White/Non-Hispanic	117 346	48 067	41.0	10 379	3885	37.4	106 967	44 182	41.3
Asian/Pacific Islander	117 346	5978	5.1	10 379	446	4.3	106 967	5532	5.2
Other Non-Hispanic	117 346	2611	2.2	10 379	235	2.3	106 967	2376	2.2
Hypertension	118 012	46 455	39.4	10 409	3142	30.2	107 603	43 313	40.3
Diabetes	117 620	13 495	11.5	10 364	941	9.1	107 256	12 554	11.7
Antenatal steroids	117 771	104 186	88.2	10 368	9125	87.4	107 403	95 061	88.2
Chorioamnionitis	118 175	14 903	12.7	10 438	1845	17.8	107 737	13 058	12.2
Multiple gestation	118 646	28 643	24.1	10 501	2225	21.2	108 145	26 418	24.4
Vaginal delivery	118 632	30 011	25.3	10 499	3466	33.0	108 133	26 545	24.5
Infant characteristics									
BW, g	118 644	—	1110 (834–1340)	10 499	—	760 (612–985)	108 145	—	1140 (875–1350)
GA, wk	118 646	—	28 (26–30)	10 501	—	25 (24–27)	108 145	—	29 (27–30)
Small for GA	118 323	22 662	19.2	10 406	1631	15.7	107 917	21 031	19.5
Male sex	118 626	59 415	50.1	10 498	5764	54.9	108 128	53 651	49.6
Inborn	118 650	102 492	86.4	10 501	8418	80.2	108 149	94 074	87.0
Congenital anomaly	118 639	6386	5.4	10 499	854	8.1	108 140	5532	5.1
Early onset sepsis	118 614	1353	1.1	10 491	217	2.1	108 123	1136	1.1
NEC	118 636	5799	4.9	10 498	1693	16.1	108 138	4106	3.8
Pneumothorax	118 615	4725	4.0	10 492	784	7.5	108 123	3.941	3.6
Severe intraventricular hemorrhage	109 722	8315	7.6	10 230	1802	17.6	108 123	6513	6.5
Periventricular leukomalacia	110 816	2919	2.6	10 251	653	6.4	99 492	2266	2.3
Chronic lung disease	101 125	30 034	29.7	8155	5059	62.0	92 970	24 975	26.9
Retinopathy of prematurity	95 179	30 313	31.8	8304	5121	61.7	86 875	25 192	29.0
Length of stay, d	118 650	—	64 (42–94)	10 501	—	102 (63–141)	108 149	—	62 (41–89)
Length of stay among survivors, d	110 807	—	66 (45–96)	8199	—	114 (86–150)	102 608	—	64 (44–91)

Infants with >1 pathogen identified were counted once. —, not applicable.

compared with survivors without late-onset sepsis (Table 5).

DISCUSSION

In this large, nationally representative sample of very preterm infants from 2018 to 2020, we observed lower overall incidence rates of late-onset sepsis compared with previous US reports.[10–13] However, incidence among infants born at the lowest GAs who survived >3 days was substantial, approaching 1 in every 3 infants born ≤23 weeks' GA. CONS was the most-common pathogen, but the highly pathogenic *S. aureus* accounted for nearly a quarter of all cases. Remarkably, 34 different pathogens were identified. Very preterm infants with late-onset sepsis died at higher rates, and those who survived had increased adjusted risks of technology-dependent, chronic morbidities upon discharge. The results of this study have important implications for clinicians who care for very preterm infants at risk for late-onset sepsis, choose empirical antibiotic regimens, and discuss prognostication with families. Furthermore, the study results highlight a current challenge in neonatal care. Despite ongoing national quality improvement efforts aimed at late-onset sepsis prevention, and attention paid by local and national public health agencies, as well as insurers, late-onset sepsis persists among very preterm infants. This suggests that prevention efforts and related reductions have likely plateaued.

Our contemporary findings do suggest declines in late-onset sepsis incidence compared with data published over the past 3 decades, although the use of different populations of preterm infants complicates comparisons. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN) collects data from select high-risk academic centers. Among 7861 infants born with BW <1500 g from 1991 to 1993 who survived >3 days after birth, 25% developed late-onset sepsis.[1] Among 6956 preterm

TABLE 2 Incidence of Late-Onset Sepsis Pathogen Types by Study Year and Gestational Age Category

Category	*N*	All Late-Onset Sepsis[a] (No., %)	Incidence Rate Per 1000 Eligible Infants[a] (99% CI)	CONS[b] (No., %)	GBS[b] (No., %)	Other GP[b] (No., %)	GN[b] (No., %)	Fungal[b] (No., %)
Overall	118 650	10 501 (8.9)	88.5 (86.4–90.7)	3549 (3.0)	569 (0.5)	3436 (2.9)	3692 (3.1)	620 (0.5)
Study year								
2018	40 295	3514 (8.7)	87.2 (83.7–90.9)	1224 (3.0)	196 (0.5)	1153 (2.9)	1228 (3.1)	213 (0.5)
2019	40 727	3609 (8.9)	88.6 (85.1–92.3)	1193 (2.9)	203 (0.5)	1182 (2.9)	1261 (3.1)	201 (0.5)
2020	37 628	3378 (9.0)	89.8 (86.0–93.6)	1132 (3.0)	170 (0.5)	1101 (2.9)	1203 (3.2)	206 (0.6)
GA category, completed wk[c]								
≤23	5708	1838 (32.2)	322.0 (306.3–338.1)	611 (10.7)	68 (1.2)	516 (9.0)	766 (13.4)	224 (3.9)
24–25	16 781	3669 (21.9)	218.6 (210.5–227.0)	1270 (7.6)	149 (0.9)	1235 (7.4)	1330 (7.9)	229 (1.4)
26–27	23 368	2583 (11.1)	110.5 (105.4–115.9)	889 (3.8)	159 (0.7)	865 (3.7)	838 (3.6)	104 (0.5)
28–29	32 590	1579 (4.9)	48.5 (45.5–51.6)	509 (1.6)	124 (0.4)	507 (1.6)	530 (1.6)	44 (0.1)
>29	40 199	832 (2.1)	20.7 (18.8–22.6)	270 (0.7)	69 (0.2)	313 (0.8)	228 (0.6)	19 (0.1)

GN, gram-negative; GP, gram-positive.

[a] Infants with >1 pathogen identified were counted once. There were 9067 infants with 1 pathogen identified (7.6% of total and 86.3% of infants with infection), 1270 infants with 2 pathogens identified (1.1% of total and 12.1% of infants with infection), and 164 infants with 3 or more pathogens identified (0.14% of total and 1.6% of infants with infection). Infants with >1 pathogen identified had polymicrobial infection and/or multiple distinct, late-onset sepsis episodes.

[b] Infants with >1 pathogen identified were counted separately in each relevant group.

[c] Four infants with missing GA were not included in the GA-specific counts.

infants born 1998 to 2000 in NRN centers, similar findings were reported in incidence and pathogen distribution.[11] Data from 313 pediatric NICUs from 1997 to 2010 found that 12.2% of very low BW infants suffered from late-onset sepsis.[14] Previous reporting from VON centers found the proportion of very preterm infants with late-onset sepsis declined from 21.1% in 2000 to 15.0% in 2009 and 10.1% in 2014.[12,13] Analysis by GA at birth rather than BW results in higher-reported incidence of infection, but a trend to improvement is still apparent. NRN data encompassing 10 131 infants born <27 weeks' GA born 2000 to 2011 found decreasing rates over time, with 41% suffering late-onset sepsis if born 2000 to 2005, compared with 34% of those born 2006 to 2011.[10] In our study, 24.5% of infants born ≤25 weeks' GA and 17.6% born ≤27 weeks' GA had late-onset sepsis (Table 2), suggesting that further reductions in infection have been accomplished over the past decade among the lowest-GA infants who survive.

Pathogen surveillance informs optimal empirical antibiotic choices, sheds light on the effects of infection prevention efforts, and can detect shifting infection patterns. Historically, CONS was the most-common late-onset sepsis pathogen among very preterm infants and was isolated in more than half of cases in previous reports from US and international cohorts.[1,4,10,11,15–17] In the current study, which included >12000 isolates, only 29.3% of late-onset sepsis was caused by CONS, whereas 23.0% was caused by *S. aureus*. Variable definitions of CONS infection may partially explain the proportional difference, though the overall decline in late-onset sepsis incidence combined with the increasing proportion of *S. aureus* infections may indicate infection prevention practices have disproportionately reduced CONS infections. The pathogenesis of CONS infections is such that certain infection prevention practices may be particularly effective (for example, bundles aimed at reducing central line-associated bloodstream infection).[18] The biologic origins of *S. aureus* infections include direct invasion of colonized mucosal surfaces and may be less amenable to practice improvements focused on optimal central-line care.[19,20] Gram-negative organisms were isolated in one-third of late-onset sepsis cases, in contrast to ∼20% of cases in previous reports.[1,4,10,14] Fungal species, which accounted for up to 10% of late-onset sepsis cases in previous reports, were isolated in only 5.1% of cases.[1,10]

Our results do not clearly identify the optimal choice of empirical therapy but do inform this important clinical decision. First, the relative proportions of CONS and *S. aureus* infections and the higher survival among infants infected with CONS support efforts to reduce empirical vancomycin use.[21,22] Although we could not distinguish between MSSA and MRSA, previous studies have found that MRSA late-onset sepsis is less common than MSSA.[15,23,24] Centers that use routine MRSA surveillance may consider selective use of antistaphylococcal penicillins in place of empirical vancomycin for suspected late-onset sepsis.[25] Second, gram-negative bacteria accounted for one-third of identified pathogens, and infants with gram-negative infection had increased mortality, especially among infants

TABLE 3 Microbiology of Late-Onset Sepsis

Pathogen	No., %
Gram-positive bacteria	7621 (62.9)
Coagulase-negative staphylococci	3549 (29.3)
Staphylococcus aureus	2784 (23.0)
Enterococcus spp.	642 (5.3)
GBS	569 (4.7)
Streptococcus pneumoniae	24 (0.2)
Streptococcus pyogenes	23 (0.2)
Streptococcus anginosus	20 (0.2)
Clostridium spp.	9 (0.1)
Listeria spp.	1 (0.0)
Gram-negative bacteria	3876 (32.0)
Escherichia coli	1479 (12.2)
Klebsiella spp.	1005 (8.3)
Enterobacter spp.	441 (3.6)
Pseudomonas spp.	379 (3.1)
Serratia spp.	275 (2.3)
Citrobacter spp.	62 (0.5)
Acinetobacter spp.	52 (0.4)
Proteus spp.	46 (0.4)
Stenotrophomonas maltophilia	37 (0.3)
Haemophilus spp.	17 (0.1)
Morganella morganii	16 (0.1)
Salmonella spp.	13 (0.1)
Bacteroides spp.	11 (0.1)
Moraxella spp.	8 (0.1)
Achromobacter spp.	7 (0.1)
Pantoea spp.	7 (0.1)
Neisseria spp.	5 (0.0)
Burkholderia spp.	5 (0.0)
Flavobacterium spp.	4 (0.0)
Ralstonia spp.	2 (0.0)
Alcaligenes spp.	1 (0.0)
Campylobacter spp.	1 (0.0)
Chryseobacterium spp.	1 (0.0)
Prevotella spp.	1 (0.0)
Providencia spp.	1 (0.0)
Fungi	620 (5.1)
Total	12 117

There were 12 117 pathogens identified among 10 501 infants. Percentages are out of total number of identified pathogens. Infants with >1 pathogen identified were counted more than once. No infections were reported for *Aeromonas* species or *Pasteurella* species.

at the lowest GAs. Therefore, empirical gram-negative coverage for very preterm infants with suspected late-onset sepsis remains warranted. Although susceptibility data were not available, the paucity of *Pseudomonas* isolates in our cohort and recent reports of neonatal *E. coli* and other gram-negative pathogen susceptibilities suggest that an aminoglycoside or third-generation cephalosporin may be most appropriate for infants without risk factors for multidrug-resistant infection.[26,27] Third, although we could not account for antifungal prophylaxis, routine empirical antifungal coverage for suspected late-onset sepsis is likely not warranted in most instances: only 0.5% of infants in this cohort had fungal late-onset sepsis. Our results also support consideration of GA at birth when making empirical antimicrobial decisions. Not only were infants of the lowest GAs at highest risk of infection, 46.1% of pathogens identified among infants ≤23 weeks' GA were gram-negative or fungal organisms, with a combined incidence rate of 173 per 1000. Differential fungal infection by GA is particularly notable: 10% of pathogens identified among infants born ≤23 weeks' GA were fungal organisms (incidence rate 39 per 1000), whereas 2.5% of pathogens identified among infants born ≥28 weeks' GA were fungal organisms (incidence rate 0.9 per 1000).

We were unable to assess the temporal association of late infection and specific morbidities of prematurity. Nonetheless, the pathogen-specific association of late-onset sepsis with death and higher rates of neonatal, in-hospital morbidities suggest that either the sickest infants are also at risk for late-onset sepsis, or that late-onset sepsis contributes to preterm morbidity and mortality. Previous studies have supported causation, but the predominance of late-onset sepsis among infants born <26 weeks, ~1 of every 4 infants, suggests that the association likely goes in both directions.[1,11] Survivors of late infection also had higher adjusted risks of technology-dependent, chronic morbidities, including home oxygen, tracheostomy, and gastrostomy, which are associated with significant health burden and resource utilization, including hospital readmissions in the first year after birth.[28–30] Importantly, infants with late-onset sepsis born ≤23 weeks' GA had higher rates of survival than uninfected infants, but uninfected infants born ≤23 weeks' GA had median survival of only 10 days, suggesting survival bias.

Our findings suggest that novel approaches will be needed to make further reductions in late-onset sepsis. The predominance of highly pathogenic organisms infecting the lowest-GA infants argues that new tools need to be added to established prevention efforts, such as central-line care bundles, hand hygiene, early enteral feeding, and

TABLE 4 Survival Among Infants With or Without Late-Onset Sepsis, Overall and by Gestational Age Category

	Any Late-Onset Sepsis			No Late-Onset Sepsis			
	N	No.	%	*N*	No.	%	aRR (95% CI)
Overall	10 491	8199	78.2	108 131	102 608	94.9	0.89 (0.87–0.90)[a]
GA category, completed wk							
≤23	1837	1155	62.9	3869	2570	66.4	0.95 (0.91–0.99)[b]
24–25	3665	2790	76.1	13 106	11 216	85.6	0.90 (0.89–0.92)[b]
26–27	2579	2156	83.6	20 778	19 690	94.8	0.90 (0.88–0.91)[b]
28–29	1579	1388	87.9	31 008	30 363	97.9	0.91 (0.89–0.92)[b]
>29	831	710	85.4	39 366	38 765	98.5	0.87 (0.85–0.90)[b]

Infants with >1 pathogen identified were counted once. Twenty-eight infants were missing data on survival and were not included in the analysis.

[a] Adjusted for GA, small for GA, multiple birth, vaginal delivery, sex, inborn, and clustering of infants within hospitals.

[b] Adjusted for small for GA, multiple birth, vaginal delivery, sex, inborn, and clustering of infants within hospitals.

TABLE 5 Secondary Outcomes Among Infants With or Without Late-Onset Sepsis Who Survived to Hospital Discharge or Transfer

	Any Late-Onset Sepsis			No Late-Onset Sepsis			
Outcome	*N*	No.	%	*N*	No.	%	aRR (95% CI)[a]
Home oxygen	6891	2602	37.8	94 408	12 453	13.2	1.32 (1.26–1.38)
Tracheostomy	8197	295	3.6	102 593	582	0.6	2.89 (2.47–3.37)
Gastrostomy	8197	1198	14.6	102 593	3873	3.8	2.09 (1.93–2.56)

Infants with >1 pathogen identified were counted once. Infants who had tracheostomy or gastrostomy at the time of transfer were assumed to have these at hospital discharge; infants who were on supplemental oxygen at the time of transfer were not assumed to have this at hospital discharge.

[a] Adjusted for GA, small for GA, multiple birth, vaginal delivery, sex, inborn, and clustering of infants within hospitals.

fluconazole prophylaxis.[31–35] A better understanding of late-onset sepsis pathogenesis is needed: to the extent that some infections are because of invasive events after colonization of mucosal surfaces, strategies to prevent specific strain colonization, interrupt translocation, or promote bloodstream clearance are necessary. In addition, neonatal clinicians should recognize those infections that simply may not be preventable with current strategies. GBS disease accounted for 6.3% of late-onset sepsis among infants born ≥26 weeks' GA, with an incidence rate of 3.7 per 1000, which is 10-fold higher than the overall national incidence of late-onset GBS infection.[36] There are no effective strategies for the prevention of late-onset GBS infection. Currently, strategies exist to decrease but not eliminate the risk of NEC, and associated infections, among preterm infants.[37] Similarly, late-onset sepsis secondary to urinary tract infection is a common cause of serious bacterial infection, and there are no strategies for primary prevention unless urinary tract anomalies are recognized.[38] As resuscitation near the limit of viability increases, the imperative to improve late-onset sepsis prevention through a better understanding of pathogenesis is clear: 1 of every 2 infants born ≤23 weeks' GA in our study who survived past day 3 either died later or suffered late-onset sepsis.

The strengths of this study include prospective data collection with validation audits and access to the overall VON data set that inform robust statistical adjustment. The findings should be generalizable to most centers across the country that care for very preterm infants. The study does have limitations. Some important data were not available, including maternal and neonatal antimicrobial agents, invasive interventions which may increase the risk of infection, antimicrobial susceptibilities (including inability to distinguish between MRSA and MSSA), fungal pathogen speciation (though we speculate that most were *Candida* species), urine and other specimen culture results, and postdischarge outcomes (including later death and duration of home oxygen, tracheostomy, and gastrostomy). Importantly, we were unable to delineate timing of late infection or distinguish between polymicrobial versus multiple episodes of infection and bacteremia versus meningitis.

CONCLUSIONS

Late-onset sepsis incidence among very preterm infants remains substantial, particularly among infants born at the lowest GAs. CONS and *S. aureus* were the predominant pathogens. Infants with late-onset sepsis suffered from higher mortality, and survivors had increased risks of technology-dependent, chronic morbidities. The persistent burden and diverse microbiology of late-onset sepsis among very preterm infants underscore the need for innovative and potentially organism-specific prevention strategies.

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ABBREVIATIONS

aRR: adjusted risk ratio
BW: birth weight
CI: confidence interval
CONS: coagulase negative staphylococci
GA: gestational age
GBS: Group B *Streptococcus*
IQR: interquartile range
MRSA: methicillin-resistant *Staphylococcus aureus*
MSSA: methicillin-sensitive *Staphylococcus aureus*
NEC: necrotizing enterocolitis
NRN: Neonatal Research Network
VON: Vermont Oxford Network

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