Early-Onset Sepsis Among Very Preterm Infants

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abstract

OBJECTIVES: To determine the epidemiology and microbiology of early-onset sepsis (EOS) among very preterm infants using a nationally representative cohort from academic and community hospitals to inform empirical antibiotic guidance, highlight risk factors for infection, and aid in prognostication for infected infants.

METHODS: Prospective observational study of very preterm infants born weighing 401 to 1500 g or at 22 to 29 weeks' gestational age from January 2018 to December 2019 in 753 Vermont Oxford Network centers. EOS was defined as a culture-confirmed bacterial infection of the blood or cerebrospinal fluid in the 3 days after birth. Demographics, clinical characteristics, and outcomes were compared between infants with and without EOS.

RESULTS: Of 84 333 included infants, 1139 had EOS for an incidence rate of 13.5 per 1000 very preterm births (99% confidence interval [CI] 12.5–14.6). *Escherichia coli* (538 of 1158; 46.5%) and group B *Streptococcus* (218 of 1158; 18.8%) were the most common pathogens. Infected infants had longer lengths of stay (median 92 vs 66 days) and lower rates of survival (67.5% vs 90.4%; adjusted risk ratio 0.82 [95% CI 0.79–0.85]) and of survival without morbidity (26.1% vs 59.4%; adjusted risk ratio 0.66 [95% CI 0.60–0.72]).

CONCLUSIONS: In a nationally representative sample of very preterm infants with EOS from 2018 to 2019, approximately one-third of isolates were neither group B *Streptococcus* nor *E coli*. Three-quarters of all infected infants either died or survived with a major medical morbidity. The profoundly negative impact of EOS on very preterm infants highlights the need for novel preventive strategies.

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WHAT'S KNOWN ON THIS SUBJECT: Studies conducted in high-risk perinatal centers have identified *Escherichia coli* and group B *Streptococcus* as the most common organisms causing early-onset sepsis. Few data inform the full spectrum of pathogens or the impact of infection on outcomes among surviving infants.

WHAT THIS STUDY ADDS: Although *E coli* and group B *Streptococcus* were most common, one-third of infections were due to other pathogens. Very preterm infants with early-onset sepsis had higher adjusted risks of death and major medical morbidity compared with those uninfected.

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Early-onset sepsis (EOS) is a significant cause of morbidity and mortality among newborn infants. The overall incidence of the disease in the US birth population is ~1 case per 1000 live births but is ~10-fold higher among infants born preterm.[1] For preterm infants at the lowest gestational ages (GAs), EOS-related mortality approaches 50%.[2] Because of this risk, ~80% of very preterm infants are started on empirical antibiotics at birth, with little change over the last decade despite ongoing refinements in EOS risk assessment.[3,4]

Infection epidemiology is important to guide empirical antibiotic decisions in neonatal care. The recommended empirical antibiotic regimen for preterm infants at risk for EOS, according to the American Academy of Pediatrics (AAP) Committee on the Fetus and Newborn, is the dual combination of ampicillin and gentamicin.[2] This recommendation is based on previous reports and knowledge about the typical EOS pathogens infecting preterm infants. Previously, the most common organism causing EOS in preterm infants was *Streptococcus agalactiae* (group B *Streptococcus* [GBS]).[5] However, more recently, *Escherichia coli* has become the most common cause, followed by GBS.[1,6] Continued surveillance of EOS epidemiology is especially important in light of recent debate on the continued utility of ampicillin and gentamicin for empirical coverage.[7] In 2 separate reports, up to 1 in 10 *E coli* isolates causing neonatal EOS were resistant to both ampicillin and gentamicin.[1,8] Although the regimen provides adequate coverage for GBS, because this organism remains almost universally sensitive to ampicillin, there is concern about increasing prevalence of EOS infections due to organisms besides *E coli* and GBS, including other multidrug-resistant Gram-negative bacteria.[1,9,10] Furthermore, as the landscape of EOS microbiology continues to evolve, the impact of the disease on both short- and long-term outcomes must be continually assessed. The objective of this study was to determine the epidemiology, microbiology, and related outcomes of EOS among very preterm infants by using a large, contemporary, and nationally representative prospective cohort from both academic and community hospitals across the United States.

METHODS

Data Source and Study Population

Vermont Oxford Network (VON) is a nonprofit voluntary worldwide community of practice dedicated to improving the quality, safety, and value of care for newborns through a coordinated program of data-driven quality improvement, education, and research. VON maintains a voluntary database for collecting and benchmarking data from NICU care of very low birth weight (VLBW) (birth weight [BW] <1500 g) infants. This was a prospective observational study of infants born weighing 401 to 1500 g or at 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, 2019. Infants born at 22 to 29 weeks' GA were included regardless of BW, and infants with a BW of 401 to 1500 g were included regardless of GA. Data from 753 participating centers in 49 states across the United States were included. Infants who died in the delivery room were excluded. Data were collected from birth until hospital discharge, death, or first birthday (whichever came first). Infants who were transferred were tracked to determine their ultimate disposition and length of stay. 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

Exposure

EOS was defined as a culture-confirmed infection of the blood or cerebrospinal fluid (CSF) by a prespecified bacterial pathogen (Supplemental Information) in the first 3 days after birth. For *Staphylococcus aureus*, there was no distinction between methicillin-sensitive and methicillin-resistant isolates. Polymicrobial infections were counted once for Tables 1 and 2 and were reported individually in Table 3.

Outcomes

The primary outcome was survival to hospital discharge. There were 2 secondary outcomes: survival without morbidity by using the VON Manual of Operations definition[11] (survival without any of the following: necrotizing enterocolitis [NEC], chronic lung disease [CLD], severe intraventricular hemorrhage [IVH], pneumothorax, late-onset sepsis, or cystic periventricular leukomalacia [PVL]) and survival with major neonatal morbidity (including CLD, IVH, PVL, and/or severe retinopathy of prematurity [ROP]). The latter outcome is focused on the morbidities that may predict death after NICU discharge or survival with neurodevelopmental impairment.[12] CLD was defined for infants born at <33 weeks' GA as supplemental oxygen requirement at 36 weeks' corrected GA or as oxygen dependence at transfer if transferred at 34 or 35 weeks' GA. Severe IVH was defined as grade 3 or 4 on the basis of a cranial ultrasound, computed tomography scan, or MRI before day 28 from birth.[13] Severe ROP was defined as stage 3 to 5 ROP among infants who received an ophthalmologic examination.[14] NEC was defined as at least 1 clinical

TABLE 1 Demographics, Clinical Characteristics, and Outcomes of Infants With and Without EOS

	Overall (*N* = 84 333)	Infected (EOS) (*n* = 1139)	Not Infected (No EOS) (*n* = 83 191)
Maternal characteristics			
Race and/or ethnicity			
Black, non-Hispanic	26 109/83 539 (31.2)	375/1124 (33.4)	25 734/82 415 (31.2)
Hispanic	16 320/83 539 (19.5)	247/1124 (22.0)	16 073/82 415 (19.5)
White, non-Hispanic	34 293/83 539 (41.1)	402/1124 (35.8)	33 893/82 415 (41.2)
Asian American, non-Hispanic	4332/83 539 (5.2)	57/1124 (5.1)	4275/82 415 (5.2)
American Indian, non-Hispanic	690/83 539 (0.8)	8/1124 (0.7)	682/82 415 (0.8)
Other, non-Hispanic	1793/83 539 (2.2)	35/1124 (3.1)	1758/82 415 (2.1)
Any prenatal care	80 822/84 018 (96.2)	1067/1133 (94.2)	79 755/82 885 (96.2)
Hypertensive disorder	31 830/83 887 (37.9)	170/1126 (15.1)	31 660/82 761 (38.3)
Chorioamnionitis	10 849/83 600 (13.0)	515/1121 (45.8)	10 034/82 479 (12.5)
Diabetes	9179/83 734 (11.0)	103/1128 (9.2)	9076/82 606 (11.0)
Antenatal steroids	73 691/83 977 (87.8)	977/1134 (86.3)	72 714/82 843 (87.8)
Multiple gestation	20 555/84 329 (24.4)	177/1139 (15.6)	20 378/83 190 (24.5)
Cesarean delivery	62 594/84 322 (74.2)	659/1139 (57.9)	61 935/83 183 (74.5)
Infant characteristics			
BW, *n*	84 325	1139	83 186
Median (Q1, Q3), g	1100 (810, 1330)	870 (650, 1170)	1100 (819, 1334)
GA, *n*	84 329	1139	83 190
≤23 wk	4908/84 329 (5.8)	223/1139 (19.6)	4685/83 190 (5.6)
24–25 wk	12 482/84 329 (14.8)	324/1139 (28.5)	12 158/83 190 (14.6)
26–27 wk	16 574/84 329 (19.7)	259/1139 (22.7)	16 315/83 190 (19.6)
28–29 wk	22 762/84 329 (27.0)	229/1139 (20.1)	22 533/83 190 (27.1)
>29 wk	27 603/84 329 (32.7)	104/1139 (9.1)	27 499/83 190 (33.1)
Median (Q1, Q3), wk	28 (26, 30)	26 (24, 28)	28 (26, 30)
Apgar score at 1 min, *n*	83 416	1113	82 303
Median (Q1, Q3)	5 (3, 7)	3 (1, 5)	5 (3, 7)
SGA	16 048/84 009 (19.1)	48/1123 (4.3)	16 000/82 886 (19.3)
Female sex	41 802/84 310 (49.6)	528/1139 (46.3)	41 275/83 171 (49.6)
Outborn	11 396/84 333 (13.5)	180/1139 (15.8)	11 216/83 194 (13.5)
Congenital anomaly	4953/84 311 (5.9)	49/1139 (4.3)	4904/83 172 (5.9)
Infant individual outcomes			
NEC	3967/84 307 (4.7)	69/1139 (6.1)	3898/83 168 (4.7)
CLD	20 474/69 219 (29.6)	315/746 (42.2)	20 159/68 473 (29.4)
Late-onset sepsis	7184/81 149 (8.9)	156/946 (16.5)	7028/80 203 (8.8)
Pneumothorax	3895/84 290 (4.6)	105/1138 (9.2)	3790/83 152 (4.6)
Severe IVH	6206/76 270 (8.1)	342/990 (34.6)	5864/75 280 (7.8)
Cystic PVL	2039/76 288 (2.7)	76/990 (7.7)	1963/75 298 (2.6)
Total length of stay among survivors, *n*	75 596	763	74 833
Median (Q1, Q3), d	66 (45, 96)	92 (66, 123)	66 (45, 95)
By GA			
≤23 wk, *n*	2538	106	2422
Median (Q1, Q3), d	143 (122, 175)	148 (124, 194)	143 (122, 174)
24–25 wk, *n*	9539	191	9348
Median (Q1, Q3), d	115 (98, 142)	115 (97, 146)	115 (98, 141)
26–27 wk, *n*	14 941	191	14 750
Median (Q1, Q3), d	87 (73, 107)	90 (75, 105)	87 (73, 107)
28–29 wk, *n*	21 777	187	21 590
Median (Q1, Q3), d	63 (52, 78)	64 (53, 81)	63 (52, 78)
>29 wk, *n*	26 807	88	26 719
Median (Q1, Q3), d	40 (31, 52)	46 (37, 65)	40 (31, 52)

Data are presented as numerator/denominator (%) unless otherwise stated. Q1, quartile 1; Q3, quartile 3.

(bilious gastric aspirate or emesis, abdominal distension, occult or gross blood in stool) and at least 1 radiographic finding (pneumatosis intestinalis, hepato-biliary gas, pneumoperitoneum). Pneumothorax was diagnosed as extrapleural air by chest radiograph or thoracentesis. Late-onset sepsis was defined as culture-confirmed infection of the blood (bacterial or fungal) or CSF (bacterial), or culture-confirmed coagulase-negative *Staphylococcus* infection (blood or CSF) with signs of infection and at least 5 days of antibiotic treatment, occurring after day 3 from birth. Cystic PVL was defined as evidence based on a cranial ultrasound, computed tomography scan, or MRI scan at any time. All morbidities occurred before

TABLE 2 Incidence of Early-Onset Neonatal Infection by Study Year, BW Category, and GA Category

Category	*n*	Infected (EOS)	Incidence Rate per 1000 Births (99% CI)
Overall	84 333	1139	13.5 (12.5–14.6)
2018	41 094	534	13.0 (11.6–14.5)
2019	43 249	605	14.0 (12.6–15.5)
BW, g			
≤500	2697	55	20.4 (14.5–28.7)
501–750	14 326	355	24.7 (21.6–28.3)
751–1000	17 736	305	17.2 (14.9–19.9)
1001–1250	20 871	210	10.0 (8.4–11.9)
1251–1500	26 415	188	7.1 (5.9–8.6)
≥1501	2280	26	11.4 (6.9–18.7)
GA, completed wk			
≤23	4908	223	45.4 (38.3–53.7)
24–25	12 482	324	26.0 (22.6–29.9)
26–27	16 574	259	15.5 (13.2–18.2)
28–29	22 762	229	10.1 (8.5–11.9)
>29	27 603	104	3.8 (2.9–4.9)

NICU discharge or death; in the VON database, severe ROP, NEC, pneumothorax, late-onset sepsis, and cystic PVL are not associated with a specific timing relative to birth.

Covariates

Covariates of interest were defined per the VON Manual of Operations definitions.[11] Race and/or ethnicity, acknowledged as a social construct, was obtained by personal interview with the mother, by review of the birth certificate, or per medical record, in that order, and was included because of previously reported racial and/or ethnic disparities in care practice and outcomes (including EOS) among preterm infants in the United States.[9,15,16] The following maternal variables were defined by notation in the infant or maternal medical record: maternal hypertensive disorders, including chronic or pregnancy-induced maternal hypertension, with or without associated preeclampsia; maternal diabetes of any type or severity; and obstetric clinical diagnosis of chorioamnionitis. Prenatal care was defined as any prenatal obstetrical care before the birth admission. Antenatal steroid treatment was defined as betamethasone, dexamethasone, or hydrocortisone administered intramuscularly or intravenously to the mother at any time before delivery. Small for gestational age (SGA) was defined as BW in the <10th percentile by using the Fenton prenatal growth charts.[17] Length of stay was calculated as total days from birth to hospital discharge or death. Congenital anomalies included those on a prespecified list or, if not on the list, those that were lethal (primary cause of death) or life-threatening (treated with surgical or medical therapy to correct an anatomic anomaly or physiologic dysfunction before discharge).[11]

NICU level of care is defined in the VON database as follows: type A, restrictions on mechanical ventilation and/or major surgery not performed; type B, no restrictions on ventilation and major surgery performed; and type C, no restrictions on ventilation and major surgery performed, including cardiac surgery. Geographical region was assigned by using the US Census Bureau classifications.

Statistical Analysis

The incidence rate of EOS was determined per 1000 very preterm births overall and by GA category. The microbiology of EOS was determined by using proportions of infecting isolates overall and by Gram-positive or Gram-negative

TABLE 3 Microbiology of EOS Among 1139 Infants

Pathogen	Overall, *n* (%)
Gram-positive	382 (33.2)
GBS	218 (18.8)
S aureus	73 (6.3)
Enterococcus species	32 (2.8)
Streptococcus anginosus	20 (1.7)
Listeria monocytogenes	18 (1.6)
Streptococcus pneumoniae	15 (1.3)
Streptococcus pyogenes	9 (0.8)
Gram-negative	767 (66.8)
E coli	538 (46.5)
Haemophilus species	90 (7.8)
Klebsiella species	46 (4.0)
Enterobacter species	16 (1.4)
Citrobacter species	15 (1.3)
Morganella morganii	14 (1.2)
Pseudomonas species	12 (1.0)
Serratia species	12 (1.0)
Bacteroides species	11 (0.9)
Acinetobacter species	5 (0.4)
Proteus species	4 (0.3)
Flavobacterium species	3 (0.3)
Moraxella species	2 (0.2)
Neisseria species	2 (0.2)
Burkholderia species	1 (0.1)
Campylobacter species	1 (0.1)
Pantoea species	1 (0.1)
Total	1158 (100)

Percentages of the total number of infections. No infections were reported for *Clostridium* species, *Achromobacter* species, *Aeromonas* species, *Alcaligenes* species, *Chryseobacterium* species, *Pasteurella* species, *Providencia* species, *Prevotella* species, *Ralstonia* species, *Salmonella* species, or *Stenotrophomonas maltophilia*.

isolate status. Demographics and clinical characteristics were compared between infants with and without EOS by using standard descriptive statistics. The proportion of deaths was determined overall and by GA category. The primary outcomes were evaluated by using generalized estimating equation regressions controlling for factors present at birth known to affect outcomes, including GA, inborn or outborn status, infant sex, SGA, multiple gestation, Apgar score at 1 minute, mode of delivery, and presence of a congenital anomaly, as well as clustering of infants within hospitals. Statistical analyses were performed by using SAS 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Characteristics of the Study Participants and Centers

A total 84 333 infants born weighing 401 to 1500 g or at 22 to 29 weeks' GA were included in the analysis. For the overall cohort (Table 1), the median BW was 1100 g (interquartile range [IQR] 810–1330) and the median GA was 28 weeks (IQR 26–30). Fifty percent of infants were female, and the median length of stay was 66 days (IQR 45–95). Of the infants admitted to centers with NICU level designation available (n = 83 321), 20 440 (24.5%) were at NICU type A, 37 178 (44.6%) were at NICU type B, and 25 703 (30.8%) were at NICU type C centers. Of the infants admitted to centers with US geographic region designation available (n = 84 333), 12 539 (14.9%) were in the Northeast, 18 657 (22.1%) were in the Midwest, 16 638 (19.7%) were in the West, and 36 499 (43.3%) were in the South.

EOS Incidence Rate and Microbiology

There were 1139 infants who had EOS for an incidence rate of 13.5 per 1000 very preterm births (99% confidence interval [CI] 12.5–14.6). The incidence rate was similar between 2018 and 2019 and was highest for infants born at ≤23 completed weeks' GA (45.4 per 1000 [99% CI 38.3–53.7]; Table 2). *E coli* (538 of 1158; 46.5%) and GBS (218 of 1158; 18.8%) were the most common pathogens identified, although 402 of 1158 (34.7%) were other bacteria (Table 3). *Haemophilus* species (n = 90; 7.8%) and *S aureus* (n = 73; 6.3%) isolates were the third and fourth most common causes of EOS infections, respectively.

Comparison of Infants With and Without EOS

Infants with EOS were more often born vaginally and to mothers with chorioamnionitis and without hypertension or multiple gestation (Table 1). Infected infants were also less often SGA and had lower BWs and GAs compared with uninfected infants. There were no major differences in sex, race, or ethnicity between the 2 groups (Table 1). Including infants who died before NICU discharge, lengths of stay were longer for infants with EOS compared with uninfected infants (median 92 vs 66 days).

Outcomes

Infants with EOS had lower rates of survival to hospital discharge (67.5% vs 90.4%; adjusted risk ratio 0.82 [95% CI 0.79–0.85]; Table 4). Infants without EOS were more than twice as likely to survive to hospital discharge without morbidity (VON metric) compared with infants without EOS (Table 4). Infants with EOS who survived to discharge were at significantly increased risk for ≥1

TABLE 4 Survival and Survival Without Morbidity for Infants With and Without EOS, by GA

Outcome	Overall	Infected (EOS)	Not Infected (No EOS)	Adjusted Risk Ratio (95% CI)
`Survival	75 703/84 029 (90.1)	765/1133 (67.5)	74 938/82 896 (90.4)	0.82[a] (0.79–0.85)
By GA,[b] wk				
≤23	2358/4882 (51.6)	107/221 (48.4)	2431/4661 (52.2)	0.90 (0.77–1.05)
24–25	9569/12 387 (77.3)	191/322 (59.3)	9378/12 065 (77.7)	0.74 (0.68–0.81)
26–27	14 968/16 494 (90.8)	191/258 (74.0)	14 777/16 236 (91.0)	0.80 (0.74–0.86)
28–29	21 799/22 711 (96.0)	188/228 (82.5)	21 611/22 483 (96.1)	0.86 (0.81–0.91)
>29	26 825/27 551 (97.4)	88/104 (84.6)	26 737/27 447 (97.4)	0.86 (0.79–0.94)
Survival without morbidity[c] (VON metric)	49 390/83 941 (58.9)	294/1130 (26.1)	49 0926/82 811 (59.4)	0.66[a] (0.60–0.72)
By GA,[b] wk				
≤23	340/4877 (7.0)	5/221 (2.3)	335/4656 (7.2)	0.25 (0.09–0.64)
24–25	2560/12 372 (20.7)	43/321 (13.4)	2517/12 051 (20.9)	0.60 (0.45–0.80)
26–27	7479/16 475 (45.4)	79/258 (30.6)	7400/16 217 (45.6)	0.63 (0.52–0.76)
28–29	15 591/22 687 (68.7)	109/226 (48.2)	15 482/22 461 (68.9)	0.69 (0.61–0.79)
>29	23 416/27 526 (85.1)	58/104 (55.8)	23 358/27 422 (85.2)	0.65 (0.55–0.78)

Data are presented as numerator/denominator (%) unless otherwise stated.

[a] Adjusted for GA, inborn or outborn status, infant sex, SGA, multiple gestation, Apgar score at 1 min, mode of delivery, and presence of a congenital anomaly.

[b] Adjusted for inborn or outborn status, infant sex, SGA, multiple gestation, Apgar score at 1 min, mode of delivery, and presence of a congenital anomaly.

[c] The VON metric is defined as survival without any of the following: NEC, CLD, severe IVH, pneumothorax, late-onset sepsis, and cystic PVL.

TABLE 5 Survival With Major Neonatal Morbidity for Infants With and Without EOS

Survival With Major Neonatal Morbidity (CLD, sIVH or PVL, sROP)	Overall	Infected (EOS)	Not Infected (No EOS)	Adjusted Risk Ratio[a] (95% CI)
0 morbidities	37 805/59 841 (63.2)	286/682 (41.9)	37 519/59 159 (63.4)	Reference
1 morbidity	16 909/59 841 (28.3)	239/682 (35.0)	16 670/59 159 (28.2)	1.39 (1.22–1.57)
2 morbidities	4412/59 841 (7.4)	120/682 (17.6)	4292/59 159 (7.3)	1.92 (1.50–2.48)
3 morbidities	715/59 841 (1.2)	37/582 (5.4)	678/59 159 (1.1)	2.67 (1.83–3.90)

Data are presented as numerator/denominator (%) unless otherwise stated. sIVH, severe intraventricular hemorrhage; sROP, severe retinopathy of prematurity.
[a] Adjusted for GA, inborn or outborn status, infant sex, SGA, multiple gestation, Apgar score at 1 min, mode of delivery, and presence of a congenital anomaly.

major neonatal morbidity (CLD, IVH or PVL, ROP) when compared with infants without EOS, after adjustment for confounders (Table 5).

DISCUSSION

In this nationally representative sample of very preterm infants from 2018 to 2019, incidence rates of EOS remain substantial, particularly among infants at the lowest GAs. *E coli* was the most common EOS pathogen, but approximately one-third of EOS isolates were neither GBS nor *E coli*. Very preterm infants with EOS died at higher rates, and those who survived the infection had a significantly lower rate of surviving without VON-defined morbidities. Notably, VLBW survivors of EOS were more likely to suffer brain injury, retinopathy, and CLD, complications of prematurity that have been associated with subsequent risk of neurodevelopmental impairment or later death.[12] The results of this study have important implications for clinicians who must assess sepsis risk and choose empirical antibiotics for very preterm infants and who counsel families both before and after very preterm birth.

EOS risk assessment for preterm infants is challenged by the relatively high incidence of infection (compared with term infants), by the prevalence of traditional risk factors for perinatal infection, and by the physiologic instability inherent to very preterm infants that can be difficult, if not impossible, to distinguish from instability due to infection. Current AAP guidance for EOS risk assessment among preterm infants endorses an approach based on the etiology of preterm birth and circumstances of delivery that may be used to categorize infants as at lower or higher risk of EOS.[2] Although the clinical detail available in this study does not allow strict classification in the manner recommended by the AAP, our findings do support that approach. Consistent with the known association of intraamniotic infection as an etiology of spontaneous preterm birth,[18,19] the obstetric diagnosis of chorioamnionitis was made in the mothers of ~13% of all infants in our cohort as well as all uninfected infants, yet it was present in 46% of infected infants. AAP guidance strongly recommends evaluation and empirical treatment of preterm infants born to women with suspected or proven chorioamnionitis.[2] In contrast, diagnoses associated with medically indicated preterm birth (maternal hypertensive disorders and fetal growth restriction) were present in far lower proportions of infected infants compared with the overall and uninfected infants (Table 1). Another important finding that can aid clinicians in risk assessment is that the size of this study and available clinical detail allow further discrimination by gestational week. The incidence of EOS in our study is similar to contemporary Neonatal Research Network data.[1] In contrast to other recent EOS studies, however, we were able to the quantify the differential impact of GA. In this study, incidence of EOS was inversely related to GA. Roughly 1 of every 20 infants born at ≤23 weeks' gestation suffered EOS; in contrast, ~1 of every 100 infants born at 28 to 29 weeks' gestation were infected. Among VLBW infants born at >29 weeks' GA, incidence declined further to 1 of every 200 to 250 infants. Incidence of EOS was also inversely related to BW, except for very premature infants born weighing >1500 g. We interpret this as the impact of GA and infants born SGA, that is, heavier infants born at lower GAs are more at risk for EOS than lighter infants born at higher GAs.

The microbiology of EOS informs the content of empirical antibiotic therapies. This large and contemporary cohort largely confirms and extends the findings of Centers for Disease Control and Prevention (CDC) active surveillance conducted in 2005–2014 and the findings of a *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) study of high-risk centers conducted in 2015–2017.[1,20] Although the accounting of GA and BW differed slightly among these and the current study, approximately half of infections among VLBW infants were due to *E coli*, and 10% to 20% were due to GBS in these reports.[1,20] Antibiotic susceptibility data for each EOS isolate were not available in our data. The CDC and NICHD studies found ~8% to 10% of EOS *E coli* isolates to be resistant to both ampicillin and gentamicin.[1,20] Using known

antibiotic susceptibilities of organisms other than GBS and *E coli*, we speculate that *S aureus* (6.3% of all infections) and most of the other Gram-negative organisms in our cohort would be resistant to ampicillin. Therefore, many may not be optimally treated given that gentamicin monotherapy would not be considered sufficient therapy for such infections. These data strongly support current AAP guidance that suggests additional empirical therapy with a broader-spectrum agent may be indicated in high-risk cases until culture results are known.[2] Although we excluded coagulase-negative staphylococci (CONS) isolates in our analysis, reports from Europe, Canada, and China have found relatively high proportions of EOS caused by CONS.[21–23] It is possible that different parturient colonization patterns contribute to variation in EOS microbiology. However, the Canadian report, in particular, was unable to distinguish contaminating species from true infections,[23] a persistent challenge with interpretation of CONS isolation among neonates.

Neonatal clinicians play a key role in counseling both patients with threatened preterm birth, and families whose newborn has suffered EOS. Our study provides important and, we believe, sobering data to inform these conversations. Similar to CDC and NICHD reports,[1,20] approximately one-third of VLBW infants with EOS died, in contrast to the 90% rate of survival in the uninfected infants. The differential impact of infection on GA-specific survival is notable. Although EOS does not significantly impact the already high rate of mortality among infants born at ≤23 weeks' gestation, the relative impact is substantial for those born at ≥24 weeks' gestation, in which infected infants die at 2 to 6 times the rate of the uninfected. We speculate that the differential impact of EOS may be explained by the relative proportion of births that are due to spontaneous preterm birth prompted by intraamniotic infection at each GA week. Importantly, infants who survived EOS had a markedly lower rate of survival without specified morbidities, even when adjusted for GA and multiple other predictors of preterm morbidity. In particular, survivors of EOS had a higher adjusted risk of suffering specific morbidities that have been associated with both neurodevelopmental impairment in early childhood and risk of death after NICU discharge.[12] This information may be critically important to inform conversation and joint decision-making around obstetric management and neonatal care, particularly at the lowest GAs, when there is high obstetric concern for intraamniotic infection (chorioamnionitis) as the etiology of preterm birth.

The strengths of our study include prospective data collection by using standardized definitions and access to the overall VON data set, which informs robust statistical adjustment. Given that >700 neonatal centers from 49 states across the United States contribute data to VON, our findings are generalizable to most preterm infants cared for in the United States. The limitations of our study were primarily related to unavailable data, including maternal antibiotic data, pathogen susceptibility profile data, fungal pathogen data, and postdischarge outcomes. In addition, we were unable to distinguish bloodstream infection from meningitis.

CONCLUSIONS

In a nationally representative cohort study of very preterm infants from 2018 to 2019, the overall incidence rate of EOS was 13.5 per 1000 very preterm live births and increased significantly with decreasing GA. *E coli* was the most common infecting pathogen, but approximately one-third of isolates were neither GBS nor *E coli*. Very preterm infants with EOS died at higher rates, and survivors had significantly increased risk of morbidities compared with uninfected infants. The profoundly negative impact of EOS on very preterm infants highlights the need for novel preventive strategies among such infants.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
BW: birth weight
CDC: Centers for Disease Control and Prevention
CI: confidence interval
CLD: chronic lung disease
CONS: coagulase-negative staphylococci
CSF: cerebrospinal fluid
EOS: early-onset sepsis
GA: gestational age
GBS: group B *Streptococcus*
IVH: intraventricular hemorrhage
NEC: necrotizing enterocolitis
NICHD: *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
PVL: periventricular leukomalacia
ROP: retinopathy of prematurity
SGA: small for gestational age
VLBW: very low birth weight
VON: Vermont Oxford Network

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