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Early-Onset Neonatal Sepsis 2015 to 2017, the Rise of *Escherichia coli*, and the Need for Novel Prevention Strategies

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IMPORTANCE Early-onset sepsis (EOS) remains a potentially fatal newborn condition. Ongoing surveillance is critical to optimize prevention and treatment strategies.

OBJECTIVE To describe the current incidence, microbiology, morbidity, and mortality of EOS among a cohort of term and preterm infants.

DESIGN, SETTING, AND PARTICIPANTS This prospective surveillance study included a cohort of infants born at a gestational age (GA) of at least 22 weeks and birth weight of greater than 400 g from 18 centers of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network from April 1, 2015, to March 31, 2017. Data were analyzed from June 14, 2019, to January 28, 2020.

MAIN OUTCOMES AND MEASURES Early-onset sepsis defined by isolation of pathogenic species from blood or cerebrospinal fluid culture within 72 hours of birth and antibiotic treatment for at least 5 days or until death.

RESULTS A total of 235 EOS cases (127 male [54.0%]) were identified among 217 480 newborns (1.08 [95% CI, 0.95-1.23] cases per 1000 live births). Incidence varied significantly by GA and was highest among infants with a GA of 22 to 28 weeks (18.47 [95% CI, 14.57-23.38] cases per 1000). No significant differences in EOS incidence were observed by sex, race, or ethnicity. The most frequent pathogens were *Escherichia coli* (86 [36.6%]) and group B streptococcus (GBS; 71 [30.2%]). *E coli* disease primarily occurred among preterm infants (68 of 131 [51.9%]); GBS disease primarily occurred among term infants (54 of 104 [51.9%]), with 24 of 45 GBS cases (53.3%) seen in infants born to mothers with negative GBS screening test results. Intrapartum antibiotics were administered to 162 mothers (68.9%; 110 of 131 [84.0%] preterm and 52 of 104 [50.0%] term), most commonly for suspected chorioamnionitis. Neonatal empirical antibiotic treatment most frequently included ampicillin and gentamicin. All GBS isolates were tested, but only 18 of 81 (22.2%) *E coli* isolates tested were susceptible to ampicillin; 6 of 77 *E coli* isolates (7.8%) were resistant to both ampicillin and gentamicin. Nearly all newborns with EOS (220 of 235 [93.6%]) displayed signs of illness within 72 hours of birth. Death occurred in 38 of 131 infected infants with GA of less than 37 weeks (29.0%); no term infants died. Compared with earlier surveillance (2006-2009), the rate of *E coli* infection increased among very low-birth-weight (401-1500 g) infants (8.68 [95% CI, 6.50-11.60] vs 5.07 [95% CI, 3.93-6.53] per 1000 live births; $P = .008$).

CONCLUSIONS AND RELEVANCE In this study, EOS incidence and associated mortality disproportionately occurred in preterm infants. Contemporary cases have demonstrated the limitations of current GBS prevention strategies. The increase in *E coli* infections among very low-birth-weight infants warrants continued study. Ampicillin and gentamicin remained effective antibiotics in most cases, but ongoing surveillance should monitor antibiotic susceptibilities of EOS pathogens.

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Supplemental content

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Neonatal early-onset sepsis (EOS) remains a significant cause of morbidity and mortality. National surveillance conducted by the Centers for Disease Control and Prevention from 2005 to 2014 demonstrated that most EOS cases occur in term infants, but incidence and infection-attributable mortality are higher in preterm infants.[1] Obstetric and neonatal professional organizations have collaborated for more than 20 years to provide recommendations for the use of intrapartum antibiotics to prevent EOS.[2-4] From 2017 to 2019, the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics updated guidance for intrapartum antibiotic use in women with concern for evolving intra-amniotic infection, for antenatal screening and intrapartum antibiotic prophylaxis (IAP) to prevent group B streptococcal (GBS)-specific infection, and for administration of empirical antibiotic therapy to newborns at risk for EOS.[5-9] Optimal guidance depends on longitudinal surveillance to characterize the epidemiology, microbiology, and antibiotic susceptibilities of EOS.

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) longitudinally studies the epidemiology of EOS among extremely preterm infants through its high-risk infant registry and periodically conducts surveillance among all infants born at NRN centers.[10-12] This 2-year prospective cohort study includes a birth cohort of more than 100 000 live births per year and was undertaken to monitor rates of infection, pathogen distribution, antibiotic susceptibilities, disease severity, and outcomes.

Key Points

Question What is the incidence and microbiology of contemporary cases of neonatal early-onset sepsis?

Findings This cohort study of 217 480 infants identified 235 cases of early-onset sepsis from 2015 to 2017; *Escherichia coli* (86 [36.6%]) and group B streptococcus (71 [30.2%]) were the most common pathogens, with *E coli* most frequent among preterm infants and group B streptococcus most frequent among term infants. Of note, 6 of 77 *E coli* isolates (7.8%) were resistant to both ampicillin and gentamicin, the most commonly used agents for empirical therapy.

Meaning These findings suggest that early-onset sepsis persists despite recommended prevention strategies and requires ongoing surveillance for shifts in etiologic agents and antimicrobial resistance.

Methods

Study Period and Definitions

Prospective surveillance for EOS and early-onset meningitis was conducted from April 1, 2015, to March 31, 2017, among all infants with a gestational age (GA) of at least 22 weeks and birth weight of more than 400 g born at 18 NRN centers. Early-onset sepsis and early-onset meningitis were defined by isolation of a pathogen from blood or cerebrospinal fluid (CSF) culture obtained within 72 hours after birth and treatment with antibiotics for at least 5 days (<5 days if death occurred while receiving antibiotics). Coagulase-negative staphylococci, *Micrococcus*, *Bacillus*, *Corynebacterium*, and *Propionibacterium* species were considered contaminants unless at least 2 cultures were positive for the organism. The study was approved by each center's institutional review board, with waiver of consent, given the minimal risk of the study. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Demographic and Case Information

Centers recorded the annual number of live births with a GA of at least 22 weeks and birth weight of more than 400 g overall and by GA group, birth weight group, sex, race, and ethnicity. Maternal data included GBS screening, GBS bacteriuria, delivery of prior infant with GBS disease, use of antenatal corticosteroids, use of intrapartum antibiotics, signs or symptoms within 72 hours before delivery, duration of rupture of membranes (ROM), medical record diagnosis of chorioamnionitis, and delivery type. Neonatal data included signs of sepsis, laboratory results, antimicrobial therapy, length of stay, and final status (death, discharge home, or transfer). Microbiologic data included culture type, infecting organism, and antibiotic susceptibilities as reported by study center.

Statistical Analysis

Data were analyzed from June 14, 2019, to January 28, 2020. Rates of EOS and early-onset meningitis were estimated as the number of infected infants overall or by group, divided by the total number of live births reported for the same group. Organism-specific data analyses include individual isolates from polymicrobial infections unless otherwise stated. Wilson or Clopper-Pearson 95% CIs were estimated for each rate. Rates were compared with those from the previous NRN surveillance study[12] using data from hospitals of 14 NRN centers that participated in both studies. Statistical significance for unadjusted comparisons was determined by Fisher exact, χ^2, or Kruskal-Wallis tests. Comparisons adjusted for GA were made using linear or logistic regression models with statistical significance determined by F or Wald χ^2 tests. Poisson regression with robust variance estimators[13] was used to estimate the adjusted relative risk of death and 95% CI for infants with *Escherichia coli* compared with GBS infection, adjusting for GA. Two-sided $P < .05$ indicated significance.

Results

During the 2-year study period, 289 infants among 217 480 live births had organisms isolated from blood and CSF. The organisms isolated from 54 infants were determined to be contaminants, leaving 235 cases (127 male [54.0%] and 108 female [46.0%]). Most infections (131 of 235 [55.7%]) occurred among preterm infants with a GA of less than 37 weeks.

Pathogens and Infection Rates

Gram-positive organisms were identified in 120 of 235 infants; gram-negative organisms, in 107; and fungal organ-

Table 1. Pathogens Associated With EOS and EOM

Pathogen[a]	Infant group, No. (%)					
	All		Preterm (GA 22-36 wk)		Term (GA ≥37 wk)	
	EOS	EOM[b]	EOS	EOM	EOS	EOM
Gram-positive	120 (51.1)	3 (50.0)	38 (29.0)	1 (25.0)	82 (78.8)	2 (100)
GBS	70 (29.8)	1 (16.7)	17 (13.0)	0	53 (51.0)	1 (50.0)
Enterococcus species	13 (5.5)	0	4 (3.1)	0	9 (8.7)	0
Group A streptococcus	9 (3.8)	0	3 (2.3)	0	6 (5.8)	0
Viridans streptococci	7 (3.0)	0	4 (3.1)	0	3 (2.9)	0
Streptococcus bovis	6 (2.6)	1 (16.7)	2 (1.5)	0	4 (3.8)	1 (50.0)
Streptococcus species	5 (2.1)	0	2 (1.5)	0	3 (2.9)	0
Streptococcus pneumoniae	3 (1.3)	0	1 (0.8)	0	2 (1.9)	0
Coagulase-negative staphylococci	2 (0.9)	1 (16.7)	1 (0.8)	1 (25.0)	1 (1.0)	0
Listeria monocytogenes	2 (0.9)	0	2 (1.5)	0	0	0
Staphylococcus aureus	2 (0.9)	0	2 (1.5)	0	0	0
S aureus (methicillin-resistant)	1 (0.4)	0		0	1 (1.0)	0
Gram-negative	107 (45.5)	3 (50.0)	87 (66.4)	3 (75.0)	20 (19.2)	0
Escherichia coli	83 (35.3)	1 (16.7)	67 (51.1)	1 (25.0)	16 (15.4)	0
Haemophilus species	9 (3.8)	0	7 (5.3)	0	2 (1.9)	0
Klebsiella species	7 (3.0)	0	7 (5.3)	0	0	0
Morganella morganii	3 (1.3)	1 (16.7)	3 (2.3)	1 (25.0)	0	0
Citrobacter species	1 (0.4)	1 (16.7)	1 (0.8)	1 (25.0)	0	0
Enterobacter species	1 (0.4)	0	0	0	1 (1.0)	0
Flavobacterium species	1 (0.4)	0	1 (0.8)	0	0	0
Proteus species	1 (0.4)	0	1 (0.8)	0	0	0
Pseudomonas species	1 (0.4)	0	0	0	1 (1.0)	0
Fungi	4 (1.7)	0	4 (3.1)	0	0	0
Candida albicans	4 (1.7)	0	4 (3.1)	0	0	0
Polymicrobial	4 (1.7)	0	2 (1.5)	0	2 (1.9)	0
E coli and *Enterococcus* species	1 (0.4)	0	1 (0.8)	0	0	0
E coli and *Streptococcus* species	1 (0.4)	0	0	0	1 (1.0)	0
Haemophilus species and *V streptococci*	1 (0.4)	0	1 (0.8)	0	0	0
GBS and *E coli*	1 (0.4)	0	0	0	1 (1.0)	0
All cases	235 (100)	6 (100)	131 (100)	4 (100)	104 (100)	2 (100)

Abbreviations: EOM, early-onset meningitis; EOS, early-onset sepsis; GBS, group B streptococcus.

[a] Median time from culture drawn to culture positivity was 17.6 hours overall (95th percentile: 65.9 hours) and varied by pathogen type: gram-positive, 19.3 (95th percentile: 71.3) hours; gram-negative, 14.7 (95th percentile: 43.3) hours; fungi, 49.7 (95th percentile: 66.3) hours; and polymicrobial, 18.2 (95th percentile: 20.7) hours ($P < .001$).

[b] All 6 infants with EOM had blood and cerebrospinal fluid cultures positive for the same organism.

isms and polymicrobial infections, in 4 each (**Table 1**). Overall, *E coli* was isolated in 86 cases (36.6%) and GBS in 71 (30.2%). Gram-negative infections occurred most frequently among the 131 preterm cases, with *E coli* isolated in 68 of these (51.9%). Gram-positive infections occurred most frequently among the 104 term cases, with GBS isolated in 54 (51.9%).

The same pathogen was isolated from both blood and CSF in 6 of 235 cases; 2 of 6 CSF specimens were contaminated with blood. No case had growth in CSF only. Lumbar puncture was performed in the first week after birth for 156 infants (66.4%), with greater likelihood of lumbar puncture with increasing GA (22-28 weeks: 40.3% [n = 27]; 29-33 weeks: 70.0% [n = 35]; 34-36 weeks: 71.4% [n = 10]; ≥37 weeks: 80.8% [n = 84]). Although most infants (200 [85.1%]) with EOS had blood cultured on the day of birth, most lumbar punctures (143 [91.7%]) were performed on day 2 or later, with median time between blood and CSF cultures of 1 (interquartile range [IQR], 1-2) day. Among infants who underwent lumbar punctures, 148 (95.5%) received antibiotics before lumbar puncture.

Overall incidence of EOS was 1.08 cases (95% CI, 0.95-1.23) per 1000 live births (**Table 2**). Rates were inversely related to birth weight and GA and varied by center (range across centers: 0.39 [95% CI, 0.16-0.81] to 6.25 [95% CI, 0.16-34.33] per 1000 live births) (eTable 1 in the Supplement). Incidence was highest among infants born at GA of 22 to 28 weeks (18.47 [95% CI, 14.57-23.38] per 1000 live births) and very low-birth-weight (VLBW; 401-1500 g) infants (13.92 [95% CI, 11.31-17.12] per 1000 live births) (Table 2 and eTables 1-6 in the Supplement). Rates overall did not differ significantly by sex, race, or ethnicity (Table 2), but center differences in rates by sex, race, and ethnicity were present (eTables 7-15 in the Supplement). Incidence of *E coli* infection (0.40 [95% CI, 0.32-0.49]

Table 2. Rates of EOS per 1000 Live Births

Variable	All pathogens		GBS		*Escherichia coli*	
	No./total No.	Rate (95% CI)[a]	No./total No.	Rate (95% CI)[a]	No./total No.	Rate (95% CI)[a]
All	235/217 480	1.08 (0.95-1.23)	71/217 480	0.33 (0.26-0.41)	86/217 480	0.40 (0.32-0.49)
By birth weight, g						
401-1500	88/6322	13.92 (11.31-17.12)	10/6322	1.58 (0.86-2.91)	51/6322	8.07 (6.14-10.59)
1501-2500	39/20 743	1.88 (1.38-2.57)	7/20 743	0.34 (0.16-0.70)	14/20 743	0.67 (0.40-1.13)
>2501	108/190 415	0.57 (0.47-0.68)	54/190 415	0.28 (0.22-0.37)	21/190 415	0.11 (0.07-0.17)
By GA, wk						
22-28	67/3628	18.47 (14.57-23.38)	5/3628	1.38 (0.59-3.22)	44/3628	12.13 (9.05-16.24)
29-33	50/8056	6.21 (4.71-8.17)	9/8056	1.12 (0.59-2.12)	20/8056	2.48 (1.61-3.83)
34-36	14/19 195	0.73 (0.43-1.22)	3/19 195	0.16 (0.05-0.46)	4/19 195	0.21 (0.08-0.54)
≥37	104/185 970	0.56 (0.46-0.68)	54/185 970	0.29 (0.22-0.38)	18/185 970	0.10 (0.06-0.15)
By sex						
Male	127/111 543	1.14 (0.96-1.35)	39/111 543	0.35 (0.26-0.48)	50/111 543	0.45 (0.34-0.59)
Female	108/105 977	1.02 (0.84-1.23)	32/105 977	0.30 (0.21-0.43)	36/105 977	0.34 (0.25-0.47)
Total (sites included in rates by race)[b]	137/127 740	1.07 (0.91-1.27)	37/127 740	0.29 (0.21-0.40)	52/127 740	0.41 (0.31-0.53)
By race						
Black	47/40 250	1.17 (0.88-1.55)	12/40 250	0.30 (0.17-0.52)	19/40 250	0.47 (0.30-0.74)
White	70/69 140	1.01 (0.80-1.28)	20/69 140	0.29 (0.19-0.45)	26/69 140	0.38 (0.26-0.55)
Other, unknown, or not reported	20/18 089	1.11 (0.72-1.71)	5/18 089	0.28 (0.12-0.65)	7/18 089	0.39 (0.19-0.80)
Total (sites included in rates by ethnicity)[c]	176/155 831	1.13 (0.97-1.31)	56/155 831	0.36 (0.28-0.47)	59/155 831	0.38 (0.29-0.49)
By ethnicity						
Hispanic	46/39 798	1.16 (0.87-1.54)	15/39 798	0.38 (0.23-0.62)	16/39 798	0.40 (0.25-0.65)
Non-Hispanic	125/111 725	1.12 (0.94-1.33)	40/111 725	0.36 (0.26-0.49)	41/111 725	0.37 (0.27-0.50)
Unknown or not reported	5/4393	1.14 (0.49-2.66)	1/4393	0.23 (0.04-1.29)	2/4393	0.46 (0.12-1.66)

Abbreviations: EOS, early-onset sepsis; GA, gestational age; GBS, group B streptococcus.

[a] Wilson 95% CIs are reported.

[b] Data were excluded from calculations if the number of births was not reported by race (1 center) or if the number of births recorded as other, unknown, or not reported was more than 20% of the total live births reported (4 centers, 1 hospital at each of 2 additional centers) unless more than 20% of infants at the center were thought to have maternal race other than white or black as determined by center infants born 2015 to 2017 enrolled in the Neonatal Research Network high-risk registry (1 center that was 27% Asian and 1 center that was 29% American Indian/Alaska Native were not excluded).

[c] Data were excluded from calculations if the number of births was not reported by ethnicity (2 centers, 1 hospital at each of 2 additional centers) or if the number of births recorded as unknown or not reported was more than 20% of the total live births reported (1 hospital at each of 2 centers).

cases per 1000 live births) was higher than incidence of GBS infection overall (0.33 [95% CI, 0.26-0.41] cases per 1000 live births) and among infants with GA of 22 to 28 weeks (12.13 [95% CI, 9.05-16.24] vs 1.38 [95% CI, 0.59-3.22] cases per 1000 live births) (Table 2). Among term infants, rates of GBS infection were higher than rates of *E coli* infection (0.29 [95% CI, 0.22-0.38] vs 0.10 [95% CI, 0.06-0.15] cases per 1000 live births) (Table 2). Pathogen patterns across centers were generally similar (eTables 2 and 3 in the Supplement).

Microbiology

The median time from culture drawn to culture positivity was 17.6 (95th percentile: 65.9) hours overall and varied by pathogen type (gram-positive, 19.3 [95th percentile: 71.3] hours; gram-negative, 14.7 [95th percentile: 43.3] hours; fungi, 49.7 [95th percentile: 66.3] hours; and polymicrobial, 18.2 [95th percentile: 20.7] hours; $P < .001$) (Table 1). Antibiotic susceptibility data were available for 51 of 71 GBS isolates, but not all cases were tested for each antibiotic. All GBS isolates tested were susceptible to penicillin (43 tested), ampicillin (8 tested), and vancomycin (32 tested); 50.0% were susceptible to erythromycin (9 of 18 tested), and 58.1% (18 of 31 tested) were susceptible to clindamycin.

Most *E coli* isolates (81 of 86) were tested for susceptibility to ampicillin, and 60 of these (74.1%) were resistant. Among infected infants whose mothers received intrapartum ampicillin, 36 of 44 (81.8%) had isolates that were resistant to ampicillin compared with 24 of 37 (64.9%) whose mothers did not receive ampicillin ($P = .13$). Ampicillin resistance was higher among preterm (54 of 65 [83.1%]) compared with term (6 of 16 [37.5%]) infants ($P < .001$). Most *E coli* isolates (80 of 86) were tested for susceptibility to gentamicin, and 72 of these (90.0%) were susceptible. Gentamicin susceptibility did not differ for preterm (57 of 62 [91.9%]) vs term (15 of 18 [83.3%]) infants ($P = .28$). Of 77 *E coli* isolates tested for susceptibility to ampicillin and gentamicin, 6 (7.8%) were resistant to both antibiotics. Five of these 6 infants were preterm; 4 of 5 mothers received IAP (2 received ampicillin; none received gentamicin). Most *E coli* isolates tested (61 of 64 [95.3%]) were susceptible to third-

Table 3. Maternal GBS Screening and Indications for IAP for Infants With EOS

Variable	Infant group[a]				
		GA of infants with GBS, wk[c]			
	All (N = 235)[b]	22-34 (n = 14)	35-37 (n = 13)	≥38 (n = 43)	Overall (n = 70)
Screened for GBS					
Yes	158 (67.2)	10 (71.4)	10 (76.9)	25 (58.1)	45 (64.3)
No	68 (28.9)	4 (28.6)	2 (15.4)	17 (39.5)	23 (32.9)
Unknown	9 (3.8)	0	1 (7.7)	1 (2.3)	2 (2.9)
GBS screen result[d]					
Positive	41 (25.9)	9 (90.0)	5 (50.0)	7 (28.0)	21 (46.7)
Negative	115 (72.8)	1 (10.0)	5 (50.0)	18 (72.0)	24 (53.3)
Unknown	2 (1.3)	0	0	0	0
Intrapartum antibiotics given[e]					
GBS prophylaxis (with or without another indication)	47 (20.1)	3 (21.4)	2 (15.4)	2 (4.7)	7 (10.0)
Chorioamnionitis or other non-GBS indication	114 (48.7)	7 (50.0)	3 (23.1)	18 (41.9)	28 (40.0)
No intrapartum antibiotics given	73 (31.2)	4 (28.6)	8 (61.5)	23 (53.5)	35 (50.0)
Indication for intrapartum GBS prophylaxis, per CDC 2010 guidelines					
Previous infant with GBS, No. of mothers	1	0	0	0	0
Antibiotics given	1 (100)	0	0	0	0
Maternal GBS bacteriuria (without CD performed before onset of labor or ROM), No. of mothers	17	2	3	5	10
Antibiotics given	11 (64.7)	2 (100)	2 (66.7)	1 (20.0)	5 (50.0)
Positive GBS screening culture (without CD performed before onset of labor or ROM), No. of mothers	25	7	2	3	12
Antibiotics given	21 (84.0)	6 (85.7)	0	2 (66.7)	8 (66.7)
Unknown GBS status with maternal risk factor, No. of mothers[f]	62	4	0	14	18
Antibiotics given	49 (79.0)	2 (50.0)	0	10 (71.4)	12 (66.7)
Negative GBS screen >5 wk before delivery, no repeat of test, with preterm ROM, and/or labor, No. of mothers[g]	1	0	0	0	0
Antibiotics given	1 (100)	0	0	0	0
Intrapartum prophylaxis not indicated per CDC 2010 guidelines					
Negative GBS screen ≤5 wk before delivery or CD in the absence of labor or ROM, No. of mothers	99	1	4	10	15
Antibiotics given	69 (69.7)	0	1 (25.0)	6 (60.0)	7 (46.7)
Other clinical scenarios					
Negative GBS screen >5 wk before delivery without maternal risk factor, No. of mothers	4	0	0	2	2
Antibiotics given	0	0	0	0	0
Negative GBS screen result, timing unknown, with or without maternal risk factor, No. of mothers[h]	10	0	1	5	6
Antibiotics given	2 (20.0)	0	0	0	0
Unknown GBS status without maternal risk factor, No. of mothers	16	0	3	4	7
Antibiotics given	8 (50.0)	0	2 (66.7)	3 (75.0)	3 (42.8)

Abbreviations: CDC, Centers for Disease Control and Prevention; CD, cesarean delivery; EOS, early-onset sepsis; GA, gestational age; GBS, group B streptococcus; IAP, intrapartum antibiotic prophylaxis; ROM, rupture of membranes.

[a] Unless otherwise indicated, data are expressed as number (percentage). Percentages have been rounded and may not total 100.

[b] Data for 1 infant with both GBS and *E coli* were included in all patient data but excluded from GBS columns.

[c] The GA breakdown is consistent with CDC guidelines. Includes 70 EOS cases due to GBS. One polymicrobial case with both GBS and E *coli* was not included.

[d] Includes 158 mothers screened for GBS.

[e] Includes maternal antibiotics received within 72 hours before delivery; reason given was missing for 1 infant.

[f] Maternal risk factors for GBS early-onset infection were any of the following: delivery at GA of less than 37 weeks, ROM at least 18 hours before delivery, and intrapartum fever of at least 38.0 °C.

[g] According to the suggested approach for GBS prophylaxis management in the CDC 2010 guidelines for women with preterm labor (Figure 5 in the guidelines) or women with preterm ROM (Figure 6 in the guidelines),[4] a negative GBS screen result is considered valid for 5 weeks. A woman with a negative GBS screen more than 5 weeks before delivery should be rescreened and managed according to those results. Because this mother was not rescreened and GBS status was not available before labor onset before GA of 37 weeks, GBS prophylaxis was indicated.

[h] Among all patients, 6 infants had mothers with 1 or more of the specified risk factors, and 4 infants had no maternal risk factors.

generation cephalosporins; 43 of 46 tested (93.5%) were susceptible to cefepime.

Intrapartum Antibiotics and GBS Screening

Intrapartum antibiotics were administered to mothers of 162 of 235 (68.9%) infected infants. Administration differed by GA (110 of 131 [84.0%] preterm vs 52 of 104 [50.0%] term cases; $P < .001$) and by interval between maternal admission to hospital and delivery (among mothers admitted <4 hours before delivery, 17 [56.7%]; 4 to 24 hours, 34 [55.7%]; >24 hours, 111 [77.6%]; $P = .002$). Multiple reasons for intrapartum antibiotic administration were present in 101 cases (62.7%), including suspected chorioamnionitis (62 [38.5%]), premature ROM (54 [33.5%]), cesarean delivery prophylaxis (49 [30.4%]), GBS prophylaxis (47 [29.2%]), and maternal fever (40 [24.8%]).

Antenatal GBS testing was performed in 158 of 235 cases (67.2%); 41 of 158 (25.9%) were colonized with GBS (**Table 3**). Intrapartum antibiotic prophylaxis was administered to 83 of

106 mothers (78.3%) with an indication for GBS IAP. Among infants with GBS infection, 45 of 70 mothers (64.3%) were screened for GBS, but 24 screens (53.3%) had negative results (23 [71.9%] term and 1 [7.7%] preterm infants with GBS). Fifteen of 40 mothers (37.5%) of infants with early-onset GBS infection who had at least 1 indication for IAP did not receive prophylaxis. Failure to administer GBS IAP was found in association with multiple recommended indications for antibiotic prophylaxis (Table 3).

Clinical Characteristics of Mothers and Infants

The median GA of infected infants was 34 (IQR, 27-39) weeks, and median birth weight was 2260 (IQR, 1150-3262) g. Most infants with *E coli* were preterm (68 of 86 [79.1%]) with median GA of 28 (IQR, 25-33) weeks and median birth weight of 1230 (IQR, 800-2090) g. Most GBS infections were in term infants (54 of 71 [76.1%]) with median GA of 39 (IQR, 37-40) weeks and birth weight of 3199 (IQR, 2550-3440) g. Mothers of infants with *E coli* infections were more likely than mothers of infants with GBS infections to have received antibiotics within 72 hours before delivery (72 of 85 [84.7%] vs 35 of 70 [50.0%]) and to have had ROM at least 18 hours before delivery (63 of 85 [74.1%] vs 22 of 70 [31.4%]) (**Table 4**). Among preterm infants with *E coli* or GBS, 82 (97.6%) were born by vaginal or cesarean delivery after preterm ROM or onset of labor, whereas only 2 (2.3%) were born by cesarean delivery in the absence of preterm labor or ROM. Most of the cases were associated with preterm ROM with or without preterm labor (69 [81.2%]), and 45 mothers (52.9%) had a clinical diagnosis of chorioamnionitis.

Nearly all infected infants had signs of instability within 72 hours after birth (220 of 235 [93.6%]). Of the 15 infants without signs of illness throughout the first 72 hours, 14 were term and 1 was born at a GA of 33 weeks. Among infected infants born to mothers with documented chorioamnionitis, 59 of 60 preterm infants (98.3%) had signs at birth; the only well-appearing preterm infant developed signs within 72 hours of birth. Among 43 term infants born to mothers with chorioamnionitis, 11 (25.6%) appeared healthy at birth; 4 (9.3%) of these developed signs within 72 hours, but 7 (16.3%) remained healthy throughout the first 72 hours (eFigure in the Supplement). All 7 well-appearing infants had cultures taken on the day of birth and antibiotic therapy started empirically. Most infected infants (198 of 235 [84.3%]) received intensive care (Table 4), especially preterm infants, but 22 of 104 term infants (21.2%) were cared for in well-baby nurseries.

All infected infants received antibiotics, except 1 who died shortly after birth. Most infants (182 of 234 [77.8%]) were treated empirically with 2 antibiotics, most frequently ampicillin sodium and gentamicin sulfate. Initial antibiotic regimens were changed for 138 of 234 (59.0%) in response to culture results. Cefotaxime or another cephalosporin, penicillin G, or vancomycin hydrochloride were the antibiotics most frequently added or substituted.

Mortality

Most infants with EOS (197 of 235 [83.8%]) survived to discharge (eTables 16 and 17 in the Supplement). Case fatality was inversely related to GA: 38 of 131 infants born at GA of 22 to 36 weeks (29.0%) died, including 27 infants (39.7%) with *E coli* infection, but all term infants survived. The median GA of infants who died was 25.5 (IQR, 24-28) weeks, and median birth weight was 850 (IQR, 680-1370) g. Half the deaths occurred within 3 days of birth. Although a larger proportion of all infants with *E coli* than GBS infection died (27 [31.8%] vs 4 [5.7%]), risk of death was not significantly different when adjusted for GA (adjusted relative risk, 1.66 [95% CI, 0.66-4.16]; $P = .28$). Of note, 2 infants with early deaths were infected with *E coli* strains that were resistant to both ampicillin and gentamicin, the antibiotics they were receiving.

Comparison of Surveillance Studies

Rates of EOS and mortality were compared to those of an earlier NRN surveillance study (2006-2009).[12] Among infants born at the 14 centers that participated in both studies, the overall rate of infection was 1.16 (95% CI, 1.01-1.33) per 1000 live births in the current study vs 1.00 (95% CI, 0.90-1.10) per 1000 live births in the earlier study ($P = .08$) (**Table 5**). Among VLBW infants, the EOS rate was 15.05 (95% CI, 12.08-18.74) per 1000 live births in the current study vs 11.00 (95% CI, 9.26-13.06) per 1000 live births in the earlier period ($P = .03$). The rate of GBS infection did not change significantly, but the *E coli* infection rate among VLBW infants increased in the current study (8.68 [95% CI, 6.50-11.60] vs 5.07 [95% CI, 3.93-6.53] per 1000 live births; $P = .008$). No significant changes in infection-associated mortality were observed.

Discussion

This study reviews the current epidemiology of EOS across the GA spectrum to inform issues that concern clinicians: the use and efficacy of obstetric prevention measures and neonatal clinical assessment, treatment, and outcomes. Although the study is not population based, EOS cases were identified from a cohort of 217 480 infants born at academic centers in 14 states. The cohort was enriched for preterm infants, with proportions born at a GA of less than 37 weeks (30 879 [14.2%]) and VLBW (6322 [2.9%]) exceeding national incidences (9.9% and 1.4%, respectively).[14] In addition to providing an important opportunity to evaluate issues relevant to preterm infants, the study included 185 970 term births and is generalizable to the population of US term newborns. The study has several important messages for clinicians, investigators, and policy makers. First, EOS disproportionately occurred in preterm infants, a reminder of the public health consequences of preterm birth. Second, the microbiology and antimicrobial susceptibility profiles of EOS pathogens bear close monitoring, with the increase in *E coli* infection among VLBW infants particularly concerning. Third, missed opportunities for GBS prevention continue to adversely affect newborns, underscoring the importance of adherence to GBS screening and IAP recommendations. Finally, additional, innovative clinical and public health approaches to prevent EOS are urgently needed, including efforts to prevent maternal intra-amniotic infection.

The rate of early-onset *E coli* sepsis among VLBW infants was significantly higher in the current study than in the

Table 4. Characteristics, Clinical Presentation, and Care of Infants With EOS

Characteristic	All (N = 235)[a]	Preterm (GA 22-36 wk) with GBS or *E coli*		Term (GA ≥37 wk) with GBS or *E coli*		All with GBS or *E coli*		*P* value[b]	
		GBS (n = 17)	*E coli* (n = 68)	GBS (n = 53)	*E coli* (n = 17)	GBS (n = 70)	*E coli* (n = 85)	Unadjusted	Adjusted
Birth weight, g									
401-1500	88 (37.4)	10 (58.8)	51 (75.0)	0	0	10 (14.3)	51 (60.0)	<.001	.67
1501-2500	39 (16.6)	6 (35.3)	14 (20.6)	1 (1.9)	0	7 (10.0)	14 (16.5)		
>2500	108 (46.0)	1 (5.9)	3 (4.4)	52 (98.1)	17 (100)	53 (75.7)	20 (23.5)		
Sex									
Male	127 (54.0)	9 (52.9)	41 (60.3)	30 (56.6)	9 (52.9)	39 (55.7)	50 (58.8)	.75	.79
Female	108 (46.0)	8 (47.1)	27 (39.7)	23 (43.4)	8 (47.1)	31 (44.3)	35 (41.2)		
Maternal race/ethnicity									
Black, non-Hispanic	76 (34.2)	2 (12.5)	21 (33.3)	25 (49.0)	6 (35.3)	27 (40.3)	27 (33.8)	.53	.77
White, non-Hispanic	68 (30.6)	6 (37.5)	22 (34.9)	10 (19.6)	4 (23.5)	16 (23.9)	26 (32.5)		
Hispanic	60 (27.0)	7 (43.8)	17 (27.0)	11 (21.6)	6 (35.3)	18 (26.9)	23 (28.8)		
Other	18 (8.1)	1 (6.3)	3 (4.8)	5 (9.8)	1 (5.9)	6 (9.0)	4 (5.0)		
Mother's age, mean (SD), y	28.4 (6.7)	29.4 (6.6)	29.6 (6.6)	26.2 (6.6)	26.3 (5.5)	26.9 (6.7)	28.9 (6.5)	.06	.38
Antibiotics within 72 h before delivery	162 (68.9)	11 (64.7)	62 (91.2)	24 (45.3)	10 (58.8)	35 (50.0)	72 (84.7)	<.001	.01
Antenatal corticosteroids within 72 h before delivery	85 (36.2)	10 (58.8)	44 (64.7)	NA	NA	NA	NA	.78	.91[c]
Type of delivery									
Vaginal	127 (54.5)	9 (56.3)	26 (38.2)	39 (75.0)	11 (64.7)	48 (70.6)	37 (43.5)	<.001	.02
CD with labor, with ROM before	63 (27.0)	2 (12.5)	20 (29.4)	13 (25.0)	6 (35.3)	15 (22.1)	26 (30.6)		
CD with labor, without ROM before	10 (4.3)	2 (12.5)	1 (1.5)	0	0	2 (2.9)	1 (1.2)		
CD without labor, with ROM before	28 (12.0)	2 (12.5)	20 (29.4)	0	0	2 (2.9)	20 (23.5)		
CD without labor, without ROM before	5 (2.1)	1 (6.3)	1 (1.5)	0	0	1 (1.5)	1 (1.2)		
ROM ≥18 h before delivery	115 (48.9)	8 (47.1)	53 (77.9)	14 (26.4)	10 (58.8)	22 (31.4)	63 (74.1)	<.001	<.001
Spontaneous ROM with or without labor before 37 weeks	93 (39.6)	12 (70.6)	57 (83.8)	NA	NA	NA	NA	.30	.16[d]
Symptoms within 72 h before delivery									
Maternal temperature ≥38.0 °C	72 (30.6)	3 (17.6)	22 (32.4)	20 (37.7)	8 (47.1)	23 (32.9)	30 (35.3)	.87	.16
Uterine or abdominal tenderness	34 (14.5)	0	23 (33.8)	1 (1.9)	0	1 (1.4)	23 (27.1)	<.001	.03
Foul-smelling vaginal discharge or amniotic fluid	20 (8.5)	1 (5.9)	10 (14.7)	3 (5.7)	1 (5.9)	4 (5.7)	11 (12.9)	.17	.55
Maternal tachycardia (>100 bpm)	135 (57.4)	10 (58.8)	46 (67.6)	20 (37.7)	11 (64.7)	30 (42.9)	57 (67.1)	.003	.05
Fetal tachycardia (>160 bpm)	94 (40.2)	3 (17.6)	35 (52.2)	22 (41.5)	3 (17.6)	25 (35.7)	38 (45.2)	.25	.34
Chorioamnionitis documented in the medical record	103 (43.8)	5 (29.4)	40 (58.8)	23 (43.4)	8 (47.1)	28 (40.0)	48 (56.5)	.05	.09
Placental pathologic examination performed	174 (74.0)	16 (94.1)	62 (91.2)	33 (62.3)	7 (41.2)	49 (70.0)	69 (81.2)	.13	.22
Histologic chorioamnionitis[e]	141 (81.0)	12 (75.0)	54 (87.1)	26 (78.8)	5 (71.4)	38 (77.6)	59 (85.5)	.33	.89
Highest care level									
Well-baby nursery	25 (10.6)	0	2 (2.9)	13 (24.5)	2 (11.8)	13 (18.6)	4 (4.7)	.02	.31
Intermediate, step-down, or transitional	12 (5.1)	0	2 (2.9)	4 (7.5)	2 (11.8)	4 (5.7)	4 (4.7)		
Intensive care	198 (84.3)	17 (100)	64 (94.1)	36 (67.9)	13 (76.5)	53 (75.7)	77 (90.6)		
Any signs of sepsis in the first 72 h									
Yes	220 (93.6)	17 (100)	67 (98.5)	45 (84.9)	16 (94.1)	62 (88.6)	83 (97.6)	.04	.58
No	15 (6.4)	0	1 (1.5)	8 (15.1)	1 (5.9)	8 (11.4)	2 (2.4)		

(continued)

Table 4. Characteristics, Clinical Presentation, and Care of Infants With EOS (continued)

Characteristic	All (N = 235)[a]	Preterm (GA 22-36 wk) with GBS or *E coli*		Term (GA ≥37 wk) with GBS or *E coli*		All with GBS or *E coli*		*P* value[b]	
		GBS (n = 17)	*E coli* (n = 68)	GBS (n = 53)	*E coli* (n = 17)	GBS (n = 70)	*E coli* (n = 85)	Unadjusted	Adjusted
Signs of sepsis[f]									
Temperature ≥38.0 °C	42 (19.1)	1 (5.9)	13 (19.4)	10 (22.2)	4 (25.0)	11 (17.7)	17 (20.5)	.83	.17
Temperature ≤36.0 °C	40 (18.2)	2 (11.8)	17 (25.4)	6 (13.3)	3 (18.8)	8 (12.9)	20 (24.1)	.14	.32
Cyanosis with use of supplemental oxygen (>60 min)	90 (40.9)	7 (41.2)	36 (53.7)	11 (24.4)	3 (18.8)	18 (29.0)	39 (47.0)	.04	.92
Tachypnea (respiratory rate >60 breaths/min) for ≥30 min documented twice	132 (60.0)	11 (64.7)	38 (56.7)	27 (60.0)	9 (56.3)	38 (61.3)	47 (56.6)	.61	.57
Grunting, flaring, retractions	144 (65.5)	11 (64.7)	45 (67.2)	27 (60.0)	8 (50.0)	38 (61.3)	53 (63.9)	.86	.63
Hypotension[g]	92 (41.8)	8 (47.1)	41 (61.2)	12 (26.7)	6 (37.5)	20 (32.3)	47 (56.6)	.004	.19
Acidosis[h]	116 (52.7)	10 (58.8)	50 (74.6)	16 (35.5)	3 (18.8)	26 (41.9)	53 (63.9)	.01	.89
Tachycardia (heart rate >160 bpm)	154 (70.0)	12 (70.6)	59 (88.1)	20 (44.4)	9 (56.3)	32 (51.6)	68 (81.9)	<.001	.15
Apnea and/or intermittent bradycardia	69 (31.4)	5 (29.4)	32 (47.8)	6 (13.3)	3 (18.8)	11 (17.7)	35 (42.2)	.002	.15
Lethargy	51 (23.2)	5 (29.4)	21 (31.3)	12 (26.7)	1 (6.3)	17 (27.4)	22 (26.5)	>.99	.41
Irritability	31 (14.1)	4 (23.5)	5 (7.5)	4 (8.9)	3 (18.8)	8 (12.9)	8 (9.6)	.60	.74
Hypoglycemia (lowest blood glucose level <40 mg/dL)	61 (27.7)	2 (11.8)	24 (35.8)	13 (28.9)	6 (37.5)	15 (24.2)	30 (36.1)	.15	.09
Neutropenia (ANC<1000/μL)	44 (20.0)	5 (29.4)	20 (29.9)	4 (8.9)	3 (18.8)	9 (14.5)	23 (27.7)	.07	.46
Bleeding, petechiae, thrombocytopenia (platelets <10^5/μL)	42 (19.1)	2 (11.8)	20 (29.9)	8 (17.8)	2 (12.5)	10 (16.1)	22 (26.5)	.16	.98
Abdominal distention or >1 episode of bilious emesis	11 (5.0)	1 (5.9)	7 (10.4)	0	0	1 (1.6)	7 (8.4)	.14	.21
Clinical seizures (proven or suspect)	9 (4.1)	0	6 (9.0)	2 (4.4)	0	2 (3.2)	6 (7.2)	.47	.35

Abbreviations: ANC, absolute neutrophil count; CD, cesarean delivery; *E coli*, *Escherichia coli*; EOS, early-onset sepsis; GA, gestational age; GBS, group B streptococcus; NA, not applicable; ROM, rupture of membranes.

SI conversion factors: To convert ANC to ×10^9 per liter, multiply by 0.001; glucose to millimoles per liter, multiply by 0.0555; platelet count to ×10^9 per liter, multiply by 1.0.

[a] Data for 1 infant with both GBS and *E coli* were included in all patient data but excluded from GBS and *E coli* columns. Among all infants, information was missing for maternal race/ethnicity in 13, delivery type in 2, and fetal tachycardia in 1. Unless otherwise indicated, data were expressed as number (percentage) of patients. Percentages have been rounded and may not total 100.

[b] Indicates difference between infants overall with GBS vs *E coli* by Fisher exact test or the Kruskal-Wallis test (mother's age) and adjusting for GA (continuous) in a linear (mother's age; *F* test) or logistic regression model (Wald χ^2 test).

[c] Indicates difference between preterm infants with GBS vs *E coli*, unadjusted and adjusting for GA (continuous) in a logistic regression model. No term infants received antenatal corticosteroids.

[d] Indicates difference between preterm infants with GBS vs *E coli*, unadjusted and adjusting for GA (continuous) in a logistic regression model.

[e] Includes mothers for whom placental pathologic examination was performed.

[f] Includes infants with at least 1 sign.

[g] Defined as mean arterial pressure less than estimated GA or treated with fluid boluses or pressors (such as dopamine, epinephrine, norepinephrine, or vasopressin).

[h] Defined as peripheral or cord blood gas analysis with pH of less than 7.25.

previous NRN study,[12] with no significant changes in the rate of GBS infection or in the overall rate of EOS. Notably, the rate of EOS among preterm infants born at a GA of 22 to 28 weeks was more than 30-fold higher than that observed among infants with a GA of at least 37 weeks. The rate among even moderately preterm infants with a GA of 29 to 33 weeks was 11-fold higher than among term infants. Diagnosis of meningitis was infrequent; however, only 66.4% of infants with EOS had lumbar punctures, most of these after starting antibiotic therapy. Death occurred in 29.0% of infected infants with a GA of 22 to 36 weeks, including 39.7% of infants with *E coli* infection; no deaths occurred in term infants. Although preterm infants with GBS and *E coli* were almost all ill and cared for in intensive care settings, using clinical presentation alone to assess infection risk in preterm infants remained difficult. Most of the infected infants had signs compatible with sepsis, including respiratory distress and hypotension, but these are common findings among VLBW infants.[15,16] Delivery characteristics may be more useful to predict EOS: 82 (97.6%) preterm infants with *E coli* or GBS infection were born by vaginal or cesarean delivery after preterm ROM or onset of labor, whereas only 2 (2.3%) were born by cesarean delivery in the absence of preterm labor or ROM. These findings are consistent with a recent NRN study[17] that linked specific delivery characteristics with lower risk of EOS among extremely preterm infants. Most preterm *E coli* or GBS cases (69 [81.2%]) were

Table 5. Change in Rates of EOS Over Time: EOS1 vs EOS2

Variable	Rate per 1000 live births[a]		*P* value[b]
	EOS1 (2006-2009)	EOS2 (2015-2017)	
All	1.00 (0.90-1.10)	1.16 (1.01-1.33)	.08
No./total No.	362/363 567	207/178 104	NA
All by birth weight, g			
401-1500	11.00 (9.26-13.06)	15.05 (12.08-18.74)	.03
No./total No.	128/11 639	78/5182	NA
1501-2500	1.31 (0.97-1.75)	1.78 (1.25-2.54)	.22
No./total No.	44/33 700	30/16 830	NA
>2500	0.60 (0.52-0.69)	0.63 (0.52-0.77)	.62
No./total No.	190/318 228	99/156 092	NA
GBS	0.42 (0.36-0.50)	0.36 (0.29-0.47)	.35
No./total No.	154/363 567	65/178 104	NA
GBS by birth weight, g			
401-1500	1.98 (1.32-2.96)	1.74 (0.91-3.30)	.85
No./total No.	23/11 639	9/5182	NA
1501-2500	0.39 (0.23-0.66)	0.42 (0.20-0.86)	.82
No./total No.	13/33 700	7/16 830	NA
>2500	0.37 (0.31-0.44)	0.31 (0.24-0.41)	.37
No./total No.	118/318 228	49/156 092	NA
E coli	0.27 (0.22-0.33)	0.40 (0.32-0.51)	.01
No./total No.	98/363 567	72/178 104	NA
E coli by birth weight, g			
401-1500	5.07 (3.93-6.53)	8.68 (6.50-11.60)	.008
No./total No.	59/11 639	45/5182	NA
1501-2500	0.47 (0.29-0.77)	0.53 (0.28-1.02)	.83
No./total No.	16/33 700	9/16 830	NA
>2500	0.07 (0.05-0.11)	0.12 (0.07-0.18)	.14
No./total No.	23/318 228	18/156 092	NA

Abbreviations: *E coli*, *Escherichia coli*; EOS, early-onset sepsis; GBS, group B streptococcus; NA, not applicable.

[a] EOS1 includes infants born February 1, 2006, through December 31, 2009, and EOS2 includes infants born April 1, 2015, through March 31, 2017. Rates are based on infants born at the 14 centers in both cohorts. Wilson 95% CIs are shown.

[b] *P* value by Fisher exact test for a difference in rates between the cohorts.

associated with preterm ROM with or without preterm labor, and approximately half of mothers had a clinical diagnosis of chorioamnionitis. These findings support current recommendations focusing on the reason for and mode of delivery to identify preterm infants at lowest risk for EOS who may not require empirical antibiotic therapy, while recommending empirical antibiotic administration for infants born after preterm labor, preterm ROM, or chorioamnionitis.[7]

Term infants had more variable perinatal risk factors and clinical presentation. In some cases, a blood culture was performed because of maternal risk factors for infection, with no signs of illness in the infant. Among term infants with EOS, 21.2% were well enough to be cared for in well-baby nurseries. On the other hand, our rates of respiratory distress among term infants with GBS and *E coli* infection far exceeded what has been reported in uninfected term infants.[18,19] Single perinatal risk factors, such as ROM at least 18 hours before delivery and clinical chorioamnionitis, were observed in fewer than half of term infants with GBS or *E coli*. Similar to national surveillance of GBS disease in the era of IAP,[20,21] most term infants with GBS disease were born to mothers with negative GBS screen results. No GBS or *E coli* cases occurred among term infants born by cesarean delivery in the absence of labor or ROM before delivery. These findings support approaches to neonatal risk assessment among term and late preterm infants that use a combination of perinatal risk factors and clinical condition.[6,9]

Most infants received empirical antibiotics, generally ampicillin and gentamicin. Most isolates were susceptible to one or both of these medications, supporting the continued recommendation of ampicillin and gentamicin as empirical therapy for most infants at risk for EOS.[4,5] Ampicillin-resistant *E coli* was more frequent among preterm infants (83.1% vs 37.5% term; $P < .001$). Gentamicin resistance increased from 3% to 11% in the years since the earlier NRN study (14 centers in both studies)[12]; 7.8% of *E coli* isolates were resistant to both ampicillin and gentamicin in the present study. The deaths of 2 preterm infants infected with strains resistant to both ampicillin and gentamicin underscore the current American Academy of Pediatrics recommendation that clinicians may consider broader-spectrum antibiotics for the most critically ill newborns,[6,7] particularly severely ill VLBW infants born after prolonged preterm ROM or after prolonged antepartum use of ampicillin. Ongoing surveillance for EOS pathogens and their antibiotic susceptibility profiles is important to ensure that ampicillin and gentamicin remain appropriate empirical therapy in most cases.

With 3 855 500 births reported in the United States in 2017,[14] our observed rates reflect an estimated EOS burden of 3125 infants annually, with approximately 343 deaths in

preterm infants and considerable costs. Contemporary cases demonstrate the limits of current prevention strategies. We continue to identify missed opportunities for GBS prevention. Despite recommendations, many pregnant women were not screened for GBS, many women with indications did not receive IAP, and most troubling, term infants with GBS disease were often born to women with negative GBS screen results. The association of preterm EOS with preterm ROM, preterm labor, and chorioamnionitis[22] underscores the important link between intra-amniotic infection and pregnancy complications. By the time the woman seeks medical attention and is admitted for management of preterm labor, it may be too late to prevent fetal and neonatal infection. Further reduction in EOS will require alternate means of GBS prevention (eg, maternal vaccines and rapid intrapartum detection of colonization), as well as novel approaches to preventing the onset of intra-amniotic infection.

Strengths and Limitations

Strengths of this study include the large NRN birth cohort, detailed maternal and newborn information collected prospectively, and the ability to compare rates of infection and mortality among centers that participated in both surveillance studies. However, the NRN centers are academic referral centers. Although the birth cohort is large, this is not a population-based national sample. Limitations of the study include lack of data on methods used for maternal GBS screening and blood cultures and drug dosage and frequency in infants.

Conclusions

In this cohort study, EOS remained a significant cause of morbidity and mortality among newborns, particularly those born preterm, who were increasingly infected with ampicillin-resistant, gram-negative infections. Continued surveillance is warranted to identify changes in pathogen distribution and/or antibiotic susceptibilities. Novel prevention strategies, including efforts to prevent intra-amniotic infection, are needed to effect further declines in the incidence of early-onset infection.

ARTICLE INFORMATION

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Correction: This article was corrected on December 14, 2020, to fix a misleading definition of thrombocytopenia in Table 4.

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