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Antimicrobial Susceptibility Profiles Among Neonatal Early-Onset Sepsis Pathogens

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Abstract

Background: Empiric administration of ampicillin and gentamicin is recommended for newborns at risk of early-onset sepsis (EOS). There are limited data on antimicrobial susceptibility of all EOS pathogens.

Methods: Retrospective review of antimicrobial susceptibility data from a prospective EOS surveillance study of infants born ≥22 weeks' gestation and cared for in Neonatal Research Network centers 4/2015–3/2017. Non-susceptible was defined as intermediate or resistant on final result.

Results: We identified 239 pathogens (235 bacteria, 4 fungi) in 235 EOS cases among 217,480 live-born infants. Antimicrobial susceptibility data were available for 189/239 (79.1%) isolates. Among 81 gram-positive isolates with ampicillin and/or gentamicin susceptibility data, all were susceptible *in vitro* to either ampicillin or gentamicin. Among gram-negative isolates with ampicillin and/or gentamicin susceptibility data, 72/94 (76.6%) isolates were non-susceptible

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to ampicillin, 8/94 (8.5%) were non-susceptible to gentamicin, and 7/96 (7.3%) isolates were non-susceptible to both. Five percent or less of tested gram-negative isolates were non-susceptible to each of 3rd or 4th generation cephalosporins, piperacillin-tazobactam and carbapenems. Overall, we estimated that 8% of EOS cases were caused by isolates non-susceptible to both ampicillin and gentamicin; these were most likely to occur among preterm, very-low birth weight infants.

Conclusions: The vast majority of contemporary EOS pathogens are susceptible to the combination of ampicillin and gentamicin. Clinicians may consider the addition of broader-spectrum therapy among newborns at highest risk of EOS, but we caution that neither the substitution nor the addition of one single antimicrobial agent is likely to provide adequate empiric therapy in all cases.

Keywords

neonatal sepsis; antimicrobial resistance; empiric

INTRODUCTION

Empiric antibiotics are administered to 5–10% of term newborns and up to 90% of extremely preterm infants due to risk for early-onset sepsis (EOS).[1,2] The American Academy of Pediatrics updated guidance on management of EOS continues to recommend the combination of ampicillin and gentamicin as empiric therapy in most instances.[3,4] The AAP guidance cautions, however, that broader-spectrum empiric therapies might be warranted for critically ill infants at highest risk for EOS.[3,4] In particular, reports of ampicillin resistance among the majority of *Escherichia coli* infections raise the concern that empiric administration of a cephalosporin or carbapenem antibiotic may be indicated.[5] Widespread use of antibiotics may increase the risk of later resistant infections, necrotizing enterocolitis, and death, and may have negative long-term impacts on the development of the neonatal microbiome.[6–9] Further, although Group B *Streptococcus* (GBS) and *E. coli* are the most common organisms isolated in EOS cases, roughly one third of all cases are caused by a variety of other pathogens.[10,11] Large-scale surveillance from multiple centers of antimicrobial susceptibility data for all organisms' causing EOS is therefore critically important to inform optimal empiric antibiotic prescription practices and antibiotic stewardship in the newborn population.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN) studies the epidemiology of EOS among extremely preterm infants through the NRN's high risk infant registry and periodically conducts surveillance among term and preterm infants born at NRN centers.[12–14] Most recently, EOS pathogens and antimicrobial susceptibility data were collected during a 2-year prospective surveillance study of over 200,000 live births at NRN centers in 14 states (2015–2017).[11] While this study reported ampicillin and gentamicin susceptibility of *E. coli* and GBS, full susceptibility data for these and other infecting organisms were not reported. In addition, specific antibiotic-resistant organisms are identified as urgent threats by the Centers for Disease Control and Prevention (CDC)[15], and the neonatal prevalence of infection with such organisms is unknown. Therefore, the objective of this study was to determine antimicrobial susceptibility profiles of all EOS pathogens identified in this surveillance study.

MATERIALS AND METHODS

Data Source and Study Population:

This is a secondary analysis of data collected for the NRN EOS Surveillance Study II.[11] Prospective surveillance for EOS was conducted among infants born at ≥22 weeks gestational age (GA) with birth weight (BW) >400 g from April 1, 2015 to March 31, 2017 at 18 NRN centers. The study was approved by the institutional review board at each center, with waiver of consent, given the minimal risk. Data collected included culture type, infecting organism, and antimicrobial susceptibilities if available. Antimicrobial susceptibility profiles of organisms considered pathogenic and included in the primary analysis were reviewed for this study. Profiles of organisms considered contaminants were not collected. Coagulase-negative staphylococci (CONS), *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp., and *Propionibacterium* spp. were considered contaminants unless ≥2 cultures were positive for the organism.

Study Definitions:

EOS was defined as isolation of a pathogen from blood or cerebrospinal fluid (CSF) culture obtained within 72 hours of birth and treatment with antibiotics for 5 or more days (or <5 days if death occurred while receiving antibiotic therapy). Antimicrobial susceptibility was reported as susceptible (S), intermediate (I), or resistant (R). For this study, non-susceptible was defined as I or R on final result. Agents tested to determine antimicrobial susceptibility were recorded using a prespecified list in the study Manual of Operations; all other agents were recorded as “other” and not further specified. In some cases, for example, levofloxacin and ertapenem, the drug name was available from comments recorded by the study center. To be considered susceptible to an antibiotic, a bacterial isolate had to be tested for susceptibility to that antibiotic or to an antibiotic with narrower spectrum whose susceptibility routinely predicts susceptibility to later generation agents of the same class (for example, GBS susceptible to penicillin would be considered susceptible to ampicillin, even if not tested for susceptibility to ampicillin.) Antimicrobial susceptibility was evaluated separately for each organism isolated in polymicrobial infections. If the same organism was isolated from more than one clinical specimen (e.g., two blood cultures or blood and CSF culture), susceptibility results reported for each culture were reviewed for concordance. If the organism was reported as susceptible to a drug in one culture and resistant or intermediate to the same drug in the other culture, the non-susceptible result was reported (2 cases—see Table 1 footnotes). Methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococci (VRE), carbapenem-resistant *Enterobacterales* (formerly *Enterobacteriaceae*; CRE), and extended-spectrum β-lactamase (ESBL)-producing *Enterobacterales* were defined using definitions recently updated and reported by CDC.[15] MRSA, VRE, CRE, ESBL-producing *Enterobacterales* as well as gentamicin or carbapenem non-susceptible *Pseudomonas* spp. were considered as urgent or serious threats by the CDC.[15] In addition, we defined resistant organisms of neonatal priority as ampicillin non-susceptible bacteria, gentamicin non-susceptible bacteria, and combined ampicillin and gentamicin non-susceptible bacteria.

Determination of optimal antibiotic therapy:

To estimate the overall proportion of EOS cases for which ampicillin and gentamicin would not be optimal therapy, we made several assumptions based on available study data and generally-accepted recommendations for optimal antimicrobial therapy. First, we assumed that *Staphylococcus aureus*, CONS and *viridans streptococci* isolates would not be adequately treated *in vivo* with gentamicin monotherapy even if susceptible to gentamicin *in vitro*.[16] Second, we had no information on antibiotic susceptibility for the single *Flavobacterium* spp. isolate, but this organism is highly resistant to most antibiotics including ampicillin and gentamicin, and therefore was considered sub-optimally treated.[17] Third, if there was no antimicrobial susceptibility data for an isolate, we assumed the isolate would have been adequately treated with ampicillin and gentamicin.

Statistical analysis:

Antimicrobial susceptibility results were first examined for each organism individually. Non-susceptible proportions were reported with the number of isolates non-susceptible to the drug or drug class in the numerator and the total number tested in the denominator. Not all drugs were tested for each isolate. For reporting susceptibility to drug classes (e.g., 2nd generation cephalosporins, macrolides), an isolate was classified as non-susceptible to that group if it was intermediate or resistant to any drug in the group; isolates tested against any of the drugs in the group were included in the denominator. The neonatal priority resistant organisms were defined as noted above with non-susceptible isolates included in the numerator and total isolates tested in the denominator. Priority resistant organisms with more than one non-susceptible result were also reported by study year (April 1, 2015 – March 31, 2016; April 1, 2016 – March 31, 2017). Statistical significance for tests of differences by year was determined by Fisher's exact test. Characteristics of infants with isolates for which ampicillin and gentamicin was estimated to provide adequate versus suboptimal therapy were compared with statistical significance determined by F, Wilcoxon, Fisher's exact, or chi-square test.

RESULTS

A total of 235 infants with EOS were identified among 217,480 term and preterm neonates born during the two-year study period.[11] Cases included 4 polymicrobial infections for a total of 239 infecting isolates. There were 61 contaminant organisms cultured from 54 infants, and 2 cases of CONS were included as pathogens. Antimicrobial susceptibility data appropriate to the organism were available for 189/239 (79.1%) isolates.

Antimicrobial susceptibility of individual organisms:

All GBS, Group A Streptococcus, Enterococci spp. and 3/6 viridans Streptococci isolates tested were susceptible to ampicillin and/or penicillin (Table 1). Of the GBS isolates tested, 13/31 (41.9%) were non-susceptible to clindamycin and 9/18 (50.0%) were non-susceptible to erythromycin. *S. aureus* isolates tested were susceptible to vancomycin and variably susceptible to penicillin and gentamicin. For the 2 CONS isolates, one was resistant to gentamicin and was not tested for ampicillin, and the other was resistant to ampicillin but susceptible to gentamicin.

The majority of *E. coli* isolates tested (63/81, 77.8%) were non-susceptible to ampicillin, 10% (8/80) were non-susceptible to gentamicin and 7/79 (8.9%) were non-susceptible to both antibiotics. All 30 *E. coli* isolates tested were susceptible to amikacin but 7/56 (12.5%) were non-susceptible to tobramycin. Among cephalosporins, 11/51 (21.6%), 3/56 (5.4%) and 3/46 (6.5%) *E. coli* isolates were non-susceptible to cefazolin, ceftriaxone or cefepime, respectively. The majority of *E. coli* isolates tested were non-susceptible to ampicillin-sulbactam (30/50, 60%) but only 2/62 (3.2%) were non-susceptible to piperacillin-tazobactam. The only antibiotic class to which all *E. coli* isolates were susceptible was carbapenems.

Among all EOS infections, 25/239 (10.5%) were caused by gram-negative organisms other than *E. coli*. Few *Haemophilus* spp. isolates had susceptibility testing; none of the 3 tested were resistant to ampicillin, but 1 of 2 tested was resistant to ceftriaxone. *Klebsiella* spp. isolates were uniformly resistant to ampicillin. *Klebsiella* spp. as well as the remaining gram-negative isolates were susceptible to gentamicin, cephalosporins, piperacillin-tazobactam and carbapenems, with the exception of one *Morganella morganii* isolate that was intermediate to carbapenems. *Candida albicans* isolates were susceptible to fluconazole but none tested against amphotericin.

Priority resistant organisms:

Among all tested isolates, 74/173 (42.8%) were non-susceptible to ampicillin, 10/106 (9.4%) non-susceptible to gentamicin and 7/177 (4%) were non-susceptible to both antibiotics (Table 2). The 7 isolates non-susceptible to both ampicillin and gentamicin were each from different centers. Only 3/77 isolates (all *E. coli*, no *Klebsiella* spp.) were found to be ESBL-producing. Both the proportion of isolates non-susceptible to gentamicin, and the proportion non-susceptible to both ampicillin and gentamicin increased significantly between study year 1 and year 2 (Table 2). Among other priority organisms, only one case of MRSA and no cases of EOS caused by VRE, CRE or gentamicin/carbapenem-resistant *Pseudomonas* spp. were identified.

Clinical significance of infection with pathogens non-susceptible to both ampicillin and gentamicin:

Although not all pathogens had available susceptibility testing to ampicillin and gentamicin, we estimate that 19/239 (7.9%) of isolates (7 *E. coli*, 3 *S. aureus*, 2 CONS, 1 *Flavobacterium spp.*, 4 *Candida spp.*, and 2 *viridans Streptococci*) might not be adequately treated with empiric ampicillin and gentamicin. The addition of a carbapenem agent such as meropenem would provide coverage for all *E. coli* and methicillin-sensitive *S. aureus* isolates, but only the addition of vancomycin, a carbapenem, and an antifungal agent together with ampicillin and gentamicin would provide adequate empiric antibiotic coverage for all 239 isolates.

To determine the clinical characteristics of infants who might benefit from the addition of empiric therapy beyond ampicillin and gentamicin, we compared infants infected with isolates for which ampicillin and gentamicin was estimated to be suboptimal empiric treatment to those with adequate treatment (Table 3). For infants with polymicrobial infection, if at least one isolate was sub-optimally treated then the infant was categorized

that way. Infants infected with an isolate for which ampicillin and gentamicin would be suboptimal empiric treatment (N=19) were more often born preterm and of lower birth weight (Table 3). For infants with EOS born 22–28 weeks' GA and/or with BW ≤1500 g, approximately 12% were infected with isolates for which ampicillin and gentamicin would be suboptimal empiric treatment, in contrast to only 4% of those born ≥37 weeks' GA and/or with BW >2500 g (Table 3). There was no overall difference in mortality between the comparison groups.

DISCUSSION

In this multicenter U.S. study conducted from 2015–2017, we found that the majority of all pathogens causing EOS were susceptible to the combination of ampicillin and gentamicin. Published studies on antimicrobial susceptibility of organisms causing neonatal EOS have focused on the two most common organisms, GBS and *E. coli*. However, approximately one-third of EOS infections are caused by a variety of other organisms.[26] Therefore in this study we assessed all available antimicrobial susceptibility data. From the perspective of the clinician who must make decisions regarding empiric antibiotic therapy for newborns at risk for EOS, this report contains good news and bad news. The good news is that the currently recommended combination of empiric ampicillin and gentamicin would likely be, at least initially, appropriate therapy for 92% of cases identified in this study. Other good news derives from a very low prevalence of infection caused by priority resistant organisms, and little evidence of infection with ESBL-producing *Enterobacterales*. However, we did find increasing resistance to gentamicin, which increased the proportion of bacteria non-susceptible to the combination of empiric ampicillin and gentamicin based on available data.

Most infants treated with antibiotics from birth due to risk of EOS are ultimately found to be uninfected. However, a substantial proportion of term infants and up to 90% of extremely preterm infants are empirically treated.[1,33] Such frequent antibiotic exposure combined with the high risk of morbidity and mortality among infants with EOS, particularly those born preterm, underscores the importance of continually assessing the appropriateness of therapeutic regimens.[18] In a longitudinal single center study of resistance rates among cases of neonatal *E. coli*, investigators found 54% of cases from 1997–2006 were resistant to ampicillin, yet none were resistant to gentamicin.[19] A prior NRN study of *E. coli* EOS isolates from 2008–2009 also found no gentamicin resistance.[20] CDC active surveillance during 2005–2014, however, found that 66% of *E. coli* EOS isolates were resistant to ampicillin and 10% were resistant to gentamicin, similar to percentages in our study.[21] More recently, a large study of neonatal *E. coli* isolate susceptibility from 2009–2017 using the Premier Health Database found on average 67% ampicillin non-susceptibility and 17% aminoglycoside non-susceptibility, and notably, 10% of EOS *E. coli* isolates were non-susceptible to both ampicillin and gentamicin.[5] The current study demonstrates that the threat of infection with ampicillin and gentamicin-resistant *Enterobacterales* is real and persistent across diverse U.S. centers. Our study provides some insight into the clinical profile of infants most likely to be infected with such strains. Although we found that such infants are more likely to be born with very low birth weight and gestational age <33 weeks, in the setting of histologically-confirmed chorioamnionitis – these characteristics

were not defining. Some dual resistance infections occurred in term infants, and histologic chorioamnionitis was present on placental pathology in nearly 80% of cases without dual resistance. Larger case series with detailed clinical and microbiologic data will be needed to help clinicians accurately identify those at highest risk of resistant infection. In the meantime, our findings support the use of ampicillin and gentamicin empiric therapy, with the addition of a broader-spectrum antibiotic when there is significant clinical concern for serious infection, particularly among premature infants or when there is a high suspicion for meningitis.

Despite ongoing endorsement of screening-based approaches to GBS prevention, one-third of infections in this study were caused by GBS. Reassuringly, GBS isolates tested were susceptible to ampicillin, penicillin, vancomycin, and cephalosporins. However, GBS were commonly resistant to clindamycin (42%) and macrolides (50%), consistent with CDC U.S. surveillance from 2016.[22] These data have important implications for intrapartum antibiotic prophylaxis (IAP) for pregnant women colonized with GBS. Current guidance from both the AAP and the American College of Obstetricians and Gynecologists recommend clindamycin as an alternative IAP agent for colonized women with penicillin allergy and high risk of anaphylaxis, and clindamycin or azithromycin when preterm pre-labor rupture of membranes is also present.[23,24] The use of such medications for IAP without evidence of isolate susceptibility is not supported by our findings. The data justify current AAP guidance that the administration of clindamycin as GBS IAP should not be considered adequate when performing newborn infection risk assessment.[23]

In 2019 the CDC released a report of the top antibiotic resistance threats in the US and called for immediate attention to such pathogens among all populations.[15] Our findings directly address an important knowledge gap: what are the recent rates of these priority resistant organisms among neonates with EOS? Infections caused by organisms on the list of urgent or serious threats in the CDC report were not common in our cohort. Of 77 *E. coli* and *Klebsiella* spp. isolates tested, 3 (3.9%) were ESBL-producing; all were *E. coli*, the organism of most concern in terms of evolving EOS resistance.[3,4] There were no resistant *Candida* species, VRE, or CRE, although one case of *M. morganii* intermediate to carbapenems was identified. Continued attention to pathogen susceptibility surveillance remains important, given the increase in gentamicin resistance observed during the two-year study period and evolving reports of multi-drug resistant bacteria emerging as predominant EOS pathogens, particularly in low and middle income countries.[25–30] Our finding that infants infected with isolates sub-optimally treated with ampicillin/gentamicin were born at lower GAs suggests that mechanisms of EOS pathogenesis specific to the premature population may predispose to resistant gram-negative infection, and requires further investigation as well as consideration of alternative antimicrobial therapies. Although the unadjusted comparisons in Table 3 did not show a difference in death, consistent with findings from a recent study[5] of neonatal early-onset *E. coli* infection, they do suggest a more complex hospital stay among those infected with isolates not optimally treated with ampicillin and gentamicin.

Strengths of this study include the large contemporary cohort of infants from 18 centers in 14 states across the U.S. and the collection of detailed antimicrobial susceptibility data

for numerous pathogens. While the cohort is large, NRN centers are primarily tertiary academic neonatal centers and the cohort is not a population-based sample which may limit the generalizability of our findings. The unadjusted comparison of infants with isolates for which ampicillin/gentamicin is estimated to be suboptimal vs adequate therapy was limited by small sample size in the suboptimal group. Antimicrobial susceptibility patterns are dynamic, and the data collected during the two-year study period from 2015 to 2017 may not reflect current susceptibility patterns. Another limitation of our study is that we relied on antimicrobial "S/R/I" result designations reported by the study center and did not have quantitative data on minimum inhibitory concentration. Finally, we do not have data on subsequent blood cultures that may have been obtained after initiation of empiric antibiotic therapy, limiting our ability to determine potential differences between *in vitro* susceptibility data and *in vivo* efficacy.

CONCLUSIONS

Most EOS pathogens were susceptible to the combination of ampicillin and gentamicin during the 2015–2017 study period. Our findings support the primary use of this antibiotic combination as empiric therapy in most cases, with the addition of a broader-spectrum antibiotic when there is significant clinical concern for serious infection, particularly among premature infants. Large-scale assessments of antimicrobial susceptibility profiles among organisms causing EOS in the U.S. are crucial to inform optimal empiric therapy.

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Data collected at participating sites of the NICHD NRN were transmitted to RTI International, the data coordinating center for the network, which stored, managed, and analyzed the data included in this study. On behalf of the NRN, RTI International had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

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Table 1a.

Antimicrobial susceptibility of Gram-positive and Gram-negative organisms causing early-onset sepsis

Organism	Total # of isolates[2]	# Non-susceptible / # Tested (% Non-susceptible)[1]						
		Ampicillin[3]	Gentamicin	Ampicillin AND Gentamicin[4]	Penicillin	Amikacin	Tobramycin	Vancomycin
Gram-positive								
GBS	71	0/48 (0.0)		0/48 (0.0)	0/43 (0.0)			0/32 (0.0)
Enterococcus spp.	14	0/14 (0.0)	1/6 (16.7)	0/14 (0.0)	0/7 (0.0)			0/13 (0.0)
GAS	9	0/2 (0.0)		0/2 (0.0)	0/2 (0.0)			0/2 (0.0)
Viridans Streptococci	8	1/4 (25.0)	0/1 (0.0)	0/3 (0.0)	3/6 (50.0)			0/6 (0.0)
Streptococcus spp.	6	0/2 (0.0)		0/2 (0.0)	0/2 (0.0)			0/2 (0.0)
S. bovis	6	0/5 (0.0)		0/5 (0.0)	0/5 (0.0)			0/4 (0.0)
S. aureus	3		0/3 (0.0)	0/3 (0.0)	2/2 (100.0)			0/3 (0.0)
S. pneumoniae	3	0/2 (0.0)		0/2 (0.0)	0/2 (0.0)			0/3 (0.0)
CONS	2	1/1 (100.0)	1/2 (50.0)	0/1 (0.0)	0/1 (0.0)			0/2 (0.0)
L. monocytogenes	2	0/1 (0.0)		0/1 (0.0)	0/1 (0.0)			
Gram-negative								
E. coli	86	63/81 (77.8)	8/80 (10.0)	7/79 (8.9)		0/30 (0.0)	7/56 (12.5)	
Haemophilus spp.	10	0/3 (0.0)		0/3 (0.0)				
Klebsiella spp.	7	6/6 (100.0)	0/7 (0.0)	0/7 (0.0)		0/2 (0.0)	0/4 (0.0)	
M. morganii	3	2/2 (100.0)	0/3 (0.0)	0/3 (0.0)		0/1 (0.0)	0/2 (0.0)	
Citrobacter spp.	1		0/1 (0.0)	0/1 (0.0)		0/1 (0.0)	0/1 (0.0)	
Enterobacter spp.	1	1/1 (100.0)	0/1 (0.0)	0/1 (0.0)				
Proteus spp.	1	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)			0/1 (0.0)	
Pseudomonas spp.	1		0/1 (0.0)	0/1 (0.0)				
Flavobacterium spp.	1							

Table 1b.

Antimicrobial susceptibility of Gram-positive and Gram-negative organisms causing early-onset sepsis

Organism	Total # of isolates[2]	# Non-susceptible / # Tested (% Non-susceptible)[1]						
		Cefazolin[5]	2nd gen. ceph.[6]	Ceftriaxone	Other 3rd gen. ceph.[7]	Cefepime	Oxacillin	Piperacillin
Gram-positive								
GBS	71			0/16 (0.0)	0/11 (0.0)	0/11 (0.0)		
Enterococcus spp.	14		1/1 (100.0)					
GAS	9			0/2 (0.0)				
Viridans Streptococci	8			0/5 (0.0)	0/3 (0.0)	0/2 (0.0)		
Streptococcus spp.	6			0/2 (0.0)	0/1 (0.0)	0/2 (0.0)		
S. bovis	6			1/4 (25.0)				
S. aureus	3						1/3 (33.3)	
S. pneumoniae	3			0/2 (0.0)	0/1 (0.0)			
CONS	2			0/1 (0.0)			1/2 (50.0)	
L. monocytogenes	2							
Gram-negative								
E. coli	86	11/51 (21.6)	1/33 (3.0)	3/56 (5.4)	3/34 (8.8)	3/46 (6.5)		1/4 (25.0)
Haemophilus spp.	10			1/2 (50.0)				
Klebsiella spp.	7	0/4 (0.0)	1/4 (25.0)	0/6 (0.0)	0/2 (0.0)	0/5 (0.0)		
M. morganii	3	1/1 (100.0)		0/1 (0.0)	0/1 (0.0)	0/1 (0.0)		
Citrobacter spp.	1	0/1 (0.0)		0/1 (0.0)		0/1 (0.0)		0/1 (0.0)
Enterobacter spp.	1	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)		
Proteus spp.	1	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)		
Pseudomonas spp.	1					0/1 (0.0)		
Flavobacterium spp.	1							

Table 1c.

Antimicrobial susceptibility of Gram-positive and Gram-negative organisms causing early-onset sepsis

Organism	Total # of isolates[2]	# Non-susceptible / # Tested (% Non-susceptible)[1]								
		Aztreonam	TMP-SMX	Piperacillin-tazobactam	Ampicillin-sulbactam/ Amoxicillin-clavulanate[8]	Quinolones[9]	Carbapenems[10]	Clindamycin[11]	Macrolides[12]	Linezolid
Gram-positive										
GBS	71					0/6 (0.0)	0/6 (0.0)	13/31 (41.9)	9/18 (50.0)	0/8 (0.0)
Enterococcus spp.	14							1/1 (100.0)	1/1 (100.0)	0/7 (0.0)
GAS	9					0/1 (0.0)		0/2 (0.0)	0/2 (0.0)	
Viridans Streptococci	8					0/1 (0.0)	0/2 (0.0)	1/3 (33.3)	1/1 (100.0)	0/2 (0.0)
Streptococcus spp.	6					0/1 (0.0)	0/1 (0.0)	2/3 (66.7)	3/3 (100.0)	0/1 (0.0)
S. bovis	6					0/1 (0.0)	0/1 (0.0)	1/3 (33.3)	1/2 (50.0)	0/3 (0.0)
S. aureus	3		0/3 (0.0)			0/1 (0.0)		1/3 (33.3)	1/3 (33.3)	0/2 (0.0)
S. pneumoniae	3		0/2 (0.0)					0/1 (0.0)	0/1 (0.0)	0/1 (0.0)
CONS	2		0/1 (0.0)		0/1 (0.0)	0/1 (0.0)		2/2 (100.0)	2/2 (100.0)	0/1 (0.0)
L. monocytogenes	2		0/1 (0.0)							
Gram-negative										
E. coli	86	1/23 (4.3)	23/60 (38.3)	2/62 (3.2)	30/50 (60.0)	11/57 (19.3)	0/43 (0.0)			
Haemophilus spp.	10									
Klebsiella spp.	7	0/2 (0.0)	0/4 (0.0)	0/6 (0.0)	1/4 (25.0)	0/6 (0.0)	0/6 (0.0)			
M. morganii	3		0/1 (0.0)	0/2 (0.0)	0/1 (0.0)		1/1 (100.0)			
Citrobacter spp.	1		0/1 (0.0)			0/1 (0.0)	0/1 (0.0)			
Enterobacter spp.	1			0/1 (0.0)	1/1 (100.0)	0/1 (0.0)	0/1 (0.0)			
Proteus spp.	1		0/1 (0.0)	0/1 (0.0)	0/1 (0.0)					
Pseudomonas spp.	1									
Flavobacterium spp.	1									

GBS (Group B *Streptococcus*); GAS (Group A *Streptococcus*); CONS (coagulase-negative Staphylococci)

[1] Non-susceptible was defined as intermediate or resistant to the drug or drug group shown. If an isolate was intermediate or resistant to any drug in a combination group, it was classified as non-susceptible to that group; the denominator includes isolates tested against any of the drugs in the group.

[2] Isolates from single organism and polymicrobial cases counted.

[3] The numerator includes isolates non-susceptible to ampicillin or amoxicillin. The denominator includes isolates susceptible or non-susceptible to ampicillin or amoxicillin or susceptible to penicillin. One *Enterococcus* spp. isolate reported as intermediate to ampicillin and susceptible to penicillin was classified as susceptible to ampicillin. One CONS isolate reported as resistant to ampicillin and susceptible to penicillin was classified as non-susceptible to ampicillin.

[4] Isolates non-susceptible to ampicillin or amoxicillin and non-susceptible to gentamicin are included in the numerator. The denominator includes isolates non-susceptible to ampicillin or amoxicillin and gentamicin or isolates susceptible to ampicillin or amoxicillin or gentamicin or penicillin. Thus, combined ampicillin and gentamicin susceptibility is defined differently than for other groups in this table involving more than one drug (as stated in note 1).

[5] Cefazolin was the only 1st generation cephalosporin tested.

[6] 2nd generation cephalosporins tested were cefoxitin, cefuroxime, and cefotetan.

[7] Other 3rd generation cephalosporins tested were cefotaxime, ceftazidime, ceftizoxime, and cefixime.

[8] For one case, *E. coli* was reported as susceptible to ampicillin-sulbactam on blood culture but non-susceptible on CSF culture. This *E. coli* case was counted as non-susceptible to ampicillin-sulbactam.

[9] Quinolones tested were ciprofloxacin, levofloxacin, and moxifloxacin.

[10] Carbapenems tested were imipenem, meropenem, and ertapenem.

[11] For one case, CONS was reported as susceptible to clindamycin on first blood culture but resistant on repeat blood culture. This CONS case was counted as non-susceptible to clindamycin.

[12] Macrolides tested were erythromycin and azithromycin.

Table 2.

Priority resistant organisms causing early-onset neonatal sepsis by study year

Organism	Overall	Year 1 April 2015 – March 2016	Year 2 April 2016 – March 2017	P-value[5]
Ampicillin and gentamicin non-susceptible bacteria (any species)[1]	7/177 (4.0)	1/99 (1.0)	6/78 (7.7)	0.04
Ampicillin non-susceptible bacteria (any species)[2]	74/173 (42.8)	39/96 (40.6)	35/77 (45.5)	0.54
Ampicillin non-susceptible gram-negative bacteria[2]	72/94 (76.6)	38/51 (74.5)	34/43 (79.1)	0.63
Gentamicin non-susceptible bacteria (any species)[3]	10/106 (9.4)	2/58 (3.4)	8/48 (16.7)	0.04
Gentamicin non-susceptible gram-negative bacteria[3]	8/94 (8.5)	2/51 (3.9)	6/43 (14.0)	0.14
ESBL-producing *Enterobacterales*[4]	3/77 (3.9)	0/40 (0.0)	3/37 (8.1)	0.11

Non-susceptible = resistant (R) or intermediate (I).

[1]Isolates non-susceptible to ampicillin or amoxicillin and non-susceptible to gentamicin are included in the numerator. The denominator includes isolates non-susceptible to ampicillin or amoxicillin and gentamicin or isolates susceptible to ampicillin or amoxicillin or gentamicin or penicillin. The 177 isolates in the denominator include: 23 sensitive to ampicillin or amoxicillin, gentamicin not tested; 10 sensitive to gentamicin, ampicillin/amoxicillin not tested; 50 sensitive to penicillin, ampicillin/amoxicillin and gentamicin not tested; 94 tested for both ampicillin and gentamicin—23 sensitive to both, 64 sensitive to one or the other (63 susceptible to gentamicin, 1 to ampicillin), 7 non-susceptible to both drugs.

All 7 non-susceptible isolates were E. coli: 6 were resistant to both ampicillin and gentamicin; 1 was intermediate to ampicillin and resistant to gentamicin.

[2]The numerator includes isolates non-susceptible to ampicillin or amoxicillin. The denominator includes isolates susceptible or non-susceptible to ampicillin or amoxicillin or susceptible to penicillin. *Klebsiella* spp. were included.

The 173 isolates in the denominator include: 46 sensitive to ampicillin (includes one intermediate to ampicillin and sensitive to penicillin coded as susceptible to ampicillin); 2 sensitive to amoxicillin, not tested for ampicillin; 51 sensitive to penicillin, ampicillin/amoxicillin not tested; 74 resistant or intermediate to ampicillin or amoxicillin (70 resistant to ampicillin, 3 intermediate to ampicillin, 1 intermediate to amoxicillin not tested for ampicillin). 70 isolates were resistant to ampicillin (1 CONS, 60 *E. coli*, 6 *Klebsiella* spp., 1 *Enterobacter* spp., 2 M. morganii), 3 were intermediate to ampicillin (*E. coli*) and 1 was intermediate to amoxicillin (viridans Streptococci).

[3]The numerator includes isolates non-susceptible to gentamicin. The denominator includes isolates susceptible or non-susceptible to gentamicin. All 10 non-susceptible isolates were resistant to gentamicin (1 CONS, 1 *Enterococcus* spp., 8 *E. coli*).

[4]Includes *E. coli* and *Klebsiella* spp. (not Klebsiella aerogenes). Isolates non-susceptible to cefotaxime, ceftriaxone, ceftazidime, or cefepime are included in the numerator. The denominator includes isolates with a susceptible or non-susceptible result to cefotaxime, ceftriaxone, ceftazidime, cefepime or the same isolate with at least 2 reported susceptible results to ampicillin, piperacillin, aztreonam, or cefazolin.[15] The 3 ESBL-producing isolates were *E. coli* resistant to 3rd and 4th generation cephalosporins.

[5]P-value for difference by year by Fisher's exact test

Table 3.

Infants with isolates for which ampicillin/gentamicin is estimated to be suboptimal vs adequate therapy[1]

N (column %) or as shown	Suboptimal (N=19)	Adequate (N=216)	P-value[2]
Maternal and delivery characteristics			
Mother's age, mean (SD)	29.5 (5.6)	28.3 (6.8)	0.46
Maternal race/ethnicity			0.51
Black, non-Hispanic	5/17 (29.4)	71/205 (34.6)	
White, non-Hispanic	7/17 (41.2)	61/205 (29.8)	
Hispanic	5/17 (29.4)	55/205 (26.8)	
Other	0/17 (0.0)	18/205 (8.8)	
Antibiotics within 72 h before delivery	17 (89.5)	145 (67.1)	0.07
Received ampicillin or amoxicillin within 72 h before delivery	7 (36.8)	85 (39.4)	1.0
Received gentamicin within 72 h before delivery	4 (21.1)	48 (22.2)	1.0
Antenatal steroids within 72 h before delivery	11 (57.9)	74 (34.3)	0.05
Chorioamnionitis documented in the medical record	9 (47.4)	94 (43.5)	0.81
Placental pathology performed	16 (84.2)	158 (73.1)	0.42
Histologic chorioamnionitis	16/16 (100.0)	125/158 (79.1)	0.04
Rupture of membranes ≥ 18 h before delivery	7 (36.8)	108 (50.0)	0.34
Type of delivery			0.64
Vaginal	10 (52.6)	117 (54.4)	
C-section with labor	5 (26.3)	69 (32.1)	
C-section without labor	4 (21.1)	29 (13.5)	
Infant characteristics			
Study year of birth			0.02
April 2015-March 2016	5 (26.3)	122 (56.5)	
April 2016-March 2017	14 (73.7)	94 (43.5)	
Gestational age (w), mean (SD)	30.6 (6.1)	33.5 (6.1)	0.05
Gestational age category			0.03
22–28	8 (42.1)	59 (27.3)	
29–33	6 (31.6)	44 (20.4)	
34–36	1 (5.3)	13 (6.0)	
37+	4 (21.1)	100 (46.3)	
Birth weight (g), mean (SD)	1704 (1097)	2273 (1152)	0.04
Birth weight category			0.02
401–1500	11 (57.9)	77 (35.6)	
1501–2500	4 (21.1)	35 (16.2)	
2501+	4 (21.1)	104 (48.1)	
Sex			0.63
M	9 (47.4)	118 (54.6)	

N (column %) or as shown	Suboptimal (N=19)	Adequate (N=216)	P-value[2]
F	10 (52.6)	98 (45.4)	
Highest care in first 72 h			0.18
Well baby nursery	0 (0.0)	25 (11.6)	
Intermediate care/ step down	2 (10.5)	10 (4.6)	
Intensive care	17 (89.5)	181 (83.8)	
Status at 120 days			0.03
Discharged home	12 (63.2)	171 (79.2)	
Still in hospital	2 (10.5)	6 (2.8)	
Transferred	2 (10.5)	4 (1.9)	
Death[3]	3 (15.8)	35 (16.2)	
Timing of death, day of life			0.29
1–3	2/3 (66.7)	17/35 (48.6)	
4–7	1/3 (33.3)	5/35 (14.3)	
8–14	0/3 (0.0)	5/35 (14.3)	
15+	0/3 (0.0)	8/35 (22.9)	

[1]Infants with isolates for which ampicillin and gentamicin was estimated to be suboptimal therapy included 7 infants with *E. coli* that was non-susceptible based on study test results, 1 with *Flavobacterium* spp., 2 with CONS, 3 with *S. aureus*, 2 with viridans Streptococci, and 4 with *C. albicans*. Of the 8 infants in the cohort with viridans Streptococci, one with viridans Streptococci that was non-susceptible to ampicillin and was not tested for gentamicin, and one with viridans Streptococci that was not tested for susceptibility to ampicillin or gentamicin but was resistant to penicillin were included in the suboptimal therapy group.

[2]P-value by F test (mother's age, gestational age, birth weight), chi-square or Fisher's exact test.

[3]The difference in the proportion of infants who died was not significant, P=1.0 by Fisher's exact test.