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Epidemiology and Etiology of Invasive Bacterial Infection in Infants ≤60 Days Old Treated in Emergency Departments

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Abstract

Objectives—To help guide empiric treatment of infants ≤60 days old with suspected invasive bacterial infection (IBI) by describing pathogens and their antimicrobial susceptibilities.

Study design—Cross-sectional study of infants ≤60 days old with IBI (bacteremia and/or bacterial meningitis) evaluated in the emergency departments (EDs) of 11 children's hospitals between July 1, 2011 and June 30, 2016. Each site's microbiology laboratory database or electronic medical record system was queried to identify infants from whom a bacterial pathogen was isolated from either blood or cerebrospinal fluid (CSF). Medical records of these infants were reviewed to confirm the presence of a pathogen and to obtain demographic, clinical, and laboratory data.

Results—Of the 442 infants with IBI, 353 (79.9%) had bacteremia without meningitis, 64 (14.5%) had bacterial meningitis with bacteremia, and 25 (5.7%) had bacterial meningitis without bacteremia. The peak number of cases of IBI occurred in the second week of life; 364 (82.4%) infants were febrile. Group B streptococcus (GBS) was the most common pathogen identified (36.7%), followed by *Escherichia coli* (30.8%), *Staphylococcus aureus* (9.7%), and *Enterococcus* spp. (6.6%). Overall, 96.8% of pathogens were susceptible to ampicillin plus a third-generation cephalosporin, 96.0% to ampicillin plus gentamicin, and 89.2% to third-generation cephalosporins alone.

Conclusions—For most infants ≤60 days old evaluated in a pediatric ED for suspected IBI, the combination of ampicillin plus either gentamicin or a third-generation cephalosporin is an appropriate empiric antimicrobial treatment regimen. Of the pathogens isolated from infants with IBI, 11% were resistant to third-generation cephalosporins alone.

Keywords

bacteremia; meningitis; febrile infant; pathogen

Infants ≤60 days old are at increased risk of bacterial infections due to exposure to bacterial pathogens in the perinatal period and lack of vaccine-induced immunity.[1,2] Although viral infections cause most episodes of fever in infants ≤60 days of age,[3] 2–5% of these infants have bacteremia and/or bacterial meningitis, [4–7] ie, invasive bacterial infection (IBI).[7,8] These infants routinely undergo extensive diagnostic evaluation and are frequently hospitalized for treatment with empiric intravenous antimicrobials.[9] Understanding the

epidemiology of IBI in young infants could inform the selection of empiric antimicrobials while awaiting bacterial culture results in infants with suspected IBI.

Due in large part to broadened screening and perinatal antimicrobial prophylaxis for Group B streptococcus (GBS),[2] as well as expanded vaccines for infants in the United States,[10–13] the epidemiology of IBI in young infants has changed since the 1990s. Recent multicenter studies of bacteremia and/or bacterial meningitis in young infants ≤90 days of age predominantly reported *Escherichia coli* as the most common pathogen.[14–19] Though ampicillin is effective for the treatment of GBS,[20] 47- 58% of *E. coli* and other gram negative pathogens are resistant to ampicillin.[15,19] Furthermore, *Enterococcus* spp. and *Listeria monocytogenes*, pathogens typically susceptible to ampicillin but intrinsically resistant to third-genergation cephalosporins,[21] were uncommon in these prior studies,[14–19,22] raising concerns about the need for routine use of ampicillin as empiric therapy in young infants with suspected IBI.[15] However, many of the recent studies focused either on infants with bacteremia[14–18,23] or with bacterial meningitis[19,22] rather than including those with bacteremia and/or bacterial meningitis. Additionally, most of the investigations included older infants (>60 days of age) in whom the rates of these infections are lower[14–16,19,22,23]

Given the higher risk of bacteremia and bacterial meningitis and the uncertainty of optimal empiric antimicrobial selection for infants ≤60 days old with suspected IBI, we conducted a large, multicenter investigation of infants with IBI in this younger age group. Our objective was to describe the bacterial pathogens identified and their antimicrobial susceptibilities in infants ≤60 days old with bacteremia and/or bacterial meningitis evaluated in the emergency department (ED).

METHODS

We identified infants ≤60 days of age with bacteremia and/or bacterial meningitis evaluated in the ED at one of 11 geographically diverse children's hospitals between July 1, 2011 and June 30, 2016. The study was approved by each site's institutional review board with permission for data sharing.

Study Population

We searched the microbiology laboratory database or the electronic medical record system at each hospital to identify positive blood or cerebrospinal fluid (CSF) cultures obtained in the ED from infants ≤60 days of age. We defined pathogenic bacteria *a priori* through expert consensus (Appendix 1 (available at www.jpeds.com) for list of pathogens).[18,24–26] For eligible infants with growth of a pathogen from culture, we reviewed the medical records and included infants who were documented to have received an antimicrobial treatment course commensurate for an IBI,[14,22,23] defined as bacteremia and/or bacterial meningitis. We excluded infants whose positive culture was documented to have been treated as a contaminant by the treating physician and those with bacterial cultures positive for contaminant species.[14,22,23] Pathogens that grew only from CSF enrichment broth cultures were considered contaminants if the blood culture had no growth and there was no CSF pleocytosis.[26]

Data Collection

For each eligible infant, we extracted the following variables: demographics (age, sex), past medical history (prematurity or presence of a complex chronic condition), temperature (at home, in an outpatient clinic, in triage, and highest recorded in the ED), clinical appearance, presence of a clinically apparent infection on physical examination, laboratory data (complete blood count, urinalysis, and CSF cell count), bacterial culture results (urine, blood, CSF), and antimicrobial susceptibilities. Data were entered directly into a Research Electronic Data Capture (REDCap) tool hosted at Yale University.[27]

Study Definitions

Fever was defined as a documented temperature ≥38.0° C (100.4° F) at home, in an outpatient clinic, or in the ED obtained via any method (e.g., rectal, axillary). Ill-appearance was defined as any of the following words documented on the physical examination in the ED: “ill-appearing,” “toxic,” “limp,” “unresponsive,” “gray,” “cyanotic,” “apnea,” “weak cry,” “poorly perfused,” “grunting,” “listless,” “lethargic,” or “irritable.”[28] If none of these terms were documented, the infant was classified as not ill-appearing. In cases with contradictory documentation of appearance between the attending physician and a trainee, the attending physician’s documentation was used. We defined complex chronic conditions as severe medical conditions expected to last ≥12 months, and that involve ≥1 organ system and/or require pediatric specialty care.[29,30] CSF pleocytosis was defined as CSF WBC ≥20 cells/mm^3 for infants ≤28 days and ≥10 cells/mm^3 for infants 29 to 60 days of age.[31]

Bacterial Infections

Bacteremia and bacterial meningitis were defined *a priori* as growth of a pathogen from blood or from CSF, respectively.[8,18,32] Bacteremia with CSF pleocytosis but negative CSF culture was classified as bacterial meningitis if antimicrobials were administered prior to CSF collection.[19,33] Urinary tract infection (UTI) was defined as either 1) a urine culture obtained by catheterization with ≥50,000 colony-forming units (CFUs)/mL of a single pathogen or 10,000–50,000 CFUs/mL of a single pathogen with an abnormal urinalysis (i.e., positive nitrite or leukocyte esterase on urine dipstick or >5 WBCs/hpf on urine microscopy),[32,34–36] or 2) ≥100,000 CFUs/mL of a single pathogen on culture obtained from a bagged urine specimen or from an unknown method of collection, if the pathogen was simultaneously identified in the blood.[37,38] Clinically apparent infection was defined as the presence of any of the following that were either documented in the ED or confirmed in the inpatient records: cellulitis, abscess, omphalitis, osteomyelitis/septic arthritis, myositis, lymphadenitis, parotitis, surgical site infection, or necrotizing enterocolitis.

Antimicrobial Susceptibilities

In vitro antimicrobial susceptibilities were categorized as susceptible or resistant based on microbiology reports.[39] Additionally, as *in vitro* susceptibility testing may not be performed due to assumed susceptibility or resistance for certain pathogen-antimicrobial combinations, Clinical and Laboratory Standards Institute M100-S27 was consulted and used to determine intrinsic resistance, and predictable and inferred susceptibility.[21] All isolates from infants

with bacterial meningitis were considered resistant to gentamicin due to poor CSF penetration.[40]

Statistical Analyses

Descriptive analyses were stratified by type of IBI (bacteremia without meningitis or bacterial meningitis [with or without bacteremia]) and, for pathogens and antimicrobial susceptibilities, by age group (≤28 days and 29–60 days of age). We used chi-square tests to compare the distribution of antimicrobial resistance with binary demographic, clinical, and laboratory factors. We then used mixed-effects logistic regression for the adjusted analysis, with variables selected at a p-value ≤0.1 from the unadjusted analysis. Statistical significance was determined as a two-sided p-value <0.05. Statistical analyses were performed using Stata Data Analysis and Statistical Software version 15.0 (StataCorp, Inc, College Station, Texas).

RESULTS

During the 5-year study period, there were 20,896 blood cultures and 10,635 CSF cultures obtained from infants ≤60 days old evaluated in the ED. We identified 497 infants with a blood and/or CSF culture that grew a potential bacterial pathogen. Fifty-five of these infants were excluded: 45 had bacteria that were treated as contaminants (34 from CSF and 11 from blood culture), 7 infants did not have an ED visit, and 3 infants had CSF bacterial detection from broth culture alone with no concurrent CSF pleocytosis. Of the 442 infants with an IBI, 353 (79.9%) had bacteremia without meningitis, 64 (14.5%) had bacterial meningitis with bacteremia, and 25 (5.7%) had bacterial meningitis without bacteremia. Overall, 417/20,896 (2.0%) blood cultures and 76/10,635 (0.7%) CSF cultures demonstrated growth of a pathogen. Thirteen infants had bacteremia and CSF pleocytosis but negative CSF culture after receipt of antimicrobials prior to CSF collection.

Clinical and Laboratory Characteristics of Infants with IBI

The peak number of cases of IBI occurred in the second week of life (Figure; **available at** www.jpeds.com). Though IBI declined in the second month of life as compared with the first, the number of infants with bacteremia was similar from the fifth to the eighth week of life. Characteristics of infants with IBI are shown in Table I. Over 80% of infants were febrile at the time of presentation and 29% had a concomitant UTI. Among infants with bacterial meningitis, 20% had an abnormal urinalysis and 9% had a UTI. Three infants with meningitis had ventriculo-peritoneal (VP) shunts.

Bacteremia Without Meningitis

The bacterial pathogens isolated in infants with bacteremia without meningitis are listed in Table II. *E. coli* was the most common pathogen overall (33.7%) though GBS accounted for a higher proportion of bacteremia in the second month of life. Of the 119 infants with *E. coli* bacteremia without meningitis, 98 (82.4%) had a UTI. *S. aureus* was isolated in 40 (11.3%) infants; 11 (27.5%) of these infants had a clinically apparent infection, including 5 infants with cellulitis, 3 with surgical site infections, 2 with myositis, and 1 with parotitis. Twenty-seven (7.6%) infants had *Enterococcus* spp. and 12 (3.4%) *had Klebsiella* spp., including 4

(33.3%) with UTI. Among the 238 febrile infants without a complex chronic condition or a clinically apparent infection, *E. coli* was the most common pathogen isolated (40.8%). Sixteen (6.7%) of the infants had *S. aureus* and 15 (6.3%) had *Enterococcus* spp., 6 (40%) with concomitant UTI.

Over 96% of infants with bacteremia without meningitis had pathogens susceptible to a combination of ampicillin plus either gentamicin or a third-generation cephalosporin (defined as cefotaxime or ceftriaxone) [Table III]. However, 11.5% (95% confidence interval [CI]: 8.5–15.2%) had pathogens resistant to third-generation cephalosporins alone, including 10.2% (95% CI: 6.6–15.6%) of those 29–60 days of age. Resistance patterns were similar among febrile and afebrile infants; 8.5% of febrile infants without a chronic condition or a clinically apparent infection had a pathogen resistant to a third-generation cephalosporin.

Bacterial Meningitis

Among infants with bacterial meningitis, GBS was the most common pathogen isolated in both age groups (Table II). Four febrile infants aged 11 to 24 days from 3 different study sites had meningitis due to *Listeria monocytogenes*. One infant (who was ill-appearing) had concomitant bacteremia, and none had a complex chronic condition. Among the 13 infants with bacteremia and CSF pleocytosis but negative CSF culture after receipt of antimicrobials prior to CSF collection, GBS was the most common pathogen isolated (46.2%) followed by *E. coli* (23.1%).

All but one infant with bacterial meningitis had pathogens susceptibile to a combination of ampicillin plus a third-generation cephalosporin (Table III). This infant was a febrile 53-day old infant with a ventriculo-peritoneal shunt and *Pseudomonas aeruginosa* meningitis.

Resistance to Third-Generation Cephalosporins

Across sites, the median proportion of infants with a cephalosporin-resistant pathogen was 13.3% (range 0–17%). Resistance to third-generation cephalosporins was predominantly due to *Enterococcus* spp., and to a lesser extent *Enterobacter* spp. and *S. aureus* (Table IV; **available at** www.jpeds.com). Four of 43 (9.3%) *S. aureus* isolates were methicillin-resistant. Of the 9 infants with bacteremia without meningitis who had pathogens susceptible to a combination of ampicillin plus gentamicin but resistant to ampicillin plus a third-generation cephalosporin, 5 (55.6%) had *Enterobacter* spp. Resistance to third-generation cephalosporins occurred more commonly among infants with complex chronic conditions (Table V); this association persisted on adjusted analysis (odds ratio 3.8; 95% CI: 1.9–7.5).

DISCUSSION

In this multicenter study of infants ≤60 days of age with IBI evaluated in the ED, the overall prevalence of IBI was similar to previous studies.[15,18] GBS accounted for a greater proportion of all cases of IBI including in the second month of life.[14–19,41–43] We also found a higher prevalence *of Enterococcus* spp., and a similar proportion of cases due to *E. coli*.[14–19,22,41–43] Overall, nearly 11% of isolates were resistant to third-generation cephalosporins.

Due to increasing antimicrobial resistance[15,19,44] and potential detrimental effects of antimicrobials on the infantile gut microbiome,[45] clinicians increasingly need to practice antimicrobial stewardship, even for the youngest infants. Infants at low-risk of IBI do not warrant empiric antimicrobial therapy.[46,47] For the empiric treatment of infants ≤60 days of age with suspected IBI, clinicians should select the narrowest spectrum antimicrobial therapy with the most tolerable side effect profile. Our study informs this important issue by identifying the most prevalent pathogens and their antimicrobial susceptibilities. Ampicillin plus gentamicin has traditionally been used for the empiric treatment of IBI in young infants.[48] However, concerns about gentamicin toxicity,[49] sub-optimal therapy with gentamicin alone in the setting of an ampicillin-resistant pathogen (up to 35% of isolates in this population),[15,19,39,44] and the low prevalence *of Listeria monocytogenes*[14,50,51] have all contributed to the common use of third-generation cephalosporins as empiric antimicrobial therapy for young infants, particularly in the second month of life.[9] However, we found that 11% of isolates, including those from infants in the second month of life, were resistant to third-generation cephalosoporins. Our finding that *Enterococcus* spp. accounted for a greater proportion of bacteremia than prior reports[14,15,18] partially explains this level of resistance to third-generation cephalosporins. Additionally, 10 infants had bacteremia due to *Enterobacter* spp. and 3 had *Citrobacter* spp.; both of these pathogens can have inducible beta-lactamases.[52] Although resistance to third-generation cephalosporins was more common in children with complex chronic conditions, two-thirds of infants with a cephalosporin-resistant pathogen did not have a complex chronic condition. Therefore, our findings support the empiric use of ampicillin plus gentamicin for most infants with suspected bacteremia while awaiting bacterial culture results, particularly given the lower risk of toxicity with once daily dosing[49] and the association of third-generation cephalosporin use with development of resistant bacteria.[53] When a pathogen is identified, which frequently occurs within 24 hours,[23] the antimicrobial regimen can be adjusted to provide definitive therapy.

However, *in vitro* susceptibilities do not necessarily correlate with *in vivo* effectiveness,[39] and it is unknown if discordant empiric antimicrobial selection in the ED is associated with adverse clinical outcomes.[54,55] Therefore, despite the high rate of *in vitro* pathogen susceptibility to a combination of ampicillin plus gentamicin in infants with bacteremia without meningitis, there are several circumstances in which an alternative empiric antimicrobial regimen would be more appropriate. First, we identified *S. aureus* as the pathogen for 11% of infants with bacteremia. Though most *S. aureus* had *in vitro* susceptibility to a combination of ampicillin plus gentamicin, this regimen would not provide appropriate *in vivo* coverage, particularly for methicillin-resistant *S. aureus*.[54] Clinician suspicion of *S. aureus* should prompt broadening of empiric coverage to include vancomycin or another anti-staphylococcal antimicrobial. Suspicion for *S. aureus* may be elicited by the presence of Gram-positive cocci in clusters on blood and/or CSF culture or by a clinically apparent infection, although unlike older children,[56] only 27.5% of infants with *S. aureus* had a clinically apparent infection.

For cases in which the clinical suspicion for bacterial meningitis is high (i.e., ill-appearance, bacteria identified on CSF Gram stain, or CSF pleocytosis with a neutrophil predominance),[57,58] an alternative presumptive antimicrobial regimen with better CSF penetration and a

broader spectrum of coverage is necessary. As 99% of infants with bacterial meningitis had a pathogen susceptible to the combination of ampicillin plus a third-generation cephalosporin, our findings support the use of this antimicrobial regimen for most infants with bacterial meningitis, though local antimicrobial susceptibilities may better guide empiric therapy, particularly when meningitis due to a gram-negative pathogen is suspected.[19,39] Clinicians may also initiate empiric antimicrobial therapy for infants with suspected IBI prior to the availability of CSF cell counts. In this scenario, initial treatment in the ED with ampicillin plus a third-generation cephalosporin would provide adequate empiric coverage for most infants.

Our study has several limitations. First, we classified *a priori* defined pathogens as either contaminants or pathogens based on treatment by the medical team, a definition used in prior investigations.[14,22,23] It is possible that some isolates classified as pathogens would have been eradicated without treatment. However, the time to detection on blood and/or CSF culture was significantly shorter for pathogens vs. contaminants, and the proportion of pathogens detected within 24 hours, including *Enterococcus* spp. and *Klebsiella* spp., was similar to a prior multicenter study (data not shown).[23] Additionally, although *Enterococcus* spp. may sometimes be considered a contaminant, the proportion of febrile infants with *Enterococcal* bacteremia with associated UTI was similar to prior investigations.[14,39,41]

We relied on medical records for historical features and physical examination findings of prematurity, complex chronic conditions, and ill-appearance. Although we used an established definition of ill-appearance to mitigate the potentially subjective nature of medical record documentation, this definition may not accurately reflect clinical appearance in young infants with IBI.[28] Our antimicrobial susceptibility data is partially based on intrinsic resistance patterns and inferred susceptibility for certain pathogen-antimicrobial combinations.[21] Fourth, limiting inclusion to the ED setting likely underrepresents IBI in the 0–7 day age range, as some infants with IBI would have been identified prior to hospital discharge, particularly if premature.[59] As 47 infants had pathogens resistant to third-generation cephalosporins, our study may have been underpowered to find an association between certain clinical or laboratory factors and resistance to third-generation cephalosporins. The current study was designed to inform the selection of empiric antimicrobial therapy for infants ≤60 days old with suspected IBI, not susceptibility-derived definitive antimicrobial therapy after bacterial culture results are available. While our results and recommendations are focused on bacteremia and bacterial meningitis, the optimal antimicrobial regimen may differ for more common infections such as UTI. Lastly, our study was limited to EDs at children's hospitals, rendering our findings less generalizable to other clinical settings.

In conclusion, the optimal empiric antimicrobial treatment for IBI in young infants presenting to the ED remains a challenge for the clinician. Our results support the use of a combination of ampicillin plus gentamicin for the empiric treatment of bacteremia in most young infants, though ampicillin plus a third-generation cephalosporin may be used, particularly if bacterial meningitis is suspected. As 11% of isolates were resistant to third-generation cephalosporins, our data highlight potential consequences of using third-generation cephalosporins alone as empiric therapy for infants with suspected IBI.

Additional investigation is needed to determine if initially discordant antimicrobial treatment has an impact on clinical outcomes for infants ≤60 days old with IBI.

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Abbreviations

CI	Confidence Interval
CFU	Colony-Forming Unit
CSF	Cerebrospinal Fluid
ED	Emergency Department
GBS	Group B streptococcus
IBI	Invasive Bacterial Infection
UTI	Urinary Tract Infection
VP	Ventriculo-peritoneal
WBC	White Blood Cell

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Appendix 1. Definition of Pathogens (a priori) for Organisms Isolated from Blood and/or Cerebrospinal Fluid Culture

Any organism isolated from both blood *and* CSF [exception: coagulase-negative staphylococci]
Gram-positive organisms: *Enterococcus* spp., *Listeria monocytogenes, Staphylococcus aureus, Streptococcus agalactiae* (GBS), *Streptococcus pneumoniae, Streptococcus pyogenes* (Group A streptococcus), *Streptococcus alactolyticus, Streptococcus gallolyticus, Streptococcus bovis*
Gram-negative organisms: *Acinetobacter* spp., *Citrobacter* spp., *Enterobacter* spp., *Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella* spp., *Moraxella* spp., *Neisseria meningitidis, Pasteurella multocida, Proteus mirabilis, Pseudomonas aeruginosa, Salmonella* spp., *Serratia marcescens*

Organisms treated as contaminants or isolated only from CSF broth cultures were considered contaminants

Abbreviations: CSF: cerebrospinal fluid; GBS: Group B streptococcus

Appendix 2. Collaborators in the Febrile Young Infant Research Collaborative

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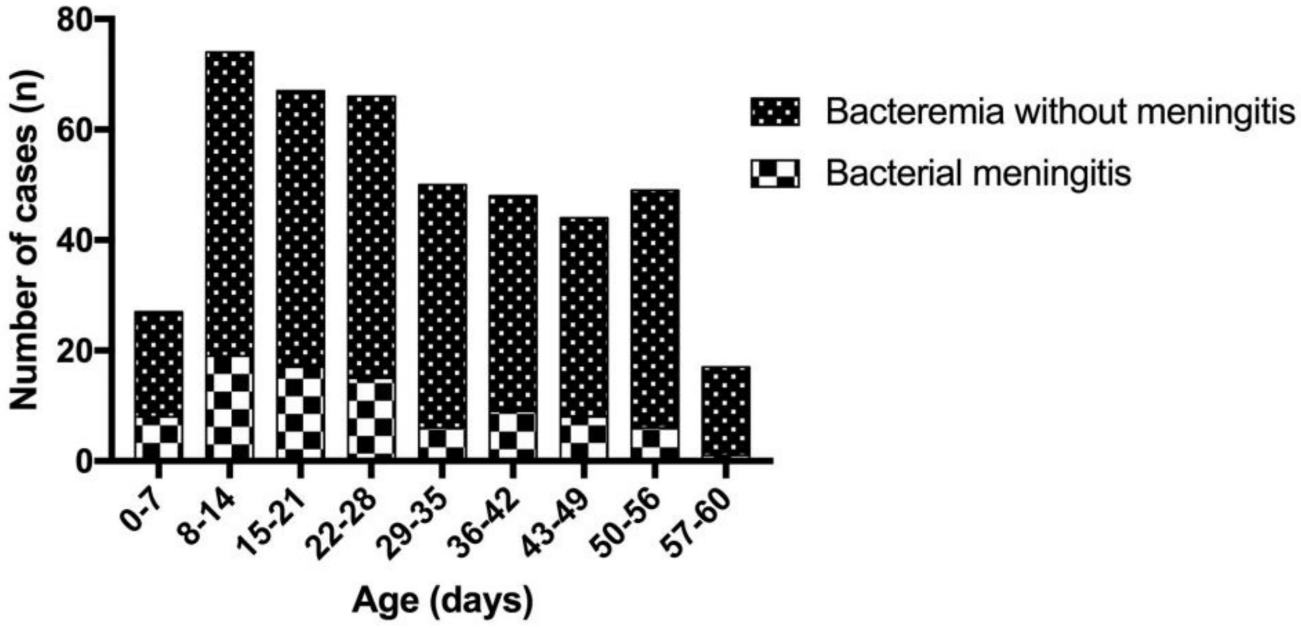

Figure.

online; Cases of invasive bacterial infection by week of life

Table I

Characteristics of Infants with Invasive Bacterial Infection

Characteristic	Total N (%) n=442	Bacteremia without meningitis N (%) n=353	Bacterial Meningitis[1] N (%) n=89
Demographics			
Age Group			
≤28 days	*234 (52.9)*	*175 (49.6)*	*59 (66.3)*
29–60 days	*208 (47.1)*	*178 (50.4)*	*30 (33.7)*
Male	256 (57.9)	204 (57.8)	52 (58.4)
Past Medical History			
Prematurity (<37w0d)	70 (15.8)	53 (15.0)	17 (19.1)
Complex Chronic Condition	64 (14.5)	55 (15.6)	9 (10.1)
Temperature at the Time of Presentation			
Fever	364 (82.4)	291 (82.4)	73 (82.0)
At home only	*77 (17.4)*	*62 (17.6)*	*15 (16.9)*
In ED	*287 (64.9)*	*229 (64.9)*	*58 (65.2)*
Physical Examination			
Ill-appearing	148 (33.5)	101 (28.6)	47 (52.8)
Clinically Apparent Infection	35 (7.9)	32 (9.1)	3 (3.4)
Laboratory			
Abnormal Urinalysis[3]	164 (37.1)	146 (41.4)	18 (20.2)
Peripheral WBC <5K or >15K	192 (43.4)	141 (39.9)	51 (57.3)
CSF Cell Count Obtained	357 (80.8)	275 (77.9)	82 (92.1)
CSF Pleocytosis[4]	*123 (34.5)*	*52 (18.9)*	*71 (86.6)*
Urinary Tract Infection	130 (29.4)	122 (34.6)	8 (9.0)

[1] Infants with bacterial meningitis with or without bacteremia

[2] Includes fever first recorded in the ED

[3] Positive nitrite or leukocyte esterase, or >5 WBC/high-powered field

[4] Percentages reported of infants tested

Abbreviations: CSF, cerebrospinal fluid; ED, emergency department; WBC, white blood cell

Table II

Pathogens Isolated in Infants with Invasive Bacterial Infection

INFANTS ≤28 DAYS OF AGE			
Pathogen	**Total N (%) (n=234[1])**	**Bacteremia without meningitis N (%) (n=175[1])**	**Bacterial Meningitis[2] N (%) (n=59)**
E. coli	72 (30.8)	62 (35.4)	10 (16.9)
Group B streptococcus	71 (30.3)	41 (23.4)	30 (50.8)
S. aureus	29 (12.4)	26 (14.9)	3 (5.1)
Enterococcus spp.	17 (7.3)	16 (9.1)	1 (1.7)
Klebsiella spp.	13 (5.6)	11 (6.3)	2 (3.4)
Other Gram Negative[3]	9 (3.8)	8 (4.6)	1 (1.7)
Group A streptococcus	8 (3.4)	8 (4.6)	0
Other Gram Positive[4]	7 (3.0)	1 (0.6)	6 (10.2)
Enterobacter spp.	5 (2.1)	4 (2.3)	1 (1.7)
L. monocytogenes	4 (1.7)	0	4 (6.8)
Salmonella spp.	2 (0.9)	1 (0.6)	1 (1.7)
S. pneumoniae	0	0	0
INFANTS 29–60 DAYS OF AGE			
Pathogen	**Total N (%) (n=208[1])**	**Bacteremia without meningitis N (%) (n=178[1])**	**Bacterial Meningitis[2] N (%) (n=30)**
Group B streptococcus	91 (44.3)	73 (41.0)	18 (60.0)
E. coli	64 (30.8)	57 (32.0)	7 (23.2)
S. aureus	14 (6.7)	14 (7.9)	0
Enterococcus spp.	12 (5.8)	11 (6.2)	1 (3.3)
Other Gram Negative[3]	7 (3.4)	4 (2.2)	3 (10.0)
Enterobacter spp.	6 (2.9)	6 (3.4)	0
S. pneumoniae	6 (2.9)	5 (2.8)	1 (3.3)
Salmonella spp.	4 (1.9)	4 (2.2)	0
Group A streptococcus	3 (1.4)	3 (1.7)	0
Other Gram Positive[4]	2 (1.0)	2 (1.1)	0
Klebsiella spp.	1 (0.5)	1 (0.6)	0
L. monocytogenes	0	0	0

[1] Some cultures grew >1 organism.

[2] Infants with bacterial meningitis with or without bacteremia

[3] Includes *Citrobacter* spp. (3 infants overall), *Pseudomonas aeruginosa* (2), *Neisseria meningitidis* (2), *Moraxella* spp. (2), *Haemophilus influenzae* non-typeable (2), *Haemophilus parainfluenzae* (1), *Proteus* spp. (1), *Serratia* spp. (1), *Pasteurella* spp. (1), *Acinetobacter* spp. (1)

[4] Includes *Streptococcus gallolyticus* (4 infants overall), *Streptococcus bovis* (4), *Paenibacillus* spp. (1)

Table III

Antimicrobial Susceptibilities of Isolates

ALL INFANTS[1,2]			
Antimicrobial(s)	**Total N (%)**[3]	**Bacteremia without meningitis N (%)**	**Bacterial Meningitis**[4] **N (%)**
Individual			
Ampicillin	306/429 (71.3)	233/344 (67.7)	73/85 (85.9)
3rd generation cephalosporin	388/435 (89.2)	309/349 (88.5)	79/86 (91.9)
Combination			
Ampicillin/gentamicin	411/428 (96.0)[5]	338/343 (98.5)	73/85 (85.9)[5]
Ampicillin/3rd generation cephalosporin	422/436 (96.8)	337/350 (96.3)	85/86 (98.8)
Vancomycin/ampicillin/gentamicin	429/434 (98.9)[5]	345/349 (98.9)	84/85 (98.8)[5]
Vancomycin/3rd generation cephalosporin	424/432 (98.2)	341/348 (98.0)	83/84 (98.8)
INFANTS ≤28 DAYS OF AGE[2]			
Antimicrobial(s)	**Total N (%)**[3]	**Bacteremia without meningitis N (%)**	**Bacterial Meningitis**[4] **N(%)**
Individual			
Ampicillin	152/229 (66.4)	105/173 (60.7)	47/56 (83.9)
3rd generation cephalosporin	202/229 (88.2)	151/173 (87.3)	51/56 (91.1)
Combination			
Ampicillin/gentamicin	217/228 (95.2)[5]	170/172 (98.8)	47/56 (83.9)[5]
Ampicillin/3rd generation cephalosporin	224/230 (97.4)	168/174 (96.6)	56/56 (100)
Vancomycin/ampicillin/gentamicin	227/230 (98.7)[5]	172/174 (98.9)	55/56 (98.2)[5]
Vancomycin/3rd generation cephalosporin	225/227 (99.1)	171/173 (98.8)	54/54 (100)
INFANTS 29–60 DAYS OF AGE[2]			
Antimicrobial(s)	**Total N (%)**[3]	**Bacteremia without meningitis N (%)**	**Bacterial Meningitis**[4] **N(%)**
Individual			
Ampicillin	154/200 (77.0)	128/171 (74.9)	26/29 (89.7)
3rd generation cephalosporin	186/206 (90.3)	158/176 (89.8)	28/30 (93.3)
Combination			
Ampicillin/gentamicin	194/200 (97.0)[5]	168/171 (98.3)	26/29 (89.7)[5]
Ampicillin/3rd generation cephalosporin	198/206 (96.1)	169/176 (96.0)	29/30 (96.7)
Vancomycin/ampicillin/gentamicin	202/204 (99.0)[5]	173/175 (98.9)	29/29 (100)[5]
Vancomycin/3rd generation cephalosporin	199/205 (97.1)	170/175 (97.1)	29/30 (96.7)

[1] 5 infants had missing antimicrobial susceptibilities (3 with bacteremia without meningitis, 2 with bacterial meningitis)

[2] Denominators represent infants with available susceptibility testing

[3] N (%) susceptible

[4] Infants with bacterial meningitis with or without bacteremia

[5]Gentamicin has poor cerebrospinal fluid penetration; pathogen considered ampicillin/gentamicin resistant if infant had bacterial meningitis and pathogen was ampicillin-resistant

Table IV

Pathogen Susceptibilities to Common Empiric Antimicrobial Regimens

Pathogen	**Ampicillin/Gentamicin N (%)[123]**	**3rd generation cephalosporin N (%)[12]**
Group B streptococcus	162/162 (100)	162/162 (100)
E. coli	124/135 (91.9)	132/135 (97.8)
S. aureus[4]	35/37 (94.6)	39/43 (90.7)
Enterococcus spp.[4]	28/28 (100)	0/29 (0)
Other Gram Negative[5]	10/11 (90.9)	9/11 (81.8)
Klebsiella spp.	12/14 (85.7)	12/14 (85.7)V
Enterobacter spp.	10/11 (90.9)	6/11 (54.5)
Group A streptococcus	11/11 (100)	11/11 (100)
Other Gram Positive[6]	8/8 (100)	8/8 (100)
Salmonella spp.	6/6 (100)	6/6 (100)
S. pneumoniae	6/6 (100)	6/6 (100)
L. monocytogenes	4/4 (100)	0/4 (0)
Total	416/433 (96.1)	391/440 (88.9)

[1] Denominators represent isolates with available susceptibility testing

[2] Some cultures grew >1 organism

[3] Gentamicin has poor cerebrospinal fluid penetration; pathogen considered ampicillin/gentamicin resistant if infant had bacterial meningitis and pathogen was ampicillin-resistant

[4] 6 isolates of *S. aureus* and 1 isolate of *Enterococcus* spp. had available susceptibility testing to third-generation cephalosporins but not to ampicillin/gentamicin

[5] Includes *Citrobacter* spp. (3), *Pseudomonas aeruginosa* (2), *Neisseria meningitidis* (2), *Moraxella* spp. (2), *Haemophilus influenzae* non-typeable (2), *Haemophilus parainfluenzae* (1), *Proteus* spp. (1), *Serratia* spp. (1), *Pasteurella* spp. *(1), Acinetobacter* spp. (1)

[6] Includes *Streptococcus gallolyticus* (4), *Streptococcus bovis* (4), *Paenibacillus* spp. (1)

Table V

Distribution of Resistance to Third-Generation Cephalosporins by Demographic, Clinical, and Laboratory Factors

	Proportion Resistant to 3rd Generation Cephalosporins[1] N (%)	P-value
Age Group		*0.49*
≤28 days	27/229 (11.8)	
29–60 days	20/206 (9.7)	
Gestational Age[2]		*0.58*
Preterm (<37w0d)	6/69 (8.7)	
Term	38/348 (10.9)	
Complex Chronic Condition		*<0.001*
Yes	16/64 (25.0)	
No	31/371 (8.4)	
Fever		*0.11*
Yes	35/359 (9.8)	
No	12/76 (15.8)	
Clinical Appearance		*0.83*
Ill-Appearing	15/145 (10.3)	
Not Ill-Appearing	32/290 (11.0)	
Abnormal Urinalysis[3,4]		*0.52*
Yes	17/163 (10.4)	
No	19/223 (8.5)	
Peripheral WBC <5K or >15K[5]		*0.42*
Yes	18/188 (9.6)	
No	29/241 (12.0)	

[1] 435 infants had isolates with available susceptibility testing to third-generation cephalosporins

[2] 18 infants had missing data for gestational age

[3] Positive nitrite or leukocyte esterase, or >5 WBC/high-powered field

[4] 49 infants had no urinalysis results

[5] 6 infants had no peripheral WBC results

Abbreviations: WBC, white blood cell