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

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

Study design Cross-sectional study of infants ≤60 days old with invasive bacterial infection (bacteremia and/or bacterial meningitis) evaluated in the emergency departments 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. 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 invasive bacterial infection, 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 invasive bacterial infection occurred in the second week of life; 364 (82.4%) infants were febrile. Group B streptococcus 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 emergency department for suspected invasive bacterial infection, 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 invasive bacterial infection, 11% were resistant to third-generation cephalosporins alone. *(J Pediatr 2018;■■:■■-■■).*

Infants ≤60 days old are at increased risk of bacterial infections because of 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).[7,8] These infants routinely undergo extensive diagnostic evaluation and are frequently hospitalized for treatment with empiric intravenous antimicrobials.[9] Understanding the epidemiology of invasive bacterial infection in young infants could inform the selection of empiric antimicrobials while awaiting bacterial culture results in infants with suspected invasive bacterial infection.

Because of broadened screening and perinatal antimicrobial prophylaxis for GBS,[2] as well as expanded vaccines for infants in the US,[10-13] the epidemiology of invasive bacterial infection in young infants has changed since the 1990s. Recent multicenter studies of bacteremia and/or bacterial meningitis in young infants

CFU	Colony-forming unit
CSF	Cerebrospinal fluid
ED	Emergency department
GBS	Group B streptococcus
UTI	Urinary tract infection

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≤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-generation 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 invasive bacterial infection.[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. In addition, 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 invasive bacterial infection, we conducted a large, multicenter investigation of infants with invasive bacterial infection 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 invasive bacterial infection,[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 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 (eg, 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 white blood cell ≥20 cells/mm^3 for infants ≤28 days and ≥10 cells/mm^3 for infants 29-60 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 (ie, positive nitrite or leukocyte esterase on urine dipstick or >5 white blood cells/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] In addition, 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]

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