Published in final edited form as:

J Pediatr. 2019 January ; 204: 177–182.e1. doi:10.1016/j.jpeds.2018.08.066.

Factors Associated with Adverse Outcomes among Febrile Young Infants with Invasive Bacterial Infections

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The authors declare no conflicts of interest.

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Abstract

Objective—To determine factors associated with adverse outcomes among febrile young infants with invasive bacterial infections (IBI), i.e., bacteremia and/or bacterial meningitis.

Study design—Multicenter, retrospective cohort study (July 2011 – June 2016) of febrile infants 60 days of age with pathogenic bacterial growth in blood and/or cerebrospinal fluid. Subjects were identified by query of local microbiology laboratory and/or electronic medical record systems, and clinical data were extracted by medical record review. Mixed-effect logistic regression was employed to determine clinical factors associated with 30-day adverse outcomes, which were defined as death, neurologic sequelae, mechanical ventilation, or vasoactive medication receipt.

Results—350 infants met inclusion criteria; 279 (79.7%) with bacteremia without meningitis and 71 (20.3%) with bacterial meningitis. Forty-two (12.0%) infants had a 30-day adverse outcome: 29/71 (40.8%) with bacterial meningitis vs. 13/279 (4.7%) with bacteremia without meningitis (36.2% difference, 95% CI 25.1% to 48.0%; $P < .001$). On adjusted analysis, bacterial meningitis (adjusted odds ratio [aOR] 16.3, 95% CI 6.5 to 41.0; $P < 0.001$), prematurity (aOR 7.1, 95% CI 2.6 to 19.7; $P < 0.001$), and ill appearance (aOR 3.8, 95% CI 1.6 to 9.1; $P = 0.002$) were associated with adverse outcomes. Among infants who were born at term, not ill appearing, and had bacteremia without meningitis, only 2/184 (1.1%) had adverse outcomes, and there were no deaths.

Conclusions—Among febrile infants 60 days old with IBI, prematurity, ill appearance, and bacterial meningitis (vs bacteremia without meningitis) were associated with adverse outcomes. These factors can inform clinical decision-making for febrile young infants with IBI.

Keywords

bacteremia; bacterial meningitis; prematurity

Fever is a common reason for infants to visit the emergency department (ED)(1) and may herald the presence of bacterial infections in very young infants. Due to perinatal bacterial exposure, vaccine naivety, and relative immune immaturity, infants 60 days old are particularly susceptible to bacterial infections.(2–4) Invasive bacterial infections (IBI), defined as bacteremia and/or bacterial meningitis, are associated with significant morbidity and mortality in this patient population.(5–8)

Although prior studies have examined rates and predictors of IBI in young infants in the ED, most of the literature focused on IBI does not describe patient outcomes,(9, 10) and none has reported the association of clinical factors at presentation with adverse outcomes. Knowledge of these factors would help inform management decisions for young infants with IBI. The objective of our study was to describe outcomes of febrile infants 60 days of age with IBI and to identify clinical factors associated with adverse outcomes for these infants.

METHODS

We performed a retrospective cohort study of febrile infants 60 days of age with proven IBI resulting from evaluation in the participating EDs of 11 United States children's hospitals. Study approval with agreements for data sharing and waivers of informed consent were obtained from each site's institutional review board.

Infants 60 days of age with an ED visit between July 1, 2011 and June 30, 2016 were screened for inclusion. We identified subjects by first querying each hospital's microbiology laboratory and/or electronic medical record system for positive blood and/or cerebrospinal fluid (CSF) bacterial cultures. After subsequent medical record review, infants were included if they 1) had a blood and/or CSF culture positive for an *a priori* determined pathogen that was not treated as a contaminant,(11, 12) as previously described (13); 2) were febrile at home or in the ED; and 3) had no clinically apparent source of infection (eg, cellulitis, omphalitis) on ED physical examination. Pathogens that grew only from CSF broth cultures were considered contaminants if there was no CSF pleocytosis and the blood culture was negative.(14)

Data Collection

The following variables were extracted by medical record review: patient demographics (age, sex), past medical history (prematurity, presence of a complex chronic condition), temperature (prior to and during ED visit), clinical appearance, bacterial culture results (blood, CSF), and *in vitro* antimicrobial susceptibilities. Antimicrobial agents administered, ED disposition (discharge home; inpatient or intensive care unit admission), adverse outcomes, and repeat ED visits or readmissions within 30 days also were recorded. Data were entered directly into a Research Electronic Data Capture (REDCap®) tool hosted at Yale University.(15)

Clinical Definitions

Bacteremia and bacterial meningitis were defined as growth of a pathogen from blood or CSF, respectively.(16, 17) Bacteremia with CSF pleocytosis but negative CSF culture was classified as bacterial meningitis if antimicrobial therapy was administered prior to CSF collection.(18, 19) Urinary tract infection (UTI) was defined per published criteria, as previously described.(13) We defined fever as a documented temperature $\geq 38.0^{\circ}\text{C}$ (100.4°F) at home, in an outpatient clinic, or in the ED.(20) Prematurity was defined as gestational age <37 weeks.(21) Complex chronic conditions were defined as severe medical conditions expected to last ≥ 12 months involving ≥ 1 organ system, and/or requiring specialty care.(22, 23) Ill appearance was defined by the presence of any of the following terms documented in the ED physical examination: “ill appearing,” “toxic,” “limp,” “unresponsive,” “gray,” “cyanotic,” “apnea,” “weak cry,” “poorly-perfused,” “grunting,” “listless,” “lethargic,” or “irritable.”(24) If none of these terms was documented, the infant was classified as not ill appearing. Contradictory documentation between attending and trainee physicians was reconciled by using the attending physician’s documentation. Empiric antimicrobial therapy was defined as antimicrobial therapy administered within 12 hours following ED triage. Antimicrobial therapies were cross-referenced with *in vitro* antimicrobial susceptibilities test results for isolates, to determine concordance. As *in vitro* susceptibilities may not have been performed due to assumed susceptibility or resistance for certain pathogen-antimicrobial combinations, we used existing criteria to determine intrinsic antimicrobial resistance, along with predicted and inferred susceptibilities.(25) Infants were considered to have received concordant antimicrobial therapy if, within 12 hours of ED arrival, they were administered an antimicrobial agent to which the isolated pathogen was susceptible as determined by reported *in vitro* test results.

Outcomes

We defined a 30-day adverse outcome as any of the following occurring within 30 days after the ED encounter: death; neurologic sequelae (defined as hearing loss, seizures, or any abnormal cranial imaging); need for mechanical ventilation; or receipt of vasoactive medications. To determine adverse outcomes, records were reviewed from the index ED visit, as well as all inpatient or outpatient records within 30 days subsequent to the ED encounter.

Statistical Analyses

Categorical variables are described with frequencies and percentages, and were compared using Chi-square or Fisher exact tests, where appropriate. To determine clinical factors associated with adverse outcomes in infants with IBI, we employed a mixed-effects logistic regression approach(26, 27) to account for outcome variability due to clustering of patients by study site. The model estimated the variance of the random effect due to site, which we then used to calculate an intra-class correlation. The following clinically relevant covariates were considered in the linear predictor of the model: age ≥ 28 days, prematurity, complex chronic condition, ill appearance, bacterial meningitis (vs. bacteremia without meningitis), and empiric antimicrobial receipt. Covariates with $P < 0.10$ from the unadjusted models were retained for the multivariable regression model; age was also retained due to its association

with risk of IBI.(20) We considered all possible two-way interactions in the final models. Findings are presented as adjusted odds ratios with 95% confidence intervals (95% CI). We conducted bootstrap analysis using 10,000 replicates to confirm our findings. Statistical analyses were performed using Stata version 15.0 (StataCorp), with two-sided p-values <0.05 considered statistically significant.

RESULTS

We identified 497 infants with a blood and/or CSF culture that grew a potential bacterial pathogen. Of these, 147 were excluded after medical record review: 93 infants had a potential pathogen on culture, but did not have a history of febrile temperature measured at home and were afebrile in the ED; 32 had bacterial isolates treated as contaminants; 12 infants had a clinically apparent source of infection; 7 infants lacked an ED encounter; and 3 had growth in CSF broth culture alone (*Enterococcus* spp., *Escherichia coli*, and *Streptococcus agalactiae*) without CSF pleocytosis or positive blood culture. Of the 350 febrile infants with an IBI, 174 patients (49.7%) were ≥ 28 days old. Two hundred seventy-nine infants (79.7%) had bacteremia without meningitis (252 [90.3%] of whom had CSF testing), 51 (14.6%) had bacterial meningitis with bacteremia, and 20 (5.7%) had bacterial meningitis without bacteremia. Six infants with bacterial meningitis (8.5% of meningitis cases) had a concomitant UTI; 4 of these patients were ≥ 28 days of age, 2 were ill appearing, and 5 had bacteremia. One hundred thirteen infants with bacteremia without meningitis (40.5%) had a concomitant UTI.

Outcomes

Table I describes ED disposition, empiric antimicrobial therapy, and outcomes for the study cohort. Forty-two infants (12.0%) with IBI experienced one or more adverse outcomes in the 30-day period following the ED encounter. Five infants (1.4%) died. A higher proportion of infants with bacterial meningitis experienced an adverse outcome compared with infants with bacteremia without meningitis (29/71 [40.8%] vs. 13/279 [4.7%], 36.2% difference, 95% CI 25.1% to 48.0%; $P < 0.001$) (Table I). Ten infants classified as having bacterial meningitis had bacteremia and CSF pleocytosis but negative CSF culture after receipt of antimicrobial therapy prior to CSF collection; 4/10 (40.0%) had an adverse outcome. Table II displays adverse outcomes by pathogen for infants with IBI.

Clinical Factors Associated with 30-Day Adverse Outcomes

Mixed-effects logistic regression revealed the following factors to be significantly associated with adverse outcomes: prematurity, ill appearance, and bacterial meningitis (vs. bacteremia without meningitis) (Table III). Age ≥ 28 days, presence of a complex chronic condition, and lack of concordant antimicrobial therapy were not associated with adverse outcomes. Results did not materially differ in bootstrap analysis. Among febrile infants who were born at term, not ill appearing, and had bacteremia without meningitis, 2/184 (1.1%) had adverse outcomes, and there were no deaths.

Receipt of Discordant or No Empiric Antimicrobial Therapy

Of the 10 infants who initially received discordant empiric antimicrobial therapy, 9 had bacteremia without meningitis, 1 had bacterial meningitis, and none experienced an adverse outcome. The pathogens isolated from these 10 infants were *Enterobacter* (3), *Escherichia coli* (3), *Acinetobacter* spp. (1), *Enterococcus* spp. (1), *Klebsiella* spp. (1), and *Pseudomonas aeruginosa* (1). Nine of the infants underwent CSF testing and all had repeat blood cultures, 2 of which were positive for the previously isolated organism (*E. coli* and *Klebsiella* spp.). Four of these infants (40.0%) had a concomitant UTI.

Of the 15 infants who received no empiric antimicrobial therapy, 7 were hospitalized and 8 were discharged home from the ED. Of the 7 hospitalized infants, 5 underwent CSF testing and all had repeat blood cultures, 2 of which were positive. Both infants with positive repeat blood cultures (one with *Streptococcus pneumoniae* bacteremia and meningitis, the other with *Enterococcus* spp. bacteremia) had an adverse outcome. The 8 infants discharged from the ED without empiric antimicrobial therapy returned within 48 hours of their index visit and were subsequently hospitalized. Seven of the 8 infants underwent CSF testing, and all had repeat blood cultures with no growth of bacteria. All 8 infants had bacteremia without meningitis; none had an adverse outcome. Pathogens isolated from these infants were *E. coli* (3), *Streptococcus agalactiae* (2), *Salmonella* spp. (1), *Staphylococcus aureus* (1), and *Streptococcus pyogenes* (1). Two of these 8 infants (25.0%) had a concomitant UTI.

DISCUSSION

In this large, multicenter study of febrile infants <60 days of age evaluated in the ED who had confirmed IBI, 12% of infants had an adverse outcome, including 41% of infants with bacterial meningitis compared with 5% of those with isolated bacteremia. Prematurity, ill appearance, and bacterial meningitis were associated with 30-day adverse outcomes. These results may help inform management of febrile infants <60 days of age at risk for IBI.

Of the clinical factors identifiable at the time of presentation, prematurity and ill appearance were associated with increased odds of adverse outcome, but younger age was not. Although a small number of studies have demonstrated worse outcomes for younger infants with IBI, most have focused solely on mortality, and age cutoffs defining younger infants differed. (28–32) Some studies on IBI in young infants have excluded premature infants altogether; (33, 34) and very few have reported outcomes data in relation to prematurity. (18) Age-stratified outcomes data for infants with IBI, particularly febrile infants, has been identified as a research priority. (35) Although febrile infants <28 days of age have a higher prevalence of IBI than older infants, our data indicate that, when adjusting for other clinical factors, they may not have a higher rate of adverse outcomes.

In our study, ill appearing infants with IBI more commonly experienced adverse outcomes within 30 days of their ED visit compared with non-ill appearing infants. The existing literature on clinical appearance of infants with suspected IBI is conflicting. Most of this research has focused on clinical appearance in terms of the presence or absence of bacterial infections, and much less on clinical outcomes. The majority of these studies have demonstrated a significant association between ill appearance and bacterial infections, (9, 28,

30–32, 34, 36–38) yet some have called into question the reliability of either objective or subjective determinations of ill appearance in identifying infants with IBI.(39, 40) Although important to note that our cohort excludes infants with suspected IBI whose cultures are negative, our data nonetheless identify ill appearance at presentation as a poor prognostic indicator when IBI is present.

Forty-one percent of infants with bacterial meningitis in our cohort had a 30-day adverse outcome, significantly more than infants with bacteremia without meningitis. Moreover, all adverse outcomes, except for death, occurred more frequently in infants with bacterial meningitis. Though perhaps intuitive that infants 60 days old with bacterial meningitis have a higher rate of adverse outcomes than those with bacteremia without meningitis, few previous studies on both types of IBI have explored clinical outcomes.(41, 42) Importantly, few infants with bacteremia without meningitis, or with bacterial meningitis, died (1.1% and 2.8%, respectively).

Our findings have several clinical implications. Given the high rate of adverse outcomes in our relatively large population of young infants with bacterial meningitis, this knowledge can help clinicians assess the risk and prognosis for the infant in the ED for whom bacterial meningitis is suspected (because the diagnosis often cannot be confirmed in the ED). Additionally, awareness of this and other risk factors for adverse outcomes can help practitioners discuss with parents the need for lumbar puncture and empiric antimicrobial therapy for infants in the ED for whom there is a high clinical suspicion for IBI. In our cohort, just over 1% of infants with none of our identified “high-risk” clinical factors had adverse outcomes, and there were no deaths. This knowledge, as well as the pathogen-specific outcome data, can assist the clinician in making management decisions for hospitalized infants with culture-proven IBI. Of note, for *E. coli*, the most common pathogen isolated in our cohort, only 1.8% of infants with bacteremia without meningitis experienced an adverse outcome. Future research could analyze how the presence or absence of these risk factors for adverse outcomes might inform decisions surrounding duration of therapy or transition to enteral antimicrobial agents, decisions for which recommendations exist,(43) but for which there is scant evidence.

Our study has several limitations. As our study is ED-based, our findings may not be generalizable to infants with IBI identified prior to newborn hospital discharge, or to other clinical settings. Adverse outcomes were derived from medical record review, and could have been underestimated if documentation was lacking in the record. We did not assess adverse outcomes beyond 30 days following the ED visit; additional adverse outcomes may be recognized after this timeframe, especially among children with bacterial meningitis. Given the retrospective study design, historical and physical examination factors were obtained from the medical record, which is prone to subjective interpretation. Perhaps most important to the present study is the documentation of complex chronic conditions and ill appearance on physical examination. We sought to mitigate this limitation by utilizing a specific, previously published list of complex chronic conditions.(23) Though we used an established definition of ill appearance with high inter-rater reliability(24) that is more rigorous than those used in many previous studies,(30, 36–38) this method of classification may not accurately reflect clinical appearance on arrival to the ED for infants with suspected

IBI. We also classified 10 infants with bacteremia and CSF pleocytosis (but with negative CSF cultures) as having bacterial meningitis if antimicrobial therapy was administered prior to CSF collection. Although this introduces a potential for misclassification, the adverse outcome rate was similar for these infants (40%) and the bacterial meningitis group as a whole (41%). Additionally, we excluded 3 infants with pathogen growth from CSF broth culture only without bacteremia or CSF pleocytosis; it is possible that these infants had bacterial meningitis. Finally, concordance of empiric antimicrobial therapy was determined by *in vitro* antimicrobial susceptibility test results, and thus may not reflect actual *in vivo* antimicrobial activity against specific organisms.

In this study of IBI in febrile infants < 60 days of age, adverse outcomes were common and disproportionately occurred in infants with bacterial meningitis. Prematurity, ill appearance at ED presentation, and the presence of bacterial meningitis portend worse outcomes for infants with IBI. These factors, therefore, can assist clinicians in discussing testing and treatment with parents, and may inform inpatient management of infants < 60 days with IBI. Further prospective research is needed to evaluate the impact of such management decisions on adverse outcomes for febrile infants < 60 days with IBI.

Acknowledgments

Supported by the National Center for Advancing Translational Science (NCATS), a component of the National Institutes of Health (NIH) (KL2 TR001862 [to P.A.]). The NIH had no role in study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the manuscript for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Abbreviations:

ED	emergency department
IBI	invasive bacterial infection
CSF	cerebrospinal fluid
UTI	urinary tract infection

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Table I.

Management and outcomes of febrile infants with invasive bacterial infections.

Characteristic	Overall No. (%) n=350	Bacteremia without Meningitis No. (%) n=279	Bacterial Meningitis No. (%) n=71 ^a	P
Disposition				
Hospitalization at index visit	335 (95.7)	265 (95.0)	70 (98.6)	0.18
Empiric Therapy^b				
Parenteral antimicrobial therapy	333 (95.1)	264 (94.6)	69 (97.2)	0.37
Oral antimicrobial therapy	2 (0.6)	1 (0.4)	1 (1.4)	0.29
No antimicrobial therapy	15 (4.3)	14 (5.0)	1 (1.4)	0.18
30-Day Outcomes				
Any adverse outcome	42 (12.0)	13 (4.7)	29 (40.9)	<0.0001
Death	5 (1.4)	3 (1.1)	2 (2.8)	0.27
Neurologic disability	29 (8.3)	5 (1.8)	24 (33.8)	<0.0001
Mechanical ventilation	27 (7.7)	10 (3.6)	17 (23.9)	<0.0001
Vasopressor support	14 (4.0)	5 (1.8)	9 (12.7)	0.0008
Intensive care unit admission	60 (17.1)	29 (10.4)	31 (43.7)	<0.0001
ED revisit or readmission	67 (19.1)	58 (20.8)	9 (12.7)	0.12

P values represent comparisons between bacteremia without meningitis and bacterial meningitis.

^a51 infants with meningitis (14.6% overall, 71.8% of meningitis cases) had bacteremia.^bWithin 12 hours of arrival.

Table II.

Outcomes of febrile infants with invasive bacterial infections by organism.

Organism	Outcomes ^a		
	Any 30-day adverse outcome, No. (%)	Death, No. (%)	Neurologic Disability, No. (%)
Bacteremia without Meningitis (No.), n = 279^{b,c}			
<i>Escherichia coli</i> (109)	2 (1.8)	1 (0.9)	1 (0.9)
<i>Streptococcus agalactiae</i> (91)	7 (7.7)	2 (2.2)	4 (4.4)
<i>Staphylococcus aureus</i> (23)	1 (4.3)	0	0
<i>Enterococcus</i> spp. (19)	2 (10.5)	0	0
<i>Klebsiella</i> spp. (9)	0	0	0
<i>Enterobacter</i> (8)	0	0	0
Other Gram negative (7) ^d	1 (14.3)	0	0
<i>Streptococcus pyogenes</i> (7)	0	0	0
<i>Streptococcus pneumoniae</i> (4)	0	0	0
<i>Salmonella</i> spp. (4)	0	0	0
Other Gram positive (2) ^e	0	0	0
Bacterial Meningitis (No.), n = 71^f			
<i>Streptococcus agalactiae</i> (39)	16 (41.0)	1 (2.6)	12 (30.8)
<i>Escherichia coli</i> (13)	4 (30.8)	0	4 (30.8)
Other Gram positive (5) ^g	2 (40.0)	0	1 (20.0)
<i>Listeria monocytogenes</i> (4)	1 (25.0)	0	1 (25.0)
Other Gram negative (3) ^h	2 (66.7)	1 (33.3)	2 (66.7)
<i>Staphylococcus aureus</i> (3)	2 (66.7)	0	2 (66.7)
<i>Streptococcus pneumoniae</i> (2)	2 (100)	0	2 (100)
<i>Enterococcus</i> spp. (1)	0	0	0
<i>Klebsiella</i> spp. (1)	0	0	0

^a Percentages represent proportion of outcomes for respective organism.^b Some infants' cultures grew multiple organisms.^c 113/279 (40.5%) infants with bacteremia without meningitis had concomitant UTI: 91/109 (83.5%) with *E. coli*, 7/19 (36.8%) with *Enterococcus* spp., 4/9 (44.4%) with *Klebsiella* spp., 4/8 (50.0%) with *Enterobacter*, 4/91 (4.4%) with *S. agalactiae*, 3/23 (13.0%) with *S. aureus*, and 1/7 (14.3%) with other Gram negative (*Citrobacter*). (One infant had both *Klebsiella* spp. and *Enterococcus* spp. bacteremia.)^d *Acinetobacter* spp. (1), *Citrobacter* (1), *Haemophilus influenzae* non-typeable (1), *Moraxella* spp. (1), *Neisseria meningitidis* (1), *Pseudomonas aeruginosa* (1), *Serratia* spp. (1).^e *Streptococcus bovis* (1), *Streptococcus gallolyticus* (1).^f 6/71 (8.5%) infants with bacterial meningitis had concomitant UTI: 3/13 (23.1%) with *E. coli* meningitis, 1/39 (2.6%) with *S. agalactiae*, 1/3 (33.3%) with *S. aureus*, and 1/1 (100%) with *Klebsiella* spp.

^g *Streptococcus gallolyticus* (3), *Streptococcus bovis* (1), *Paenibacillus* spp. (1).

^h *Neisseria meningitidis* (1), *Pasteurella* spp. (1), *Pseudomonas aeruginosa* (1).

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Table III.

Factors associated with 30-day adverse outcomes for febrile infants with invasive bacterial infections (IBI).

	Proportion with Adverse Outcomes (%)	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI) ^a
Age Group			
29–60 days	19/176 (10.8)	ref.	ref.
0–28 days	23/174 (13.2)	1.3 (0.7–2.4)	1.7 (0.7–4.0)
Gestational Age^b			
Term	24/293 (8.2)	ref.	ref.
Premature	17/45 (37.8)	6.8 (3.3–14.2)	7.1 (2.6–19.7)
Chronic Condition			
No Complex Chronic Condition	33/306 (10.8)	ref.	ref.
Complex Chronic Condition	9/44 (20.5)	2.1 (0.9–4.8)	2.1 (0.7–6.7)
Clinical Appearance			
Not Ill-Appearing	13/244 (5.3)	ref.	ref.
Ill-Appearing	29/106 (27.4)	6.7 (3.3–13.5)	3.8 (1.6–9.1)
Type of IBI			
Bacteremia without Meningitis	13/279 (4.7)	ref.	ref.
Bacterial Meningitis	29/71 (40.8)	14.1 (6.8–29.3)	16.3 (6.5–41.0)
Empiric Therapy^c			
Concordant Antimicrobial Therapy	39/322 (12.1)	ref.	*
Discordant Antimicrobial Therapy	0/10 (0)	0.3 (0.02–5.9)	*
No Empiric Therapy	2/15 (13.3)	1.1 (0.2–5.1)	*

^a Adjusted for age group, gestational age, chronic condition, clinical appearance, and IBI type, with study site as a random effect.

^b 12/350 subjects (3.4%) lacked gestational age data.

^c 3/350 patients (0.9%) excluded due to missing susceptibility data.

Bold: associated with more adverse outcomes (P<0.05).

* Not included in multivariable model.