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Neonatal *Escherichia coli* Bloodstream Infections: Clinical Outcomes and Impact of Initial Antibiotic Therapy

Stephen P. Bergin, MD^{*}, Joshua Thaden, MD^{*}, Jessica E. Ericson, MD^{†,‡}, Heather Cross, DPhil[‡], Julia Messina, MD^{*,‡}, Reese H. Clark, MD[§], Vance G. Fowler Jr., MD, MHS^{*,‡}, Daniel K. Benjamin Jr., MD, PhD^{†,‡}, Christoph P. Hornik, MD, MPH^{†,‡}, and P. Brian Smith, MD, MPH, MHS^{†,‡} for the Antibacterial Resistance Leadership Group

^{*}Department of Medicine, Duke University School of Medicine, Durham, NC

[†]Department of Pediatrics, Duke University School of Medicine, Durham, NC

[‡]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC

[§]Pediatrix-Obstetrix Center for Research and Education, Sunrise, FL

Abstract

Background—*Escherichia coli* is a common cause of bloodstream infections (BSI) in infants and is associated with high mortality and morbidity among survivors. The clinical significance of antibiotic resistance and timing of appropriate antimicrobial therapy in this population is poorly understood.

Methods—We identified all infants with *E. coli* BSIs discharged from 77 neonatal intensive care units managed by the Pediatrix Medical Group in 2012. We used multivariable logistic regression to evaluate the association between 30-day mortality and ampicillin-resistant *E. coli* BSI, as well as the number of active empiric antimicrobial agents administered, controlling for gestational age, small-for-gestational age status, early- versus late-onset BSI, oxygen requirement, ventilator support, and inotropic support on the day of the first positive blood culture.

Results—We identified 258 episodes of *E. coli* BSI, including 123 (48%) ampicillin-resistant isolates. Unadjusted 30-day mortality did not significantly differ between infants with ampicillin-resistant vs. -susceptible *E. coli* BSI (11/123 [9%] vs. 7/135 [5%]; $p=0.33$; adjusted odds ratio=1.37 [95% confidence interval 0.39, 4.77]). Among ampicillin-resistant *E. coli* BSIs, 30-day mortality was not significantly lower for infants treated with at least one empiric antimicrobial active against ampicillin-resistant *E. coli* vs. infants receiving no active empiric agent (adjusted odds ratio=1.50 [0.07, 33.6]).

Conclusions—In this population of infants with *E. coli* BSI, ampicillin resistance was not associated with significantly increased mortality. Among the subset of infants with ampicillin-resistant *E. coli*, appropriate empirical antibiotic therapy was not associated with lower mortality.

Keywords

Escherichia coli; antimicrobial resistance; early-onset sepsis; late-onset sepsis; bacteremia

Escherichia coli is a frequent cause of early-onset bloodstream infection (BSI) among infants, accounting for 24% of all BSIs.^{1,2} Over the past two decades, *E. coli* has become the most common cause of early-onset BSI in premature infants and a frequent cause of late-onset BSI.^{3–5} In hospitalized infants, BSIs caused by *E. coli* are associated with higher mortality compared with those caused by gram-positive organisms.⁶

Several contemporary studies have reported increasing ampicillin resistance, ranging from 59–85% of *E. coli* isolates causing BSIs in infants.^{1–3,5,7–11} Higher mortality among infants with ampicillin-resistant *E. coli* BSI has been reported, but multiple confounders, primarily prematurity, were noted, and small sample sizes limited detailed analysis.^{8,11,12} Risk factors for antimicrobial-resistant *E. coli* BSI, clinical implications of infection with resistant organisms, and the impact of appropriate empiric antimicrobial therapy in infants with infection are poorly understood. Clinicians need this information to inform the balance between potential risk for excess morbidity and mortality associated with ineffective empiric antimicrobial therapy and the side effects of routine use of broad-spectrum empiric antimicrobial therapy.¹³

The aims of this study were to: 1) compare the clinical characteristics of infants with ampicillin-susceptible and -resistant *E. coli* BSIs; 2) compare the outcomes of infants with ampicillin-susceptible and -resistant *E. coli* BSIs; and 3) evaluate the impact of appropriate empiric antimicrobial therapy for infants with ampicillin-resistant *E. coli* BSIs.

METHODS

We identified all infants with *E. coli* BSI discharged from one of 77 U.S. neonatal intensive care units (NICUs) managed by the Pediatrix Medical Group in 2012. Data were obtained from an electronic medical record that prospectively captures information from notes generated by clinicians on all infants cared for by the Pediatrix Medical Group. Data are extracted, de-identified, and stored in the Pediatrix Clinical Data Warehouse. Information stored for infants on a daily basis includes maternal history, demographics, medications ordered, laboratory results, microbiology results, diagnoses, and procedures.¹⁴ Antimicrobial susceptibility data for microbiologic isolates are reported as the presence or absence of resistance to several common antibiotics. Comprehensive antimicrobial resistance patterns are not captured in the database.

We identified all blood cultures positive for *E. coli* during the first 120 days of life. All positive cultures obtained within 21 days of each other were analyzed as single infectious episodes. We assumed the same antimicrobial resistance for all positive blood cultures obtained within a single BSI episode. We defined the duration of bacteremia as the difference between the day of the first and last positive blood cultures within a single episode. We defined an early-onset BSI as an initial positive blood culture within the first 3

postnatal days and a late-onset BSI as an initial positive blood culture after the first 3 postnatal days.

We defined empiric antimicrobial therapy as any antimicrobial administered on the day of the first positive blood culture for each episode of bacteremia. For ampicillin-resistant *E. coli* isolates, we categorized the number of effective empiric antimicrobials received on the day of first positive blood culture as none or 1. We considered the following antimicrobials effective empiric therapy against ampicillin-resistant *E. coli*: beta-lactam/lactamase inhibitor combinations, cephalosporins, anti-pseudomonal penicillins, aztreonam, carbapenems, aminoglycosides, fluoroquinolones, and trimethoprim/sulfamethoxazole. We defined inotropic support as exposure to any inotrope (dobutamine, dopamine, epinephrine, milrinone/amrinone, norepinephrine, or phenylephrine), supplemental oxygen requirement as any fraction of inspired oxygen >21%, and mechanical ventilation as any need for invasive mechanical ventilation on the day of the first positive blood culture for each episode of bacteremia. We categorized *E. coli* isolates as ampicillin-susceptible or ampicillin-resistant as reported by each site.

The primary outcome of our study was mortality within 30 days of the first positive blood culture. Secondary outcomes were duration of BSI, mortality within 7 days of the first positive blood culture, and mortality at hospital discharge. We used standard summary statistics including counts (percentages) and medians (interquartile ranges) to describe the categorical and continuous study variables, respectively. We compared study variables across groups using Wilcoxon rank sum and chi-square tests of association where appropriate. We used multivariable logistic regression to compare outcomes between ampicillin-susceptible and -resistant *E. coli* BSI. The following covariates were included in a full model: *E. coli* ampicillin-susceptible vs. -resistant, birth weight, male gender, gestational age (GA), small-for-gestational age status (SGA), early- vs. late-onset BSI, and inotropic, ventilator, or oxygen support on the day of the first positive culture. Reduced models were then constructed by removing pre-specified groups of covariates and comparing the reduced model to the full model using likelihood ratio tests. The most parsimonious model that fit the data well was retained and contained the following covariates in addition to ampicillin resistance: GA, SGA, early- vs. late-onset BSI, and inotropic, ventilator, or oxygen support on the day of the first positive culture. Lastly, we accounted for the clustering of data by fitting separate random intercepts for each NICU. We used standard graphing techniques and statistical tests to evaluate the assumptions of our models. To evaluate the impact of effective empiric antimicrobial therapy, 30-day mortality was compared between infants with ampicillin-resistant *E. coli* BSI receiving 0 or 1 empiric antimicrobial agents known to be effective against ampicillin-resistant isolates. Multivariable logistic regression was used to compare 30-day mortality for infants with ampicillin-resistant *E. coli* BSI receiving 0 versus 1 empiric antimicrobial agents active against ampicillin-resistant *E. coli*. Covariates incorporated into the model included: GA, SGA, early- vs. late-onset BSI, and inotropic, ventilator, or oxygen support on the day of the first positive culture. Finally, median duration of BSI for infants with ampicillin-resistant *E. coli* isolates receiving 0 versus 1 effective empiric antimicrobial agents was compared. We used Stata 13.0 (College Station, TX) to conduct all analyses and considered a $p < 0.05$

statistically significant. The Duke University Health System Institutional Review Board determined that the study met the definition of research not involving human subjects and was, therefore, exempt.

RESULTS

Infant Characteristics

We identified 267 episodes of *E. coli* BSI in 267 infants. No episodes of recurrent *E. coli* BSI were identified. We excluded 9 episodes of extended spectrum beta-lactamase producing *E. coli* BSI from further analysis. Ampicillin resistance was noted for 123/258 (48%) remaining isolates. Early-onset BSI accounted for 109/258 (42%) cases. The proportion of ampicillin-resistant isolates did not significantly differ between early-onset and late-onset BSI (53/109 [49%] vs. 70/149 [47%], $p=0.80$). The median GA (29 weeks [interquartile range; 24, 34] vs. 28 weeks [26, 34], $p=0.67$) and birth weight (1220 g [690, 2470] vs. 1140 g [810, 2080], $p=0.48$) did not significantly differ between infants with ampicillin-resistant and -susceptible *E. coli* BSI, respectively (Table 1). The median postnatal age on the date of first positive blood culture was similar between infants with ampicillin-resistant and -susceptible infections: 4 days (0, 12) vs. 6 (0, 13), $p=0.57$. More infants with ampicillin-resistant *E. coli* BSI were exposed to antenatal antibiotics: 80/123 (65%) vs. 65/135 (48%), $p=0.008$. The proportion of infants receiving at least one active empiric antimicrobial agent was not significantly different between those with ampicillin-resistant and -susceptible *E. coli* BSI: 100/123 (81%) vs. 104/135 (77%), $p=0.45$. Among the 135 episodes of ampicillin-susceptible *E. coli* BSI, the most commonly administered antibiotics on the day of first positive culture were gentamicin (61%), ampicillin (46%), vancomycin (19%), cefotaxime (10%), piperacillin-tazobactam (9%), and nafcillin (6%). For the 123 episodes of ampicillin-resistant *E. coli* BSI, the most commonly administered antibiotics on the day of first positive culture were gentamicin (67%), ampicillin (47%), vancomycin (22%), cefotaxime (15%), piperacillin-tazobactam (8%), and ceftazidime (4%).

Outcomes

Unadjusted 30-day mortality was similar for infants with ampicillin-resistant (11/123 [9%]) and ampicillin-susceptible isolates (7/135 [5%], $p=0.33$). On adjusted analysis, there was no significant difference in odds of death at 30 days for infants with ampicillin-resistant versus ampicillin-susceptible *E. coli* BSI (odds ratio [OR]=1.37 [0.39, 4.77]). Additionally, no significant difference in death at 7 days or hospital discharge was noted (Table 2). Median duration of *E. coli* BSI was similar for infants with ampicillin-resistant (1 day [range; 1, 10]) and ampicillin-susceptible isolates (1 day [1, 6], $p=0.43$).

Among ampicillin-resistant *E. coli* isolates, unadjusted odds of death at 30 days was not significantly lower for infants treated with 1 active empiric antimicrobial agent (10/100 [10%]) versus those receiving no active empiric antimicrobial agent (1/23 [4%], $p=0.69$). On adjusted analysis, odds of death at 30 days were similar for infants receiving 1 versus no active empiric antimicrobial therapy (OR=1.50 [0.07, 33.6]). Median duration of BSI was similar among infants with ampicillin-resistant *E. coli* BSI treated with 1 effective empiric

antimicrobial agent (1 day [range; 1, 10]) versus those receiving no active empiric antimicrobial agent (1 day [1, 2], $p=0.24$).

DISCUSSION

This study compares clinical characteristics and outcomes of infants with ampicillin-susceptible and -resistant *E. coli* BSIs. It is among the largest studies of *E. coli* BSIs in infants reporting antimicrobial resistance data and the impact of effective empiric antimicrobial therapy among resistant isolates. Compared with previous reports, the prevalence of ampicillin resistance in this study was lower: 46% vs. 59–85%. Cases of BSI caused by ESBL-producing isolates were infrequent (3%) in this cohort.

Clinical factors associated with increased risk of antimicrobial resistant *E. coli* BSI are poorly defined. In this study, only antenatal antibiotic exposure was associated with ampicillin-resistant *E. coli* BSI ($p=0.008$). These findings are consistent with prior studies of both early- and late-onset sepsis.^{5,15,16} The strength of this association may be exaggerated, however, as these analyses lack a control group and cannot account for ampicillin-susceptible isolates eradicated with antenatal antibiotics.¹⁷ Notably, the only case-control study evaluating this association showed no significant difference in risk of antimicrobial-resistant infection, demonstrating an overall protective effect of intrapartum antimicrobial prophylaxis.⁷

We found no significant increase in unadjusted or adjusted 30-day mortality for infants with ampicillin-resistant *E. coli* BSI. Notably, birth weight and GA were similar among infants with ampicillin-resistant and -susceptible BSI in this study. These findings are in contrast to prior reports of *E. coli* BSI that identified trends toward increased mortality among infants infected with ampicillin-resistant isolates.^{8,11} In previous reports, ampicillin resistance was significantly more common in premature infants. Our results are consistent with those previously reported in a study of late-onset sepsis that controlled for prematurity,⁵ but our analysis also includes data from 114 episodes of early-onset BSI.

Among infants with ampicillin-resistant *E. coli* BSI, no significant association between mortality and the number of active empiric antimicrobial agents administered was noted. This study is among the first to evaluate the impact of empiric antimicrobial therapy for infants with ampicillin-resistant *E. coli* BSI. The adequacy of empiric antimicrobial regimens must be continually reevaluated as the emergence of more extensively drug-resistant organisms is observed. The number of extensively drug-resistant *E. coli* isolates in this study was small, and results may not be applicable to centers reporting higher rates of extensive drug resistance.^{12,18}

To date, our study represents the largest series of *E. coli* BSIs in infants reporting antimicrobial resistance data and associated outcomes. Strengths of the study include a large sample size obtained from a wide variety of NICUs in the U.S., incorporation of both early- and late-onset BSI cases, and evaluation of the impact of empiric antimicrobial therapy not previously reported.

There are several limitations to this analysis. Details regarding antenatal antimicrobial exposure, including the specific agent administered, indication, timing, dosing, or duration of exposure, were not captured within this dataset, thus limiting the ability to evaluate a potential association between exposure and risk of infection with antimicrobial-resistant *E. coli*. Previous studies demonstrated the importance of considering these aspects of antenatal antimicrobial exposure.^{7,16,19} Comprehensive antimicrobial resistance profiles were not captured within the dataset. Ampicillin resistance secondary to narrow spectrum beta-lactamases does not reliably predict resistance to first-generation cephalosporins. In our analysis, first-generation cephalosporins were considered effective empiric antimicrobial therapy for ampicillin-resistant *E. coli*, potentially diminishing our ability to detect differences between infants receiving zero and at least one active empiric antimicrobial agent. Additionally, this dataset did not capture doses of empiric antimicrobials or administration schedules. Suboptimal prescribing of these agents may limit our ability to discern differences in outcomes based upon choice of empiric antimicrobial alone. Our outcome analyses incorporated the confounders of prematurity and severity of illness at the onset of BSI, but it is possible additional contributors to infant mortality were not included in this dataset or the multivariable regression model of this retrospective study. Despite a relatively large sample size, mortality was an infrequent occurrence; thus, our study may not have been adequately powered to detect important differences in the outcomes associated with resistant infections or inadequate empiric antimicrobial therapy.

In conclusion, ampicillin resistance was not associated with significantly increased mortality in this cohort of infants with *E. coli* BSI. Among infants with ampicillin-resistant *E. coli* BSI, empiric treatment with an antimicrobial active against resistant *E. coli* was not associated with decreased mortality. Changes in the epidemiology of BSI and increasing antimicrobial resistance represent important areas of concern in the management of this significant cause of infant morbidity and mortality. Continued monitoring of antimicrobial resistance patterns and further prospective studies are needed to better evaluate risk factors for infection with drug-resistant *E. coli* and the optimal empiric antimicrobial strategy to employ in this important clinical entity.

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TABLE 1

Demographics

	Ampicillin-susceptible <i>E. coli</i> N=135 (%)	Ampicillin-resistant <i>E. coli</i> N=123 (%)
Gestational age, weeks		
25	32 (24)	45 (37)
26–28	37 (28)	16 (13)
29–32	27 (20)	21 (17)
33–36	16 (12)	15 (12)
37	21 (16)	26 (21)
Birth weight, g		
<1000	51 (38)	54 (44)
1000–1499	32 (24)	17 (14)
1500–2499	24 (18)	23 (19)
2500–3499	14 (10)	24 (20)
3500	14 (10)	5 (4)
Race/ethnicity		
White	52 (39)	42 (35)
African American	44 (33)	39 (32)
Hispanic	28 (21)	33 (27)
Other	10 (8)	7 (6)
Male	79 (59)	71 (58)
5-minute APGAR		
0–3	8 (6)	10 (9)
4–6	31 (24)	34 (29)
7–10	88 (69)	73 (62)
Cesarean section	62 (47)	58 (48)
Antenatal antibiotic exposure	65 (48)	80 (65)
Early-onset BSI	56 (42)	53 (43)
Mechanical ventilation on day of culture	66 (52)	55 (47)
Inotrope support on day of culture	14 (10)	20 (16)
Supplemental oxygen on day of culture	70 (52)	68 (55)

TABLE 2

Mortality by antimicrobial resistance pattern

	Ampicillin-susceptible <i>E. coli</i> N=135 (%)	Ampicillin-resistant <i>E. coli</i> N=123 (%)	Adjusted odds ratio* (95% CI)
Death within 30 days of culture	7 (5)	11 (9)	1.37 (0.39, 4.77)
Death within 7 days of culture	6 (4)	8 (7)	1.25 (0.35, 4.39)
Death at hospital discharge	8 (7)	16 (15)	1.74 (0.65, 4.67)

* Odds of death for infection with ampicillin-resistant vs. -susceptible *E. coli*. Covariates included: gestational age, small-for-gestational age status, early- vs. late-onset BSI, and inotropic, ventilator, or oxygen support on the day first positive culture obtained.

CI, confidence interval.