

Empiric Combination Therapy for Gram-Negative Bacteremia



WHAT'S KNOWN ON THIS SUBJECT: Existing data do not demonstrate a need for combination therapy after antimicrobial susceptibility data indicate adequate in vitro activity with β -lactam monotherapy. However, the role of empirical combination therapy for the treatment of Gram-negative bacteremia in children remains unsettled.



WHAT THIS STUDY ADDS: We conducted a retrospective, propensity-score matched study demonstrating no improvement in 10-day mortality of children who have Gram-negative bacteremia receiving empirical β -lactam and aminoglycoside combination therapy compared with β -lactam monotherapy, unless the bacteremic episode was attributable to a multidrug-resistant organism.

abstract

BACKGROUND: Empirical combination antibiotic regimens consisting of a β -lactam and an aminoglycoside are frequently employed in the pediatric population. Data to demonstrate the comparative benefit of empirical β -lactam combination therapy relative to monotherapy for culture-proven Gram-negative bacteremia are lacking in the pediatric population.

METHODS: We conducted a retrospective cohort study of children treated for Gram-negative bacteremia at The Johns Hopkins Hospital from 2004 through 2012. We compared the estimated odds of 10-day mortality and the relative duration of bacteremia for children receiving empirical combination therapy versus empirical monotherapy using 1:1 nearest-neighbor propensity-score matching without replacement, before performing regression analysis.

RESULTS: We identified 226 matched pairs of patients well balanced on baseline covariates. Ten-day mortality was similar between the groups (odds ratio, 0.84; 95% confidence interval [CI], 0.28 to 1.71). Use of empirical combination therapy was not associated with a decrease in the duration of bacteremia (-0.51 days; 95% CI, -2.22 to 1.48 days). There was no survival benefit when evaluating 10-day mortality for the severely ill (pediatric risk of mortality III score ≥ 15) or profoundly neutropenic patients (absolute neutrophil count ≤ 100 cells/mL) receiving combination therapy. However, a survival benefit was observed when empirical combination therapy was prescribed for children growing multidrug-resistant Gram-negative organisms from the bloodstream (odds ratio, 0.70; 95% CI, 0.51 to 0.84).

CONCLUSIONS: Although there appears to be no advantage to the routine addition of an aminoglycoside to a β -lactam as empirical therapy for children who have Gram-negative bacteremia, children who have risk factors for MDRGN organisms appear to benefit from this practice. *Pediatrics* 2014;133:e1148–e1155

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KEY WORDS

combination therapy, empiric therapy, aminoglycoside, β -lactam, Gram-negative bacteremia

ABBREVIATIONS

ANC—absolute neutrophil count

CI—confidence interval

JHH—Johns Hopkins Hospital

MDRGN—multidrug-resistant Gram-negative organism

OR—odds ratio

PRISM III score—pediatric risk of mortality III score

Dr Sick conducted data collection, carried out the initial analyses, and wrote the first draft; Drs Tschudin-Sutter and Weissman assisted with conceptualizing the study and reviewed and revised the manuscript; Dr Turnbull assisted with statistical support and critically reviewed and revised the manuscript; Dr Tamma conceptualized and designed the study, designed the data collection instruments, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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POTENTIAL CONFLICT OF INTEREST: Dr Weissman has a patent application pending for a point-of-care diagnostic test to optimize the initial selection of antibiotics for urinary tract infections. The method remains in the developmental stage, and Dr Weissman has received no financial compensation for or benefit from the patented entity. The other authors have indicated they have no potential conflicts of interest to disclose.

Gram-negative bacteremia continues to plague the pediatric population and will remain an ongoing concern as advancements in healthcare produce greater numbers of children requiring long-term intravenous catheters and increasingly complex medical procedures.^{1,2} Definitive or culture-directed therapy for Gram-negative bacteremia has been evaluated in previous pediatric and adults studies.³⁻⁵ Existing data do not demonstrate a continued need for both β -lactam and aminoglycoside therapy after antimicrobial susceptibility data indicate adequate in vitro activity with β -lactam monotherapy (“definitive combination therapy”). However, the role of empirical combination therapy for the treatment of Gram-negative bacteremia in children remains unsettled.

Although the likelihood that an empirical antibiotic regimen will provide adequate coverage for potential infectious pathogens may increase with the use of 2 antimicrobial agents compared with a single agent, later generations of β -lactams with broader spectra of activity may obviate any additional benefit offered by aminoglycosides.⁶ Kumar and colleagues conducted a retrospective, propensity-score matched multicenter cohort study in an adult ICU population and found that empirical combination therapy was associated with decreased 28-day mortality.⁷ This benefit was only present where the β -lactam agent was a first- or second-generation cephalosporin and was not observed with β -lactam agents with broader spectra of activity.

In the pediatric population, comparative effectiveness studies of empirical β -lactam monotherapy and β -lactam/aminoglycoside combination therapy are limited to neonatal sepsis and neutropenic fever.⁸⁻¹⁶ Furthermore, exceedingly small numbers of patients in these studies had culture-proven Gram-negative bacteremia, making

comparisons between the 2 empirical treatment strategies difficult. If there is a benefit of empirical combination therapy, it is unknown whether it extends to all children or whether this approach should be reserved for particular subgroups such as severely ill patients, profoundly neutropenic patients, or patients with risk factors for multidrug-resistant organisms. We conducted a retrospective, cohort study to evaluate the role of empirical combination therapy for children who have Gram-negative bacteremia.

METHODS

Setting and Subjects

All children who had monomicrobial Gram-negative bacteremia (*Acinetobacter baumannii*, *Escherichia coli*, *Enterobacter* spp, *Klebsiella* spp, *Citrobacter* spp, *Pseudomonas* spp, *Serratia marcescens*) hospitalized at The Johns Hopkins (JHH) Charlotte R. Bloomberg Children’s Center from January 1, 2004 until December 31, 2012 with clinical signs and symptoms suggestive of infection, given age-based normal values (temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, leukopenia, leukocytosis, apnea, bradycardia, tachycardia, or hypotension) were included.¹⁷ Excluded from the study were children not admitted to the hospital and children who were not receiving a β -lactam antibiotic as part of their empirical antimicrobial therapy at the time the Gram-stain identified a Gram-negative organism. Additionally, all infants ≤ 2 months of age were excluded, as these patients routinely receive empirical combination therapy with ampicillin and gentamicin in our institution.

Exposures and Outcomes

The primary exposure was receipt of a β -lactam antibiotic (piperacillin-tazobactam, ceftriaxone, cefepime, aztreonam, or meropenem) either with

or without an aminoglycoside as empirical therapy for bacteremia. Empirical aminoglycoside administration was administered as gentamicin 2.5 mg/kg per dose every 8 hours (90% of patients) and amikacin 5 to 7.5 mg/kg per dose every 8 hours (10% of patients) per the JHH pediatric aminoglycoside dosing guidelines.¹⁸ Aminoglycoside dosage adjustments were made as appropriate for renal function. Similarly, all β -lactam dosing followed the recommended dosing in the JHH “Guidelines for the Management of Bloodstream Infections in Neonatal and Pediatric Patients.”¹⁹ Of note, no patients received prolonged infusion β -lactam therapy or extended-interval aminoglycoside dosing.

The primary outcome was mortality within 10 days of the day the first positive blood culture was obtained. Day 10 vital status could be captured for the vast majority of patients as greater than 97% of children in the cohort had subsequent return visits to JHH inpatient or outpatient services. The secondary outcome was duration of bacteremia. At the JHH Children’s Center, it is routine to collect blood cultures daily until clearance of clinically-relevant bacteremia is documented.²⁰ Empirical therapy was defined as antibiotic therapy prescribed within 24 hours from the time the first positive blood culture was obtained. Monotherapy was defined as empirical therapy that consisted only of a β -lactam antibiotic; combination therapy was defined as empirical therapy that consisted of both a β -lactam antibiotic and an aminoglycoside.

Data Collection

Patients growing Gram-negative organisms in the bloodstream during the study period were identified by using the hospital’s microbiology database. Baseline data were collected for the first day of detectable bacteremia,

including demographics, preexisting medical conditions, presumed source of bacteremia, absolute neutrophil count (ANC), presence of a central venous catheter, vasopressor or mechanical ventilator requirement, severity of illness (pediatric risk of mortality III [PRISM] score), other microorganisms cultured from the bloodstream, and antimicrobial susceptibility testing results. Data collected for each subsequent day of hospitalization included daily central line status, blood culture results, and vital status for 10 days.

Patients who (1) received corticosteroid therapy ≥ 2 mg/kg or ≥ 20 mg daily for at least 14 days, (2) received biologic agents in the preceding 30 days, (3) received a solid organ transplant, (4) received a hematopoietic stem cell transplant in the preceding 1 year, (5) received cancer chemotherapy within 6 months, (6) had a congenital immunodeficiency, or (7) had HIV with CD4 ≤ 200 cells/mL were categorized as immunocompromised.²¹

Multidrug resistant Gram-negative (MDRGN) organisms were defined as organisms not susceptible (resistant or intermediate) to at least 1 agent in at least 3 of 6 antimicrobial drug classes, including aminoglycosides, anti-pseudomonal penicillins, third-generation cephalosporins, anti-pseudomonal fluoroquinolones, aztreonam, or carbapenems.²² *Escherichia coli* and *Klebsiella* spp were identified as extended spectrum β -lactamase (ESBL) producing when there was an increase in the zone of inhibition of ≥ 5 mm with either ceftazidime or cefotaxime discs when tested in combination with discs containing clavulanic acid.²³ Enterobacteriaceae resistant to ertapenem and ceftriaxone and positive by the Modified Hodge Test were reported as carbapenamase producers.²⁴ This study was approved by The Johns Hopkins University School of Medicine Review Board with a waiver of informed consent.

Statistical Analysis

We developed a multivariable logistic regression model to estimate a propensity score for each patient's likelihood of receiving empirical combination antibiotic therapy. The covariates used to generate these scores included age, number of preexisting medical conditions, PICU admission, vasopressor requirement, mechanical ventilation, pediatric risk of mortality III (PRISM) score, time from admission to first day of detectable bacteremia, immunocompromised status, ANC ≤ 100 $\mu\text{g}/\text{mL}$, MDRGN organism as the cause of bacteremia, receipt of definitive combination antibiotic therapy, and presence of a central line on day 1 of bacteremia. Children receiving monotherapy and combination therapy were then matched by their propensity score using 1:1 nearest-neighbor matching without replacement. Standardized biases were used to measure covariate balance, whereby a standardized bias > 0.10 represented imbalance. Patients without an eligible match were excluded from additional analysis to reduce the risk of bias from nonexchangeable subjects. Continuous data were described by medians and interquartile range and compared by using the Wilcoxon rank-sum test. Categorical data and proportions were compared by using the χ^2 test. McNemar's test and the paired sample *t* test were used to analyze baseline characteristics after matching. After matching, the association between combination empirical therapy and (a) 10-day mortality, and (b) duration of bacteremia were estimated by using logistic regression and linear regression, respectively. Variables with standardized biases > 0.10 were included in the regression analyses to further adjust for any remaining covariate imbalance after matching. Interaction terms were included to assess any effect modification for the association between (1)

PRISM III scores ≥ 15 , (2) ANC ≤ 100 cells/mL, and (3) bacteremia attributable to an MDRGN for the outcome of 10-day mortality, as it was decided a priori that these children were in high-risk categories that may benefit from combination empirical therapy. Analyses were performed by using the R programming language (version 3.0.1; R Development Core Team, MatchIt package).²⁵ All tests were 2-tailed and values of $P < .05$ were considered statistically significant.

RESULTS

Baseline Characteristics

There were 714 children meeting eligibility criteria with 488 (68%) receiving empirical β -lactam and aminoglycoside combination therapy and 226 (32%) receiving β -lactam monotherapy (Table 1). Children receiving combination therapy were more likely to be immunocompromised, profoundly neutropenic, have a central line on the first day of bacteremia, and continue to receive combination therapy after antibiotic susceptibilities were finalized (Table 1). After matching on propensity scores, we identified 226 well-balanced pairs, producing a cohort of 452 patients. Because no patient received aztreonam as part of an empirical combination regimen, patients receiving aztreonam were excluded from the matched-pair cohort analysis evaluating 10-day mortality and duration of bacteremia.

10-Day Mortality

Thirty-five (7.7%) of the 452 patients died within 10 days of bacteremia, regardless of treatment strategy. Ten-day mortality among patients receiving combination therapy and monotherapy was 8.4% and 7.1%, respectively. There was no difference in the unadjusted odds of 10-day mortality among children receiving combination therapy

TABLE 1 Characteristics of Patients Hospitalized With Gram-Negative Bacteremia Between 2004 and 2012

Variable	Complete Cohort (n = 714)			Propensity-Score Matched Patients (n = 452)		
	Monotherapy (n = 226; 32%)	Combination Therapy (n = 488; 68%)	P value	Monotherapy (n = 226)	Combination Therapy (n = 226)	P value
Age; median (IQR)	5.5 (1–14)	5 (1–13)	0.95	5.5 (1–14)	4 (1–13)	0.62
Admitted to ICU ^a	32.3%	36.5%	0.23	32.3%	35.0%	0.32
Vasopressors ^a	13.8%	17.4%	0.21	13.8%	15.0%	0.79
Mechanical ventilation ^a	16.4%	19.7%	0.29	16.4%	18.1%	0.71
Pediatric risk of mortality III score, median (IQR) ^a	5 (2–8)	4 (2–7)	0.07	5 (2–8)	4 (2–7)	0.46
Days from admission to first positive blood culture, median (IQR)	1 (1–12)	1 (1–9)	0.58	1 (1–12)	1 (1–10)	0.38
Number of preexisting medical conditions, median (IQR)	1 (1–2)	1 (1–3)	0.09	1 (1–2)	1 (1–2)	0.40
Immunocompromised	19.1%	25.8%	0.04	19.1%	21.2%	0.64
Absolute neutrophil count $\leq 100 \mu\text{g}/\text{mL}$	10.4%	18.4%	0.001	10.4%	11.5%	0.35
Central line in place on day 1 of bacteremia	63.2%	81.9%	<0.001	63.2%	71.2%	0.09
Central line in place on day 3 of bacteremia	35.8%	41.0%	0.21	35.8%	39.0%	0.56
Multidrug-resistant Gram-negative organism	12.6%	14.6%	0.49	9.3%	11.1%	0.65
β -lactam and aminoglycoside use for ≥ 48 h after culture and susceptibility results finalized	61%	70%	0.02	61%	61%	0.99

IQR, interquartile range.

^a On day 1 of detectable bacteremia.

compared with those receiving monotherapy (odds ratio [OR], 0.79; 95% confidence interval [CI], 0.26 to 1.85; Table 2). The relative odds of mortality remained largely unchanged after adjusting for the presence of a central line on day 1 of bacteremia (standardized biases >0.10 in the post-match sample; OR, 0.84; 95% CI, 0.28 to 1.71).

There was no 10-day survival benefit of adding an aminoglycoside to the β -lactam on an empirical basis for

children who had PRISM III scores ≥ 15 or ANCs ≤ 100 cells/mL ($P = .77$ and $P = .21$, respectively). However, among children who had bacteremia attributable to an MDRGN organism, those receiving combination therapy with an aminoglycoside had lower 10-day mortality (OR, 0.70; 95% CI, 0.51 to 0.84; $P < .01$; Fig 1).

There were 46 children who had MDRGN bacteremia. Of these, 45.6% and 54.3% of children in the monotherapy and

combination therapy arms, respectively, received at least 1 empirical agent with in vitro activity against the isolated pathogen. The MDRGN organisms recovered in the matched cohort included the following: ESBL *E. coli* or *Klebsiella* spp ($n = 12$), multidrug-resistant *Pseudomonas aeruginosa* ($n = 15$), multidrug-resistant *Enterobacter* spp ($n = 14$), multidrug-resistant *Citrobacter* spp ($n = 2$), and multidrug-resistant *Serratia marcescens* ($n = 3$). There were no carbapenemase-resistant Enterobacteriaceae identified. Eighty-seven percent of patients experiencing MDRGN bacteremia were previously colonized or infected with an MDRGN.

Duration of Bacteremia

The median duration of bacteremia for children in the monotherapy and combination therapy arms was 1.9 and 2.1 days, respectively. There was no significant difference in the duration of bacteremia in the matched samples, even after adjusting for time to central line removal or drainage of intra-abdominal abscesses (-0.51 days; 95% CI, -2.22 to 1.48 days). Among children who had MDRGN bacteremia, there was a nonsignificant trend toward longer durations of bacteremia for patients

TABLE 2 10-Day Mortality for 452 Children Receiving Either Empirical Combination Therapy or Empirical Monotherapy

Covariate	Unadjusted Analysis of Matched Cohort (n = 226)		Adjusted ^a Analysis of Matched Cohort (n = 226)	
	OR (95% CI)	P value	OR (95% CI)	P value
Empirical combination therapy	0.79 (0.26 to 1.85)	0.46	0.84 (0.28 to 1.71)	0.41
Age (per 1-y increase)	0.98 (0.91 to 1.06)	0.69	—	—
Pediatric risk of mortality III score ≥ 15	15.8 (5.7 to 44)	<0.001	—	—
Number of days of combination therapy from day 1 to 10 (per day increase)	0.82 (0.38 to 1.79)	0.48	—	—
Number of preexisting medical conditions (per unit increase)	1.23 (0.57 to 2.68)	0.59	—	—
Central line retained beyond 48 h after positive blood culture	4.72 (1.07 to 20.90)	0.04	—	—
ICU admission	4.38 (1.51 to 12.67)	<0.01	—	—
Vasopressors within 48 h	5.96 (2.20 to 16.14)	<0.001	—	—
Mechanical ventilation within 48 h	10.02 (3.43 to 29.23)	<0.001	—	—
Absolute neutrophil count ≤ 100 cells/mL	2.40 (0.89 to 6.49)	0.08	—	—
Immunocompromised status	2.31 (0.86 to 6.24)	0.10	—	—
Current infection is attributable to an MDRGN ^b	10.53 (3.86 to 26.73)	<0.001	—	—

—, analysis not performed.

^a Adjusting for central line present at the time of admission.^b Multidrug-resistant Gram-negative organism resistant to at least 1 agent in 3 or more classes of antibiotics.

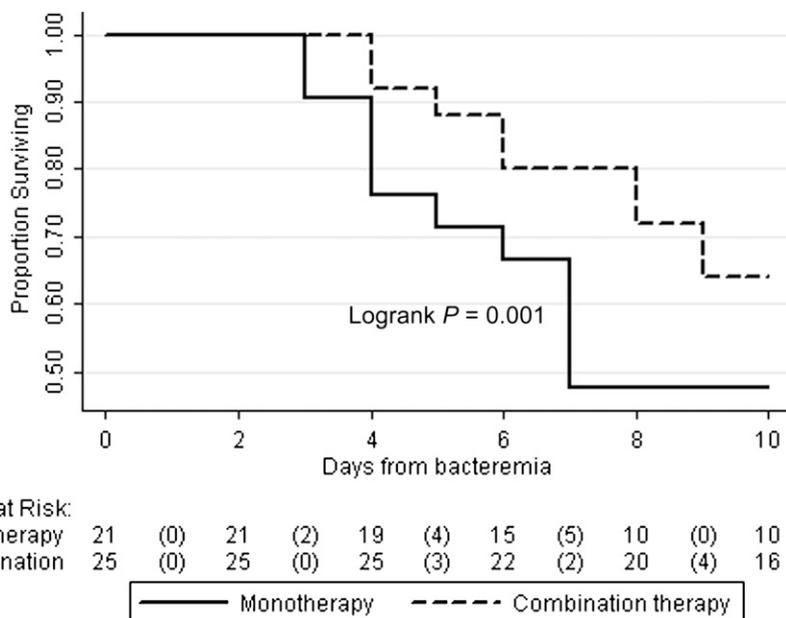


FIGURE 1 Kaplan-Meier curve comparing 10-day mortality of patients who have multidrug-resistant Gram-negative bacteremia receiving empirical combination antibiotic therapy or monotherapy.

receiving β -lactam monotherapy (0.85 days; 95% CI, -0.04 to 2.10 days).

In Vitro Activity of Agents Selected

Evaluating the entire cohort of eligible patients ($n = 714$), aztreonam had the lowest activity against cultured organisms (Fig 2). Aztreonam if prescribed as a single agent would have had in vitro activity against the organism recovered in only 81% of patients prescribed this agent. The addition of an aminoglycoside increased activity to 88% ($P < .01$). There was no difference in coverage proportions between piperacillin-tazobactam, cefepime, or carbapenems for organisms growing in patients receiving these agents. The addition of an aminoglycoside increased ceftriaxone activity by 4% (evaluating only the children prescribed ceftriaxone), most notably for *P. aeruginosa* and *Enterobacter* spp. There was an increase in activity against the infecting organism with the addition of an aminoglycoside to all β -lactams evaluated for children infected with MDRGNs, with the exception of meropenem (Fig 3).

DISCUSSION

Our study demonstrates that the routine use of empirical combination therapy with a β -lactam and aminoglycoside does not appear to decrease 10-day mortality or duration of bacteremia for children who have Gram-negative bacteremia. However, there may be a benefit to the addition of an aminoglycoside for empirical therapy in children who have risk factors for MDRGN bacteremia, particularly when receiving agents other than carbapenems.

Selecting an appropriate β -lactam for empirical therapy may be more important than the reflexive addition of an aminoglycoside to all patients who have Gram-negative bacteremia. Our study demonstrated that only 81% of children were bacteremic with an organism susceptible to aztreonam if it had been prescribed as monotherapy. Similarly, aztreonam had 83% in vitro activity in a pediatric study of some 33 000 diverse-source Gram-negative isolates.²⁶ Patients who have an inability to tolerate penicillins may benefit from the routine addition of an

aminoglycoside to aztreonam on an empirical basis. In contrast, monotherapy with ceftriaxone (when hospital-acquired Gram-negative infections are unlikely), piperacillin-tazobactam, cefepime, or meropenem will likely suffice. Specifically, the addition of an aminoglycoside only increased in vitro activity against the organisms isolated between 0% and 4% for patients receiving these β -lactam agents.

When an MDRGN is suspected, our results suggest the empirical antibiotic approach should include combination antibiotic therapy. Of the various β -lactam agents evaluated for children bacteremic with MDRGNs, meropenem had the broadest spectrum of activity at 83% with the susceptibility of other agents ranging from 38% (ceftriaxone) to 66% (cefepime). When a patient has risk factors for MDRGNs (eg, a history of previous colonization or infection with an MDRGN, broad-spectrum antibiotic therapy within 30 days, a prolonged current hospitalization, or a high prevalence of MDRGNs in the community),^{27,28} the addition of an aminoglycoside as empirical therapy appears prudent.

There are few comparative studies in the pediatric population evaluating clinical outcomes of children receiving empirical combination therapy versus monotherapy for confirmed Gram-negative infections, and the vast majority of patients in these studies had culture-negative sepsis, limiting the generalizability of findings.⁸⁻¹⁶ Kumar and colleagues conducted a retrospective, propensity-matched multicenter cohort study in the adult ICU population and found that empirical combination therapy was associated with decreased 28-day mortality. This benefit was most pronounced for early generation cephalosporins but did not persist when β -lactams with broader spectrums of activity were prescribed.⁷ These results were similar to the

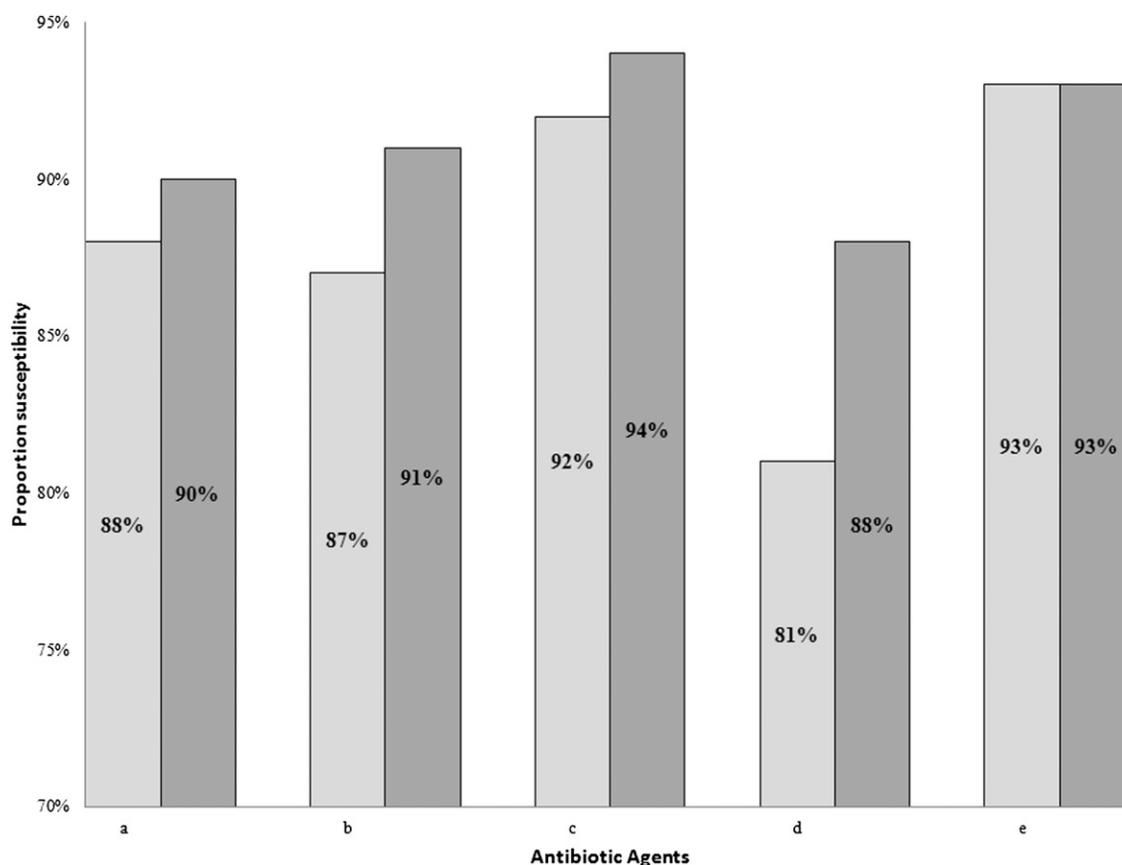


FIGURE 2

Percent of in vitro activity of β -lactam agents prescribed empirically for patients subsequently having qualifying Gram-negative organisms recovered in the bloodstream ($n = 714$). a, piperacillin-tazobactam; b, ceftriaxone; c, cefepime; d, aztreonam; e, meropenem. Light gray bars represent β -lactam alone, dark gray bars represent β -lactam plus aminoglycoside therapy. P value not significant when comparing broadened spectrum of activity of monotherapy and combination therapy for each β -lactam except for aztreonam ($P < .01$).

results of 2 other large studies conducted in adults who had Gram-negative bacteremia, which concluded that although routine combination empirical therapy did not provide a survival advantage for adults who had Gram-negative bacteremia, empirical combination therapy contributed to the survival of patients infected with MDRGN organisms.^{29,30} These studies further support our conclusion that if a sufficiently broad-spectrum β -lactam agent is selected, in the absence of risk factors for MDRGN organisms, β -lactam monotherapy should be adequate.

Although we did not evaluate children in our cohort for untoward effects of aminoglycoside therapy, there are important potential disadvantages to combination therapy worth acknowl-

edging. Aminoglycosides, whether administered using traditional dosing or using extended-infusion strategies, have been known to cause ototoxicity and nephrotoxicity,^{6,31} which could be exacerbated by the concomitant administration of additional agents frequently started on an empirical basis for sepsis, such as vancomycin. Additionally their use requires therapeutic drug monitoring, and their relatively frequent administration can lead to complex treatment schedules, potentially leading to drug interactions and further toxicities.

There are some limitations to consider with our findings. First, this is a single-center study conducted at a tertiary care referral center. The epidemiology of microorganisms at our institution

and the proportion of β -lactams with in vitro activity against the recovered pathogens may not be generalizable to other pediatric populations. Our β -lactam and aminoglycoside antibiotic susceptibility percentages, however, appear consistent with a study evaluating antibiotic susceptibility data from 55 contributing institutions caring for children in the United States.²⁶

Second, although we did not find a benefit of combination therapy in a subgroup analysis of children who had ANCs ≤ 100 cells/mL or PRISM III scores ≥ 15 , there were only 49 and 114 children in these categories, respectively, and we may have been unable to detect a difference in the clinical outcomes of children comparing combination therapy versus monotherapy, if a difference

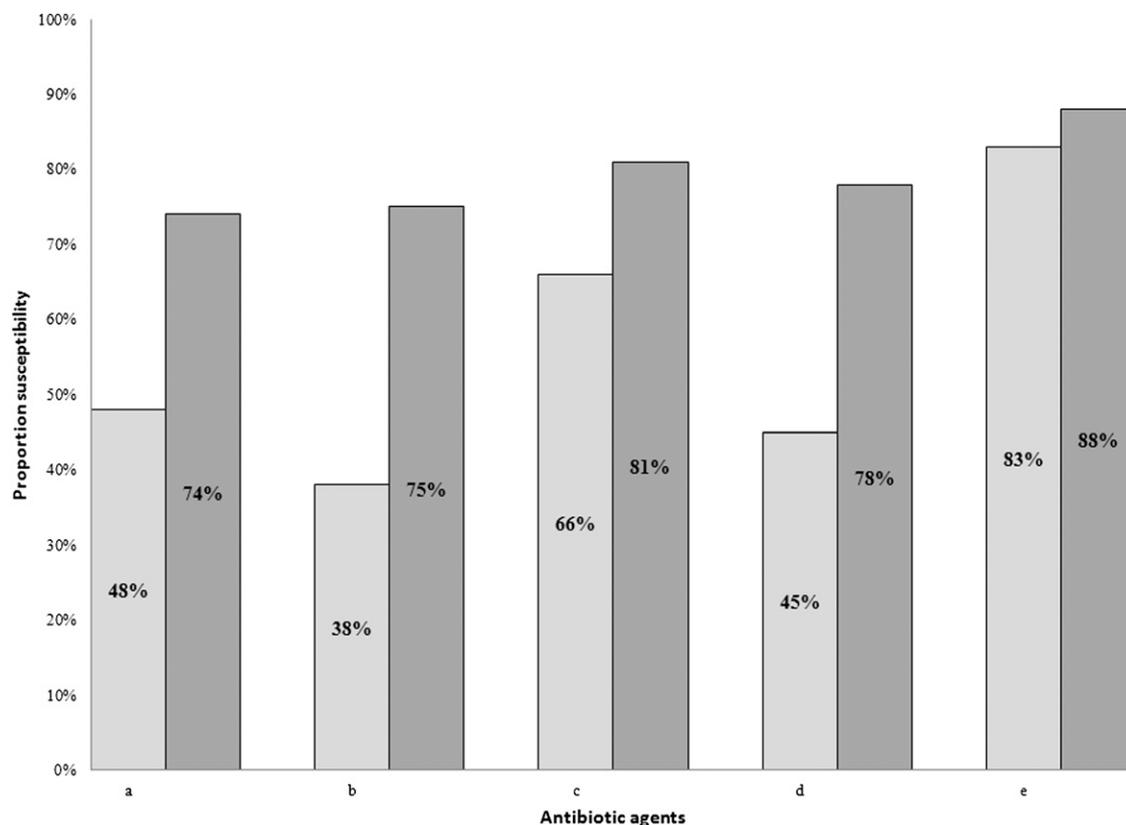


FIGURE 3

Percent of in vitro activity of β -lactam agents prescribed empirically for patients subsequently having multidrug-resistant Gram-negative organisms in the bloodstream ($n = 46$). a, piperacillin-tazobactam; b, ceftriaxone; c, ceftipime; d, aztreonam; e, meropenem. Light gray bars represent β -lactam alone, dark gray bars represent β -lactam plus aminoglycoside therapy. P value significant when comparing broadened spectrum of activity of monotherapy and combination therapy for each β -lactam except for meropenem ($P < .01$).

exists. Further prospective studies are needed to evaluate patients in these risk categories.

Finally, despite our use of propensity scores to account for differences in baseline characteristics between the treatment groups and the reassuring covariate balance within the matched pairs, unmeasured residual confounding may have still occurred. However, when analyzing our outcomes data, we

adjusted for baseline characteristics that may still cause some minor inequalities between the treatment groups to decrease residual bias and increase precision.

CONCLUSIONS

Our findings indicate that combination empirical therapy does not appear to add a clinical benefit for the routine

management of children who have Gram-negative bacteremia when an appropriately broad β -lactam agent guided by local epidemiology is selected. Combination empirical therapy improves the outcomes of patients growing MDRGN organisms in the bloodstream and careful review of patient risk factors is needed to identify these patients to ensure early, appropriate therapy is prescribed.

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