BRIEF REPORT

Increased 30-Day Mortality Associated With Carbapenem-Resistant Enterobacteriaceae in Children

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In this multicenter study, we identified an increased risk of 30-day mortality among hospitalized children with carbapenem-resistant Enterobacteriaceae (CRE) isolated from clinical cultures compared with those with carbapenem-susceptible Enterobacteriaceae. We additionally report significant variation in antibiotic treatment for children with CRE infections with infrequent use of combination therapy.

Keywords. Gram-negative resistance; *Klebsiella pneumoniae* carbapenemase; pediatrics; multidrug-resistant organism.

Carbapenem-resistant *Enterobacteriaceae* (CRE) are increasingly identified in children, with mortality rates from associated infections as high as 50% [1–3]. The reasons for these high mortality rates are likely multifactorial, including delays in appropriate antibiotic therapy, lack of available antibiotics active against CRE, and underlying comorbid conditions and illness severity placing patients at high baseline risk for mortality. Indeed, oncologic conditions, prematurity, and intensive care unit (ICU) stay are frequently reported in available case series of pediatric CRE infections. In addition, a recent comparative study identified prior surgery, mechanical ventilation, and ICU stay as risk factors for colonization or infection with CRE [2, 4–6]. A number of studies in adults suggest that carbapenem-containing combination antibiotic therapy is the treatment strategy associated with the lowest mortality for invasive infections due to CRE, though this has not been evaluated in children [7, 8]. The objective of this study was to evaluate the impact of CRE identified in clinical culture on 30-day mortality as compared with carbapenem-susceptible Enterobacteriaceae (CSE) among children hospitalized at 3 tertiary care institutions in the United States.

METHODS

Study Design and Population

We performed a matched cohort study to assess the impact of isolation of CRE from a clinical culture on 30-day all-cause mortality relative to isolation of CSE. All patients younger than 21 years old hospitalized at Boston Children's Hospital (395 beds, Boston, MA), Children's Hospital of Philadelphia (527 beds, Philadelphia, PA), or The Johns Hopkins Hospital (250 beds, Baltimore, MD) between January 1, 2011, and July 1, 2016, were eligible for inclusion. Patients with index clinical cultures positive for CRE were matched in a 2:1 ratio to patients with clinical cultures positive for CSE on the following criteria: (1) hospitalization at the same institution, (2) age strata (infant <1 year; child 1–12 years; adolescent ≥13 years), (3) year of positive culture, (4) clinical source of positive culture, and (5) definite infection vs possible infection or colonization. CRE was defined as an isolate resistant to imipenem, meropenem, doripenem, or ertapenem [9]. Carbapenem resistance was defined per the Clinical and Laboratory Standards Institute guidelines throughout the study period as an imipenem, doripenem, or meropenem minimum inhibitory concentration (MIC) ≥4 μg/mL or ertapenem MIC ≥2 μg/mL [10]. All blood and intra-abdominal fluid cultures were considered representative of definite infection; urine, respiratory, and wound cultures were classified as definite infection vs possible infection or colonization based on modified National Healthcare Safety Network (NHSN) surveillance definitions by infectious diseases–trained physicians at each site [11]. Cultures obtained from the gastrointestinal tract were considered representative of definite colonization and were excluded from the study. This study was approved by the institutional review board at each institution with a waiver of informed consent.

Data Collection

Demographic and clinical data were abstracted from the electronic medical record onto a standardized data collection form by an infectious diseases–trained physician at each site. Empiric antibiotic therapy was defined as agents administered within 3 days of the date of culture collection. Definitive antibiotic therapy was defined as the agent(s) administered 3 or more

days after the positive culture for at least 3 days. Patients were considered to have received combination therapy if 2 or more CRE-active agents were administered for 3 or more days simultaneously. CRE-active agents included carbapenems, aminoglycosides (if susceptible), fluoroquinolones (if susceptible), tigecycline, colistin, or ceftazidime-avibactam.

Statistical Analysis

To account for the matched cohort design, conditional Poisson regression was utilized to evaluate the impact of CRE isolated from a clinical culture on 30-day mortality. The calculated incidence rate ratios (IRRs) resulting from the conditional Poisson model approximate risk ratios (RRs) for a matched cohort study [12, 13]. Because of the small number of events in this cohort, only bivariable analysis was performed. All analyses were performed using Stata, version 14 (StataCorp, College Station, TX).

RESULTS

Impact of CRE on 30-Day Mortality

During the 5.5-year study period, 72 patients with a clinical culture positive for CRE were identified and matched to 144 control patients with a clinical culture positive for CSE. Sixty-three patients (33%) were younger than 1 year of age, 93 (49%) were between 1 and 12 years of age, and 11 (17%) were older than 13 years of age. Thirty-one (43%) met criteria for definite infection, and the remaining patients were considered to have possible infections or colonization. Sources of the positive culture included urine (39%), respiratory (35%), wound (13%), blood (11%), and intra-abdominal fluid (3%). Relative to patients with CSE, patients with CRE were more often hospitalized in the ICU (61% vs 40%) and more often had health care–associated infections (71% vs 38%). Crude 30-day mortality for patients with CRE was 8.3% (6/72 patients), compared with 1.4% for patients with CSE (2/144 patients). Accounting for matching on age strata, year, hospital, clinical source, and definite infection vs possible infection or colonization, the RR of 30-day mortality for patients with CRE was 6.00 (95% confidence interval [CI], 1.21–29.7; $P = .03$). Among patients with definite infections, 30-day infection-related mortality for patients with CRE was 6.5% (2/31), and it was 0% in patients with CSE.

Microbiologic Characteristics and Antibiotic Treatment Regimens

Among the 31 patients with definite CRE infections, 21 isolates were tested for carbapenemase production, and 11 (52%) carbapenemase-producing organisms were identified. Of the 31 isolates, 13 were classified as CRE based only on ertapenem resistance, including 3 KPC-producing organisms. Nine of the 31 patients (29%) received a CRE-active antibiotic within 3 days of the positive culture (ie, appropriate empiric therapy), compared with 53 of the 62 patients (85%) with CSE. Definitive treatment regimens are summarized in Table 1. Of note, CRE-active combination therapy was utilized in only 23% of patients, and extended-infusion carbapenem therapy in only 10%. Both

patients who died were treated empirically and definitively with CRE-active monotherapy. Infectious diseases was consulted in 65% of cases with CRE infection, including in 100% of patients who received combination therapy and 54% of those receiving monotherapy or no active therapy.

DISCUSSION

We performed a multicenter matched cohort study evaluating the effect of CRE on 30-day mortality among hospitalized children and found that patients with CRE had a 6-fold greater risk of mortality relative to patients with CSE. Further, we identified substantial variability in antibiotic treatment regimens, including frequent use of cephalosporin, carbapenem, and ciprofloxacin monotherapy and relatively infrequent use of combination therapy, even among patients with bloodstream infections. Our findings provide the first comparative data demonstrating the effect of CRE on mortality in children and further identify significant variation in antibiotic prescribing practices, highlighting a potential opportunity for improved standardization.

Our finding of increased mortality associated with CRE isolated from a clinical culture is consistent with adult and available pediatric literature, though the mortality of 8.3% in our cohort was substantially lower than the 40% mortality generally reported in adult series [2, 14]. This relatively lower mortality in children is not surprising, and in this particular study may be driven in part by bacteremia representing a relatively uncommon source of infection. The higher mortality associated with CRE vs CSE could be due in part due to delays in appropriate antibiotic therapy, infrequent use of combination therapy, or residual confounding due to underlying comorbidities. It is notable that infectious diseases consulted on all patients receiving combination therapy, potentially underscoring the importance of this expertise in defining antibiotic treatment regimens for CRE, as has been shown in other populations with multidrug-resistant organisms [15].

Our study has several limitations. First, given the retrospective nature, we were unable to definitively determine whether positive cultures were representative of true infection. We therefore matched patients based on definite vs possible infection or colonization using standardized definitions of definite infection, so misclassification on this characteristic should not affect assessment of risk of death due to CRE. Mortality was infrequent in the cohort, and as such, we were unable to evaluate mortality in the subset of patients who had definite infections or perform multivariable analysis adjusting for other risk factors that may confound the evaluation of the impact of a positive clinical culture for CRE on 30-day mortality, including baseline illness severity and comorbid medical conditions. Still, we did account for differences in mortality that would be expected between definite infection vs possible infection or colonization, as well as different sources of the positive culture, by matching

Table 1. Definitive Treatment Regimens Prescribed for a Cohort of 31 Children With Carbapenem-Resistant Enterobacteriaceae Infections[a]

Antibiotic(s)	Organism	Carbapenemase Identified	Source	Outcome at 30 d
CRE-active combination therapy (n = 7)[c]				
Meropenem (extended infusion) + amikacin	*K. pneumoniae*	KPC	Blood	Survived
Meropenem + amikacin	*E. coli*	No carbapenemase detected	Wound	Survived
Imipenem + gentamicin	*E. aerogenes*	No carbapenemase detected	Blood	Survived
Meropenem + levofloxacin	*K. pneumoniae*	No carbapenemase detected	Peritoneal fluid	Survived
Ciprofloxacin + amikacin	*E. cloacae*	Carbapenemase detected, phenotypic test only	Blood	Survived
Ceftazidime-avibactam + amikacin	*K. pneumoniae*	KPC	Urine	Survived
Imipenem + amikacin + ciprofloxacin	*K. pneumoniae*	Not tested	Blood	Survived
Non-CRE-active combination therapy[b] (n = 3)				
Cefepime + tigecycline	*E. cloacae*	Not tested	Peritoneal fluid	Survived
Piperacillin-tazobactam + gentamicin	*K. pneumoniae*	NDM	Wound	Survived
Piperacillin-tazobactam + TMP-SMX	*E. cloacae*	KPC	Wound	Survived
Monotherapy (n = 15)				
Cephalexin	*K. pneumoniae*	Not tested	Urine	Survived
Cefotaxime	*C. freundii*	KPC	Urine	Survived
Ceftriaxone	*E. cloacae*	No carbapenemase detected	Wound	Survived
Cefepime	*C. freundii*	Carbapenemase detected, phenotypic test only	Urine	Survived
Cefepime	*E. cloacae*	No carbapenemase detected	Blood	Survived
Ciprofloxacin	*E. cloacae*	KPC	Urine	Survived
Ciprofloxacin	*E. cloacae*	Not tested	Urine	Survived
Ciprofloxacin	*E. aerogenes*	Not tested	Urine	Survived
Ciprofloxacin	*E. cloacae*	Not tested	Blood	Died
Gentamicin	*K. pneumoniae*	Not tested	Urine	Survived
Meropenem (extended infusion)	*S. marcescens*	No carbapenemase detected	Respiratory	Survived
Meropenem (extended infusion)	*K. pneumoniae*	No carbapenemase detected	Wound	Survived
Meropenem	*K. pneumoniae*	No carbapenemase detected	Blood	Died
Meropenem	*S. marcescens*	Not tested	Blood	Survived
Imipenem	*E. coli*	No carbapenemase detected	Urine	Survived
No antibiotic treatment (n = 6)				
	K. pneumoniae	NDM	Wound	Survived
	E. coli	No carbapenemase detected	Urine	Survived
	S. marcescens	No carbapenemase detected	Respiratory	Survived
	E. cloacae	No carbapenemase detected	Wound	Survived
	E. cloacae	KPC	Wound	Survived
	E. coli	NDM, OXA	Urine	Survived

[a]Definitive treatment defined as treatment administered 3 or more days after the culture date or at the time of death if the patient died less than 3 days from the culture date.

[b]Combination therapy defined as more than 1 CRE-active antibiotic administered for 3 or more days.

[c]CRE-active agents include carbapenems, aminoglycosides (if reported susceptible), fluoroquinolones (if reported susceptible), tigecycline, colistin, and ceftazidime-avibactam [10].

Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; TMP-SMX, trimethoprim-sulfamethoxazole.

on these characteristics. Finally, we were unable to assess the effect of various antibiotic treatment strategies, including use of CRE-active vs CRE-inactive agents on mortality, given the small sample size.

In conclusion, we have demonstrated an increased mortality risk among children with CRE relative to those with CSE and identified significant variation in antibiotic treatment strategies among infected patients. Future studies should evaluate the efficacy of various antibiotic treatment approaches among children and evaluate new antibiotics in this increasingly complex population.

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