Risk factors and outcomes for children with carbapenem-resistant Enterobacteriaceae: a multicenter case series

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Abstract

- Background. Carbapenem-resistant Enterobacteriaceae (CRE) are increasingly identified causes of healthcare-associated infections in adults, but little is known about the epidemiology of CRE in children.
- Objectives. To describe risk factors and outcomes for pediatric patients with CRE infection or colonization hospitalized in three tertiary care pediatric centers.
- Methods. All patients <21 years old with CRE isolated from a clinical culture between 2011-2015 were included. Data were obtained by primary medical record review.
- Results. Prior antibiotic use, medical care abroad, medical devices, and comorbid medical conditions were commonly identified in patients with CRE. Attributable mortality was 11%.
- Conclusions. Our study identified several important risk factors for CRE and highlights key differences from adult patients.

Background

- CRE is one of the Centers for Disease Control and Prevention's top 3 urgent antibiotic resistance threats.
- The microbiology, molecular epidemiology, risk factors and outcomes for pediatric patients with CRE are poorly characterized and may differ from adult patients.

Objectives

- To describe risk factors and outcomes for pediatric patients with CRE.
- To describe microbiologic features of pediatric CRE isolates.

Methods

- All children <21 years old admitted to Boston Children's Hospital, The Children's Hospital of Philadelphia, or Johns Hopkins Children's Center with CRE isolated from any clinical culture between January 1st, 2011 and October 15th, 2015 were included.
- CRE was defined per the 2015 CDC definition as an isolate with imipenem, doripenem, or meropenem minimum inhibitory concentration (MIC) $\geq$ 4 µg/mL, or an ertapenem MIC $\geq$ 2 µg/mL.
- Clinical characteristics, treatment strategies, and outcomes were obtained through primary medical record review at each center.

Table 1. Clinical Characteristics of Children with CRE

Variable	N=62
Median age, months (IQR)	24 (5,144)
Median length of stay, days (IQR)	50 (16,119)
Long-term care facility resident, n (%)	3 (5)
Healthcare abroad, n (%)	10 (16)
India	1 (10)
Pakistan	1 (10)
Kuwait	4 (40)
United Arab Emirates	3 (30)
Saudi Arabia	1 (10)
ICU care, n (%)	37 (60)
Prior acute care admission, n (%)	31 (50)
Recent surgery, n (%)	40 (65)
Comorbidities, n (%)	
Hematopoietic stem cell transplant	1 (2)
Solid organ transplant	7 (11)
Malignancy	8 (13)
Prematurity	11 (18)
Renal/urologic	13 (21)
Devices, n (%)	
Central line	38 (61)
Tracheostomy/Endotracheal tube	18 (30)
Urinary catheter	11 (18)
Anti-pseudomonal antibiotic exposure, n (%)	44 (71)
Carbapenem exposure, n (%)	23 (37)

Results

- Sixty-two unique patients with CRE were identified.
- Prior broad-spectrum antibiotic exposure, underlying medical conditions, and medical devices were commonly identified in our cohort.
- *Enterobacter* species were isolated in almost half of patients with *Klebsiella* species and *Escherichia coli* identified in 27% and 6%, respectively.
- Half of isolates were tested for carbapenemase production and 61% of these were positive.
- Most isolates retained susceptibility to aminoglycosides and fluoroquinolones.
- Of the 27 patients with CRE infection, 5 (19%) were were treated with combination antibiotic therapy.
- Sixty-day attributable mortality was 11% among patients with CRE infection.

Table 2. Microbiologic Data

Variable	N=62
Organism	
Klebsiella pneumoniae	16 (26)
Klebsiella oxytoca	1 (2)
Escherichia coli	4 (6)
Enterobacter cloacae	28 (45)
Enterobacter aerogenes	7 (11)
Enterobacter species	1 (2)
Serratia marcescens	5 (8)
Source	
Blood	9 (15)
Urine	21 (34)
Respiratory	21 (34)
Peritoneal fluid	2 (3)
Wound	9 (15)
Carbapenemase Testing Performed	33 (53)
Carbapenemase Detected	20 (61)
Modified Hodge test only	14 (70)
Klebsiella pneumoniae carbapenemase	3 (15)
New Delhi metallo-β-lactamase	2 (10)
Verona integron-encoded metallo-β-lactamase	1 (5)

Conclusions

- CRE is an emerging threat in children, but little data exist informing optimal treatment and prevention strategies.
- Our study identifies several important risk factors for CRE in children and highlights key differences from adult patients, including a predominance of *Enterobacter* species, infrequent use of combination therapy, and substantially lower mortality.
- Prior antibiotic exposure and medical device use are potentially modifiable risk factors for CRE, and immunocompromised patients and patients receiving medical care abroad may be candidate populations for targeted active surveillance.
- Further research is needed to characterize these risk factors and targets for active surveillance, optimal treatment strategies, and the molecular epidemiology of pediatric CRE.

Table 3. Susceptibility Profile for Pediatric CRE Isolates[1]

Antibiotic	Sensitive, n (%)	Intermediate, n (%)	Resistant, n (%)	Not tested, n (%)
Gentamicin	41 (66)	2 (3)	19 (31)	0 (0)
Tobramycin	29 (47)	4 (6)	20 (32)	9 (15)
Amikacin	57 (92)	2 (3)	3 (5)	0 (0)
Ceftriaxone	4 (7)	6 (10)	46 (74)	6 (10)
Cefepime	25 (40)	12 (19)	25 (40)	0 (0)
Piperacillin-tazobactam	9 (15)	8 (13)	34 (55)	11 (18)
Ciprofloxacin	44 (71)	2 (3)	16 (26)	0 (0)
Ertapenem	2 (3)	0 (0)	37 (60)	23 (37)
Imipenem	10 (16)	4 (6)	25 (40)	23 (37)
Meropenem	33 (53)	1 (2)	23 (37)	5 (8)
Tigecycline[2]	7 (11)	0 (0)	7 (11)	48 (77)
Colistin[3]	8 (13)	0 (0)	2 (3)	52 (84)

[1] Susceptibilities based on 2015 Clinical and Laboratory Standards Institute breakpoints unless otherwise noted
[2]Tigecycline sensitive defined as MIC $\leq$ 1 ug/mL and resistant defined as MIC $\geq$ 2
[3]Colistin sensitive defined as MIC) $\leq$ 2 ug/mL and resistant defined as MIC > 2 ug/mL