Epidemiological characteristics and risk factors of nosocomial carbapenem-resistant *Enterobacteriaceae* infections in children

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Carbapenem-resistant *Enterobacteriaceae* (CRE) have spread worldwide as a global threat and CRE infection is associated with a significant mortality. However, data on epidemiology and treatment of CRE infection in children are comparatively lacking.[1] Therefore, we retrospectively conducted a matched case-control study to summarize the epidemiological characteristics, risk factors, treatment, and outcomes of nosocomial CRE infections in a children patient population, and also to identify the antimicrobial resistance and resistance genotyping of CRE isolates.

Children with nosocomially-acquired CRE infection between January 1, 2009 and December 31, 2018 were matched in a 1:2 ratio to control patients with carbapenem-susceptible *Enterobacteriaceae* infection during the same period. Matching was based on the age category and clinical type of infection. This study was approved by the Ethics Committee of The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (No. L-2020-20). Informed consent was obtained from all patients. All isolates were identified by VITEK Compact-2 automatic system (BioMérieux, France). The antimicrobial minimum inhibitory concentration breakpoints were determined according to the Clinical and Laboratory Standards Institutes Guidelines at the time of testing.[2] The presence of carbapenemases was determined by polymerase chain reaction. Statistical analysis was performed using SPSS 25.0 (IBM Corporation, Armonk, NY, USA). Continuous variables were compared by the Mann-Whitney *U*-test or *t*-test. Categorical variables were evaluated using χ^2 test or Fisher exact test. Logistic regression analysis was performed to evaluate factors associated with CRE infection.

Fifty-one CRE-infected children were identified and 102 controls were consecutively selected [Supplementary Table 1, http://links.lww.com/CM9/A271]. It was found that independent risk factors for children with CRE infection were previous exposure to third-generation cephalosporins, β-lactam/β-lactamase inhibitors, mechanical ventilation, and indwelling urethral catheter [Table 1].

Fifty-seven CRE isolates were identified, 98.2% (56/57) of which was multidrug-resistant. The antimicrobial susceptibility of CRE isolates is shown in Supplementary Table 2, http://links.lww.com/CM9/A271. The highest sensitivity was found in tigecycline (100%), followed by amikacin (91.3%) and levofloxacin (75.4%). Phenotypes and genotypes were performed on 23 CRE isolates [Supplementary Table 3, http://links.lww.com/CM9/A271]. *Klebsiella pneumoniae* carbapenemase-2 (*KPC-2*) and New Delhi metallo-β-lactamase-1 were detected in 17 (73.9%) and 3 (13.0%) isolates, respectively. Twenty-one isolates were found to carry at least one extended spectrum β-lactamase and/or AmpC cephalosporinase gene, including two non-carbapenemase-producing strains. Antimicrobial treatment and outcomes are summarized in Supplementary Table 4, http://links.lww.com/CM9/A271. Seven CRE-infected patients died, in contrast with six of the controls ($P = 0.126$). Twenty-two (43.1%) CRE-infected patients received combination therapy. There was no statistical difference in mortality between monotherapy and combination therapy in CRE-infected children (17.2% *vs.* 9.1%, $P = 0.685$). Eight cases who were given fosfomycin-based combination therapy all survived.

Similar to other studies,[3,4] previous exposure to third-generation cephalosporins, β-lactam/β-lactamase inhibitors was associated with CRE infections. This may be due to the widespread use of antibiotics and the altered gastrointestinal flora, which results in the selection for antibiotic-resistant

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Table 1: Risk factors associated with nosocomially-acquired CRE infection.

Characteristics	CRE ($n=51$)	CSE ($n=102$)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*P*	OR (95% CI)	*P*
Gender, *n* (%)						
Male	28 (54.9)	60 (58.8)	0.85 (0.43–1.67)	0.644		
Female	23 (45.1)	42 (41.2)				
Underlying diseases, *n* (%)						
Yes	35 (68.6)	66 (64.7)	1.19 (0.58–2.45)	0.629		
No	16 (31.4)	36 (35.3)				
Previous antibiotic exposure, *n* (%)						
Third-generation cephalosporins						
Yes	18 (35.3)	19 (18.6)	2.38 (1.11–5.10)	0.023	3.46 (1.09–10.96)	0.035
No	33 (64.7)	83 (81.4)				
β-lactam/β-lactamase inhibitors						
Yes	32 (62.7)	24 (23.5)	5.47 (2.64–11.35)	<0.001	6.93 (2.17–22.15)	0.001
No	20 (37.3)	78 (76.5)				
Carbapenems						
Yes	16 (31.4)	10 (9.8)	4.21 (1.74–10.15)	0.001		
No	35 (68.6)	92 (90.2)				
Vancomycin						
Yes	9 (17.6)	4 (3.9)	5.25 (1.53–18.00)	0.01		
No	42 (82.4)	98 (96.1)				
Previous admission in ICU, *n* (%)						
Yes	37 (72.5)	47 (46.1)	3.09 (1.49–6.40)	0.002		
No	14 (27.5)	54 (53.9)				
Previous invasive procedures, *n* (%)						
Mechanical ventilation						
Yes	29 (56.9)	19 (18.6)	5.76 (2.73–12.13)	<0.001	4.80 (1.32–17.46)	0.017
No	22 (43.1)	83 81.3				
Indwelling gastric tube						
Yes	32 (62.7)	25 (24.5)	5.19 (2.51–10.71)	<0.001		
No	20 (37.3)	77 (75.5)				
Indwelling urethral catheter						
Yes	20 (39.2)	9 (8.8)	6.67 (2.75–16.16)	<0.001	3.94 (1.12–13.79)	0.032
No	32 (62.7)	103 (91.2)				
Central venous catheter						
Yes	26 (51.0)	20 (19.6)	4.26 (2.04–8.89)	<0.001		
No	25 (49.0)	82 (80.4)				
Previous surgery, *n* (%)						
Yes	22 (43.1)	20 (19.6)	3.11 (1.49–6.51)	0.002		
No	29 (56.9)	81 (80.4)				
Previous systemic corticosteroid use, *n* (%)						
Yes	20 (39.2)	22 (10.8)	2.35 (1.13–4.89)	0.021		
No	31 (60.8)	80 (89.2)				
Length of hospital stay (days), median	37	19		<0.001		

CRE: Carbapenem-resistant *Enterobacteriaceae*; CSE: Carbapenem-susceptible *Enterobacteriaceae*; OR: Odds ratio; CI: Confidence interval; ICU: Intensive care unit.

organisms. Our results also suggested that mechanical ventilation and indwelling urethral catheter were associated with CRE infection, which was consistent with previous studies.[1,3] Frequent invasive operations and tube indwelling could cause mucosal barrier injury, and increased the possibility of CRE infection. Our findings showed the importance of antimicrobial stewardship and minimizing the use of invasive devices in preventing CRE infection.

Consistent with an Italy pediatric study,[5] *KPC* was the most frequently isolated carbapenemase. CRE isolates remained relatively sensitive to tigecycline, amikacin, and levofloxacin. However, tigecycline is not recommended in children aged <8 years for the risk of dental staining. Besides, fluoroquinolones are only allowed to be used in children aged <18 years in China when no effective drugs are available for serious infection. Therefore, the treatment of CRE-infected children is challenging. Fosfomycin, defined as "critically important" by the World Health Organization, is active against multidrug-resistant bacteria, including Enterobacterales resistant to carbapenems.[6,7] It also presents an excellent safety profile in children.[7] Fosfomycin, when

used as monotherapy, resistance can develop rapidly. However, its unique mechanism allows for synergistic action with other antibiotics and makes cross-resistance uncommon, particularly when used as combination therapy.[7] Although fosfomycin was not included in the antimicrobial susceptibility testing, eight children received fosfomycin-based combination therapy were all cured. Thus, we consider it preferable for CRE-infected children to be treated with fosfomycin-based combination therapy.

Despite its retrospective design and small size, our study has evaluated risk factors and treatment of pediatric CRE infection. Hopefully, it might offer useful information for the treatment of CRE-infected children.

Conflicts of interest

None.

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