A matched case-control study to assess the carbapenem-resistant *Enterobacteriaceae* infections among hospitalized children at King Fahad Medical City, Riyadh, Saudi Arabia

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ABSTRACT

الأهداف: لتحديد عوامل الخطر المرتبطة بالتهابات الأمعاء والبكتيريا المقاومة للكاربينيم (CRE) بين الأطفال في المستشفيات في مدينة الملك فهد الطبية، الرياض، المملكة العربية السعودية.

المنهجية: أجريت دراسة الحالات والشواهد المتطابقة بأثر رجعي في مرضى الأطفال الذين يعانون من عدوى CRE في مدينة الملك فهد الطبية، الرياض، المملكة العربية السعودية خلال الفترة من يناير 2016م ويناير 2017م.

النتائج: خلال فترة الدراسة، تم تحديد 19 حالة CRE و 37 مجموعة الشاهد للتحليل. اشتملت الدراسة على الأطفال ≥ 17 سنة (متوسط العمر [SD] للحالات والشواهد 43.9 [46] أشهر و 29.2 [52.2] أشهر ، على التوالي) في الدراسة. تم تحديد العديد من العوامل المرتبطة بالتهابات CRE، والتي شملت، وضع خط CVC (القيمة الإحصائية=0.023؛ فاصل الثقة 0.97 إلى 85.77)، والإجراءات الجراحية الحديثة (القيمة الإحصائية= 0.006؛ فاصل الثقة 1.30 إلى 9.28)، الإجراءات الجراحية ($p<0.001$؛ فاصل الثقة 1.98 إلى 21.18)، الاستخدام المسبق للمضادات الحيوية (القيمة الإحصائية= 0.008؛ فاصل الثقة 1.38 إلى 24.62)، والتعرض للكاربابينيم في الأشهر الثلاثة الماضية (القيمة الإحصائية= 0.004؛ فاصل الثقة 1.09 إلى 12.20). من بين الحالات، كان الالتهاب الرئوي كليبسيلا الأكثر شيوعا (47%) تليها الإشريكية القولونية (31%). وارتبطت مقاومة للكاربينيم مع زيادة الأمراض المصاحبة والاستشفاء لفترات طويلة ولكن لم يتم الإبلاغ عن وفيات.

الخلاصة: حددت هذه الدراسة التعرض للمضادات الحيوية السابقة والجراحة الحديثة واستخدام الإجراءات الجراحية كعوامل خطر كبيرة للعَدْوَى الاسْتِعْماريّة أو عدوى CRE. أيضًا، يتم إبراز الحاجة إلى الوعي العام والتعليم المستمر لأخصائيي الرعاية الصحية والاستخدام الأمثل للأجهزة الجراحية والمراقبة المعززة والإدارة الجيدة على مضادات الميكروبات هنا والتي يمكن أن تحد من انتقال CRE في مرافق الرعاية الصحية.

Objectives: To identify risk factors associated with carbapenem-resistant *Enterobacteriaceae* (CRE) infections among hospitalized children at King Fahad Medical City, Riyadh, Saudi Arabia.

Methods: A retrospective matched case-control study was conducted in pediatric patients with CRE infection at King Fahad Medical City, Riyadh, Saudi Arabia between January 2016-2017.

Results: During the study period, 19 CRE cases and 37 controls were identified for analysis. Children ≤17 years (mean age±SD for cases was 43.9±46 months and controls was 29.2±52.2 months) were included in the study. Several factors associated with CRE infections were identified, which included, central venous catheter (CVC) line placement (p=0.023; confidence interval [CI]: 0.97-85.77), recent surgical procedures (p=0.006; CI: 1.30-9.28), invasive procedures (p<0.001; CI: 1.98-21.18), use of prior antibiotics (p=0.008; CI: 1.38-24.62), and carbapenem exposure in the past 3 months (p=0.004; CI: 1.09-12.20). Among the cases, *Klebsiella pneumonia* was the most commonly identified (47%) followed by *Escherichia coli* (31%). Carbapenem-resistant *Enterobacteriaceae* was associated with increased comorbidities and prolonged hospitalization however, no mortalities were reported.

Conclusion: This study identified prior antibiotic exposure, recent surgery and the use of invasive procedures as significant risk factors for colonization or infection with CRE. Also, the need for public awareness, continuing education for healthcare professionals, optimum use of invasive devices, enhanced surveillance, and antimicrobial stewardship are highlighted here which can limit CRE transmission in healthcare facilities.

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Carbapenem is a broad-range antibiotic which acts against metallo-ß-lactamase (MBL) as well as extended spectrum ß-lactamases (ESBL) produced by many gram-negative pathogens.[1-3] However, the emergence of carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* (CP-CRE) has threatened the clinical utility of this antibiotic and in fact poses a significant clinical and public health concern.[4] *Klebsiella species* and *Escherichia coli* (*E. coli*), the common organisms in human gut microbiota, can become carbapenem-resistant.[5] *Klebsiella pneumoniae* carbapenemase (KPC) and New Delhi metallo-beta-lactamase (NDM) are enzymes conferring resistance to carbapenems verona integron-mediated metallo-ß-lactamase (VIM) from *Pseudomonas*, imipenemase (IMP) from *Enterobacter aerogenes* and oxacillinase-48-type carbapenemases (OXA-48) from *Acinetobacter baumannii* are also reported to be carbapenem degrading enzymes.[5,6] The highest rates of CRE infection are reported in Greece, Italy, Brazil, and China, followed by several other countries including the United States and Colombia.[7] Oxacillinase-48-type carbapenemases (OXA-48)-producing isolates are commonly observed in cases returning from endemic areas like the Middle East.[7]

Carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* infections are associated with ≥30% case fatality rates and are typically seen in patients with prior healthcare exposure.[8] Contaminated medical devices are a common risk factor for CRE acquisition.[9] Other risk factors are poor functional status, exposure to an intensive care unit and overseas hospitalization.[10-12] Though sporadic, CRE infections in children are on the rise with an increasing number of cases being reported globally.[13] Also, little is known about the associated risk factors in this patient population. A 2017 study by Chiotos et al,[14] showed antipseudomonal antibiotic exposure, prior surgery and mechanical ventilation to be the major risk factors for colonization or infection with CRE in hospitalized children. Thus, rampant use of antibiotics (antibiotic misuse), extensive international travel and poor infection control practices play a role in development of carbapenem-resistance.

In this context, owing to its geographical location, annual hosting of mass gathering events and population flow from the Middle East and India, the Kingdom of Saudi Arabia (KSA) is a potential hotspot for collection and spread of these resistance determinants.[15] A recent study by Khan et al,[16] revealed that *Enterobacteriaceae* isolates in particular *K. pneumoniae* co-harboring (KPC), NDM-1, and OXA-48 genes are emerging in Western region, KSA. The risk factors for CRE infections identified in this region are: higher mean Charlson comorbidity index (CCI), former antibiotic use, intensive care unit (ICU) admission, and receipt of invasive procedures.[17] Also, CRE infections registered a higher mortality rate when compared to matched controls (p=0.031).[17] Mortality was associated with increased age, presence of comorbidities and length of ICU stay.[17] However, literature evidence regarding the burden of CRE infections in children from this region is scarce and so is the information on the associated risk factors. Also, effective antibiotic therapy, have not been formally characterized. Thus, this study aims to identify the prevalence and risk factors of infections due to CRE among hospitalized children, aiming to develop effective prevention strategies including strict infection control measures and close adherence to antibiotic stewardship.

Methods. The source population for the study included patients who were hospitalized at King Fahad Medical City (KFMC), Riyadh, KSA between January 2016-2017.

We performed a retrospective matched case-control study to identify the risk factors for CRE colonization or infection in the pediatric population at KFMC. Patients ≤17 years of age, positive for CRE and hospitalized for ≥24 hours were included. Outpatients and patients who had cultures performed in the Emergency department and not admitted were excluded. Subjects were matched for the anatomic site of infection and the causative organism. The study was focused on the first episode of hospital-acquired infection even if recurrent infections occurred. All data were captured retrospectively, and no additional tests were performed. A microbiology laboratory personnel identified the pathogenic CRE (mainly *K. pneumonia*, *E. coli*, *Enterobacter sp.*, and *Citrobacter sp.*) from the microbiology laboratory database. Patients with clinical cultures positive for CRE were included as case-patients. Carbapenem-resistant *Enterobacteriaceae* was defined according to the 2015 Centers for Disease Control and Prevention (CDC) definition.[18] Patients with positive cultures for carbapenem susceptible *Enterobacteriaceae* (CSE) were treated as controls. Because of the scarcity of infection with some of the above-stated organisms, controls were selected without randomization. All identified eligible controls were screened for inclusion. Carbapenem resistance and susceptibility were defined per the

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2017 Clinical and Laboratory Standards Institute (CLSI) guidelines.[19] Two different control groups were selected in order to get a better representation of the total base population. The criteria for selecting control patients were: (i) hospitalization at same institution, (ii) comparable age stratification, (iii) the year of positive culture, (iv) a clinical source of positive culture, and (v) infection versus colonization status. Instances where more than 2 eligible controls were identified for a single case, the ones with the cultures closest in date to that of the case patient were selected. If for a case there were fewer than 2 eligible controls, the case was excluded from the analysis.

Data were collected using a pre-designed data collection sheet adopted from a previous study conducted by Garbati et al.[17] Collected demographic data included: age, gender, and patient source (home, hospital, long-term care facility). Clinical data included the duration of current hospitalization, site of infection, treatment for the index infection, and the outcome. The severity of illness was assessed by (i) hospitalization within the last 3 months; (ii) patient location at the time of infection; (iii) admission to ICU; (iv) using antibiotics within 3 months before admission; (v) use of central venous catheter (CVC); (vi) use of urinary catheter mechanical ventilation; and (vii) dialysis. Also, the comorbid conditions (cardiovascular disease, lung disease, diabetes mellitus, solid tumors or hematological malignancy, liver disease, renal failure, and chemotherapy) were recorded. The causative organisms isolated from the sites of infection, the date of isolation, and the in vitro susceptibilities of the organisms to various antibiotics, including colistin and tigecycline for participants with more than one episode of infection; data were only collected and analyzed for the first episode. These cases were reviewed to identify the received treatment and also their outcomes. Exposure to several risk factors was considered for the analysis only if it had happened before the acquisition of the infection. Prior antibiotic exposure was considered significant for analysis only if (i) that exposure had occurred within 3 months prior to the hospitalization and (ii) the antibiotic was administered for at least 72 hours.

Articles related to our research were identified through a search of the literature in different databases including Embase, PubMed, GoogleScholar, and ScienceDirect. The search was not limited by country of publication, study design, carbapenem resistance mechanism, or patient characteristics. Studies pertaining to clinical trials, systematic reviews, and meta-analysis, and case reports were included. Articles published only in English language not earlier than 2014 were considered for the drafting of this manuscript.

Ethical approval was obtained from KFMC Institutional Review Board and the research was carried out in accordance to the Declaration of Helsinki.

Statistical analysis. Data were described as mean±SD and percentages. Least significant difference will be measured at 95% CI. Intergroup comparison for metric data were carried out by Student's t-test, whereas Chi-square test and odds ratio will be used for nonmetric variables. Binary logistic regression analysis for multivariate comparison and Kaplan-Meir survival analysis predicted final outcome of the study. Statistical Package for Social Sciences (SPSS) for Windows version 20.0 (IBM Corp., Armonk, NY, USA) was used for data analysis.

Results. *Baseline characteristics of the study population.* During the one-year study period, 19 cases with index clinical cultures positive for CRE and 38 matched control patients were identified. However, one matched control was excluded because of data incompleteness. The mean age±SD of cases was recorded to be 43.9±46 months (age range: 2-144 months) and that for controls was 29.2±52.2 months (age range: 0-204 months; p=0.301). There were 56.8% males among the cases and 57.9% males among the controls (p=0.935). Forty-seven percent (n=9) of the cases and 59% (n=22) of the controls were identified at their home. Cases were admitted into either medical (38.9%), surgical (11.1%) or ICU (50%) wards; among controls the rates of admission in the medical ward was 31.4%, surgical ward was 14.3% and ICU ward was 54.3%. These values were not statistically different (p=0.84). It was also noted that CRE was associated with increased comorbidities and prolonged hospitalization (**Table 1**).

Risk factors for colonization or infection with CRE. In a univariate analysis, several variables were associated with colonization or infection with CRE. Compared to matched control patients with CSE, patients with CRE were more likely to have CVC line placement (odds ratio [OR]=9.12; 95% confidence interval [CI]: [0.97-85.77]; p=0.023), have had a recent surgical procedure (OR=3.47; 95% CI: [1.30-9.28]; p=0.006), have undergone any invasive procedures (OR=6.48; 95% CI: [1.98-21.18]; p<0.001), use of prior antibiotics (OR=5.83; 95% CI: [1.38-24.62]; p=0.008) and carbapenem exposure in past 3 months (OR=19.73; 95% CI: [1.09-12.20]; p=0.004; **Table 2**).

Microbiology of CRE isolates and characterization of the infection sites. Among the CRE index cases, the most commonly identified species were *Klebsiella*

Table 1 - Clinical and sociodermographic characteristics of the study participants.

Variables	Case (n=19)	Control (n=37)	*P*-value
Age (Mean±SD), [minimum-maximum]	43.9±46 [2-144]	29.2±52.2 [0-204]	0.304
Gender			≠0.898
Female	8 (42.1)	16 (43.2)	
Male	11 (57.9)	21 (56.8)	
Admission unit			0.894
Intensive care	9 (50.0)	19 (54.3)	
Medical	7 (38.9)	11 (31.4)	
Surgical	2 (11.1)	5 (14.3)	
Source of patient			0.395
Home	9 (47.4)	22 (59.5)	
Hospital	7 (36.8)	13 (35.1)	
Long-term care facility	3 (15.8)	2 (5.4)	
Source of specimen			0.152
Body fluid	9 (47.4)	11 (29.7)	
Urinary tract	8 (42.1)	15 (40.5)	
Bloodstream	2 (10.5)	3 (8.1)	
Skin and soft tissue	0 (0)	8 (21.6)	
Isolated organisms			0.898
Klebsiella pneumonia	9 (47.4)	18 (48.6)	
Escherichia coli	6 (31.6)	13 (35.1)	
Others	4 (21.1)	6 (16.2)	
Duration of prior hospitalization in the past 3 months (days)±SD) [minimum-maximum]	57.2±42.9 [4-90]	28.4±26.1 [2-68]	0.003
Duration of current hospitalization (mean days)±SD) [minimum-maximum]	167±140.8 [5-480]	50.4±73.4 [1-326]	<0.001
Total number of comorbidities	18 (94.7)	33 (89.2)	0.491
Number of procedures	15 (78.9)	28 (75.7)	0.784

Data presented either as number and percentage or mean and standard deviation

pneumoniae (47.4%; n=9) and *Escherichia coli* (31.6%; n=6) while other prevalent species included *Enterobacter sp.*, *Citrobacter sp.*, *Kluyvera Ascorbata* and *Proteus* (21.1%; n=4). Similar microbiological profile was seen in matched controls (*K. pneumoniae* 48.6% [n=18]; *E. coli* 35.1% [n=13] and other species 16.2% [n=6]).

Infections in body fluids (pleural, pericardial, peritoneal, cerebrospinal, biliary, tracheal, and abscess contents) and wound discharge were the most common (47.4% each; n=9), followed by urinary tract (42.1%; n=8), and bloodstream infections (10.5%; n=2). The corresponding outcomes for infection sites among controls were 29.7% (n=11), 40.5% (n=15), 8.1% (n=3), and 21.6% (n=8).

Mortality was not reported in the CRE group while one patient died in the control group.

Discussion. This study was a single-center retrospective study evaluating risk factors for CRE colonization or infection in children over a period of one-year. Central venous catheter line placement, recent surgery, invasive procedure, prior antibiotic use and carbapenem exposure in past 3 months were significant risk factors for CRE colonization or infection.

In response to increasing multidrug-resistance in the last era in many regions of the Middle East region, this case-control study was conducted at KFMC in Riyadh, KSA, to evaluate our understanding of the prevalent risk factors for CRE colonization or infection among the pediatric age group.

Our study showed that receipt of carbapenem antibiotics in the last 3 months was a significant risk factor for colonization or infection with CRE in children. This is consistent with a United States of America multicenter study with pediatric population which revealed a 3-month exposure to antipseudomonal antibiotics is associated with CRE infection or colonization.[14] Some available pediatric case series also support this finding.[20,21] This can likely be attributed to rampant antibiotics use which alters the gastrointestinal flora and results in multidrug resistance. This also highlights the importance of antibiotic stewardship interventions in limiting unnecessary exposure to antibiotics in pediatric cases.

Also, CVC line placement and prior surgery were significantly associated with subsequent CRE colonization or infection, and the association with invasive procedures reached statistical significance. This was in accordance to the study of Chiotos et al.[14] In one case-control study (from KFMC) about CRE infection among adult hospitalized patients, it was reported that the duration of index admission, prior antibiotic use, ICU stay, and invasive procedures were associated with CRE infection and higher mortality rates.[17] Most of the literature reported risk factors, are in line with our present study which mainly included prolonged duration of hospitalization, prior surgery, and use of invasive procedures, especially the placement of the CVC line.

Our results revealed that CRE was associated with prolonged hospitalization; however, there was no mortality reported. A 2015 study reported a 30-day mortality rate to be 50% (23/46) among patients with CRE infections.[22] Similarly, a study from Middle-Western part of Taiwan projected a 40.8% mortality rate.[19] Study conducted at a single medical center of Northern Taiwan during 2012-2013 showed that a single CRE isolate (with an imipenem minimum inhibitory concentration [MIC] ≥16 mg/L) independently

Table 2 - CRE and CSE infections associated risk factors.

Characteristics	CRE (n=19)	CSE (n=37)	Univariate OR [95% CI]	*P*-value
	n (%)			
Comorbid conditions				
Pulmonary disease	3 (15.8)	4 (10.8)	1.56 [0.32-7.48]	0.594
Cardiovascular disease	5(26.3)	7(18.9)	1.52 [0.44-5.28]	0.523
Renal disease	3 (15.8)	10 (27.0)	0.55 [0.14-2.19]	0.346
Liver disease	2 (10.5)	1 (2.7)	4.22 [0.37-48.63]	0.218
Neurologic disease	5 (26.3)	7 (18.9)	1.52 [0.44-5.28]	0.523
Malignancy	3 (15.8)	2 (5.4)	3.23 [0.51-20.52]	0.197
Clinical characteristics				
CVC line placement	4 (21.1)	1 (2.7)	9.12 [0.97-85.77]	0.023
Urinary catheter	3 (15.8)	8 (21.6)	0.72 [0.18-2.95]	0.603
ICU stay	9 (47.4)	20 (54.1)	0.86 [0.33-2.22]	0.635
Surgery	13 (68.4)	11 (29.7)	3.47 [1.30-9.28]	0.006
Mechanical ventilation	5 (26.3)	6 (16.2)	1.81 [0.5-6.5]	0.368
Dialysis	0 (0)	1 (2.7)	0.95 [0.00-54.84]	0.470
Invasive procedure	11 (57.9)	5 (13.5)	6.48 [1.98-21.18]	<0.001
Antibiotic use				
Prior antibiotic use	7 (36.8)	3 (8.1)	5.83 [1.38-24.62]	0.008
Penicillin	11 (57.9)	29 (78.4)	0.38 [0.11-1.26]	0.108
Aminoglycoside	9 (47.4)	14 (37.8)	1.48 [0.48-4.53]	0.492
Carbapenem	6 (31.6)	7 (18.9)	1.98 [0.56-7.04]	0.288
Cephalosporin	3 (15.8)	8 (21.6)	0.68 [0.16-2.93]	0.603
Quinolone	2 (10.5)	0 (0)	8.71 [0.37-203.53]	0.044
Prior Carbapenem exposure in past 3 months	4 (21.1)	0 (.0)	19.73 [1.09-12.203251]	0.004

OR - odds ratios, CRE - carbapenem-resistant enterobacteriaceae, CSE - carbapenem-susceptible enterobacteriaceae, CI - confidence interval, CVC - central venous catheter, ICU - intensive care unit.

predicted 14-day mortality among patients regardless of the isolate was from infection or colonization.[23] A possible explanation for this is that, though some multidrug-resistant organisms have limited therapeutic options, timely and accurate treatment can benefit the patients.

The results of this study also provide a comprehensive description of the microbiology of pediatric CRE isolates. The most commonly identified isolates included *K. pneumonia* (47%), *E. coli* (31%), and others (21%) (*Enterobacter sp.*, *Citrobacter sp.*, *Kluyvera Ascorbata* and *Proteus*). This was in accordance to Khan et al,[16] where it was showed that multidrug-resistant *Enterobacteriaceae* isolates in particular *K. pneumoniae* co-harboring (KPC), NDM-1 and OXA-48 genes are emerging in Western region, KSA. The findings were also supported by a study from the same region which indicated that in KSA, OXA-48 and NDM-1 are the dominant carbapenemases among the *Enterobacteriaceae*.[24]

Study limitations. This study has several potential limitations, (i) the retrospective nature of the study which does not guarantee the accuracy and the completeness of the data captured; however, in order to minimize the shortcomings of the retrospective study nature we limited our cohort to inpatients and urged for a comprehensive medical record review by trained physicians; (ii) the sample size in this study is small and warrants more extensive trials; (iii) the results of this study might not be generalizable to other centers as this study was a single-center study; (iv) infected and colonized patients were combined into one group which precluded the evaluation of risk factors (especially for infection). However, since the gastrointestinal tract is generally colonized with antibiotic resistant organisms before the actual infection takes course, the risk factors are likely to be similar. Also, while collecting the data, it was kept in mind that samples isolated from sterile sites and fluids only were to be included and not any isolate without any clinical evidence for infection.

In conclusion, this observational case-control study demonstrates that prior antibiotic exposure (namely carbapenem), recent surgery and use of invasive procedures (in particular CVC) were significant risk factors for colonization or infection with CRE in pediatric population. Also, infection with CRE is also associated with higher morbidity (prolonged hospitalization) as compared with CSE. This underscores the importance of improved hygiene, barrier nursing, continuing education, optimum use of invasive devices, enhanced surveillance, and antimicrobial stewardship in limiting CRE transmission in healthcare facilities. Also, effective antibiotic therapy has not been formerly

characterized among the pediatric age group where the need for development of novel antimicrobial agents with reliable efficacy against *Multidrug-resistant Gram-negative rods* is a priority.

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