Journal of Infection and Public Health 12 (2019) 465–471

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: http://www.elsevier.com/locate/jiph

Carbapenem-Resistant *Enterobacteriaceae*: An update narrative review from Saudi Arabia

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ARTICLE INFO

Article history:
Received 24 November 2018
Received in revised form 23 March 2019
Accepted 31 March 2019

Keywords:
Carbapenem-resistant *Enterobacteriaceae* (CRE)
Saudi Arabia

ABSTRACT

Carbapenem-Resistant *Enterobacteriaceae* (CRE) is a worldwide urgent public health problem. Similar to other countries, Saudi Arabia is facing the challenge of increasingly reported cases of CRE. The aim of this review is to bring and update on the prevalence, epidemiology and microbiological characteristics of CRE reported from Saudi Arabia.

Contents

Introduction

Carbapenem-Resistant *Enterobacteriaceae* is a serious emerging public health issue [1,2]. Recently, there is a global dissemination of multi-resistant strains of *Enterobacteriaceae* that are usually resistant to cephalosporins producing extended-spectrum β-lactamases (ESBLs) and carbapenemases such as KPC and New Delhi metallo-β-lactamase NDM [3,4]. Currently, treatment options for carbapenem-resistant *Enterobacteriaceae* (CRE) infections are limited to few antibiotics including polymyxins, tigecycline, fosfomycin, and aminoglycosides, alone or in combination with other antibiotics. Combination therapy is associated with better clinical outcome compared to monotherapy. There are different therapeutic strategies such as high-dose prolonged colistin regimen, high-dose infusion of carbapenem (for CRE strains with low MICs (up to 4 μg/ml), and double carbapenem therapy [5]. Other promising treatment options are the recently approved β-lactam/β-lactamases inhibitors, ceftazidime-avibactam (CAZ-AVI), active only against KPC and OXA-48-producing *Enterobacteriaceae* but not metallo-β-lactamase-producing CRE [5]. Recently, in a clinical trial, meropenem-vaborbactam (active against KPC producers) was compared with best available therapy and was associated with decreased mortality and clinical cure [6]. However, a worrisome increase in resistance to these last resource agents is a major health

https://doi.org/10.1016/j.jiph.2019.03.024

challenge [4]. Antibiotic misuse, genetic mobile elements, international travel and ineffective infection control measures are the main predisposing factors for the emergence of resistance [7,8]. Like other Gulf countries, Saudi Arabia is facing the pressure of the spread of multi-resistant strains such as carbapenem resistant *Enterobacteriaceae* (CRE). Travelling within and outside the Gulf region is a major risk factor for transmission of resistant strain of *Enterobacteriaceae* [2]. Those strains were reported from many studies and reports including sporadic cases and outbreaks from various regions of Saudi Arabia [9–26]. The aim of this paper is to review the available data reported on CRE from Saudi Arabia.

Methods

A PubMed search of the literature (from 2013 to 2018) was performed using the terms: 'Enterobacteriaceae', '*Escherichia coli*', '*Klebsiella*', 'Saudi Arabia', 'carbapenem', 'β-lactam', 'β-lactamase', 'resistant', and 'carbapenemase'. Peer-reviewed Saudi journals were searched for published articles. In addition, articles describing CRE infections published in international journals on CRE infections from Saudi Arabia were included.

Epidemiology

Prevalence and regional distribution of CRE reports from Saudi Arabia

Carbapenem resistance is increasingly reported among the species of *Enterobacteriaceae* in Saudi Arabia. Increased prevalence of CRE producers and the dissemination of carbapenem-resistance genes are of particular health concern to the health care providers and the Ministry of health in Saudi Arabia. Most reports related to CRE came from the central part of the country, Riyadh. On the other hand, only few studies describing the susceptibility pattern of *Enterobacteriaceae* against carbapenem with few data on their molecular characteristics were reported from other regions of Saudi Arabia. In a recent study from Madinah, assisting the antibiotic susceptibility of *E. coli* from different clinical sources found all the isolates were susceptible to imipenem [9]. In another recent study, Al-Zahrani and Alasiri studied the molecular characteristics of 54 carbapenem non-susceptible *K. pneumoniae* isolates obtained from clinical specimens in two of the largest hospitals in the Southern province of Saudi Arabia. The major type of carbapenemases found was OXA-48 (81.5%) followed by (NDM) (7.4%) and only one isolate of Verona integrin encoded metallo-β-lactamase (VIM) [10]. In two phenotypic non-molecular studies from Makah [11,12], *K. pneumoniae* positive for carbapenemase production contributed to 48.4% and 38% respectively. Interestingly, the first study in Saudi Arabia and the Gulf region evaluating the digestive tract colonization of CRE and carbapenem-resistant *Pseudomonas aeruginosa* (CRPAE) was reported from Dammam. In this study, the prevalence of gastrointestinal tract colonization of CRE in patients admitted to the intensive care units was as low as 0.5% (1/200) [13]. One of the other interesting studies from Jeddah city reported high incidence of *blaNDM-1*-positive *E. coli* detected in the local wastewater around the Hajj event in October 2013. *BlaNDM-1* was detected at concentrations ranging from 10^4 to 10^5 copies per m^3 of untreated wastewater [14]. Most of the other studies were reported from Riyadh, the central region of Saudi Arabia [15–25]. These included reports describing small outbreaks [15,16], molecular characterization of CRE [17–22], studies highlighting the emergence and persistence of certain carbapenem resistance genetic determents in hospitals [23,16–25] and a matched case-control study [26]. Table 1 describes the regional distribution, number of cases, molecular characteristics of CRE isolates and the main conclusions of almost all reported CRE studies from Saudi Arabia.

Prior hospitalization and travel history

The emergence of NDM and OXA- 48 carbapenemases in Saudi Arabia might be a consequence of the spread of resistant strains of the *Enterobacteriaceae* harboring the resistance determinants imported to the kingdom from different countries because of international travel. The massive people transfer particularly during Hajj seasons between the Kingdom and other countries such as India, where NDM is endemic, might explain the emergence and increasing dissemination of CRE. Foreign travel was documented in 23.3% of CRE infected patients from the Gulf region. India followed by Africa and Pakistan are the most common travel destinations [27]. Moreover, travel involving the Middle East countries such as Saudi Arabia was found to be the source of OXA- 48 carbapenemases in some reports [27]. In fact, the first case of OXA-48-producing carbapenem-resistant *Klebsiella pneumoniae* in the United States was identified in a patient with recent hospitalization in Saudi Arabia [28].

Compared to $bla_{OXA\text{-}48\text{-}like}$ and bla_{VIM}, the bla_{NDM} gene, was identified mostly among isolates obtained from patients with travel history [27].

Prior hospitalization is an important risk factor for CRE acquisition and was recorded in 72.3% of the patients from one study [26]. In addition, multi-resistant pattern to antibiotics other than carbapenem was observed in isolates obtained from patients with travel and prior hospitalization history [26]. However, in 69.8% of the 96 CRE cases collected from the Gulf region, no travel or foreign hospitalization were documented [27]. We can therefore conclude that the Middle East and other Asian countries are considered source of transmission of CRE to Europe and other distant places. Early detection and screening of patients previously hospitalized in the Middle East for CRE, particularly the highly transmissible strains such as the NDM-1 producers, was found to be an effective infection control measure [29].

Types of CRE species

Among the genus *Enterobacteriaceae*, carbapenemases are more prevalent in *K. pneumoniae* isolates, which usually causes hospital acquired infections and outbreaks. Balkhy et al. [15] reported the first nosocomial outbreak involving 23 cases caused by carbapenem-resistant *K. pneumonia*.

In a study from Makah [12], *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter* sp. were among the most commonly isolated species.

Apart from a large study describing the molecular characterization of the β- lactamases in *E. coli* and *K. pneumoniae* from a tertiary care hospital in Riyadh, in which carbapenemase genes were detected more frequently among *K. pneumoniae* (63%) compared with *E. coli* (55%), the total numbers of all reported *Enterobacteriaceae* species from Saudi Arabia is illustrated in Fig. 1.

Risk factors associated with the acquisition, emergence and spread of CRE

Several risk factors are associated with the emergence and spread of CRE in Saudi Arabia. Expectantly, the extensive use of carbapenems as first line management of invasive infections caused by ESBL producing *Enterobacteriaceae* is a major risk factor for the emergence of CRE.

Unrestricted use of antibiotics, lack of effective stewardship programs along with the huge influx of different populations, especially from the Asian continent such as India are considered major risk factors for the emergence and spread of CRE strains in Saudi Arabia and the Gulf region [27]. International travel during the religious occasions and country-to-country transfer of patients har-

Table 1
Publications from Saudi Arabia of CRE reports during the period of 2010 and 2018.

Number	Author and Year of publication	Region of study	Type of publication	Number of cases	Molecular analysis carbapenemase type	Type of species	Outcome and conclusions
1	El Ghany M[21] (2018)	*Riyadh*	Research article	Ten	NDM-1 and 5, and OXA-181 in all carbapenem-resistant UPEC strains	*MDR-uropathogenic Escherichia coli isolates*	data identified an emerging public health concern and highlight the need to use comprehensive approaches to detect the structure of MDR *E. coli* populations associated with CA-UTIs in KSA.
2	Al-Zahrani IA,Alasiri BA.[10] (2018)	*from 2 hospitals in the Southern (Asir) province*	Research article	49	OXA-48, 81.5% (n=44) and New Delhi metallo-s-lactamas (NDM) 7.4% (n=4) of isolates while Verona integronencoded metallo-β-lactamase (VIM) only in one isolate.	*K. pneumoniae*	increasing age and intensive care unit admission were associated with CRKP isolation. No producers of blaIMP and blaKPC were detected among all tested isolates
3	Zaman T et al.[20] (2018)	*Riyadh*	Research article	71 isolates	OXA-48 gene detected in 48/71(67.6%) isolates. NDM-1 alone in 9/71 (12.7%) isolates	*Klebsiella pneumoniae*	A polyclonal OXA-48 gene was the most common carbapenemase followed by NDM-1.Coproduction of OXA-48 and NDM-1 in 6/71 (8.5%)
4	Al-Agamy MH. et al.[17] (2018)	*Riyadh*	Research article	31 isolates	blaOXA-48-type and blaNDM.	21 K. pneumoniae and 10 E. coli)	The predominant carbapen-emases in the isolates that had carbapenem MIC ≤4 _g/ml and MIC≥12 _g/ml were blaOXA-48-type and blaNDM-type respectively.
5	Fawzia E. Alotaibi[23] et al. (2017)	*Riyadh*	Research Article	Nine patients	blaNDM and one as OXA-48.	*Klebseilla pneumoniae* (5),*Escherichia coli*(3), and one Enterobacter aerogenes (1).	Four died
6	Faidah HS [12] (2017)	Makah western part of SA	Research article	515 isolates	NO	*Klebsiella pneumoniae*(459) *Escherichia coli* (56)	Majority of resistant strains were isolated from ICU, followed by surgery unit
7	Mantilla-Calderon D[14] (2016)	*Jeddah*	Epidemiological study	–	*blaNDM-1* was detected at concentrations from $10^4$to 10^5copies /$m^3$of untreated wastewater	*Escherichia coli*	the first report of a *blaNDM-1*-positive*E. coli* isolated from a non-nosocomial environment in Saudi Arabia. high incidence of *blaNDM-1 blaNDM-1* in the local wastewater.
8	M. A. Garbati[26] et al. (2016)	*Riyadh*	Research Article Matched Case-Control Study	29 cases 58 controls	No	*Klebsiella pneumoniae (15).*	Nine of the cases died compared with 7 of the controls. Infections due to CRE resulted in a significantly increased mortality. Combination antibiotic therapy was associated with reduced mortality.
9	B. Abdalhamid[13] (2016)	Dammam, Eastern part of SA	Research Article	One CRE (200 nonduplicated rectal swab specimens screened at ICU admission)	CTX-M-15	*Klebsiella pneumoniae*	digestive tract colonization of CRE
10	Khan MA, Faiz A[11]. (2016)	Makah	Research article	31 isolates	No	Of 31 *K. pneumoniae* isolates, 15 were found positive for carbapenemase.	the first report from Makkah reporting carbapenamse producing K.pneumoniae. Of 12% potential carbapenemase producing K.pneumoniae, 48.4% were found positive for carbapenemase production.
11	Yezli S, Shibl AM and Memish ZA [22] (2015)	Riyadh	Review article (from 1990 to 2014)		OXA-48 and NDM-1.	Primarily among *K. pneumoniae*.	Carbapenem resistance is mainly due to OXA-48 and NDM-1.

Table 1 (*Continued*)

Number	Author and Year of publication	Region of study	Type of publication	Number of cases	Molecular analysis carbapenemase type	Type of species	Outcome and conclusions
12	Memish ZA e tal. [19] (2015)	Riyadh	Research article	Unknown	OXA-48 and NDM-1 are the dominant carbapenemases among Enterobacteriaceae with low prevalence of VIM.	*K. pneumoniae Enterobacter*	No KPC or IMP genes were detected.the first report of OXA-48, NDM-1, and VIM-4 enzymes in*Enterobacter*from the Kingdom.
13	Zowawi et al[32]. (2014)	Riyadh	Research article	62 isolates	35 isolates (34 *K. pneumoniae* and 1 *E. coliE. coli*) were OXA-48-type and 16 (15 *K. pneumoniae K. pneumoniae* and 1 *E. coliE. coli*) were NDM-type. Six isolates coproduce NDM type and OXA-48 type,	53 were *K. pneumoniae*, and 9 were*E. coli*	Multiple clones were detected with seven clusters of clonally related Klebsiella pneumoniae. Awareness of CRE in GCC countries is important in controlling the spread of CRE in the Middle East
14	Zaman TU e tal. [16] (2014)	Riyadh	Research article (Outbreak)	23 isolates	OXA-48 gene, CTX-M and SHV genes were detected in all isolates. Disruption of the Omp-36 gene detected in four isolates	*K. pneumoniae*	ST29, a clone not reported from this region before, was the major clone responsible. KPC, NDM, OXA-A, -B, -C, VIM, and IMP genes were absent
15	Al-Agamy MH. et al.[17] (2013)		Research article	9 isolates	OXA-48 and NDM (77.7 % and 22.2%). None of the isolates harboured KPC, VIM or IMP, but all carried the SHV gene.	*K. pneumoniae*	
16	Shibl et al[24]. (2013)	Riyadh	Research article	60 isolates	47 carried the OXA-48 gene, NDM-1 in (12) and VIM in (1) of the isolates.	*K. pneumoniae*	Multidrug-resistant K. pneumoniae isolates harboring blaOXA-48, blaNDM, and colistin resistance are emerging in Saudi Arabia
17	Marie et al[18]. (2013)	Riyadh	Research article	2337	NDM in 55% of the isolates IMP and VIM in, respectively, 9 and 7% of the isolates,	E. coli ; 1779 (53%) K. pneumonia ; 558 (63%)	KPC and OXA-48 was not detected in any of the isolates. carbapenemase more frequently in K. pneumoniae isolates,
18	Balkhy HH et al.[15] (2012)	Riyadh	Research article (Outbreak)	Eight patients in the adult (ICU).	Not available	*K. pneumoniae*	The first described carbapenem-resistant *Klebsiella pneumoniae* CRKP outbreak in a tertiary care hospital. 38% died during hospitalization
19	Al-Qadheeb et al.[31] (2010)	Riyadh	Case report	One	The first case of KPC-producing K. pneumoniae in the Kingdom,	*K. pneumoniae* isolated from a 75-year-old immune-compromised patient. The strain was MDR (including colistin),	Evolved in the same patient from susceptible to resistant to tigecycline during the course of treatment.

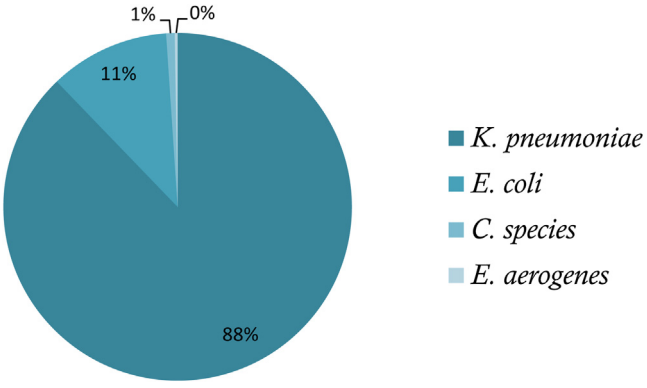

Fig. 1. Prevalence of CRE species reported from Saudi Arabia.

boring resistant strains are well-known risk factors for the spread of multi-resistant organisms like CRE [27]. Other potential and specific risk factors were reported from Saudi Arabia, in a matched case-control study involving 29 cases and 58 controls of Saudi hospitalized patients, the presence of comorbidities, prior uses of carbapenem, the duration of hospitalization and invasive procedures were significantly associated with CRE infections. In addition, renal disease requiring dialysis was independently associated with CRE infection [26].

Classification and mechanisms of resistance with relevance to Saudi Arabia

The acquisition of easily transmissible genes encoding carbapenemases is the main mechanism causing carbapenem resistance in *Enterobacteriaceae*. Based on the amino acid sequence homology, three classes of carbapenemases were identified. Classes

A and D are serine carbapenemases, while class B carbapenemases are metallo-β-lactamases (MBL) [30]. Class A carbapenemases include the most prevalent and clinically significant KPC (*Klebsiella pneumoniae* carbapenemase), and less commonly the SME, IMI and GES. On the other hand, Class B carbapenemases which are usually inhibited by ethylenediaminetetraacetic (EDTA), include IMP, VIM, GIM and NDM-1 [30].

NDM-1is a relatively new metallo-β-lactamase originated in 2008 from India and spreads rapidly through international travel to many countries including Saudi Arabia [10,14,17–25]. Class D carbapenemases was first identified in *Acinetobacter baumannii* and *Pseudomonas Aeruginosa.*

Carbapenem-resistant *Klebsiella pneumoniae* producing OXA-48 enzyme encoded by the bla_{OXA-48} gene was reported in many studies from Saudi Arabia [10,16–25]. *Klebsiella pneumonia,* carrying the OXA-48 gene and showing variations in outer membrane protein 36, was associated with an outbreak in a tertiary care hospital in Riyadh caused by multi-drug carbapenem-resistant [16].

Molecular characterization of CRE reported from Saudi Arabia

Up to the date of writing this review, NDM and OXA-48 enzymes are the major carbapenemases causing resistance in *Enterobacteriaceae* reported from the Gulf region and Saudi Arabia [10,14,16–25]. Other carbapenemases and isolates possessing *K pneumoniae* carbapenemase (KPC) enzymes, such as KPC-1, KPC-2 and KPC-3, are rare in Saudi Arabia and other Gulf countries. The first KPC-producing *K pneumoniae* isolate was described in an elderly Saudi male who acquired the resistant strain after prolonged hospitalization in the critical care unit [31]. In addition, of 200 carbapenem non-susceptible *Enterobacteriaceae* isolates collected in 16 hospitals of the Gulf regions including Saudi Arabia, no KPC-isolates were detected [27]. Referred to the same study, the most frequently identified carbapenemase gene was bla_{NDM-1} followed by $bla_{OXA-48-like}$ gene. Three major clones of bla_{NDM-1} carrying *Klebsiella pneumoniae* of ST152 were detected in 22 isolates obtained from Saudi Arabia [27].

Interestingly, more than half of NDM and OXA-48-like isolates were not linked to foreign exposure, travel or prior hospitalization [27]. Similar data describing the molecular characteristics and mechanisms of resistance of CRE in hospitals from the Gulf region was reported [27,32–35].

More important, those multi-resistant strains harboring plasmid encoded genes are associated with outbreaks and endmicity. Co-expression of OXA- 48 and CTX-M-15 ESBLs type was found in *K. pneumoniae* isolates in an outbreak in a tertiary care hospital in Riyadh [16].

Zowawi et al. [32] determined The molecular characterization of CRE in hospitals in the countries of the Gulf region. Among the 45 carbapenemase producers identified, the most common carbapenemases were of the OXA-48 (35 isolates) and NDM (16 isolates) types; six isolates were found to coproduce the OXA-48 and NDM types. No KPC-type, VIM-type, or IMP-type producers were detected. For 17 isolates, no carbapenemase activity or carbapenemase genes were identified. Other mechanisms of resistance such as porin loss and ESBL production associated with decreased permeability of the outer membrane were suggested [32]. Similar findings were found in another study [20], in which OXA-48 gene alone was the most common carbapenemase detected in (67.6%) of *Klebsiella pneumoniae* isolates followed by NDM-1 alone in (12.7%) of the isolates.

The presence of carbapenem-resistant uropathogenic *E. coli* in the community was investigated as well. NDM-1 and 5, and OXA-181 were identified in ten carbapenem-resistant *E. coli* strains causing urinary tract infection [21].

In conclusion, The Gulf region reported a high rate of extended-spectrum-β-lactamase (ESBL) and increasingly reported cases of CRE. The most prevalent genotypes are CTX-M-15, OXA-48, and NDM-1. However, less common enzymes were identified including PER-7, GES-11, and PME-1. [27].

Treatment and outcomes of CRE infection

In a metaanalysis of nine studies published before 2012 on the deaths attributable to CRE infections revealed that carbapenem resistance was independently associated with 26%–44% of deaths in seven studies caused mainly by *Klebsiella pneumoniae* [36].

PubMed searches identify only few published clinical studies describing the clinical characteristics and outcomes of patients infected with CRE in Saudi Arabia. Four of nine patients reported from Saudi Arabia died due to septic shock refractory to treatment [23]. Similarly, nine of 29 patients (31%) with CRE infection died compared with 7/58 (12.1%) of their matched controls [26]. The mortality was associated with old age, comorbidities, prior use of carbapenem, ICU admission, mechanical ventilation and central line insertion. The author concluded that combination antibiotic therapy was associated with reduced mortality [26]. On the other hand, there are no clinical studies with strong evidence supporting combination therapies compared with colistin monotherapy against CRE invasive infections. However, in a systematic review of 20 studies, bacteremia representing the majority of infections in 8 of them, mortality was the lowest for tigecycline-gentamicin combination (50%) compared with tigecycline-colistin, and carbapenem-colistin combinations (64% and 67% respectively) [37]. (In addition, only Three studies reported significantly lower mortality using combination therapies compared with monotherapy in critically ill patients with bacteremia. Ceftazidime-avibactam is a recent lactam–lactamase inhibitor combination approved to treat serious infections caused by carbapenem-resistant organisms. Unfortunately, plasmid-borne mutations (bla_{KPC-3}) in three *K. pneumoniae* isolates emerged in three patients after ceftazidime-avibactam treatment for 10 to 19 days. (Emergence of Ceftazidime-Avibactam Resistance Due to Plasmid-Borne *bla*KPC-3

Mutations during Treatment of Carbapenem-Resistant *Klebsiella pneumoniae* Infections. [38]. Other treatment options, other than polymyxin and Aminoglycoside, included fosfomycin, tigecycline, minocycline and the more recent combination therapies such as meropenem-vaborbactam, imipenem-relebactam, plazomicin, and Eravacycline [39]

In conclusion, CRE infection is a serious clinical challenge associated with high mortality due to difficult treatment of usually pan-resistant strains and lack of optimum therapeutic regimen.

Public health concerns

There are several public health concerns related to the spread and acquisition of CRE in Saudi Arabia. First: the massive importation of people during Hajj seasons and the transfer of patients for health care purposes. Second; the non-restricted use of antibiotics. Third; the presence of poor and inadequate waste disposal system in the western province of Saudi Arabia with the possibility of transmission of intestinal CRE strains to the sources of drinking water. This possibility arises due to the high incidence of *blaNDM-1* found in the local wastewater of Jeddah city [14]. Fourth and final issue is the increasing prevalence of clones of carbapenem resistant genes among species of the *Enterobacteriaceae* associated with community-acquired infections such as urinary tract infection (UTI). These clones include the *bla*NDM-1 isolates related to intestinal strains encoding genes such as *bla*NDM-5 and *bla*OXA-181 [21].

Conclusion

Carbapenem-resistant *Enterobacteriaceae* (CRE) including the highly transmissible plasmid mediated carbapenemase-producing *Enterobacteriaceae* (CPE) is a growing threat and serious health concern spreading in Saudi Arabia and worldwide. Due to the high mortality related to CRE infection, strict infection control practices particularly among hospitalized patients in high dependency units combined with early and accurate detection of CRE strains and appropriate managements of patients are essential preventive measures. Colistin, tigecycline, and combination of carbapenem-containing regimen are the mainstay of the current treatment options. However, new antimicrobials such as avibactam, plazomicin, or siderophore cephalosporins are promising and the need for new and effective anti-CRE therapies is urgent.

Funding

No funding sources.

Competing interests

None declared.

Ethical approval

Not required.

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