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Emergence of carbapenem-resistant *Enterobacteriaceae* isolated from patients in a university hospital in Saudi Arabia. Epidemiology, clinical profiles and outcomes

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ABSTRACT

Carbapenemase-producing *Enterobacteriaceae* have been steadily spreading worldwide during the last decade. Nine patients were identified prospectively and were followed during their hospitalization course to identify the epidemiology, clinical profiles and outcomes. These patients had one or more cultures positive for a CRE isolate, contributing to a total of eleven positive cultures from various sites without including duplicates of isolates obtained from the same site. Isolates from these patients included five *Klebseilla pneumoniae*, three *Escherichia coli*, and one *Enterobacter aerogenes*. Five isolates were grown from blood cultures, three from wound cultures, one from urine cultures, one from respiratory cultures and one from an abscess collection. Five survived the hospital course. The other five patients died due to severe sepsis, septic shock or multi-organ failure. Of the nine isolates of CRE identified for which molecular analysis were available, four *K. pneumonia* were confirmed as blaNDM and one as OXA-48. For the purpose of controlling the spread of CRE in our institution, we recommend considering active surveillance cultures and screening patients transferred from other hospitals or coming from highly endemic settings at admission for these organisms.

Introduction

Carbapenemase-producing *Enterobacteriaceae* (CRE) including the non-fermenters, has caused a major public health concern all over the world [1,2]. International travel, migration, and contaminated food products have been responsible for the spread of these microorganisms to several countries beyond their origin [3,4]. The extensive use of carbapenems in hospital settings, particularly when the infection control practices are inadequate, has contributed to an increased prevalence of carbapenem resistant *Enterobacteriaceae* (CRE) [5]. Spread of infection is mediated by the potential of these organisms for widespread transmission via mobile genetic elements [5,6]. Spread of *Escherichia coli* acquiring the plasmid-borne carbapenemase has been reported [7]. Carbapenemase-producing Gram-negatives can cause serious nosocomial infections particularly in critically ill patients, and are associated with increased mortality rate (ranged from 44% to 70%, for bacteremia was 50%) and sometimes outbreaks [8–12]. In addition, spread of CRE into the community is a major concern. They usually demonstrate resistant to other commonly used antibiotics such as quinolones and aminoglycosides [13–15]. Recently, pan-resistance to all antimicrobial agents including colistin and tigecycline has also been reported [16]. The limited therapeutic options available to treat patients infected with CRE have made these organisms of epidemiologic and diagnostic importance. Until date, no clear data on effective therapy of infections caused by CRE are available. Combination treatment of two or more antibiotics was shown to be more effective than monotherapy for infections caused by CRE [17,18]. Active surveillance to detect colonized patients, implementation of strict infection control measures and contact precautions, are important ways of preventing the introduction and transmission of these bacteria in healthcare settings. Increasing prevalence of CRE isolates including CRE outbreaks in

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some hospitals is a growing problem in Saudi Arabia [19,20,21,22]. The main purpose of this case series is to evaluate and describe the important clinical and epidemiological features of CRE infections in our institution.

Methods

Data collection

A prospective chart review was conducted using the hospital (King Khalid University Hospital) and laboratory patient's information (computerized data or documents made by physicians) during the period from, October 2011 and October 2013. The hospital epidemiologic database was used to identify admitted patients with blood, respiratory, urine, or wound cultures positive for CRE. The inclusion criteria included age 18 years and older and signs and symptoms of infection. Patients with colonization without evidence of infection were excluded. The implication of CRE as a colonizer or true infection was unclear in some patients.

Microbiology identification and susceptibility testing

In this study, All *Enterobacteriaceae* isolates was defined as carbapenem nonsusceptible (MIC, $\geq$1 μg/ml) based on the CLSI 2016 guidelines [23]. The identification of isolates as well as the antibiotics susceptibility testing was carried out on the automated system Vitek 2 (bioMérieux, Marcy l'Etoile, France). Tested antibiotics included extended-spectrum cephalosporins (ceftriaxone, ceftazidime, and cefepime), carbapenems (ertapenem, imipenem, and meropenem), aminoglycosides (amikacin and gentamicin), quinolones (ciprofloxacin), tigecycline, and colistin. Nonduplicate carbapenem-nonsusceptible isolates, and resistant to all third-generation cephalosporins were selected for the investigation. The modified Hodge test (MHT) and the MBL E-test were performed as confirmatory test for some selected isolates. Four of the nine Carbapenem-nonsusceptible isolates for which kits were available, were PCR tested using primers targeting blaNDM-1, blaIMP, blaVIM, blaGES, blaKPC, and blaOXA-48.

Results

Nine patients infected with CRE organisms were identified. These patients had one or more cultures positive for a CRE isolate during their hospital course, contributing to a total of eleven positive cultures from various sites without counting duplicates of isolates obtained from the same site. Isolates from these patients included five *Klebseilla pneumoniae*, three *E. coli*, and one *Enterobacter aerogenes*. Five isolates were obtained from blood cultures, three from wound cultures, one from urine cultures, one from respiratory cultures and one from an abscess collection. Of the nine isolates of CRE identified, three *K. pneumonia* were confirmed by molecular analysis as *blaNDM-1* and one *K. pneumonia* isolated from blood was identified as *bla*OXA-48. Molecular analysis was not available for five isolates. Table 1 summarizes the key comorbid conditions, isolates, treatment, and outcomes. The full susceptibility profile, as determined by the Clinical and Laboratory Standards Institute (CLSI) E test method is shown in Table 2. Comorbid conditions, diabetes mellitus, malignancy, chronic kidney disease, catheter placement, surgical procedures, and prior hospitalization within 90 days were identified among our patients. Five patients had diabetes mellitus, three patients had renal insufficiency, two had a history of a malignancy, five had ischemic heart disease/hypertension or rheumatic heart disease, and one had renal transplant. Six patients had either prior ICU admission or spent time in the intensive care during their hospitalization course. The other

Table 1
Clinical characteristics and laboratory findings of the nine CRE infected patients.

Case no.	Sex	Age	Clinical features	Underlying disease	Organism	Site	Treatment	Outcome
1	M	77	Urosepsis, Fever, dysuria, & decrease level of consciousness	IHD, HPT, Post prostatectomy, CA bladder	*Klebsiella pneumonia*	Urine	Gentamicin, imipenem, ceftriaxone.	Discharged
2	M	75	Septic shock Fever, hypotension	DM, IHD, bilateral DVT	*E. coli*	Blood	Meropenem + gentamicin	Died
3	F	50	Septic shock Bedsores, VAP, multi-organ failure	DM, chronic kidney disease, rheumatic heart disease with severe stenosis	*K. pneumonia*	Blood & tracheal aspirate.	Colistin, meropenem, vancomycin, amikacin tigecycline and caspofungen	Died
4	M	74	Cardiac arrest Septic shock Infected bed sore	Bedridden, HTN, DM	*E. coli*	Blood, wound	Piperacillin-tazobactam & vancomycin	Died
5	M	50	Acute pancreatitis with multi-organ failure Refractory septic shock	Alcoholism	*K. pneumonia*	Blood.	Colistin + meropenem	Died
6	F	35	Diabetic foot infection, leg amputation.	DM, renal failure	*K. pneumonia*	Wound.	Ampicillin, gentamicin, vancomycin and caspofungen	Discharged
7	M	38	Fever, chills, diarrhea and abdominal pain.	Renal transplant on cycloserine & steroid.	*K. pneumonia*	Blood.	Colistin + meropenem	Discharged
8	M	65	Recurrent left iliopsoas abscess	Recto-sigmoid adenocarcinoma, chronic kidney disease, HTN	*E. coli*	abscess	Imipenem Tigecycline	Improved
9			Infected bedsore complicated with osteomyelitis	DM, bedridden & dementia, right femoral fracture.	*Enterobacter aerogenes*	Wound	Piperacillin-tazobactam & wound dressing.	Chronic infection

DM: diabetes. IHD: iscemic heart disease. HTN: hypertension. DVT: deep vein thrombosis. CA: cancer.

Table 2
Antimicrobial susceptibility of the nine CRE isolates to the tested antimicrobial agents.

Antibiotics[a]	Species[b]								
	KPN	EC	KPN[c]	EC	KPN	KPN	KPN	EC	ECL
AMK	>256	0.5	32	256	0.5	256	256	0.5	<16
CTX	256	64	128	32	16	32	>256	>256	>8
FEP	256	16	32	64	16	128	>256	32	16
CAZ	128	64	32	>256	128	256	>64	64	>16
CIP	>32	16	0.25	32	16	>32	32	16	<1
POL	0.125	0.38	8	0.047	0.094	0.25	0.5	0.25	0.25
GM	>32	32	0.5	32	32	0.5	>32	0.5	<4
TZP	256	64	256	64	16	64	256	64	>64
TGC	2	0.25	2	2	2	0.12	1	0.25	1.5
IPM	32	6	8	32	3	6	32	3	32
MEP	32	8	12	32	1	8	32	32	12
Carbapenemase genes	blaNDM-1	NA	blaNDM-1	NA	blaOXA-48	NA	blaNDM-1	NA	NA

AMK: amikacin; CTX: cefotaxime; FEP: cefepime; CAZ: ceftazidime; CIP: ciprofloxacin; POL: polymixin B; GM: gentamicin; TZP: pipracillin-tazobactam; TGC: tigecycline; IPM: imipenem; MEP: imipenem.

[a] Minimum inhibitory concentration MIC (μg/ml).

[b] EC, *Escherichia coli*; ECL, *Enterobacter cloacae*; KPN, *Klebsiella pneumoniae*.

[c] The patient had a repeated infection with a resistant strain to colistin.

five patients died due to severe sepsis, septic shock and multi-organ failure. Six patients had been hospitalized within 90 days or transferred from other hospitals prior to their current admission and received antibiotics previously. Four patients had surgical procedure within 90 days of the onset of infection. Infectious diseases physicians were consulted for treatment recommendations in all nine cases presented in this series. Except for one isolate which was colistin resistant (8 μg/ml), the CRE isolates identified in these nine patients were susceptible to colistin but showed variable susceptibilities to aminoglycosides (MIC range, 0.5 to >256 μg/ml) and fluoroquinolones (MIC range, 0.25 to >32 μg/ml). All the carbapenemase producers were highly resistant to the third and fourth generation cephalosporin, including piperacillin-tazobactam (MIC range, 8 to >256 μg/ml). Tigecycline was the only antimicrobial agent active against all isolates (MICs, 0.12–2 μg/ml). Prior treatment with carbapenems were documented in three patients. Four patients were given aminoglycosides, three were given colistin, and none were given fluoroquinolones. Six patients received combination treatment including carbapenem. Only two patients received tigecycline, one for septicemia and ventilator associated pneumonia caused by *K. pneumonia* (died) and the other for psoas abscess caused by *E. coli* (discharged). Interestingly, one patient had a history of surgery for hip fracture in India 3 months prior to his presentation and another patient was transferred from Egypt. Carbapenemase genes were detected in 4 of the 9 clinical isolates.

Case 1

A 77 years old male from Najran (south region of Saudi Arabia), known to have hypertension, ischemic heart disease, benign prostatic hyperplasia partially (resected 3 years ago), and long standing rheumatoid arthritis treated with steroids. He had multiple admissions due to urinary tract infection and urinary retention with urosepsis. He was presented to the emergency two months prior to admission with upper gastro intestinal bleeding (melena). He had a Foley catheter put in for urinary obstruction associated with hematuria and generalized joint pain post prostatectomy. Urine culture showed *Candida albicans* which was treated with fluconazole for 7 days. Repeated urine culture showed high WBCs and bacteria treated with ciprofloxacin. He was admitted electively for endoscopy and further evaluation. He was physically well and afebrile (T 36 °C) (BP 90/46 mm HG). Lab investigation showed very low hemoglobin, and hypocalcemia. After 7 days, urine culture showed >100,000 cfu/ml *Klebsiella pneumonia* which was resistant to all antibiotics including carbapenems and sensitive only to colistin. The patient was started on empirical ceftriaxone (1 g IV daily) and imipenem (500 mg IV Q6 hours) for 7 days. He also received two doses of gentamicin. He was discharged home after repeating the urine culture which showed negative result.

Case 2

A 75 years old male came to the emergency room on May 15, 2015, in septic shock presenting with high-grade fever and low blood pressure. He is known to have advanced bladder cancer (stage IV), with metastasis requiring surgery, chemotherapy and radiotherapy. He also had diabetes mellitus, ischemic heart disease, bilateral deep vein thrombosis (DVT) on medication. His previous records revealed multiple admissions due to urinary tract infections with positive blood culture which grew *E. coli*, ESBL producer treated with meropenem (1 g IV q 8 h for 14 days). The patient was discharged after completing 2 months in the intensive care (ICU) when blood culture showed negative result. Two weeks later (current admission), he came back to the emergency room with severe sepsis, septic shock and UTI. His blood pressure was low and he had lower limb swelling, high WBCs and low hemoglobin. He received one unit of packed blood. Blood and urine cultures showed *E. coli* (>100,000 cfu/ml), ESBL and carbapenemase producer. The patient was admitted to the ICU and started on gentamicin and meropenem for 14 days. He also received one dose of Ceftriaxone. His clinical condition continued to deteriorate and he had episodes of confusion and loss of consciousness due to severe sepsis. He was managed aggressively in the ICU and was given many regimens of antimicrobial agents but he continued to deteriorate until he died on August 16, 2015. Blood and urine cultures were positive for *E. coli*, ESBL and carbapenemase producer, sensitive only to colistin, amikacin and tigecycline.

Case 3

A 50 years old woman was transferred to our intensive care unit from a private hospital on November 11, 2014 in septic shock. She had diabetes mellitus, chronic kidney disease on dialysis, and rheumatic heart disease with severe mitral and aortic stenosis. The patient presented two months ago to a private hospital with shortness of breath, repeated cardiac arrest, intubated and stayed in the ICU for two months. She developed bedsores in her back with large abscess requiring incision and drainage. During hospitalization, she had ventilator-associated pneumonia due to *Stenotrophomonas multophilia* and blood stream infection with a multidrug resis-

tant *Acinetobacter spp.* for which she received multiple antibiotics including vancomycin, linezolid, imepenem, tigecycline and ceftazidime. On referral to our hospital for further ICU care, the patient was sedated, hemodynamically unstable with low level of consciousness (10/15), and signs of septic shock (hypotension (123/69 mm HG), hypothermia (36 °C) bradycardia (52 beats/min). The patient was intubated (oxygen requirement of 35% pressure support) and on low dose vasopressors dose, dopamine, noradrenaline, hydrocortisone and insulin infusion. She has central venous catheter, nasogastric tube, and folly's catheter. Both pupil were dilated (5 mm) with sluggish reaction to light. Examination of the back showed a big (7 × 8 cm) infrascapular abscess. Chest examination revealed bilateral basal crepitation. Lab investigation showed hemoglobin of 9.4, WBCs 6.9 cells/mm^3, platelets 33, Na 133, K 308, INR 21, urea 31, creatinine 167, and albumin 27. She was started empirically on colistin (3IU IV Q12hr), meropenem (Igm IV Q12Hr), vancomycin (500 mg IV OD) and amikacin (500 mg IVOD). Two days after admission, caspofungin (50 mg OD) was given and Trans-esophageal echocardiogram (TEE) was done to exclude infective endocarditis, which was ruled out as no vegetation was seen. Over the next few days, she was stable and vancomycin was suspended. Two weeks after admission, septic work up from two consecutive blood cultures (from central line and dialysis line) showed blood stream infection with *K. pneumoniae* resistant to all antibiotic including carbapenem except colistin. The same isolate was grown from the tracheal aspirate. The isolate was shown to be a New-Delhi Metallo-beta-lactamase producer (NDM). Accordingly, she was started on colistin, tigecycline and the central line was changed. Repeated blood cultures were negative. On the next two days, the patient showed mild improvement in her clinical condition. After two weeks while on treatment, she developed a breakthrough fever and septic workup was done. *Candida glabrata* and multi-drug resistant *Pseudomonas aeroginosa* were isolated from the blood. Tigecycline was discontinued and all the lines were changed. A repeated echocardiogram and ultrasound of abdomen were done. Ophthalmology team was consulted for suspected disseminated candidemia. The patient clinically improved and became afebrile. During her hospitalization stay, she developed persistent watery diarrhea for which colonoscopy and *Clostridium difficile* toxin antigen detection test were negative. Repeated blood culture grew carpapenem resistant *K. pneumonia* (CRE) resistant to all antimicrobial agents including colistin. The patient developed hyperkalemia (6.1), severe metabolic acidosis and deteriorated renal function, acute adult respiratory distress syndrome (ARDS) and her blood pressure dropped to 80/40 mm HG. She had multiorgan failure due to refractory septic shock and was arrested and died after 2 month of hospitalization. Laboratory testing revealed, meropenem and imipenem MICs (>32 μg/ml) as determined by E-test. The isolate was confirmed as a carbapenemase producer by the modified Hodge test of the CLSI. PCR and sequencing confirmed the presence of *bla*NDM-1, and plasmid analysis revealed this was carried on a 98 kb. Gene-expert analysis using *Xba*I was carried out on the two *K. pneumonia* isolates from the patient (the carbapenem-resistant *K. pneumoniae* from the blood and tracheal aspirate)

Case 4

A 74 years old bed ridden male known to have diabetes mellitus, hypertension, old ischemic stroke, and infected bedsores. He presented to the emergency room in cardiac arrest on December 20, 2015. Cardiopulmonary resuscitation (CPR) was started immediately with high flow of O_2 (100%), inotropes, antibiotics and blood volume monitoring. He was diagnosed to have urinary tract infection (UTI) on a private clinic one week prior to his presentation. He had a history of surgery for hip fracture in India 3 months ago. The patient is hemodynamically unstable, afebrile, on high dose vasopressor (noradrenaline IVI 60 mcg/min). Lab investigation showed WBCs 30 cells/mm^3, Hb 75, lactic acid 14, creatinine 170, PH 6.9. Coagulation profile showed a picture of disseminated intravascular coagulation (DIC), explained by (high PTT 70, low platelets count 105 and low fibrinogen 1.54), secondary to septicemia. He was given 2 unites of PRBCs and Vitamin K stat dose. He was started empirically on vancomycin and tazocin. During his ICU stay, he developed deep vein thrombosis (DVT) and acute lower limb ischemia (bluish discoloration, swelling and gangrene) with bilateral iatrogenic emphysema. Heparin was started. The patient's condition was complicated with acute renal failure (DIC) and septic shock due to aspiration pneumonia and UTI. He was arrested and died on the second day of admission due to multiple comorbidities. Two days after his death, blood culture grew *E. coli*, ESBL producer, multidrug-resistant and carbapenem resistant and the tracheal aspirate culture grew heavy growth of *K. pneumonia* resistant to all antibiotics except carbapenem and colistin, and moderate growth of multi-resistant *Acinetobacter baumannii*. Wound culture (deep infected bedsore) also showed heavy growth of *E. coli*, ESBL producer, carbapenem resistant and few growth of *Pseudomonas aeruginosa*.

Case 5

A 53-years-old alcoholic male was transferred to our intensive care unit from a private hospital in Egypt on October 18, 2015 in a state of confusion, disturbed conscious level and diffuse abdominal pain. He was diagnosed as acute pancreatitis with multiple organ failure. He presented with severe sepsis secondary to community-acquired pneumonia (CAP) and pancreatitis. He was admitted to the Intensive Care Unit (ICU) because of acute respiratory distress syndrome (ARDS). He was intubated in septic shock and required inotropes. During transfer, the patient had one attack of generalized tonic-clonic seizure. He was immediately started on Keppra (500 mg BID). The patient was sedated, hemodynamically unstable and unconscious (coma scale: 6/15) (BP 134/68 mm HG) (hyperthermia 39 °C) (tachycardia 127 beats/min). Laboratory investigation showed: hemoglobin 12.7 g/L, WBCs 18 109/L, platelets 332 109/L, albumin 25 g/L, creatinine 160 mcmol/L, Troponin-I 0.37 mcg/L. He was started empirically on tazocin. During his stay in the ICU, he had spikes of high temperature (40 °C). Blood culture grew gram negative bacilli which was identified as *K. pneumonia* (CRKP, MDRO), resistant to Tazocin, Imipenem and Ciprofloxacin and sensitive to Meropenem and Amikacin. Tazocin was suspended and Meropenem combined with Amikacin were started. Sputum culture grew *Acinetobacter spp*. (MDRO), sensitive to Colistin. The patient was screened for MERS CoV and H1N1, which were negative but he was still symptomatic, and the infection control team recommended continuing airborne and contact isolation. The patient condition became worse, as he had aspiration pneumonia post seizure attack. He also developed new infiltration on CXR with more requirements for inotropic support. He was started on Colistin, Vancomycin and Caspofungen and continued on Meropenem and Amikacin. The patient became in a critical condition; he was in a refractory septic shock in spite of good coverage with many broad spectrum antibiotics. He deteriorated rapidly and died on November 7, 2015. Gene expert analysis revealed *K. pneumonia* isolate from the blood culture as carbapenemase producer (OXA-48+).

Case 6

A 35 years old female known to have type 1 diabetes mellitus on insulin for more than 15 years came to the emergency department as a case of infected right diabetic foot and sepsis on March 22, 2016. She had renal impairment secondary to diabetic nephropathy and

history of ICU admission and left big toe amputation two months prior to his presentation. On admission, her BP was (116/64 mm HG), and was found to have abnormal renal parameters: urea 26.1, creatinine 350, k 4.4, sodium (Na) 121, calcium (Ca) 2.27. Other laboratory investigations showed: glucose >27, Hb 8.6 with MCV 79.1, WBC 14 cells/mm^3. After initial clinical evaluation, her clinical condition required immediate transfer to the operating room for below knee amputation and to start her empirically on tazocin. Blood culture showed *C. glabrata* and *Enterococcus faecalis* sensitive to ampicillin. She was started on caspofungen and vancomycin. After three days, she developed right leg gangrene at the site of amputation and debridement was done and tissue specimens were sent for culture. Wound culture from the right foot ulcer and the tissue specimen from the infected amputated site showed heavy growth of ESBL producing *K. pneumonia*, resistant to carbapenem and heavy growth of *E. faecalis*. She was started on ampicillin and gentamicin. Infection control recommendation is to place the patient on contact isolation. After forty days of admission in the surgical intensive care (SICU), the patient condition improved and she was discharged home.

Case 7

A 38-year-old female admitted with one week history of fever, chills, diarrhea and abdominal pain. She gave a history of renal transplant 7 years ago on cycloserine and steroid. On admission, her BP was 120/68 mm HG, pulse; 112 RR; 20. Her temperature was 39 °C, serum creatinine, 184. The patient was started empirically on tazocin. Blood culture grew ESBL producing *K. pneumonia*, resistant to all antibiotic except colistin. After the blood culture and sensitivity testing result, the patient was started on intravenous colistin (6 million unit loading dose followed by 2 million units every 12 h along with meropenem 1 g every 12 h) for 14 days. She showed improvement and was discharged in good condition.

Case 8

A 65 year-old male, known to have hypertension and invasive recto-sigmoid adenocarcinoma with perforation, recurrent intra-abdominal and left iliopsoas abscess, chronic kidney disease, history of renal stone and hydronephrosis. She underwent diverting transverse loop colostomy and percutaneous pig tail drainage of the abscess collection one month prior to presentation. The patient was admitted electively for chemotherapy. During admission, he complained of left loin pain, radiating to the groin area, and a left thigh swelling was noticed. Abdominal CT scan showed no improvement regarding the size and appearance of the recto-sigmoid mass with re-accumulation of the abdominal wall and left pelvic cavity collections (abscess). The diagnosis was left psoas abscess with pelvic and abdominal wall collection. No recent distant metastasis to the abdomen or chest seen. The abscess collection was drained and sent to the microbiology laboratory and a left pigtail was inserted. The patient was started empirically on imipenem. Culture from the abscess grew *E. coli*, ESBL and carbapenemase producer (Intermediate to imipenem and sensitive to tigecycline). Based on the sensitivity result, and as recommended by the infectious team, meropenam was discontinued and tigecycline was started (50 mg Q12 hrs). Seven days after treatment, CT-abdomen with contrast showed significant regression in the size of the left psoas abscess with no residual measurable drainable collection. tigecycline was continued for 28 days. The duration of the antibiotic depends on complete resolution of collection based on clinical, laboratory and radiological findings. He became stable with no complication or complains. Repeated CT scan abdomen and pelvis revealed complete resolution of the psoas abscess. The patient clinical condition improved and he was discharged and given 2 weeks appointment for CT abdomen and pelvis to assess for possible re-collection of abscess or metastasis.

Case 9

An 80 year old female, known to have uncontrolled DM type II, vascular dementia, right distal femoral fracture, bedridden with bedsores admitted on August 2016 with UTI and infected (grade 4) sacral bedsore complicated with osteomyelitis. Her family noted lack of sleep and discomfort. Physical examination showed infected bed sore, bilateral lung crepitation, and tender abdomen. Vitals and measurements revealed *T*: 36.4 °C (Axillary) RR: 18 BP: 130/84 SpO_2: 97%. She is on NGT feeding with Foley's catheter. Blood culture grew *K. pneumoniae* ESBL producer. Wound culture from the bedsore grew *E. coli* ESBL producer and *Morganella morganii*. She was started on imipenem (500 mg q6 hourly) and Piperacillin-tazobactam (4.5 g IV, q8hr), for a total of 6 weeks. She was seen by a plastic surgeon for debridement and cleaning of the sacral sore using povidone soaked dressing and flamazine twice daily. Her blood sugar was adjusted by regular insulin sliding scale (Regular insulin 100 units/ml Subcutaneous INJ). During admission, she had hematuria and Foleys catheter wash was done. Over the weekend the patient condition deteriorated, she was arrested admitted to the ICU and her resuscitation was successful. The infectious disease team suggested continuing meropenem for 6 weeks. The patient completed 6 weeks of imipenem and seven days piperacillin-tazobactam along with dressing for the infected bed sore. She was not showing clinical improvement, looked sick, afebrile (O_2 saturation = 88%), and chest examination showed reduced air bilaterally. Complete blood count showed leukocytosis [20]. CXR showed aspiration pneumonia. The overall response was poor. Repeated culture from the bedsore grew *E. aerogenes*, resistant to carpapenem. The infectious disease impression was that, the patient has chronic osteomyelitis and the recommendation was to repeat ESR, CRP, and MRI for bone assessment.

Discussion

The comorbidities, prior hospital stay and surgical procedures observed within this cohort is consistent with previously described risk factors identified in retrospective studies of CRE infection or sporadic outbreaks [12,13]. Exposure to health care systems and carbapenems have been identified as major risk factors for CRE acquisition or infection. [9,14]. A study of invasive infections due to carbapenem-resistant *K. pneumoniae* (CRKP) as compared to carbapenem-susceptible *K. pneumoniae* found an association with mechanical ventilation, exposure to antimicrobials, longer length of stay, and recent organ transplantation. [15]. Admission to intensive care unit have also been associated with the acquisition of CRKP. [15].

Carbapenems are frequently used to treat severe infections caused by multiresistant AmpC- or extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*. Unfortunately, Carbapenem-resistant *Enterobacteriaceae* has been reported in many countries [5–7,13]. Carbapenemases and porin loss combined with AmpC enzyme hyperproduction are the main two mechanisms of resistance [24–32]. Carbapenem resistance can be mediated through the production of acquired metallo-β-lactamases (MBLs) such as VIM and IMP, or non-metallo-carbapenemases of the IMI/NMC, SME, OXA or KPC families. [26–28]. Alterations or losses of porins in members of the *Enterobacteriaceae* have also been reported [26,30,32]. Results from large hospital-based surveillance studies in China of the genotypic characterization of 49 isolates of *Enterobacteriaceae* with decreased susceptibility to carbapenems has shown that, moderate- to high-level carbapenem resistance

was mainly due to loss or decreased expression of both major porins combined with production of AmpC or ESBL enzymes, while other carbapenemase (KPC-2, IMP-4, and IMP-8) was associated with a low to moderate level of carbapenem resistance. [24]. On the other hand, a review of 171 clinical *Klebsiella* and *Enterobacter spp.* isolates from UK reference laboratory found that very few had true carbapenemases production combined with impermeability [25].

Although, in our case series, molecular analysis was performed on only few of the isolates, carbapenemase genes of the *blaNDM* type seems to predominate. This finding is similar to previous reports from Saudi Arabia and the gulf region [19–21]. In a report by Zowawi et al. investigating the molecular epidemiology and mechanisms of resistance of CRE obtained from the countries of the gulf region including Saudi Arabia, The most common carbapenemases were of the OXA-48 and NDM types. No KPC-type, VIM-type, or IMP-type producers were detected [20]. In fact, the first two clinical cases of OXA-48-type carbapenemase-producing *Enterobacteriaceae* in the United States were isolated from patients recently hospitalized in Saudi Arabia and India [33].

Enterobacteriaceae can cause both hospital and community infections, increases the chance of spread of CRE into the community. In hospitalized patients, it is important to identify CRE infections before these organisms are transmitted in the same hospital or to other health care facilities. Effective infection control policy including implementation of a notification system and infection-prevention measures when CRE are identified in the laboratory is highly recommended. Identified CRE infected or colonized patients should be placed on contact precautions [34]. Surveillance cultures from patients with epidemiologic links to CRE case-patients should be considered to identify additional unrecognized CRE colonized patients. Early detection of colonized cases allows appropriate implementation of contact precautions and prevents transmission to other patients and staff [35]. Active surveillance cultures have been used as part of an effective policy to interrupt transmission of KPC-producing *K. pneumoniae* in several investigations [36–39]. Only few remaining antibiotics are currently in use to treat CRE infections including, polymyxins, tigecycline, aminoglycosides, fosfomycin, and temocillin. Combination therapy with 2 or more drugs is superior to monotherapy and associated with better survival rate [40–42]. In this series four patients died due to septic shock refractory to treatment. The combination Ceftazidime-avibactam have been approved by the Food and Drug Administration (FDA) for treating complicated urinary tract and complicated intra-abdominal infections caused by CRE isolates that produce KPC and AmpC and partial activity against OXA enzymes; however, this drug is not active against metallo-β-lactamases such as NDM, VIM, or IMP [43]. Although, all those patients had severe underlying diseases, the lack of or delay in initiating appropriate treatment might contributed to the poor outcome.

Limitations of this case series include lack of data related to prior patent's stay in other hospitals, difficulty in following patients after discharge for final outcome, reliance on physician's notes to distinguish infection from colonization. Identification of CRKP in the urine is not always associated with urinary tract infection. Case 1 in this series, had carbapenem-resistant *K. pneumonia* bacteriuria (CRKP) bacteriuria during his elective admission for endoscopy, which most probably represents colonization rather than real infection. Qureshi ZA, et al. has found that, the majority of patients (80%) with CRKP identified from urine, are having asymptomatic bacteriuria rather than UTI [44]. Molecular diagnosis was not performed and actual resistance mechanisms were not identified in all isolates. In conclusion, CRE infections is a growing problem in our hospital and are expected to increase in prevalence and involve other hospitals. We believe that, antibiotic stewardship and strict infection control measures are essential for preventing further spread of CRE. For the purpose of controlling the spread of CRE in our institution, we recommend considering active surveillance cultures and screening patients transferred from other hospitals or coming from highly endemic settings at admission for these organisms. Finally, more research is needed from our institution from all over the world to identify the epidemiology and molecular profile of the involved CRE associated infections.

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Ethical approval

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