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Case Report

COMPLICATED URINARY TRACT INFECTION WITH EXTENSIVE DRUG-RESISTANT *KLEBSIELLA PNEUMONIAE* TREATED WITH COMBINATORIAL THERAPY OF CEFTRIAXONE+SULBACTAM+EDTA ALONG WITH CARBAPENEMS: A CASE REPORT AND THE REVIEW OF LITERATURE

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ABSTRACT

Colistin is considered one of the last available therapeutic options to treat infections caused by carbapenem-resistant Klebsiella pneumoniae (CRKP). However, with an increase in the use of colistin to treat CRKP infections, colistin resistance is emerging and there are no standard treatment regimens for these type of infections. In the present case report, we are discussing a case of 64-year-old male patient having complicated urinary tract infection (cUTI) by CRKP, treated successfully with ceftriaxone+sulbactam+EDTA (CSE-1034) and carbapenem combination therapy. Conclusively, CSE-1034 in combination with or without carbapenems could be a successful therapeutic option for the treatment of CRKP cUTI cases.

Keywords: Catheter-associated urinary tract infections, Carbapenems, Extended spectrum beta lactamases, Metallo-beta-lactamases

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INTRODUCTION

Catheter-associated urinary tract infections (UTIs) attributed to the use of indwelling urethral catheters is one of the most prevalent hospital-associated infections accounting for around 70–80% of all UTIs [1]. The burden of hospital-associated infections is further complicated by rising antimicrobial resistance among the causative agents. Over the past two decades, various species of Enterobacteriaceae family have witnessed a sharp rise in resistance toward carbapenems [2]. Most importantly, the carbapenem-resistant Klebsiella pneumoniae (CRKP) constitutes a major fraction of all carbapenem-resistant Enterobacteriaceae and are associated with a high rate of mortality, morbidity, and overall treatment cost [2]. Colistin is considered to have very important place in antibiotic treatment regimen for infections caused by carbapenem-resistant strains [3]. However, an increased use of colistin accompanied with a rise in carbapenem resistance is leading to the emergence of pathogens resistant to even colistin. The sharp global emergence of multidrug-resistant urinary pathogens to the antibiotics of last resort spotlights the need for alternate therapeutic strategies to combat UTIs [4,5]. In the present case report, we are discussing a case of 64-year-old male patient having cUTI due to CRKP, treated successfully with CSE-1034 in combination with carbapenems.

CASE REPORT

A 64-year-old male patient presented to our emergency department with symptoms of pyrexia, chills, and decreased appetite past one day. Physical examination revealed that the patient was having high body temperature (103°F), tachycardia (110/min), and blood pressure (130/80 mm Hg). Medical history revealed a history of hydronephrosis with ureteropelvic junction obstruction in the left kidney, and the patient was operated for retrograde pyelogram pyeloplasty with double J (DJ) stenting for left kidney about 9 days before presenting to the hospital. After surgery, he had normal blood counts and was afebrile. Moreover, the patient was a known case of hypertension and ischemic heart disease.

Hematology test reports (Table 1) done immediately on the day of admission show deranged white blood cell (WBC) count; however, hemoglobin (Hb) and platelet count were normal. Peripheral blood film was normal, and no parasite was reported. Biochemical investigations revealed normal serum creatinine levels (Table 1). A urine sample was sent for culture and susceptibility (C/S) testing, and the patient was put empirically on meropenem (2 g IV/8 h). The patient continued to have a fever even after 48 h of meropenem. On the 3rd day of admission, blood sample was sent for C/S testing along with other hematological and biochemical investigations. Repeat hematology report also showed deranged WBC count (30160/cumm) and Hb - 10.1 g/dL. Urine examination revealed the presence of protein (traces), blood (occult blood - positive), and pus cells - 10–12/high power field. The provisional urine culture susceptibility report showed extensive drug-resistant (XDR) *K. pneumoniae* resistant to most antibiotics including colistin. The pathogen isolated showed susceptibility only toward ceftriaxone+sulbactam+EDTA (CSE-1034).

The patient was started on CSE-1034 (3 g) given IV every12 h, injection ertapenem (1 g) IV every 24 h, and injection meropenem (2 g) IV every 24 h (3 h infusion) utilizing the role of ertapenem as a suicide penem, and CSE-1034 was used as the only active antibiotic in this case. Meanwhile, the blood C/S report also confirmed XDR *K. pneumoniae* as a pathogen. Symptomatic improvement in terms of normal body temperature was observed on the 6th day of admission. Hematological investigations (Hb - 10.3 g/dl and WBC - 9210) and other parameters confirmed the *patient's* improvement. CSE-1034 3 g every 12 h IV was continued along with meropenem and ertapenem. On the 9th day of admission, repeat hematological reports available revealed Hb: 11.9 g/dl and total leukocyte count (TLC): 12830/cu mm. Moreover, blood culture report available revealed no growth. However, the patient was reported to have low procalcitonin levels (0.128 ng/ml), so antibiotics were deescalated. Both carbapenems (meropenem and ertapenem) were stopped, and CSE-1034 (3 g q12 h IV) was continued for 7 more days. The patient responded well to given treatment with complete bacteriological eradication (sterile blood and urine culture), and clinical improvement was achieved. After the completion of treatment, the patient was reported to have normal TLC, normal platelet count (Table 1), and normal body temperature. The patient was discharged on the 16th day with advice to continue injection CSE-1034 (3 g) IV every 12 h at home for 7 more days.

Table 1: Various laboratory parameters of the patients captured with the progression of treatment

Parameters	Before admission	Baseline (day of admission)	Day 3	Day 6	Day 9	16th day discharge day
Hb (g/dl)		11.0	10.1	10.3	11.9	10.7
TLC (/cu mm)		27720	30160	9210	12830	10050
Platelet count (cu mm)		270,000	-	-	-	483000
Serum creatinine (mg/dl)		1.18	-		-	-
Procalcitonin (ng/ml)	-	-	-	-	0.128	-

Hb: Hemoglobin, TLC: Total leukocyte count

Table 2: Primers used in the study

S. No.	Gene	Forward	PCR conditions
1	NDM-1	NDM-1-F 5-GGTTTGGCGATCTGGTTTTC-3 NDM-1-R 5-CGGAATGGCTCATCACGATC-3	10 min at 94°C and 36 cycles of amplification consisting of 30 s at 94°C, 40 s at 52°C, and 50 s at 72°C, with 5 min at 72°C for the final extension
2	VIM	VIM-F 5-GATGGTGTTTGGTCGCATA-3 VIM-R 5-CGAATGCGCAGCACCAG-3	10 min at 94°C and 36 cycles of amplification consisting of 30 s at 94°C, 40 s at 52°C, and 50 s at 72°C, with 5 min at 72°C for the final extension
3	Amp-C	Amp-C F-5-CCCCGCTTATAGAGCAACAA-3 Amp-CR 5-TCAATGGTCGACTTCACACC-3	5 min at 95°C and 35 cycles of amplification consisting of 60 s at 94°C, 2 min at 58°C, and 3 min at 72°C, with 5 min at 72°C for the final extension

PCR: Polymerase chain reaction, NDM-1: New Delhi metallo-beta-lactamase-1, VIM: Verona integron metallo-beta-lactamases

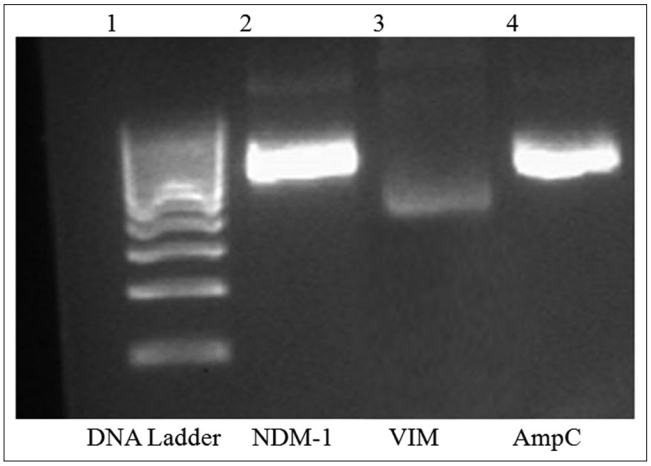

Fig. 1: Gel electrophoresis showing amplification of New Delhi metallo-beta-lactamase-1, Verona integron metallo-beta-lactamases, and Amp-C

The genotypic characterization of extended spectrum beta lactamases (ESBL) and metallo-beta-lactamases (MBL) encoding genes in multidrug-resistant *K. pneumoniae* isolate was also performed. The DNA was extracted from the clinical sample using phenol-chloroform method and used in polymerase chain reaction (PCR) to amplify different ESBLs and MBLs including New Delhi metallo-beta-lactamase-1 (NDM-1), Verona integron metallo-beta-lactamases (VIM), IMP, TEM, SHV, Amp-C, and CTX-M. For PCR amplification, 20 ng DNA was added to 20 µl mixture containing 0.5 mM of dNTPs, 1.25 µM of each primer (Table 2), and 3.0 µl of Taq polymerase (Bangalore Genei) in ×1 PCR buffer. Among all the tested genes, the isolate tested positive for only AmpC (ESBL), VIM, and NDM-1 (MBLs) (Fig. 1).

DISCUSSION

Over the past few decades, *K. pneumoniae,* a Gram-negative pathogen, has emerged as a pathogen of concern posing serious challenges to the treatment regimens [6,7]. Carbapenems are considered as the drug of choice for treating infections by ESBL strains of *K. pneumoniae.* However, various studies have shown the rising antibiotic resistance patterns to this drug also. In India, CRKP is as high as 44%. Various mechanisms described for CRKP include the production of enzymes including ESBL or carbapenemases, hyperproduction of AmpC β-lactamase, and variety of drug efflux mechanisms [8]. CRKP shows coresistance to various classes of antimicrobials including beta-lactam antibiotics, extended-spectrum cephalosporins, carbapenems, aminoglycosides, and fluoroquinolones and thus limits the treatment options completely [9]. In such situations, colistin remains the mainstay of therapy [10,11].

In the present case, the patient was diagnosed with cUTI following pyeloplasty with DJ stenting of the left kidney. This is a typical case of health-care-associated UTI following renal surgery. Health-care-associated infections are the biggest threat faced by the hospitalized patients in the health-care settings. cUTI is one of the most frequent and prevalent hospital-acquired infections accounting for around 30% of nosocomial cases [12]. The prime risk factors associated with nosocomial UTI include urological surgery, indwelling urinary catheters, poor health status, weak immunocompromised status, surgical drains, wound bandage, elderly male patients, and debilitating diseases [12]. Thus, in this elderly male case, surgical intervention combined with underlying comorbidities could be prime contributing factors toward the acquired infection.

In the present case, the patient was put on the empirical treatment of meropenem but did not respond to the therapy. The culture susceptibility test confirmed the infection with XDR *K. pneumoniae* resistant to all major classes of antibiotics including carbapenems and colistin except CSE-1034. Colistin also called as polymyxin E has been reserve drug for CRKP infections [3,13]. Despite being a reserve drug, with the sudden rise in the rate of resistance to carbapenems witnessed in the last decade, the usage of colistin has increased leading to slow emergence of colistin resistance as well. In the past few years, there have been sporadic reports of colistin-resistant, carbapenem-resistant Enterobacteriaceae cases worldwide. Giani *et al.* [4] have reported an outbreak of colistin-resistant KPC-producing K. pneumoniae in 93 patients over 4 years from 2009 to 2012. In one of the surveillance studies between 2012 to 2014 in Greece, 86 colistin-resistant/carbapenem-resistant clinical isolates were reported [14]. Likewise, outbreaks of colistin-resistant, carbapenem-resistant Enterobacteriaceae cases have been reported worldwide including Israel involving 15 patients over 10 months in 2006 [15], South Korea [5], and Detroit [16]. Colistin belongs to the family of cationic polypeptides with a lipophilic fatty acyl side chain [17,18]. The electrostatic attractions between the positively charged polymyxins and the negatively charged phosphate group of lipopolysaccharide (LPS), a part of the outer membrane, actually leads to the binding of colistin to the bacterial wall [18]. After entering the

outer membrane, polymyxin crosses the periplasm and intercalates into the inner membrane leading to pore formation and resulting in lysis. Modification of LPS, the initial site of action of colistin, is the most common mechanism of colistin resistance.

The genotypic characterization has shown the isolate positive for Amp C (ESBL), VIM, and NDM-1. VIM, oxacillinase-48 (OXA-48), NDM-1, imipenemase (IMP), and KPC are the carbapenemases which are the most commonly reported mechanism of carbapenem resistance in K. pneumoniae [19]. According to SENTRY antimicrobial surveillance study conducted, NDM was the most common gene isolated (38.4%) followed by OXA-48 in India [20]. The first isolate from India known to produce NDM was reported in a retrospective study in 2006 [21]. NDM producers have been detected in >10 major population centers in India, traversing both the north and south of the country [22-24]. The study by Nagaraj *et al.* [25] found 27 of 36 *K. pneumonia* isolates (75%) and 10 of 15 *Escherichia coli* isolates (66%) to be NDM positive by PCR. The study could not detect any KPCs among carbapenem-resistant isolates. KPCs could not be identified in the present case also. Dwivedi *et al*., in 2009, reported 12 carbapenem-resistant Enterobacteriaceae isolates harboring metallo-β-lactamases (5 IMP, 4 VIM, 2 IMP, and SIM and VIM and SIM) [26]. A study by Solanki *et al*., in 2014 [27], from Hyderabad, showed bla_{NDM} to be the most common gene (59/100), followed by bla_{KPC} (15/100) and least frequently bla_{VIM} (6/100).

As the patient was reported to be susceptible to CSE-1034 only, hence, the patient was started with CSE-1034 along with ertapenem and meropenem. The double-carbapenem regimen of ertapenem and meropenem was used where ertapenem was utilized as a suicide penem. Various studies in the past have reported the synergistic effect of double carbapenem regimen for infections in humans due to carbapenemase-producing pan-drug-resistant *K. pneumoniae* [28]. CSE-1034 was the only active antibiotic in the antibiotic regimen prescribed. After switching to this therapy, various laboratory parameters started improving after 48h and the patient recovered within 21 days of post-CSE-1034 therapy. CSE-1034 is a novel combination of ceftriaxone, sulbactam, and disodium edetate, and the high susceptibility of CSE-1034 could be attributed to the synergistic effect of ceftriaxone, sulbactam, and disodium edetate. Various studies have reported a high efficacy of CSE-1034 against a vast number of bacterial infections [29-31]. In an antimicrobial susceptibility pattern study, ESBL-producing K. pneumoniae clinical isolates were reported to be highly susceptible (67–81%) to CSE-1034 [32]. Bhatia *et al.* [33] have also reported an overall success rate of >75% of CSE-1034 against ~61% in meropenem for the treatment of various Gram-negative bacterial infections.

CONCLUSION

cUTI is one of the common hospital-acquired infections in the hospital settings. The growing incidence of MDR among various bacterial strains and the promiscuous rise in carbapenemase-producing K. pneumoniae has posed a big challenge in treating these infections. Conclusively, the present case highlights the importance of antibiotic adjuvant entities for the treatment of bacterial infections which are caused by pathogens resistant to both carbapenems and colistin.

AUTHORS' CONTRIBUTIONS

Sanjith Saseedharan has conceived the concept, written, and revised the manuscript.

CONFLICTS OF INTEREST

All the authors declare that there is no potential conflict of interest and any source of funding involved.

REFERENCES

1. Al-Hazmi H. Role of duration of catheterization and length of hospital stay on the rate of catheter-related hospital-acquired urinary tract infections. Res Rep Urol 2015;7:41-7.
2. Centers for Disease Control and Prevention (CDC). Guidance for control of infections with carbapenem-resistant or carbapenemase-producing *Enterobacteriaceae* in acute care facilities. MMWR Morb Mortal Wkly Rep 2009;58:256-60.
3. Paterson DL, Harris PN. Colistin resistance: A major breach in our last line of defence. Lancet Infect Dis 2016;16:132-3.
4. Giani T, Arena F, Vaggelli G, Conte V, Chiarelli A, Henrici De Angelis L, *et al*. Large nosocomial outbreak of colistin-resistant, carbapenemase-producing *Klebsiella pneumoniae* traced to clonal expansion of an Mgrb deletion mutant. J Clin Microbiol 2015;53:3341-4.
5. Suh JY, Son JS, Chung DR, Peck KR, Ko KS, Song JH. Nonclonal emergence of colistin-resistant *Klebsiella pneumoniae* isolates from blood samples in South Korea. Antimicrob Agents Chemother 2010;54:560-2.
6. Moemen D, Masallat DT. Prevalence and characterization of carbapenem-resistant *Klebsiella pneumoniae* isolated from intensive care units of Mansoura University hospitals. Egypt J Basic Appl Sci 2017;4:37-41.
7. El-mahdy TS, Abdelaziz MO, El-domany RA. Prevalence and molecular characterization of extended spectrum β-lactamases in *Klebsiella pneumoniae* isolates from cancer patients and others. Int J Pharm Pharm Sci 2015;7:122-7.
8. Blair JM, Webber MA, Baylay AJ, Ogbolu DO, Piddock LJ. Molecular mechanisms of antibiotic resistance. Nat Rev Microbiol 2015;13:42-51.
9. Schwaber MJ, Carmeli Y. Carbapenem-resistant *Enterobacteriaceae*: A potential threat. JAMA 2008;300:2911-13.
10. Souli M, Galani I, Antoniadou A, Papadomichelakis E, Poulakou G, Panagea T, *et al*. An outbreak of infection due to beta-Lactamase *Klebsiella pneumoniae* carbapenemase 2-producing *K. pneumoniae* in a Greek University hospital: Molecular characterization, epidemiology, and outcomes. Clin Infect Dis Off Publ Infect Dis Soc Am 2010;50:364-73.
11. Woodford N, Zhang J, Warner M, Kaufmann ME, Matos J, Macdonald A, *et al*. Arrival of *Klebsiella pneumoniae* producing KPC carbapenemase in the United Kingdom. J Antimicrob Chemother 2008;62:1261-4.
12. Iacovelli V, Gaziev G, Topazio L, Bove P, Vespasiani G, Agrò F, *et al*. Nosocomial urinary tract infections: A review. Riv Urol 2014;81:222-7.
13. Shah PG, Shah SR, Kamat SD, Kamat DV. Colistin-carbapenem combination therapy against carbapenem resistant gram negative bacilli infections: Clinical and an *in vitro* synergy study. Int J Pharm Pharm Sci 2014;6:497-500.
14. Oikonomou O, Sarrou S, Papagiannitsis CC, Georgiadou S, Mantzarlis K, Zakynthinos E, *et al*. Rapid dissemination of colistin and carbapenem resistant *Acinetobacter baumannii* in Central Greece: Mechanisms of resistance, molecular identification and epidemiological data. BMC Infect Dis 2015;15:559.
15. Samra Z, Ofir O, Lishtzinsky Y, Madar-Shapiro L, Bishara J. Outbreak of carbapenem-resistant *Klebsiella pneumoniae* producing KPC-3 in a tertiary medical centre in Israel. Int J Antimicrob Agents 2007;30:525-9.
16. Marchaim D, Chopra T, Pogue JM, Perez F, Hujer AM, Rudin S, *et al*. Outbreak of colistin-resistant, carbapenem-resistant *Klebsiella pneumoniae* in metropolitan Detroit, Michigan. Antimicrob Agents Chemother 2011;55:593-9.
17. Gao R, Hu Y, Li Z, Sun J, Wang Q, Lin J, *et al*. Dissemination and mechanism for the MCR-1 colistin resistance. PLOS Pathog 2016;12:e1005957.
18. Wanty C, Anandan A, Piek S, Walshe J, Ganguly J, Carlson RW, *et al*. The structure of the neisserial lipooligosaccharide phosphoethanolamine transferase A (LptA) required for resistance to polymyxin. J Mol Biol 2013;425:3389-402.
19. Nordmann P, Nass T, Poirel L. Global spread of carbapenemase-producing *Enterobacteriaceae*. Emerg Infect Dis 2017;17:1791-8.
20. Castanheira M, Deshpande LM, Mathai D, Bell JM, Jones RN, Mendes RE. Early dissemination of NDM-1- and OXA-181-producing *Enterobacteriaceae* in Indian hospitals: Report from the SENTRY antimicrobial surveillance program, 2006-2007. Antimicrob Agents Chemother 2011;55:1274-8.
21. Ashour HM, El-Sharif A. Species distribution and antimicrobial susceptibility of gram-negative aerobic bacteria in hospitalized cancer patients. J Transl Med 2009;7:14.
22. Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, *et al*. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: A molecular, biological, and epidemiological study. Lancet Infect Dis 2010;10:597-602.
23. Charan J, Mulla S, Ryavanki S, Kantharia N. New Delhi metallo-beta lactamase-1 containing *Enterobacteriaceae*: Origin, diagnosis,

treatment and public health concern. Pan Afr Med J 2012;11:22.
24. Swaminathan A, Ardra M, Manoharan A, Nair KP, Girija KR. Characterisation of carbapenemase-producing gram-negative bacilli among clinical isolates in a tertiary care centre in Kerala, South India. J Acad Clin Microbiol 2016;18:100.
25. Nagaraj S, Chandran SP, Shamanna P, Macaden R. Carbapenem resistance among *Escherichia coli* and *Klebsiella pneumoniae* in a tertiary care hospital in south India. Indian J Med Microbiol 2012;30:93.
26. Dwivedi M, Mishra A, Azim A, Singh RK, Baronia AK, Prasad KN, *et al*. Ventilator-associated pneumonia caused by carbapenem-resistant *Enterobacteriaceae* carrying multiple metallo-beta-lactamase genes. Indian J Pathol Microbiol 2009;52:339-42.
27. Solanki R, Vanjari L, Subramanian S, Aparna B, Nagapriyanka E, Lakshmi V, *et al.* Comparative evaluation of multiplex PCR and routine laboratory phenotypic methods for detection of carbapenemases among gram negative bacilli. J Clin Diagn Res 2014;8:DC23-6.
28. Bulik CC, Nicolau DP. Double-carbapenem therapy for carbapenemase-producing *Klebsiella pneumoniae*. Antimicrob Agents Chemother 2011;55:3002-4.
29. Shameem M, Mir MA. Management of pneumonia and blood stream infections with new antibiotic adjuvant entity (ceftriaxone + sulbactam + disodium edetate) - A novel way to spare carbapenems. J Clin Diagn Res 2016;10:LC23-7.
30. Chaudhary M, Mir MA, Ayub SG, Protocol 06 Group. Safety and efficacy of a novel drug elores (ceftriaxone+sulbactam+disodium edetate) in the management of multi-drug resistant bacterial infections in tertiary care centers: A post-marketing surveillance study. Braz J Infect Dis Off Publ Braz Soc Infect Dis 2017;21:408-17.
31. Chaudhary M, Ayub SG, Mir MA. Comparative efficacy and safety analysis of CSE-1034: An open labeled phase III study in community acquired pneumonia. J Infect Public Health 2018;11:691-7.
32. Sahu M, Sanjith S, Bhalekar P, Keny D. Waging war against extended spectrum beta lactamase and metallo betalactamase producing pathogens-novel adjuvant antimicrobial agent Cse1034- an extended hope. J Clin Diagn Res 2014;8:DC20-3.
33. Bhatia P. Alternative empiric therapy to carbapenems in management of drug resistant gram negative pathogens: A new way to spare carbapenems. Res J Infect Dis 2015;3:2.