Case Report

Compassionate use of β-lactam enhancer/β-lactam combination zidebactam/cefepime (WCK 5222) for the treatment of recurrent pyelonephritis caused by extensively drug-resistant *Klebsiella pneumoniae* with high zidebactam/cefepime: A case report

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ABSTRACT

Infections in immunocompromised individuals often present as recalcitrant or recurrent infections. Due to recurrent healthcare system exposure, these patients are at risk of infections due to multidrug-resistant organisms. Due to limited treatment options available, such infections pose a challenge to successful treatment outcomes in this population. Zidebactam/cefepime (WCK 5222) is a β-lactam enhancer/β-lactam combination being studied in a Phase 3 trial for use in adult patients with complicated urinary tract infections. Here, we report a case of complicated pyelonephritis caused by colistin and carbapenem-resistant *Klebsiella pneumonia* in a 62-year-old patient with ovarian carcinoma using this drug under compassionate use grounds with a successful treatment outcome.

Key words: Cefepime-zidebactam, Multidrug-resistant organism, Urinary tract infections

Immunocompromised patients, such as those with cancer, are prone to infections from multidrug-resistant (MDR) Gram-negative pathogens due to frequent exposure to healthcare settings. These infections often present as recalcitrant or recurrent infections in the immunocompromised state. Zidebactam/cefepime (WCK 5222) is a β-lactam enhancer/β-lactam combination being studied in a Phase 3 trial for use in adult patients with complicated urinary tract infections (UTIs) [1,2]. Efficacy of zidebactam/cefepime rides on a novel enhancer mechanism that bestows the combination with a pharmacokinetic (PK)/pharmacodynamic scope to treat infections caused by isolates with minimum inhibitory concentrations (MIC) up to 64 mg/L; hence, a Clinical and Laboratory Standards Institute investigational MIC susceptibility breakpoint of ≤64 mg/L was granted to the combination.

This is a case report describing the successful treatment of complicated pyelonephritis caused by colistin and carbapenem-resistant *Klebsiella pneumonia* (CRKP) in a patient with ovarian carcinoma using this drug under compassionate use grounds. This case report is being discussed as traditionally available agents, in our country, such as colistin and ceftazidime-avibactam, could not be used for this patient due to resistance.

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CASE PRESENTATION

A 62-year-old woman with ovarian carcinoma underwent laparotomy, including *en bloc* resection of the uterus, ovaries, fallopian tubes, lower abdominal peritoneum, left iliac node dissection, and omentectomy.

She was later admitted with right pyelonephritis and a renal abscess (Table 1). A pigtail catheter (Fig. 1) was inserted twice to drain pus, which cultured CRKP and was later found to harbor NDM-5. Based on susceptibility testing, she received ceftazidime-avibactam and aztreonam for 3 weeks, along with cystoscopy and double J (DJ) stenting. After 1.5 months, she was readmitted with fever and loin pain.

Repeat computed tomography scan of the abdomen showed resolution of the right peri-nephric abscess. Interval appearance of ill-defined hypoenhancing areas at the upper pole of the left kidney with peri-nephric fat stranding. Suspecting a stent-related infection, the DJ stent was removed, and intravenous colistin was initiated (Fig. 2). Cultures from the stent and intraoperative urine again grew CRKP. Colistin was discontinued after 7 days due to symptomatic improvement following stent removal.

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Table 1: Patient's biochemical test results before & after treatment with zidebactam/cefepime

	CRP (mg/L)	Procalcitonin (ng/mL)	WBC (x109/L)	Creatinine (mg/dL)	Bilirubin (mg/dL)
Before WCK 5222 Treatment	48	0.12	5.1	1.4	1.2
After WCK 5222 Treatment	35	0.10	8.6	1.2	1.4

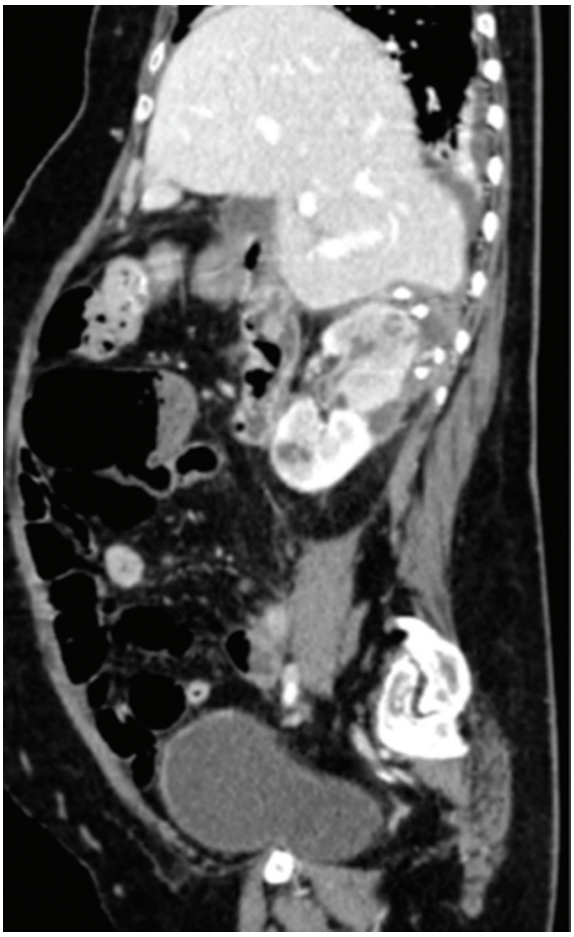

Figure 1: Sagittal section contrast CT images showing hypo-enhancing areas in the upper pole of right kidney-suggestive of pyelonephritis with peri-nephric abscess. Note made of the pigtail catheter within the collection

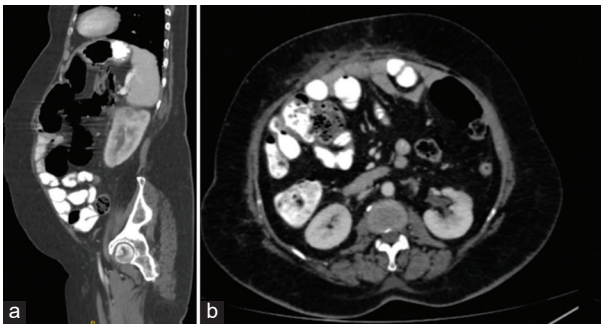

Figure 2: (a) Contrast enhanced CT showing normal enhancement of right kidney with interval resolution of right peri-nephric abscess. Interval appearance of ill-defined hypoenhancing areas at the upper pole of left kidney with peri-nephric fat stranding. Proximal tip of DJ stent seen within left renal pelvis; (b) Axial contrast CT showing normal enhancement of left kidney with interval resolution of perinephric fat stranding and thickening of left pararenal fascia. Interval reduction in dilatation of left renal pelvis is seen when compared to previous CT. Previously seen left DJ stent has been removed.

However, 4 weeks later, she returned with fever and abdominal pain, with cultures isolating colistin and CRKP. Due to recurrent, extensively drug-resistant (XDR) UTI with no other treatment options, she was started on zidebactam/cefepime (WCK 5222) under compassionate use with Central Drugs Standard Control Organisation approval (Table 2). Institutional ethics committee approval was also obtained (APH-001/02-2024). Prior testing confirmed susceptibility to WCK 5222 (MIC 32 mg/L). The regimen (1 g zidebactam + 2 g cefepime, every 8 h, 60-min infusion) was well tolerated for 7 days with no drug-related adverse effects. She showed clinical improvement, with resolution of fever and abdominal pain, a mild reduction in renal abscess size, and was discharged in stable condition.

Table 2: Antibiotic susceptibility and genotypic resistance profile of XDR *Klebsiella pneumoniae* recovered from the patient

Antibiotics	MIC in mg/L (Interpretation as per CLSI)*	Molecular determinants antibiotic resistance identified from WGS
WCK 5222	32 (S)**	TEM-1, SHV-11, CTXM-15, NDM-5
Imipenem	128 (R)	
Imipenem/relebactam	128 (R)	
Meropenem	128 (R)	
Ceftazidime/avibactam	>128 (R)	
Ceftazidime/ avibactam+Aztreonam	<0.5 (S)***	
Ceftolozane/tazobactam	128 (R)	
Piperacillin/tazobactam	>128 (R)	
Colistin	64 (I)	
Amikacin	>128 (R)	
Levofloxacin	128 (R)	

* As per CLSI 2023 interpretation;
** WCK 5222 MIC was determined in 1:1 ratio; susceptibility was interpreted based on CLSI investigational breakpoint of ≤64 mg/L
*** Susceptibility was interpreted based on standalone aztreonam's CLSI breakpoint of ≤4 mg/L

Show the radiological images during the first episode of pyelonephritis with abscess, pre- and post-treatment with zidebactam/cefepime. This patient is currently on follow-up with no further episodes of UTI (Table 1).

DISCUSSION

Rising antimicrobial resistance due to repeated exposure to antibiotics and the immunocompromised status of the patient, posing a risk for recurrent infections, forms a vicious cycle that makes treatment of resistant Gram-negative infections very challenging in the cancer population. Furthermore, effective treatment options for XDR Gram-negative pathogens are limited. However, WCK 5222 is a unique β-lactam enhancer/β-lactam combination of cefepime with

bicyclo-acyl hydrazide zidebactam, which acts as a β-lactam enhancer [2,3]. Besides protecting hydrolysis of cefepime by serine-β-lactamases, zidebactam also has standalone antibacterial properties, due to the potent penicillin-binding protein 2 binding in Gram-negative bacteria [4].

There are case reports and case series that describe the use of WK5222 for the treatment of XDR *Pseudomonas aeruginosa* [2-5]. Although ceftolozane-tazobactam, imipenem-relebactam, and ceftazidime-avibactam are effective combinations against certain carbapenem-resistant *P. aeruginosa* isolates, they are ineffective against MBL-producing isolates [4]. Furthermore, due to the non-availability of ceftolozane-tazobactam and imipenem-relebactam in India, polymyxins are the major treatment options in such situations. However, literature for the use of WCK 5222 for XDR *Klebsiella* or *Escherichia coli* producing metallo-β-lactamases is probably scarce due to widespread availability of agents such as intravenous tigecycline, fosfomycin, ceftazidime-avibactam, and aztreonam combinations as other therapeutic options in our country [6,7]. This case report describes the use of WCK 5222 in niche situations where the above agents are either resistant or ineffective due to PK properties, such as tigecycline or polymyxin B, for use in UTIs due to XDR/MDR Klebsiella or *E. coli*. In a study by Bakthavatchalam *et al*, zidebactam/cefepime demonstrated potent activity with MIC_{50} and MIC_{90} of 1 and 2 mg/L, respectively, against carbapenem- and colistin-resistant *K. pneumonia*e isolates while MIC_{90}s of amikacin, ceftazidime/avibactam, and imipenem/relebactam were >32 mg/L [8]. To the best of our knowledge, this is the first case report in the literature describing the successful use of WCK 5222 for monomicrobial infection caused by XDR *K. pneumoniae* under compassionate use grounds.

CONCLUSION

The zidebactam/cefepime MIC for the carbapenem- and colistin-resistant *K. pneumoniae* strain in the case was 32 mg/L. Zidebactam/cefepime demonstrated clinical efficacy in this patient, supporting its therapeutic scope for infections with MICs up to 64 mg/L.

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