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CASE REPORT

Cefiderocol in the Successful Treatment of Complicated Hospital-Acquired K. pneumoniae NDM, OXA48 Intraabdominal Infection

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Background: *Klebsiella pneumoniae* MDR/XDR constitutes a difficult to treat bacteria in a number of infections as there are few therapeutic options. Promising drugs in such cases can be cefiderocol, aztreonam and ceftazidime/avibactam or meropenem/vaborbactam.

Case Presentation: A 72-year-old female patient with sepsis caused by KP NDM, OXA 48 was admitted to the Intensive Care Unit, immediately after an emergency graftectomy (of a recently transplanted kidney) complicated with bleeding. Because of suspicion of intra-abdominal infection, a broad-spectrum empirical antibiotic therapy was initiated (meropenem, vancomycin, colistin). The patient underwent an abdominal revision 48 hours after admission. On the 3rd day of hospitalization, diagnosis of a septic shock with etiology of KP NDM, OXA 48 was made. The strain had sensitivity to a colistin and a cefiderocol. On 13th day in the ICU a relaparotomy was performed. Again, KP strains with sensitivity to cefiderocol only, were cultured from intra-abdominal fluid. Aztreonam, in combination with meropenem/vaborbactam, were included in the treatment and were used together with colistin and tigecycline. In the following days, the inflammatory markers decreased slightly, but the patient's general condition did not improve. On day 27 ceftazidime/avibactam and aztreonam were added, while colistin, meropenem/vaborbactam and fosfomycin were discontinued. On 37th day of hospitalization, cefiderocol became available in hospital and was included in the treatment. Cefiderocol monotherapy was continued for 8 days. After 4 days of cefiderocol treatment, the inflammatory markers CRP and PCT decreased and a significant improvement in patient's condition were observed. On day 56, the patient was transferred to another department.

Conclusion: A surgical debridement of a source infection, and usage of meropenem/vaborbactam or ceftazidime/avibactam together with aztreonam and colistin allowed survival of the patient but not full recovery. Ultimately, only the cefiderocol monotherapy was effective in treatment of the patient with septic shock of KP NDM OXA 48 etiology.

Keywords: cefiderocol, meropenem/vaborbactam, ceftazidime/avibactam, Klebsiella pneumoniae NDM, septic shock

Introduction

Ever-increasing resistance of microorganisms causes gradual loss of effectiveness of longer available antimicrobials including colistin. The problem is profoundly pronounced in Poland where drug resistance of several bacteria has reached alarming levels.[1]

Cefiderocol, ceftazidime/avibactam, meropenem/vaborbactam, eravacycline, plazomicin are novel formulations introduced in order to counter the increasing number of multi-drug resistant Gram-negative pathogens, especially carbapenem-resistant Enterobacterales.[2–4]

Cefiderocol (a siderophore cephalosporin) was introduced in the European Union in 2020. Its primary indication are infections with limited therapeutic options caused by susceptible Gram-negative microorganisms. It was also approved by FDA for the treatment of complicated urinary tract infections (cUTI), hospital-acquired pneumonia (HAP) including

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ventilator associated pneumonia (VAP). Cefiderocol is stable to the hydrolytic effect of all Ambler classes of beta-lactamases, including class B metallo-beta-carbapenemases (MBLs). [2,5]

Meropenem/vaborbactam was approved for medical use in Europe in 2018 and its indication for use are cUTI, complicated intra-abdominal infections (cIAI) and HAP including VAP. It is stable to beta lactamases class A (eg ESBL, KPC) and class C (eg AmpC).[3] Ceftazidime/avibactam was approved by EMA for medical use in 2016 for the treatment HAP, VAP, cUTI, cIAI, bacteremia and Gram-negative aerobic infections with limited therapeutic options.[3] It is stable to beta lactamases class A (eg ESBL, KPC), class C (eg AmpC) and some class D (eg OXA 48). Ceftazidime/avibactam and meropenem/vaborbactam are not stable to MBLs. The addition of aztreonam to ceftazidime/avibactam or meropenem/vaborbactam has been successful, but not in this case.

Klebsiella pneumoniae, a Gram-negative bacterium, causes numerous community acquired and hospital infections. Its MDR strains with various resistance mechanisms (including New Delhi metallo-beta-lactamase 1, and OXA-48 carbapenemase) became one of the most important dangers for patients in hospital settings. KP NDM and OXA-48 is in recent years an emerging threat both in Wroclaw University Hospital and Poland (authors' materials;[6]).

NDM strains are resistant to all β-lactams except aztreonam, while OXA-48 enzyme activity varies allowing different groups of β-lactams to be hydrolyzed, most predominantly penicillin and carbapenems.[7,8]

In this paper, we report the successful use of cefiderocol after others novel beta-lactam antibiotics combinations usage in a life-threatening case of an intra-abdominal infection caused by *K. pneumoniae* NDM, OXA-48 ultimately resistant to colistin.

Case Presentation

A 72-year-old woman, underwent kidney transplant in Wroclaw University Hospital. The surgery was complicated by a venous thrombosis of the graft and, two days later, thrombectomy of the renal vein was performed. Four weeks later, a marked increase of C-reactive protein and procalcitonin were noted, and the CT scan of the abdomen revealed multiple intra-abdominal abscesses, mostly around the transplanted kidney. Cultures from the patient's blood grew *Klebsiella pneumoniae* NDM, OXA-48 and meropenem in combination with colistin were started. Graftectomy of the transplanted kidney was performed and the patient was admitted to the ICU with the diagnosis of intraabdominal sepsis.

Patient's medical history included end-stage renal failure due to an interstitial non-bacterial nephritis, peritoneal dialysis, parenchymal goiter, Graves-Basedow disease, secondary hyperparathyroidism, atherosclerosis, mild carotid artery stenosis, moderate aortic stenosis, esophageal hernia, chronic gastritis, sigmoid diverticulitis, rectal polyps and mixed hyperlipidemia.

On admission to the ICU, the patient was sedated with propofol and fentanyl, was intubated and mechanically ventilated with 40% oxygen, blood pressure was 110/65 mmHg with norepinephrine infusion 13 microgram per minute, pulse was 74 beats per minute. Temporary abdominal wall closure was used due to surgical packing for hemostasis. Meropenem and colistin were continued and vancomycin was added. Results of the cultures obtained from the patient during ICU stay are shown in Table 1.

Continuous veno-venous hemodiafiltration with citrate anticoagulation was started. Detailed analysis of infection biomarkers is presented in Figure 1.

During hospitalization, the patient had persistent coagulation disorders with intermittent anemia compensated by transfusions of red blood cell concentrate and fresh frozen plasma.

The patient underwent an abdominal revision 48 hours after admission to the ICU, during which the hemostatic packing was removed, and the abdominal wall was closed.

Due to persistent hypotension, high-dose norepinephrine and vasopressin infusions were continued in the following days. Atrial fibrillation was treated with amiodarone.

On ICU day 3, there was a marked increase of CRP and procalcitonin level and antibiotic therapy was changed to meropenem/vaborbactam and linezolid. Septic shock was diagnosed.

Antibiotics administered throughout the ICU stay are shown in Table 2, and selected values of infection markers at admission/discharge from ICU, and in relation to the initiation and/or the end of antibiotic treatment are presented in Table 3.

Table 1 Pathogens Isolated from the Patient During Stay at the ICU

Place of Isolation	Name of Pathogen	Type of Drug Resistance
Abdomen	*Klebsiella pneumoniae* *Staphylococcus spp.*	NDM, OXA-48
Blood	*Klebsiella pneumoniae*	NDM, OXA-48, MDR
Surgical wound	*Klebsiella pneumoniae*	NDM, OXA-48, MDR
Bronchi	*Pseudomonas aeruginosa*	XDR/MDR
Throat	*Klebsiella pneumoniae* *Pseudomonas aeruginosa*	NDM, OXA-48, PDR XDR, CRPA
Rectum	*Klebsiella pneumoniae* *Enterococcus faecium*	NDM, OXA-48, MDR HLAR/GRE
Urine	*Enterococcus faecium* *Candida albicans*	HLCR

On ICU day 5, ultrasonography of the abdomen revealed a fluid collection in the right lateral abdominal region and the skin in the corresponding area became reddened.

On ICU day 6, CRP level reached 674,74 mg/L while PCT level dropped to 12.45 ng/mL. A CT scan performed on the next day showed striated fluid collections in the place of graftectomy in the right iliac fossa, corresponding morphologically to abscesses. Fosfomycin and tigecycline were added to the treatment, while linezolid was discontinued.

On the following day, due to anisocoria and a suspicion of stroke, a CT scan of the head was performed, which revealed a mediocre hyperdense sign of the right middle cerebral artery in section M3/4, possibly suggesting fresh

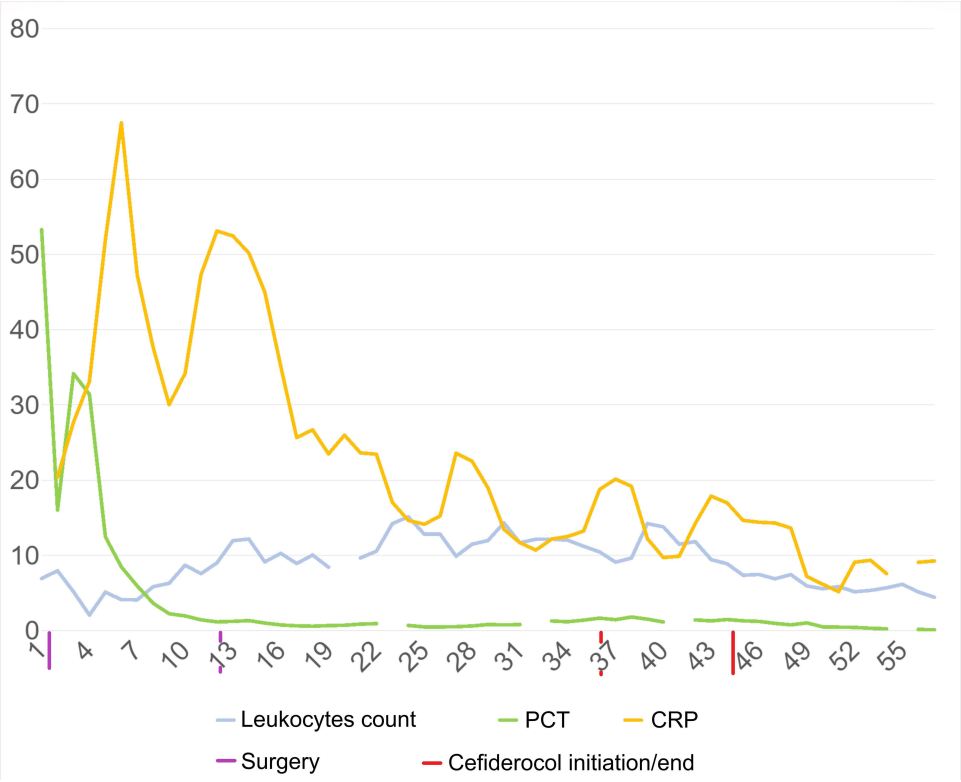

Figure 1 CRP, PCT and leukocytes count of the patient throughout hospitalization at the ICU with marked surgeries and cefiderocol therapy.

Table 2 Antibiotics Administered Throughout Hospitalization at ICU. Data Was Shown as Days from Admission to ICU

Name of antibiotic	Initiation and Finish of Antibiotic Administration
Meropenem	1–4
Vancomycin	1–3
Colistin	1–27
Linezolid	3–7
Fosfomycin	3–13; 20–27
Meropenem / vaborbactam	4–17
Aztreonam	13–21; 28–37
Fluconazole	11–27
Tigecycline	13–20
Ceftazidime / avibactam	28–37
Amikacin	30–37
Cefiderocol	37–44
Ceftazidime	45–50
Piperacillin / tazobactam	50–56

Table 3 Selected Infection Markers at Admission/Discharge from ICU, in Relation to the Initiation and/or the End of a Chosen Antimicrobial Treatment

	Admission	COL + LIN + FOS + MEV, 1	COL + LIN + FOS + MEV, 2	COL + FOS + MEV + AZT, 1	COL + FOS + MEV + AZT, 2	COL + FOS + MEV + AZT + FLC, 1	COL + FOS + MEV + AZT + FLC, 2; COL + AZT + FLC + TIG, 1	COL + AZT + FLC + TIG, 2	CTV + AZT, 1	CTV + AZT, 2; CID, 1	CID, 2	Discharge
Leucocyte count [1000/μL]	7.4	5.1	4.07	5.82	8.67	7.55	11.93	9.02	11.46	9.08	8.87	5.75
Neutrophils [% Leukocyte count]									76%	75%	70%	51%
CRP[mg/L]	203.97	331.23	472.51	375.97	341.6	473.21	524.54	259.63	224	201	146	92
PCT [ng/mL]	53.29	31.39	5.91	3.61	1.93	1.41	1.2	0.69	0.79	1.43	1.2	0.09

Abbreviations: COL, colistin; LIN, linezolid; FOS, fosfomycin; MEV, meropenem / vaborbactam; AZT, aztreonam; FLC, fluconazole; TIG, tigecycline; CTV, ceftazidime / avibactam; AMI, amikacin; CID, cefiderocol; 1, initiation; 2, end. For eg - COL, 1, initiation of colistin.

ischemia. According to the neurological consultation, this did not allow a definite diagnosis of stroke. Coagulation abnormalities and the risk of abdominal bleeding precluded anticoagulant treatment.

On ICU day 10, an inflammatory infiltrate appeared along the surgical wound, with a small leakage of purulent discharge from the lower end of the wound. Wound cultures yielded Klebsiella pneumoniae NDM, OXA-48 strains sensitive to colistin and cefiderocol. An ultrasound examination of the area of the wound on the 10th day showed inflammatory infiltration with strips of fluid. On ICU day 13, a relaparotomy was performed and an abdominal drain was placed. A culture of the purulent

contents, taken intraoperatively, grew a strain of Klebsiella pneumoniae NDM resistant to colistin and sensitive only to cefiderocol. Aztreonam, in combination with meropenem/vaborbactam, colistin and tigecycline, were prescribed.

In the following days, the inflammatory biomarkers decreased slightly, but the patient's general condition did not improve – the blood pressure was supported with vasopressors and cardiac arrhythmias were present. Despite renal replacement therapy and albumin supplementation, massive peripheral edema persisted.

Elevated inflammatory markers persisted after surgery, the post-operative wound did not heal and a purulent discharge leaked out. The wound was treated with antiseptic lavage. During subsequent days, a negative pressure wound therapy (VAC – Vacuum-Assisted Closure of a wound) was applied.

On ICU day 23, a tracheostomy was performed and the patient was gradually weaned off sedation. In the following days, the patient regained consciousness and opened her eyes, but was very weak and could hardly move her limbs.

On ICU day 27, antimicrobial therapy was modified. Ceftazidime/avibactam and aztreonam were started, while colistin and fosfomycin were discontinued. On ICU day 30, amikacin was also added. These interventions caused a decrease in CRP level to 124,88 mg/L, but in the following day inflammatory markers increased again, while cultures from bronchial aspirate grew *Pseudomonas aeruginosa* and cultures from surgical wound grew *Klebsiella pneumoniae* NDM.

On ICU day 37, cefiderocol (Fetcroja, Shionogi B.V., Netherlands) became available at the hospital pharmacy and it was immediately included in the treatment, while other antibiotics were discontinued. Cefiderocol therapy was continued for 8 days with a good clinical response. After 4 days of the cefiderocol therapy, inflammatory markers decreased and there was a marked improvement in the abdominal wound healing. On ICU day 42, the VAC therapy of the wound could be discontinued. After completion of cefiderocol therapy ventilation associated tracheobronchitis developed and treatment with ceftazidime followed by piperacillin/tazobactam in targeted therapy was included. Culture from bronchial aspirate grew *Pseudomonas aeruginosa* XDR. Also on ICU day 47, urinary tract infection was diagnosed and linezolid was added for Enterococcus faecium cultured in urine. This resulted in a further decrease of infection biomarkers. With each day the patient was improving. The muscle strength was better and, by the ICU day 47, she was weaned from mechanical ventilation. The norepinephrine infusion was stopped on ICU day 52, and the tracheostomy tube was removed on ICU day 54. She could speak and move her limbs in bed. She had plans to return to painting landscapes when she returned home. On ICU day 56, continuous renal replacement therapy was stopped and on the next day she was transferred to Nephrology Department for further treatment, hemodialysis and rehabilitation. One month later, she was finally discharged home.

Selected infection markers at admission/discharge from ICU, in relation to the initiation and/or the end of a chosen antimicrobial treatment are presented in Table 3.

Discussion

Intra-abdominal infections are a common clinical presentation of surgical infections.[9] The results of a Polish study indicate that surgical infections were the most common cause of sepsis, affecting 56% of the analyzed patients admitted to the ICU, and IAIs were the most common causes of surgical infections (49%).[10] IAIs were shown to have an out-of-hospital source in 86.7% and a hospital source in only 13.3%.[9]

Complicated IAIs treated in the ICU often have a character of a generalized infection (sepsis or septic shock) and have a mortality rate of up to 31.2%.[11] According to the results of a recently published study, infectious complications of surgical site infections/other after kidney transplantation in elderly patients occur in 22.7% of patients.[12]

The case presented here is an example of a complicated intra-abdominal infection in a renal transplant patient classified as a deep/intestinal surgical site infection. Complicated IAI with peritoneal involvement and abscess formation with the clinical picture of sepsis requires management according to the Surviving Sepsis Campaign recommendations, among which prognostic significance are: removal of the source of infection, rapid microbiological diagnosis, antibiotic therapy and fluid resuscitation, extracorporeal therapies like CRRT.[13] Beginning from the ICU admission, the patient presented symptoms of a septic shock with cardiovascular, respiratory and renal failure.

The diagnostic and treatment methods used were in accordance with international recommendations for the diagnosis and treatment of sepsis.[13]

Upon admission to the ICU, the patient's blood was drawn for culture and empirical, broad-spectrum treatment (carbapenem and vancomycin) was administered. This was in accordance with SSC recommendations for the treatment of sepsis, as well as with Infectious Diseases Society of America recommendations for the treatment of nosocomial intra-abdominal infections.[13,14] Because Resistance of Gram-negative bacterial strains, especially Enterobacterales to third-generation cephalosporins, carbapenems, as well as vancomycin resistance among enterococci is a global problem.[1,15–17] In the case presented here, the source of sepsis was IAI. The targeted colistin used for treatment at admission was directed against a multidrug-resistant strain of Klebsiella pneumoniae NDM, OXA 48 isolated from blood 3 days before admission to the ICU. In the local hospital for many years, the predominant pathogens of nosocomial infections have been *Acinetobacter baumannii* XDR and *Klebsiella pneumoniae* with an increasing proportion of NDM strains.[18,19] Hospital procedures for the treatment of infections that take into account microbiological mapping of the ward allow the use of colistin (in combination treatment with other drugs depending on the clinical form of the infection) for empirical treatment of HAIs (also in IAIs).

The use of appropriate methods of diagnostic imaging (including abdominal CT) and surgical eradication of the source of infection are essential elements of proper treatment of sepsis according to the recommendations of numerous scientific bodies, as was the case here.[13,14]

The most dire problem in the described clinical situation was the increasing resistance of the *Klebsiella pneumoniae* strain to colistin, despite its use in the recommended dose. This forced the use of antibiotic combinations recommended in the literature for the treatment of G- negative MDR, MBL bacteria strains infections in the hope to aid in patient survival during the long wait for cefiderocol, which is available in Poland only for direct emergency import.[20–23] The use of the association meropenem/vaborbactam with aztreonam and ceftazidime/avibactam with aztreonam are described in the literature as potentially effective associations for the treatment of *Klebsiella pneumoniae* NDM MBL infections.[20–23] In the case described here, these drugs did significantly improve inflammatory parameters and allowed effective treatment of septic shock and kept the patient alive despite not being able to eradicate the KP strain. Hovewer, complete recovery, including significant improvement on neurological state, was made possible by cefiderocol treatment. Efficacy of cefiderocol in the treatment of infections was shown in a number of case reports and analyses including ICU patients.[24–26]

In an era of increasing strain resistance to the antibiotics used, infections with MDR *Klebsiella pneumoniae* strains, in addition to *Acinetobacter baumannii* MDR and enterococci VRE strains, contribute to higher mortality rates than infections caused by other pathogens.[27]

The presented case is unique in that it shows a severe infection with *Klebsiella pneumoniae* MBL NDM XDR strain with a rare colistin resistance, treated with a regimen never described to the best of the authors' knowledge. A combination therapy against KP MBL with meropenem/vaborbactam and later with added aztreonam followed by ceftazidime/avibactam + aztreonam allowed effective treatment of the septic shock and a survival of patient in wait for the cefiderocol shipment.

Nevertheless, the treatment with cefiderocol in monotherapy, an antibiotic used for one of the initial times in Poland, allowed definitive cure of IAI infection and a recovery of the patient. Following the patient's response to cefiderocol, it is vital to underline that earlier availability could have positively influenced on earlier patient recovery.

Despite cefiderocol efficacy in the treatment, it should be noted that there are already strains of bacteria resistant to this novel drug.[28]

This case report has several limitations. It should be noted that the success of the aforementioned combination therapy cannot be determined conclusively, as other drugs were also used in the treatment of the IAI, as shown in Tables 2 and 3. These drugs, in conjunction with the antibiotics mentioned above, may have contributed to the improvement in the clinical condition. Given the limited number of antibiotics potentially effective against Gram-negative strains with MBL resistance mechanisms, it would be beneficial to assess the MIC for cefiderocol. Additionally, cefiderocol should be made available in all hospitals, particularly if local epidemiology indicates a high prevalence of such strains in the hospital environment.

Conclusion

This case has shown that a surgical debridement of a source infection, an intensive therapy of multiorgan failure and an appropriate targeted antibiotic therapy can improve septic patient condition. Despite the usage of meropenem/vaborbactam or ceftazidime/avibactam together with aztreonam and colistin, ultimately only the cefiderocol monotherapy was successful in the treatment of the septic shock with *Klebsiella pneumoniae* NDM OXA 48 etiology.

Abbreviations

Amp.C, batalactamase AmpC; cIAIs, complicated intra-abdominal infections; CRE, carbapenem-resistant enterobacteriales; CRP, C reactive protein; cUTIs, complicated urinary tract infections; CVVHDF Ci-Ca, continuous veno-venous hemodiafiltration with citrate anticoagulation; ESBL, extended spectrum beta-lactamase; HAP, hospital-acquired pneumonia; IAIs, intra-abdominal infections; ICU, Intensive Care Unit; KP, Klebsiella pneumoniae; KPC, Klebsiella pneumoniae carbapenemase; MDR, multidrug resistant; NDM, New Delhi metallo-beta-lactamase 1; VAP, ventilator associated pneumonia.

Ethical Statement and Informed Consent

This case report received approval from the Bioethics Committee of Wroclaw Medical University (Approval No. KB–369/2024) and it was prepared in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from the patient for the publication of this case report.

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Disclosure

The authors report no conflicts of interest in this work.

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