



Case report

Carbapenemase-producing *Klebsiella pneumoniae* intra-abdominal infection successfully treated with ceftazidime/avibactam plus tigecycline



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ARTICLE INFO

Article history:

Received 11 January 2020

Received in revised form 8 March 2020

Accepted 8 March 2020

Keywords:

Intra-abdominal infection
Carbapenemase-producing *Klebsiella pneumoniae*
Ceftazidime/avibactam
Tigecycline

ABSTRACT

Ceftazidime/avibactam combines ceftazidime with a new beta-lactam that successfully that inhibits Amber Class A and D carbapenemases.

We report a clinical case of a 61 year-old man with a carbapenemase-producing *Klebsiella pneumoniae* intra-abdominal infection after an elective abdominal hernia repair. The infection was successfully managed with multiple abdominal surgeries, drainage and combined antibiotic therapy with ceftazidime/avibactam plus tigecycline.

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Introduction

Carbapenemase-producing *Klebsiella pneumoniae* (CP-Kp) is a global health problem [1]. Infections by this microorganism are associated with high mortality [2,3].

Ceftazidime/avibactam is a combination of a well-known third generation cephalosporin with broad-spectrum activity against Gram-negative pathogens [4] and a novel β -lactamase inhibitor that is active against Ambler class A and some class D carbapenemases [5].

We report a clinical case of a CP-Kp intra-abdominal infection successfully treated with ceftazidime/avibactam plus tigecycline.

Case presentation

A 61 year-old man with history of open sigmoidectomy with colostomy for intestinal occlusion was admitted to perform a prosthetic ventral incisional hernia repair. As a complication from this procedure the patient developed secondary peritonitis with an intra-abdominal abscess initially managed with antibiotic therapy

(piperacillin/tazobactam plus vancomycin) and abscess drainage. However, one week after stopping previous antibiotic therapy, the patient presented clinical deterioration with fever, hypotension (blood pressure 85/54 mmHg) and purulent drainage from the surgical wound.

Investigations

The blood analysis revealed high inflammatory markers (white blood count $11 \times 10^9/L$ and C reactive protein 382.1 mg/L) and abdominal computed tomography (CT) described infected soft tissues with necrosis. Exploratory laparotomy was performed which confirmed presence of various intra-abdominal abscesses with necrosis and pus. Peritoneal debridement and cleaning as well as hernia prosthesis removal were performed. In the samples collected during this surgical intervention a multi-susceptible *Proteus mirabilis* and extended-spectrum beta-lactamase (ESBL) producing *Escherichia coli* were identified. (Table 1) Antibiotic therapy was changed to vancomycin (dose adjusted by plasmatic therapeutic drug monitoring) plus meropenem 1 g every 8 h. Despite this optimized antibiotic treatment, the patient maintained fever, purulent fluid drainage from the surgical wound, increasing inflammatory markers (C reactive protein 290 mg/L) and increased intra-abdominal collections. The microbiological analysis of newly collected surgical wound pus identified a

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Table 1
Antibiotic susceptibility of the microbiological isolates.

Sample	Peritoneal fluid (13/Jul/18)		Surgical wound pus (18/Jul/18)			Peritoneal fluid (08/Aug/18)		Peritoneal fluid (21/Aug/18)		Respiratory samples (28/Aug/18) Klebsiella pneumoniae
	<i>Proteus mirabilis</i>	<i>Escherichia coli</i>	Klebsiella pneumoniae	<i>Proteus mirabilis</i>	<i>Escherichia coli</i>	Klebsiella pneumoniae	<i>Escherichia coli</i>	Klebsiella pneumoniae	<i>Escherichia coli</i>	
Amikacin	S	S	S	S	S	S	S	S	S	S
Amoxicillin/ Clavulanic Acid	S	R	R	–	R	R	R	R	R	R
Ampicilin	S	R	R	–	R	R	R	R	R	R
Cefepime	S	S	R	S	S	R	I	R	I	R
Cefotaxime	S	R	R	–	R	R	R	R	R	R
Ceftazidime	S	R	R	S	R	R	R	R	R	R
Cefuroxime	S	R	R	–	R	R	R	R	R	R
Ciprofloxacin	S	S	R	S	S	R	S	R	S	R
Colistin	–	–	S (MIC 0,5 µg/mL)*	–	–	S (MIC 0,25 µg/mL)*	S (MIC 0,25 µg/mL)*	S (MIC 0,25 µg/mL)*	S (MIC 0,25 µg/mL)*	R (MIC 16 µg/mL)*
Ertapenem	S	S	R (MIC 16 µg/mL)**	–	S	R (MIC 6 µg/mL)**	R (MIC 1,5 µg/mL)**	R (MIC > 32 µg/mL)**	R (MIC 2 µg/mL)**	R (MIC > 32 µg/mL)**
Fosfomycin	–	–	–	–	–	–	–	R	S	–
Imipenem	–	–	R (MIC > 32 µg/mL)**	S	–	I (MIC 6 µg/mL)**	I (MIC 4 µg/mL)**	R (MIC > 32 µg/mL)**	(MIC 4 µg/mL)**	R (MIC > 32 µg/mL)**
Gentamicin	S	S	S	S	S	S	S	S	S	S
Meropenem	–	–	R (MIC 16 µg/mL)**	–	–	I (MIC 4 µg/mL)**	S (MIC 1 µg/mL)**	R (MIC > 32 µg/mL)**	(MIC 0,5 µg/mL)**	R (MIC > 32 µg/mL)**
Piperacilin/ Tazobactam	S	R	R	S	R	R	R	R	R	R
Tigecycline	–	–	I	–	–	–	–	S	S	S (MIC 1 µg/mL)
Trimetoprim/ Sulfametoxazol	S	S	R	S	S	R	R	R	R	R
ESBL[#]	–	Positive	Negative	–	Negative	Negative	Positive	Negative	Negative	Negative
KPC^{##}	–	Negative	Positive	–	–	Positive	Positive	–	–	–

Legend: Susceptibility testing performed with: VITEK[®]2 bioMérieux. R, resistant; S, sensitive; I, intermediate.
MIC: Minimum inhibitory concentration. ESBL, Extended-Spectrum Beta-Lactamase. KPC, *Klebsiella pneumoniae* Carbapenemase.

* Microdilution; EUCAST cut-off.

** E-test; EUCAST cut-off.

Vitek[®] 2 Advanced Expert System.

Xpert[®] Carba-R assay.

KPC-producing *Klebsiella pneumoniae* and an infectious diseases consultation was requested.

Treatment

Antibiotic therapy was changed to meropenem 2 g every 8 h plus colistin 4.5 million IU every 12 h (after a loading dose of 9 million IU) plus gentamicin 5 mg/kg every 24 h and susceptibility testing to colistin, tigecycline and ceftazidime/avibactam was requested.

The microbiology laboratory confirmed *Klebsiella pneumoniae* susceptibility to colistin (minimum inhibitory concentration of 0,5 µg/mL) and intermediate susceptibility to tigecycline (although unable to determine the minimum inhibitory concentration), however the susceptibility test to ceftazidime/avibactam was not available. As such, with this information, we decided to change antibiotic therapy to colistin 4.5 million IU every 12 h plus high dose tigecycline 100 mg every 12 h. Moreover, a new laparotomy with peritoneal debridement and drainage through the surgical wound with a vacuum system was performed. The microbiological samples collected during this procedure identified the same microorganisms as before (Table 1).

The patient was admitted to intensive care unit (ICU) due to a nosocomial pneumoniae. During ICU admission the antibiotic therapy was changed to vancomycin plus meropenem 1 g every 8 h plus colistin 4.5 million IU every 12 h. No microorganisms were identified in the respiratory samples, 5 days of vancomycin were completed and combined therapy with low dose meropenem plus colistin was continued for 32 days. At exploration during vacuum system replacement, there was a progressive decline in the purulent discharged and inflammatory signs of the surgical wound and the control abdominal CT scan showed reduction in dimension and number of intra-abdominal collections with only one small abscess of 23 mm. The microbiological samples collected during vacuum system replacement identified the same microorganisms as before but the respiratory samples collected during ICU stay identified a *K. pneumoniae* resistant to colistin. (Table 1)

The patient was discharged to the surgical ward and seven days after stopping antibiotics a second infectious disease consultation was requested due to fever. On physical exploration there was an abundant purulent discharged from the vacuum system, with the remaining physical exam unremarkable. Blood analysis showed increased inflammatory parameters (white blood count $22 \times 10^9/L$ and C reactive protein 52.1 mg/L) with normal glomerular filtration rate (GFR) [151 mL/min/1.73m² (MDRD Equation)].

The diagnosis of a relapsed intra-abdominal surgical site infection was made. Assuming the high probability of the same microorganisms being implicated in this infection, and considering also the known respiratory colonization with a carbapenemase-producing colistin-resistant *Klebsiella pneumoniae* and the long course of therapy with colistin, we decided to re-start antibiotic therapy with a combined regimen using ceftazidime/avibactam 2.5 g every 8 h plus high dose tigecycline (100 mg every 12 h after a loading dose of 200 mg).

Outcome and follow-up

A total of 13 days of combined therapy with ceftazidime/avibactam plus tigecycline was completed without any adverse events. The inflammatory markers decreases (white blood count $9 \times 10^9/L$ and C reactive protein 10 mg/L) and abdominal CT scan showed no signs of intra-abdominal infection. The patient was discharged 3 months after hospital admission without clinical signs of intra-abdominal infection.

Discussion

We report a clinical case of a Cp-Kp intra-abdominal infection successfully managed with ceftazidime/avibactam plus tigecycline.

Even though our patient was exposed to well-known risk factors for carbapenem-resistant Enterobacteriaceae (CRE) acquisition (long length of intensive care unit stay, multiple surgeries and use of broad-spectrum antibiotic therapy) [6], the ongoing KPC-producing *Klebsiella pneumoniae* outbreak in the Surgical Ward during his admission certainly played a role in colonization and subsequent infection.

Ceftazidime/avibactam was approved in Europe in 2016 for treatment of complicated intra-abdominal infections (cIAI) [4]. Recent studies have reported increased clinical and microbiological cure, decreased mortality and a better safety profile in treatment of CRE infections with ceftazidime/avibactam [7,8], when compared to other antibiotic regimens (colistin or aminoglycoside monotherapy or combined therapy with carbapenem plus aminoglycoside or colistin) [9,10].

In the absence of the susceptibility test to ceftazidime/avibactam, initially we decided to use combined therapy with meropenem plus colistin, taking in consideration that combined therapy in CRE infections had been associated with increased survival when compared to monotherapy [2,11–13].

Unfortunately, the selection of colistin resistance in a strain of *Klebsiella pneumoniae* in the respiratory tract during therapy and the relapsed intra-abdominal infection posed a therapeutic challenge. Outbreaks with colistin-resistant and carbapenemase-producing *K. pneumoniae* isolates have been reported worldwide and are associated with even higher mortality rates owing to limited treatment options [14,15].

Ceftazidime/avibactam should be considered for the treatment of carbapenemase-producing gram negative microorganisms when the susceptible test is available. However, its use as the backbone drug in a combined regimen is still a matter of debate. With the widespread use of this new antibiotic we expect selection of ceftazidime/avibactam resistance. Microbiologic failure due to selection of resistant strains has already been reported [7] with resistance to this new antibiotic related to the increased expression of KPC-3 and mutations in the OmpK35 porin gene [16–19]. To overcome this problem, some authors recommend addition of aminoglycoside or polymyxin B in severe infections or when source control is an issue [20].

Taking in consideration the intra-abdominal infection, the antimicrobial susceptibility profile available and the current available evidence, we decided to use combined therapy with ceftazidime/avibactam plus double dose tigecycline and successful clinical recovery was achieved.

Conclusion

Ceftazidime/avibactam is an option to overcome the limitations of carbapenemase-producing *Klebsiella pneumoniae* infections treatment.

Colistin should be used with caution, especially in high inoculum infections, due to increasing selection of resistance.

More studies should be performed in order to access the benefits of adding a non β-lactam antibiotic to the ceftazidime/avibactam backbone.

Antimicrobial stewardship and infection prevention and control teams are important to improve patient outcome, especially in settings with high prevalence of extremely drug resistant bacteria.

Ethical considerations

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor in-Chief of this journal on request.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

CRediT authorship contribution statement

Mariana Guedes: Conceptualization, Methodology, Investigation, Writing - original draft, Writing - review & editing. **Raquel Duro:** Writing - review & editing. **Telma Fonseca:** Writing - review & editing. **Isabel Abreu:** Writing - review & editing. **Nuno Rocha-Pereira:** Writing - review & editing, Supervision.

Declaration of Competing Interest

None.

Acknowledgements

None.

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