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Short Communication

KPC-producing *Klebsiella pneumoniae* gut decolonisation following ceftazidime/avibactam-based combination therapy: A retrospective observational study☆

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ABSTRACT

Objectives: KPC-producing *Klebsiella pneumoniae* (KPC-Kp) gut colonisation is a major risk factor for developing systemic infection. Ceftazidime/avibactam (CAZ/AVI) may have a role as decolonisation therapy in special situations.
Methods: This was a retrospective, observational, multicentre study. The KPC-Kp gut decolonisation rate of CAZ/AVI-based therapy (Group A) was compared with other antimicrobial regimens (Group B) in patients with KPC-Kp infection.
Results: Among 12 patients in Group A, 11 (91.7%) achieved gut decolonisation. None of the 24 patients of Group B were decolonised.
Conclusion: CAZ/AVI-based therapy could be useful in KPC-Kp gut decolonisation in high-risk patients.

1. Introduction

Ceftazidime/avibactam (CAZ/AVI) is a novel combination of an old third-generation cephalosporin (ceftazidime) and a new β-lactamase inhibitor (avibactam) with activity against Ambler class A, C and, with certain variability, class D β-lactamases that has been recently approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [1]. Nowadays, CAZ/AVI represents the drug of choice for the treatment of *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* (KPC-Kp) infections [2].

KPC-Kp gut colonisation is recognised as a substantial risk factor for developing KPC-Kp systemic infection [3,4]. Several decontamination strategies have been previously investigated with satisfactory but not conclusive results. Oral gentamicin alone [4–7] and a combination of gentamicin with colistin [8] achieved decolonisation rates of 42–71% and 60%, respectively. Although patients tend to be rapidly re-colonised following discontinuation of the decolonising regimen and/or further antibiotic treatment [3,4,7,8], decolonisation reduced the risk of mortality and infections [3] and might be useful in specific high-risk situations [3,4]. Systemic therapy with CAZ/AVI might have a role in these situations, and its adjunctive 'decoloniser' effect might be useful for infection control and/or clinical purposes.

2. Patients and methods

An observational, retrospective, multicentre study was conducted to evaluate KPC-Kp gut decolonisation as a secondary effect

☆ The results of this study have been presented as a poster presentation at the 28th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), 21–24 April 2018, Madrid Spain.

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of CAZ/AVI-based antimicrobial therapy. Data for all patients with a KPC-Kp infection and gut colonisation who were treated with compassionate use of a CAZ/AVI-based regimen and who underwent at least a second evaluation of their KPC-Kp carriage state at the end of treatment (Group A) from May 2017 to February 2018 were retrospectively analysed. As a historical control group, patients with a KPC-Kp infection and gut colonisation with the following criteria were selected: (i) patients were treated with a different antimicrobial regimen; and (ii) oral decolonisation was not administered (Group B). Groups A and B were on a 1:2 ratio. Rectal swabs were performed for every patient coming from another hospital or ward and/or with exposure to healthcare in the previous 3 months. Gut colonisation was defined as a positive culture on selective medium and a positive molecular test on two different rectal swabs performed at the same time. Rectal swab collection followed the manufacturer's instructions. All enrolled patients suffered from a microbiologically and clinically confirmed infection due to KPC-Kp. KPC enzyme production was confirmed in all enrolled patients by boronic acid disk test (Diatabs phenylboronic acid; Rosco Diagnostica, Taastrup, Denmark) and a molecular test (Xpert® Carba-R; Cepheid, Sunnyvale, CA); VIM- and OXA-48-type enzymes were also ruled out by an immunochromatographic assay (Resist-3 O.K.N. K-Set; Coris BioConcept, Gembloux, Belgium). Decolonisation was defined as detection of the negativity of two consecutive cultures and at least one molecular test on rectal swabs at the end of antimicrobial treatment.

An antimicrobial regimen was established following ad hoc disk diffusion test to determine the synergistic activity of CAZ/AVI with meropenem, imipenem, fosfomycin, colistin, amikacin, gentamicin and tigecycline. All antibiotics were administered at standard dosages. In particular, CAZ/AVI 2.5 g every 8 h (q8 h), meropenem 2 g q8 h, imipenem 1 g every 6 h (q6 h), fosfomycin 4 g q6 h, colistin 4.5 million units (MU) every 12 h (q12 h) following a 9 MU loading dose, amikacin 15 mg/kg/day, gentamicin 3 mg/kg/day and tigecycline 100 mg q12 h following a 200 mg loading dose. In the case of renal impairment, the dose was reduced according to the instructions provided by the manufacturer.

Fisher's exact test was performed to evaluate the statistical significance of the results. A P-value of <0.05 was considered as the threshold of significance.

3. Results

A total of 12 patients in Group A and 24 patients in Group B were enrolled in the study. Table 1 summarises the primary infections, antimicrobial regimens and decolonisation results for the patients in both groups.

The median patient age was 63.5 years in Group A and 69.5 years in Group B. There were 8/12 (66.7%) males in Group A and 14/24 (58.3%) males in Group B ($P > 0.05$). Moreover, 11/12 patients (91.7%) in Group A and all patients (24/24; 100%) in Group B were treated with combination antimicrobial therapy ($P > 0.05$).

Table 1
Patient characteristics, antimicrobial regimens and rectal decolonisation.

Patient/sex	Infection	Therapy	Rectal decolonisation
Group A			
A01–M	ABSSSI	CAZ/AVI, meropenem and fosfomycin	Yes
A02–F	cIAI and sepsis	CAZ/AVI, meropenem and fosfomycin	Yes
A03–F	Spondylodiscitis	CAZ/AVI, meropenem and fosfomycin	Yes
A04–F	Surgical wound infection	CAZ/AVI, meropenem and fosfomycin	Yes
A05–M	HAP	CAZ/AVI and colistin	Yes
A06–M	HAP	CAZ/AVI and gentamicin	Yes
A07–F	Osteomyelitis	CAZ/AVI and gentamicin	Yes
A08–M	cIAI	CAZ/AVI	No
A09–M	cIAI	CAZ/AVI, gentamicin and tigecycline	Yes
A10–M	cIAI	CAZ/AVI, amikacin and tigecycline	Yes
A11–M	Sepsis	CAZ/AVI, colistin and tigecycline	Yes
A12–M	cIAI	CAZ/AVI, colistin and tigecycline	Yes
Group B			
B01–F	Sepsis	Imipenem and tigecycline	No
B02–M	Surgical wound infection	Colistin, rifampicin and tigecycline	No
B03–F	Sepsis	Colistin, fosfomycin and tigecycline	No
B04–M	Catheter-associated UTI	Colistin, imipenem, fosfomycin and tigecycline	No
B05–F	HAP	Tigecycline and fosfomycin	No
B06–F	Surgical wound infection	Tigecycline and gentamicin	No
B07–M	Sepsis	Tigecycline and gentamicin	No
B08–F	Sepsis	Colistin, meropenem and amikacin	No
B09–M	cIAI	Colistin, fosfomycin and tigecycline	No
B10–M	Sepsis	Colistin, meropenem and tigecycline	No
B11–M	cIAI	Tigecycline, meropenem and gentamicin	No
B12–F	HAP	Tigecycline, rifampicin, ertapenem and gentamicin	No
B13–M	HAP	Colistin, rifampicin and tigecycline	No
B14–F	Sepsis	Colistin, meropenem and tigecycline	No
B15–M	HAP	Colistin, meropenem and tigecycline	No
B16–M	cIAI	Colistin, fosfomycin and tigecycline	No
B17–M	Sepsis	Colistin, meropenem, gentamicin and tigecycline	No
B18–M	HAP	Colistin and tigecycline	No
B19–M	Sepsis	Colistin and tigecycline	No
B20–M	Sepsis	Colistin, meropenem and tigecycline	No
B21–M	Sepsis	Colistin, rifampicin, meropenem and tigecycline	No
B22–F	cIAI	Meropenem and tigecycline	No
B23–F	Surgical wound infection	Colistin, rifampicin and tigecycline	No
B24–F	Surgical wound infection	Imipenem and ertapenem	No

M, male; F, female; ABSSSI, acute bacterial skin and skin-structure infection; cIAI, complicated intra-abdominal infection; HAP, hospital-acquired pneumonia; UTI, urinary tract infection; CAZ/AVI, ceftazidime/avibactam.

In Group A, 11/12 (patients 91.7%) were decolonised. The mean follow-up was 39.5 days (range 4–74 days). Only one patient in Group A had a persistently positive rectal swab for KPC-Kp and was the only patient treated with CAZ/AVI monotherapy. Successful treatment of the infection with CAZ/AVI monotherapy or combination therapy was achieved in 9/12 patients (75.0%) in Group A.

None of the Group B patients were decolonised ($P < 0.01$).

4. Discussion and conclusions

CAZ/AVI has shown promising results against multidrug-resistant (MDR) Gram-negative micro-organisms both in pivotal and real-life trials [9–11]. Moreover, as previously described in an anecdotal report [12], CAZ/AVI may have a potential role in gut decolonisation. The findings of the present study show that 11/12 patients treated with a CAZ/AVI-based therapy were decolonised and this success rate was higher than those reported by other decolonising treatments such as gentamicin or a combination of gentamicin plus colistin [4–8]. Oren et al. described a 44% eradication rate with the development of resistance to gentamicin and colistin, which was described in 6/26 and 1/16 cases, respectively [7]. Some cases of CAZ/AVI resistance, although rare, have been reported [13], representing one of the main matters of concern of the scientific community. This concern should restrict CAZ/AVI use to severe MDR Gram-negative infections. In the current study, KPC-Kp gut decolonisation represents, besides clinical efficacy, a secondary unexpected outcome during the treatment of a KPC-Kp infection; it might reduce the rate of resistance selection.

KPC-Kp gut colonisation is a well-known risk factor for KPC-Kp systemic infection, especially in neutropenic patients and in the case of major surgery [3,7,14]. In these special situations, more effective decolonisation could be useful to reduce the risk of systemic infection, and CAZ/AVI administration could be taken into account.

According to the findings of the present study, combination therapy appears to be more effective than CAZ/AVI monotherapy in gut decolonisation. The only non-decolonised patient in Group A was treated with CAZ/AVI alone. Since a definite conclusion regarding the best therapy for KPC-Kp infection between CAZ/AVI monotherapy and combination therapy is still not available [14], to avoid the possible emergence of resistant strains combination therapy could be preferable also for gut decolonisation.

This study presents several limitations since it is retrospective, non-randomised and with a small sample size, thus any conclusions in the use of CAZ/AVI for gut decolonisation should be taken with caution. Nevertheless, these data suggest that CAZ/AVI-based combination therapy could be used for gut decolonisation in high-risk patients with KPC-Kp infection with an expected very high success rate. Larger studies are needed to confirm the findings of our experience.

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Competing interests

CT has received funds for speaking at symposia organised on behalf of Pfizer, Novartis, Merck, Thermo Fisher, Gilead, Angelini and Astellas; CP has received funds for speaking at symposia organised on behalf of Merck, Angelini and Bristol-Myers Squibb; MBa has participated in advisory boards and/or received speaker honoraria from Achaogen, Angelini, Astellas, AstraZeneca, Bayer, Basilea, Cidara, Gilead, Menarini, MSD, Paratek, Pfizer, Roche, The Medicines Company, Shionogi, Tetraphase, VenatoRx and Vifor. All other authors declare no competing interests.

Ethical approval

Not required. Patients provided their consent for data analysis and submission.

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