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Short Communication

Infections by OXA-48-like-producing *Klebsiella pneumoniae* non-co-producing extended-spectrum beta-lactamase: Can they be successfully treated with cephalosporins?

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ABSTRACT

Background: OXA-48 is an Ambler class D β-lactamase that hydrolyses penicillin and imipenem but has poor hydrolytic activity against cephalosporins. However, very few clinical experiences of treating extended-spectrum β-lactamase (ESBL)-negative OXA-48 producers with cephalosporins have been published.
Objectives: The aim of this study was to report clinical experience of infections due to ESBL-negative OXA-48-producing *Klebsiella pneumoniae* (*K. pneumoniae*) treated with cephalosporins.
Patients and methods: A retrospective study was conducted at Vall d'Hebron University Hospital, in Barcelona (Spain). It reviewed all microbiological isolates of OXA-48-producers that did not co-produce ESBL from May 2014 to May 2017, and included only clinical strains of patients treated with a cephalosporin for ≥72 h.
Results: From the 75 isolations of OXA-48 producers, there were 17 isolations of ESBL-negative OXA-48-producing *K. pneumoniae*. Three patients were treated with cephalosporins with successful outcomes: a pneumonia in a neutropenic patient treated with cefepime and amikacin; an acute focal nephritis of a renal graft treated with ceftriaxone; and an intrabdominal post-surgical infection treated with cefepime in combination with tigecycline at the beginning, and ciprofloxacin afterwards.
Conclusions: Cephalosporins could be an alternative treatment in selected patients with ESBL-negative OXA-48-producing *K. pneumoniae* infections, especially to avoid carbapenem use. However, it remains unknown if they should be given in combination.
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1. Introduction

Due to their rapid spread and challenging treatment, infections caused by multidrug-resistant Enterobacteriaceae have become a matter of major concern [1]. An example of this is the OXA-48-like-producing *Klebsiella pneumoniae* (*K. pneumoniae*) initially identified from a carbapenem-resistant *K. pneumoniae* isolate from Istanbul, Turkey, in 2001 [2], which has caused many outbreaks in different countries since then [3–6]. OXA-48-like carbapenemases are Ambler class D β-lactamases that hydrolyse penicillin and imipenem, but have low hydrolytic activity against cephalosporins and do not confer cephalosporin resistance [2,7,8]. However, most OXA-48-like producers are also extended-spectrum-β-lactamase (ESBL) producers [9,10]. Ceftazidime has shown antibacterial activity against OXA-48-like producers lacking ESBLs or AmpC in animal models [11,12], but very little clinical experience has been published [13,14]. The aim of this study was to report clinical experience treating non-ESBL OXA-48-like-producing *K. pneumoniae* infections with cephalosporins.

2. Patients and methods

A retrospective study was performed at Vall d'Hebron University Hospital, a 1000-bed tertiary referral hospital, in Barcelona (Spain). All positive cultures of OXA-48-like-producers that did not co-produce ESBL (one culture per patient) from May

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2014 to May 2017 were reviewed. Surveillance cultures were discarded and only patients who had received at least 72 h of treatment with a cephalosporin were included. Demographic, clinical, and microbiological data were retrospectively collected through an electronic chart review and entered in a database specifically created for the study. This study adhered to the principles of the Declaration of Helsinki, formulated by the World Medical Association.

Susceptibility to β-lactams was determined by disc diffusion, and in cases of carbapenems – including meropenem, ertapenem and imipenem – additionally by MIC gradient strip test (Etest, bioMérieux, Marcy l'Étoile, France), following EUCAST recommendations [15]. Detection of ESBLs in Enterobacteriaceae was based on non-susceptibility to cefotaxime and ceftazidime, and synergy between clavulanate and at least one of the following antibiotics: cefotaxime, ceftazidime, aztreonam and cefepime. Evidence suggestive of carbapenemase production was determined using EUCAST screening cut-off values (disk inhibition zones of <28 mm for meropenem and <25 for ertapenem; or MICs > 0.125 mg/L for meropenem and/or ertapenem). Additionally, phenotypic testing for carbapenemase production – including Modified Hodge test, Temocillin susceptibility, and double-disk synergy test method with meropenem combined with boronic acid, cloxacillin or dipicolinic acid – was performed on isolates with suggestive production of carbapenemase [16,17]. If phenotypic testing was positive, the presence of the genes encoding carbapenemases OXA-48-like, KPC, VIM, IMP, IMI, and NDM were screened by PCR, as previously described.

3. Results

From the 75 cultures in which an OXA-48-like Enterobacteriaceae was obtained during the study period, 17 (22.7%) corresponded to non-ESBL OXA-48-like-producing *K. pneumoniae* (Fig. 1), three of which were treated with cephalosporins (Table 1).

The first case was a 60-year-old female who was neutropenic due to an acute myeloid leukaemia and had a rectal colonisation with a non-ESBL OXA-48-like-producing *K. pneumoniae.* She was admitted for pneumonia with positive blood cultures for the same microorganism that was successfully treated with cefepime (2 g every 8 h) and amikacin (1 g every 24 h) for 14 days. However, 1 week after discharge and finishing antibiotic therapy, she was still neutropenic and had a new episode of bacteraemia, without pneumonia, probably due to gastrointestinal translocation. Blood cultures were positive again for non-ESBL OXA-48-like-producing *K. pneumoniae,* which remained susceptible to cefepime, and she was treated with amikacin (1 g every 24 h) for 7 days. During the 12 months of follow-up, she did not present with any more infectious complications.

The second case was a 76-year-old female with a kidney transplant who presented with an acute focal renal graft pyelonephritis with urine culture positive for a non-ESBL OXA-48-like-producing *K. pneumoniae.* She initially received 2 days of ceftazidime (2 g every 8 h) that, due to good clinical course, was changed to ceftriaxone (2 g every 24 h) so she could continue treatment on an outpatient basis for 3 weeks. At 10 months of follow-up, she did not have any new urinary tract infections.

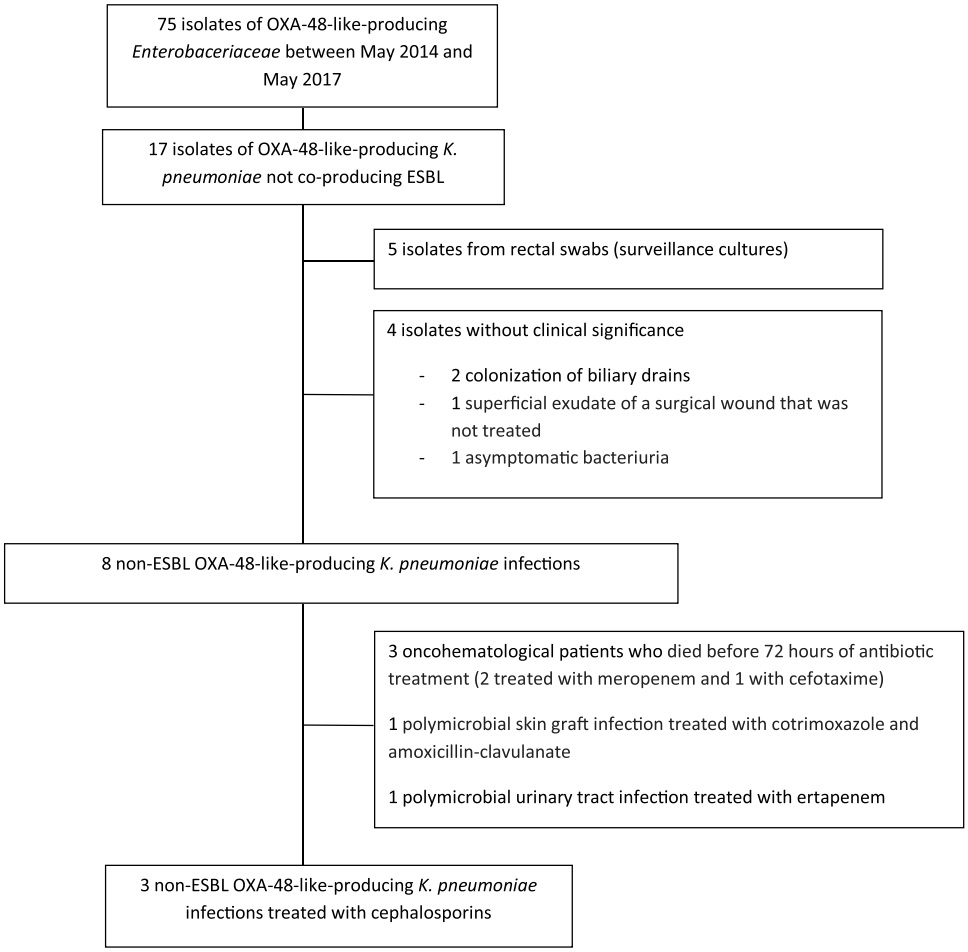

Fig. 1. Flowchart of included patients.

Table 1
Demographic, clinical and microbiological characteristics of the three non-ESBL OXA-48-like-producing *Klebsiella pneumoniae* infections treated with cephalosporins.

Case (sex, age)	Main comorbidities	Type of infection	Sample	Antimicrobial MICs (μg/mL) and EUCAST interpretation												Antimicrobial treatment and duration	Clinical outcome at the end of treatment
				AMC	CXM	CTX	CAZ	FEP	IPM	MEM	AMK	CIP	SXT	FOF	NIT	TGC	
Case 1 (female, 60 years)	Acute myeloid leukaemia and neutropenia	Pneumonia	Blood cultures	>256 (R)	64 (R)	0.75 (S)	0.75 (S)	1 (S)	3 (I)	3 (I)	1 (S)	>32 (R)	>32 (R)	32 (S)	NA	2 (I)	Cefepime 2 g q8h IV and amikacin 1 g q24 h IV (14 d)	Cure
Case 2 (female, 76 years)	Kidney transplant	Acute focal nephritis of the renal graft	Urine culture	>256 (R)	16 (R)	0.38 (S)	0.25 (S)	0.5 (S)	0.75 (S)	1.5 (S)	2 (S)	>32 (R)	>32 (R)	32 (S)	64 (I)	0.75 (S)	Ceftazidime 2 g q8h IV (2 d) and then ceftriaxone 2 g q24 h IV (21 d)	Cure
Case 3 (male, 78 years)	Cephalic duodeno-pancreatectomy due to an ampullary carcinoma	Post-surgical intraabdominal infection and acute pancreatitis	Blood cultures	>256 (R)	12 (R)	0.5 (S)	0.125 (S)	0.5 (S)	4 (I)	>32 (R)	1 (S)	0.023 (S)	0.38 (S)	24 (S)	NA	0.5 (S)	Cefepime 2 g q8h IV and tigecycline 100 mg q12 h IV (18 d) and then cefepime 2 g q8h IV, ciprofloxacin 400 mg q12 h IV, metronidazole 500 mg q8h IV (12 d)	Cure

Abbreviations: MIC, minimal inhibitory concentration; AMC, amoxicillin-clavulanic acid; CXM, cefuroxime; CTX, cefotaxime; CAZ, ceftazidime; FEP, cefepime; IPM, imipenem; MEM, meropenem; AMK, amikacin; CIP, ciprofloxacin; SXT, trimethoprim-sulfamethoxazole; FOF, fosfomycin; NIT, nitrofurantoin; TGC, tigecycline; IV, intravenous.

The third case was a 78-year-old male who underwent a scheduled cephalic duodenopancreatectomy due to an ampullary carcinoma. He presented with a post-surgical intraabdominal infection and acute pancreatitis with positive blood cultures for non-ESBL OXA-48-like-producing *K. pneumoniae* and *Escherichia coli* (only resistant to ampicillin). He was initially treated with cefepime (2 g every 8 h) and tigecycline (100 mg every 12 h) but after 18 days he developed a coagulation disorder related to tigecycline. Antibiotic therapy was changed to cefepime (2 g every 8 h), ciprofloxacin (400 mg every 12 h) and metronidazole (500 mg every 8 h), finishing 30 days of treatment with good clinical outcome at the end of treatment and no relapses at 6 months of follow-up.

4. Discussion

This paper presents three different non-ESBL OXA-48-like-producing *K. pneumoniae* infections that were successfully treated with expanded-spectrum cephalosporins in high doses; two of the cases were in combination with a second antimicrobial. Although OXA-48-like producers show low-level resistance or susceptibility to several carbapenems, there is currently little clinical experience in treating these infections with carbapenems, at least in monotherapy, with contradictory results, since several failures of imipenem-containing therapy to treat OXA-48 infections have been reported [3,4,18–20]. In addition, there is a theoretical risk of selecting in vivo mutants with increased levels of resistance to carbapenems [1,7]. Therefore, it is worth focusing on carbapenem-sparing regimens.

OXA-48-like producers that do not co-produce ESBL hydrolyse cefotaxime very poorly and do not significantly hydrolyse ceftazidime nor cefepime [2,7]. An experimental lethal peritonitis model was induced in mice with an OXA-48-producing *K. pneumoniae* isolate that did not co-produce an ESBL [11]. This strain exhibited decreased susceptibility to carbapenems and susceptibility to broad-spectrum cephalosporins. Administration of a single dose of the antibiotics piperacillin-tazobactam, imipenem-cilastatin, ertapenem, or cefotaxime had little or no impact on lethality, in contrast to ceftazidime, which had the highest efficacy in vivo, which mirrored the in vitro activity. It is believed that there are only two more clinical case reports about successfully treating ESBL-negative and OXA-48-producing Enterobacteriaceae with cephalosporins: a new-born infection treated with a combination of cefotaxime and amikacin [13], and a central-catheter infection in a woman with acute lymphoblastic leukaemia treated with ceftazidime plus colistin and catheter removal [14].

No randomized clinical trials have compared combination therapy with monotherapy for patients with infections due to carbapenemase producers. Two of the current patients were treated in combination, since they were considered to be difficult-to treat infections. Published data suggest that combination therapy may be beneficial for high-risk patients, depending on the source of infection, and presence of septic shock, but also suggest that monotherapy may be enough for lower-risk patients. As more studies are needed, selection of the appropriate therapy should be made case-by-case [1,7,20].

This study had some limitations, mainly its retrospective nature and the difficulty in assessing clinical cure with combination therapy. However, all patients with non-ESBL OXA-48-like-producing *K. pneumoniae* isolates were analysed and the three-mentioned difficult-to-treat infections were successfully treated with cephalosporins.

5. Conclusions

In conclusion, cephalosporins in high doses could be an alternative treatment in selected patients with non-ESBL OXA-

48-like-producing *K. pneumoniae* infections, especially to avoid carbapenem use. However, their use in monotherapy or combined therapy remains unknown and further clinical studies should be performed to investigate this issue. Until then, each case should be individualised.

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None.

Competing interests

None.

Ethical approval

This study adhered to the 60 principles of the Declaration of Helsinki, formulated by the World Medical Association.

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