Journal of Antimicrobial Chemotherapy

J Antimicrob Chemother
doi:10.1093/jac/dkx496

Clinical outcomes after combination treatment with ceftazidime/avibactam and aztreonam for NDM-1/OXA-48/CTX-M-15-producing *Klebsiella pneumoniae* infection

Evelyn Shaw[1,2]*, Alexander Rombauts[1], Fe Tubau[3,4], Ariadna Padullés[5], Jordi Càmara[3], Toni Lozano[5], Sara Cobo-Sacristán[5], Núria Sabe[1,2], Imma Grau[1,4,6], Raül Rigo-Bonnin[7], M. Angeles Dominguez[2,3,6] and Jordi Carratalà[1,2,6]

[1]*Department of Infectious Diseases, Hospital Universitari de Bellvitge-IDIBELL, Barcelona, Spain;* [2]*Spanish Network for Research in Infectious Diseases (REIPI RD12/0015/0008 and REIPI RD16/0016/0005), Instituto de Salud Carlos III, Madrid, Spain;* [3]*Department of Microbiology, Hospital Universitari de Bellvitge-IDIBELL, Barcelona, Spain;* [4]*CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain;* [5]*Department of Pharmacy, Hospital Universitari de Bellvitge-IDIBELL, Barcelona, Spain;* [6]*University of Barcelona, Barcelona, Spain;* [7]*Department of Clinical Laboratory, Hospital Universitari de Bellvitge-IDIBELL, Barcelona, Spain*

*Corresponding author. Department of Infectious Diseases, Hospital Universitari de Bellvitge-IDIBELL, Feixa Llarga s/n 08907 Hospitalet de Llobregat, Barcelona, Spain. Tel: +34-93-2607274; Fax: +34-93-2607637; E-mail: eshawp@gmail.com

Sir,

The growing spread of bacteria producing carbapenemases, such as the New Delhi MBL (NDM),[1] has created an urgent need to identify effective therapeutic options that can treat serious infections caused by these XDR bacteria. Ceftazidime/avibactam has been successfully used to treat infection caused by carbapenem-resistant Enterobacteriaceae;[2,3] however, the combination lacks activity against strains producing NDM. These carbapenemases remain susceptible to aztreonam, although most MBL-producing isolates also harbour ESBLs or other β-lactamases that confer resistance to aztreonam.[4] The combination of aztreonam and avibactam has demonstrated potent *in vitro* activity against MBL-producing Enterobacteriaceae including those isolates that also carry other β-lactamases.[5] However, this combination is currently in clinical development and unavailable for clinical use.

In our hospital, we experienced an outbreak of *Klebsiella pneumoniae* ST147 in late 2015 caused by an XDR strain producing NDM-1 + OXA-48 + CTX-M-15 (KP-HUB-ST147).[6] Herein, we retrospectively review the outcomes of 10 patients treated with ceftazidime/avibactam plus aztreonam between January 2016 and June 2017 at Bellvitge University Hospital, Barcelona, Spain. All patients were attended by an infectious diseases physician after informing the patient about the need for using the combination therapy and obtaining oral consent. As ceftazidime/avibactam was still not approved by the Spanish Medicines Agency, this antibiotic was obtained on a compassionate basis. This study had the approval of the local Ethics Committee (reference: EPA033/17). Clinical success was defined as survival and the absence of recurrence at day 30 after the onset of the infection, with resolution of the signs and symptoms of infection, and sterilization of site-specific cultures within 7 days of starting combination therapy.[7] To check for long-term recurrence, patients were followed up for 90 days after the onset of infection. Recurrence was defined as a new positive culture with the reappearance of clinical signs and symptoms of infection after clinical success.

The MICs of antibiotics were determined via microdilution, using a commercial NC53 panel by the MicroScan system (Beckman Coulter, Inc.) and a DKMGN panel by the Sensititre™ system (TREK Diagnostic Systems Ltd). The synergistic activity of ceftazidime/avibactam and aztreonam was tested *in vitro*, using disc diffusion [ceftazidime/avibactam (30/20 μg) and aztreonam (30 μg)]. All isolates showed synergistic activity. MIC clinical breakpoints were defined according to EUCAST.[8]

Ten patients received ceftazidime/avibactam and aztreonam; five of them (50%) were receiving immunosuppressant therapy (three were liver recipients, one was a kidney recipient and one was receiving long-term corticosteroid therapy). In total, five (50%) infections were bacteraemic (four were secondary and one was primary). All infections were caused by a KP-HUB-ST147, which was resistant to β-lactam antibiotics, including aztreonam (MIC >32 mg/L), ceftazidime/avibactam (MIC >16/4 mg/L), meropenem (MIC >16 mg/L), imipenem (MIC >16 mg/L), aminoglycosides, fluoroquinolones and trimethoprim/sulfamethoxazole, and only showed intermediate susceptibility to tigecycline (MIC = 2 mg/L). In four patients, the strain was resistant to colistin (MIC >8 mg/L). Clinical success was achieved in 6 of the 10 patients (60%). Failures were due to death ($n = 3$) and recurrence ($n = 1$). Two of the six patients with clinical success (33.3%) had a recurrence within 90 days, but these were patients with structural anomalies at the site of infection. One infection was a bacteraemic cholangitis in a liver recipient and the other was a febrile urinary tract infection in a patient with radical cystoprostatectomy with Studer reconstruction. Recurrences occurred 30 days and 12 days after the antibiotic therapy had been withdrawn. The 30 day mortality rate was 30% (3/10) and the median number of days to death was 20 days (range, 17–21 days). None of the deaths was considered related to the infection. Moreover, there were no adverse events related to the combination therapy during follow-up. Table 1 summarizes patient characteristics.

Consistent with our findings, a recent investigation has demonstrated *in vitro* synergistic activity and bactericidal effect of the combination of ceftazidime/avibactam and aztreonam. The authors also reported successfully treating a patient with a

Table 1. Characteristics and outcomes of patients treated with ceftazidime/avibactam and aztreonam

Patient	Age (sex)	Underlying disease	Charlson (SOFA[a])	Type of infection	Bacteraemia	Previous therapies[b] (intravenous)	Aztreonam dose	Ceftazidime/ avibactam dose	Glomerular filtration rate (mL/min/1.73 m^2)	Overall days of therapy	Clinical outcome at day 30	Recurrence at day 90
1	59 (M)	liver transplant	3 (2)	cholangitis[c]	yes	meropenem plus ertapenem plus tigecycline plus aztreonam	2 g q8h	2.5 g q8h	100	28	success	yes
2	62 (F)	renal transplant	4 (12)	hospital-acquired pneumonia	no	meropenem plus tigecycline plus colistin	2 g q24h (CI)	1.25 g q24h (EI)	17	10[e]	failure (death)	–
3	70 (M)	bladder cancer	5 (0)	cUTI	yes	colistin	3 g q24h (CI)	2.5 g q8h (EI)	100	14	success	yes
4	77 (M)	liver transplant	9 (4)	cUTI	no	colistin	2 g q24h (CI)	940 mg q12h (EI)	28	10	failure (death)	–
5	80 (M)	metastatic bone prostate cancer	13 (2)	catheter-related bacteraemia	yes	–	1 g q8h	2.5 g q8h	50	3[f]	failure (death)	–
6	82 (F)	kidney stones	6 (1)	pyelonephritis	yes	colistin	3 g q24h (CI)	2.5 g q8h (EI)	68	14	success	no
7	61 (F)	kidney stones	2 (1)	pyelonephritis[d]	no	–	3 g q24h (CI)	1.25 g q8h	41	10	failure (recurrence)	–
8	58 (M)	liver transplant	5 (2)	biliary peritonitis[c]	yes	–	1 g q8h	2.5 g q8h	73	18[g]	success	no
9	59 (M)	cirrhosis	4 (9)	hospital-acquired pneumonia	no	–	3 g q24h (CI)	2.5 g q8h	90	14	success	no
10	77 (M)	oesophageal cancer	6 (4)	mediastinitis[c]	no	–	3 g q24h (CI)	2.5 g q8h	90	28	success	no

M, male; F, female; cUTI, complicated urinary tract infection; CI, continuous infusion; EI, extended infusion.
[a]SOFA was recorded at onset of the infection.
[b]They included targeted therapies to treat the infection.
[c]Patient required surgical drainage.
[d]Patient required a ureteral stent placement (JJ stent).
[e]Patient received concomitantly inhaled colistin.
[f]Patient received only 3 days of therapy because he had improved after the catheter removal. Blood cultures at the end of therapy were negative.
[g]Patient received concomitantly intravenous tigecycline and inhaled colistin.

hip arthroplasty site infection caused by an XDR NDM-1-producing strain of *Enterobacter cloacae*.[9] A successful experience has also been recently reported using this combination for treating a patient with a suppurated thrombophlebitis and persistent bacteraemia due to an OXA-48/NDM-1-producing *K. pneumoniae*.[10]

Although the safety of combination therapy with ceftazidime/avibactam and aztreonam could be a legitimate cause for concern among clinicians, we observed no adverse events in our series. However, it should be noted that the retrospective nature of the study and the small number of patients may have limited our ability to detect non-severe adverse events.

In summary, our clinical data suggest that combination therapy with ceftazidime/avibactam plus aztreonam would be a safe therapeutic option for treating severe infection caused by Enterobacteriaceae harbouring NDM plus other β-lactamases and carbapenemases. Therefore, this combination could be considered in the absence of alternative therapeutic options.

Funding

This work was supported by Planes Nacionales de I+D+i 2008–2011/2013–2016 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Ministerio de Economía y Competitividad, Spanish Network for Research in Infectious Diseases (REIPI RD12/0015/0008 and REIPI RD16/0016/0005) co-financed by European Development Regional Fund 'A way to achieve Europe' and Operative programme Intelligent Growth 2014–2020 (E. S., N. S., M. A. D. and J. C.) and by grants from CIBER de Enfermedades Respiratorias, CIBERES (CB06/06/0037), Instituto de Salud Carlos III (F. T. and I. G.).

Transparency declarations

None to declare.

References

1 Albiger B, Glasner C, Struelens M *et al*. Carbapenemase-producing Enterobacteriaceae in Europe: assessment by national experts from 38 countries, May 2015. *Euro Surveill* 2015; **20**: pii=30062.

2 Temkin E, Torre-Cisneros J, Beovic B *et al*. Ceftazidime–avibactam as salvage therapy for infections caused by carbapenem-resistant organisms. *Antimicrob Agents Chemother* 2017; **61**: e01964-16.

3 Shields RK, Nguyen MH, Chen L *et al*. Ceftazidime–avibactam is superior to other treatment regimens against carbapenem-resistant *Klebsiella pneumoniae* bacteremia. *Antimicrob Agents Chemother* 2017; **61**: e00883-17.

4 Nordmann P, Naas T, Poirel L. Global spread of carbapenemase-producing Enterobacteriaceae. *Emerg Infect Dis* 2011; **17**: 1791–8.

5 Karlowsky JA, Kazmierczak KM, de Jonge BLM *et al*. *In vitro* activity of aztreonam–avibactam against Enterobacteriaceae and *Pseudomonas aeruginosa* isolated by clinical laboratories in 40 countries from 2012 to 2015. *Antimicrob Agents Chemother* 2017; **61**: e00472-17.

6 Càmara J, Shaw E, Cubero M *et al*. Outbreak due to an extensively drug-resistant *Klebsiella pneumoniae* harbouring bla_{NDM-1} and/or bla_{OXA-48} in Barcelona, Spain. In: *Abstracts of the Twenty-seventh European Congress of Clinical Microbiology and Infectious Diseases, Vienna, Austria, 2017*. Abstract OS0290. ESCMID, Basel, Switzerland.

7 Shields RK, Potoski BA, Haidar G *et al*. Clinical outcomes, drug toxicity, and emergence of ceftazidime–avibactam resistance among patients treated for carbapenem-resistant Enterobacteriaceae infections. *Clin Infect Dis* 2016; **63**: 1615–8.

8 EUCAST. *Breakpoint Tables for Interpretation of MICs and Zone Diameters, Version 7.1*. 2017. http://www.eucast.org.

9 Marshall S, Hujer AM, Rojas LJ *et al*. Can ceftazidime–avibactam and aztreonam overcome β-lactam resistance conferred by metallo-β-lactamases in Enterobacteriaceae? *Antimicrob Agents Chemother* 2017; **61**: e02243-16.

10 Davido B, Fellous L, Lawrence C *et al*. Ceftazidime–avibactam and aztreonam, an interesting strategy to overcome β-lactam resistance conferred by metallo-β-lactamases in Enterobacteriaceae and *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2017; **61**: e01008-17.