justifications for aztreonam dosing, then $fT_{>MIC}$ between 45% and 70% would seem appropriate. This is longer than the Gram-negative $fT_{>MIC}$ targets for cephalosporins of 30%–40%[7] and for carbapenems of 20%–35%[8] and more similar to that for penicillins of 30%–60%.[9] All the above data show the robustness of dilutional *in vitro* models in defining pharmacodynamic target sizes and their close alignment with animal models. Previous concerns about washout have also been shown to be baseless[10] and indeed dilutional models may be superior to hollow-fibre systems in terms of cost-effectiveness, biofilm formation and modelled drug concentrations.

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Transparency declarations

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Successful rescue treatment of sepsis due to a pandrug-resistant, NDM-producing *Klebsiella pneumoniae* using aztreonam powder for nebulizer solution as intravenous therapy in combination with ceftazidime/avibactam

Elske Sieswerda[1]*, Marre van den Brand[2], Roland B. van den Berg[3], Joris Sträter[4], Leo Schouls[5], Karin van Dijk[1] and Andries E. Budding[6]

[1]Department of Medical Microbiology and Infection Control, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; [2]Department of Medical Microbiology, Meander Medical Centre, Amersfoort, The Netherlands; [3]Department of Clinical Pharmacology and Pharmacy, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; [4]Department of Nephrology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; [5]Centre for Infectious Diseases Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands; [6]inBiome, Amsterdam, The Netherlands

*Corresponding author. E-mail: e.sieswerda@amsterdamumc.nl

Sir,

Pandrug-resistant *Klebsiella pneumoniae* that produces New Delhi MBL (NDM) is increasingly reported worldwide.[1] These strains contain multiple β-lactamase genes but also may have acquired resistance to last-resort options such as colistin and tigecycline. Combining aztreonam and avibactam is potentially effective in MDR, NDM-producing Enterobacterales.[2] Avibactam inhibits class A, C and D ESBLs, cephalosporinases and carbapenemases, while aztreonam is stable to hydrolysis by class B MBLs such as NDM. Until this drug combination becomes available, one could combine

aztreonam and ceftazidime/avibactam to treat serious infections with such strains. A small number of studies have reported on 13 patients with serious infections with NDM-producing Enterobacterales who were successfully treated with aztreonam and ceftazidime/avibactam.[3–7] Evidence of clinical efficacy and safety is therefore limited at present. Also, aztreonam for IV use is not registered and readily available in many countries, including the Netherlands. We describe successful rescue treatment of a patient with sepsis due to a pandrug-resistant, NDM-producing *K. pneumoniae* using aztreonam powder for nebulizer solution as IV therapy in combination with ceftazidime/avibactam.

A woman in her sixties who had received a kidney transplant 2 months earlier underwent routine urinary culture screening. The culture grew *K. pneumoniae* resistant to all antimicrobial classes (Table 1). An in-house carbapenemase PCR showed that the strain carried an NDM carbapenemase gene. As she was asymptomatic, no treatment was started, but 9 days later she presented signs and symptoms of a kidney transplant pyelonephritis. We regarded aztreonam combined with ceftazidime/avibactam as the only promising treatment option for the pandrug-resistant *K. pneumoniae*. However, it was not clear whether we could import aztreonam for IV use to the Netherlands within a reasonable time. As the patient's condition deteriorated, we decided to administer aztreonam powder for nebulizer solution intravenously (1000 mg three-times daily, prepared from 14 vials of 75 mg, in extended infusion) in combination with ceftazidime/avibactam (2000 + 500 mg three-times daily by continuous infusion). The subsequent day the blood culture became positive with the pandrug-resistant *K. pneumoniae*. Immunosuppressive therapy was reduced and the patient received supportive care for sepsis. Her condition improved within 1 day after the start of combination therapy and she recovered completely with 14 days of therapy without signs of adverse events. Aztreonam for IV solution was imported from France 11 days after our urgent request to the Dutch Government. The patient had one mild pyelonephritis recurrence with the same strain and unchanged susceptibility pattern 1 month later and recovered with the same treatment. She consented to the publication of this report.

Table 1 shows phenotypic characteristics of the isolate. We assessed *in vitro* synergy by using gradient test superposition as previously described in this journal.[5] We compared MICs of the gradient test superposition with MICs of single gradient tests. We only found clinically relevant synergy (i.e. inhibition of the strain at drug concentrations below the breakpoints of both antimicrobials with gradient test superposition compared with single gradient tests) when combining aztreonam and ceftazidime/avibactam (Table 1).

Next-generation sequencing (HiSeq 2500 sequencer, BaseClear, Leiden, the Netherlands) reads were uploaded to the European nucleotide archive (accession number PRJEB33296) and used to perform resistome and replicome composition analysis (ResFinder, version 2.1, PlasmidFinder, version 1.3). These analyses showed that the isolate (MLST ST15) carried the bla_{NDM-1} carbapenemase gene, as well as the bla_{CMY-6}, $bla_{CTX-M-15}$, bla_{OXA-1}, bla_{OXA-10}, bla_{SHV-28} β-lactamase genes and *aac(3)-IIa*, *aac(6′)Ib-3* resistance genes, among others, conferring resistance to all β-lactams, aminoglycosides and fluoroquinolones. Similar to a previously described comparable strain, we did not identify resistance genes conferring resistance to colistin and tigecycline.[1]

Table 1. Phenotypic characteristics of the pandrug-resistant *K. pneumoniae*

Method	Antimicrobial	MIC (mg/L)	Interpretation[a]
Single susceptibility testing			
Vitek-2®			
	amoxicillin/clavulanic acid	≥32	resistant
	cefotaxime	≥64	resistant
	ceftazidime	≥64	resistant
	cefoxitin	≥64	resistant
	ciprofloxacin	≥4	resistant
	trimethoprim/sulfamethoxazole	≥320	resistant
	gentamicin	≥16	resistant
	imipenem	≥16	resistant
	meropenem	≥16	resistant
	nitrofurantoin	256	resistant
	piperacillin/tazobactam	≥128	resistant
	tobramycin	≥16	resistant
Gradient test			
	amikacin	>256	resistant
	aztreonam	>256	resistant
	ceftazidime/avibactam	>256	resistant
	ceftolozane/tazobactam	>256	resistant
	doripenem	>32	resistant
	eravacycline	4	resistant
	fosfomycin	>256	resistant
	imipenem	>32	resistant
	meropenem	>32	resistant
	plazomicin	>256	unknown
	sulbactam	>256	unknown
	tigecycline	6	resistant
Broth microdilution			
	colistin	16	resistant

Antimicrobial	MIC mg/L: single	MIC mg/L: combined with aztreonam	Interpretation[b]
Gradient test superposition			
amoxicillin/clavulanic acid	>256	12	synergy
ceftazidime/avibactam	>256	0.5	synergy
ceftolozane/tazobactam	>256	48	synergy
colistin	8	12	no synergy
meropenem	>32	16	synergy
piperacillin/tazobactam	>256	32	synergy

[a]According to EUCAST (www.eucast.org).
[b]Synergy was defined as the occurrence of an inhibition zone when an antimicrobial was combined with aztreonam.

We considered carefully before using aztreonam powder for nebulizer solution as off-label and unlicensed IV therapy. Aztreonam powder for nebulizer solution is a sterile product, without any additives that are known to be harmful. Also, it has a similar composition to the IV product. We expected that the benefits of

the product, i.e. potential survival and no other treatment alternatives, weighed against potential risks of the product, i.e. unexpected side effects. Before providing aztreonam powder for nebulizer solution intravenously, we asked for consent from the patient and the medical director of our hospital.

In conclusion, we report successful rescue treatment of a patient with sepsis due to a pandrug-resistant, NDM-producing *K. pneumoniae* using aztreonam powder for nebulizer solution as IV therapy in combination with ceftazidime/avibactam and reducing immunosuppressive therapy. As such strains have been reported worldwide, we request the pharmaceutical industry to make aztreonam for IV use and ceftazidime/avibactam readily available in all countries. When aztreonam for IV use is not registered in a country, our case demonstrates that rescue treatment with aztreonam powder for nebulizer solution as IV therapy may be considered after careful assessment of the potential benefits and harms. Future studies are awaited to define the efficacy and safety of the promising treatment combination of aztreonam and avibactam in patients with serious infections due to pandrug-resistant, NDM-producing *K. pneumoniae* and other Enterobacterales.

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Clinically significant drug interaction: letermovir and voriconazole

Arianne Duong [1,2], Ania Sweet[2,3], Rupali Jain[1,3,4], Joshua A. Hill[2–5], Steven A. Pergam [2–5], Michael Boeckh[2–5] and Catherine Liu[2–5]*

[1]School of Pharmacy, University of Washington, Seattle, WA, USA; [2]Seattle Cancer Care Alliance, Seattle, WA, USA; [3]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [4]Division of Allergy and Infectious Diseases, University of Washington, Seattle, WA, USA; [5]Clinical and Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

*Corresponding author. E-mail: catherine.liu@fredhutch.org

Sir,

Human cytomegalovirus (CMV) remains a serious complication of HSCT. In 2017, letermovir was approved for prophylaxis of CMV infection for high-risk patients following allogeneic HSCT.[1,2] Letermovir is an inhibitor of CYP3A4 and inducer of CYP2C19/2C9, which are common enzymatic pathways for many medications used in HSCT, including voriconazole.[2–4] Voriconazole is metabolized by CYP2C9 and CYP2C19, and co-administration with letermovir may lead to reduced voriconazole exposure through induction of these pathways.[3,4] In a study of healthy subjects who received letermovir 480 mg daily with voriconazole, voriconazole AUC and maximum serum concentration were reduced by 44% and 39%, respectively.[4] In addition, interpatient variability can be significant, with plasma concentrations of voriconazole varying up to 100-fold between patients.[5] Although letermovir is known to reduce voriconazole exposure, there are limited published data describing the implications of this interaction in clinical practice. Here, we report two cases of a clinically significant drug interaction between voriconazole and letermovir.