justifications for aztreonam dosing, then \( f_{T_{-MIC}} \) between 45% and 70% would seem appropriate. This is longer than the Gram-negative \( f_{T_{-MIC}} \) targets for cephalosporins of 30%–40% and for carbapenems of 20%–35% and more similar to that for penicillins of 30%–60%. All the above data show the robustness of dilutional washout have also been shown to be baseless 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**

None to declare.

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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**

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Sir,

Pandrug-resistant *Klebsiella pneumoniae* that produces New Delhi MBL (NDM) is increasingly reported worldwide. 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 Enterobacteriales. 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...
K. pneumoniae, the only promising treatment option for the pandrug-resistant strain. 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. 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 resistance and replicon composition analysis (ResFinder, version 2.1, PlasmidFinder, version 1.3). These analyses showed that the isolate (MLST ST15) carried the blaSHV-28, blaTX-M-15, blaCTX-M-1, and blaOXA-10 carbapenemase gene, as well as the blaOXA-1, blaOXA-10, and blaOXA-1 carbapenemase genes, and that the isolate carried the aac(3)-IIa, aac(6')-Ib 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.

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

| Method                  | Antimicrobial                          | MIC (mg/L) | Interpretation⁴ |
|-------------------------|----------------------------------------|------------|-----------------|
| **Single susceptibility testing** |                                        |            |                 |
| Vitek-2⁵                 | 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 | Interpretation⁵ |
|------------------------|----------|-----------------|
| **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     |

⁴According to EUCAST (www.eucast.org).
⁵Synergy 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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Transparency declarations
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Clinically significant drug interaction: letermovir and voriconazole

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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.3 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.