Ceftazidime/avibactam alone or in combination with aztreonam against colistin-resistant and carbapenemase-producing Klebsiella pneumoniae

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Sir,
The spread of carbapenemase-producing Klebsiella pneumoniae is a major public health concern since such isolates are basically resistant to most available antibiotics, including β-lactams, fluoroquinolones and aminoglycosides. Infections due to carbapenemase-producing K. pneumoniae are therefore commonly treated with a regimen containing colistin. However, acquired resistance to colistin now occurs frequently and has few therapeutic options. Outbreaks with colistin-resistant and carbapenemase-producing K. pneumoniae isolates have been reported worldwide and mortality rates are high owing to limited treatment options.

Recently, a new therapeutic option, namely ceftazidime/avibactam, combining a broad-spectrum cephalosporin and a novel β-lactamase inhibitor, has been marketed. The addition of avibactam expands the spectrum of activity of ceftazidime to many MDR Enterobacteriaceae including producers of ESBLs and carbapenemases. Indeed, avibactam is active against all types of ESBLs and against carbapenemases of class A (KPC) and of some class D (OXA-48 and its derivatives), but is not active against class B β-lactamases (MBLs).

In two reports, the combination of ceftazidime/avibactam with aztreonam demonstrated a synergistic effect against MBL-producing Gram-negative pathogens, but only a small number of isolates were tested.

The objective of this study was to determine the in vitro activity of ceftazidime/avibactam, alone (for class A and D carbapenemase producers) or in combination with aztreonam (for class B carbapenemase producers), against a collection of colistin-resistant and carbapenemase-producing K. pneumoniae isolates. A collection of 63 K. pneumoniae isolates recovered from clinical samples in France, Colombia and Turkey were tested in this study. All the isolates were resistant to colistin (MICs of colistin ranging from 8 to >128 mg/L) and produced a carbapenemase. The nature of the carbapenemase and the mechanisms responsible for colistin resistance have been previously characterized. Our collection included 11 KPC-like producers, 32 OXA-48 producers, 5 OXA-181 producers, 8 NDM-like producers and 7 isolates that co-produced two carbapenemases (NDM and OXA-48 or NDM and OXA-181) (Table S1, available as Supplementary data at JAC Online). The mechanisms responsible for colistin resistance were various and are indicated in Table S1.

MICs of ceftazidime/avibactam were determined using MIC test strips (Liofilchem, I2A, Montpellier, France) according to the manufacturer’s guidelines. Following the EUCAST breakpoints (http://www.eucast.org/), isolates with an MIC of ceftazidime/avibactam of ≤8 mg/L were categorized as susceptible, whereas those with an MIC >8 mg/L were categorized as resistant. All the K. pneumoniae isolates producing a class A (KPC) or class D (OXA-48 and OXA-181) carbapenemase alone were susceptible to ceftazidime/avibactam with MICs ranging from 0.12 to 6 mg/L. As expected, the isolates producing a class B carbapenemase (NDM alone or associated with another carbapenemase) presented a high level of resistance to ceftazidime/avibactam (MIC ≥256 mg/L) (Table S1).

For the 15 isolates producing an MBL, MICs of aztreonam were also determined using MIC test strips (Liofilchem). According to EUCAST breakpoints, isolates with an MIC of ≤1 mg/L were categorized as susceptible, whereas those with an MIC >4 mg/L were categorized as resistant. Out of the 15 isolates, only a single isolate was actually susceptible to aztreonam. Resistance to aztreonam was mainly due to production of ESBLs (data not shown).

The in vitro synergy of ceftazidime/avibactam and aztreonam against MBL-positive isolates was studied using MIC test-strip-based synergy methods as previously described. The combination was tested by first applying a ceftazidime/avibactam strip to the Mueller–Hinton agar, removing it after 5 min, then applying an aztreonam strip to the exact same location and replacing the ceftazidime/avibactam strip on top of the aztreonam strip. Despite a high level of resistance to each antibiotic, the combination was synergistic for all the isolates with MICs of the combination <2 mg/L (Figure 1).

This study further suggests that ceftazidime/avibactam is an effective therapeutic option for treating infections caused by colistin-resistant and KPC- or OXA-48-producing K. pneumoniae. Moreover, the association of ceftazidime/avibactam and aztreonam is effective against NDM-producing K. pneumoniae. This combination was efficient in particular against K. pneumoniae isolates producing two carbapenemases. The synergy of the combination of...
ceftazidime/avibactam with aztreonam against NDM producers could be explained by the neutralization of the ESBL activity by avibactam allowing a restoration of the susceptibility to aztreonam. This study suggests that further commercialization of aztreonam/avibactam as a pharmaceutical preparation could be an interesting option to treat infections caused by MBL producers. Notably, synergy of ceftazidime/avibactam and aztreonam can be easily evaluated using MIC test-strip synergy assays in clinical microbiology laboratories. Further investigations using experimental models and clinical trials are required to further confirm that this might be a relevant and effective therapeutic option in clinical practice.

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**Transparency declarations**
None to declare.

**Supplementary data**
Table S1 is available as Supplementary data.

**References**