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Short Communication

# Continuous infusion, therapeutic drug monitoring and outpatient parenteral antimicrobial therapy with ceftazidime/avibactam: a retrospective cohort study

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ABSTRACT

*Objectives:* Based on recent pharmacokinetic/pharmacodynamic (PK/PD) evidence, continuous-infusion (CI) $\beta$-lactam administration is increasingly recommended for serious infections. Since 2016, the combination ceftazidime/avibactam (CAZ/AVI) is administered as per the manufacturer's instructions as an intermittent infusion of 2.5 g every 8 h. Thus, CI has not yet been evaluated in clinical trials.

*Methods:* We aimed to evaluate the use of CI of CAZ/AVI in a retrospective case series from December 2016 to October 2019. All isolates displayed in vitro susceptibility to CAZ/AVI according to EUCAST definitions. Patients were initially given CAZ/AVI as CI of 5 g every 12 h, and dosages were adjusted according to therapeutic drug monitoring of ceftazidime with a therapeutic goal of $\geq$4–5 $\times$ MIC in plasma and/or at the site of infection.

*Results:* CAZ/AVI was administered by CI in 10 patients with infections mainly caused by multidrug-resistant *Pseudomonas aeruginosa* (54.5%) and *Klebsiella pneumoniae* (36.4%). Bacteraemia occurred in 30% of cases. Sepsis or septic shock was present in 20% of cases. CAZ/AVI was used as monotherapy in 60% of cases. Clinical cure and microbiological eradication were achieved in 80% and 90% of cases, respectively. The 30-day mortality after CAZ/AVI treatment onset was 10%. The therapeutic goals of $\geq$4–5 $\times$ MIC in plasma and/or at the site of infection were achieved in 100% and 87.5% of cases, respectively, without adverse events.

*Conclusion:* Despite a limited number of patients, CI of CAZ/AVI provided promising results after optimisation of PK/PD parameters both in plasma and at the site of infection.



## 1. Introduction

The spread of multidrug-resistant (MDR) infections caused by Gram-negative bacteria has complicated therapeutic strategies in recent years, particularly because of the increasing prevalence of extended-spectrum $\beta$-lactamase (ESBL)-producing pathogens [1]. This prompted the World Health Organization (WHO) to publish a list of priority pathogens (including *Acinetobacter baumannii, Pseudomonas aeruginosa*, and carbapenem-resistant and third-generation cephalosporin-resistant *Enterobacterales*) to promote research and development of new antibiotics [2]. Also, continuous or extended infusions of $\beta$-lactam antibiotics have been advocated for maximising the time that the antimicrobial concentration remains above the minimum inhibitory concentration (MIC) and optimising pharmacokinetic/pharmacodynamic (PK/PD) targets, allowing higher clinical cure rates and lower mortality, particularly in critical care patients [3,4]. In in vitro studies, the novel $\beta$-lactam/$\beta$-lactamase inhibitor combination ceftazidime/avibactam (CAZ/AVI) showed high activity against many carbapenem-resistant *Enter-*

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*obacterales* and *Pseudomonas aeruginosa*, but clinical data for documented MDR infections remain limited [1,5]. Moreover, CAZ/AVI is administered as per the manufacturer's instructions as an intermittent infusion over 2 h of 2.5 g (2 g of ceftazidime plus 0.5 g of avibactam) every 8 h, thus continuous infusion (CI) has not yet been evaluated in clinical trials [1]. The present study aimed to assess the use of CI of CAZ/AVI in a retrospective case series from December 2016 to October 2019.

## 2. Materials and methods

Patients treated in our Belgian tertiary hospital, with an isolate with in vitro-confirmed susceptibility to CAZ/AVI (≤8 mg/L) according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint definitions [6] and who received a 24-h CI of CAZ/AVI for ≥48 h, were included in this study. MICs of CAZ/AVI were determined by either Etest (bioMérieux) or broth microdilution using Sensititre® panels (Thermo Fisher Scientific). After a loading dose of 2.5 g administered in 2 h, patients were initially given CAZ/AVI as a CI of 5 g every 12 h (q12h) diluted in 250 mL of normal saline, with initial dosage adjustment depending on renal function as follows: creatinine clearance ($CL_{Cr}$) ≥60 mL/min, 5 g q12h; $CL_{Cr}$ <60 mL/min and ≥30 mL/min, 2.5 g q12h; and $CL_{Cr}$ <30 mL/min and ≥15 mL/min, 1.25 g q12h. We used this initial posology to avoid (i) waste (only available as 2.5 g bottle) and (ii) initial low plasma concentration [7,8]. The cartridge was changed every 12 h. Indeed, the diluted CAZ/AVI solution has been shown to be stable for 12 h at concentrations up to 40 mg/mL for ceftazidime (CAZ) and up to 10 mg/mL for avibactam (AVI) [9]. CAZ/AVI dosages were thereafter adjusted according to therapeutic drug monitoring (TDM) of CAZ performed in plasma at steady-state (i.e. >24 h after initiation) with a therapeutic goal of ≥4–5 × MIC in plasma and/or at the site of infection. The concentration at the site of infection was extrapolated from published data regarding the ratio of the concentration at the site of infection/plasma concentration for CAZ. This ratio was ≈100% for upper complicated urinary tract infection, ≈50% for complicated intra-abdominal infection, ≈30–35% for ventilator-associated pneumonia and bone and joint infection and ≈15% for prostatitis [10–15]. A therapeutic goal was considered as achieved at the site of infection if the site of infection/plasma ratio was reached (e.g. for an MIC of 2 mg/L and a ratio of 30–35%, the therapeutic goal was 8–10 at the site of infection and 24–30 in plasma). Each initiation of treatment and adaptation of TDM were supervised by an infectious diseases specialist. Selection for CI was at the discretion of the infectious diseases specialist but was systematically considered in intensive care unit patients, deep-seated infections and/or 'high' MIC (i.e. ≥2 mg/L). Clinical and microbiological responses were evaluated at 1 month after the start of CAZ/AVI (excepted for bone and joint infection, where this period was extended to 12 months) or at the end of therapy if the duration of treatment exceeded 30 days. Clinical evaluation was based on the evolution of signs and symptoms of the index infection and was defined as: (i) 'cure' if complete resolution or significant improvement occurred, meaning that no surgical drainage nor change of antibiotic therapy was deemed necessary after 96 h from the start of CAZ/AVI; (ii) 'failure' if death was related to the index infection, or persistence or worsening of the majority of signs and symptoms; and (iii) 'indeterminate' if death occurred but was clearly not related to the index infection. Microbiological response was considered as: (i) 'eradication' if an adequate source specimen demonstrated absence of the original baseline pathogen if culture at the site of infection returns negative after treatment; (ii) 'presumed eradication' if an adequate source specimen was not available to culture and the patient was assessed as clinically cured; and (iii) 'failure' if culture at the site of infection remained positive for the same pathogen after >5 days of therapy [16,17]. The concentrations of total CAZ in plasma were determined by a validated chromatographic method [18].

## 3. Results

CAZ/AVI was administered through CI in ten patients. The demographic and clinical characteristics as well as PK/PD data are presented in Tables 1 and 2, respectively. The infections were mainly caused by MDR *Pseudomonas aeruginosa* (6/10 cases) and *Klebsiella pneumoniae* (4/10 cases), including one case with concomitant infection by both bacteria. Bacteraemia occurred in 30% of cases, and sepsis or septic shock was present in 20% of cases. Other antibiotic(s) before initiation of CAZ/AVI were prescribed in 50% of cases with a median [interquartile range (IQR)] duration of 13 (9–14) days, and CAZ/AVI was initiated empirically or based on documented infection in the remainder of the patients. In four of the five patients who were prescribed other antibiotics before the start of CAZ/AVI, the offending strain was resistant or developed resistance to empirical therapy (sulfamethoxazole/trimethoprim + gentamicin in Patient 2, meropenem in Patients 3 and 4 and tigecycline in Patient 10). In one patient, the strain was susceptible to empirical therapy (meropenem in Patient 8) but the switch was performed to allow outpatient parenteral antimicrobial therapy (OPAT) because no CI of meropenem is performed in our institution owing to lack of data regarding the stability of meropenem for OPAT.

The median (IQR) duration of CI of CAZ/AVI was 12 (7–23.7) days, which represents 79.1% of the total duration of CAZ/AVI treatment. Clinical cure and microbiological eradication were achieved in 80% and 90% of cases, respectively. The median (IQR) time to microbiological eradication after initiation of CAZ/AVI was 6 (4–17) days (Patients 3, 5, 6, 7 and 10); for Patient 1, all per-operative samples (6/6) were negative during total knee replacement performed 6 months later. The 30-day mortality after CAZ/AVI treatment onset was 10% and concerned one patient whose death was clearly not related to the index infection, which was ventilator-associated tracheobronchitis. Treatment dosage adjustments based on CAZ TDM were made in 20% of cases (Patients 2 and 9). Neither drug-related adverse events nor CAZ/AVI resistance were noted during the follow-up period. Furthermore, CAZ/AVI was stable for 12-h infusions: no visible haze, particulate formation or colour changes were observed. Regarding OPAT, all three patients achieved therapeutic goals both in plasma and at the site of infection as well as clinical and microbiological cure.

## 4. Discussion

To the best of our knowledge, this is the first report on use of CI of CAZ/AVI in clinical practice. Bacterial killing of Gram-negative pathogens occurs when bacteria are exposed to a concentration of $\beta$-lactams exceeding the MIC for a defined period of time and is maximised at 4–5 times the MIC achieved in plasma [3,4,19]. In complicated circumstances such as in critically-ill patients in sepsis or septic shock with increased MICs and/or deep-seated infections, this therapeutic goal could be increased to $100\%fT_{>4-8\times\ MIC}$ (concentration of free drug exceeds 4–8 × MIC for 100% of the dosing interval) and CI offers advantages over intermittent infusion to reach this goal [7,8]. Since most infections occur in the extravascular space, antimicrobial concentrations at the site of infection seem determinant to achieve rapid bacterial killing and to limit the emergence of resistance, but no clinical study has yet documented whether the magnitudes of the PD parameters of $\beta$-lactam antibiotics at the site of infection are the same as those proposed for plasma to reach these goals and to improve clinical outcome [13,20]. We tried to achieve a probable concentration of CAZ of ≥4–5 × MIC of the isolated pathogen at the site of infection (which

**Table 1**
Clinical and microbiological characteristics of patients treated with continuous infusion (CI) of ceftazidime/avibactam (CAZ/AVI)

| Clinical characteristics | *n* (%)[a] |
|---|---|
| **Patient variables (*n* = 10)** | |
| Age (years) [median (IQR)] | 61.5 (54.2–63) |
| Male sex (%) | 7 (70) |
| eGFR (CKD-EPI) (mL/min/1.73m$^2$) [median (IQR)][b] | 95 (92–112) |
| At the onset of infection ($n$ = 10) (%) | |
| - Sepsis | 1 (10) |
| - Septic shock | 1 (10) |
| - Bacteraemia | 3 (30) |
| Ward | |
| - Medical | 6 (60) |
| - ICU | 4 (40) |
| Type of infection ($n$ = 10) | |
| - cIAI[c] | 2 (20) |
| - cUTI/prostatitis[d] | 2 (20) |
| - VAP | 2 (20) |
| - VAT | 2 (20) |
| - BJI | 1 (10) |
| - PJI | 1 (10) |
| Type of organism ($n$ = 11) [e] | |
| - *Pseudomonas aeruginosa* | 6 (54.5) |
| - KPC-producing *Klebsiella pneumoniae* | 2 (18.2) |
| - ESBL-producing *Klebsiella pneumoniae* | 2 (18.2) |
| - *Enterobacter aerogenes* | 1 (9.1) |
| **CAZ/AVI treatment results** | |
| Previous antibiotic(s) for index infection | 5 (50) |
| - Duration (days) [median (IQR)] | 13 (9–14) |
| Duration of CAZ/AVI (days) [median (IQR)] | |
| - Total | 13.5 (8.2–33.2) |
| - CAZ/AVI as a 24-h CI | 12 (7–23.7) |
| Proportion of duration of CI CAZ/AVI compared with total duration of CAZ/AVI treatment (days) (%) [f] | 155/196 (79.1) |
| - Monotherapy | 6 (60) |
| - Combination therapy with CAZ/AVI [g] | 4 (40) |
| - OPAT | 3 (30) |
| Outcomes | |
| Clinical response | |
| - Cure (including 3/3 OPAT) | 8 (80) |
| - Indeterminate | 1 (10) |
| - Failure | 1 (10) |
| Microbiological response | |
| - Eradication | 6 (60) |
| - Presumed eradication | 3 (30) |
| - Failure | 1 (10) |
| 30-day mortality after the onset of CAZ/AVI treatment [h] | 1 (10) |

CAZ/AVI, ceftazidime/avibactam; IQR, interquartile range; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ICU, intensive care unit; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis; BJI, bone and joint infection; PJI, prosthetic joint infection; ESBL, extended-spectrum $\beta$-lactamase; OPAT, outpatient parenteral antimicrobial therapy.

[a] Values are number (%) unless indicated otherwise.

[b] At the onset of CAZ/AVI therapy (within 24 h).

[c] Both cases occurred after complex liver surgery.

[d] Both cases were relapsing acute prostatitis.

[e] For one patient, nosocomial pneumoniae was due to concomitant ESBL-producing *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, with both confirmed as susceptible to CAZ/AVI.

[f] In three patients, CAZ/AVI was initiated as intermittent infusion and then switched to continuous infusion, and in one patient it was changed from initial continuous infusion to intermittent infusion owing to initiation of continuous venovenous haemofiltration.

[g] For details regarding combination therapy, see Table 2.

[h] Or until the end of therapy if duration >30 days; the death was not directly attributed to multidrug-resistant infection (see definition of clinical response in the text).

was extrapolated from obtained plasma concentrations and published data regarding the ratio of concentration at the site of infection/plasma concentration for CAZ), and this goal was achieved in 7/8 cases, with a median concentration at the site of infection/MIC ratio of 5.7. Use of an individual MIC value to guide antibacterial dosing may not be appropriate owing to high variability in MIC determination (varying by one to two dilutions in both directions) leading to a potential four-fold variation in PK concentrations and PK/PD targets [21,22]. Considering the worst scenario, i.e. a higher MIC variation of two dilutions and high interindividual variability in terms of PKs, it seems reasonable to target 4–5 × MIC at the site of infection to expect to have ≥1 × MIC in the majority of patients [7,21,22]. In doing so, we used a median (IQR) daily dose of CAZ/AVI of 10 (5–10) g with a relatively high median level of CAZ in plasma (63.6 mg/L), which was still below the maximum value of 80 mg/L considered by Guilhaumou et al. [8]. This was correlated with a high plasma concentration/MIC ratio (median of 13.3), without neurological or haematological toxicity, outlining the wide therapeutic range of $\beta$-lactams [20]. Based on TDM of CAZ, our strategy allowed to achieve a high rate of clinical cure and microbiological eradication of 80% and 90%, respectively. Treatment adjustments were made in 20% of cases and a reduction or an increase of dosage was possible but not performed in an additional 30% (Patients 7, 8 and 10) and 10% (Patient 3), respectively. The fact

**Table 2**
Detailed characteristics and pharmacokinetic/pharmacodynamic (PK/PD) data of patients treated with continuous infusion of ceftazidime/avibactam (CAZ/AVI)

| Patient | Type of infection | Type of organism(s) | Daily dose of CAZ/AVI (g) | CAZ/AVI MIC (mg/L) | Mean CAZ plasma conc. by TDM (mg/L) | Estimated site of infection/plasma ratio | Mean estimated conc. at site of infection by TDM (mg/L) | Achieved ratio concentration/MIC in fold | | Samples for CAZ TDM (*n*) | OPAT | Clinical response | Microbiological response |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Plasma | Site of infection | | | | |
| 1 [a] | BJI | KPC-producing *Klebsiella pneumoniae* | 10 | 2 | 35.1 | 0.3–0.35 | 10.5–12.3 | 17.5 | 5.2–6.1 | 5 | Yes | Cure | Erad. |
| 2 | cUTI and bacteraemia | KPC-producing *Klebsiella pneumoniae* | 7.5 for 18 days | 8 | 47.6 | 1.0 | 47.6 | 6 | 6 | 4 | Yes | Cure | PE |
| | | | 5 for 5 days | | 44.6 | 1.0 | 44.6 | 5.6 | 5.6 | | | | |
| 3 [a] | VAP and empyema | *Pseudomonas aeruginosa* | 10 | 8 | 84.3 | 0.3–0.35 | 25.3–29.5 | 10.5 | 3.2–3.7 [b] | 5 | No | Cure | Erad. |
| 4 [a] | VAT | *Pseudomonas aeruginosa* | 5 | 8 | 82.0 | NA | NA | 10.2 | NA | 2 | No | Cure | PE |
| 5 | VAT | *Pseudomonas aeruginosa* | 10 | 0.5 | 124 | NA | NA | 248 | NA | 1 | No | Indeterminate [c] | Erad. |
| 6 [a] | cIAI | *Enterobacter aerogenes* | 5 | 6 | ≥80 | 0.5 | ≥40 | 13.3 | 6.7 | 2 | No | Cure | Erad. |
| 7 | VAP | ESBL-producing *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* | 10 | ESBL-producing *K. pneumoniae*, 1 *Pseudomonas aeruginosa*, 2 | 76.2 | 0.3–0.35 | 22.9–26.7 | 38.1 | 11.4–13.3 | 2 | No | Cure | Erad. |
| 8 | cUTI (prostatitis) | ESBL-producing *Klebsiella pneumoniae* | 5 | 0.25 | 17.6 | 0.15 | 2.6 | 70.4 | 10.4 | 7 | Yes | Cure | PE |
| 9 | PJI and bacteraemia | *Pseudomonas aeruginosa* | 10 for 3 days | 4 | 51.5 | 0.3–0.35 | 15.4–18.0 | 12.9 | 3.8–4.5 | 4 | No | Failure [c] | Failure |
| | | | 7.5 for 5 days | | 48.1 | 0.3–0.35 | 14.4–16.8 | 12.0 | 3.6–4.2 | | | | |
| | | | 10 for 4 days | | 63.6 | 0.3–0.35 | 19.1–22.3 | 15.9 | 4.8–5.6 | | | | |
| 10 | cIAI and bacteraemia | *Pseudomonas aeruginosa* | 10 | 2 | 67.4 | 0.5 | 33.7 | 33.7 | 16.8 | 3 | No | Cure | Erad. |
| **Median (IQR)** | | | 10 (5–10) | 2 (1.5–7) | 63.6 (47.6–80) | / | 24.8 (16.1–36.8) | 13.3 (10.5–33.7) | 5.7 (4.7–8.5) | 3.5 (2–4.7) | | | |

CAZ/AVI, ceftazidime/avibactam; CAZ, ceftazidime; MIC, minimum inhibitory concentration; TDM, therapeutic drug monitoring; OPAT, outpatient parenteral antimicrobial therapy; BJI, bone and joint infection; Erad., eradication; cUTI, complicated urinary tract infection; PE, presumed eradication; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis; NA, not applicable; cIAI, complicated intra-abdominal infection; ESBL, extended-spectrum $\beta$-lactamase; PJI, prosthetic joint infection; IQR, interquartile range.

[a] Combination therapy: Patient 1, local resorbable gentamicin with combined aggressive large repeated debridements; Patient 3, colistin plus aerosolised tobramycin; Patient 4, aerosolised tobramycin; and Patient 6, colistin plus tigecycline.

[b] The therapeutic goal of >4–5 × MIC was not achieved.

[c] Patient 5 died <15 days after the end of CAZ/AVI therapy but the death was not related to this specific episode of infection; Patient 9 had persistent infection despite repeated aggressive surgery including resection of the foreign material and died 7 weeks after initiation of CAZ/AVI, which was replaced by meropenem after 12 days owing to the lower MIC for meropenem.

that adaptation of doses was relatively infrequent could partly be explained by the turnaround time for the TDM result, which was as long as 72–96 h. Monotherapy was used in 60% of cases, which is higher than in recent reports (21–34%) [23,24]. Moreover, there were difficult-to-treat pathogens with high MICs: the median MIC was 2 mg/L, but there were three cases with an MIC of 8 mg/L and one case with an MIC of 6 mg/L, all of which were considered clinically and microbiologically cured. Three patients were successfully discharged with OPAT, which was easy to perform with a change of cartridge every 12 h.

We acknowledge notable limitations of the present study. No drug monitoring of AVI was performed, but we considered that AVI had similar PKs to CAZ hence with similar volumes of distribution, time-dependent activity, low plasma protein binding and renal elimination. Also, they both exhibit short plasma half-lives of ~2 h at least in plasma and epithelial lining fluid [1]. We took into consideration the total (and not free drug) concentration of CAZ owing to expected low protein binding of ~10% [8]. Furthermore, we acknowledge a limited sample size and the retrospective setting of the study. Finally, reducing the delay between blood sampling and obtaining a TDM result should have been a priority in order to improve opportunities to perform efficacious treatment dosage adjustments.

## 5. Conclusion

In patients with limited treatment options, CI of CAZ/AVI allowed to achieve high clinical and microbiological cure rates, including when used as OPAT. Further larger studies should be performed to confirm these results in order to establish recommendations for the clinical use of CI of CAZ/AVI.

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## Competing interests

None declared.

## Ethical approval

Not required.

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