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CEFTAZIDIME-AVIBACTAM FOR THE TREATMENT OF INFECTIONS DUE TO AEROBIC GRAM-NEGATIVE ORGANISMS IN PATIENTS WITH LIMITED TREATMENT OPTIONS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background and Objective

- Antimicrobial resistance (AMR) is a global concern of particular importance in Gram-negative bacteria infections, because of the fewer available treatment options. In the last two decades, the paucity of novel antibiotics with which to treat multidrug-resistant (MDR) infections has led to the re-introduction of colistin as a therapeutic option.[1,2,3]
- Ceftazidime-avibactam (CAZ-AVI) is a new fixed dose combination of a β-lactam (ceftazidime) with a new β-lactamase inhibitor (avibactam) indicated for the treatment of infections due to aerobic Gram-negative organisms in patients with limited treatment options.[4]
- Our objective was to evaluate the effectiveness of CAZ-AVI compared to colistin for the treatment of infections due to aerobic Gram-negative organisms, in particular MDR *Enterobacteriaceae* and *Pseudomonas* infections, in adult patients with limited treatment options, defined as carbapenem resistance.

Methods

- Electronic search in Medline, EMBASE and ClinicalTrials.gov databases up to June 2018.
- Reference lists of retrieved studies and review papers were cross-checked. Data were screened, extracted, and appraised independently.

Inclusion criteria: PICOS	
Population	Patients with MDR *Enterobacteriaceae* or *Pseudomonas* infections
Intervention	CAZ-AVI
Comparison	Colistin
Outcomes	Clinical cure, recurrence, mortality, nephrotoxicity and neurotoxicity
Study design	Random and non-random interventional studies

Exclusion criteria
Studies providing aggregated results on patients with infections caused by *Staphylococcus aureus*, *Enterococcus spp.*, *Stenotrophomonas maltophilia* or *Acinetobacter spp.*, since *in vitro* data suggest that these species are not susceptible to CAZ-AVI.
Studies with less than 10 patients
Studies whose patients were included in subsequent publications

- Data were pooled through a random-effect meta-analysis weighted by inverse variance method. Heterogeneity between studies was assessed with χ2 and I2 tests.
- A meta-regression was performed to estimate treatment effect of CAZ-AVI compared to colistin, adjusted for study design, using R software.

Results

- 804 references were retrieved from the electronic search. After screening, a total of 37 non randomized studies (evaluating 361 patients treated with CAZ-AVI and 1,363 treated with colistin) were included (24 studies in Enterobacteriaceae, 16 in Pseudomonas and 3 studies reported results for both infections).

Patients characteristics (N=1,724, 37 studies)	**Carbapenem-resistant *Enterobacteriaceae* infections**	***MDR Pseudomonas* infections**
Age (years, min-max)	54 - 70	35 - 68
Male proportion (min-max)	47% - 70%	46% - 86%
Main pathogen	*Klebsiella pneumoniae* (77%)	*Pseudomonas aeruginosa* (33%)
Main infection site	Primary bacteraemia (37%) Pulmonary infections (32%)	Primary bacteremia (29%) Respiratory (52%)
Comorbidities		
Cardiovascular disease	26%	30%
Diabetes mellitus	23%	23%
Chronic respiratory disease	21%	26%
Malignant tumors	20%	21%
Mean treatment duration (days)		
CAZ-AVI	12.8	16.0
Colistin	14.1	16.0

Clinical results (CAZ-AVI *vs.* Colistin)	**Carbapenem-resistant *Enterobacteriaceae* infections**	***MDR Pseudomonas* infections**
Clinical cure	OR: 1.99 (95%CI: 0.99-4.04)	OR: 1.27 (95%CI: 0.19-10.81)
30 day mortality	OR: 0.45 (95%CI: 0.12-1.62)	OR: 0.69 (95%CI: 0.16-3.07)
Nephrotoxicity	12% (95%CI: 7-20) *vs.* 26% (95%CI: 20-34)	
Neurotoxicity	NR *vs.* 3% (95%CI: 2-5)	

CI: Confidence interval; NR, not reported; OR: Odds ratio.

- In patients with carbapenem-resistant *Enterobacteriaceae* infections, the results suggest that CAZ-AVI is associated with higher clinical cure and lower 30-day mortality in comparison to colistin.
- In patients with MDR *Pseudomonas* infections, the OR also favored CAZ-AVI over colistin for both clinical cure and 30-day mortality.
- CAZ-AVI was associated with a lower nephrotoxicity rate in comparison to colistin-treated patients (12% vs. 26%), with no neurotoxicity events reported (0% *vs*. 3%).

STUDY LIMITATIONS

- Observational data;
- Sample size (range, 10 to 529 patients);
- Only one study provided a direct comparison between CAZ-AVI and colistin (regarding mortality in *Enterobacteriaceae* infections); [5]
- Only one study provided the clinical cure and mortality rate associated with CAZ-AVI treatment In MDR *Pseudomomas* infections; [6]

Conclusions

- Despite the scarcity of data and the methodological limitations of the analysis, the available evidence suggests that CAZ-AVI is associated with a **better efficacy and safety profile** compared to colistin in patients with limited therapeutic options for infections caused by Gram-negative aerobic organisms, in particular carbapenem-resistant *Enterobacteriaceae* and MDR *Pseudomonas* infections.

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