**South African National Essential Medicine List**
**Primary Healthcare and Adult Hospital Level of Care Medication Review Process**
**Component: Critical care, Antibiotics**

# MEDICINE REVIEW

**Title: Ceftazidime-avibactam for the treatment of carbapenem-resistant Enterobacterales (CRE) bacteraemia**
**Date: 21 September 2023**

## EXECUTIVE SUMMARY

**Date:** 6 July 2023
**Medicine (INN):** Ceftazidime-avibactam
**Medicine (ATC):** J01DD52
**Indication (ICD10 code):** B96.89

**Patient population:** Adults with CRE bacteraemia
**Prevalence of condition:**

- In Sub-Saharan African region, 27.3 deaths per 100 000 people associated with antimicrobial resistance. (1)
- In South Africa, NICD surveillance data reports 2 144 patients identified with CRE bacteremia over 24 months across 16 tertiary public hospitals in 4 provinces (2)

**Level of Care:** Adult Hospital Level
**Prescriber Level:** Medical Doctor, Specialist
**Current standard of Care:**

- Various antimicrobials depending on isolate susceptibility and drug availability, alone or in combination. Regimens may include tigecycline, colistin, amikacin and high-dose meropenem.

**Efficacy and safety estimates:**

- In the treatment of carbapenem-resistant K. pneumoniae bloodstream infections specifically, ceftazidime-avibactam containing treatment regimens are associated with a 61% reduction in odds of 30-day all-cause mortality, compared to other appropriate antimicrobial therapies. (4 studies, n = 493, 28.6% vs. 44.0%; OR 0.39; 95% confidence interval (CI) 0.25, 0.60; $p < 0.0001$; $I^2$=0%; NNT 7 (NNT 6.46 95% CI 4.16, 14.48))(3)
- In the treatment of carbapenem-resistant Enterobacterales bacteraemia, ceftazidime-avibactam containing treatment regimens are associated with a 45% reduction in risk of 30-day all-cause mortality, compared to other appropriate antimicrobial therapies (11 studies, n = 1205, RR 0.55; 95% CI 0.45, 0.68; $p < 0.00001$; $I^2 = 0\%$; NNT 6 (NNT 5.52 95% CI 4.21, 8.00))(4)
- In the treatment of carbapenem-resistant Enterobacterales bacteraemia, ceftazidime-avibactam containing treatment regimens are associated with a 52% reduction in risk of 30-day all-cause mortality, compared to colistin containing regimens (RR 0.48 95% CI 0.33, 0.69, $I^2 = 36\%$, $p < 0.0001$; NNT 5 (NNT 4.39 95% CI 3.11, 7.47))(4)
- Ceftazidime-avibactam containing regimens are associated with a reduced risk of nephrotoxicity when compared to other appropriate antibiotic regimens for the treatment of carbapenem-resistant Enterobacterales bacteraemia (5 studies; 380 patients; RR 0.41; 95% CI 0.20, 0.84; $I^2$= 2%; p = 0.02; NNT 13 (NNT 12.20 95% CI 7.17, 40.81)).(4)

**Motivator/reviewer name(s):** Gayle Tatz, Jessica Taylor, Jeremy Nel, Marc Blockman

**Secretariat support:** Milli Reddy
**PTC affiliation:** Marc Blockman (Western Cape provincial pharmacy therapeutics committee)

**KEY FINDINGS**

- We conducted a systematic review of the evidence for the safety and efficacy of ceftazidime-avibactam-containing therapy in the management of carbapenem-resistant Enterobacterales (CRE) bacteraemia.
- Current standard of care for CRE bacteraemia is dependent on sensitivity testing and may include therapies such as aminoglycosides, colistin, tigecycline and high-dose carbapenems, usually given as a combination regimen comprising two drugs.
- Concerns over poor efficacy, increasing resistance, and serious potential toxicities associated with these agents has driven the development of novel antimicrobials such as ceftazidime-avibactam.
- Due to the nature of the infection being researched, studies identified were largely observational and it is unlikely that interventional data will become available in the future.
- Two systematic reviews with meta-analysis, and 8 primary observational studies were included in the review.
- Ceftazidime-avibactam-containing therapy was associated with a reduction in mortality (NNT 5 – 7) and nephrotoxicity (NNT 13) compared to other appropriate antibiotic regimens in populations with high proportions of *Klebsiella pneumoniae* CRE infections that produce KPC and OXA-48 carbapenemases.
- Recent NICD surveillance suggests comparable CRE epidemiology in South Africa, with the largest proportion of CRE bacteraemia being caused by *Klebsiella pneumoniae* producing OXA-48.
- However, CRE isolates producing metallo-beta-lactamases will not be susceptible to ceftazidime-avibactam. Local data suggest that almost 25% of CRE isolates fall into this category. These isolates can be identified by standard laboratory testing.
- At the current price, the incremental cost effectiveness ratio suggests an additional cost of ZAR 109 786.21 to prevent one death (when compared to a regimen of tigecycline with amikacin), and an additional cost of ZAR 84 613.32 to prevent one death (when compared to a regimen of tigecycline and colistin). A formal pharmacoeconomic analysis is recommended to guide further decision making

**PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:**

| | We recommend against the option and for the alternative **(strong)** | We suggest not to use the option **(conditional)** | We suggest using either the option or the alternative **(conditional)** | We suggest using the option **(conditional)** | We recommend the option **(strong)** |
|---|---|---|---|---|---|
| **Type of recommendation** | | | | **x** | |

**Recommendation:** The PHC Adult Hospital Level ERC suggests using ceftazidime-avibactam in selected patients with bacteraemia due to carbapenem resistant organisms. In view of the cost and antibiotic stewardship concerns the decision to use this agent should not be based solely on sensitivity of the cultured organism to ceftazidime-avibactam.

The decision should be made in consultation with a multidisciplinary antibiotic stewardship team and use should be avoided in patients with a very poor prognosis.

**(Conditional: Low Certainty Evidence)**

*Rationale: Systematic reviews and meta-analyses of observational data suggest a large reduction in mortality associated with treatment with ceftazidime-avibactam. At the current price, the incremental cost-effectiveness ratio suggests an additional cost of ZAR* 109 786.21 *to prevent one death (when compared to a regimen of tigecycline with amikacin), and an additional cost of ZAR* 84 613.32 *to prevent one death (when compared to a regimen of tigecycline and colistin). A formal pharmacoeconomic analysis is recommended to guide further decision-making.*

**Level of Evidence:** *Systematic reviews of observational trials.* **(Low Certainty Evidence)**

**Review indicator: Evidence of harm and new cost data**

**NEMLC RECOMMENDATION (MEETING OF 12 OCTOBER 2023):**
**NEMLC supported the PHC Adult Hospital Level ERC recommendation to use ceftazidime-avibactam in selected patients with bacteraemia due to carbapenem resistant organisms. Use must be based on sensitivity of the cultured organism to ceftazidime-avibactam in consultation with a multidisciplinary antibiotic stewardship team (for example microbiologists or infectious disease specialists). Use of ceftazidime-avibactam should be avoided in patients with a very poor prognosis.**

NEMLC did not recommend a full pharmacoeconomic evaluation at this time.

**Monitoring and evaluation considerations**

**Research priorities**


**NAME OF AUTHOR(S)/MOTIVATOR(S)**

Gayle Tatz[1], Jessica Taylor[1], Jeremy Nel[2], Marc Blockman[1]

**AUTHOR AFFILIATION AND CONFLICT OF INTEREST DETAILS**

[1]Division of Clinical Pharmacology, Department of Medicine, University of Cape Town and Groote Schuur Hospital
[2]Division of Infectious Diseases, Department of Medicine, Helen Joseph Hospital and the University of Witwatersrand.

There are no conflicts of interest to declare.


**BACKGROUND**

Antimicrobial resistance (AMR) is increasingly being recognised as a major threat to public health with the potential for widespread adverse implications in the treatment and prevention of bacterial infections over the next two decades. One review estimated that approximately 4.9 million deaths were associated with AMR in 2019 globally, while the western Sub-Saharan African region was deemed to have the highest rate of death associated with AMR at 27.3 deaths per 100 000 people. (1) The loss of efficacy of antimicrobial agents impacts the security of future healthcare provision, and at worst, could lead to the spread of untreatable pathogens resulting in mortality rates reminiscent of the pre-antibiotic era.

The societal and economic costs of AMR are also significant and require consideration. According to the Centre for Disease Control and Prevention in the United States of America (USA), AMR results in additional direct healthcare costs of USD 20 billion in the USA (ZAR 344 billion). (5) This figure excludes indirect and societal costs, such as loss of productivity. Local data are sparse but likely to echo international literature. As micro-organism resistance to initial treatment options increases, more costly and resource-intensive interventions are required. It is therefore imperative that measures to improve the use of available antimicrobials are formulated, implemented, evaluated, and optimised. Promotion of the appropriate use of antimicrobials is one of the key strategies that has been included in the national framework to slow the development and spread of AMR. This can be achieved with the availability of updated, evidence-based standard treatment guidelines and the South African Essential Medicines List. (6)

**Carbapenem-resistant Enterobacterales**

Carbapenem-resistant Enterobacterales (CRE) are Gram-negative bacteria not susceptible to at least one of the carbapenem antibiotics, or which produce a carbapenemase, a type of beta-lactamase. Beta-lactamases are categorised as class A, B, C or D using the Ambler classification system. Carbapenemases comprise class A (e.g., Guinea extended-spectrum beta-lactamase (GES) and Klebsiella pneumoniae carbapenemase (KPC)), class B (e.g., imipenem metallo-beta-lactamase (IMP), New Delhi metallo-beta-lactamase (NDM) and Verona integron-encoded metallo-beta-lactamase (VIM)) and class D beta-lactamases (e.g., oxacillinase-48-like (OXA-48)).(7) Infections caused by CRE are associated with increased morbidity and mortality as effective treatment options are severely limited. (3)

**South African Perspective**

In South Africa, over a 24-month period spanning January 2019 to December 2020, surveillance conducted by the National Institute of Communicable Disease (NICD) identified 2 144 patients with CRE bacteraemia across 16 public sector tertiary academic hospitals.(2). One third of the study population (35.6%) were aged 19 years or younger, 50.1% were adults aged 20 – 59 years, and 14.2% were adults aged 60 years and older. Klebsiella pneumoniae was identified as the causative pathogen in most CRE isolates (79.8%), and the most frequently detected carbapenemase genes identified across isolates was $bla_{OXA\text{-}48\text{-}LIKE}$ (76.8%), followed by $bla_{NDM}$ (21.1%) and $bla_{VIM}$ (1.3%). The in-hospital mortality rate was 36.6% and increasing age, comorbidities and history of previous antimicrobial use were associated with increased odds of death. Approximately 30.6% of CRE isolates in the study were resistant to amikacin, 19.8% of isolates were resistant to tigecycline and 18.6% of isolates were resistant to colistin (an absolute increase of 5.6% from the previous surveillance period). Susceptibility of isolates to the carbapenems was low, with sensitivity to doripenem, imipenem or meropenem ranging from 41.2% to 44.9% and only 11.5% of isolates were sensitive to ertapenem.

**Ceftazidime-avibactam**

At present, combination antibiotic regimens that include high-dose carbapenems, amikacin, tigecycline and colistin, are employed as last resort treatment options for CRE. However, concerns about poor efficacy, increasing resistance

and serious potential toxicities associated with these agents has driven the development of novel antimicrobials such as ceftazidime-avibactam. (8)

Ceftazidime-avibactam (CAZ-AVI) is an extended-spectrum beta-lactam and beta-lactamase inhibitor antimicrobial. Ceftazidime induces bacterial cell lysis by attaching to penicillin-binding proteins and inhibiting bacterial peptidoglycan synthesis. Avibactam exhibits no clinically relevant antibacterial activity itself but prevents the inactivation of ceftazidime by class A, class C and some class D carbapenemases (such as OXA-48). Avibactam is not active against the class B metallo-beta-lactamase producing bacteria (such as NDM, VIM and IMP). (4, 9) CAZ-AVI is currently registered in South Africa for the treatment of complicated intra-abdominal infections (in combination with metronidazole), hospital- and ventilator-associated bacterial pneumonias (HAP and VAP) and complicated urinary tract infections (cUTIs). (9)

A recent study conducted by Perovic et al. determined in vitro activity of CAZ-AVI against E. Coli and K. pneumoniae isolated from positive blood cultures from sentinel South African hospitals. In 30% of the E. Coli isolates, and 61% of the K. pneumonia isolates, multidrug resistance was detected. However, all isolates were found to be highly susceptible to CAZ-AVI, with a 96% and 100% susceptibility rate reported for E. Coli and K. pneumoniae isolates respectively.(10)

The objective of this review is to appraise and assess the efficacy and safety data for CAZ-AVI-based antimicrobial treatment regimens in the treatment of CRE infections.

**RESEARCH QUESTION**

"Is ceftazidime-avibactam-based therapy more effective and/or safer than colistin or tigecycline or aminoglycoside-based treatment regimens in the management of carbapenem-resistant Enterobacterales bacteraemia?"

**OBJECTIVES**

Our PICO framework for the review is outlined in *Table 1.*

**Table 1. PICO Framework**

| | |
|---|---|
| **Population** | • Adults with CRE bacteremia |
| **Intervention** | • Ceftazidime-avibactam-based therapy |
| **Comparators** | • Colistin-based therapy<br>• Tigecycline-based therapy<br>• Aminoglycoside-based therapy |
| **Outcomes** | • Clinical cure<br>• Mortality |

| | |
|---|---|
| | • Safety |
| **Study type** | • Systematic reviews with meta-analysis (pairwise or network meta-analysis) of randomised controlled trials or observational studies<br>• Randomised controlled trials<br>• Observational studies (retrospective or prospective)<br>• Health technological assessments |

## METHODS

### Data sources

We searched the following databases for reviews and primary research: MEDLINE, Epistemonikos, and the Cochrane database of systematic reviews. For health technology assessments (HTAs), the following databases were searched: National Institute for Health Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Scottish Medicines Consortium (SMC), and the International HTA Database. All studies from database inception until 17 April 2023 - the date the search was performed - were considered eligible. No search of the grey literature was conducted. However, additional references brought to the reviewers' attention while reviewing reference lists of included studies were considered eligible for inclusion.

### Search Strategy

We conducted our search on 17 April 2023.

| Database | Search Strategy |
|---|---|
| PubMed | ((carbapenem-resistant) OR (CRE)) AND (ceftazidime) AND (avibactam) AND ((colistin) OR (tigecycline) OR (aminoglycoside)) AND ((clinical cure) OR (mortality) OR (safety)) |
| Epistemonikos | CRE AND ceftazidime AND avibactam AND clinical cure OR mortality OR safety |
| HTA databases | ceftazidime/avibactam OR ceftazidime-avibactam |

We removed duplicates and screened titles and abstracts, followed by full-text screening using Endnote citation manager software. Screening was performed at both stages by two reviewers (GT and JT). Disagreements between reviewers at each stage of the selection process were resolved through discussion until a consensus was reached.

### Additional Inclusion and Exclusion Criteria

We included studies conducted in adult patients with CRE bacteraemia that compared CAZ-AVI-based therapy to colistin- or tigecycline- or aminoglycoside-based therapies, which reported on safety and/or clinical efficacy outcomes.

Narrative reviews and systematic reviews without meta-analysis were excluded from the review, but their reference lists were examined to identify studies for inclusion. Language of included studies was restricted to English.

Considering the barriers to performing randomised clinical trials in this field of research, both primary observational studies and systematic reviews with meta-analyses of observational studies were considered eligible for inclusion.

**Data Extraction**

A tool for data extraction was developed in Excel by JT and GT. (11) We extracted data pertaining to study design, sample size, population, site of infection, organism, effect size and dosing regimens for intervention and comparator.

**Assessment of evidence quality**

All included studies underwent quality assessment. We assessed the quality of included systematic reviews with meta-analyses using the AGREE II grading tool.(12) We assessed the quality of included randomised controlled trials using the Cochrane risk of bias tool. (13) We assessed the quality of included observational studies using the ROBINS-I assessment tool. (14)

**Data Analysis and Presentation**

Data are summarised in a tabular format and in a narrative summary with relevant figures and graphs. Numbers needed to treat to benefit (NNT) or harm (NNH) for significant findings are also presented where possible.

**RESULTS:**

The results of the search and the study selection process are reported in the results section below and presented using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram (figure 1).(15)

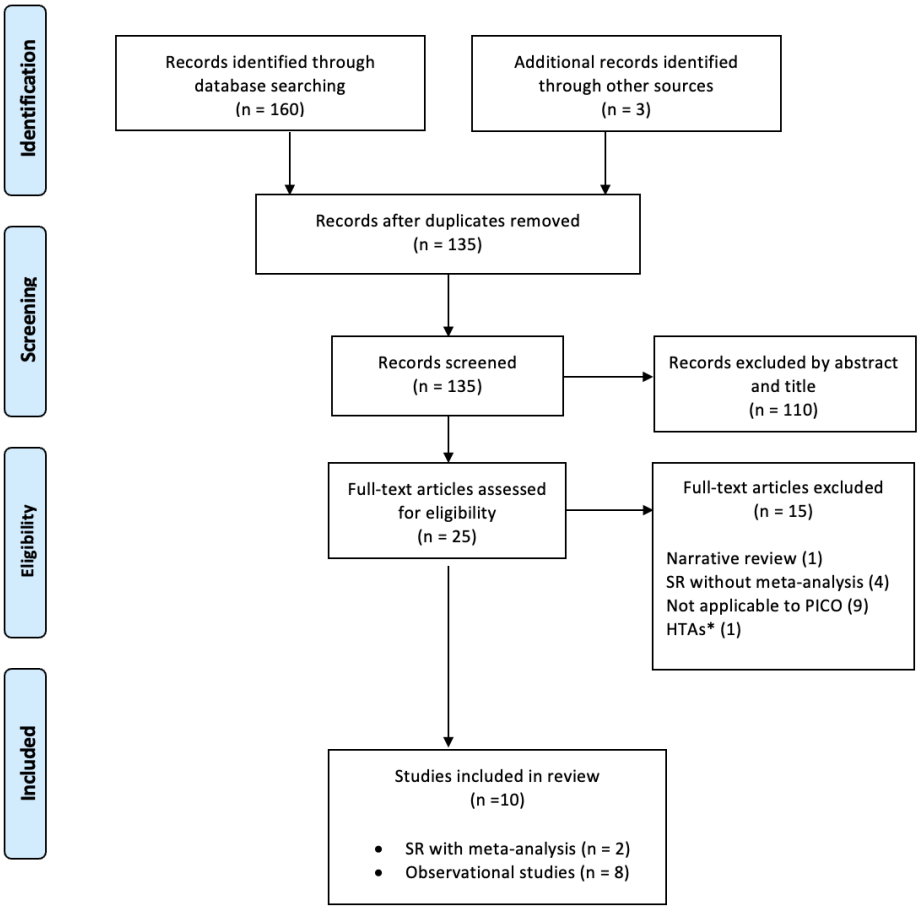

*Figure 1. PRISMA flow-diagram detailing study identification, selection, and exclusion*

One hundred and sixty studies were identified using the search strategy outlined above, with 3 additional studies identified through other sources. Once 28 duplicates were removed, 135 records were screened by title and abstract. After excluding 110 studies, the remaining 25 studies underwent full text review.

On full text review, a further 15 studies were excluded for reasons as outlined in *Figure 1* and *Table 2*, including the National Institute of Clinical Excellence (NICE) HTA.(16-30) The primary objective of this HTA was to estimate the benefits associated with the use of CAZ-AVI to patients and the UK National Health Service (NHS) over time, to inform delinked compensation to Pfizer (the manufacturer of CAZ-AVI) and to incentivise the development of antimicrobials for drug resistant infections. Considering the delinked system of payment (which is not applicable to South Africa) and the differences in epidemiology of drug resistant infections, the findings of this HTA, including the projected QALYS gained per year, cannot be extrapolated to the South African setting or be included in our review. However, the references were reviewed for primary efficacy studies meeting inclusion criteria.

After full text screening, we included 10 studies: 2 systematic reviews with meta-analyses of observational data, and 8 observational studies.(3, 4, 31-38) Five of the 8 observational studies identified for inclusion were analysed as part of the 2 systematic reviews with meta-analyses and are therefore not discussed or presented separately here.(34-38)

*Table 2. Reasons for study exclusion*

| Study | Reason for exclusion |
|---|---|
| Hu et al. 2022 (17) | Systematic review without meta-analysis |
| Chen et al. 2021 (18) | Not applicable to PICO (outcome) |
| Durante-Mangoni et al. 2019 (19) | Systematic review without meta-analysis |
| Cultrera et al. 2020 (20) | Not applicable to PICO (population and comparator) |
| Hsu et al. 2019 (21) | Not applicable to PICO |
| Kanji et al. 2022 (22) | Systematic review without meta-analysis |
| Katchanov et al. 2018 (23) | Not applicable to PICO (outcome) |
| King et al. 2017 (24) | Not applicable to PICO (comparator and study design) |
| Meng et al. 2022 (25) | Not applicable to PICO (population) |
| Shen et al. 2021 (26) | Not applicable to PICO (study design) |
| Shi et al. 2021 (27) | Not applicable to PICO (population) |
| Soriano et al. 2021 (28) | Systematic review without meta-analysis |
| Zhen et al. 2022 (29) | Narrative review |
| Zhong et al. 2018 (30) | Not applicable to PICO (population and comparator) |
| NICE Health Technology Assessment (16) | See text |

**Evidence synthesis**: Efficacy

Two systematic reviews with meta-analyses were identified for inclusion (*Table 3*). On quality assessment using AMSTAR II, both reviews were assessed as of critically low-quality *(Appendix 1).* There was a 37.5% overlap of primary studies included in the two systematic reviews, calculated using the corrected covered area (CCA) method described by Hennessy and Johnson (*Appendix 3)*.(39) However, since the target populations differed between the systematic reviews, both are discussed below. The 3 observational studies identified in the search that were not included in the

systematic reviews, reported similar findings (*Table 4*). (31-33)The observational study judged to be at the lowest risk of bias is discussed in more detail below.(33)

**Chen et al.** (4)

Chen et al. conducted a systematic review of 11 observational studies (5 case-control studies and 6 cohort studies) of adults with CRE blood stream infection (BSI) or bacteraemia. Three studies were conducted prospectively, and 8 studies were conducted retrospectively. All 11 studies (n = 1205) reported on the primary study outcome of mortality. Nine of 11 included studies were assessed to be of high quality, with Newcastle Ottawa scores (NOS) ≥ 7. The remaining 2 studies had scores of 6, but were still included in the meta-analysis. No sensitivity analysis with the excluded lower quality studies was performed.

Six studies (n = 567) reported on the secondary outcome of clinical cure, 4 studies (n = 455) on the secondary outcome of relapse and 5 studies (n = 380) on the secondary outcome of nephrotoxicity. The primary sites of infection varied. In 6 studies, all participants were infected with *Klebsiella pneumoniae*. In the remaining 5 studies, multiple organisms were identified, of which the majority (79 – 88%) were *Klebsiella pneumoniae*. In the majority of included studies, most participants were admitted to the intensive care unit. Specifically, 1 study was conducted predominantly in those with haematological malignancies.

The predominant carbapenemase identified was KPC (> 70%) in 6 of the included studies, OXA-48 in 2 studies and metallo-beta-lactamases in 1 study. CAZ-AVI was administered mostly in combination therapy with carbapenems and tigecycline. Control groups received varied regimens but most contained tigecycline or colistin. The most common combination regimen identified in control arms consisted of both tigecycline and colistin.

The primary outcome of the study was 30-day all-cause mortality, which was reported in 11 studies consisting of 1 205 patients. Participants treated with CAZ-AVI-containing regimens had a statistically significant 45% reduction in the relative risk of mortality compared to those treated with other appropriate antibiotics (RR 0.55; 95% confidence interval (CI) 0.45, 0.68; $I^2$= 0%, p < 0.00001; NNT 6 (NNT 5.52 95% CI 4.21, 8.00)) (*Figure 2*). When specifically compared to colistin-containing treatment regimens, those treated with CAZ-AVI-containing regimens were also found to have a significantly lower relative risk of mortality (RR 0.48; 95% CI 0.33, 0.69; $I^2$ = 36%; p < 0.0001, NNT 5 (NNT 4.39 95% CI 3.11, 7.47)) (*Figure 3*). Interestingly, when stratified by type of carbapenemase, CAZ-AVI was also associated with reduced mortality risk in those infected with CRE-producing metallo-beta-lactamases (RR 0.44; 95% CI 0.23, 0.83; P = 0.01) (*Figure 4*).

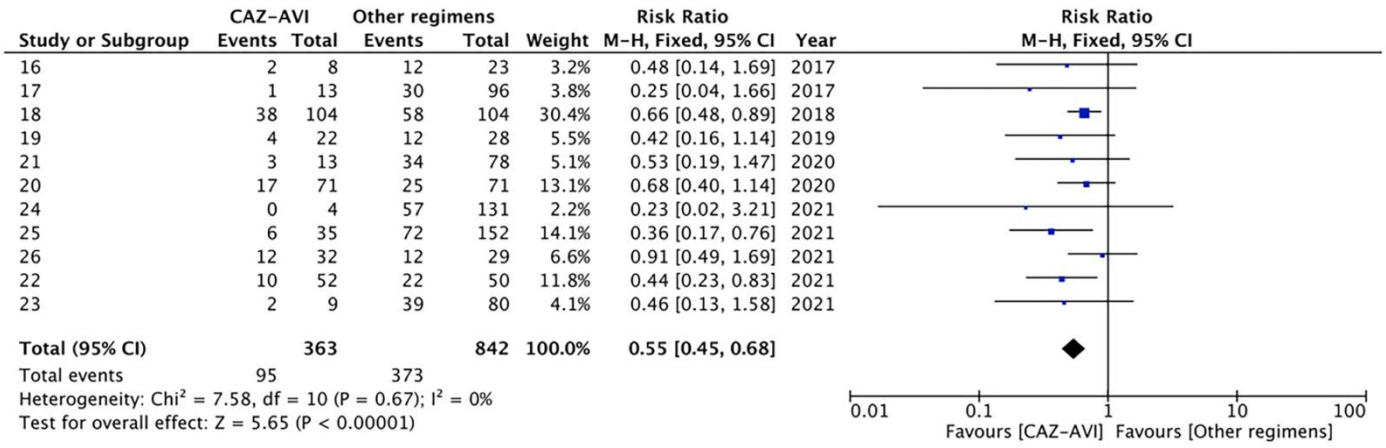


*Figure 2. Thirty-day all-cause mortality of ceftazidime-avibactam (CAZ-AVI) regimens compared to other appropriate antibiotic controls in carbapenem-resistant Enterobacterales bloodstream infection from Chen et al. (4)*

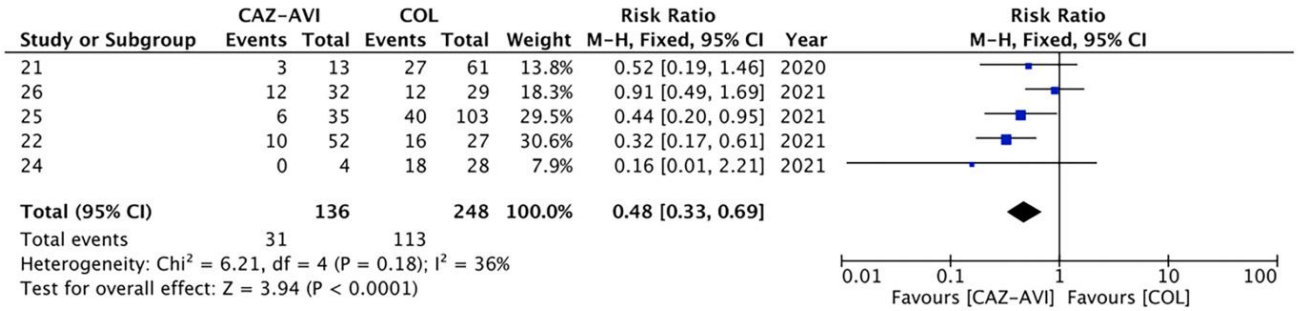


*Figure 3. Subgroup analysis of 30-day all-cause mortality in those treated with ceftazidime-avibactam (CAZ-AVI)-based regimens compared to colistin-containing regimens from Chen et al.(4)*

A higher rate of clinical cure was associated with CAZ-AVI-containing regimens (RR 1.85; 95% CI 1.57, 2.18; $I^2$ = 0%, p < 0.00001; NNT 3 (NNT 2.94 95% 2.37, 3.88)). No difference was found in the relapse rate in those treated with CAZ-AVI containing regimens as compared to other appropriate antibiotics, although only 4 studies with 455 contributed to this outcome (RR 0.69; 95% CI 0.29, 1.66; $I^2$ = 54%; p = 0.86). Additionally, the definitions of relapse varied significantly among included studies. Furthermore, a reduction in nephrotoxicity was reported for the groups receiving CAZ-AVI-containing regimens as compared to other appropriate antibiotic regimens (RR 0.41; 95% CI 0.20, 0.84; $I^2$= 2%; p = 0.02; NNT 13 (NNT 12.20 95% CI 7.17, 40.81))(*Figure 5*). The studies included in the review included a majority of CRE infections likely to be susceptible to CAZ-AVI (KPC or OXA-48 producing) and a minority of CRE infections unlikely to be susceptible (MBL-producing). If the entire population had been susceptible, CAZ-AVI may have performed even better. The proportion of CRE isolates likely to be susceptible to CAZ-AVI in the review, is comparable to that of South Africa. In the study, KPC dominated, while locally OXA-48 is the most prevalent carbapenemase.

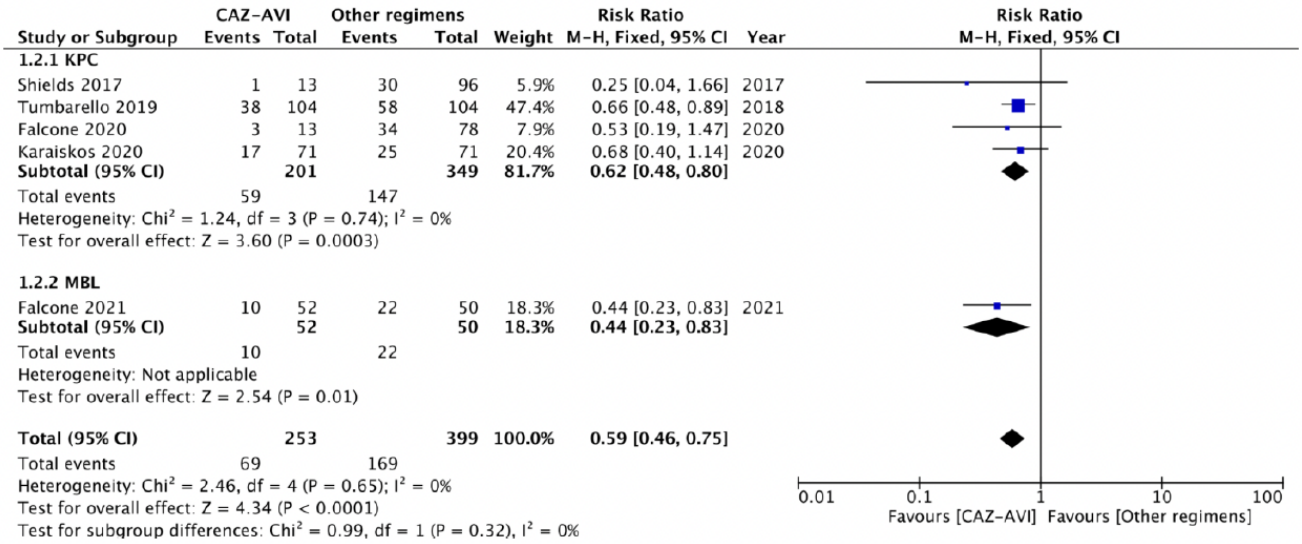


*Figure 4. Subgroup analysis by identified carbapenemase of 30-day all-cause mortality in those treated with ceftazidime-avibactam (CAZ-AVI)-based regimens compared to other appropriate antibiotic controls from Chen et al.(4)*


*Figure 5. Nephrotoxicity of the ceftazidime-avibactam (CAZ-AVI) regimens compared with control in carbapenem-resistant Enterobacterales (CRE) bloodstream infection (BSI) from Chen et al.(4)*

**Karampatakis et al.(3)**

Karampatakis et al. conducted a systematic review and meta-analysis to assess the efficacy and safety of CAZ-AVI containing treatment regimens (monotherapy or combination therapy) compared to other antimicrobials in adults with CRE *K. pneumoniae* infections. Similar to Chen et al., since no randomised controlled data was available, the authors analysed 11 observational studies. The methodological quality of included studies was assessed using the Critical Appraisal Skills Programme (CASP) checklist for observational studies. Three studies were classified as of poor-quality, and the remaining 8 studies were classified as high-quality studies. Eight of the included studies were conducted retrospectively and three were prospectively performed. Comparator regimens varied among included studies and consisted of tigecycline or colistin monotherapy or various treatment combinations of colistin, tigecycline, aminoglycosides, aztreonam or fosfomycin.

For the primary outcome, the CAZ-AVI treatment arms had greater odds of clinical success than treatment arms consisting of other appropriate antibiotics (7 studies; 652 patients; OR 3.55; 95% CI 2.42, 5.19; p < 0.00001; $I^2$ = 6%) (*Figure 6*). CAZ-AVI treatment was associated with a similar increased odds of clinical success in those patients with bloodstream infections specifically (3 studies; 261 patients; OR 3.96; 95% CI 2.08, 7.54; p < 0.0001, $I^2$ = 0%). Furthermore, CAZ-AVI treatment was also associated with higher odds of microbiological eradication (5 studies; 430 patients; OR 5.39; 95% CI 2.20, 13.21; p = 0.0002; $I^2$ = 69%). CAZ-AVI was reportedly associated with a 67% reduction in odds of 30-day mortality (7 studies; 774 patients; OR 0.33; 95% CI 0.23, 0.48; p 0.00001; $I^2$ = 0%; NNT 6 (NNT 5.32 95% CI 3.94, 8.18)) (*Figure 7*). In those studies that examined bloodstream infections only, a similar reduction in the odds of mortality by day 30 were reported for CAZ-AVI treatment (4 studies; 493 patients; OR 0.39; 95% CI 0.25, 0.60; p < 0.0001; $I^2$ = 0%, NNT 7 (NNT 6.46 95% CI 4.16, 14.48)). Only 3 studies included reported on prevalence of various carbapenemases per cohort precluding any subgroup analysis and therefore no conclusion can be drawn for effectiveness by carbapenemase produced. No meta-analysis of safety outcomes was able to be performed due to lack of data.

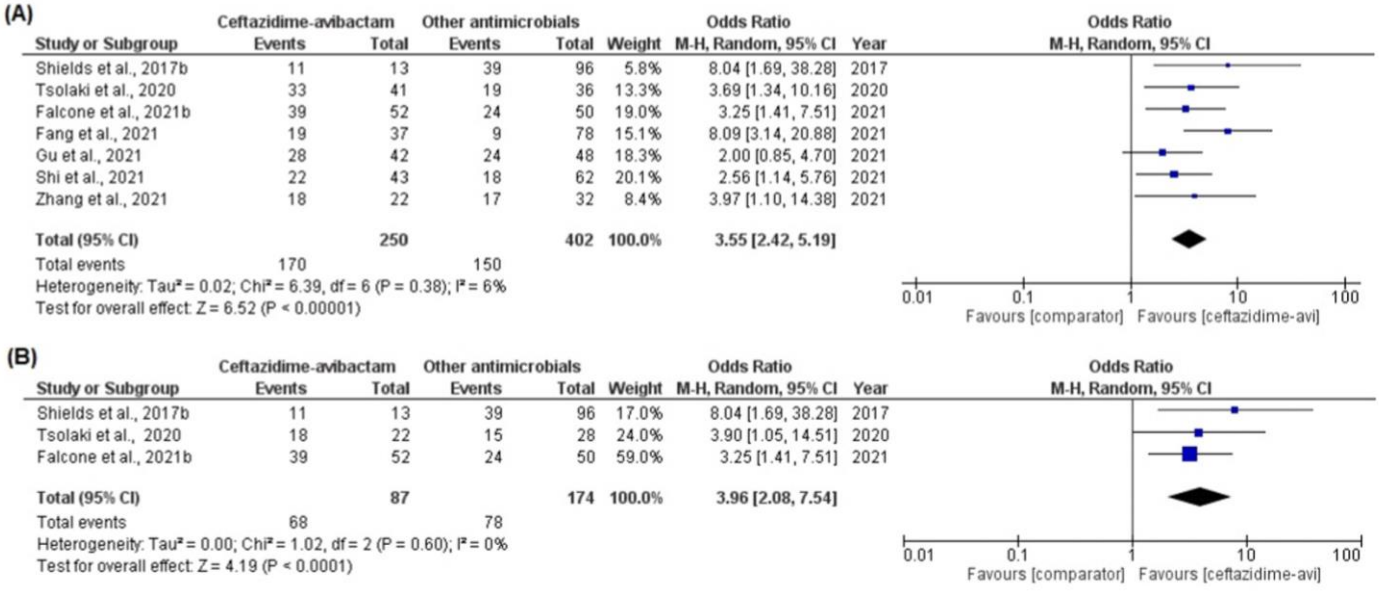


*Figure 6. Clinical success of CAZ-AVI vs. comparators in the treatment of CRE K. pneumoniae infections (A) and in CRE K. pneumonia BSIs specifically (B), Karampatakis et al. (3)*

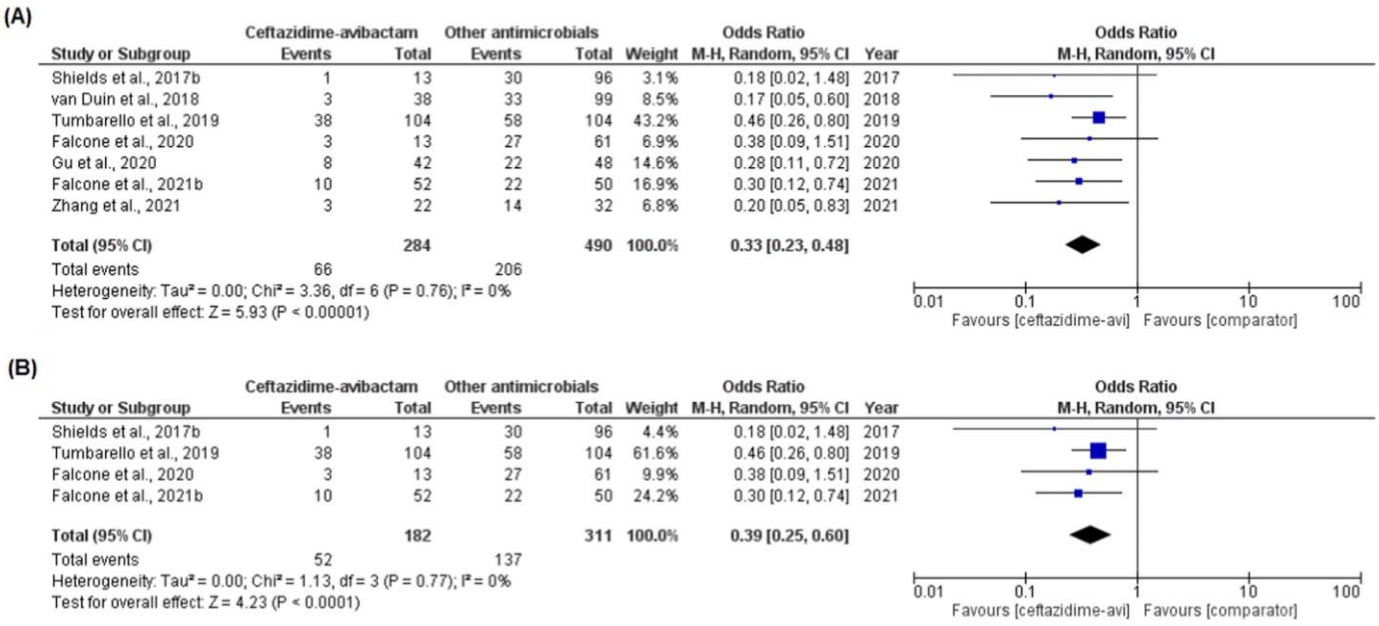


*Figure 7. 30-day mortality of CAZ-AVI vs. comparators in the treatment of CRE K. pneumoniae infections (A) and in CRE K. pneumoniae BSIs specifically (B), Karampatakis et al. (3)*

**Caston et al. (33)**

Caston et al. conducted an industry-sponsored multicentred retrospective observational study comparing outcomes in participants with carbapenemase-producing Enterobacterales (CPE) infections treated with CAZ-AVI or best available alternative therapies. The study, conducted in the Spanish Public Healthcare system, enrolled 339 participants and was assessed to be at moderate risk of bias using the ROBINS-I tool. (14) Complicated urinary tract infection (38.1%) and bloodstream infections (32.7%) were the most frequently reported CPE infections. Of the cases with bacterial isolates available (n = 174), the most frequently reported causative organism was *K. pneumoniae (*163), and the most frequent carbapenemase was OXA-48 (109), followed by KPC (62).

CAZ-AVI treatment was used in combination drugs such as amikacin (30.3%), tigecycline (26.8%), colistin (17.9%) , gentamycin (10.7%), fosfomycin (10.7%), tobramycin (1.8%) and aztreonam (1.8%). Various combinations of these antimicrobials made up the regimens in the comparator arm. A multivariate logistic regression model and adjustment for propensity scores were used to control or confounding.

In terms of baseline characteristics between the two groups, at the start of treatment the CAZ-AVI group had significantly greater proportion of participants with diabetes mellitus, acute renal failure, haematological malignancies, septic shock and CPE bloodstream infections. In the multivariate analysis, after adjustment for propensity score, treatment with CAZ-AVI was associated with improved survival (OR 0.41; 95% CI 0.20, 0.80; p = 0.01). Interestingly, this survival benefit was most pronounced in patients with higher risk of morality based on an INCREMENT-CPE score > 7 points (*Figure 8 and 9*). The INCREMENT-CPE score predicts mortality associated with CRE bacteraemia, considering variables such as severe sepsis or septic shock, Pitt score ≥ 6, Charlson comorbidity index ≥

2, source of bacteraemia other than urinary or biliary tract and inappropriate early targeted therapy.(40) CAZ-AVI containing therapy was also identified as an independent predictor of clinical response (OR 2.43; 95% CI 1.16, 5.12; p =0.02). and microbiological response (OR 0.40; 95% CI 0.18; 0.85; p = 0.02).

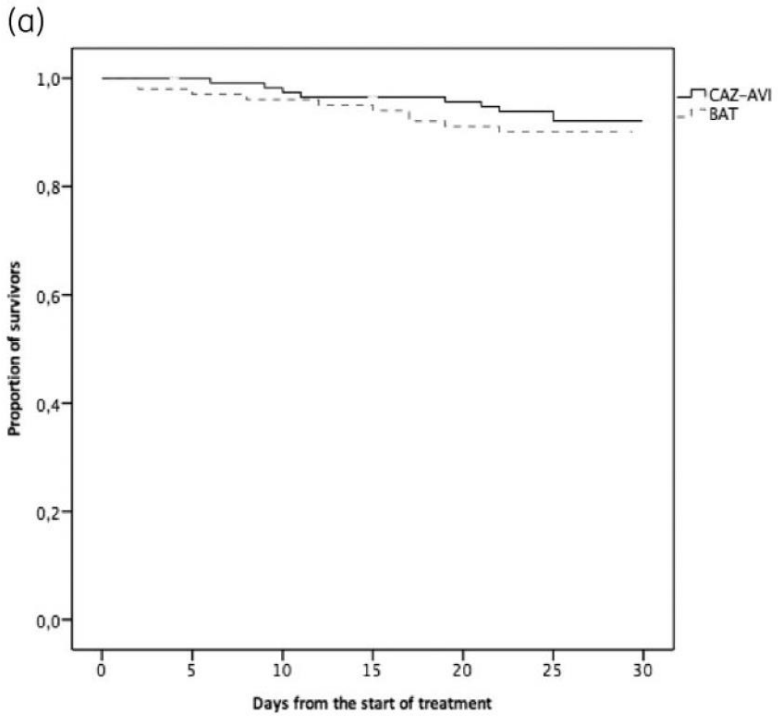


*Figure 8. Survival in patients with INCREMENT-CPE score ≤ 7 points treated with ceftazidime-avibactam (CAZ-AVI) (solid line) or best alternative therapy (discontinuous line) for infections caused by carbapenemase-producing Enterobacterales (CPE) (log rank p = 0.73), Caston et al. (32)*

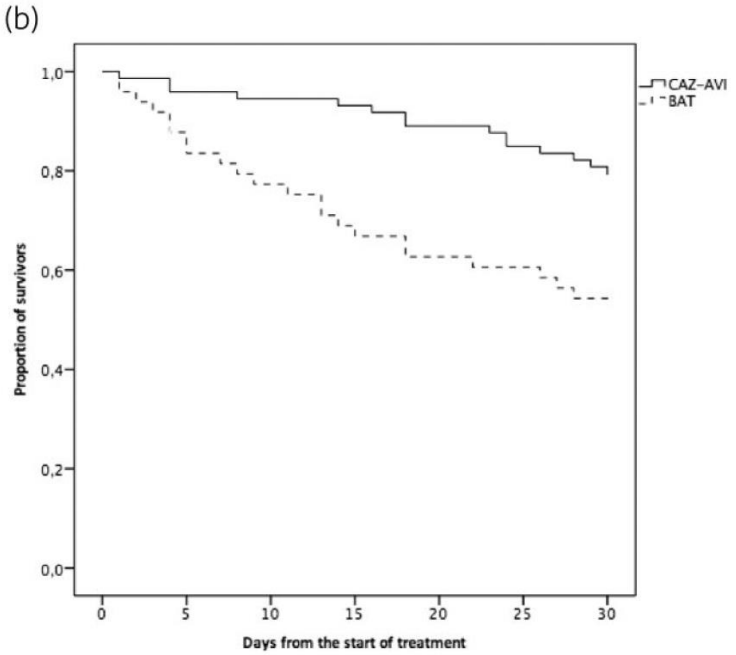


*Figure 9. Survival in patients with INCREMENT-CPE score > 7 points treated with CAZ-AVI (solid line) or best alternative therapy (discontinuous line) for infections caused by CPE. (log rank p = 0.004), Caston et al. (32)*

**Evidence Synthesis:** Safety

The most commonly reported adverse reactions associated with CAZ-AVI treatment are nausea, diarrhoea and a positive direct antiglobulin or Coombs tests. This seroconversion to Coombs positivity, while very common, has not yet been associated with the development of haemolysis. (9) Furthermore, in patients with renal impairment, failure to dose adjust ceftazidime has been associated with neurological adverse events such as tremor, convulsions and encephalopathy.(9)

Safety outcomes were not extensively investigated in the included systematic reviews. Karampatakis et al. did not perform meta-analysis of safety outcomes in their study due to lack of data.(3) Chen et al. reported only on nephrotoxicity.(4) CAZ-AVI containing regimens were associated with a reduction in risk of nephrotoxicity as compared to other appropriate antibiotic regimens (5 studies; 380 patients; RR 0.41; 95% CI 0.20, 0.84; $I^2$= 2%; p = 0.02; NNT 13 (NNT 12.20 95% CI 7.17, 40.81)).(4)

In terms of safety, in the study by Caston et al., treatment with CAZ-AVI was associated with less adverse events (AEs) than alternative antibiotic regimens (5.8% vs. 20%; p < 0.001). (33) Although diarrhoea was more frequently reported in the CAZ-AVI treatment arm, this was not statistically significant (45.4% vs. 13.3%; p = 0.07). Renal failure occurred more frequently in patients receiving comparator regimens (10% vs 1.6%; p ≤ 0.01), despite the higher baseline proportion of participants with acute renal failure in the CAZ-AVI arm. In total 10 participants experienced AEs resulting in treatment discontinuation. Eight participants in the comparator arm discontinued treatment early, 7

as a result of renal failure. Two participants treated with CAZ-AVI discontinued treatment early due to Clostridium difficile colitis.

| Table 3. Summary of systematic reviews with meta-analyses | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Name of systematic review** | **Primary study sites** | **Population** | Number of primary studies (N) **Total number of participants (n)** | **Site of Infection** | **Organism** | **Intervention** | **Comparator** | **Primary Outcomes** | **Secondary** | AMSTAR II Rating **(see appendices)** |
| Y Chen et al. 2022**(4)** | USA Europe China | Adults with CRE BSI | N = 11 observational studies (n = 1205) | UTI, respiratory tract, IAI, catheter-related | K. pneumoniae (6 studies)<br><br>Multiple pathogens of which 79 – 88% K. pneumoniae (5 studies) | CAZ-AVI-based combination therapy. | OAA (Most common combination regimen in control group was colistin + tigecycline) | **30-day all-cause mortality:**<br>CAZ-AVI vs. OAA, 11 studies, n=1205<br>RR 0.55; 95% CI 0.45, 0.68 p < 0.00001; $I^2$ = 0%<br>NNT 6<br><br>CAZ-AVI vs. colistin-containing therapy.<br>RR 0.48 95% CI 0.33, 0.69, $I^2$ =36%, p<0.0001<br>NNT 5 | **Clinical cure:**<br>CAZ-AVI vs. OAA 6 studies, n = 567<br>RR 1.85, 95% CI 1.57, 2.18, $I^2$ = 0%, p < 0.00001<br>NNT 3<br>**Relapse rate:**<br>CAZ-AVI vs. OAA 4 studies, n = 455<br>RR 0.69, 95% CI 0.29, 1.66, $I^2$ = 54%, p =0.41<br>**Nephrotoxicity:**<br>CAZ-AVI vs. OAA 5 studies, n = 380<br>RR 0.41, 95% CI 0.2, 0.84, $I^2$ = 2%, p =0.02<br>NNT 13 | Critically Low Quality |
| Karampatakis et al. 2023**(3)** | USA Europe China | Adults with CRE K. pneumonia infection | N = 11 observational studies (n = 1213) | All (4)<br>BSI (3) | CRE K. pneumoniae | CAZ-AVI monotherapy or combination therapy | OAA (Monotherapy or combination therapy) | **Clinical success:**<br>CAZ-AVI vs. OAA, 7 studies, n=652 68% vs. 37.3%; OR 3.55;<br>95% CI 2.42, 5.19; p < 0.00001, $I^2$ 6%<br>**Clinical success for studies of patients with BSIs only:**<br>CAZ-AVI vs. OAA, 3 studies, n=261<br>78.2% vs. 44.8%; OR 3.96<br>95% CI 2.08, 7.54; p < 0.0001; $I^2$ = 0%<br>NNT 3 | **28-day mortality:**<br>CAZ-AVI vs. OAA, 4 studies, n = 439<br>18.2% vs. 35.2%, OR 0.38;<br>95% CI 0.21, 0.71; p = 0.002; $I^2$ =38%<br>**28-day mortality for patients with BSIs only:**<br>CAZ-AVI vs. OAA, 2 studies, n = 192<br>18.3% vs. 41.4%; OR 0.32;<br>95% CI 0.16, 0.61; p = 0.0007; $I^2$ = 0%<br>**30-day mortality:**<br>CAZ-AVI vs. OAA, 7 studies, n = 774<br>23.2% vs. 42.0%; OR 0.33;<br>95% CI 0.23, 0.48; p < 0.00001; $I^2$ = 0%; NNT 6<br>**30-day mortality for patients with BSIs:**<br>CAZ-AVI vs. OAA, 4 studies, n = 493<br>28.6% vs. 44.0%; OR 0.39; 95% CI 0.25, 0.60; p < 0.001; $I^2$=0%; NNT 7 | Critically Low Quality |

ICU = intensive care unit; CAZ-AVI = ceftazidime-avibactam; OAA = other appropriate antibiotic; UTI – urinary tract infection; IAI = intraabdominal infection; CRE = carbapenem resistant Enterobacterales; BSIs = blood stream infections

| Table 4. Summary of primary studies | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Name** | **Study Type** | **Study Site** | **Population** | **n** | **Site of Infection** | **Microbiology** | **Intervention** | **Comparator** | **Primary Outcome** | **Secondary Outcome** | **Comments** | **ROBINS Quality** |
| Almangour et al. 2022 (31) | Retrospective cohort | Saudi Arabia | Hospitalised adults with CRE infections.<br><br>Mean age: 58 years<br><br>Males: 62%<br><br>ICU: 65%<br><br>Mechanically ventilated: 48% | 230 | HAP (26%), UTI (19%), Wound infection (16%), IAI (13%), VAP (10%), BSIs (26%) | K. Pneumonia (87%).<br><br>In CAZ-AVI arm 78% of isolates were susceptible to CAZ-AVI.<br><br>In colistin arm 76% of isolates were susceptible to colistin.<br><br>Patients were excluded if isolate identified was non-susceptible to the study drug being investigated. | CAZ-AVI (n = 149)<br>2.5g 8 hourly<br><br>In combination with:<br>Tigecycline (11%)<br>Aminoglycoside (5%) | Colistin-based regimen (n = 81)<br>9 MIU as loading dose, followed by at least 9 MIU given in divided doses. *<br><br>In combination with:<br>Carbapenem (58%)<br>Tigecycline (10%)<br>Aminoglycoside (7%) | **Clinical cure at the end of treatment:**<br>CAZ-AVI 71% vs. colistin 52%<br>OR 2.29; 95% CI 1.31, 4.01; p < 0.004, NNT 5<br>**In-hospital mortality:**<br>CAZ-AVI 35% vs. colistin 44%<br>OR 0.67; 95% CI 0.39, 1.16; p = 0.156 | **Infection-related mortality:**<br>CAZ-AVI 28% vs. colistin 33%<br>OR 0.79;<br>95% CI 0.44, 1.41; p = 0.418<br>**AKI:**<br>CAZ-AVI 15% vs. colistin 33%<br>OR 0.37, 95% CI 0.19,0.69; p = 0.002, NNT 6<br>**Length of hospital stay, ICU stay, duration of mechanical ventilation, 30-day readmission or 30 and 90-day recurrence:**<br>No statistically significant difference | No statistically significant difference in time to active therapy and time to study drug.<br><br>Combination therapy more commonly used in the colistin arm (70% VS. 23%, P < 0.001).<br><br>Higher incidence of heart failure and peripheral vascular disease in CAZ-AVI arm.<br><br>Median comorbidity index higher in CAZ-AVI arm.<br><br>Higher median baseline creatinine in CAZ-AVI arm.<br><br>Median APACHE score 15 in CAZ-AVI and 16 Colistin. | Serious risk of bias |
| Alraddadi et al. 2019 (32) | Retrospective cohort | Saudi Arabia | Adults who received >24 hours CAZ-AVI for clinically established CRE infections.<br><br>Mean age (CAZ-AVI): 59.5 years<br>Mean age (comparator): 61.5 years<br><br>Males (CAZ-AVI): 80% Males (comparator): 57.1% | 38 | BSIs (CAZ-AVI): 70%<br>BSIs (comparator): 53.6% | In CAZ-AVI group:<br>K. Pneumonia 70%<br>E. Coli 30%<br>OXA-48 80%<br><br>In comparator group:<br>K. Pneumonia (82.1%<br>E. Coli 17.9%<br>OXA-48 68% | CAZ-AVI (n =10)<br>Dosing not specified | OAA (n = 28)<br><br>25 of 28 patients received combination therapy:<br><br>Colistin 75%<br>Carbapenem 75%<br>Tigecycline31.1%<br>Aminoglycoside 28.6%<br><br>Dosing not specified | **Clinical remission:**<br>CAZ-AVI vs. OAA<br>80% vs. 53.6%, p = 0.14 | **30-day mortality:**<br>CAZ-AVI vs. OAA<br>50% vs. 57.1%; p = 0.7<br>**Relapse with same isolate:**<br>CAZ-AVI vs. OAA<br>20% vs. 3.6%, p = 0.1 | Underpowered<br><br>Risk of chronological bias as CAZ-AVI only available from December 2017.<br><br>Comparator group selected from those with CRE infections between Jan and Nov. 2017 compared to intervention group selected between Dec. 2017 and Aug. 2018. | Critical risk of bias |

| Table 4. Summary of primary studies | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Name** | **Study Type** | **Study Site** | **Population** | **n** | **Site of Infection** | **Microbiology** | **Intervention** | **Comparator** | **Primary Outcome** | **Secondary Outcome** | **Comments** | **ROBINS Quality** |
| Caston et al. 2022 (33) | Retrospective cohort. | Spain | Adults with cUTI, HAP, IAI or BSI with confirmed CPE, and received ≥ 48 hours of CAZ-AVI.<br><br>Median age: 70 years<br><br>Males (CAZ-AVI): 66.1%<br>Males (comparator): 57.3% | 339 | BSIs (CAZ-AVI): 38.1%<br><br>BSI (comparator): 26% | In CAZ-AVI group:<br>K. pneumoniae 89.9%<br>OXA-48 73.5%<br>KPC 25.5%<br><br>In comparator group:<br>K. pneumoniae 94%<br>OXA-48 77.3%<br>KPC 22.7% | CAZ-AVI (n = 189)<br>Monotherapy 70.4%<br><br>In combination with:<br>Amikacin 30.3%<br>Tigecycline 26.8%,<br>Colistin 17.9%<br>Gentamicin 10.7%<br>Fosfomycin 10.7%<br>Tobramycin 1.8%<br>Aztreonam 1.8%<br><br>Dosing not specified | OAA (n = 150)<br>Monotherapy 42.6%<br><br>Dosing not specified | **30-day crude mortality after diagnosis of infection**:<br>CAZ-AVI vs. OAA<br>13.7% vs. 22%; p = 0.04<br><br>**Mortality rate in BSI subgroup:**<br>CAZ-AVI vs. OAA<br>13.9% vs. 30.8%; p = 0.03<br><br>**Mortality rate for CAZ-AVI monotherapy vs. CAZ-AVI combination therapy**:<br><br>14.3% vs. 12.5%; p = 0.82<br><br>**In multivariate analysis with adjustment for propensity score:**<br><br>CAZ-AVI was associated with increased survival<br>OR 0.41; 95% CI 0.20, 0.80; p = 0.01 | **21-day clinical response:**<br>CAZ-AVI vs. OAA<br>89.4% vs. 79.3%; p = 0.01<br><br>**CAZ-AVI containing therapy was an independent predictor of clinical response on multivariate analysis:**<br>OR 2.43; 95% CI 1.16, 5.12;<br>p = 0.02<br>**Microbiological eradication:**<br>CAZ-AVI vs. OAA<br>83.3% vs. 69.4%; p = 0.02.<br>**CAZ-AVI containing therapy was only factor independently associated with microbiological response on multivariate analysis:**<br>OR 0.40; 95% CI 0.18, 0.85;<br>p = 0.02<br>**Adverse events:**<br>CAZ-AVI vs. OAA<br>5.8% vs. 20%; p < 0.001<br>**Renal failure:**<br>CAZ-AVI vs. OAA<br>1.6% vs. 10%; p ≤ 0.01 | | Moderate risk of bias<br>Industry sponsored. |

*(1 MIU = 80mg of prodrug colisthimethate sodium)

ICU = intensive care unit; CAZ-AVI = ceftazidime-avibactam; OAA = other appropriate antibiotic; UTI – urinary tract infection; cUTI = complicated urinary tract infection; IAI = intraabdominal infection; CRE = carbapenem resistant enterobacterales; BSIs = blood stream infections; OAA = other appropriate antibiotics; CPE = carbapenemase producing Enterobacterales

**CONCLUSION**

This review suggests that ceftazidime-avibactam-containing therapy is associated with a reduction in mortality (NNT 5 – 7) and nephrotoxicity (NNT 13), and improved clinical cure when compared to other appropriate antibiotic regimens in populations with high proportions of Klebsiella pneumoniae CRE infections that produce KPC and OXA-48 carbapenemases. Recent NICD surveillance suggests comparable CRE epidemiology in South Africa, with the largest proportion of CRE bacteraemia being caused by Klebsiella pneumonia producing OXA-48. However, based on this local data, a significant proportion of CRE isolates (almost 25%) are still unlikely to be susceptible to ceftazidime-avibactam therapy (metallo-beta-lactamases) and thus culture and sensitivity must be used to guide its usage.

At present, CAZ-AVI is available at some tertiary facilities on a named-patient basis due to high cost and to prevent resistance. Standardised guidance on the appropriate use of CAZ-AVI should occur, to improve appropriate access; and in turn to limit resistance with improve health equity.

**Our recommendations:**

- The use of ceftazidime-avibactam in proven CRE bacteraemia should be restricted to infections with organisms that are proven to be sensitive to the drug and resistant to cheaper, equally effective alternatives.
- Access should be limited to, or after discussion with infectious disease sub-specialists or microbiologists, following strict antibiotic stewardship principles.
- A formal pharmacoeconomic analysis should be conducted to guide financial decision-making.
- Ongoing national surveillance for the development of CAZ-AVI resistance should be prioritized.

**Limitations:**

- This review cannot inform decision-making regarding empiric treatment of suspected CRE infections with CAZ-AVI therapy or monotherapy with CAZ-AVI compared with CAZ-AVI-containing combination therapy.
- The findings of this report, including the costing analyses, cannot be generalised to CRE infections other than bacteraemia.

| Version | Date | Reviewer(s) | Recommendation and Rationale |
|---|---|---|---|
| 1 | 21 September 2023 | GT, JT, JN, MB | The PHC Adult Hospital Level ERC suggests using ceftazidime-avibactam in selected patients with bacteraemia due to carbapenem resistant organisms. In view of the cost and antibiotic stewardship concerns the decision to use this agent should not be based solely on sensitivity of the cultured organism to ceftazidime-avibactam. The decision should be made in consultation with a multidisciplinary antibiotic stewardship team and use should be avoided in patients with a very poor prognosis.<br><br>**Rationale:** Systematic reviews and meta-analyses of observational data suggest a large reduction in mortality associated with treatment with ceftazidime-avibactam. At the current price, the incremental cost-effectiveness ratio suggests an additional cost of ZAR 109 786.21 to prevent one death (when compared to a regimen of tigecycline with amikacin), and an additional cost of ZAR 84 613.32 to prevent one |

| | | | |
|---|---|---|---|
| | | | death (when compared to a regimen of tigecycline and colistin). A formal pharmacoeconomic analysis is recommended to guide further decision-making. |

**EVIDENCE TO DECISION FRAMEWORK**

| | JUDGEMENT | EVIDENCE & ADDITIONAL CONSIDERATIONS |
|---|---|---|
| QUALITY OF EVIDENCE OF BENEFIT | **What is the certainty/quality of evidence?**<br>High: ☐ Moderate: ☐ Low: x Very low: ☐<br>*High quality:* confident in the evidence<br>*Moderate quality:* mostly confident, but further research may change the effect<br>*Low quality:* some confidence, further research likely to change the effect<br>*Very low quality:* findings indicate uncertain effect | Observational data of low quality.<br>No randomised controlled trial data available. |
| EVIDENCE OF BENEFIT | **What is the size of the effect for beneficial outcomes?**<br>Large: x Moderate: ☐ Small: ☐ None: ☐ | <u>Chen et al.</u><br><br>Reduced 30-day all-cause mortality: 11 studies; 1 205 participants:<br>• RR 0.55 (95% confidence interval (CI) 0.45, 0.68)<br>• p < 0.00001<br>• $I^2$= 0%<br>• ARR 0.18 (95% CI 0.12; 0.24)<br>• NNT 6 (NNT 5.52; 95% CI 4.21, 8.00)<br><br>Improved clinical cure*: 6 studies; 567 participants:<br>• RR 1.85 (95% CI 1.57, 2.18)<br>• p < 0.00001<br>• $I^2$ = 0%,<br>• ARR 0.34 (95% 0.26; 0.42)<br>• NNT 3 (NNT 2.94; 95% CI 2.37, 3.88)<br><br>Lower risk of nephrotoxicity:5 studies; 380 participants:<br>• RR 0.41 (95% CI 0.20, 0.84)<br>• p = 0.02<br>• $I^2$= 2%<br>• ARR 0.08 (95% 0.02; 0.14)<br>• NNT 13 (NNT 12.20 95% CI 7.17, 40.81<br><br><u>Karampatakis et al.(3)</u><br><br>Reduced 30-day all-cause mortality: 7 studies; 774 patients;<br>• OR 0.33 (95% CI 0.23, 0.48)<br>• P = 0.00001<br>• $I^2$ = 0%<br>• ARR 0.19 (95% CI 0.12, 0.25)<br>• NNT 6 (NNT 5.32 95% CI 3.94, 8.18) |

| | JUDGEMENT | EVIDENCE & ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | | Reduced 30-day all-cause mortality (bloodstream infections only): 4 studies; 493 patients;<br>• OR 0.39 (95% CI 0.25, 0.60)<br>• p < 0.0001<br>• $I^2$ = 0%<br>• ARR 0.15 (95% CI 0.07, 0.24)<br>• NNT 7 (NNT 6.46 95% CI 4.16, 14.48)<br><br>Improved clinical success*: 7 studies; 652 patients;<br>• OR 3.55(95% CI 2.42, 5.19)<br>• p < 0.00001<br>• $I^2$ = 6%<br>• ARR 0.31 (95% CI 0.23, 0.38)<br>• NNT 4 (NNT 3,26; 95% CI 2.62, 4.31)<br><br><u>Caston et al.(33)</u><br>In participants with INCREMENT-CPE > 7 (severe illness), CAZ-AVI therapy was associated with statistically significant improved survival at 30-days<br>78.1% vs. 53.1%; p-value = 0.004 |
| **QUALITY OF EVIDENCE OF HARM** | **What is the certainty/quality of evidence?**<br>High ☐ Moderate ☐ Low ☒ Very low ☐<br>*High quality:* confident in the evidence<br>*Moderate quality:* mostly confident, but further research may change the effect<br>*Low quality:* some confidence, further research likely to change the effect<br>*Very low quality:* findings indicate uncertain effect | Observational data of low quality.<br>Systematic reviews with meta-analyses only reported on mortality and nephrotoxicity. |
| **EVIDENCE OF HARMS** | **What is the size of the effect for harmful outcomes?**<br>Large ☐ Moderate ☐ Small ☒ None ☐ | <u>Caston et al.(33)</u><br>Risk of any adverse events associated with CAZ-AVI compared with best available therapy:<br>5.8% vs. 20%; p < 0.001<br><br>Risk of diarrhoea associated with CAZ-AVI compared with best available therapy:<br>45.4% vs. 13.3%; p = 0.07 |
| **BENEFITS & HARMS** | **Do the desirable effects outweigh the undesirable harms?**<br>Favours intervention ☒ Favours control ☐ Intervention = Control *or* Uncertain ☐ | |
| **THERAPEUTIC INTERCHANGE** | Therapeutic alternatives available:<br>Yes ☐ No ☒<br><br>List the members of the group.<br><br>List specific exclusion from the group: | Rationale for therapeutic alternatives included:<br>Not applicable<br><br>References:<br>Not applicable<br><br>Rationale for exclusion from the group: |

<table>
<tr><th></th><th>JUDGEMENT</th><th>EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td></td><td></td><td>Not applicable<br><br>References: Not applicable</td></tr>
<tr><td>FEASABILITY</td><td>Is implementation of this recommendation feasible?<br>Yes [ ] No [ ] Uncertain [x]</td><td>Evidence suggests a clear mortality benefit (NNT 5 – 7). The budgetary impact, however, is substantial. At the current price, the ICER suggests an additional cost of ZAR 109 786.21 to prevent one death (when compared to a regimen of tigecycline with amikacin), and an additional cost of ZAR 84 613.32 to prevent one death (when compared to a regimen of tigecycline and colistin).<br>The willingness to pay per death prevented is undefined.<br>The feasibility of implementation of the recommendation is thus uncertain.</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?<br>More intensive [x] Less intensive [ ] Uncertain [ ]</td><td>Price of medicines/ treatment course
<table>
<tr><th>Medicine</th><th>Tender price (ZAR)</th><th>SEP (ZAR)</th></tr>
<tr><td>CAZ-AVI (2g/0.5g)</td><td>1 174.62</td><td>1 628.07</td></tr>
<tr><td>Colistin (1 MU)*</td><td>69.67</td><td>69.67</td></tr>
<tr><td>Tigecycline (50mg/ml)</td><td>308.26</td><td></td></tr>
</table>
*Section 21; current cost price<br><br>We strongly recommend a formal pharmacoeconomic analysis to guide decision making.<br><br><u>DIRECT COSTS CAZ-AVI:</u><br>7-day course:<br>(1174.62)*(3)*(7) = ZAR 24 667.02<br><br>5 to 14-day course:<br>(1174.62)*(3)*(5) to (1174.62)*(3)*(14) =<br>ZAR 17 619.30 – 49 334.04<br><br>TOTAL BUDGETARY COSTs:<br>Based on NICD surveillance data:<br>2 144 x 76,8% = 1647 cases potentially susceptible to CAZ-AVI over 24 months<br>1647 x 0.5 = 824 cases potentially susceptible to CAZ-AVI per annum<br><br>Gross budgetary cost of CAZ-AVI to treat all cases in a year for 7-days:<br>(24 667.02*824)<br>ZAR 20 325 624.48<br><br>Gross budgetary cost of TIG+AMIK to treat all cases in a year for 7 days:<br>ZAR 3 924 530.72<br><br>Excess cost per annum of CAZ-AVI over TIG+AMIK:</td></tr>
</table>

| | JUDGEMENT | EVIDENCE & ADDITIONAL CONSIDERATIONS |
|---|---|---|
| | | **ZAR 16 401 093.76**<br><br>Gross budgetary cost of TIG+COLISTIN to treat all cases in a year for 7 days:<br>**ZAR 7 685 139**<br><br>Excess cost per annum of CAZ-AVI over TIG+COLISTIN<br>**ZAR 12 640 485.48**<br><br>**ICER (TO PREVENT ONE DEATH):**<br>**CAZ-AVI vs. TIG+AMIK:**<br>Difference in cost: 19 904.24 per course<br>Difference in mortality: -0.1813<br>ICER: ZAR 109 786.21 per death prevented<br>**CAZ-AVI vs. TIG+COLISTIN:**<br>Difference in cost: 15 340.40 per course<br>Difference in mortality: -0.1813<br>ICER: ZAR 84 613.32 per death prevented<br>**Other resources:**<br>CAZ-AVI review Costing calculations |
| **VALUES, PREFERENCES, ACCEPTABILITY** | **Is there important uncertainty or variability about how much people value the options?**<br>Minor: ☐ Major: ☐ Uncertain: x<br><br>**Is the option acceptable to key stakeholders?**<br>Yes: x No: ☐ Uncertain: ☐ | Likely to be acceptable to stakeholder<br><br>2022:<br>Total vials of Zavicefta® supplied to public sector by Pfizer: 590<br><br>Jan. 2023 to June 2023:<br>Total vials of Zavicefta® supplied to public sector: 780 |
| **EQUITY** | **Would there be an impact on health inequity?**<br>Yes: ☐ No: ☐ Uncertain: x | Favours health equity by improving access to all patients at all facilities, however, high budgetary costs may detract financial resources from other areas of care. |

## REFERENCES


1. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399(10325):629-55. 10.1016/s0140-6736(21)02724-0.
2. Lowe M, Shuping L, Perovic O. Carbapenem-resistant Enterobacterales in patients with bacteraemia at tertiary academic hospitals in South Africa, 2019 - 2020: An update. S Afr Med J. 2022;112(8):542-52. 10.7196/SAMJ.2022.v112i8.16351. https://www.ncbi.nlm.nih.gov/pubmed/36214398.
3. Karampatakis T, Tsergouli K, Behzadi P. Carbapenem-Resistant Klebsiella pneumoniae: Virulence Factors, Molecular Epidemiology and Latest Updates in Treatment Options. Antibiotics (Basel). 2023;12(2). 10.3390/antibiotics12020234. https://www.ncbi.nlm.nih.gov/pubmed/36830145.
4. Chen Y, Huang HB, Peng JM, Weng L, Du B. Efficacy and Safety of Ceftazidime-Avibactam for the Treatment of Carbapenem-Resistant Enterobacterales Bloodstream Infection: a Systematic Review and Meta-Analysis. Microbiol Spectr. 2022;10(2):e0260321. 10.1128/spectrum.02603-21. https://www.ncbi.nlm.nih.gov/pubmed/35377233.
5. Dadgostar P. Antimicrobial Resistance: Implications and Costs. Infect Drug Resist. 2019;12:3903-10. 10.2147/idr.S234610.
6. South African National Department of Health. Antimicrobial Resistance National Strategy Framework. 2014 - 2024. https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-04/Antimicrobial%252520resistance%252520national%252520strategy%252520framework%2525202014-2024.pdf.
7. Queenan AM, Bush K. Carbapenemases: the versatile beta-lactamases. Clin Microbiol Rev. 2007;20(3):440-58, table of contents. 10.1128/cmr.00001-07.
8. Morrill HJ, Pogue JM, Kaye KS, LaPlante KL. Treatment Options for Carbapenem-Resistant Enterobacteriaceae Infections. Open Forum Infect Dis. 2015;2(2):ofv050. 10.1093/ofid/ofv050. https://www.ncbi.nlm.nih.gov/pubmed/26125030.
9. Zavicefta [package insert]. South Africa. Pfizer Laboratories (Pty) Ltd; 2021.
10. Perovic O, Singh-Moodley A, Lowe M. In Vitro Activity of Ceftolozane-Tazobactam against Escherichia coli, Klebsiella pneumoniae and Pseudomonas aeruginosa Obtained from Blood Cultures from Sentinel Public Hospitals in South Africa. Antibiotics (Basel). 2023;12(3). 10.3390/antibiotics12030453.
11. Microsoft Corporation. Microsoft Excel [Internet]. 2018. Available from: https://office.microsoft.com/excel.
12. AGREE Next Steps Consortium (2013). The AGREE II Instrument [Electronic version]. Retrieved May 26, 2023, from http://www.agreetrust.org.
13. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. 10.1136/bmj.l4898. https://www.ncbi.nlm.nih.gov/pubmed/31462531.
14. Sterne JAC, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. 10.1136/bmj.i4919. https://www.ncbi.nlm.nih.gov/pubmed/27733354.
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. 10.1136/bmj.n71. https://www.bmj.com/content/bmj/372/bmj.n71.full.pdf.
16. NICE. Antimicrobial health technology evaluation guidance. Ceftazidime with avibactam for treating severe drug-resistant gram-negative bacterial infections. 2022. https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials/ceftazidime-with-avibactam.
17. Hu Q., Chen J., Sun S., Deng S. Mortality-Related Risk Factors and Novel Antimicrobial Regimens for Carbapenem-Resistant Enterobacteriaceae Infections: A Systematic Review. Infect Drug Resist. 2022;15:6907-26. 10.2147/idr.S390635.
18. Chen J., Yang Y., Yao H., Bu S., Li L., Wang F., et al. Prediction of Prognosis in Adult Patients With Carbapenem-Resistant Klebsiella pneumoniae Infection. Front Cell Infect Microbiol. 2021;11:818308. 10.3389/fcimb.2021.818308.
19. Durante-Mangoni E., Andini R., Zampino R. Management of carbapenem-resistant Enterobacteriaceae infections. Clin Microbiol Infect. 2019;25(8):943-50. 10.1016/j.cmi.2019.04.013.
20. Cultrera R., Libanore M., Barozzi A., d'Anchera E., Romanini L., Fabbian F., et al. Ceftolozane/Tazobactam and Ceftazidime/Avibactam for Multidrug-Resistant Gram-Negative Infections in Immunocompetent Patients: A Single-Center Retrospective Study. Antibiotics (Basel, Switzerland). 2020;9(10):1-11. 10.3390/antibiotics9100640. http://www.epistemonikos.org/documents/5172ff0a11e117a2f6de6531fb91d75369dcb543.
21. Hsu J. Y., Chuang Y. C., Wang J. T., Chen Y. C., Hsieh S. M. Healthcare-associated carbapenem-resistant Klebsiella pneumoniae bloodstream infections: Risk factors, mortality, and antimicrobial susceptibility, 2017-2019. J Formos Med Assoc. 2021;120(11):1994-2002. 10.1016/j.jfma.2021.04.014.
22. Kanj S. S., Bassetti M., Kiratisin P., Rodrigues C., Villegas M. V., Yu Y., et al. Clinical data from studies involving novel antibiotics to treat multidrug-resistant Gram-negative bacterial infections. Int J Antimicrob Agents. 2022;60(3):106633. 10.1016/j.ijantimicag.2022.106633.
23. Katchanov J., Asar L., Klupp E. M., Both A., Rothe C., König C., et al. Carbapenem-resistant Gram-negative pathogens in a German university medical center: Prevalence, clinical implications and the role of novel β-lactam/β-lactamase inhibitor combinations. PLoS One. 2018;13(4):e0195757. 10.1371/journal.pone.0195757.
24. King M., Heil E., Kuriakose S., Bias T., Huang V., El-Beyrouty C., et al. Multicenter Study of Outcomes with Ceftazidime-Avibactam in Patients with Carbapenem-Resistant Enterobacteriaceae Infections. Antimicrobial agents and chemotherapy. 2017;61(7). 10.1128/AAC.00449-17. http://www.epistemonikos.org/documents/c1d0d83e9c6a0f358992f659b46defaab747f665.
25. Meng H., Han L., Niu M., Xu L., Xu M., An Q., et al. Risk Factors for Mortality and Outcomes in Hematological Malignancy Patients with Carbapenem-Resistant Klebsiella pneumoniae Bloodstream Infections. Infect Drug Resist. 2022;15:4241-51. 10.2147/idr.S374904.
26. Shen L., Lian C., Zhu B., Yao Y., Yang Q., Zhou J., et al. Bloodstream Infections due to Carbapenem-Resistant Klebsiella pneumoniae: A Single-Center Retrospective Study on Risk Factors and Therapy Options. Microb Drug Resist. 2021;27(2):227-33. 10.1089/mdr.2019.0455.

27. Shi Y., Hu J., Liu P., Wang T., Wang H., Liu Y., et al. Ceftazidime-Avibactam-Based Versus Tigecycline-Based Regimen for the Treatment of Carbapenem-Resistant Klebsiella pneumoniae-Induced Pneumonia in Critically Ill Patients. Infect Dis Ther. 2021;10(4):2721-34. 10.1007/s40121-021-00542-3.
28. Soriano A., Carmeli Y., Omrani A. S., Moore L. S. P., Tawadrous M., Irani P. Ceftazidime-Avibactam for the Treatment of Serious Gram-Negative Infections with Limited Treatment Options: A Systematic Literature Review. Infectious diseases and therapy. 2021;10(4):1989-2034. 10.1007/s40121-021-00507-6. http://www.epistemonikos.org/documents/fa2386728599f03476216d9e2f5f494a6c9f97b3.
29. Zhen S., Wang H., Feng S. Update of clinical application in ceftazidime-avibactam for multidrug-resistant Gram-negative bacteria infections. Infection. 2022;50(6):1409-23. 10.1007/s15010-022-01876-x.
30. Zhong H., Zhao X. Y., Zhang Z. L., Gu Z. C., Zhang C., Gao Y., et al. Evaluation of the efficacy and safety of ceftazidime/avibactam in the treatment of Gram-negative bacterial infections: a systematic review and meta-analysis. Int J Antimicrob Agents. 2018;52(4):443-50. 10.1016/j.ijantimicag.2018.07.004.
31. Almangour TA, Ghonem L, Aljabri A, Alruwaili A, Al Musawa M, Damfu N, et al. Ceftazidime-Avibactam versus Colistin for the Treatment of Infections Due to Carbapenem-Resistant Enterobacterales: A Multicenter Cohort Study. Infect Drug Resist. 2022;15:211-21. 10.2147/idr.S349004.
32. Alraddadi BM, Saeedi M, Qutub M, Alshukairi A, Hassanien A, Wali G. Efficacy of ceftazidime-avibactam in the treatment of infections due to Carbapenem-resistant Enterobacteriaceae. BMC Infect Dis. 2019;19(1):772. 10.1186/s12879-019-4409-1. https://www.ncbi.nlm.nih.gov/pubmed/31484510.
33. Caston JJ, Cano A, Perez-Camacho I, Aguado JM, Carratala J, Ramasco F, et al. Impact of ceftazidime/avibactam versus best available therapy on mortality from infections caused by carbapenemase-producing Enterobacterales (CAVICOR study). J Antimicrob Chemother. 2022;77(5):1452-60. 10.1093/jac/dkac049. https://www.ncbi.nlm.nih.gov/pubmed/35187577.
34. Gu J, Xu J, Zuo TT, Chen YB. Ceftazidime-avibactam in the treatment of infections from carbapenem-resistant Klebsiella pneumoniae: Ceftazidime-avibactam against CR-KP infections. J Glob Antimicrob Resist. 2021;26:20-5. 10.1016/j.jgar.2021.04.022. https://www.ncbi.nlm.nih.gov/pubmed/34020072.
35. Hakeam HA, Alsahli H, Albabtain L, Alassaf S, Al Duhailib Z, Althawadi S. Effectiveness of ceftazidime-avibactam versus colistin in treating carbapenem-resistant Enterobacteriaceae bacteremia. Int J Infect Dis. 2021;109:1-7. 10.1016/j.ijid.2021.05.079. https://www.ncbi.nlm.nih.gov/pubmed/34091006.
36. Chen L, Han X, Li Y, Li M. Assessment of Mortality-Related Risk Factors and Effective Antimicrobial Regimens for Treatment of Bloodstream Infections Caused by Carbapenem-Resistant Enterobacterales. Antimicrob Agents Chemother. 2021;65(9):e0069821. 10.1128/AAC.00698-21. https://www.ncbi.nlm.nih.gov/pubmed/34228539.
37. Tsolaki V, Mantzarlis K, Mpakalis A, Malli E, Tsimpoukas F, Tsirogianni A, et al. Ceftazidime-Avibactam To Treat Life-Threatening Infections by Carbapenem-Resistant Pathogens in Critically Ill Mechanically Ventilated Patients. Antimicrob Agents Chemother. 2020;64(3). 10.1128/AAC.02320-19. https://www.ncbi.nlm.nih.gov/pubmed/31818820.
38. van Duin D, Lok JJ, Earley M, Cober E, Richter SS, Perez F, et al. Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae. Clin Infect Dis. 2018;66(2):163-71. 10.1093/cid/cix783. https://www.ncbi.nlm.nih.gov/pubmed/29020404.
39. Hennessy EA, Johnson BT. Examining overlap of included studies in meta-reviews: Guidance for using the corrected covered area index. Res Synth Methods. 2020;11(1):134-45. 10.1002/jrsm.1390. https://www.ncbi.nlm.nih.gov/pubmed/31823513.
40. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, Hsueh PR, Viale P, Paño-Pardo JR, et al. A Predictive Model of Mortality in Patients With Bloodstream Infections due to Carbapenemase-Producing Enterobacteriaceae. Mayo Clinic Proceedings. 2016;91(10):1362-71. https://doi.org/10.1016/j.mayocp.2016.06.024. https://www.sciencedirect.com/science/article/pii/S0025619616303664.

## APPENDICES

### Appendix 1: AMSTAR

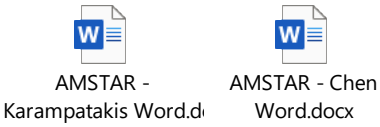


*Figure A1: AMSTAR Assessment of Included Systematic reviews with meta-analyse*

### Appendix 2: ROBINS-I

| | Almangour et al. 2022 (31) | Alradaddi et al. 2019 (32) | Caston et al. 2022 (33) |
|---|---|---|---|
| Bias due to confounding | Moderate | Critical | Moderate |
| Bias in selection of participants into study | Serious | Low | Low |
| Bias in classification of interventions | Moderate | Low | Low |
| Bias due to deviations from intended interventions | Low | Low | Low |
| Bias due to missing data | Low | Low | Low |
| Bias in measurement of outcomes | Moderate | Serious | Low |
| Bias in selection of reported result | Low | Low | Low |
| Overall | Serious | Critical | Moderate |

*Table A2 ROBINS-I Asssessment of Included Primary Research*

Appendix 1**:** Table of primary study overla**p**

| | | Systematic Review | |
|---|---|---|---|
| **Row** | **Primary Study** | 1. Chen, 2022 | 2. Karampatakis, 2023 |
| **1** | Shields 2017 | 1 | 1 |
| **2** | Tumbarello, 2019 | 1 | 1 |
| **3** | Tsolaki, 2020 | 1 | 1 |
| **4** | Karaiskos, 2021 | 1 | 1 |
| **5** | Falcone, 2020 | 1 | 1 |
| **6** | Falcone, 2021 | 1 | 1 |
| **7** | Shen, 2021 | 1 | 0 |
| **8** | Zhou, 2021 | 1 | 0 |
| **9** | Chen, 2021 | 1 | 0 |
| **10** | Hakeam, 2021 | 1 | 0 |
| **11** | Caston, 2017 | 1 | 0 |
| **12** | Fang, 2021 | 0 | 1 |
| **13** | Gu, 2021 | 0 | 1 |
| **14** | Shi, 2021 | 0 | 1 |
| **15** | Zhang, 2021 | 0 | 1 |
| **16** | Van Duin, 2018 | 0 | 1 |
| | **TOTAL** | **11** | **11** |

*Table A3 of primary studies included in two systematic reviews used in this review of the evidence and the overlap thereof*

Appendix 4: **Calculation of CCA**

$$CCA = \frac{N - r}{(r \times c) - r},$$

$$CCA = (22 - 16)/((16*2) - 16) = 0.375$$

$$= 37.5\%$$

N = total number of included publications (including double counting) = 22
r = number of rows (number of index publications) = 16
c = number of reviews = 2

*Figure A4 Calculation of study overlap of primary studies included in two systematic reviews used in this review of the evidence using the corrected covered area (CCA) method by Hennessy & Johnson.*