KZN SPECIALIST NETWORK – ANTIMICROBIAL STEWARDSHIP INITIATIVE

CARBAPENEM RESISTANT ENTEROBACTERALES (CRE) BLOOD STREAM INFECTIONS IN KZN (PRIVATE SECTOR) : GUIDELINE FOR TARGETED ANTIMICROBIAL THERAPY

Endorsed by the KZN Specialist Network (KZNSN), the KZN Branch of Critical Care Society of Southern Africa (CCSSA) and the KZN Branch of the South African Society of Clinical Pharmacy (SA SOCP).

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DISCLAIMER

It is important to realize that guidance cannot always account for individual variation among patients and are not intended to supplant physician judgment with respect to particular patients or special clinical situations. Permission is granted to physicians and health care providers solely to copy and use the guidance in their professional practices and clinical decision-making.

DEFINITIONS

What are Enterobacterales?

A large family of Gram-negative bacteria that includes a number of pathogens such as *Klebsiella*, *Enterobacter*, *Citrobacter*, *Salmonella*, *Escherichia coli*, *Shigella*, *Proteus*, *Serratia* and other species. (DOES NOT INCLUDE Pseudomonas spp, Acinetobacter spp).

Carbapenem Resistant Enterobacterales (CRE) are Enterobacterales that test resistant to at least one of the carbapenem antibiotics (ertapenem, meropenem, doripenem, or imipenem) or produce a carbapenemase (an enzyme that can make them resistant to carbapenem antibiotics).

INTRODUCTION

Carbapenem-Resistant Enterobacterales (CRE) are a serious threat to public health. Infections with CRE are difficult to treat and have been associated with mortality rates of up to 50% for hospitalized patients.

Enterobacterales that produce metallo beta-lactamases e.g., NDM are a particular and growing problem worldwide. The optimization of antibiotic therapy is challenging.

We note with concern the increase in carbapenem resistant metallo beta-lactamase producing CREs in KwaZulu-Natal with most testing positive for the NDM-1 carbapenemase accounting for two thirds of all clinical isolates in the region (personal correspondence, Lancet and Ampath Laboratories).

In South Africa, carbapenems, polymyxins, Fosfomycin, Tigecycline and Amikacin have until recently been the only available treatment options for serious infections caused by CREs. Ceftazidime-Avibactam (CA), a β-lactam/ β-lactamase inhibitor combination (BLBLI), has recently been registered for use in SA.

Optimal management requires identification of the site of infection (lung, abdomen and blood stream most commonly), a focus on the enzyme types associated with the CREs and provision of timely and accurate therapy in the context of appropriate antimicrobial stewardship.

The objectives of our recommended approach are to:

- Optimise patient outcomes in settings where there has been increasing dependence on colistin as salvage therapy.
- Avoid redundant and inappropriate use of CA from an antibiotic stewardship and cost-containment point-of-view.
- Ensure the longevity of existing broad-spectrum and the new antibiotics.

In an effort to do so, the KZN Specialist Network's Antimicrobial Stewardship Initiative (KZNSN ASI) committee convened a panel of clinicians, microbiologists and pharmacists to consider appropriate therapeutic guidelines for the treatment of **blood culture positive** carbapenemase producing Enterobacterales.

TREATMENT SELECTION

It is important to note that no treatment regimen has been clearly defined to be superior to another, as registration trials have been non-inferiority based.

The guide below has been adapted taking into consideration both Infectious Diseases Society of America and European Society of Clinical Microbiology and Infectious Diseases guidelines. A dosage table has also been included.

TABLE 1: ANTIMICROBIAL CHOICES FOR THE TARGETED TREATMENT CRE BSIs IN KZN

CRE ENZYME TYPE	FIRST LINE OPTIONS	ALTERNATIVES
OXA 48 ONLY	Ceftazidime-Avibactam [1]	Carbapenem Based Regime[2] OR Polymyxin/Colistin Based Regime[3,4] OR Cefiderocol
NDM ONLY	Ceftazidime-Avibactam plus Aztreonam	Polymyxin/Colistin Based Regime[3,4] OR Cefiderocol
NDM PLUS OXA 48	Ceftazidime-Avibactam plus Aztreonam	Polymyxin/Colistin Based Regime[3,4] OR Cefiderocol
NO ENZYME DETECTED	Treatment Based on Susceptibility Report	

Notes:
[1] CEFTAZIDIME-AVIBACTAM
[2] CONSIDER IF MEROPENEM MICs <=8ug/ml
[3] RECOMMEND USE AS PART OF COMBINATION THERAPY WITH SECOND SUSCEPTIBLE AGENT
[4] POLYMYXIN IS PREFERRED OVER COLISTIN TO MINIMISE ADVERSE RENAL EVENTS

TABLE 2. RECOMMENDED DOSAGE, SPECTRUM OF COVERAGE, COST & AVAILABILITY IN SA

	ESBLs	OXA	NDM	DOSING IV	COST & AVAILABILITY
CEFTAZIDIME AVIBACTAM	YES	YES	NO	2,5G 8 HOURLY	Available in South-Africa R1 415.71/ 2.5g vial (excl. VAT) **R4 247.13/ day**
AZTREONAM	NO	NO	+/-	2G 8 HOURLY	SECTION 21 R688.00/ 1g vial **R4 128.00/ day**
CEFIDEROCOL	YES	YES	YES	2G 6-8 HOURLY	SECTION 21 (Fetroja®) R4577.00/ 1g vial (excl. VAT) **R36 616/ day**
COLISTIN	YES	YES	YES	LOADING DOSE 12MU THEN 9MU/DAY IN 2-3 DIVIDED DOSES	SECTION 21 R73.63/ 1MU vial (excl. VAT) **R662.67/ day**
FOSFOMYCIN	YES	+/-	+/-	LOADING DOSE 8G FOLLOWED BY 16-24G CONTINUOUS INFUSION	SECTION 21 R741.42/ 2g vial (excl. VAT) **R8 897.04/ day**
MEROPENEM	YES	+/-	+/-	2G 8HRLY EXTENDED INFUSION OVER 4 HOURS	Readily available. Generic +/- R80.00/ 1g vial (excl. VAT) **Approx. R480.00 /day** Original Meronem® 1g: R383.66/vial (excl. VAT) **R2 301.97/day**
POLYMYXIN B	YES	YES	YES	25 000 UNITS/KG LOADING DOSE FOLLOWED BY 15 000 UNITS/KG 12 HRLY	SECTION 21 R166.92/vial (500 000U per vial) **R1 335.36/day**
TIGECYCLINE **(Last resort antibiotic for BSI)**	+/-	+/-	+/-	200MG LOADING DOSE THEN 100MG 12 HOURLY	Readily available. Generic +/- R585.00 /50mg vial (excl. VAT) **Approx. R2 340.00/ day** Original Tygacil ® R726.00 / 50mg vial (excl. VAT) **R2902.00/ day**

LABORATORY TESTING AND REPORTING

- **Carbapenems, polymyxin, colistin, aminoglycosides and tigecycline** will be tested and reported on all isolates (except polymyxin/colistin for Serratia species).
- **Ceftazidime-avibactam** will be tested and reported on all OXA isolates.
- **Ceftazidime-avibactam and Aztreonam synergy testing** will be performed and reported on all NDM-1 isolates (blood culture isolate only).
- **Fosfomycin and Cefiderocol** testing will be performed on request.

CONCLUSION

Recommended therapeutic options are either ceftazidime/avibactam or in combination with aztreonam or cefiderocol. Colistin, Fosfomycin, Tetracyclines and Aminoglycosides are also frequently effective in vitro, but are associated with less bactericidal activity or more toxicity.

Treatment should be individualised with close collaboration amongst clinicians ,microbiologists and pharmacists.

Without the implementation of aggressive stewardship measures for last-line, potentially life-saving antibiotics, we will likely rapidly lose efficacy of these, with few or no treatment options in the near-future.

REFERENCES

1. Al-Tawfiq JA, Kattan RF, Memish ZA. June 2022. Antibiotics in the pipeline: a literature review (2017-2020). *Infection* 2022 Jun;50(3):553-564.

Abstract:
There are a limited number of antibiotics against high priority organisms such as multi-drug-resistant Pseudomonas aeruginosa, and carbapenem-resistant Enterobacteriaceae. New antimicrobial agents directed against the top priority organisms as classified by the World Health Organization are urgently needed.

2. Antonello RM, Di Bella S, Maraolo AE, et al. Fosfomycin in continuous or prolonged infusion for systemic bacterial infections: a systematic review of its dosing regimen proposal from in vitro, in vivo and clinical studies. *European Journal of Clinical Microbiology & Infectious Diseases* (2021) 40:1117–1126.

Abstract:
Fosfomycin (FOS) administered intravenously has been recently rediscovered for the treatment of systemic infections due to multidrug-resistant bacteria. Its pharmacokinetic properties suggest a time-dependent dosing schedule with more clinical benefits from prolonged (PI) or continuous infusion (CI) than from intermittent infusion. We revised literature concerning PI and CI FOS to identify the best dosing regimen based on current evidence. We performed a MEDLINE/PubMed search. Ninety-one studies and their pertinent references were screened. Seventeen studies were included in the present review. The activity of FOS against Gram-negative and Gram-positive bacteria was evaluated in fourteen and five studies, respectively. Six studies evaluated FOS activity in combination with another antibiotic. Daily dosing of 12, 16, 18 or 24 g, administered with different schedules, were investigated. These regimens resulted active against the tested isolates in most cases. Emergence of resistant isolates has been shown to be preventable through the coadministration of another active antibiotic. FOS is a promising option to treat systemic infections caused by multidrug-resistant bacteria. Coadministration with another active molecule is required to prevent the emergence of resistant bacterial strains. The results of our review suggest that a therapeutic regimen including a loading dose of FOS 8 g followed by a daily dose of 16 g or 24 g CI could be the best therapeutic approach for patients with normal renal function. The dosing regimens in patients with renal insufficiency and CI or PI superiority compared with intermittent infusion in clinical settings should be further investigated.

3. Bakthavatchalama YD, Routrayb A, Maneb A, et al. (2022). In vitro activity of Ceftazidime−Avibactam and its comparators against Carbapenem resistant Enterobacterales collected across India. *Diagnostic Microbiology and Infectious Disease*. Volume 103, Issue 1, May 2022, 115652.

4. Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infectious Diseases* (2021) Feb;21(2):226-240. doi: 10.1016/S1473-3099(20)30796-9.

Abstract:
Cefiderocol had similar clinical and microbiological efficacy to best available therapy in this heterogeneous patient population with infections caused by carbapenem-resistant Gram-negative bacteria. Numerically more deaths occurred in the cefiderocol group, primarily in the patient subset with Acinetobacter spp infections. Collectively, the findings from this study support cefiderocol as an option for the treatment of carbapenem-resistant infections in patients with limited treatment options.

5. Brink AJ, Coetzee J, Richards GA, et al. October 2022. Best practices: Appropriate use of the new β-lactam/ β-lactamase inhibitor combinations, ceftazidime-avibactam and ceftolozane-tazobactam in South Africa. *Southern African Journal of Infectious Diseases.* Vol 37 No 1. DOI: https://doi.org/10.4102/sajid.v37i1.453

Abstract:
The prevalence of infections caused by difficult-to-treat resistant Gram-negative bacteria (DTR-GNB) is rapidly increasing, and along with constantly evolving epidemiology, represents a major challenge to the management of hospital-acquired infections (HAIs). In this regard, DTR describes treatment-limiting resistance to all first-line agents, that is, all β-lactams, including carbapenems and previous generation β-lactamase inhibitor combinations (BLICs), and fluoroquinolones. Arguably, the greatest threat from DTR-GNB comes in the form of carbapenem-resistant Enterobacterales (CRE) such as carbapenemase-producing *Klebsiella pneumoniae*.

6. Boyd SE, Holmes A, Peck R, et al. Aug 2022. OXA-48-Like β-Lactamases: Global Epidemiology, Treatment Options, and Development Pipeline. *Antimicrobial Agents Chemotherapy*. 16;66(8):e0021622. doi: 10.1128/aac.00216-22.

Abstract:
Over the past 20 years, OXA-48 and "OXA-48-like" enzymes have proliferated to become the most prevalent enterobacterial carbapenemases across much of Europe, Northern Africa, and the Middle East. OXA-48-like enzymes are notoriously difficult to detect because they often cause only low-level *in vitro* resistance to carbapenems, meaning that the true burden is likely underestimated. Despite this, they are associated with carbapenem treatment failures. A highly conserved incompatibility complex IncL plasmid scaffold often carries $bla_{\text{OXA-48}}$ and may carry other antimicrobial resistance genes, leaving limited treatment options. High conjugation efficiency means that this plasmid is sometimes carried by multiple *Enterobacterales* in a single patient. Producers evade most β-lactam-β-lactamase inhibitor combinations, though promising agents have recently been licensed, notably ceftazidime-avibactam and cefiderocol. The molecular machinery enabling global spread, current treatment options, and the development pipeline of potential new therapies for *Enterobacterales* that produce OXA-48-like β-lactamases form the focus of this review.

7. Castón JJ, Cano A, Pérez-Camacho I, et al. April 2022. Impact of ceftazidime/avibactam versus best available therapy on mortality from infections caused by carbapenemase-producing Enterobacterales (CAVICOR study). *Journal of Antimicrobial Chemotherapy.* 2022 Apr 27;77(5):1452-1460.

Abstract:
Background: Infections caused by carbapenemase-producing Enterobacterales (CPE) are not well represented in pivotal trials with ceftazidime/avibactam. The best strategy for the treatment of these infections is unknown.
Methods: We conducted a multicentre retrospective observational study of patients who received ≥48 h of ceftazidime/avibactam or best available therapy (BAT) for documented CPE infections. The primary outcome was 30 day crude mortality. Secondary outcomes were 21 day clinical response and microbiological response. A multivariate logistic regression model was used to identify factors predictive of 30 day crude mortality. A propensity score to receive treatment with ceftazidime/avibactam was used as a covariate in the analysis.
Results: The cohort included 339 patients with CPE infections. Ceftazidime/avibactam treatment was used in 189 (55.8%) patients and 150 (44.2%) received BAT at a median of 2 days after diagnosis of infection. In multivariate analysis, ceftazidime/avibactam treatment was associated with survival (OR 0.41, 95% CI 0.20-0.80; P = 0.01), whereas INCREMENT-CPE scores of >7 points (OR 2.57, 95% CI 1.18-1.5.58; P = 0.01) and SOFA score (OR 1.20, 95% CI 1.08-1.34; P = 0.001) were associated with higher mortality. In patients with INCREMENT-CPE scores of >7 points, ceftazidime/avibactam treatment was associated with lower mortality compared with BAT (16/73, 21.9% versus 23/49, 46.9%; P = 0.004). Ceftazidime/avibactam was also an independent factor of 21 day clinical response (OR 2.43, 95% CI 1.16-5.12; P = 0.02) and microbiological eradication (OR 0.40, 95% CI 0.18-0.85; P = 0.02).
Conclusions: Ceftazidime/avibactam is an effective alternative for the treatment of CPE infections, especially in patients with INCREMENT-CPE scores of >7 points. A randomized controlled trial should confirm these findings.

8. Chen Yan. April 2022. Efficacy and Safety of Ceftazidime-Avibactam for the Treatment of Carbapenem-Resistant Enterobacterales Bloodstream Infection: a Systematic Review and Meta-Analysis. *Microbiology Spectrum*. 10(2):e0260321.

Abstract:
Patients with CRE BSIs were often enrolled in small-sized clinical studies, together with other sites of infections, which reported pooled results. In this meta-analysis, the efficacy and safety were compared between CAZ-AVI and any other regimens used against CRE infections. The findings suggest that patients in the CAZ-AVI group had a significantly lower 30-day mortality than any other regimens and than colistin-based regimens. This paper provides a rationale for the use of CAZ-AVI in one of the most urgent antimicrobial-resistant infections of CRE bloodstream infections.

9. Chen Y, Huang H, Peng J, et al. April 2022. Efficacy and Safety of Ceftazidime-Avibactam for the Treatment of Carbapenem-Resistant Enterobacterales Bloodstream Infection: A Systematic Review and Meta-Analysis. *Microbiology Spectrum*. Volume 10 Issue 2.

10. Corbella L, Fernández-Ruiz M, Ruiz-Ruigómez M, et al. 2022. Prognostic factors of OXA-48 carbapenemase-producing Klebsiella pneumoniae infection in a tertiary-care Spanish hospital: A retrospective single-center cohort study. *International Journal of Infectious Diseases*. Volume 119, June 2022, Pages 59-68.

Abstract:
Appropriate antimicrobial treatment was protective for 30-day mortality in OXA-48-Kp infections. Carbapenems are usually active, whereas combination therapy appeared not to confer additional benefit.

11. Cruz-Lo´pez F, Martinez-Mele´ndez A, Morfin-Otero R, et al. 2022. Efficacy and In Vitro Activity of Novel Antibiotics for Infections With Carbapenem-Resistant Gram-Negative Pathogens. *Frontiers in Cellular and Infection Microbiology.* www.frontiersin.org. May 2022, Volume 12, Article 884365.

Abstract:
Infections by Gram-negative multi-drug resistant (MDR) bacterial species are difficult to treat using available antibiotics. Overuse of carbapenems has contributed to widespread resistance to these antibiotics; as a result, carbapenem-resistant Enterobacterales (CRE), A. baumannii (CRAB), and P. aeruginosa (CRPA) have become common causes of healthcare-associated infections. Carbapenems, tigecycline, and colistin are the last resource antibiotics currently used; however, multiple reports of resistance to these antimicrobial agents have been documented worldwide. Recently, new antibiotics have been evaluated against Gram-negatives, including plazomicin (a new aminoglycoside) to treat CRE infection, eravacycline (a novel tetracycline) with in vitro activity against CRAB, and cefiderocol (a synthetic conjugate) for the treatment of nosocomial pneumonia by carbapenem-non-susceptible Gram-negative isolates. Furthermore, combinations of known b-lactams with recently developed b-lactam inhibitors, such as ceftazidime avibactam, ceftolozane-tazobactam, ceftazidime-tazobactam, and meropenemvaborbactam, has been suggested for the treatment of infections by extended spectrum b-lactamases, carbapenemases, and AmpC producer bacteria. Nonetheless, they are not active against all carbapenemases, and there are reports of resistance to these combinations in clinical isolates. This review summarizes and discusses the in vitro and clinical evidence of the recently approved antibiotics, b-lactam inhibitors, and those in advanced phases of development for treating MDR infections caused by Gram-negative multi-drug resistant (MDR) bacterial species.

12. Di Bellaa S, Roberto D, Alberto G, et al. 2021. Resistance to ceftazidime/avibactam in infections and colonisations by KPC-producing Enterobacterales: a systematic review of observational clinical studies. *Journal of Global Antimicrobial Resistance*. 25 (2021) 268–28.

Abstract:
Taken together, these data highlight the need for prompt susceptibility testing including CAZ-AVI for Enterobacterales, at least in critical areas. Resistance to CAZ-AVI is an urgent issue to monitor in order to improve both empirical and targeted CAZ-AVI use as well as the management of patients with infections caused by CAZ-AVI-resistant strains.

13. Falagas ME, Vouloumanou EK, Samonis G, et al. April 2016. Fosfomycin. *Clinical Microbiology Review*. Volume 29 Number 2.

Abstract:
The treatment of bacterial infections suffers from two major problems: spread of multidrug-resistant (MDR) or extensively drug resistant (XDR) pathogens and lack of development of new antibiotics active against such MDR and XDR bacteria. As a result, physicians have turned to

older antibiotics, such as polymyxins, tetracyclines, and aminoglycosides. Lately, due to development of resistance to these agents, Fosfomycin has gained attention, as it has remained active against both Gram-positive and Gram-negative MDR and XDR bacteria. New data of higher quality have become available, and several issues were clarified further. In this review, we summarize the available Fosfomycin data regarding pharmacokinetic and pharmacodynamic properties, the in vitro activity against susceptible and antibiotic-resistant bacteria, mechanisms of resistance and development of resistance during treatment, synergy and antagonism with other antibiotics, clinical effectiveness, and adverse events. Issues that need to be studied further are also discussed.

14. Falcone M. 2021. Efficacy of Ceftazidime-avibactam Plus Aztreonam in Patients with Bloodstream Infections Caused by Metallo-β-lactamase–Producing Enterobacterales.

Abstract:
In vitro data support the use of combination of aztreonam (ATM) with ceftazidime-avibactam (CAZ-AVI), but clinical studies are lacking. The aim of our study was to compare the outcome of patients with bloodstream infections (BSIs) due to metallo-β-lactamase (MBL)–producing Enterobacterales treated either with CAZ-AVI plus ATM or other active antibiotics (OAAs). Methods. This was a prospective observational study including patients admitted to 3 hospitals in Italy and Greece. The primary outcome measure was 30-day all-cause mortality. Secondary outcomes were clinical failure at day 14 and length of stay after BSI diagnosis. Cox regression analysis including a propensity score (PS) for receiving CAZ-AVI + ATM was performed to evaluate primary and secondary outcomes. A PS-based matched analysis was also performed. Results. We enrolled 102 patients with BSI; 82 had infections caused by NDM-producing (79 Klebsiella pneumoniae and 3 Escherichia coli) and 20 by VIM-producing (14 K. pneumoniae, 5 Enterobacter species, 1 Morganella morganii) strains. The 30-day mortality rate was 19.2% in the CAZ-AVI + ATM group vs 44% in the OAA group (P = .007). The PS-adjusted analysis showed that the use of CAZ-AVI + ATM was associated with lower 30-day mortality (hazard ratio [HR], 0.37 [95% confidence interval {CI}, .13–.74]; P = .01), lower clinical failure at day 14 (HR, 0.30 [95% CI, .14–.65]; P = .002), and shorter length of stay (sub distributional HR, 0.49 [95% CI, .30–.82]; P = .007). The PS-matched analysis confirmed these findings. Conclusions. The CAZ-AVI + ATM combination offers a therapeutic advantage compared to OAAs for patients with BSI due to MBL-producing Enterobacterales. Further studies are warranted.

15. Falcone M, Daikos GL, Tiseo G, et al. (2021). Efficacy of Ceftazidime-avibactam Plus Aztreonam in Patients With Bloodstream Infections Caused by Metallo-β-lactamase–Producing Enterobacterales. cid 2021:72 (1 June).

Abstract:
Results. We enrolled 102 patients with BSI; 82 had infections caused by NDM-producing (79 Klebsiella pneumoniae and 3 Escherichia coli) and 20 by VIM-producing (14 K. pneumoniae, 5 Enterobacter species, 1 Morganella morganii) strains. The 30-day mortality rate was 19.2% in the CAZ-AVI + ATM group vs 44% in the OAA group (P = .007). The PS-adjusted analysis showed that the use of CAZ-AVI + ATM was associated with lower 30-day mortality (hazard ratio [HR], 0.37 [95% confidence interval {CI}, .13–.74]; P = .01), lower clinical failure at day 14 (HR, 0.30 [95% CI, .14–.65]; P = .002), and shorter length of stay (sub distributional HR, 0.49 [95% CI, .30–.82]; P = .007). The PS-matched analysis confirmed these findings. Conclusions. The CAZ-AVI + ATM combination offers a therapeutic advantage compared to OAAs for patients with BSI due to MBL-producing Enterobacterales. Further studies are warranted.

16. Hakeam HA, Alsahli H, Albabtain L, et al. August 2021. Effectiveness of ceftazidime-avibactam versus colistin in treating carbapenem-resistant Enterobacteriaceae bacteraemia. *Clinical Microbiology Review*. Multicentre Study Int J Infect Dis 2021 Aug;109:1-7.

Abstract:
Ceftazidime-avibactam was associated with a lower risk of 14-day mortality than colistin in patients with CRE bacteraemia.

17. Ikuta KS, Swetschinski LR, Aguilar GR, et al. November 2022. Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet.* DOI: https://doi.org/10.1016/S0140-6736(22)02185-7

18. Jean-François Timsit Antibiotics (Basel). Feb 2022. Treatment of Severe Infections Due to Metallo-Beta lactamases Enterobacterales in Critically Ill Patients. 11(2): 144. https://doi.org/10.3390%2Fantibiotics11020144

Abstract:
Metallo-beta-lactamases-producing (MBL) *Enterobacterales* is a growing problem worldwide. The optimization of antibiotic therapy is challenging. The pivotal available therapeutic options are either the combination of ceftazidime/avibactam and aztreonam or cefiderocol. Colistin, Fosfomycin, tetracyclines and aminoglycosides are also frequently effective in vitro, but are associated with less bactericidal activity or more toxicity. Prior to the availability of antibiotic susceptibility testing, severe infections should be treated with a combination therapy. A careful optimization of the pharmacokinetic/pharmacodynamic properties of antimicrobials is instrumental in severe infections. The rules of antibiotic therapy are also reported and discussed. To conclude, treatment of severe MBL infections in critically ill patients is difficult. It should be individualized with a close collaboration of intensivists with microbiologists, pharmacists and infection control practitioners.

19. Labuschagnea Q, Schellacka N, Gousa A, et al. COLISTIN: adult and paediatric guideline for South Africa. *Southern African Journal of Infectious Diseases* 2016; 31(1):3–7. http://dx.doi.org/10.1080/23120053.2016.1144285

Abstract:
Loading dosage
During life-threatening infections, it is important to achieve therapeutic concentrations of colistin (CMS) rapidly. Patients who are critically ill have capillary leakage, which increases their volume of distribution 4-15-fold. According to Landersdorfer & Nation (2015) CMS is converted to colistin slowly. This fact, combined with the long half-life of formed colistin, may result in a time interval of 2-3 days to reach an adequate therapeutic plasma concentration, in the absence of a loading dosage. Therefore, it is very important to initiate colistin (CMS) therapy with a loading dosage of 12 MU – regardless of kidney function – to reach therapeutic concentrations quicker. The high loading dosage does not affect the renal function; only the subsequent maintenance dosages would need to be adjusted.

20. Lasko MJ and Nicolau DP. 2020. Carbapenem-Resistant Enterobacterales: Considerations for Treatment in the Era of New Antimicrobials and Evolving Enzymology. *Springer Science + Business Media.*

Abstract:
Purpose of Review Gram-negative resistance is a growing concern globally. Enterobacterales, formerly Enterobacteriaceae, have developed resistance mechanisms to carbapenems that leave very few antimicrobial options in the clinician's armamentarium. Recent Findings New antimicrobials like ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, cefiderocol, and plazomicin have the potential to overcome resistance mechanisms in Enterobacterales including different classes of carbapenemases. Summary Novel β-lactam/β-lactamase inhibitors, plazomicin, and cefiderocol give the clinician options that were once not available. Utilizing these options is of the utmost importance when treating carbapenem-resistant Enterobacterales

21. Lodise TP, Nicholas O'Donnell J, Raja S, et al. 2022. Safety of Ceftazidime-Avibactam in Combination with Aztreonam (COMBINE) in a Phase I, Open-Label Study in Healthy Adult Volunteers. *American Society of Microbiology.* DOI: https://doi.org/10.1128/aac.00935-22

Abstract:
This phase I study evaluated the safety of the optimal ceftazidime-avibactam (CZA) with aztreonam (ATM) regimens identified in hollow fiber infection models of MBL-producing Enterobacterales. Eligible healthy subjects aged 18 to 45 years were assigned to one of six cohorts: 2.5 g CZA over 2 h every 8 h (approved dose), CZA continuous infusion (CI) (7.5 g daily), 2 g ATM over 2 h every 6 h, ATM CI (8 g daily), CZA (approved dose) with 1.5 g ATM over 2 h every 6 h, and CZA (approved dose) with 2 g ATM over 2 h every 6 h. Study drug(s) were administered for 7 days. The most frequently observed adverse events (AEs) were hepatic aminotransferase (ALT/AST) elevations (n = 19 subjects). Seventeen of the 19 subjects with ALT/AST elevations received ATM alone or CZA-ATM. The incidence of ALT/AST elevations was comparable between the ATM-alone and CZA-ATM cohorts. Two subjects in the ATM CI cohort experienced severe ALT/AST elevation AEs. All subjects with ALT/AST elevations were asymptomatic with no other findings suggestive of liver injury. Most other AEs were of mild to moderate severity and were similar across cohorts, except for prolonged prothrombin time (more frequent in CZA-ATM cohorts). These results suggest that CZA-ATM administered as 2-h intermittent infusions is safe and that some caution should be exercised with the use of ATM CI at an ATM dose of 8 g daily. If CZA-ATM is prescribed, clinicians are advised to monitor liver function, hematologic, and coagulation parameters. Future controlled studies are required to better define the safety and efficacy of the CZA-ATM regimens evaluated in this phase I study.

22. Lodise TP, Nicholas O'Donnell J, Belavic S, et al. 2022. Pharmacokinetics of Ceftazidime-Avibactam in Combination with Aztreonam (COMBINE) in a Phase 1, Open-Label Study of Healthy Adults. DOI: https://doi.org/10.1128/aac.00936-22

Abstract:
Scant pharmacokinetic (PK) data are available on ceftazidime-avibactam (CZA) and aztreonam (ATM) in combination, and it is unknown if CZA-ATM exacerbates alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevations relative to ATM alone. This phase 1 study sought to describe the PK of CZA-ATM and assess the associations between ATM exposures and ALT/AST elevations. Subjects (n = 48) were assigned to one of six cohorts (intermittent infusion [II] CZA, continuous infusion [CI] CZA, II ATM, CI ATM [8 g/daily], II CZA with II ATM [6 g/daily],

and II CZA with II ATM [8 g/daily]), and study product(s) were administered for 7 days. A total of 19 subjects (40%) had ALT/AST elevations, and most (89%) occurred in the ATM/CZA-ATM cohorts. Two subjects in the CI ATM cohort experienced severe ALT/AST elevations, which halted the study. All subjects with ALT/AST elevations were asymptomatic with no other signs of liver injury, and all ALT/AST elevations resolved without sequalae after cessation of dosing. In the population PK (PopPK) analyses, CZA-ATM administration reduced total ATM clearance by 16%, had a negligible effect on total ceftazidime clearance, and was not a covariate in the avibactam PopPK model. In the exposure-response analyses, coadministration of CZA-ATM was not found to augment ALT/AST elevations. Modest associations were observed between ATM exposure (maximum concentration of drug in serum [Cmax] and area under the concentration-time curve [AUC]) and ALT/AST elevations in the analysis of subjects in the II ATM/CZA-ATM cohorts. The findings suggest that administration of CZA-ATM reduces ATM clearance but does not exacerbate AST/ALT elevations relative to ATM alone. The results also indicate that CI ATM should be used with caution.

23. Michael S. Niederman, et al. 2021. Initial antimicrobial management of sepsis. *Critical Care.* volume 25, Article number: 307.

Abstract:
Sepsis is a common consequence of infection, associated with a mortality rate > 25%. Although community-acquired sepsis is more common, hospital-acquired infection is more lethal. The most common site of infection is the lung, followed by abdominal infection, catheter-associated blood steam infection and urinary tract infection. Gram-negative sepsis is more common than gram-positive infection, but sepsis can also be due to fungal and viral pathogens. To reduce mortality, it is necessary to give immediate, empiric, broad-spectrum therapy to those with severe sepsis and/or shock, but this approach can drive antimicrobial overuse and resistance and should be accompanied by a commitment to de-escalation and antimicrobial stewardship. Biomarkers such a procalcitonin can provide decision support for antibiotic use, and may identify patients with a low likelihood of infection, and in some settings, can guide duration of antibiotic therapy. Sepsis can involve drug-resistant pathogens, and this often necessitates consideration of newer antimicrobial agent.

24. Paul M, Carrara E, Retamar P, et al. 2022. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). *Clinical Microbiological Infection.* 2022 Apr;28(4):521-547.

Abstract:
Scope: These ESCMID guidelines address the targeted antibiotic treatment of third-generation cephalosporin-resistant Enterobacterales (3GCephRE) and carbapenem-resistant Gram-negative bacteria, focusing on the effectiveness of individual antibiotics and on combination versus monotherapy. Methods: An expert panel was convened by ESCMID. A systematic review was performed including randomized controlled trials and observational studies, examining different antibiotic treatment regimens for the targeted treatment of infections caused by the 3GCephRE, carbapenem-resistant Enterobacterales, carbapenem-resistant Pseudomonas aeruginosa and carbapenem-resistant Acinetobacter baumannii. Treatments were classified as head-to-head comparisons between individual antibiotics and between monotherapy and combination therapy regimens, including defined monotherapy and combination regimens only. The primary outcome was all-cause mortality, preferably at 30 days and secondary outcomes included clinical

failure, microbiological failure, development of resistance, relapse/ recurrence, adverse events and length of hospital stay. The last search of all databases was conducted in December 2019, followed by a focused search for relevant studies up until ECCMID 2021. Data were summarized narratively. The certainty of the evidence for each comparison between antibiotics and between monotherapy and combination therapy regimens was classified by the GRADE recommendations. The strength of the recommendations for or against treatments was classified as strong or conditional (weak). Recommendations: The guideline panel reviewed the evidence per pathogen, preferably per site of infection, critically appraising the existing studies. Many of the comparisons were addressed in small observational studies at high risk of bias only. Notably, there was very little evidence on the effects of the new, recently approved, b-lactam/b-lactamase inhibitors on infections caused by carbapenem-resistant Gram-negative bacteria. Most recommendations are based on very-low- and low-certainty evidence. A high value was placed on antibiotic stewardship considerations in all recommendations, searching for carbapenem-sparing options for 3GCephRE and limiting the recommendations of the new antibiotics for severe infections, as defined by the sepsis-3 criteria. Research needs are addressed.

25. Pranita D Tamma, et al. Sept 2022. Infectious Diseases Society of America Guidance on the Treatment of AmpC β-Lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia Infections. *Clinical Infectious Diseases*. 1:ciac698. doi: 10.1093/cid/ciac698.

Abstract:
Here, guidance is provided for treating AmpC β-lactamase-producing Enterobacterales (AmpC-E), carbapenem-resistant Acinetobacter baumannii (CRAB), and Stenotrophomonas maltophilia infections. A panel of 6 infectious diseases specialists with expertise in managing antimicrobial-resistant infections formulated questions about the treatment of AmpC-E, CRAB, and S. maltophilia infections. Answers are presented as suggested approaches and corresponding rationales. In contrast to guidance in the previous document, published data on the optimal treatment of AmpC-E, CRAB, and S. maltophilia infections are limited. As such, guidance in this document is provided as "suggested approaches" based on clinical experience, expert opinion, and a review of the available literature. Because of differences in the epidemiology of resistance and availability of specific anti-infectives internationally, this document focuses on the treatment of infections in the United States.

26. Tabah A, Lipman J, Barbier F, et al. Review Use of Antimicrobials for Bloodstream Infections in the Intensive Care Unit, a Clinically Oriented Review. *Antibiotics* 2022. 11(3), 362; https://doi.org/10.3390/antibiotics11030362.

Abstract:
Bloodstream infections (BSIs) in critically ill patients are associated with significant mortality. For patients with septic shock, antibiotics should be administered within the hour. Probabilistic treatment should be targeted to the most likely pathogens, considering the source and risk factors for bacterial resistance including local epidemiology. Source control is a critical component of the management. Sending blood cultures (BCs) and other specimens before antibiotic administration, without delaying them, is key to microbiological diagnosis and subsequent opportunities for antimicrobial stewardship. Molecular rapid diagnostic testing may provide faster identification of pathogens and specific resistance patterns from the initial positive BC. Results allow for antibiotic optimisation, targeting the causative pathogen with

escalation or de-escalation as required. Through this clinically oriented narrative review, we provide expert commentary for empirical and targeted antibiotic choice, including a review of the evidence and recommendations for the treatments of extended-spectrum β-lactamase-producing, AmpC-hyperproducing and carbapenem-resistant Enterobacterales; carbapenem-resistant Acinetobacter baumannii; and Staphylococcus aureus. In order to improve clinical outcomes, dosing recommendations and pharmacokinetics/pharmacodynamics specific to ICU patients must be followed, alongside therapeutic drug monitoring.

27. Tamma PD, Aitken SL, Bonomo RA, et al. 19 April 2022. Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance. *Clinical Infectious Diseases*. 268. doi: 10.1093/cid/ciac268.

Abstract:
The Infectious Diseases Society of America (IDSA) is committed to providing up to-date guidance on the treatment of antimicrobial-resistant infections. The initial guidance document on infections caused by extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with difficult-to-treat resistance (DTR-P. aeruginosa) was published on September 17th, 2020. Over the past year, there have been a number of important publications furthering our understanding of the management of ESBL-E, CRE, and DTR-P. aeruginosa infections, prompting a rereview of the literature and this updated guidance document. Methods: A panel of six infectious diseases specialists with expertise in managing antimicrobial-resistant infections reviewed, updated, and expanded previously developed questions and recommendations about the treatment of ESBL-E, CRE, and DTR-P. aeruginosa infections. Because of differences in the epidemiology of resistance and availability of specific anti-infectives internationally, this document focuses on the treatment of infections in the United States. Results: Preferred and alternative treatment recommendations are provided with accompanying rationales, assuming the causative organism has been identified and antibiotic susceptibility results are known. Approaches to empiric treatment, duration of therapy, and other management considerations are also discussed briefly. Recommendations apply for both adult and paediatric populations. Conclusions: The field of antimicrobial resistance is highly dynamic. Consultation with an infectious diseases specialist is recommended for the treatment of antimicrobial-resistant infections. This document is current as of October 24th, 2021. The most current versions of IDSA documents, including dates of publication, are available at www.idsociety.org/practiceguideline/amr-guidance/

28. Tan X, Kim HS, Baugh K. Feb 2021. Therapeutic Options for Metallo-β-Lactamase-Producing Enterobacterales. *Infection and Drug Resistance*. Volume 14: 595-596.

Abstract:
The spread of metallo-β-lactamase (MBL)-producing Enterobacterales worldwide without the simultaneous increase in active antibiotics makes these organisms an urgent public health threat. This review summarizes recent advancements in diagnostic and treatment strategies for infections caused by MBL-producing Enterobacterales. Adequate treatment of patients infected with MBL-producing Enterobacterales relies on detection of the β-lactamase in the clinic. There are several molecular platforms that are currently available to identify clinically relevant MBLs as well as other important serine-β-lactamases. Once detected, there are several antibiotics that have historically been used for the treatment of MBL-producing Enterobacterales. Antimicrobials

such as aminoglycosides, tetracyclines, Fosfomycin, and polymyxins often show promising in vitro activity though clinical data are currently lacking to support their widespread use. Ceftazidime-avibactam combined with aztreonam is promising for treatment of infections caused by MBL-producing Enterobacterales and currently has the most clinical data of any available antibiotic to support its use. While cefiderocol has displayed promising activity against MBL-producing Enterobacterales in vitro and in preliminary clinical studies, further clinical studies will better shed light on its place in treatment. Lastly, there are several promising MBL inhibitors in the pipeline, which may further improve the treatment of MBL-producing Enterobacterales.

29. Tan X, Kim HS, Baugh K, et al. 2021. Therapeutic Options for Metallo-β-Lactamase producing Enterobacterales. *Infection and Drug Resistance* 2021:14 125–142.

Abstract:
The spread of metallo-β-lactamase (MBL)-producing Enterobacterales worldwide without the simultaneous increase in active antibiotics makes these organisms an urgent public health threat. This review summarizes recent advancements in diagnostic and treatment strategies for infections caused by MBL-producing Enterobacterales. Adequate treatment of patients infected with MBL-producing Enterobacterales relies on detection of the β-lactamase in the clinic. There are several molecular platforms that are currently available to identify clinically relevant MBLs as well as other important serine-β-lactamases. Once detected, there are several antibiotics that have historically been used for the treatment of MBL-producing Enterobacterales. Antimicrobials such as aminoglycosides, tetracyclines, Fosfomycin, and polymyxins often show promising in vitro activity though clinical data are currently lacking to support their widespread use. Ceftazidime-avibactam combined with aztreonam is promising for treatment of infections caused by MBL-producing Enterobacterales and currently has the most clinical data of any available antibiotic to support its use. While cefiderocol has displayed promising activity against MBL-producing Enterobacterales in vitro and in preliminary clinical studies, further clinical studies will better shed light on its place in treatment. Lastly, there are several promising MBL inhibitors in the pipeline, which may further improve the treatment of MBL-producing Enterobacterales.

30. Timsit J, Paul M, Shields RK, et al. Cefiderocol for the Treatment of Infections due to Metallo-Beta-Lactamase-Producing Pathogens in the CREDIBLE-CR And APEKS-NP Phase 3 Randomized Studies. *Clinical Infectious Diseases* (2022 Feb 11). DOI: 10.1093/cid/ciac078.

Abstract:
In the CREDIBLE-CR and APEKS-NP studies, cefiderocol treatment was effective against Gram-negative bacteria producing metallo-beta-lactamases; rates of clinical cure (70.8% [17/24]), microbiological eradication (58.3% [14/24]), and Day-28 all-cause mortality (12.5% [3/24]) compared favourably with comparators of best available therapy and high-dose meropenem (40.0% [4/10]; 30.0% [3/10]; 50.0% [5/10]), respectively.

31. Yaghoubi S, Zekiy AO, Krutova M, et al. 2022. Tigecycline antibacterial activity, clinical effectiveness, and mechanisms and epidemiology of resistance: narrative review. *European Journal of Clinical Microbiology & Infectious Diseases* (2022) 41:1003–1022.

Abstract:

Tigecycline is unique glycylcycline class of semisynthetic antimicrobial agents developed for the treatment of polymicrobial infections caused by multidrug-resistant Gram-positive and Gram-negative pathogens. Tigecycline evades the main tetracycline resistance genetic mechanisms, such as tetracycline-specific efflux pump acquisition and ribosomal protection, via the addition of a glycyclamide moiety to the 9-position of minocycline. The use of the parenteral form of tigecycline is approved for complicated skin and skin structure infections (excluding diabetes foot infection), complicated intra-abdominal infections, and community acquired bacterial pneumonia in adults. New evidence also suggests the effectiveness of tigecycline for the treatment of severe Clostridioides difficile infections. Tigecycline showed in vitro susceptibility to Coxiella spp., Rickettsia spp., and multidrug resistant Neisseria gonnorrhoeae strains which indicate the possible use of tigecycline in the treatment of infections caused by these pathogens. Except for intrinsic, or often reported resistance in some Gram-negatives, tigecycline is effective against a wide range of multidrug-resistant nosocomial pathogens. Herein, we summarize the currently available data on tigecycline pharmacokinetics and pharmacodynamics, its mechanism of action, the epidemiology of tigecycline resistance, and its clinical effectiveness.

32. Yahiya Y. Syed. (2021). Cefderocol: A Review in Serious Gram Negative Bacterial Infections. *Drugs*. 81:1559–1571. https://doi.org/10.1007/s40265-021-01580-4

Abstract:
Infections caused by carbapenem-resistant (CR) Enterobacterales and non-fermenters (such as Pseudomonas, Acinetobacter, Stenotrophomonas, Burkholderia) are a major global health threat. Cefderocol, a cephalosporin with activity against CR Enterobacterales and non-fermenters, uses the bacteria's own iron uptake system to gain cell entry, like a Trojan horse. Once inside, the drug disrupts the formation of the bacterial cell wall, killing the bacteria. Cefderocol is approved for the treatment of serious Gram-negative bacterial infections. In clinical trials, Cefderocol was effective versus carbapenems or best available therapy for complicated urinary tract infections, nosocomial pneumonia and bloodstream infections/sepsis, including those caused by CR bacteria. The drug had a good tolerability and safety profile. Thus, cefiderocol is a useful addition to the current treatment options for adults with cefiderocol-susceptible Gram-negative bacterial infections for whom there are limited treatment options.

33. Zhanel GG, Golden AR, Zelenitsky S, et al. Feb 2019. Cefiderocol: A Siderophore Cephalosporin with Activity Against Carbapenem-Resistant and Multidrug-Resistant Gram-Negative Bacilli. *Drugs.* 79(3):271-289. doi: 10.1007/s40265-019-1055-2.

Abstract:
Cefiderocol is an injectable siderophore cephalosporin discovered and being developed by Shionogi & Co., Ltd., Japan. As with other β-lactam antibiotics, the principal antibacterial/bactericidal activity of cefiderocol occurs by inhibition of Gram-negative bacterial cell wall synthesis by binding to penicillin binding proteins; however, it is unique in that it enters the bacterial periplasmic space as a result of its siderophore-like property and has enhanced stability to β-lactamases. The chemical structure of cefiderocol is similar to both ceftazidime and cefepime, which are third- and fourth-generation cephalosporins, respectively, but with high stability to a variety of β-lactamases, including AmpC and extended-spectrum β-lactamases (ESBLs).