Early and Appropriate Use of Ceftazidime-Avibactam in the Management of Multidrug-Resistant Gram-Negative Bacterial Infections in the Indian Scenario

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Abstract

The increasing prevalence of antibiotic-resistant pathogens exerts a substantial burden on the healthcare infrastructure worldwide. The World Health Organization (WHO) has declared that multidrug-resistant (MDR) Gram-negative pathogens, especially, carbapenem-resistant Enterobacterales (CRE), Acinetobacter baumannii, and Pseudomonas aeruginosa are considered by the World Health Organization (WHO) as the highest priority while developing newer antimicrobials. The increasing prevalence of infectious diseases caused by MDR Gram-negative bacteria also poses a challenge when choosing the empiric antimicrobial therapy for seriously ill hospitalized patients. The infections caused by MDR Gram-negative organisms ultimately result in increased mortality, morbidity, prolonged hospital stay, and increased cost of management. To tackle these challenges, newer antimicrobials like ceftazidime-avibactam were explored. The article also discusses the in vitro activity and therapeutic efficacy of ceftazidime-avibactam along with its pharmacokinetic properties and the role it will play in the management of MDR Gram-negative organisms in the Indian setting. Several studies have highlighted the role of early and appropriate antibiotic use in the reduction of mortality in patients with Gram-negative infections. Timely initiation of appropriate antibiotic therapy for serious infections leads to favorable clinical outcomes. Early and appropriate use of ceftazidime-avibactam while treating MDR Gram-negative infections has been associated with improved clinical outcomes. The aim of this review is to highlight the efficacy of ceftazidime-avibactam in the treatment of MDR Gram-negative infections. We have also summarized the information on outcomes achieved by early and appropriate use of ceftazidime-avibactam.

Introduction And Background

The emerging widespread antibiotic-resistant pathogens exert a significant burden on the healthcare infrastructure. The multidrug-resistant (MDR) Gram-negative pathogens including carbapenem-resistant Enterobacterales (CRE), Acinetobacter baumannii, and Pseudomonas aeruginosa are considered by the World Health Organization (WHO) as the highest priority while developing newer antimicrobials. [1,2]. The carbapenem resistance in Enterobacterales is driven by carbapenemases such as New Delhi metallo-ß-lactamase (NDM), and Oxacillinase-48-like (OXA-48-like) VIM, IMP and KPC [3,4]. In India, high carbapenem resistance among Enterobacterales has been reported by the Indian Council of Medical Research (ICMR) with resistance rates up to 30% for Escherichia coli and 30% for Klebsiella pneumoniae [5]. OXA-48-like gene was identified in 52% of the carbapenem-resistant (CR)-K. pneumoniae isolates while 20% isolates possessed NDM gene and 27% isolates had both NDM with OXA-48-like gene. However, in carbapenem-resistant (CR)-E. coli, NDM was identified in 68% of isolates followed by OXA-48-like in 24% isolates and 8% isolates carried both NDM with OXA-48-like gene [5].

The increasing prevalence of infectious diseases caused by MDR Gram-negative bacteria places a hurdle in the selection of appropriate empiric antimicrobial therapy for seriously ill hospitalized patients [2]. The management of infections caused by CREs is more challenging owing to limited antimicrobial options. CREs exhibit resistance against conventional first-line antimicrobials including cephalosporins, ß-lactam-ß-lactamase inhibitors, carbapenems, and fluoroquinolones [6].

Infections caused by MDR organisms are responsible for increased mortality, morbidity, prolonged hospital stay, and increased cost of management [7]. They pose a serious threat to the healthcare infrastructure owing to their difficult management. Early detection of MDR organisms can facilitate the start of appropriate antibiotic treatment and better therapeutic decisions to ensure favorable clinical outcomes and survival rates [7]. Early diagnosis can thus help in implementing improved patient management strategies and appropriate antibiotic use.

There is no concrete consensus for optimal regimens in various guidelines or experts’ opinions. Colistin and tigecycline have been used as first-line therapy for managing infections caused by CREs [8]. However, tigecycline does not attain the required plasma concentrations, and hence may not be used for treating bloodstream infections [5]. Colistin has been associated with prominent toxicity (both nephrotoxicity and neurotoxicity), which may limit its clinical use [8]. Hence, these two regimens can be avoided since newer treatment modalities are available. These challenges have led to the development of newer antimicrobials such as ceftolozane-tazobactam, imipenem-cilastatin-relebactam, plazomicin, meropenem-vaborbactam, ceftazidime-avibactam, eravacycline, and ceftiderococ [8].

How to cite this article
Swaminathan S, Routray A, Mane A (August 22, 2022) Early and Appropriate Use of Ceftazidime-Avibactam in the Management of Multidrug-Resistant Gram-Negative Bacterial Infections in the Indian Scenario. Cureus 14(8): e28283. DOI 10.7759/cureus.28283
Ceftazidime–avibactam, a combination of the third-generation cephalosporin ceftazidime and non-β-lactam–β-lactamase inhibitor avibactam, is an intravenously administered antimicrobial [9]. Ceftazidime–avibactam is indicated for the treatment of following infections in adults i.e. complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), including pyelonephritis, hospital–acquired pneumonia (HAP) including ventilator-associated pneumonia (VAP) with susceptible Gram-negative microorganism and treatment of patients with bacteremia that occurs in association with, or is suspected to be associated with, any of the infections mentioned above [10]. Ceftazidime–avibactam has been proven to be clinically efficacious in pivotal phase III non-inferiority trials in comparison with carbapenems [11–13].

The in vitro activity of ceftazidime–avibactam has been established against extended-spectrum β-lactamase (ESBLs), AmpC β-lactamate, Klebsiella pneumoniae carbapenemase (KPC), and OXA–48 producing Enterobacteriales and Pseudomonas aeruginosa isolates [9]. Real–world evidence globally has demonstrated the effectiveness and safety of ceftazidime–avibactam in the management of MDR Gram-negative infections including CRE. Similarly, a few real–world evidence studies have published data supporting the use of ceftazidime–avibactam to treat MDR Gram-negative infections in Indian patients.

The aim of this review is to highlight the efficacy of ceftazidime–avibactam in the management of MDR Gram-negative infections. The article also discusses the in vitro activity and therapeutic efficacy of ceftazidime–avibactam along with its pharmacokinetic properties and the role it will play in the management of MDR Gram-negative organisms in the Indian setting.

Review

Methodology

An in–depth literature search was conducted using PubMed and Google Scholar databases. There were no predefined inclusion/exclusion criteria for article selection. The articles were selected on the basis of their suitability and relevance to the pre–decided outline by the authors.

Mechanism of action

Ceftazidime prevents bacterial cell wall synthesis which causes bacterial cell death [14]. It binds to penicillin–binding proteins (PBPs) of Gram–negative bacteria which decreases the cross–linking activity of peptidoglycan and leads to the inhibition of cell wall synthesis [15]. Avibactam is a non–β-lactam, β-lactamase inhibitor which causes covalent acylation of the β-lactamase to inactivate susceptible β-lactamases [9]. This structure is not hydrolyzed and is slowly separated. Avibactam is then reversed to its original structure. Avibactam does not possess antibacterial properties [16]. In vitro, avibactam exhibits activity against Ambler (a classification system for β-lactamases) class A, including TEM, SHV, CTX-M, KPC, GES, PER, SME; plasmid class C including FOX, MOX, LAT, ACC, DHA and chromosomal class C (AmpC); and class D including OXA–48 [16]. Additionally, inhibitors such as sulbactam and tazobactam are penicillin–based sulfones and lack the ability to inhibit carbapenemases [17]. Avibactam does not inhibit class B metallo–β-lactamases (NDM, VIM, IMP, VEB, PER), and OXA–23 and OXA–24/40 carbapenemases [17].

In vitro activity

In vitro activity of ceftazidime–avibactam was analyzed on isolates collected from nine centers across India between 2018 to 2019, as a part of the ATLAS (Antimicrobial Testing and Surveillance) program. The in vitro activity of ceftazidime–avibactam and comparator drugs was analyzed against E. coli (n = 458) and K. pneumoniae (n = 455) isolates. An overall susceptibility rate of over 70% was reported among K. pneumoniae and E. coli isolates. Around 51% of carbapenem–resistant (CR)–K. pneumoniae and 24% of CR–E. coli isolates were found to be susceptible to ceftazidime–avibactam [5].

The global ATLAS data collected between 2012 and 2016 reported in vitro susceptibilities of Gram–negative isolates against ceftazidime–avibactam. The study reported susceptibility of CR–E. coli to be 72.3% using Clinical Laboratory and Standards Institute (CLSI) breakpoints against ceftazidime–avibactam. Similarly, susceptibility of CR–K. pneumoniae was reported to be 85.6% using CLSI breakpoints [18].

Pharmacokinetics

The steady–state volumes of distribution of ceftazidime and avibactam were approximately 22 and 18 L. The human protein binding of both ceftazidime and avibactam is approximately 10% and 8%, respectively [9]. Around 80–90% of the injected ceftazidime is eliminated by the kidneys in its unchanged form with the renal clearance of 115 mL/min. Avibactam is excreted via the urine without alteration and has a renal clearance of ~158 mL/min. In healthy adults, with normal renal function, the half–life (t1/2) of both ceftazidime and avibactam is 2.76 hours and 2.71 hours, respectively [19]. Dose adjustment is required in patients with mild, moderate, or severe renal impairment to avoid an accumulation of the drug [20]. Neither ceftazidime nor avibactam is observed to undergo significant hepatic metabolism. The potential of drug–drug interactions is low for ceftazidime–avibactam. Patients with hepatic impairment require no dose adjustments. Age, weight, gender, or ethnicity do not impact the pharmacokinetics of ceftazidime–avibactam therefore dosage adjustment is not essential [9].

Compartmental pharmacokinetic studies have shown that ceftazidime (52%), as well as, avibactam (42%) penetrate into epithelial lining fluid (ELF), which is greater than previously calculated at plasma concentrations relevant for efficacy (~ 8 mg/L for ceftazidime and ~ 1 mg/L for avibactam). These results suggest epithelial lining fluid (ELF) exposures of both drugs exceeded levels required for efficacy in plasma [21,22]. The efficacy of an antibiotic to successfully mitigate pneumonia depends on the concentration of the
unbound drug available at the pulmonary infection site [22].

**Therapeutic efficacy**

*Landmark Trials*

The efficacy and safety profile of ceftazidime-avibactam has been studied by a number of randomized, multicenter, controlled phase III trials. In all studies, patients assigned to ceftazidime-avibactam received a combination of 2.5 g ceftazidime-avibactam as a two-hour intravenous infusion every eight hours. Dose adjustment was applied for patients with moderate renal impairment at baseline (estimated Cockcroft-Gault-calculated creatinine clearance (CrCl), >30 to ≤50 mL/min). Most of these trials had separate primary endpoints based on US Food and Drug Administration (FDA) guidance; and European Medicines Agency (EMA) guidance (Table 1) [9].

| Sr.No | Trial name | Indication | Treatment | Primary Outcome | Conclusion |
|-------|------------|------------|-----------|----------------|------------|
| 1     | REPRISE    | cIAI/ cUTI, including pyelonephritis | CAZ-AVI + Metronidazole (n=10), BAT (n=11) cUTI: CAZ-AVI (n= 144), BAT (n = 137) | Clinical cure at the test-of-cure visit (7–10 days after last infusion of study therapy) in the mMITT population*: CAZ-AVI: 91% (95% CI 85.6 to 94.7), BAT: 91% (95% CI 85.9 to 95.0) *Patients in the mMITT population are defined as carrying a pathogen at the start of treatment and who received at least one dose of study drug. | Numerically higher proportion of patients on ceftazidime – avibactam achieved a favorable microbiological response |
| 2     | RECAPTURE - 1 and -2 | cUTI including pyelonephritis | CAZ-AVI (n = 516) Doripenem (n= 517) | Clinical cure at the test-of-cure visit (21–25 days after randomization) mMITT*: CAZ-AVI (n = 393): 90.3% Doripenem (n = 417): 90.4% Difference, % (95% CI): -0.1 (-4.23 to 4.03) *The mMITT population comprised all randomized patients with minimum disease criteria and eligible baseline pathogen(s). | Ceftazidime-avibactam was non-inferior to doripenem in the treatment of hospitalized patients with cUTI or acute pyelonephritis |
| 3     | RECLAIM - 1 and -2 | cIAI | CAZ-AVI + Metronidazole (n = 532) Meropenem (n= 534) | Clinical cure at the test-of-cure visit (28-35 days after randomization) MITT* CAZ-AVI (n = 520): 82.5% Meropenem (n= 523): 84.9% Difference, % (95% CI): -2.4 (-6.90 to 2.10) *Patients in the MITT population are defined as patients who received study drug and met the clinical disease criteria. | Ceftazidime-avibactam plus metronidazole was non-inferior to meropenem |
| 4     | RECLAIM Indian subset | cIAI | CAZ-AVI + Metronidazole (n = 61 Meropenem (n = 63) | Clinical cure at TOC In mMITT population: CAZ-AVI + Metronidazole – 83.3%, meropenem – 77.1% Difference 6.2 (-14.31 to 25.65) In CE population: CAZ-AVI + Metronidazole – 97.8%, meropenem – 95.5% Difference 2.4 (-7.41 to 13.33) | Ceftazidime-avibactam can be considered as an alternative to carbapenems for treating resistant pathogens in the ICU setting The results of the study were in line with the results of the overall results |
| 5     | RECLAIM -3 | cIAI | CAZ-AVI + Metronidazole (n = 215) Meropenem (n= 217) | Clinical cure at the test-of-cure visit (28-35 days after randomization) CE: CAZ-AVI + Metronidazole (n = 166): 93.8% Meropenem (n = 173): 94.0% Difference, % (95% CI): -0.2 (-5.53 to 4.97) | Ceftazidime-avibactam plus metronidazole was non-inferior to meropenem |

Clinical cure at the test-of-cure visit (21–25 days after
6 **REPROVE**  HAP/ VAP

| CAZ-AVI (n = 405) | Meropenem (n = 403) |
|------------------|---------------------|
| mITT population CAZ-AVI (n = 356) | Meropenem (n = 370) |
| CE population CAZ-AVI (n = 257) | Meropenem (n = 270) |

*randomization*  mITT: CAZ-AVI (n = 245): 68.8%, Meropenem (n = 270): 73.0%. Difference, % (95% CI): -4.2 (-10.76 to 2.46)  CE: CAZ-AVI (n = 199): 77.4%, Meropenem (n = 211): 78.1%. Difference, % (95% CI): -0.7 (-7.86 to 6.39)  *The clinically evaluable population comprised patients with minimum disease criteria but excluded patients with only non-target pathogens.**  **The clinically evaluable population comprised patients in the mITT population who received an adequate course of treatment and had an assessable clinical outcome within the assessment window, no protocol deviation that could affect the assessment of efficacy, and no unacceptable previous or concomitant antibiotics.

7 **REPROVE**  Indian subset  HAP

| CAZ-AVI (n = 36) | Meropenem (n = 42) |

Clinical cure at TOC  In mITT population: CAZ-AVI – 80.6%, meropenem – 71.8%. Difference 8.9 (-12.09 to 28.27)  In CE population: CAZ-AVI – 88.0%, meropenem – 77.1%. Difference 10.9 (-10.39 to 29.77)

Ceftazidime-avibactam was non-inferior to meropenem for the management of nosocomial pneumonia. The results of the study were in-line with the results of the overall results.

8 Pooled data of RECAPTURE-1 and -2, RECLAIM-1 and -2 and REPRISE trials

| Enterobacteriaceae – 105/2240 i.e., 46.9% were MDR  | P. aeruginosa – 95/272 i.e., 34.9% were MDR |
|-----------------------------------------------------|---------------------------------------------|

Microbiological response at TOC for all Enterobacteriaceae: CAZ-AVI – 78.4% Comparators - 79.6%  Clinical cure at TOC: CAZ-AVI - 85.4% Comparators – 86.1%

Ceftazidime-avibactam demonstrated similar clinical efficacy to predominantly carbapenem comparators against MDR pathogens.

**TABLE 1: Efficacy and Safety Profile of Ceftazidime-Avibactam and Comparators from the Phase III Clinical Trials**

| Categorization | Type of Infection | Treatment | Causative | Key Outcomes |
|----------------|-------------------|-----------|-----------|-------------|

**Real-World Evidence**

The efficacy of ceftazidime-avibactam is corroborated by mounting clinical evidence. Several studies have been published in various types of primary infections including, but not limited to IAIs, UTIs, HAP, and VAP, and bacteraemia secondary to these [11,29-33]. A summary of the findings has been presented in Table 2. The real-world evidence is indicative of favorable efficacy results which were consistent even in MDR infections.

**Sr.**  **Reference**  **Type of Infection**  **Treatment**  **Causative**  **Key Outcomes**

| Sr. | Reference | Type of Infection | Treatment | Causative | Key Outcomes |
|-----|-----------|-------------------|-----------|-----------|-------------|

2022 Swaminathan et al. Cureus 14(6): e28283. DOI 10.7759/cureus.28283
| No. | Infection/s | group/s | Organisms |
|-----|-------------|---------|-----------|
| 1   | Pneumonia - 32% (50% VAP, 50% HAP), IAI - 11%, Pyelonephritis - 11% | CAZ-AVI (n = 37) Monotherapy - 26 patients | CR-K. pneumoniae - 84% CE-E. coli – 8% CR-Enterobacter cloacae – 5% CR-Enterobacter aerogenes – 3% |
|     | Shields et al., 2016 | | 30-day survival rate – 76% 90-day survival rate – 62% Clinical success rate – 59% Microbiological failure – 27% |
|     | | | |
| 2   | Bacteremia with CR-Kp Secondary bacteremia – 81/109 | CAZ-AVI (n = 13) Carbapenem + aminoglycoside (n = 25) Carbapenem + colistin (n = 30) Others (n = 41) | CR-K. pneumoniae |
|     | Shields et al., 2017 | | Clinical success CAZ-AVI – 85% Carbapenem + Aminoglycoside – 48% Carbapenem + Colistin – 40% Others – 37% 30-day survival rate CAZ-AVI – 92% Carbapenem + Aminoglycoside – 68% Carbapenem + Colistin – 70% Others – 68% 90-day survival rate CAZ-AVI – 92% Carbapenem + Aminoglycoside – 56% Carbapenem + Colistin – 63% Others – 49% |
|     | | | For KPC-producing Enterobacterales: Microbiological cure - 75% Clinical cure - 68% Survival to hospital discharge – 77% For OXA-48-producing Enterobacterales: Microbiological cure - 25% Clinical cure - 32% Survival to hospital discharge - 23% Clinical cure, by infection site IAI – 66.7% Pneumonia – 42.9% UTI – 66.7% Microbiological cure, by infection site IAI – 40% Pneumonia – 42.9% UTI – 66.7% Adverse events reported in 16% patients |
| 3   | Bacteremia - 68% IAI - 39% Pneumonia - 18% UTI - 8% | CAZ-AVI (n=38) Monotherapy – 13 patients | K. pneumoniae (n = 34) P. aeruginosa (n =2) K. oxytoca (n = 1) E. coli (n = 1) |
|     | Temkin et al., 2017 | | For KPC-producing Enterobacterales: Microbiological cure - 75% Clinical cure - 68% Survival to hospital discharge – 77% For OXA-48-producing Enterobacterales: Microbiological cure - 25% Clinical cure - 32% Survival to hospital discharge - 23% Clinical cure, by infection site IAI – 66.7% Pneumonia – 42.9% UTI – 66.7% Microbiological cure, by infection site IAI – 40% Pneumonia – 42.9% UTI – 66.7% Adverse events reported in 16% patients |
| 4   | UTI - 28% Pneumonia - 27% IAI - 7% | CAZ-AVI (n=60) Monotherapy: 55% | CRE infections caused by: K. pneumonia – 83% E. coli – 8% Others – 9% |
|     | King et al., 2017 | | In hospital mortality: 32% Microbiological cure: 53% Clinical success: 65% |
| 5   | Pneumonia - 22% UTI - 14% | CAZ-AVI ( n = 38); monotherapy – 37% Colistin (n = 99) | KPC-producing Enterobacterales |
|     | Van Duin et al., 2018 | | 30-day adjusted all-cause-hospital mortality – CAZ-AVI: 9% Colistin: 32% |
| 6   | Pneumonia - 46% Intra-abdominal - 15% | CAZ-AVI (n = 10) Monotherapy – 5 patients | P. aeruginosa, Citrobacter freundii, Enterobacter aerogenes 13/21 isolates met the Magiorakos criteria of MDR infections |
|     | Santevecchi et al., 2018 | | Ceftazidime-avibactam median MIC was 1.5 mg/L (range 0.5-8 mg/L) Microbiological cure - 67% (n = 6/9) Clinical success - 70% (n = 7/10) All-cause mortality - 30% (n = 3/10) No adverse events reported |
| 7   | Intra-abdominal - 28% Respiratory - 26% Urinary - 25% | CAZ-AVI (n = 57) Monotherapy – 46 (81%) patients | OXA-48-producing Enterobacteriaceae |
|     | Sousa et al., 2018 | | Mortality at 14 days – 14% Recurrence rate at 90 days – 10% |
| 8   | HAP – 38.8%, cUTI – 28.9%, cIAI – 21.1% | CAZ-AVI (n = 10) Comparative group (n = 28) | Carbapenem-resistant Enterobacteriaceae K. pneumonia – 78.9% E. coli – 21.1% |
|     | Airaddadi et al., 2019 | | All-cause mortality at 30 days – 50% with CAZ-AVI and 57% with comparator |
| 9   | Respiratory tract infections - 37% UTI - 20% IAI - 19.7% | CAZ-AVI (n = 203) Monotherapy – 68 patients | MDR Gram-negative bacteria 117 - CRE (63.2% CR-K. pneumoniae and 14.5% CR-E. coli) 63 - Pseudomonas spp. |
|     | Jorgensen et al., 2019 | | Composite clinical failure and 30-day mortality: 59 (29.1%) CRE patients and 35 (17.2%) Pseudomonas spp. patients Outcomes when the treatment was initiated within 48 hours: Clinical success rate - 33.3% Clinical failure - 18.6% |
| 10  | Intraabdominal - 29% Urinary - 25% Respiratory - 21% | CAZ-AVI (n = 24) | OXA-48 CPE Klebsiella pneumoniae - 95.8% episodes Escherichia coli in one episode |
|     | Caffé et al., 2019 | | 30-day mortality – 8.3% 90-day mortality - 20.8% Clinical cure at 30 days - 62.5% of episodes |
Early and appropriate use of ceftazidime-avibactam

Early detection of MDR organisms helps in deciding the appropriate antibiotic for the treatment of infections. Thus, facilitating better therapeutic decisions to ensure favorable clinical outcomes and survival rates. Conventional specimen culture is one such diagnosis method that is used to identify causative organisms in about 48 hours [7]. The causative organisms after isolation can be subjected to molecular testing (also known as genotyping) or phenotypic testing of bacterial antimicrobial susceptibility at the discretion of the treating physician.

Phenotypic testing includes diffusion method, dilution method, E-test, broth macro and micro dilution, and Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectroscopy (MALDI-ToF) [43]. Molecular testing includes polymerase chain reaction (PCR), DNA microarray and DNA chips, and loop-mediated isothermal amplification (LAMP). The newer molecular diagnostic methods generate results within one to four hours. This enables physicians to optimize a targeted treatment for the patients in a timely manner. Overall, this may lead to improved clinical outcomes and decreased mortality [48].

Multiplex real-time PCR technique assay can be utilized for rapid detection of carbapenemase genes in the infection-causing isolates. It can detect five carbapenemase genes ([34]). The evolution of rapid diagnostics has reduced the time required to get the results. This has led to positive effects on clinical outcomes in patients and also has contributed to the efforts to counter antimicrobial resistance in conjunction with robust antimicrobial stewardship programs [50]. A rapid turn-around time to obtain test results leads to a shorter time to initiate optimal therapy. The subsequent advantages of using rapid diagnostic tools and antimicrobial stewardship programs include a decrease in mortality rates, shorter hospital lengths of stay, and reduced hospital costs [50]. Early diagnosis of MDR organisms can thus help in implementing improved management strategies and standardizing antimicrobial stewardship policies. The information on the turn-around time of various diagnostic tests is presented in Table 3 [44-47].

| TABLE 2: Efficacy of Ceftazidime-Avibactam – Real World Evidence on cIAI, cUTI, pyelonephritis, HAP, VAP, and secondary bacteremia |
|---------------------------------------------------------------|
| CAZ-AVI: Ceftazidime-avibactam; cIAI: complicated intra-abdominal infections; CNS: Central nervous system; CRE: Carbapenem-resistant Enterobacterales; cUTI: complicated urinary tract infections; HAP: Hospital-acquired pneumonia; MDR: Multi-drug resistant; MIC: Minimum inhibitory concentration; PDR: Pan-drug resistant; SSTI: Skin and soft tissue infection; VAP: Ventilator-associated pneumonia; XDR: Extremely drug-resistant |

**CAZ-AVI**

**11 Tumbarello et al., 2019**

| Intra-abdominal – 8.7% LRTI – 9.4% Urinary – 4.3% Bloodstream – 75.4% | All isolates were KPC-producing K. pneumoniae | Overall, 30-day mortality – 34.1% 30-day mortality in patients who received CAZ-AVI – 36.5% versus patients who were on control – 55.8% |

**12 Vena et al., 2020**

| Nosocomial pneumonia – 40% IAI – 10% | CAZ-AVI (n = 41) | 45 isolates (24% MDR, 56% XDR, 20% PDR) P. aeruginosa (80.5%) Enterobacterales (9.8%) Clinical success – 90.5% (overall) P. aeruginosa – 87.8% ESBL Enterobacterales – 100% Mixed infection – 100% Development of resistance – not detected No adverse events reported |

**13 Rathish et al., 2021**

| Pneumonia – 16% IAI – 10% UTI – 9% | CAZ-AVI (n = 103) Monotherapy – 69 patients | K. pneumoniae (48%) E. coli (4%) P. aeruginosa (4%) 12 patients had CRE infection All-cause mortality – 27% Clinical cure – 73% |

**14 Nagyek et al., 2021**

| IAI – 32% Nosocomial pneumonia – 26% Bloodstream infections – 9% cUTI – 9% | CAZ-AVI (n = 121) Monotherapy – 4 patients | 119 culture-confirmed CRE isolates K. pneumoniae – 84.21% E. coli – 15.78% Resistance mechanism: OXA 48 – 33.61% NDM + OXA 48 – 37.81% NDM – 28.57% Clinical cure rates - OXA 48 Overall – 82.35% Ceftazidime-avibactam (alone) – 100% Ceftazidime-avibactam + Polymyxin – 75% Ceftazidime-avibactam + Tigecycline – 71% Ceftazidime-avibactam + Polymyxin + Fosfomycin – 100% NDM + OXA 48 OR NDM Overall – 77.5% |

Shields et al., 2016 [34]; Shields et al., 2017 [35]; Temkin et al., 2017 [36]; King et al., 2017 [37]; Van Duin et al., 2018 [38]; Santecocchi et al., 2018 [39]; Sousa et al., 2018 [40]; Alraddadi et al., 2019 [41]; Jorgensen et al., 2019 [11]; Calle et al., 2019 [41]; Tumbarello et al., 2019 [42]; Vena et al., 2020 [43]; Rathish et al., 2021 [44]; Nagyek et al., 2021 [45]
| Test method                              | Accuracy | Turn-around time |
|-----------------------------------------|----------|-----------------|
| Modified Hodge test*                    | Moderate | Next day        |
| Carba NP test*                          | Moderate | Same day        |
| Carbapenemase inactivation method*      | High     | Next day        |
| MALDI-TOF MS*                           | High     | Same day        |
| PCR*                                    | High     | Same day        |
| Microarray*                             | High     | Same day        |

**TABLE 3: Test methods detecting carbapenemase activity/specific carbapenemase gene**

*Detection of carbapenemase activity

Detection of specific carbapenemase gene

Carba NP: Carbapenemase detection; MALDI-TOF MS: Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry; PCR: Polymerase chain reaction

Inappropriate use of broad-spectrum antimicrobials is responsible for increased antimicrobial resistance (AMR). It is also responsible for an increase in the rate of adverse events in up to 20% of patients [51]. The American College of Physicians (ACP) and the Centers for Disease Control and Prevention (CDC) have reported an estimate of over 2.6 million diseases and 35,900 deaths annually due to AMR. They also have reported the incidence of resistant infections to be 6.1/10,000 person-days after receiving antibiotics [51]. A multivariable survival analysis conducted on 789 patients suffering from *E. coli*, *Klebsiella* spp., and *P. aeruginosa* caused bacteremia, demonstrated that the patients who received an effective antibiotic early (hazard ratio (HR) - 1.26, confidence interval i.e., CI - 0.78 to 2.06) had better survival rate as compared to those who did not (HR - 1.83, CI - 1.05 to 3.20) [52]. In patients suffering from infections caused by resistant Gram-negative organisms, delayed appropriate therapy rates remain high. As a consequence, the negative impact of increased duration of therapy (+4.5 days) and delayed recovery (+4.9 days) have been observed [53]. A retrospective analysis concluded that delayed appropriate therapy is an independent factor related to unfavorable clinical outcomes as compared to timely appropriate therapy among hospitalized patients with serious infections due to Gram-negative bacteria, regardless of resistance status. The patients who received delayed appropriate therapy experienced an approximate 70% increase in length of stay, about 65% increase in total in-hospital costs and approximately 20% increase in the risk of in-hospital mortality or discharge to hospice [53]. Early and appropriate antibiotic use results in the reduction in mortality in patients with sepsis [54,55].

Several clinical studies have highlighted the importance of timely initiating antibiotic therapy for serious infections to obtain favorable clinical outcomes. The summary has been presented in Table 4 [56-58].
| Sr. No. | Reference | Type of Infection/s | Treatment group/s | Time of treatment initiation | Causative Organisms | Key Outcomes |
|--------|-----------|---------------------|-------------------|-----------------------------|---------------------|--------------|
| 1      | Jorgensen et al., 2019 | Respiratory tract infections - 37% UTI - 20% IAI - 19.7% | CAZ-AVI (n = 203) | Monotherapy – 68 patients | MDR Gram-negative bacteria 117 - CRE (63.2% CR-K. pneumoniae and 14.5% CR-E. coli) 63 - Pseudomonas spp. | Composite clinical failure and 30-day mortality: 59 (29.1%) CRE patients and 35 (17.2%) Pseudomonas spp. patients. Patients who received CAZ-AVI within 48 hours of culture collection – adjusted odds ratio – 0.409 (CI: 0.180 to 0.930) |
| 2      | Calle et al., 2019 | IAI – 29% UTI – 25% Pneumonia – 21% Others – 25% | CAZ-AVI (n = 23; 24 episodes) | Monotherapy – 59% episodes | All isolates were OXA-48 and co-produced ESBLs (except 1) | 30-day mortality - 8.3% 90-day mortality - 20.8% Clinical cure at 30 days - 62.5% of episodes Adverse events - 16.7% patients |
| 3      | Caston et al., 2022 | Bloodstream infection – 38.1% UTI – 35.4% IAI – 14.3% Pneumonia – 12.2% | CAZ-AVI (n = 189) BAT (n = 150) | After the diagnosis of infection (2 days, median) | K. pneumonia – 89.9% Enterobacter spp. – 4.8% E. coli – 3.2% Others – 2.1% | Mortality in patients with INCREMENT-CPE score of >7 points – 21.9% CAZ-AVI and 46.9% with BAT |

**TABLE 4: List of studies with < 72 hours of time to initiation of ceftazidime avibactam**

BAT: Best available therapy; CAZ-AVI: Ceftazidime-avibactam; cIAI: complicated intra-abdominal infections; CRE: carbapenem-resistant Enterobacterales; cUTI: complicated urinary tract infections; ESBL: extended-spectrum beta-lactamase; HAP: hospital-acquired pneumonia; KPC: Klebsiella pneumoniae carbapenemase; MDR: multi-drug resistant; MIC: minimum inhibitory concentration; PDR: pan-drug resistant; SSTI: skin and soft tissue infection; VAP: ventilator-associated pneumonia; XDR: extremely drug-resistant

Jorgensen et al., 2019 [11]; Calle et al., 2019 [41]; Caston et al., 2022 [59]

Early use of ceftazidime-avibactam (within 48 hours of infection onset) has been associated with improved clinical outcomes [11]. The real-world experience with ceftazidime-avibactam, reported by Jorgensen et al., 2019 also highlights the advantages of using ceftazidime-avibactam at an early stage. The study reported data from 203 patients with MDR Gram-negative infections, the types of infections included respiratory tract infections (37.4%), UTI (19.7%), IAI (18.7%), and others (24.2%). Overall, 117 patients had CRE infections (63.2% with K. pneumoniae and 14.5% with E. coli) and 63 patients were infected with Pseudomonas spp. Among the 203 patients, 91 patients received ceftazidime-avibactam within 48 hours of infection onset. The composite clinical failure was reported to be 29.1% and 30-day mortality was 17.2%. In a group of 87 patients, ceftazidime-avibactam treatment was started within 72 hours. The clinical success rate when the treatment was initiated within 48 hours was 33.3% and failure was 18.6%. Similarly, the clinical success rate when the treatment was initiated within 72 hours was 44.4%, but the failure rate was 39.0%. For patients for whom the treatment was initiated within 96 hours and within 120 hours, the clinical failure rates were 49.2% and 61.0%, respectively, while the clinical success rates were 57.6% and 69.4%, respectively. Multivariate logistic analysis regression model for clinical failure showed that ceftazidime-avibactam given within 48 hours of culture collection was protective (adjusted OR: 0.409, 95% CI: 0.180 - 0.930) (Figure 1) [11].

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*2022 Swaminathan et al. Cureus 14(8): e28283. DOI 10.7759/cureus.28283*
Guideline recommendation of usage of ceftazidime-avibactam

Infectious Diseases Society of America (IDSA) has recommended ceftazidime-avibactam as a first-line treatment against OXA-48-like and KPC-producing carbapenem-resistant Enterobacterales for pyelonephritis or cUTI and infections outside of the urinary tract, in cases with proven in vitro susceptibility to ceftazidime-avibactam [60]. The Indian Council of Medical Research (ICMR) has recommended that ceftazidime-avibactam be used as a first-line treatment option against OXA-48-like carbapenem-resistant Enterobacterales [61].

Role of ceftazidime-avibactam in the Indian setting

In India, NDM and coproduction of NDM with OXA-48-like enzymes are the most prevalent mechanisms of CRE infections [62]. Ceftazidime-avibactam has been established to be effective in patients with comorbid conditions. The real-world evidence and clinical experience published consisted of patients with comorbidities such as obesity, impaired renal function, diabetes, heart failure, liver diseases, malignancies [11], asthma, chronic pancreatitis [33], neurological diseases, bronchiectasis, etc. [31] among others. Sub-group analyses of REPROVE (ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia) and RECLAIM (Efficacy and Safety of Ceftazidime-Avibactam Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-abdominal Infection) studies were performed on data of Indian patients [26,28]. Both the analyses concluded that ceftazidime-avibactam was an effective alternative to meropenem in HAP and complicated IAIs (cIAIs) in Indian patients. The results of both the studies were in-line with the results of the overall results and the safety profile was consistent with the adverse effects previously reported for ceftazidime and cephalosporins [26,28]. The real-world studies from India have reported high susceptibility of tested CRE isolates to ceftazidime-avibactam [29] and also concluded that ceftazidime-avibactam is a viable option to treat patients with CRE infections [50].

A rise in carbapenem-resistant Gram-negative organisms has been observed worldwide. Carbapenem-resistant *P. aeruginosa*, *Acinetobacter baumannii* and CREs remain the major cause of hospital-acquired infections. This will inevitably lead to complicated treatment scenarios and more serious infections in vulnerable patient populations [63]. The current treatment options against MDR Gram-negative bacteria include polymyxins, aminoglycosides, tigecycline, carbapenems, fosfomycin, and newer β-lactam-β-lactamase inhibitors [64].

Tigecycline and colistin face challenges such as low plasma concentration and nephrotoxicity, respectively [5,65,66]. Colistin may be limited in its use due to its narrow therapeutic index, challenges with dose optimization, poor lung penetration, nephrotoxicity, and emerging antimicrobial resistance [61,65,67]. Antimicrobial resistance against colistin is emerging due to its rampant use. The susceptible category was removed from colistin by the CLSI indicating that some causative organisms might not respond to it owing to the unknown resistance mechanism [61]. Tigecycline has an expanded broad-spectrum activity which overcomes the resistance issues of tetracycline [68]. However, tigecycline has been reported to fail in achieving the required time curve and minimum inhibitory concentration ratio leading to treatment failure [69]. Tigecycline additionally faces challenges with regard to susceptibility testing due to inconsistency in results obtained from various antimicrobial susceptibility tests [70].

Ceftazidime-avibactam has been proven to be efficacious and, in some studies, non-inferior to conventional options in treating complicated infections [13,25,27]. There is limited literature available highlighting the importance of early use of antibiotics for treating infections caused by multidrug-resistant bacteria. However, clinical studies have stressed the association between delayed appropriate therapy and the risk of prolonged symptoms and treatment duration [53]. Prolonged hospital stays and treatment duration results in an increased economic burden for the patients and the healthcare infrastructures. It is hence crucial to alter the treatment practices from escalation strategies and adopt early and appropriate antibiotic therapy in
patients with serious infections caused by Gram-negative bacteria [53].

**Conclusions**

The increasing prevalence of antimicrobial resistance and infections caused by MDR Gram-negative bacteria jeopardize the current management strategies. Treating infections caused by CREs is more challenging owing to limited antimicrobial options. Ceftazidime-avibactam, a combination of the third-generation β-lactam and a non-β-lactamase inhibitor, has been proven to be clinically efficacious in pivotal phase III non-inferiority trials as well as in real world settings. A decreased mortality rate was observed with early and appropriate use of ceftazidime-avibactam for managing infections caused by pathogens which are sensitive to ceftazidime-avibactam.

Furthermore, the use of rapid diagnostic tools can support prompt administration of effective therapy and help in reducing the morbidity and mortality associated with MDR infections. Ceftazidime-avibactam fits the role of an effective antibiotic with a favorable safety and pharmacokinetic profile. The early and appropriate use of ceftazidime-avibactam yields improved clinical outcomes for the patients whose profiles are suitable to receive early treatment. Further real-world evidence studies focusing on time of ceftazidime-avibactam treatment initiation are needed to ascertain the advantages of its early and appropriate use on a larger scale.

**Additional Information**

**Disclosures**

**Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: Abhishek Routray and Akshata Mane declare(s) employment from Pfizer Ltd. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

**Acknowledgements**

Medical writing support was provided by Vaidehi Wadhwa (Medical Excellence, Emerging Markets, Pfizer Limited).

**References**

1. Mo Y, Lorenzo M, Farghaly S, Kaur K, Housman ST: What’s new in the treatment of multidrug-resistant gram-negative infections? Diagn Microbiol Infect Dis. 2019, 93:171-81. 10.1016/j.diagmicrobio.2018.08.007
2. Cerco E, Dotelizewig SB, Sherman BM, Amin AN: Multidrug-resistant gram-negative bacterial infections in the hospital setting: overview, implications for clinical practice, and emerging treatment options. Microb Drug Resist. 2016, 22:412-51. 10.1089/mdr.2015.0220
3. Devanga Ragupathi NK, Veeraraghavan B, Muthuivelan Sethuvel DP, et al.: First Indian report on genome-wide comparison of multidrug-resistant Escherichia coli from blood stream infections. PLoS One. 2020, 15:e0220428. 10.1371/journal.pone.0220428
4. Shankar C, Jacob JJ, Sugumar SG, et al.: Distinctive mobile genetic elements observed in the clonal expansion of carbapenem-resistant klebsiella pneumoniae in India. Microb Drug Resist. 2021, 27:1096-104. 10.1089/mdr.2020.0316
5. Bakhavatchalam YD, Routray A, Mane A, et al.: In vitro activity of ceftazidime-avibactam and its comparators against carbapenem resistant Enterobacteriales collected across India: results from ATLAS surveillance 2018 to 2019. Diagn Microbiol Infect Dis. 2022, 103:115652. 10.1016/j.diagmicrobio.2022.115652
6. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, et al.: Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCOREMENT): a retrospective cohort study. Lancet Infect Dis. 2017, 17:726-34. 10.1016/S1473-3099(17)30228-1
7. Bhattacharya S: Early diagnosis of resistant pathogens: how can it improve antimicrobial treatment? Virulence. 2013, 4:172-84. 10.4161/viru.23526
8. Doi Y: Treatment options for carbapenem-resistant gram-negative bacterial infections . Clin Infect Dis. 2019, 69:S65-75. 10.1093/cid/ciz830
9. Shirley M: Ceftazidime-avibactam: a review in the treatment of serious gram-negative bacterial infections . Drugs. 2018, 78:675-92. 10.1007/s40265-018-0902-x
10. Recommendations of the SEC (Antimicrobial & Antiviral) made in its 98th meeting held on 20.01.2021 at CDSCO HQ New Delhi. (2021). Accessed: 25th July 2022: https://cdsco.gov.in/openms/resources/UploadCDSCOWeb/2018/UploadCommitteeFiles/SEC%20antimicrobial%20&%20Antiviral%20Recommendations.pdf
11. Jongenans SC, Trinh TD, Zasowski RJ, et al.: Real-world experience with ceftazidime-avibactam for multidrug-resistant gram-negative bacterial infections. Open Forum Infect Dis. 2019, 6:ofi522. 10.1093/ofid/ofz522
12. Mazuzki JE, Wagenlehner F, Torres A, et al.: Clinical and microbiological outcomes of ceftazidime-avibactam treatment in adults with gram-negative bacteria: a subset analysis from the phase 3 clinical trial program. Infect Dis Ther. 2021, 10:2399-414. 10.1007/s40121-021-00556-7
13. Torres A, Zhong N, Pichl J, et al.: Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. Lancet Infect Dis. 2018, 18:285-95. 10.1016/S1473-3099(17)30747-8
14. Sharma R, Park TE, Moy S: Ceftazidime-avibactam: a novel cephalosporin β-lactamase inhibitor combination for the treatment of resistant gram-negative organisms. Clin Ther. 2016, 38:431-44. 10.1016/j.clinthera.2016.01.018
15. Buckman SA, Krekel T, Müller AE, Mazuski JE: Ceftazidime-avibactam for the treatment of complicated intra-abdominal infections. Expert Opin Pharmacother. 2016, 17:2341-9. 10.1080/14656566.2016.1249847
Matesanz M, Mensa J. Ceftazidime-avibactam. Rev Esp Quimioter. 2021, 34 Suppl 1:38-40. 10.57201/regap1.2021

Vázquez-Ucha JC, Arco-Suírez J, Bou G, Góezco A: New carbapenemase inhibitors: clearing the way for the β-lactams. Int J Mol Sci. 2020, 21:10.3390/ijms21239508

Zhang H, Xu Y, Jia P, et al.: Global trends of antimicrobial susceptibility to ceftazidime and ceftazidime-avibactam: a surveillance study from the ATLAS program (2012-2016). Antimicrob Resist Infect Control. 2020, 9:1966. 10.1186/s13756-020-00812-9

Hidalgo JA, Vinhão CM, Antony N: Ceftazidime/avibactam: a novel cephalosporin/nonbeta-lactam beta-lactamase inhibitor for the treatment of complicated urinary tract infections and complicated intra-abdominal infections. Drug Des Devel Ther. 2016, 10:2379-86. 10.2147/DDDT.S110946

Sy SK, Zhuang L, Sy S, Derendorf H: Clinical pharmacokinetics and pharmacodynamics of ceftazidime-avibactam combination: a model-informed strategy for its clinical development. Clin Pharmacokinet. 2019, 58:545-64. 10.1007/s40262-018-0705-y

Nicolaou DP, Siew L, Armstrong J, Li J, Edekii T, Learoyd M, Das S: Phase 1 study assessing the steady-state concentration of ceftazidime and avibactam in plasma and epithelial lining fluid following two dosing regimens. J Antimicrob Chemother. 2015, 70:2862-9. 10.1095/ijm.d15v17-8485

Dimelow R, Wright IG, MacPherson M, Newell P, Das S: Population pharmacokinetic modelling of ceftazidime and avibactam in the plasma and epithelial lining fluid of healthy volunteers. Drugs R D. 2018, 18:221-30. 10.1007/s40268-018-0241-0

Carrelli Y, Armstrong J, Laud PJ, Newell P, Stone G, Wardman A, Gasink LB: Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and Pseudomonas aeruginosa complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. Lancet Infect Dis. 2016, 16:661-73. 10.1016/S1473-3099(16)30044-4

Wagenlehner FM, Sobel JD, Newell P, et al.: Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: RECAPTURE, a phase 3 randomized trial program. Clin Infect Dis. 2016, 63:54-62. 10.1093/cid/ciw578

Mazuski JE, Gasink LB, Armstrong J, et al.: Efficacy and safety of ceftazidime-avibactam plus mezlocillin and meropenem in complicated intra-abdominal infections: Indian subset from RECLAIM. J Infect Dev Ctries. 2022, 16:305-15. 10.3855/jidc.14912

Qin X, Tran BG, Kim MJ, et al.: A randomised, double-blind, phase 3 study comparing the efficacy and safety of ceftazidime/avibactam plus meropenem versus meropenem for complicated intra-abdominal infections in hospitalised adults in Asia. Int J Antimicrob Agents. 2017, 49:579-88. 10.1016/j.ijantimicag.2017.01.010

Sathe P, Kamat S, Adhav C: Clinical outcomes of ceftazidime-avibactam versus meropenem in Indian patients with nosocomial pneumonia: subset analysis from the REPROVE study. Indian J Med Microbiol. 2021, 39:36-46. 10.1007/s12028-021-00459-2

Rathish B, Wilson A, Warrier G, Prakash S, Babu R, Joy S: Clinical experience with ceftazidime/avibactam for treatment of infections due to carbapenem-resistant Enterobacteriaceae. Indian J Crit Care Med. 2021, 35:9-17. 10.1007/s40262-020-00705-y

Nagayekar Y, Shah A, Usadkat VP, et al.: Clinical outcome of patients on ceftazidime-avibactam and combination therapy in carbapenem-resistant Enterobacteriaceae. Indian J Crit Care Med. 2021, 25:780-4. 10.5005/jp-journals-10071-23863

Vena A, Gläöcher DR, Castaldo N, et al.: Clinical experience with ceftazidime-avibactam for the treatment of infections due to multidrug-resistant gram-negative bacteria other than carbapenem-resistant Enterobacteriales. Antibiotics (Basel). 2020, 9:10.3390/antibiotics9020071

Strich JR, Ricotta E, Warner S, et al.: Pharmacoeconomic evaluation of ceftazidime-avibactam use: a retrospective cohort analysis of 210 US hospitals. Clin Infect Dis. 2021, 72:611-21. 10.1093/cid/ciaa616

Santrevecchi BA, Smith TP, MacVane SH: Clinical experience with ceftazidime/avibactam for treatment of antibiotic-resistant organisms other than Klebsiella pneumoniae. Int J Antimicrob Agents. 2018, 51:629-35. 10.1016/j.ijantimicag.2018.01.015

Shields RK, Potsouki BS, Haidar G, et al.: Clinical outcomes, drug toxicity, and emergence of ceftazidime-avibactam resistance among patients treated for carbapenem-resistant Enterobacteriaceae infections. Clin Infect Dis. 2016, 63:1561-5. 10.1093/cid/ciw536

Shields RK, Nguyen MH, Chen L, et al.: Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant Klebsiella pneumoniae bacteremia. Antimicrob Agents Chemother. 2017, 61:10.1128/AAC.00835-17

Temkin E, Torre-Cineros J, Bovic R, et al.: Ceftazidime-avibactam as salvage therapy for infections caused by carbapenem-resistant organisms. Antimicrob Agents Chemother. 2017, 61:10.1128/AAC.01964-16

King M, Heil E, Kurikose S, et al.: Multicenter study of outcomes with ceftazidime-avibactam in patients with carbapenem-resistant Enterobacteriaceae infections. Antimicrob Agents Chemother. 2017, 61:10.1128/AAC.00449-17

van Duin D, Lok JJ, Eurler M, et al.: Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant Enterobacteriaceae. Clin Infect Dis. 2018, 66:163-71. 10.1093/cid/ciy783

Sousa A, Pérez-Rodríguez MT, Soto A, et al.: Effectiveness of ceftazidime/avibactam as salvage therapy for treatment of infections due to OXA-48 carbapenemase-producing Enterobacteriaceae. J Antimicrob Chemother. 2018, 73:5170-5. 10.1093/jac/dky295

Alraddadi BM, Saeedi M, Qutub M, Alshukairi A, Hassanien A, Wall G: Efficacy of ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant Enterobacteriaceae. BMC Infect Dis. 2019, 19:772. 10.1186/s12879-019-4409-1

De la Calle C, Rodríguez O, Morata L, et al.: Clinical characteristics and prognosis of infections caused by OXA-48 carbapenemase-producing Enterobacteriaceae in patients treated with ceftazidime-avibactam. Int J Antimicrob Agents. 2019, 53:520-4. 10.1016/j.ijantimicag.2018.11.015

Tumbarello M, Trecarichi EM, Corona A, et al.: Efficacy of ceftazidime-avibactam salvage therapy in patients with infections caused by Klebsiella pneumoniae carbapenemase-producing K. pneumoniae. Clin Infect Dis. 2019, 68:555-64. 10.1093/cid/ciy942

Khan ZA, Siddiqui MF, Park S: Current and emerging methods of antibiotic susceptibility testing. Diagnostics (Basel). 2019, 9:10.3390/diagnostics9020049

Messacar K, Parker SK, Todd JK, Dominguez SR: Implementation of rapid molecular infectious disease
diagnostics: the role of diagnostic and antimicrobial stewardship. J Clin Microbiol. 2017, 55:715-23. 10.1128/JCM.02761-16

45. Lautringer JD, Limbago BM: The problem of carbapenemase-producing-carbapenem-resistant Entrobacteriaceae Detection. J Clin Microbiol. 2016, 54:S29-34. 10.1128/JCM.02771-15

46. De Angelis G, Grossi A, Menchinelli G, Bocci S, Sanguinetti M, Posteraro B: Rapid molecular tests for detection of antimicrobial resistance determinants in Gram-negative organisms from positive blood cultures: a systematic review and meta-analysis. Clin Microbiol Infect. 2020, 26:271-80. 10.1016/j.cmi.2019.11.009

47. Bauer KA, Perez KK, Forrest GN, Goff DA: Review of rapid diagnostic tests used by antimicrobial stewardship programs. Clin Infect Dis. 2014, 59 Suppl 3:S134-45. 10.1093/cid/ciu547

48. Sattin MJ, Chen L, Govez-Simmonds A, et al.: Impact of a rapid molecular test for Klebsiella pneumoniae carbapenemase and ceftazidime-avibactam use on outcomes after bacteremia caused by carbapenem-resistant Entrobacteriales. Clin Infect Dis. 2022, 10.1093/cid/ciu534

49. Jin X, Zhang H, Wu S, et al.: Multicenter evaluation of Xpert Carba R Assay for detection and identification of the carbapenemase genes in rectal swabs and clinical isolates. J Mol Diagn. 2021, 23:111-9. 10.1016/j.jmoldx.2020.10.017

50. Edmiston CE, Garcia R, Barnden M, DeBaun B, Johnson HB: Rapid diagnostics for bloodstream infections: a primer for infection preventionists. Am J Infect Control. 2018, 46:1060-8. 10.1016/j.ajic.2018.02.022

51. Lee RA, Censor RM, Humphrey LL, et al.: Appropriate use of short-course antibiotics in common infections: best practice advice from the American College of Physicians. Ann Intern Med. 2021, 174:822-7. 10.7326/m20-7355

52. Baltas I, Skordale T, Tausan M, et al.: Impact of antibiotic timing on mortality from gram-negative bacteriaemia in an English district general hospital: the importance of getting it right every time. J Antimicrob Chemother. 2021, 76:813-9. 10.1093/jac/dkaa478

53. Bosine NG, Berger A, Altincatal A, Wang R, Bhagvan T, Gillard P, Lodise T: Impact of delayed appropriate antibiotic therapy on patient outcomes by antibiotic resistance status from serious gram-negative bacterial infections. Am J Med Sci. 2019, 357:103-10. 10.1016/j.amjms.2018.11.009

54. Martinez ML, Plata-Menchaca EP, Ruiz-Rodriguez JC, Ferrer R: An approach to antibiotic treatment in patients with sepsis. J Thorac Dis. 2020, 12:1007-21. 10.21037/jtd.2020.01.47

55. Kim BY, Ng AM, Periwal AK, et al.: Antibiotic timing and outcomes in sepsis. Am J Med Sci. 2018, 355:524-9. 10.1016/j.amjms.2018.02.007

56. Seymour CW, Gesten F, Prescott HC, et al.: Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med. 2017, 376:2235-44. 10.1056/NEJMoa1705058

57. Raman G, Avendano E, Berger S, Menon V: Appropriate initial antibiotic therapy in hospitalized patients with gram-negative infections: systematic review and meta-analysis. BMC Infect Dis. 2015, 15:395. 10.1186/s12879-015-1125-5

58. Lodise TP Jr, Patel N, Kwa A, et al.: Predictors of 30-day mortality among patients with Pseudomonas aeruginosa bloodstream infections: impact of delayed appropriate antibiotic selection. Antimicrob Agents Chemother. 2007, 51:5510-6. 10.1128/AAC.00358-07

59. Castón JJ, Cano A, Pérez-Camacho I, 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, 77:1452-60. 10.1095/jac/dkaa049

60. Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum b-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Entrobacteriales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTRP. aeruginosa). (2022). Accessed: 25th June 2022: https://www.idsociety.org/globalassets/idsa-practice-guidelines/amr-guidance/1.0/idsa-amr-guidance-v1.1.pdf.

61. Annual Report: Antimicrobial Resistance Research and Surveillance Network . (2022). Accessed: 25th June 2022: https://main.icmr.nic.in/sites/default/files/guidelines/AMRSN_annual_report_2020.pdf.

62. Soman R, Veeraraghavan B, Hegde A, et al.: Indian consensus on the management of CRE infection in critically ill patients (ICONIC) - India. Expert Rev Ant Infect Ther. 2019, 17:647-60. 10.1080/14787275.2019.1647103

63. Brink AJ: Epidemiology of carbapenem-resistant gram-negative infections globally. Curr Opin Infect Dis. 2019, 32:609-16. 10.1097/QCO.0000000000006608

64. Bassetti M, Peghin M, Vena A, Giacobbe DR: Treatment of infections due to MDR gram-negative bacteria . Front Med (Lausanne). 2019, 6:674. 10.3389/fmed.2019.00074

65. Veeraraghavan B, Pragasam AK, Rakhitvauchal YD, Anandan S, Swaminathan S, Sundaram B: Collistin-sparing approaches with newer antimicrobials to treat carbapenem-resistant organisms: current evidence and future prospects. Indian J Med Microbiol. 2019, 37:2-94. 10.4103/ijmm.IJMM_19_215

66. Sattin MJ: Landscape uptake of ceftazidime-avibactam for carbapenem-resistant gram-negative infections and continued reliance on polymyxins. Clin Infect Dis. 2021, 72:622-5. 10.1093/cid/ciaa065

67. Soman R, Rakhitvauchal YD, Naradranarajan HT, Venkatasubramanian R, Veeraraghavan B: Is it time to move away from polymyxins?: evidence and alternatives . Eur J Clin Microbiol Infect Dis. 2021, 40:461-75. 10.1007/s10096-020-04055-w

68. Swaminathan S, Kunde P: Tigecycline: Role in the Management of cIAI and cSTI in the Indian Context. Ind J of Clin Med. 2021, 1:24-50. 10.1177/2633944211067579

69. De Pascale G, Lisi L, Cioti GM, et al.: Pharmacokinetics of high-dose tigecycline in critically ill patients with severe infections. Ann Intensive Care. 2020, 10:94. 10.1186/s13613-020-00715-2

70. Shankar C, Pragasam AK, Veeraraghavan B, Amladi A: Bad bug, no test: tigecycline susceptibility testing challenges and way forward. Indian J Med Microbiol. 2019, 57:91-4. 10.4103/ijmm.IJMM_19_207