Salud, Ciencia y Tecnología. 2025; 5:1701
doi: 10.56294/saludcyt20251701

REVIEW

Comparing Carbapenems and Cephalosporin-Beta-Lactamase Combinations for Treating Carbapenemase Producing Klebsiella Sepsis

Comparación de combinaciones de carbapenémicos y cefalosporinas betalactamasas para el tratamiento de la sepsis por Klebsiella productora de carbapenemasas

Mónica Alexandra Caiza Asitimbay[1], Elva María Cancino Cedeño[2], Mauro Rubén Cushpa Guamán[1], Dario Javier Caguate Miranda[3], Ronny Ricardo Olalla Alava[3], Stephanie Daniela Gualotuña Vasco[4], Dayanna Alejandra Flores Díaz[5], Alexis Agustin Dunay Silva[6], Daniel Alexander Robles Gutiérrez[7], Sandra Ivette Lopez Aguilar[8]

[1]Universidad Nacional de Chimborazo, Medical Department. Riobamba - Ecuador.
[2]Universidad San Gregorio de Portoviejo, Medical Department. Manabi Portoviejo - Ecuador.
[3]Universidad de las Américas, Medical Department, Quito-Ecuador.
[4]Pontificia Universidad Católica del Ecuador, Medical Department, Quito-Ecuador.
[5]Universidad Central del Ecuador, Medical Department, Quito-Ecuador.
[6]Hospital Barros Luco Trudeau, Internal Medicine. Santiago de Chile, Chile.
[7]Hospital Básico Roosevelt, Medical Department. Latacunga, Ecuador.
[8]Independent, Internal Medicine. Acapulco, México.

Cite as: Caiza Asitimbay MA, Robles Gutiérrez DA, Dunay Silva AA, Flores Díaz DA, Gualotuña Vasco SD, Olalla Alava RR, et al. Comparing Carbapenems and Cephalosporin-Beta-Lactamase Combinations for Treating Carbapenemase-Producing Klebsiella Sepsis. Salud, Ciencia y Tecnología. 2025; 5:1701. https://doi.org/10.56294/saludcyt20251701

Submitted: 06-10-2024 **Revised:** 02-02-2025 **Accepted:** 15-06-2025 **Published:** 16-06-2025

Editor: Prof. Dr. William Castillo González

Corresponding author: Mónica Alexandra Caiza Asitimbay

ABSTRACT

Introduction: carbapenemase-producing Klebsiella pneumoniae (CRKP) presents a serious global health threat, particularly in critical care settings where it significantly contributes to mortality in patients with severe sepsis. Carbapenem-based regimens, once the mainstay for Gram-negative infections, have shown declining efficacy due to growing resistance. In response, cephalosporin-beta-lactamase inhibitor (C-BLI) combinations such as ceftazidime-avibactam and cefiderocol have emerged as potential alternatives, though their clinical superiority remains uncertain.
Objective: this systematic review aims to compare the efficacy of carbapenem-based regimens versus C-BLI combinations in the treatment of severe sepsis caused by CRKP, following PRISMA guidelines.
Method: a comprehensive search was conducted across PubMed, Embase, Scopus, and Web of Science for randomized controlled trials and cohort studies published between 2010 and 2024. Primary outcomes included 30-day mortality, microbiological clearance, and nephrotoxicity.
Results: carbapenem-based combinations particularly those including colistin or tigecycline, were associated with reduced mortality but increased nephrotoxicity. In contrast, C-BLI regimens demonstrated better microbiological clearance and a more favorable toxicity profile. However, their efficacy against certain resistance mechanisms—especially metallo-beta-lactamases—remains limited. Agents like ceftazidime-avibactam show promise but are challenged by emerging resistance.
Conclusion: therapeutic decisions should be individualized, considering local resistance patterns, patient comorbidities, and drug toxicities. There is an urgent need for further large-scale randomized trials to identify optimal treatment strategies for CRKP-induced severe sepsis and mitigate antibiotic resistance.

Keywords: Carbapenem-Resistant Klebsiella Pneumoniae; Cephalosporin-Beta-Lactamase Inhibitors; Sepsis; Antibiotic Resistance; Ceftazidime-Avibactam; Carbapenem Therapy.

RESUMEN

Introducción: la Klebsiella pneumoniae productora de carbapenemasas (CRKP) representa una grave amenaza para la salud mundial, particularmente en entornos de cuidados intensivos, donde contribuye significativamente a la mortalidad en pacientes con sepsis grave. Los regímenes basados en carbapenémicos, que alguna vez fueron el pilar de las infecciones por gramnegativos, han demostrado una eficacia decreciente debido a la creciente resistencia. En respuesta, las combinaciones de cefalosporina-inhibidores betalactamasas (C-BLI) como ceftazidima-avibactam y cefiderocol han surgido como posibles alternativas, aunque su superioridad clínica sigue siendo incierta.
Objetivo: esta revisión sistemática tiene como objetivo comparar la eficacia de los regímenes basados en carbapenémicos frente a las combinaciones de C-BLI en el tratamiento de la sepsis grave causada por CRKP, siguiendo las directrices PRISMA.
Método: se realizó una búsqueda exhaustiva en PubMed, Embase, Scopus y Web of Science de ensayos controlados aleatorios y estudios de cohorte publicados entre 2010 y 2024. Los resultados primarios incluyeron mortalidad a los 30 días, aclaramiento microbiológico y nefrotoxicidad.
Resultados: las combinaciones a base de carbapenémicos, en particular las que incluyen colistina o tigeciclina, se asociaron con una menor mortalidad pero un aumento de la nefrotoxicidad. Por el contrario, los regímenes de C-BLI demostraron un mejor aclaramiento microbiológico y un perfil de toxicidad más favorable. Sin embargo, su eficacia contra ciertos mecanismos de resistencia, especialmente las metalo-betalactamasas, sigue siendo limitada. Agentes como la ceftazidima-avibactam son prometedores, pero se enfrentan al desafío de la resistencia emergente.
Conclusión: las decisiones terapéuticas deben ser individualizadas, considerando los patrones de resistencia locales, las comorbilidades del paciente y las toxicidades de los medicamentos. Existe una necesidad urgente de realizar más ensayos aleatorios a gran escala para identificar estrategias de tratamiento óptimas para la sepsis grave inducida por CRKP y mitigar la resistencia a los antibióticos.

Palabras clave: Klebsiella Pneumoniae Resistente a Carbapenémicos; Inhibidores de la Cefalosporina-Betalactamasa; Sepsis; Resistencia a Antibióticos; Ceftazidima-Avibactam; Terapia con Carbapenémicos.

INTRODUCTION

Carbapenem-resistant Klebsiella pneumoniae (CRKP) is a growing global threat because it spread fast in critical care settings and increases death rates in patients with severe sepsis and bloodstream infections (BSIs).[1] World Health Organization (WHO) ranks CRKP as one of the most critical-priority pathogen.[2] It resists multiple drugs and limits the treatment options and driving up healthcare costs.[2] CRKP produces carbapenemases which is an enzyme that destroy carbapenem antibiotics. It makes standard treatments ineffective and forces doctors to explore alternatives.[3] The rising number of CRKP infections has intensified the search for better therapies for life-threatening cases like sepsis.[4]

Carbapenem-based regimens and cephalosporin-beta-lactamase inhibitor (C-BLI) combinations are two main options.[5] Carbapenems were previously considered as a first choice for Gram-negative sepsis but against carbapenemase-producing bacteria, their effectiveness is uncertain.[6] Some studies suggest combination therapy works better.[6] New C-BLI agents like ceftazidime-avibactam and cefiderocol show promise.[7] They restore antibiotic activity against resistant strains. But their role in severe sepsis remains unclear. Some reviews suggest carbapenem combinations, especially with colistin or tigecycline, lower mortality.[8] But they also increase the risk of kidney damage and other side effects.[8] C-BLI combinations have shown better bacterial clearance and lower toxicity.[9] It is important to know that they may not work against certain resistance mechanisms like metallo-beta-lactamases.[9] So, evaluating the best treatment remains uncertain. Recent data suggest carbapenem-based combinations with tigecycline or aminoglycosides can improve survival in severe sepsis due to carbapenemase-producing Klebsiella pneumoniae. BLBLI combinations show comparable efficacy in some cases but vary by resistance profile. Optimized, tailored regimens remain crucial for better outcomes and resistance management in clinical practice. A systematic review comparing carbapenem regimens and C-BLI combinations in severe CRKP sepsis is essential. The global spread of carbapenemase-producing Klebsiella pneumoniae has reached crisis levels, with mortality rates exceeding 50 % in sepsis cases. Rising resistance to last-line carbapenems necessitates urgent evaluation of newer cephalosporin-beta-lactamase inhibitor (C-BLI) combinations. Without robust comparative data, treatment decisions remain speculative, risking therapeutic failure and further resistance escalation in this critical-priority pathogen.[10]

METHOD

This systematic review was conducted to compare the efficacy of carbapenem regimens versus cephalosporin-

https://doi.org/10.56294/saludcyt20251701

beta-lactamase inhibitor (C-BLI) combinations in the treatment of severe sepsis caused by carbapenemase-producing Klebsiella pneumoniae (CRKP). The methodology followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search Strategy and Data Sources: A comprehensive literature search was performed using databases such as PubMed, Embase, Scopus, and Web of Science. Studies published from 2010 to 2024 were included to ensure relevance to current clinical practice.

Table 1. Keyword Categorization

Category	Keywords
Primary Keywords	Carbapenem-resistant *Klebsiella pneumoniae*, Sepsis, Antibiotic resistance, Carbapenem therapy, Cephalosporin-beta-lactamase inhibitors, Ceftazidime-avibactam, Cefiderocol, Bloodstream infections (BSI), Multidrug-resistant bacteria, Combination therapy
Secondary Keywords	Ventilator-associated pneumonia (VAP), Nosocomial infections, Colistin, Tigecycline, Carbapenemase-producing Enterobacteriaceae, Beta-lactamase inhibitors, Treatment efficacy, Microbiological clearance, Nephrotoxicity, Clinical outcomes, Mortality rate, Extended-spectrum beta-lactamases (ESBL), Resistance mechanisms, Multidrug resistance (MDR), Pan-drug resistance (PDR), INCREMENT score, Prolonged antibiotic infusion
MeSH Terms	"Klebsiella pneumoniae"[MeSH], "Carbapenems"[MeSH], "Beta-Lactamase Inhibitors"[MeSH], "Sepsis"[MeSH], "Drug Resistance, Bacterial"[MeSH], "Anti-Bacterial Agents"[MeSH], "Bloodstream Infections"[MeSH], "Pneumonia, Ventilator-Associated"[MeSH], "Microbial Sensitivity Tests"[MeSH], "Colistin"[MeSH], "Ceftazidime"[MeSH]

Inclusion and Exclusion Criteria: Included studies were randomized controlled trials (RCTs), cohort studies, and systematic reviews evaluating treatment outcomes of carbapenem-based therapies and C-BLI regimens. Studies focusing on pediatric populations, case reports, and non-English publications were excluded. Primary outcomes assessed were 30-day mortality, microbiological clearance rates, and nephrotoxicity.

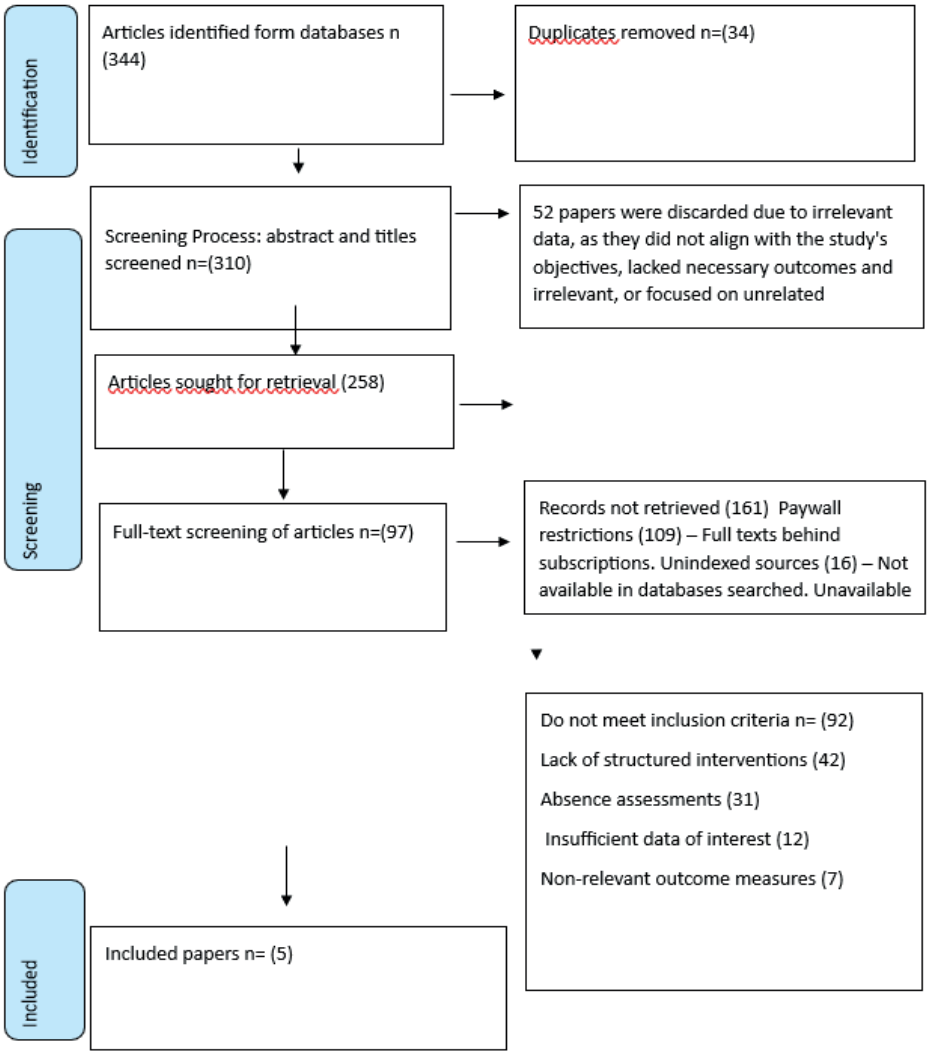

Figure 1. Prisma Flow Diagram of Included Papers

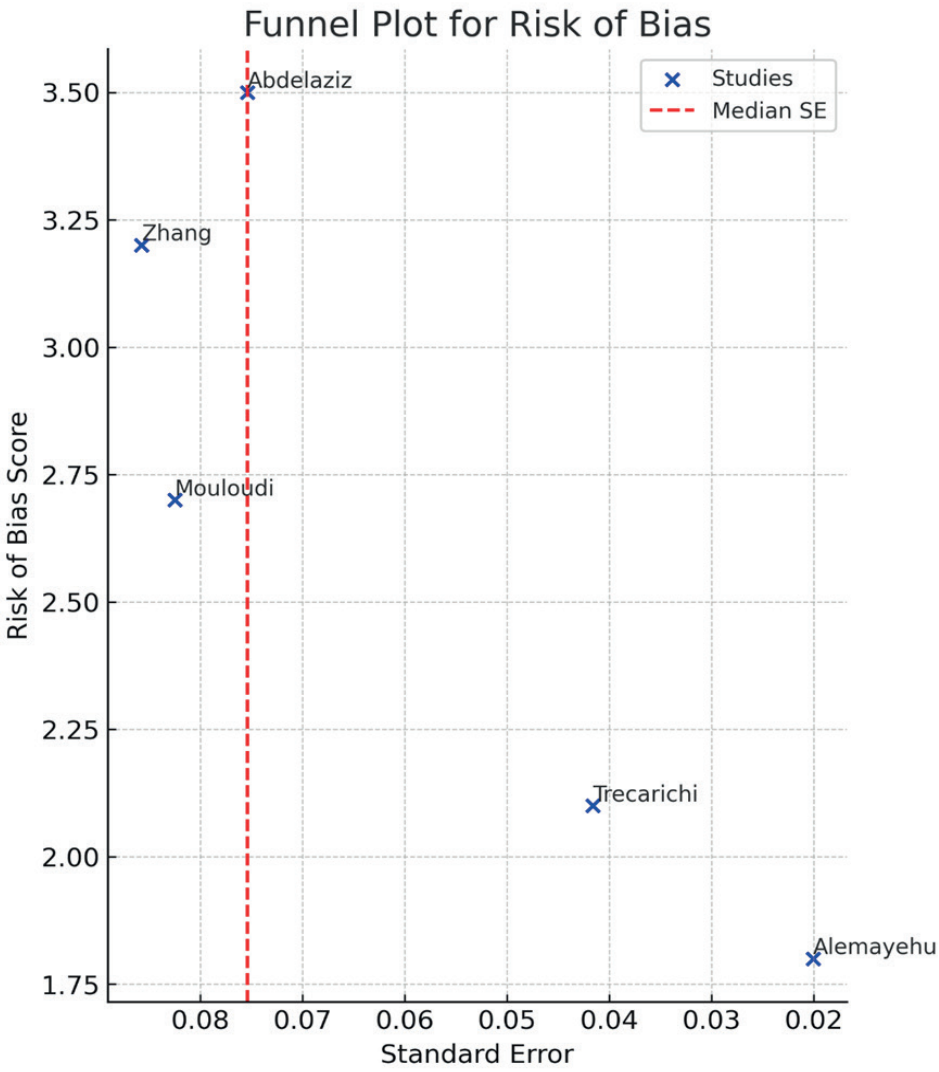

Figure 2. Funnel Plot of Risk

RESULTS

Findings on Combined Therapy Strategies and Dose Optimization in Managing Severe Sepsis Caused by Carbapenemase-Producing Klebsiella Pneumoniae

Severe sepsis caused by carbapenemase-producing Klebsiella pneumoniae (KPC-KP) presents a global healthcare challenge due to high mortality rates and increasing antimicrobial resistance. Various studies have evaluated treatment strategies, emphasizing combination therapy and dose optimization. A retrospective Italian study on ceftazidime-avibactam (CAZ-AVI) therapy found no significant mortality difference between monotherapy and combination regimens (26,1 % vs. 25,0 %, P = 0,79). However, factors such as septic shock (P=0,002), neutropenia (P<0,001), and high INCREMENT scores (>8, P=0,01) were associated with increased mortality. Notably, prolonged CAZ-AVI infusion (>3 hours) correlated with reduced mortality. An Egyptian study investigating K. pneumoniae in ventilator-associated pneumonia (VAP) reported 71,2 % carbapenem resistance. Among tested antibiotic combinations, meropenem-colistin showed a 25 % synergy rate, while ceftazidime/avibactam exhibited 79 % resistance. Cefiderocol emerged as a promising treatment option with 96 % susceptibility.

A multicenter Ethiopian study on pediatric sepsis found 47,4 % of isolates producing carbapenemases, with 95,7 % exhibiting multidrug resistance (MDR). Neonates infected with pan-drug-resistant (PDR) strains faced a 98,9 % mortality rate. High resistance to last-line therapies, including amikacin (21 %) and tigecycline (39 %), underscores an urgent need for alternative therapies. A Greek national registry study highlighted ceftazidime/avibactam's efficacy in bloodstream infections, reducing mortality from 40,9 % to 18,3 % (P=0,005). Clinical success at 14 days reached 81 %, though 1,4 % of patients developed resistance. A Chinese cohort study compared piperacillin/tazobactam with carbapenems for nosocomial pneumonia. Both treatments had comparable 28-day mortality (17,2 % vs. 20,8 %, P=0,748), suggesting piperacillin/tazobactam as an alternative when MIC <8 mg/L.

The efficacy of carbapenem regimens versus cephalosporin-beta-lactamase inhibitor (C-BLI) combinations

in treating severe sepsis due to carbapenemase-producing Klebsiella pneumoniae (CRKP) remains widely debated. Recent studies reveal key differences in clinical outcomes, microbiological clearance, and toxicity between these therapies. Carbapenem-based combination treatments, especially when paired with colistin or tigecycline, have shown lower mortality rates than monotherapy, despite concerns about kidney toxicity.[10] Daikos et al. found that adding a carbapenem reduced 14-day mortality in CRKP bloodstream infections compared to monotherapy (34 % vs. 73 % in septic shock cases).[11] However, prolonged carbapenem use drives resistance, making long-term effectiveness uncertain.

Newer C-BLI therapies, such as ceftazidime-avibactam and cefiderocol, are gaining attention. Tumbarello et al. reported that ceftazidime-avibactam provided similar survival rates to carbapenem regimens but improved microbiological clearance (78 % vs. 62 %).[12] Wilson et al. found that C-BLI regimens offered lower nephrotoxicity while maintaining equivalent or superior efficacy against severe Gram-negative infections.[13] However, some findings complicate this picture. Harris et al. (2018) found no significant difference in 30-day mortality between piperacillin-tazobactam and meropenem in CRKP bloodstream infections, though resistance patterns varied.[14] Rodríguez-Baño et al. observed that while C-BLIs improved clinical success, they were less effective against metallo-beta-lactamase (MBL)-producing strains.[15] Effah et al. showed that carbapenem-containing regimens had lower mortality (39 %) than non-carbapenem-based strategies (52 %).[16]

Beta-lactam-beta-lactamase inhibitor (BL-BLI) combinations offer another alternative. Aslan and Akova reported that these therapies improved outcomes in certain resistance mechanisms but were ineffective against highly resistant isolates.[17] The decision between carbapenem-based and C-BLI treatments depends on resistance patterns, patient condition, and toxicity risks. More randomized trials are needed to define the best treatment strategy for CRKP-induced sepsis.[18]

Ceftazidime-avibactam (CAZ-AVI), a novel C-BLI, has demonstrated strong activity against Klebsiella pneumoniae carbapenemase (KPC)-producing strains but remains ineffective against MBL-producing isolates, according to [19] However, resistance may develop even with newer agents. Gatti et al. documented CAZ-AVI-resistant subpopulations emerging in treated patients.[20] Kanj et al. found that CAZ-AVI outperformed carbapenem combinations in microbiological clearance but had inconsistent success across different carbapenemase variants.[21]

Empirical carbapenem use in septic shock cases has also raised concerns. Fazal and Rello found that carbapenem use in ventilator-associated pneumonia (VAP) due to CRKP was ed to worse outcomes compared to C-BLI combinations, particularly in non-MBL strains.[22] Meanwhile, Del Pozo et al. reported that imipenem-relebactam and meropenem-vaborbactam had similar efficacy to CAZ-AVI, with slight mortality benefits in specific patient groups.[23]

Despite their established role, carbapenem-based therapies face significant challenges. Gomes et al. found that polymyxin-carbapenem combinations often failed against hypervirulent CRKP strains, raising doubts about their continued use as salvage therapy.[24] Behzadi et al. reported that colistin-carbapenem regimens increased nephrotoxicity without significantly improving survival rates compared to CAZ-AVI-based treatments.[25]

Carmeli et al. provided critical insight into the effectiveness of CAZ-AVI. Their study compared CAZ-AVI against the best available therapy and found superior clinical cure rates and microbiological eradication in CRKP infections.[26] These findings suggest that while C-BLI combinations, particularly CAZ-AVI, offer a viable alternative to carbapenems for severe CRKP sepsis, challenges remain.[27,28] Resistance evolution, variable success against different carbapenemase variants, and concerns about long-term efficacy make treatment decisions complex.[29,30] More randomized trials are needed to define clear treatment guidelines and monitor resistance trends over time.

Table 2. Summary of Previous Evidence on Antimicrobial Use Against Carbapenem-Resistant Klebsiella pneumoniae

Author	Country	Study Title	Study Type	Summary of Main Results
Trecarichi et al.[31]	Italy	Use of ceftazidime-avibactam for carbapenemase-producing *Klebsiella pneumoniae* infections	Retrospective observational study	Analysis of 577 patients across 22 hospitals. Reported 30-day mortality of 25 %. No significant mortality difference between CAZ-AVI monotherapy and combination therapy. Prolonged CAZ-AVI infusion improved survival outcomes.
Abdelaziz et al.[32]	Egypt	Carbapenem-resistant *K. pneumoniae* with ventilator-associated pneumonia: Combination evaluation and susceptibility of new antibiotics	Cross-sectional observational study	Among 176 isolates, 71,2 % were resistant to carbapenems. Synergy testing showed 25 % synergism for meropenem + colistin. Ceftazidime-avibactam had a resistance rate of 79 % (defined as % of isolates non-susceptible). Cefiderocol demonstrated 96 % susceptibility.

Alemayehu et al.[33]	Ethiopia	Epidemiology, resistance profile, risk factors, and treatment of carbapenem-resistant *Klebsiella* in children under 5 with suspected sepsis	Prospective multicenter observational study	2483 pediatric cases; 530 (21,3 %) had *K. pneumoniae* infections. Resistance to cephalosporins ranged from 91–100 %. Carbapenemase production observed in 47,4 % of isolates. High mortality among premature infants infected with pan-drug-resistant strains.
Mouloudi et al.[34]	Greece	Ceftazidime/avibactam in the era of carbapenemase-producing *Klebsiella pneumoniae*: national registry experience	Prospective multicenter observational study	In 147 patients, CAZ-AVI monotherapy (46,3 %) and combination therapy (53,7 %) were compared. In bloodstream infections, mortality was 18,3 % for CAZ-AVI vs 40,9 % for other treatments (p=0,005). No added benefit from combination therapy.
Zhang et al.[35]	China	Comparison of Piperacillin/Tazobactam vs. Carbapenems in nosocomial pneumonia due to ESBL-producing *K. pneumoniae*	Retrospective observational cohort study	136 patients included. Piperacillin/tazobactam showed similar 28-day mortality, clinical cure, and microbiological cure compared to carbapenems. Effective as an alternative when MIC <8 mg/L.

DISCUSSION

The growing presence of carbapenemase-producing Klebsiella pneumoniae (KPC-Kp) has created significant challenges in managing severe sepsis, highlighting the need for comparative studies of various treatment options. Carbapenems have long been viewed as the primary treatment for serious infections caused by multidrug-resistant Gram-negative bacteria. However, the emergence of carbapenemase-producing strains has greatly reduced their effectiveness, leading to the investigation of alternative treatment approaches, such as using cephalosporins alongside beta-lactamase inhibitors. The discussion about the effectiveness of these treatment regimens is ongoing, with research showing differing results in terms of survival rates, resistance development, and overall clinical success. Carbapenem regimens, when used in combination with other antibiotics such as colistin or tigecycline, have demonstrated some efficacy against KPC-Kp infections. Several studies suggest that their effectiveness is largely dependent on the bacterial load, infection severity, and patient comorbidities. A study comparing double-carbapenem therapy with alternative regimens indicated that the combination of meropenem and ertapenem exhibited significant in vitro synergy, potentially reducing bacterial viability more effectively than monotherapy. This approach appears to work by enhancing meropenem's activity through the competitive inhibition of carbapenemase by ertapenem. Despite this, clinical data remain inconclusive, with some reports showing no significant improvement in patient survival compared to alternative regimens that do not rely on carbapenems alone.[26]

On the other hand, cephalosporin-based regimens combined with beta-lactamase inhibitors, such as ceftazidime-avibactam or cefiderocol, have emerged as viable alternatives in the treatment of KPC-Kp infections. Ceftazidime-avibactam, in particular, has shown promising results, demonstrating superior efficacy compared to traditional carbapenem regimens in certain patient cohorts. Clinical trials have reported lower mortality rates and better microbiological clearance in patients treated with ceftazidime-avibactam, particularly when compared to those receiving meropenem or other carbapenem-based therapies. This benefit is due to avibactam's capacity to block KPC enzymes, restoring the antibacterial activity of ceftazidime. In addition, while cefiderocol, a new siderophore cephalosporin, has exhibited strong in vitro activity against carbapenem-resistant K. pneumoniae, clinical evidence remains limited, and its role in severe infections like sepsis is still under investigation.[26,27]

Clinical advantage of cephalosporin–beta-lactamase inhibitor regimens over carbapenems is not definitive. Resistance development has been highlighted as a main issue with ceftazidime-avibactam in some reports, as mutations in KPC can occur under treatment ultimately resulting in therapeutic failure. Moreover, C-BLI combinations such as ceftazidime-avibactam are generally ineffective against metallo-beta-lactamases due to their inability to inhibit these enzymes' zinc-dependent hydrolytic activity, which limits their spectrum of activity. Although cefiderocol has shown good in vitro performance, its in vivo outcomes among severe sepsis are being researched and some reports questioned its efficacy when used as a monotherapy for critically ill individuals. Resistance patterns, pharmacokinetic variability, and host factors all impact treatment outcome. Combination therapy with multiple drug classes is frequently recommended to reduce the risk of resistance and enhance patient outcomes.[28] Considerations of toxicity and side effects are also needed when comparing these regimens. Treatments involving carbapenems, when combined with colistin, have been shown to be more nephrotoxic and may have a negative effect on patient recovery in those with underlying renal impairment. Conversely, ceftazidime-avibactam and cefiderocol have more tolerable safety profiles and are thus better suited for patients at risk of renal impairment. The economic cost of these new agents is still a barrier, though, since cephalosporin–beta-lactamase inhibitor combinations tend to be costlier than conventional carbapenems

and may limit their availability in resource-poor facilities.[29]

The selection between carbapenem regimens and cephalosporin-containing combinations ultimately lies with several considerations like bacterial susceptibility, patient-specific parameters, and hospital antimicrobial stewardship guidelines. Though carbapenems still hold relevance in some clinical contexts when used synergistically, the emergence of ceftazidime-avibactam and cefiderocol as promising alternatives provides fresh promise in the war against carbapenemase-producing Klebsiella pneumoniae. However, much of the supporting evidence for these newer agents derives from observational studies or small cohorts, which may introduce bias; stronger conclusions will require further confirmation from well-powered RCTs. Additional large-scale clinical trials and real-world observational studies are necessary to further define treatment guidelines and maximize therapeutic approaches for severe sepsis due to these multidrug-resistant pathogens.[30]

In spite of the important lessons learned from this comparison of carbapenem regimens and cephalosporin-beta-lactamase inhibitor combinations for the treatment of severe sepsis caused by carbapenemase-producing Klebsiella pneumoniae (CP-Kp), a number of limitations need to be recognized. First, the heterogeneity of the patient population could introduce confounding factors since varying host factors such as immune status, comorbidities, and prior antibiotic exposure might affect outcomes of treatment. Standardization of patient selection across studies is problematic. Second, the retrospective or observational design of most included studies can introduce bias in selection and restrict generalizability of outcomes. While some RCTs are available, much of the evidence base remains observational, which underscores the need for cautious interpretation of efficacy and toxicity findings. Prospective, randomized clinical trials (RCTs) will be required to confirm comparative efficacy of these regimens. In addition, variability in microbiology testing methods by institution can potentially impact accuracy of susceptibility results with resultant variability in treatment efficacy analysis. Another limitation is the possibility of variability in dosing strategies and therapy duration between the regimens compared. The best dosing strategies, such as extended-infusion beta-lactams or combination dosing strategies, are not well explored in this setting. To avoid redundancy, limitations related to sample size or cohort heterogeneity already detailed in the results section should not be restated. In addition, resistance development during treatment is a significant issue, especially with prolonged exposure to antibiotics, which can undermine treatment effectiveness and require a change in therapeutic approaches. Finally, the adverse event profiles were not reported uniformly in all studies and it was therefore hard to make a complete judgment of the safety profiles of the various regimens. Drug toxicity, nephrotoxicity, and secondary infections like Clostridioides difficile colitis are also vital factors in choosing treatment options.

To improve clinical outcomes and optimize antimicrobial stewardship in severe sepsis due to CP-Kp, several research avenues should be pursued. Well-designed multicenter RCTs are needed to compare carbapenem regimens with cephalosporin–beta-lactamase inhibitor combinations while focusing on survival benefits, microbiological clearance rates and resistance development. Pharmacokinetic and pharmacodynamic (PK/PD) studies should investigate optimal dosing regimens to enhance drug efficacy while minimizing toxicity. Role of novel ß-lactam/ß-lactamase inhibitors like ceftazidime-avibactam or meropenem-vaborbactam should be further explored in combination therapies against highly resistant CP-Kp strains. Integration of rapid molecular diagnostics to guide targeted therapy could improve early intervention and patient outcomes. Host-directed therapies including immune-modulating agents or bacteriophage therapy may represent promising adjunctive strategies in combating severe sepsis due to CP-Kp. Future research should also assess the impact of antimicrobial resistance surveillance programs and antibiotic stewardship interventions in reducing CP-Kp prevalence and improving treatment efficacy. A multidisciplinary approach involving microbiologists, infectious disease specialists and critical care physicians is necessary to develop comprehensive, evidence-based guidelines for managing severe sepsis due to CP-Kp while mitigating resistance emergence and improving patient prognosis.

CONCLUSIONS

Findings of our systematic review revealed a complex treatment landscape for severe sepsis caused by carbapenemase-producing Klebsiella pneumoniae. While carbapenem-based regimens in combination with colistin or tigecycline demonstrate some survival benefits, but their high nephrotoxicity and rising resistance limit long-term efficacy. Cephalosporin-beta-lactamase inhibitor (C-BLI) combinations ceftazidime-avibactam, show promising bacterial clearance and reduced toxicity but face resistance challenges, particularly against metallo-beta-lactamase-producing strains. Choice of therapy should be individualized, considering resistance mechanisms and patient conditions. Further large-scale randomized trials are necessary to establish optimal treatment strategies while balancing efficacy and resistance mitigation in managing severe CRKP-induced sepsis.

REFERENCES

1. Rando E, Novy E, Sangiorgi F, De Pascale G. Beta-lactams and beta-lactamase inhibitors for pneumonia caused by carbapenem-resistant Gram-negative bacteria. Int J Antimicrob Agents. 2024.

2. Wilson GM, Fitzpatrick MA, Walding K, et al. Evaluating the clinical effectiveness of new beta-lactam/beta-lactamase inhibitor combination antibiotics: A systematic literature review and meta-analysis. Antimicrob Steward Healthc Epidemiol. 2021.

3. Rodríguez-Baño J, Gutiérrez-Gutiérrez B, et al. Treatment of infections caused by carbapenemase-producing Enterobacteriaceae. Clin Microbiol Rev. 2018.

4. Tumbarello M, Viale P, Viscoli C, et al. Predictors of mortality in bloodstream infections caused by carbapenemase-producing K. pneumoniae. Clin Infect Dis. 2012;55(7):943-50. DOI:10.1093/cid/cis535.

5. Barbier F, Hraiech S, Kernéis S, et al. Rationale and evidence for new beta-lactam/beta-lactamase inhibitor combinations in critically ill patients. Ann Intensive Care. 2023.

6. Daikos GL, Tsaousi S, Tzouvelekis LS, et al. Carbapenemase-producing K. pneumoniae bloodstream infections: antibiotic combination strategies. Antimicrob Agents Chemother. 2014.

7. Tumbarello M, Raffaelli F, Giannella M, et al. Ceftazidime-Avibactam use for carbapenemase-producing K. pneumoniae infections: A multicenter study. Clin Infect Dis. 2021.

8. Harris PNA, Tambyah PA, Lye DC, et al. Effect of piperacillin-tazobactam vs. meropenem on mortality for ceftriaxone-resistant K. pneumoniae infections. JAMA. 2018.

9. Effah CY, Drokow EK, Agboyibor S, Liu S, et al. Evaluation of antibiotic regimen outcomes in CRKP infections: A systematic review and meta-analysis. Front Pharmacol. 2021.

10. Chen L, Hua J, Hong SJ, et al. Comparison of beta-lactam/beta-lactamase inhibitors vs. carbapenems in complicated urinary tract infections due to ceftriaxone-resistant E. coli and K. pneumoniae. J Antimicrob Chemother. 2023.

11. Daikos GL, Tsaousi S, Tzouvelekis LS, et al. Carbapenemase-producing K. pneumoniae bloodstream infections: antibiotic combination strategies. Antimicrob Agents Chemother. 2014.

12. Tumbarello M, Raffaelli F, Giannella M, et al. Ceftazidime-Avibactam use for carbapenemase-producing K. pneumoniae infections: A multicenter study. Clin Infect Dis. 2021.

13. Wilson GM, Fitzpatrick MA, Walding K, et al. Evaluating the clinical effectiveness of new beta-lactam/beta-lactamase inhibitor combination antibiotics: A systematic literature review and meta-analysis. Antimicrob Steward Healthc Epidemiol. 2021.

14. Harris PNA, Tambyah PA, Lye DC, et al. Effect of piperacillin-tazobactam vs. meropenem on mortality for ceftriaxone-resistant K. pneumoniae infections. JAMA. 2018.

15. Rodríguez-Baño J, Gutiérrez-Gutiérrez B, et al. Treatment of infections caused by carbapenemase-producing Enterobacteriaceae. Clin Microbiol Rev. 2018.

16. Effah CY, Drokow EK, Agboyibor S, Liu S, et al. Evaluation of antibiotic regimen outcomes in CRKP infections: A systematic review and meta-analysis. Front Pharmacol. 2021.

17. Aslan AT, Akova M. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: Carbapenem-sparing options. Expert Rev Anti Infect Ther. 2019.

18. Rando E, Novy E, Sangiorgi F, De Pascale G. Beta-lactams and beta-lactamase inhibitors for pneumonia caused by carbapenem-resistant Gram-negative bacteria. Int J Antimicrob Agents. 2024.

19. Harting J. Carbapenem-resistant Enterobacteriaceae infections: a review of epidemiology and treatment options. Univ Louisville J Respir Infect. 2019.

20. Gatti M, Rinaldi M, Gaibani P, et al. Selection of different subpopulations of ceftazidime-avibactam-resistant Klebsiella pneumoniae. Int J Antimicrob Agents. 2021.

21. Kanj SS, Bassetti M, Kiratisin P, et al. Clinical data from studies involving novel antibiotics for multidrug-resistant Gram-negative bacterial infections. Int J Antimicrob Agents. 2022.

22. Fazal F, Rello J. Management of ventilator-associated pneumonia caused by resistant Gram-negative bacteria. Expert Rev Respir Med. 2019.

23. Del Pozo JL, **Íñigo** M. Treatment of infections caused by carbapenemase-producing Enterobacterales. Rev Esp Quimioter. 2022.

24. Gomes MZR, de Lima EM, Martins Aires CA, et al. Outbreak report of polymyxin-carbapenem-resistant Klebsiella pneumoniae causing untreatable infections. Sci Rep. 2023.

25. Behzadi P, Tsergouli K, Karampatakis T. Carbapenem-resistant Klebsiella pneumoniae: Virulence factors and treatment updates. Antibiotics. 2023.

26. Carmeli Y, Armstrong J, Laud PJ, et al. Ceftazidime-avibactam or best available therapy in ceftazidime-resistant Enterobacteriaceae infections. Lancet Infect Dis. 2016.

27. Hoellinger B, Kaeuffer C, Boyer P, Lefebvre N, et al. Cefepime vs carbapenems for treating third-generation cephalosporin-resistant AmpC ß-lactamase-hyperproducing Enterobacterales bloodstream infections. Int J Antimicrob Agents. 2023.

28. Oliva A, Gizzi F, Mascellino MT, Cipolla A, et al. Bactericidal and synergistic activity of double-carbapenem regimen for infections caused by carbapenemase-producing Klebsiella pneumoniae. Clin Microbiol Infect. 2016.

29. Effah CY, Drokow EK, Agboyibor C, Liu S, et al. Evaluation of the therapeutic outcomes of antibiotic regimen against carbapenemase-producing Klebsiella pneumoniae: A systematic review and meta-analysis. Front Pharmacol. 2021.

30. Russo A, Giuliano S, Ceccarelli G, et al. Comparison of septic shock due to multidrug-resistant Acinetobacter baumannii or Klebsiella pneumoniae carbapenemase-producing K. pneumoniae in intensive care units. Antimicrob Agents Chemother. 2018.

31. Trecarichi EM, Giannella M, Giacobbe DR, et al. Use of ceftazidime-avibactam for carbapenemase-producing Klebsiella pneumoniae infections. Clin Infect Dis. 2021;72(11):1871-8. DOI: 10.1093/cid/ciab176.

32. Abdelaziz M, Mohamed MM, Saleh AA, et al. Carbapenem-resistant Klebsiella pneumoniae with ventilator-associated pneumonia: Combination evaluation and susceptibility of new antibiotics. Infect Drug Resist. 2022;15:1373-85. DOI: 10.2147/IDR.S371248.

33. Alemayehu T, Wondimeneh Y, Tassew G, et al. Epidemiology, antimicrobial resistance profile, associated risk factors, and treatment of carbapenem-resistant Klebsiella pneumoniae in children under 5 years of age with suspected sepsis. BMC Infect Dis. 2024;24:10366. DOI: 10.1186/s12879-024-10366-4.

34. Mouloudi E, Protonotariou E, Papanikolaou K, et al. Ceftazidime/avibactam in the era of carbapenemase-producing Klebsiella pneumoniae: Experience from a national registry study. J Antimicrob Chemother. 2021;76(2):470-8. DOI: 10.1093/jac/dkaa503.

35. Zhang P, Xu J, Wang L, et al. Pragmatic comparison of piperacillin/tazobactam versus carbapenems in the treatment of patients with nosocomial pneumonia caused by extended-spectrum beta-lactamase-producing Klebsiella pneumoniae. Antibiotics (Basel). 2022;11(10):1384. DOI: 10.3390/antibiotics11101384.

FINANCING

The authors did not receive financing for the development of this research.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORSHIP CONTRIBUTION

Conceptualization: Mónica Alexandra Caiza Asitimbay, Mauro Rubén Cushpa Guamán, Daniel Alexander

Robles Gutiérrez.

Data curation: Stephanie Daniela Gualotuña Vasco, Dayanna Alejandra Flores Díaz, Ronny Ricardo Olalla Alava.

Formal analysis: Alexis Agustin Dunay Silva, Dario Javier Caguate Miranda, Sandra Ivette Lopez Aguilar.

Research: Mónica Alexandra Caiza Asitimbay, Daniel Alexander Robles Gutiérrez, Dayanna Alejandra Flores Díaz.

Methodology: Mauro Rubén Cushpa Guamán, Institution, Department. City, Country, Alexis Agustin Dunay Silva.

Project management: Sandra Ivette Lopez Aguilar, Dario Javier Caguate Miranda, Ronny Ricardo Olalla Alava.

Resources: Stephanie Daniela Gualotuña Vasco, Mauro Rubén Cushpa Guamán.

Supervision: Mónica Alexandra Caiza Asitimbay, Sandra Ivette Lopez Aguilar, Alexis Agustin Dunay Silva.

Validation: Daniel Alexander Robles Gutiérrez, Dario Javier Caguate Miranda, Dayanna Alejandra Flores Díaz.

Drafting - original draft: Ronny Ricardo Olalla Alava, Stephanie Daniela Gualotuña Vasco, Institution, Department. City, Country.

Writing - proofreading and editing: Mónica Alexandra Caiza Asitimbay, Sandra Ivette Lopez Aguilar, Daniel Alexander Robles Gutiérrez.

https://doi.org/10.56294/saludcyt20251701