International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	CARBAPENEM-RESISTANT *ACINETOBACTER BAUMANNII*: THE ROLE OF SELECTED MICROBIOLOGICAL AND BIOCHEMICAL FACTORS IN TARGETED THERAPY SELECTION — A NARRATIVE REVIEW
DOI	https://doi.org/10.31435/ijitss.2(50).2026.5907
RECEIVED	30 March 2026
ACCEPTED	19 June 2026
PUBLISHED	23 June 2026
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

CARBAPENEM-RESISTANT *ACINETOBACTER BAUMANNII*: THE ROLE OF SELECTED MICROBIOLOGICAL AND BIOCHEMICAL FACTORS IN TARGETED THERAPY SELECTION — A NARRATIVE REVIEW

Jakub Lamorski *(Corresponding Author, Email: lamorski.jakub@gmail.com)*
Independent Public Provincial Integrated Hospital in Szczecin, Szczecin, Poland
ORCID ID: 0009-0004-5456-7413

Izabela Szubert
Independent Public Provincial Integrated Hospital in Szczecin, Szczecin, Poland
ORCID ID: 0009-0006-7162-6651

Julia Suchecka
Independent Public Provincial Integrated Hospital in Szczecin, Szczecin, Poland
ORCID ID: 0009-0001-9975-355X

Wiktor Nesterak
Pomeranian Medical University in Szczecin, Szczecin, Poland
ORCID ID: 0009-0009-5322-903X

Karolina Chudecka
Independent Public Provincial Integrated Hospital in Szczecin, Szczecin, Poland
ORCID ID: 0009-0004-0262-5036

Michał Chylewski
University Clinical Hospital No. 1 PMU in Szczecin, Szczecin, Poland
ORCID ID: 0009-0007-4789-1903

Aleksandra Kędzierska
Independent Public Provincial Integrated Hospital in Szczecin, Szczecin, Poland
ORCID ID: 0009-0008-7050-4139

Katarzyna Józwa
Independent Public Provincial Integrated Hospital in Szczecin, Szczecin, Poland
ORCID ID: 0009-0003-5615-2388

Gabriela Stępień
University Clinical Hospital No. 2 PMU in Szczecin, Szczecin, Poland
ORCID ID: 0009-0006-4505-5162

Urszula Przewoźna
University Clinical Hospital No. 2 PMU in Szczecin, Szczecin, Poland
ORCID ID: 0009-0003-2186-6604

ABSTRACT

Carbapenem-resistant *Acinetobacter baumannii* (CRAB) strains represent one of the major challenges in contemporary medicine because of features that contribute to both the high mortality rate of infections and the ease of their dissemination within the hospital environment. The aim of this study was to analyze resistance mechanisms, including the biochemical basis of selected mechanisms and their impact on the selection of targeted therapy. This review discusses the key mechanisms underlying carbapenem resistance, including enzymatic mechanisms associated with β-lactamase production, as well as non-enzymatic mechanisms involving efflux pump overexpression, alterations in membrane permeability, modification of target sites, and biofilm formation. The analysis also included the genetic background of the major resistance mechanisms. Particular attention was devoted to class B and D enzymes due to their high prevalence and broad substrate activity spectrum, which contributes to the ineffectiveness of numerous antibiotic groups. The characteristics of individual antibiotics were discussed in the context of their impact on therapeutic efficacy in infections caused by CRAB strains, together with selected novel therapeutic options, both currently used and still under investigation. The growing importance of molecular diagnostic methods, including whole-genome sequencing, as well as bioinformatics tools used both for the improvement of diagnostic methods and for monitoring the epidemiological situation at both local and global levels, was also emphasized. One of the principal conclusions of this study is the necessity for further high-quality clinical research aimed at generating more robust clinical data to support the development of effective treatment regimens.

KEYWORDS

Acinetobacter Baumannii, CRAB, Carbapenem resistance, β-lactamases, Metallo-β-lactamases, Molecular Mechanisms Of Resistance, Cefiderocol, Sulbactam–Durlobactam

CITATION

Jakub Lamorski, Izabela Szubert, Julia Suchecka, Wiktor Nesterak, Karolina Chudecka, Michał Chylewski, Aleksandra Kędzierska, Katarzyna Józwa, Gabriela Stępień, Urszula Przewoźna. (2026) Carbapenem-Resistant *Acinetobacter Baumannii*: The Role of Selected Microbiological and Biochemical Factors in Targeted Therapy Selection — a Narrative Review. *International Journal of Innovative Technologies in Social Science*. 2(50). doi: 10.31435/ijitss.2(50).2026.5907

1. Introduction

One of the most significant public health problems of the 21st century is bacterial resistance to antibiotics, driven partly by inappropriate antibiotic use, which in the coming decades will most likely lead to a substantial increase in the already high number of deaths caused by infections with multidrug-resistant bacteria (Antimicrobial Resistance Collaborators, 2022).

Acinetobacter baumannii is a non-fermenting, Gram-negative, non-motile bacillus (Karruli et al., 2023, p.1). It is a particularly dangerous bacterium for immunocompromised patients, in whom it may cause severe infections (Karampatakis et al., 2025).

It represents one of the major challenges in contemporary healthcare of modern times due to the high proportion of carbapenem-resistant strains, which has significantly increased in recent years because of the limited number of therapeutic options available against this pathogen (Iovleva et al., 2025; Zhang et al., 2024).

This results in frequent prolongation of hospital stays, including recurrent hospitalizations, while an increasing number of patients with infections caused by this microorganism are admitted to intensive care units. Inadequate hand hygiene and prolonged hospitalization may further facilitate the dissemination of *A. baumannii* and promote the selection of strains resistant to additional antimicrobial groups (Boutzoukas & Doi, 2025; Karampatakis et al., 2025).

A. baumannii may cause numerous infections, ranging from more localized forms, such as skin and soft tissue infections, to severe or systemic infections, including urinary tract infections and meningitis (Ibrahim et al., 2021). The most prevalent groups of infections are hospital-acquired pneumonia and bacteremia, with associated mortality rates ranging from 40% to as high as 70%, particularly among critically ill patients (Zhang et al., 2024; Boutzoukas & Doi, 2025). This represents an especially high proportion compared to other carbapenem-resistant pathogens (Shields et al., 2023).

The dissemination of multidrug-resistant pathogens, including *A. baumannii*, is closely associated with their resistance mechanisms, which are classified as intrinsic and acquired. β-lactamase production, mechanisms associated with the acquisition of resistance genes, and efflux pumps represent only some of the factors contributing to therapeutically challenging resistance (Zhang et al., 2024; Shields et al., 2023), which will be discussed further in this study.

Alongside the growing burden of antimicrobial resistance, advances in medical technology have created new opportunities for analyzing epidemiological and clinical data, including approaches based on artificial intelligence. These tools may support efforts to address antimicrobial resistance, particularly by facilitating molecular-level analyses of resistance mechanisms, which are essential for selecting appropriate therapy, and by enabling the monitoring of epidemiological trends at local and international levels (Karampatakis et al., 2025). They may also contribute to drug development and bioengineering, offering prospects for new effective therapeutic strategies.

2. Methodology

This study is a narrative review concerning the resistance mechanisms of carbapenem-resistant *Acinetobacter baumannii* strains and their impact on the selection of targeted therapy.

The literature analysis was conducted using the PubMed database. The search for publications was performed using the following keywords: "carbapenem resistance Acinetobacter baumannii", "CRAB", "β-lactamases", and "carbapenem resistance Acinetobacter baumannii treatment". The analysis included English-language publications published between 2018 and 2025 that addressed the mechanisms of carbapenem resistance in *Acinetobacter baumannii* and contemporary therapeutic strategies for infections caused by CRAB. Review articles, guidelines, and meta-analyses with available full text were included, which enabled a detailed analysis of the methodology, results, and conclusions presented by the authors.

Additionally, three older publications, published in 2012, 2013, and 2017, respectively, were included solely to expand the description of concepts related to well-established resistance mechanisms. These publications did not serve as the basis for discussing current therapeutic regimens. Publications not directly related to the subject of this study, duplicating previously presented data, or referring to outdated treatment regimens were excluded.

Both enzymatic and non-enzymatic resistance mechanisms were analyzed, with particular emphasis on OXA-type carbapenemases, metallo-β-lactamases, alterations in cell membrane permeability, efflux pump overexpression, and biofilm-forming capacity. The impact of these mechanisms on the effectiveness of selected therapeutic strategies was also assessed. The collected data were subjected to qualitative analysis and narrative synthesis, focusing on the relationships between resistance mechanisms and therapeutic options.

3. Results

3.1. Resistance Mechanisms

3.1.1. β-lactamases

3.1.1.1. Class A

According to the Ambler classification, class A β-lactamases, which are serine enzymes with serine in the active site, are responsible for resistance to several antibiotics, including penicillins, cephalosporins, and carbapenems. Some of these enzymes exhibit a narrow spectrum of activity; however, certain variants may acquire extended-spectrum activity through various point mutations (Kyriakidis et al., 2021; Gupta et al., 2022).

Several groups of enzymes are distinguished within this class, although it should be emphasized that class A enzymes do not constitute the principal mechanism of carbapenem resistance in Acinetobacter spp (Iovleva et al., 2025). Among CRAB strains, enzymes originating from *Klebsiella pneumoniae*—KPC enzymes—have been detected. These enzymes, first identified in Colombia and encoded by plasmids or within integron cassettes, include KPC-2, KPC-3, KPC-4, and KPC-10 (Hsu et al., 2017; de Souza et al., 2025) Bacteria producing the aforementioned enzymes were also isolated in hospitals in Puerto Rico as early as 2009. Other class A enzymes conferring carbapenem resistance in *Acinetobacter baumannii* are GES enzymes, including GES-5, which was isolated in 2010 from patients in a hospital in Riyadh (Gupta et al., 2022). Although the structural differences between GES-1 and GES-5 are not substantial, the presence of a serine residue at position 170 in GES-5, stabilizing the hydrogen bond with glutamate instead of glycine as in GES-1, significantly influences the enzymatic activity as a carbapenemase, making GES-5 more than 100 times more active in hydrolyzing imipenem (Smith et al., 2012). Genes encoding β-lactamases of this group in

Acinetobacter baumannii may be located on plasmids in the *bla*$_{GES-11}$ and *bla*$_{GES-12}$ variants; however, reports of the chromosomal *bla*$_{GES-14}$ variant have also been described (Gupta et al., 2022).

Another group of class A enzymes includes PER enzymes, which, although primarily characterized as extended-spectrum β-lactamases, may complicate the selection of therapeutic options. PER-1 has been associated with decreased susceptibility through cefiderocol hydrolysis, which frequently represents an alternative therapeutic option in infections caused by multidrug-resistant Gram-negative bacilli (de Souza et al., 2025; Yousefi et al., 2024). Four studies demonstrated that the prevalence of the *bla*$_{PER-1}$ gene ranged from 20.9% to 24.6%, respectively (Kilbas et al., 2023). Other class A enzymes whose gene detection may be useful in clinical practice and epidemiological monitoring include the TEM, VEB, and SVH groups (Kyriakidis et al., 2021).

3.1.1.2. Class B

Enzymes belonging to class B, also referred to as metallo-β-lactamases, possess carbapenemase activity capable of hydrolyzing virtually all β-lactam antibiotics except aztreonam. Zinc ions are essential for their enzymatic activity, distinguishing them from other β-lactamase classes. This class is divided into three subgroups, B1 to B3, and includes enzymes such as NDM, VIM, and IMP, as well as enzymes less characteristic for *A. baumannii*, including GIM, SPM, AIM, DIM, TMB, and FIM (Karampatakis et al., 2025, p.7). Enzymes of the B1 and B3 subgroups contain two zinc ions within their molecular structure.

The first coordinatively interacts with the oxygen atom of the substrate carbonyl group, whereas the second interacts with the carboxylate anion, which, together with the additional participation of amino acid residues, significantly stabilizes the enzyme–substrate structure during hydrolysis. In the case of B2 subgroup enzymes, stabilization is ensured by a single zinc ion (Wang & Chou, 2013). Unlike serine β-lactamases, the enzymatic mechanism is not associated with the formation of an acyl–enzyme intermediate but rather with the direct attack of a water molecule on the β-lactam ring (Wang & Chou, 2013; Smith et al., 2012).

This difference in the reaction mechanism determines the ineffectiveness of most β-lactamase inhibitors against these enzymes. Simultaneously, due to a different active-site fitting model, metallo-β-lactamases do not efficiently hydrolyze monobactams, making them a highly important therapeutic option.

Importantly, as previously mentioned, metallo-β-lactamase activity, unlike that of serine β-lactamases, is not inhibited by typical inhibitors such as clavulanic acid or sulbactam, but rather by chelating compounds such as EDTA and 1,10-o-phenanthroline. Compared with oxacillinases, which occur more frequently in *Acinetobacter spp*., MBL activity against carbapenems is 100 to 1000 times greater (Hsu et al., 2017; Gupta et al., 2022). These enzymes are encoded by mobile DNA elements, including plasmids and integrons, facilitating their transfer between different Gram-negative bacteria (Kyriakidis et al., 2021). Some enzyme variants exhibit characteristic endemic distribution. VIM-1 and VIM-4 are most commonly identified in Greece, whereas VIM-2 predominates in South Korea. The presence of other enzymes, such as IMP-1, SIM-1, and SPM, has been described not only in South Korea but also in Iran and Morocco.

Although VIM-producing strains had been reported earlier and remained predominant for some time, NDM-1- and NDM-2-producing strains had already emerged by 2012 and subsequently spread, leading to numerous outbreaks associated with severe clinical courses (Karampatakis et al., 2025). These metallo-β-lactamases, capable of efficiently hydrolyzing virtually all β-lactams, including cefiderocol, are usually plasmid-encoded by the *bla*$_{NDM}$ gene, thereby creating favorable conditions for the dissemination of infections, although the prevalence of this gene in the United States and Europe has been estimated to remain below 2% (Spernovasilis et al., 2025; Karruli et al., 2023).

Notably, the genes encoding these enzymes were particularly frequently detected in strains originating from India, where they were associated with pneumonia, catheter-related infections, and bacteremia, with mortality exceeding 50% (Jean et al., 2022). A similar situation involving a *bla*$_{NDM-1}$-positive clone causing high-mortality infections was described in a study from Pakistan (Jiang et al., 2022), emphasizing the highly dangerous nature of this phenomenon. It should be noted that phenotypic detection of MBL-producing organisms is insufficiently sensitive; therefore, next-generation molecular methods should primarily be used for this purpose (Kyriakidis et al., 2021).

3.1.1.3. Class C

Class C β-lactamases, similarly to class A and D enzymes, belong to serine enzymes. Expression of genes associated with the production of enzymes of this class may be constitutive or inducible, whereas the localization of encoding genes may be either chromosomal or plasmid-mediated (Taesoongnern et al., 2025).

These β-lactamases are capable of hydrolyzing substrates across an extended spectrum of β-lactams. An example is the cephalosporinase enzyme ADC, chromosomally encoded and naturally occurring in *A.*

baumannii strains (Karampatakis et al., 2025; Kyriakidis et al., 2021). It should be noted that these enzymes generally do not hydrolyze carbapenems; however, the β-lactamase ADC-68 has been identified as possessing carbapenemase activity, which has been experimentally confirmed (de Souza et al., 2025; Karampatakis et al., 2025). Nevertheless, the absence of direct hydrolytic activity against carbapenems in most enzymes of this group is not without significance in the context of selecting targeted therapy.

3.1.1.4. Class D

Class D β-lactamases mainly include enzymes exhibiting hydrolytic activity against oxacillin, referred to as oxacillinases. In *Acinetobacter baumannii*, numerous subgroups belonging to this enzyme class are present, including subgroup (i) enzymes: OXA-23, OXA-27, OXA-49, and OXA-239; subgroup (ii): OXA-24, OXA-25, OXA-26, OXA-40, and OXA-72; subgroup (iii): OXA-51; subgroup (iv): OXA-58; and subgroup (v): OXA-143 and OXA-231 (Hsu et al., 2017, p.4).

Despite the natural production of OXA-51 enzymes by *A. baumannii*, other enzymes such as OXA-23, OXA-40, and OXA-58, which are encoded by acquired genes, are of greater significance in the context of clinically relevant carbapenem resistance. Simultaneously, certain genetic mechanisms associated with mobile elements such as *ISAba1* may enhance OXA-51 expression, resulting in a substantial increase in carbapenem resistance (Iovleva et al., 2025; de Souza et al., 2025).

OXA-23, discovered in 1985, has spread globally and remains the dominant enzyme described in international studies. Production of this oxacillinase depends on the $bla_{\text{OXA-23}}$-like gene, and one study demonstrated that a strain acquiring this gene via a plasmid also exhibited overexpression of the AdeABC efflux pump, suggesting that the aforementioned gene may be associated with other genetic resistance mechanisms (Boutzoukas & Doi, 2025,; Ibrahim et al., 2021).

Strains producing the OXA-58 enzyme encoded by the $bla_{\text{OXA-58}}$ gene have been isolated in various countries, including the United States, the United Kingdom, Greece, and Italy, although with varying prevalence (Thacharodi et al., 2024). Although sulbactam resistance has been associated with the dissemination of OXA-23-producing strains, the introduction of durlobactam, a non-β-lactam inhibitor, significantly restores its effectiveness (Karruli et al., 2023).

3.1.2. Efflux Pumps

One of the non-enzymatic resistance mechanisms of *A. baumannii* involves efflux pumps, which are transmembrane proteins that use active transport to remove compounds toxic to the bacterium, including antibiotics, from the bacterial cell (Jiang et al., 2022; Taesoongnern et al., 2025). Among the thoroughly characterized pumps are the AdeABC, AdeFGH, and AdeIJK systems. In the context of carbapenem resistance, the most significant described pump is AdeABC, whose production is regulated by the *adeRS* gene. Together with oxacillinase production, efflux pump overexpression contributes to high-level carbapenem resistance (Thacharodi et al., 2024).

3.1.3. Alterations in Membrane Permeability

Reduced expression or mutation of porin channels located in the bacterial outer membrane constitutes another mechanism underlying bacterial resistance. Their mode of action is opposite to that of efflux pumps because, firstly, they mediate transport into the cell and, secondly, they are involved in passive transport. Several outer membrane proteins exist, including CarO, HMP-AB, and OMP; however, particular emphasis is placed on the role of the CarO protein, with a molecular weight of approximately 25 kDa, in the context of carbapenem resistance due to its decreased expression (Thacharodi et al., 2024).

An additional factor influencing membrane permeability may involve alterations in pore charge or size resulting from mutations in the gene encoding a given protein, or structural modifications associated with the composition of lipopolysaccharide located within the outer membrane, ultimately leading to impaired antibiotic diffusion (Marino et al., 2024).

3.1.4. Target Site Modifications

Mutations associated with the target sites of antibiotic action constitute a resistance mechanism affecting both β-lactam antibiotics and fluoroquinolones; however, these mechanisms differ with regard to the aforementioned “target site.” In the case of fluoroquinolones, the target is the *gyrA* gene responsible for the production of the gyrase enzyme, resulting in decreased antibiotic affinity. For β-lactam antibiotics, the targets are penicillin-binding proteins (PBPs), and structural modifications of these proteins may contribute to decreased susceptibility to carbapenems; however, it should be emphasized that some described mutations did not produce such an effect (Taesoongnern et al., 2025).

3.1.5. Overexpression of Resistance Genes

The phenomenon of gene overexpression, repeatedly described in the resistance mechanisms discussed above, represents a particularly significant process frequently resulting in a marked increase in the quantity of produced enzymes. Resistance genes may be located on chromosomes as well as on plasmids transferred between bacteria through mechanisms of horizontal gene transfer (Franzone et al., 2024). Mobile genetic elements include insertion sequences, integrons, and resistance islands (Thacharodi et al., 2024).

Due to the therapeutic importance of cefiderocol in the treatment of *A. baumannii infections*, it is worth noting that overexpression of certain proteins associated with iron transport, caused for example by a frameshift mutation, consequently led to increased MIC values for this antibiotic (McCreary et al., 2021).

Owing to advances in bioinformatics technology, whole-genome sequencing has become widespread, providing enormous amounts of information for the analysis of resistance genes and phylogenetic studies, particularly concerning strains characterized by high epidemic potential (Hamidian & Nigro, 2019).

3.1.6. Biofilm

The last resistance mechanism discussed in this section is biofilm formation. It is exceptionally significant because it impairs antibiotic penetration, particularly that of large-molecule agents, thereby contributing to the protection of bacterial cell populations embedded within it (Marino et al., 2024).

In the case of CRAB strains, adhesion to central venous catheters and other types of medical devices represents an important factor associated both with the frequency of infections and with their severe clinical course. The use of disinfectants containing antibiotics leads to the selection of highly resistant strains, while the presence of biofilm additionally creates favorable conditions for the escalation of this phenomenon (Medioli et al., 2022). In both infection prevention and treatment, the importance of bacterial biofilm removal and environmental decontamination should not be overlooked (Medioli et al., 2022).

3.2. Treatment

3.2.1. β-lactam Antibiotics

3.2.1.1. Carbapenems

In the case of CRAB infections, carbapenems are generally not used as monotherapy. However, they may constitute a component of combination therapy, provided that they are administered at high concentrations and delivered by prolonged infusion. One possible combination involves the addition of colistin to carbapenem therapy, although it should be emphasized that some analyses did not demonstrate significant differences in endpoints associated with positive therapeutic outcomes compared with colistin monotherapy (Shields et al., 2023).

3.2.1.2. Ampicillin–Sulbactam

One of the recommended combinations of a β-lactam antibiotic with a β-lactamase inhibitor in the treatment of infections caused by Acinetobacter baumannii is ampicillin combined with sulbactam, a competitive, irreversible, semisynthetic β-lactamase inhibitor. It also exhibits activity against PBP1 and PBP3 (Iovleva et al., 2025; Najafabadi & Soltani, 2024; Doi, 2019). It is characterized by good penetration into the lower respiratory tract, which places it highly within recommendations concerning invasive CRAB infections (Iovleva et al., 2025). In the case of bacteremia, ampicillin–sulbactam may also be applied therapeutically, although in combination with a carbapenem (Mancuso et al., 2021). High antibiotic doses are recommended for treatment initiation in order to quantitatively overcome resistance mechanisms against this combination, which frequently result from the production of class C and D β-lactamases (Franzone et al., 2024).

3.2.1.3. Sulbactam–Durlobactam

The combination of sulbactam with durlobactam, a novel β-lactamase inhibitor belonging to the diazabicyclooctane group, represents another promising therapeutic option against CRAB. Durlobactam strongly inhibits class A, C, and D β-lactamases, although it remains ineffective against metallo-β-lactamases. Additionally, it acts on PBP2 proteins, with which sulbactam does not interact (Choi & Kim, 2024).

Studies investigating this combination demonstrated more than a 32-fold reduction in MIC values in the treatment of *A. baumannii* strains, half of which were carbapenem-resistant, compared with sulbactam alone, (Yahav et al., 2020) while high antibiotic doses did not result in significant electrocardiographic abnormalities (McLeod et al., 2024).

3.2.1.4. Cefiderocol

This antibiotic belongs to the group of a novel siderophore cephalosporins, exhibiting a mechanism of action typical for this class, although characterized by an atypical mode of transport into the microorganism. Its molecule contains a catechol moiety enabling binding of free iron ions, after which it penetrates the bacterial

cell through the iron transport system (Piperaki et al., 2019). In the periplasmic space, cefiderocol detaches from iron ions, after which its conventional β-lactam mechanism of action begins. It should be noted that this antibiotic is inactive against Gram-positive bacteria; however, it retains activity against Gram-negative bacteria, including certain carbapenem-resistant Acinetobacter baumannii strains (Choi & Kim, 2024).

Importantly, it should be emphasized that production of metallo-β-lactamases is in many cases associated with decreased susceptibility to this antibiotic; therefore, the decision to include it in therapy should also be guided by antibiogram results (Karruli et al., 2023).

3.2.1.5. Aztreonam + Avibactam

This represents one of the combinations of a β-lactam antibiotic with a β-lactamase inhibitor; however, it is exceptional because it contains the monobactam – aztreonam. This antibiotic is unique because aztreonam is resistant to the activity of metallo-β-lactamases such as VIM and NDM, while remaining susceptible to serine β-lactamases. Nevertheless, avibactam, acting as their inhibitor, provides protection for aztreonam.

According to official EMA guidelines from 2024, this combination may be applied in the treatment of intra-abdominal infections, complicated urinary tract infections, and hospital-acquired pneumonia (Karampatakis et al., 2025). In the absence of this antibiotic, simultaneous administration of ceftazidime–avibactam together with aztreonam is possible, which has been supported by studies involving *A. baumannii* strains producing metallo-β-lactamases (Yahav et al., 2020).

3.2.2. Non-β-lactam Therapies

3.2.2.1. Polymyxins

Five types of polypeptide antibiotics are distinguished within this group. In pharmacotherapy, the most commonly encountered are polymyxin B and polymyxin E—colistin. The mechanism of action of colistin involves disruption of outer membrane function through interaction with phospholipids, causing the bacterium to lose essential components such as amino acids and nucleic acids. It is important to note that colistin demonstrates less favorable pharmacokinetics and greater nephrotoxicity compared with polymyxin B, although the majority of studies are focused on colistin (Najafabadi & Soltani, 2024). Despite increasing resistance trends, polymyxins retain substantial *in vitro* activity against CRAB strains. Although therapeutic limitations associated with pharmacokinetics and the time required to achieve adequate concentrations within the body constitute one of the reasons for including this antibiotic as a component of combination therapy, scientific evidence in this area remains inconsistent, as some studies suggest similar effects in monotherapy (Piperaki et al., 2019).

3.2.2.2. Tigecycline

This antibiotic is a semisynthetic tetracycline derivative whose mechanism of action involves inhibition of protein synthesis through binding to the ribosome, specifically the 30S subunit (Iovleva et al., 2025). Although evidence confirming the efficacy of tigecycline remains controversial, it appears as a component of complex therapeutic regimens for CRAB infections. However, it should be emphasized that one feature limiting its application in monotherapy is the inability to achieve adequate concentrations in blood and pulmonary tissue. During high-dose therapy with this antibiotic, plasma fibrinogen concentrations should be monitored particularly carefully, as their reduction represents one possible toxic effect of the antibiotic (Piperaki et al., 2019).

3.2.2.3. Apramycin

One of the investigated therapeutic options against CRAB strains is the aminoglycoside antibiotic apramycin, currently used in veterinary medicine, particularly in the treatment of gastrointestinal infections in pigs and cattle (Gontijo et al., 2021).

In vitro studies demonstrated a very high susceptibility rate of carbapenem-resistant A. baumannii to this antibiotic, exceeding 80% at an MIC value of 32 μg/mL (Isler et al., 2018). However, it should also be noted that, to date, this antibiotic has not been approved for use in humans.

4. Discussion

The analysis of the information presented in the cited publications emphasizes that carbapenem-resistant *Acinetobacter baumannii* strains are among the pathogens requiring the highest level of attention due to the microorganism's characteristics facilitating the dissemination of infections, as well as the therapeutic difficulties resulting from resistance mechanisms, which collectively contribute to high mortality rates (Antimicrobial Resistance Collaborators, 2022; Medioli et al., 2022).

Carbapenem resistance itself, although numerous independent mechanisms responsible for its induction have been identified, depends largely on their coexistence (Iovleva et al., 2025; Thacharodi et al., 2024). The

classical resistance mechanism associated with β-lactamase production may be further enhanced by additional mechanisms, including alterations in membrane permeability and modifications of antibiotic target sites, thereby reducing the effectiveness of standard therapeutic regimens (Najafabadi & Soltani, 2024).

Oxacillinases, which belong to class D enzymes, represent one of the most frequently produced enzyme groups contributing to carbapenem resistance, particularly the globally distributed OXA-23 enzyme (Boutzoukas & Doi, 2025; Jiang et al., 2022). However, the lack of therapeutic benefit associated with carbapenem administration in strains producing this enzyme becomes particularly important when considering the presence of genes responsible for overexpression, such as insertion elements (Gupta et al., 2022). Identification of these genetic elements enables an approximate qualitative and quantitative assessment of resistance intensity. A similar situation applies to alterations in the quantity or structure of PBP proteins, resulting in a reduced number of target sites. In both of the aforementioned cases, knowledge of the molecular basis of resistance indicates that the use of standard antibiotic doses will not achieve therapeutic efficacy (Bartal et al., 2022).

Another approach to counteracting the effects of specific resistance mechanisms involves the addition of β-lactamase inhibitors, which suppress enzymatic activity, including through competitive inhibition mechanisms in which the inhibitor, rather than the antibiotic, acts as the enzyme substrate (Yahav et al., 2020). It should be emphasized that, in the case of metallo-β-lactamases, no widely available substance exhibiting *in vivo* inhibitory activity against these enzymes currently exists. Nevertheless, numerous novel molecules currently undergoing clinical investigation may become effective therapeutic agents in the future.

Certain inhibitors, such as sulbactam, additionally demonstrate activity against PBP1 and PBP3 proteins; therefore, combining them with another inhibitor, for example durlobactam, promotes an alternative mechanism of antibiotic action (McLeod et al., 2024).

Cefiderocol, although its mechanism of action does not differ substantially from that of other cephalosporins, differs significantly in terms of its transport pathway into the bacterial cell. Utilization of the iron ion transport system enables circumvention of certain resistance mechanisms that could otherwise render the antibiotic ineffective. Simultaneously, however, inappropriate use of the antibiotic, including inadequate dosing, may contribute to the dissemination among bacterial strains of compensatory mechanisms associated with iron transport-dependent pathways (Yousefi et al., 2024).

Despite the large number of available studies describing the mechanisms and origins of resistance in increasingly advanced contexts, continuously expanded by novel diagnostic and research capabilities, many questions related to infections caused by CRAB strains remain unanswered or ambiguous. There is still a lack of an adequate number of high-quality clinical studies upon which unequivocal therapeutic management schemes could be established (Onorato et al., 2024; Paul et al., 2022).

Although institutions dedicated to standardizing the diagnostic process for infections exist, some diagnostic methods demonstrate varying degrees of standardization, which appears to constitute one of the reasons for difficulties in result interpretation (Gupta et al., 2022).

5. Conclusions

Knowledge of the resistance mechanisms of *Acinetobacter baumannii* is of critical importance in selecting appropriate antibiotic therapy for infections caused by this bacterium. The multiplicity of these interacting factors frequently renders monotherapy insufficient; therefore, the appropriate application of multidrug regimens targeting different resistance mechanisms appears to increase the likelihood of therapeutic success.

Further systematization and expansion of knowledge, as well as the development of therapeutic management schemes, require a greater number of high-quality clinical studies, particularly concerning novel antimicrobial agents. This may contribute both to slowing the progression of resistance associated with inappropriate antibiotic therapy and to increasing the probability of achieving favorable treatment outcomes.

Owing to emerging technologies, molecular assessment of the resistance background, supporting therapeutic decision-making alongside antibiogram results, is becoming increasingly widespread and rapid. Furthermore, the continued development of international databases associated with these technologies represents substantial potential for improving epidemiological tools, which are critically needed for the analysis of this phenomenon on a global scale.

Conflict of Interest: The authors declare no conflict of interest.

AI: Artificial intelligence tools were used exclusively to support linguistic revision of the manuscript, particularly regarding academic English and microbiological scientific terminology. AI-generated suggestions were reviewed critically and implemented only under direct human supervision. All scientific interpretation, data synthesis, and final conclusions were independently prepared by the authors.

REFERENCES

1. Antimicrobial Resistance Collaborators. (2022). Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. *Lancet, 399*(10325), 629–655. https://doi.org/10.1016/S0140-6736(21)02724-0
2. Karruli, A., Migliaccio, A., Pournaras, S., Durante-Mangoni, E., & Zarrilli, R. (2023). Cefiderocol and sulbactam-durlobactam against carbapenem-resistant *Acinetobacter baumannii*. *Antibiotics, 12*(12), 1729. https://doi.org/10.3390/antibiotics12121729
3. Karampatakis, T., Tsergouli, K., & Behzadi, P. (2025). Carbapenem-resistant *Acinetobacter baumannii*: Virulence factors, molecular epidemiology, and latest updates in treatment options. *Microorganisms, 13*(9), 1983. https://doi.org/10.3390/microorganisms13091983
4. Iovleva, A., Fowler, V. G., Jr., & Doi, Y. (2025). Treatment approaches for carbapenem-resistant *Acinetobacter baumannii* infections. *Drugs, 85*(1), 21–40. https://doi.org/10.1007/s40265-024-02104-6
5. Zhang, S., Di, L., Qi, Y., Qian, X., & Wang, S. (2024). Treatment of infections caused by carbapenem-resistant *Acinetobacter baumannii*. *Frontiers in Cellular and Infection Microbiology, 14*, 1395260. https://doi.org/10.3389/fcimb.2024.1395260
6. Boutzoukas, A., & Doi, Y. (2025). The global epidemiology of carbapenem-resistant *Acinetobacter baumannii*. *JAC-Antimicrobial Resistance, 7*(4), dlaf134. https://doi.org/10.1093/jacamr/dlaf134
7. Ibrahim, S., Al-Saryi, N., Al-Kadmy, I. M. S., & Aziz, S. N. (2021). Multidrug-resistant *Acinetobacter baumannii* as an emerging concern in hospitals. *Molecular Biology Reports, 48*(10), 6987–6998. https://doi.org/10.1007/s11033-021-06690-6
8. Shields, R. K., Paterson, D. L., & Tamma, P. D. (2023). Navigating available treatment options for carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex infections. *Clinical Infectious Diseases, 76*(Suppl. 2), S179–S193. https://doi.org/10.1093/cid/ciad094
9. Kyriakidis, I., Vasileiou, E., Pana, Z. D., & Tragiannidis, A. (2021). *Acinetobacter baumannii* antibiotic resistance mechanisms. *Pathogens, 10*(3), 373. https://doi.org/10.3390/pathogens10030373
10. Gupta, N., Angadi, K., & Jadhav, S. (2022). Molecular characterization of carbapenem-resistant *Acinetobacter baumannii* with special reference to carbapenemases: A systematic review. *Infection and Drug Resistance, 15*, 7631–7650. https://doi.org/10.2147/IDR.S386641
11. Hsu, L. Y., Apisarnthanarak, A., Khan, E., Suwantarat, N., Ghafur, A., & Tambyah, P. A. (2017). Carbapenem-resistant *Acinetobacter baumannii* and Enterobacteriaceae in South and Southeast Asia. *Clinical Microbiology Reviews, 30*(1), 1–22. https://doi.org/10.1128/CMR.masthead.30-1
12. de Souza, J., D'Espindula, H. R. S., Ribeiro, I. F., Gonçalves, G. A., Pillonetto, M., & Faoro, H. (2025). Carbapenem resistance in *Acinetobacter baumannii*: Mechanisms, therapeutics, and innovations. *Microorganisms, 13*(7), 1501. https://doi.org/10.3390/microorganisms13071501
13. Smith, C. A., Frase, H., Toth, M., Kumarasiri, M., Wiafe, K., Munoz, J., Mobashery, S., & Vakulenko, S. B. (2012). Structural basis for progression toward the carbapenemase activity in the GES family of β-lactamases. *Journal of the American Chemical Society, 134*(48), 19512–19515. https://doi.org/10.1021/ja308197j
14. Yousefi, B., Kashanipoor, S., Mazaheri, P., Alibabaei, F., Babaeizad, A., Asli, S., Mohammadi, S., Gorgin, A. H., Alipour, T., Oksenych, V., & Eslami, M. (2024). Cefiderocol in combating carbapenem-resistant *Acinetobacter baumannii*: Action and resistance. *Biomedicines, 12*(11), 2532. https://doi.org/10.3390/biomedicines12112532
15. Kilbas, E. P. K., Kilbas, I., & Ciftci, I. H. (2023). Molecular epidemiology of carbapenem-resistant *Acinetobacter baumannii* isolates in Turkiye: Systematic review. *Northern Clinics of Istanbul, 10*(4), 531–539. https://doi.org/10.14744/nci.2022.17003
16. Wang, J. F., & Chou, K. C. (2013). Metallo-β-lactamases: Structural features, antibiotic recognition, inhibition, and inhibitor design. *Current Topics in Medicinal Chemistry, 13*(10), 1242–1253. https://doi.org/10.2174/15680266113139990011
17. Spernovasilis, N., Ishak, A., Tsioutis, C., Alon-Ellenbogen, D., Agouridis, A. P., & Mazonakis, N. (2025). Sulbactam for carbapenem-resistant *Acinetobacter baumannii* infections: A literature review. *JAC-Antimicrobial Resistance, 7*(2), dlaf055. https://doi.org/10.1093/jacamr/dlaf055
18. Jean, S. S., Harnod, D., & Hsueh, P. R. (2022). Global threat of carbapenem-resistant gram-negative bacteria. *Frontiers in Cellular and Infection Microbiology, 12*, 823684. https://doi.org/10.3389/fcimb.2022.823684

19. Jiang, Y., Ding, Y., Wei, Y., Jian, C., Liu, J., & Zeng, Z. (2022). Carbapenem-resistant *Acinetobacter baumannii*: A challenge in the intensive care unit. *Frontiers in Microbiology, 13*, 1045206. https://doi.org/10.3389/fmicb.2022.104520
20. Taesoongnern, K., Thirapanmethee, K., & Chomnawang, M. T. (2025). Molecular sequence typing of carbapenem-resistant *Acinetobacter baumannii* clinical isolates: A comprehensive global update. *Infection, Genetics and Evolution, 131*, 105762. https://doi.org/10.1016/j.meegid.2025.105762
21. Thacharodi, A., Vithlani, A., Hassan, S., Alqahtani, A., & Pugazhendhi, A. (2024). Carbapenem-resistant *Acinetobacter baumannii* raises global alarm for new antibiotic regimens. *iScience, 27*(12), 111367. https://doi.org/10.1016/j.isci.2024.111367
22. Marino, A., Augello, E., Stracquadanio, S., Bellanca, C. M., Cosentino, F., Spampinato, S., Cantarella, G., Bernardini, R., Stefani, S., Cacopardo, B., & Nunnari, G. (2024). Unveiling the secrets of *Acinetobacter baumannii*: Resistance, current treatments, and future innovations. *International Journal of Molecular Sciences, 25*(13), 6814. https://doi.org/10.3390/ijms25136814
23. McCreary, E. K., Heil, E. L., & Tamma, P. D. (2021). New perspectives on antimicrobial agents: Cefiderocol. *Antimicrobial Agents and Chemotherapy, 65*(8), e0217120. https://doi.org/10.1128/AAC.02171-20
24. Franzone, J. P., Mackow, N. A., & van Duin, D. (2024). Current treatment options for pneumonia caused by carbapenem-resistant *Acinetobacter baumannii*. *Current Opinion in Infectious Diseases, 37*(2), 137–143. https://doi.org/10.1097/QCO.0000000000001001
25. Hamidian, M., & Nigro, S. J. (2019). Emergence, molecular mechanisms, and global spread of carbapenem-resistant *Acinetobacter baumannii*. *Microbial Genomics, 5*(10), e000306. https://doi.org/10.1099/mgen.0.000306
26. Medioli, F., Bacca, E., Faltoni, M., Burastero, G. J., Volpi, S., Menozzi, M., Orlando, G., Bedini, A., Franceschini, E., Mussini, C., & Meschiari, M. (2022). Is it possible to eradicate carbapenem-resistant *Acinetobacter baumannii* (CRAB) from endemic hospitals? *Antibiotics, 11*(8), 1015. https://doi.org/10.3390/antibiotics11081015
27. Doi, Y. (2019). Treatment options for carbapenem-resistant gram-negative bacterial infections. *Clinical Infectious Diseases, 69*(Suppl. 7), S565–S575. https://doi.org/10.1093/cid/ciz830
28. Mancuso, G., Midiri, A., Gerace, E., & Biondo, C. (2021). Bacterial antibiotic resistance: The most critical pathogens. *Pathogens, 10*(10), 1310. https://doi.org/10.3390/pathogens10101310
29. Choi, S. J., & Kim, E. S. (2024). Optimizing treatment for carbapenem-resistant *Acinetobacter baumannii* complex infections: A review of current evidence. *Infection & Chemotherapy, 56*(2), 171–187. https://doi.org/10.3947/ic.2024.0055
30. Yahav, D., Giske, C. G., Grāmatniece, A., Abodakpi, H., Tam, V. H., & Leibovici, L. (2020). New β-lactam–β-lactamase inhibitor combinations. *Clinical Microbiology Reviews, 34*(1), e00115-20. https://doi.org/10.1128/CMR.00115-20
31. McLeod, S. M., O'Donnell, J. P., Narayanan, N., Mills, J. P., & Kaye, K. S. (2024). Sulbactam-durlobactam: A β-lactam/β-lactamase inhibitor combination targeting *Acinetobacter baumannii*. *Future Microbiology, 19*(7), 563–576. https://doi.org/10.2217/fmb-2023-0248
32. Piperaki, E. T., Tzouvelekis, L. S., Miriagou, V., & Daikos, G. L. (2019). Carbapenem-resistant *Acinetobacter baumannii*: In pursuit of an effective treatment. *Clinical Microbiology and Infection, 25*(8), 951–957. https://doi.org/10.1016/j.cmi.2019.03.014
33. Najafabadi, M. K., & Soltani, R. (2024). Carbapenem-resistant *Acinetobacter baumannii* and ventilator-associated pneumonia: Epidemiology, risk factors, and current therapeutic approaches. *Journal of Research in Pharmacy Practice, 13*(2), 33–40. https://doi.org/10.4103/jrpp.jrpp_50_24
34. Gontijo, A. V. L., Pereira, S. L., & de Lacerda Bonfante, H. (2021). Can drug repurposing be effective against carbapenem-resistant *Acinetobacter baumannii*? *Current Microbiology, 79*(1), 13. https://doi.org/10.1007/s00284-021-02693-5
35. Isler, B., Doi, Y., Bonomo, R. A., & Paterson, D. L. (2018). New treatment options against carbapenem-resistant *Acinetobacter baumannii* infections. *Antimicrobial Agents and Chemotherapy, 63*(1), e01110-18. https://doi.org/10.1128/AAC.01110-18
36. Bartal, C., Rolston, K. V. I., & Nesher, L. (2022). Carbapenem-resistant *Acinetobacter baumannii*: Colonization, infection, and current treatment options. *Infectious Diseases and Therapy, 11*(2), 683–694. https://doi.org/10.1007/s40121-022-00597-w
37. Onorato, L., de Luca, I., Monari, C., & Coppola, N. (2024). Cefiderocol either in monotherapy or combination versus best available therapy in the treatment of carbapenem-resistant *Acinetobacter baumannii* infections: A systematic review and meta-analysis. *The Journal of Infection, 88*(3), 106113. https://doi.org/10.1016/j.jinf.2024.01.012
38. Paul, M., Carrara, E., Retamar, P., Tängdén, T., Bitterman, R., Bonomo, R. A., de Waele, J., Daikos, G. L., Akova, M., Harbarth, S., Pulcini, C., Garnacho-Montero, J., Seme, K., Tumbarello, M., Lindemann, P. C., Gandra, S., Yu, Y., Bassetti, M., Mouton, J. W., Tacconelli, E., … Rodríguez-Baño, J. (2022). European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant gram-negative bacilli endorsed by European Society of Intensive Care Medicine. *Clinical Microbiology and Infection, 28*(4), 521–547. https://doi.org/10.1016/j.cmi.2021.11.025