Review Article

Carbapenem-resistant *Acinetobacter baumannii* and Ventilator-associated Pneumonia; Epidemiology, Risk Factors, and Current Therapeutic Approaches

Malihe Kazemi Najafabadi[1], *Rasool Soltani*[1,2]

[1]Department of Clinical Pharmacy and Pharmacy Practice, Isfahan University of Medical Sciences, Isfahan, Iran

[2]Infectious Diseases and Tropical Medicine Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Received: 23-02-2024.
Revised: 07-05-2024.
Accepted: 25-05-2024.
Published: 23-12-2024.

Abstract

Acinetobacter baumannii is one of the primary pathogens responsible for healthcare-associated infections. It is related to high rates of morbidity and mortality globally, mainly because of its high capacity to develop resistance to antimicrobials. Nowadays, carbapenem-resistant *A. baumannii* (CRAB) has increased and represents a significant concern among carbapenem-resistant organisms. It is also a key pathogen associated with ventilator-associated pneumonia. CRAB was placed on the critical group of the universal priority list of the World Health Organization for antibiotic-resistant bacteria, to mention the importance of research development and the urgency of new antibiotics. Patients with severe CRAB infections currently face significant treatment challenges. Some approaches have been taken to deal with CRAB, such as combination therapy and the synergistic effect of certain antibiotics, but the best antibiotic regimen is still unknown. In this narrative review, we attempt to clarify the issues, including epidemiology, risk factors, and current treatment options for CRAB.

Keywords: *Carbapenem-resistant Acinetobacter baumannii, combination therapy, ventilator-associated pneumonia*

Introduction

Acinetobacter baumannii is a Gram-negative opportunistic microorganism that belongs to the Moraxellaceae family and is regarded as a life-threatening pathogen associated with severe community-acquired and nosocomial infections, including meningitis, sepsis, and pneumonia.[1] The most common nosocomial infection associated with *A. baumannii* is pneumonia, mainly in patients admitted to intensive care units (ICUs) and who have undergone mechanical ventilation. As is widely known, the use of mechanical ventilation is strongly associated with the occurrence of ventilator-associated pneumonia (VAP). The mortality rate from *A. baumannii*-related VAP is high, ranging from 45% to 70%. Over the last decades, this pathogen has become a significant concern for scientific attention due to extensive antimicrobial resistance. It has been related to substantial morbidity, mortality, and increased cost due to both prolonged length of hospitalization and treatment.[2,3] Carbapenem-resistant *A. baumannii* (CRAB) is a significant concern among carbapenem-resistant organisms, a global threat to human health, and a severe therapeutic challenge. It is also a key pathogen associated with VAP.[4] Carbapenem resistance is usually associated with a broad range of co-resistance to other antibiotic classes.[5] In 2017, CRAB was placed on the critical group of the universal priority list of the World Health Organization for antibiotic-resistant bacteria, to mention the importance of research development and the urgency of new antibiotics.[6] Unlike other antibiotic-resistant pathogens, CRAB poses a significant therapeutic challenge due to a lack of established treatment options to substantially lower mortality or significantly improve the outcome of patients with invasive infections.[7,8] Some approaches

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jrpp

DOI: 10.4103/jrpp.jrpp_50_24

Address for correspondence:
Dr. Rasool Soltani,
E-mail: soltani@pharm.mui.ac.ir

How to cite this article: Najafabadi MK, Soltani R. Carbapenem-resistant *Acinetobacter baumannii* and ventilator-associated pneumonia; epidemiology, risk factors, and current therapeutic approaches. J Res Pharm Pract 2024;13:33-40.

have been taken to deal with CRAB, such as combination therapy and using the synergistic effect of certain antibiotics with colistin and ampicillin/sulbactam against this pathogen.[9,10] In this narrative review, we attempt to clarify the issues, including epidemiology, risk factors, and current treatment options for CRAB.

Epidemiology

The *Acinetobacter* genus consists of over 50 species, is most ubiquitous in the natural environment, has low pathogenicity, and is most commonly found in soil and water.[11] *Acinetobacter* accounts for approximately 2% of nosocomial infections in the USA, but these rates are doubled in Asia and the Middle East, with up to 20% of infections in ICUs worldwide.[12,13] Of these, *A. baumannii* is the most well-studied genus due to its notable role in human infections and its high capacity for extensive antibiotic resistance. It is found almost exclusively in the hospital environment, particularly in ICUs.[14] As a significant pathogen in nosocomial infections in ICUs, *A. baumannii* has a high carbapenem resistance rate ranging from 50% in North America to 80% in Asia.[15] Data from the Antimicrobial Surveillance Network (CHINET) showed that the proportion of *A. baumannii* strains resistant to meropenem and imipenem increased from 30.1% and 39.0% (2005) to 71.5% and 72.3% (2021), respectively.[16] Approximately 55% of CRAB infections involve the respiratory system.[17] In a study conducted over 46 months, Lambiase *et al*. demonstrated that *A. baumannii* isolated from patients with VAP in ICUs were resistant to carbapenem with imipenem minimum inhibitory concentration (MIC) ≥16 μg/ml.[18] A retrospective study conducted from 2014 to 2017 found that the rate of isolation of CRAB from the sputum of ICU patients was specifically higher than that of non-ICU patients, and the resistance rate of CRAB showed a significantly rising trend.[19] Similarly, 80% of CRAB in ICUs were isolated from sputum specimens, and CRAB comprised more than 50% of carbapenem-resistant Gram-negative bacilli.[20] Another study showed that *A. baumannii* isolates exhibited imipenem or meropenem MICs ≥16 μg/ml, especially in pulmonary infections.[21]

The overall prevalence of multidrug-resistant (MDR) strains in patients with *A. baumannii* and VAP is estimated to be 79.9%, ranging from 56.5% in Argentina and 61.8% in Taiwan to 100% in Central America, Pakistan, Lebanon, Qatar, and Croatia. In comparison, its overall mortality can be as high as 56.2%.[22] The patterns of carbapenem resistance differ throughout Europe and also within the countries of the Arab League. Increased incidence of CRAB isolates has been observed in Northern and Eastern Europe and the Levant countries of the Arab League (Iraq, Jordan, Lebanon, Palestinian territories, and Syria).[23]

Notably, as CRAB isolates have increased in recent years, the prevention of risk factors of CRAB infections has received growing attention to reduce the risk of mortality, length of hospitalization, and associated costs.[24]

Risk Factors

Traditionally, two kinds of risk factors for nosocomial pneumonia caused by CRAB have been considered, including patient-related, infection prevention-related, and procedure-related factors as follows:

Patient-related

Acute or chronic severe disease, coma, malnutrition, prolonged hospital stays (≥14 days), hypotension, metabolic acidosis, smoking, alcohol consumption, comorbidities such as asthma, chronic obstructive pulmonary disease, diabetes, heart disease, advanced age, poor dental hygiene, a higher APACHE II score (≥16), severe burns, severity of illness.

Procedure-related

Administration of sedatives, corticosteroids, and other immunosuppressants, recent surgery or prolonged invasive procedures (especially at thoracic or abdominal level), a prolonged/inappropriate recent receipt of broad-spectrum anti-bacterial agents, intravascular devices, mechanical ventilation, presence of viral infections that compromise the respiratory tract and results in secondary bacterial colonization, admission to ICUs, contact with contaminated hospital equipment.[25-28]

Current therapeutic approaches

Due to the increase in antibiotic resistance, particularly among Gram-negative bacilli such as *A. baumannii*, the selection of empiric antibiotic therapy is complex for physicians. Patients with severe CRAB infections currently face significant treatment challenges. When patients display signs of infection, and the clinical suspicion of CRAB infection is high, appropriate treatment should be immediately provided. Unfortunately, current treatment models for CRAB are limited[29] due to antimicrobial resistance. Several mechanisms are responsible for the resistance of CRAB, such as the modification of its outer membrane, efflux pumps, resistance acquisition, and the formation of biofilms.[30] Antimicrobial optimization programs, such as the US Antimicrobial Stewardship Programs, aim to improve the clinical outcomes of patients

with nosocomial infections, minimizing side effects associated with the use of antimicrobials (including the onset and dissemination of resistance) and guaranteeing the use of cost-effective treatments.[31] Due to the limited number of antibiotics and diversity of host factors, experts have still not reached a consensus on the optimal treatment of CRAB infections. These conditions have forced clinicians to consider combination therapy. The advantages of a combination antimicrobial regimen, such as a reduction in therapeutic doses and a decrease in side effects and drug toxicity, appear to predominate those of a single regimen.[29] In the treatment of infections with limited therapeutic options and high mortality rates, such as CRAB, there is no clear superior choice of antibiotic, and it is prevalent to combine antibiotics.[32] Most clinicians prefer the use of combination therapy with agents that are individually active against this pathogen. The following sections describe current therapeutic approaches for infections caused by CRAB.

β-lactam/β-lactamase inhibitors

β-lactamase inhibitors, including clavulanic acid, sulbactam, and tazobactam, protect the β-lactam ring. Sulbactam is an irreversible competitive beta-lactamase inhibitor that can saturate penicillin-binding proteins (PBP) 1 and 3 when given in high doses and is commercially available in combination with ampicillin (a β-lactam antibiotic).[33] Although historically, ampicillin-sulbactam has been effective in treating VAP and other nosocomial infections caused by *A. baumannii*,[34] clinical resistance is increasing, and a combination of sulbactam and β-lactam antibiotics with other antibiotics has gradually become an increasingly popular choice for treating patients with CRAB infections.[35] In clinical practice, antibiotics such as polymyxins, tigecycline, minocycline, and doxycycline are typically selected for combination with sulbactam and β-lactam antibiotics based on antibiotic susceptibility testing.[36] Several clinical trials have evaluated the activity of sulbactam in combination with other antibiotics, such as fosfomycin,[37] minocycline,[38] aminoglycosides,[39] and colistin.[40] In a study conducted in 2018 by Khalili *et al*., the combination of meropenem and ampicillin/sulbactam had more curative effects than the meropenem-colistin combination in patients with severe pneumonia caused by CRAB, suggesting that ampicillin/sulbactam was an efficient treatment option for CRAB infections.[41] A systematic review reported that high-dose sulbactam (more than 6 g per day) combined with levofloxacin or tigecycline had an increased curative effect and that high-dose ampicillin-sulbactam (more than 18 g per day) combined with other drugs effectively reduced the mortality of patients with severe CRAB infections.[42] Makris *et al*. compared colistin monotherapy (n = 19) with colistin plus ampicillin/sulbactam (16/8 g daily) (n = 20) in patients with CRAB-related VAP. The 5-day clinical response, defined as an improvement of symptoms for at least 48 h, occurred in 15.8% (3/19) of patients receiving colistin monotherapy and 70% (14/20) of those receiving colistin-ampicillin/sulbactam combination therapy, respectively (odds ratio, 12.4; 95% confidence interval [CI], 2.6–59.3; P = 0.01).[43] In South Korea, a multicenter study on CRAB treatment strategies revealed that ampicillin/sulbactam treatment exhibited the lowest 7-day mortality rate (13%) and reduced the 28-day mortality rates in patients.[44] Thus, these data show that sulbactam-containing combination therapies have clinical benefits. Usually, due to the intrinsic activity of sulbactam, combination therapy of sulbactam resulted in increased efficacy of infection treatment.[33,45] Furthermore, there is evidence that even though CRAB may demonstrate laboratory non-susceptibility to ampicillin-sulbactam, providing high-dose ampicillin-sulbactam may still be an effective therapy *in vivo* through PBP saturation.[46]

Polymyxins

Polymyxins are polypeptide antibiotics classified into five types: A, B, C, D, and E, and have anti-CRAB effects. Polymyxin B has better pharmacokinetics and lower nephrotoxicity than polymyxin E (colistin); however, most studies on polymyxins have focused on colistin. Colistin destroys the permeability of the bacteria's outer membrane. It causes essential substances, such as amino and nucleic acids, to leak out of the bacteria by binding the positively charged free amino group in its molecule to the negatively charged phosphate group in the phospholipids of the cell membrane of Gram-negative pathogens, resulting in bacterial death.[32] Despite its nephrotoxicity, colistin, combined with other potent agents, such as tigecycline, ampicillin/sulbactam, meropenem, and fosfomycin, are valuable options for treating CRAB.[47] In a study conducted in 2018 by Park *et al*., the combination of colistin/rifampin was influential in the treatment of VAP caused by CRAB, so that microbiological response in the combination group was 100% in comparison to 40% in the group that received colistin alone. Still, only nine patients participated in this study, and the number of patients was minimal.[48] In another study conducted in 2012 by Aydemir *et al*., although the combination of colistin/rifampin versus colistin alone improved clinical, laboratory, radiological, and microbiological response rates in VAP patients caused by CRAB, none of these differences were statistically significant.[49] Several retrospective studies have demonstrated the effect of a colistin-combined regimen versus a tigecycline-combined

regimen for CRAB so that the colistin-combined regimen had lower mortality and clinical treatment failure rates than the tigecycline-combined regimen; however, it had a higher incidence of side effects such as nephrotoxicity.[50] Colistin combined with meropenem and high-dose ampicillin-sulbactam is another combination successfully used to treat VAP caused by CRAB.[51] In conclusion, colistin, combined with at least one other potent agent, is one of the best current options for treating CRAB infections.

Minocycline

Minocycline is a tetracycline derivative with bactericidal activity against *A. baumannii*, including CRAB, and may act synergistically when combined with other agents such as colistin, rifampin, and carbapenems.[52,53] Studies have demonstrated that intravenous minocycline injections yield a better clinical cure rate than their oral dosage form, are well tolerated in patients infected with CRAB isolates, and are recommended to be given at a high dose of 200 mg every 12 h.[54] Goff *et al*. treated 55 patients infected with MDR *A. baumannii* with minocycline, three with monotherapy, and 52 with minocycline in combination with other drugs, resulting in the successful treatment of 73% of patients. Although treatment with minocycline alone is effective, it is recommended that clinicians use this drug in combination regimens to prevent the development of resistance.[55] In an *in vitro* pharmacodynamic model, a regimen of polymyxin B and high-dose minocycline combined with continuous-infusion sulbactam exhibited the most potent bactericidal effect on CRAB isolates, with no regeneration or minimal resistance development.[56] The curative effect of minocycline on CRAB is efficient; however, this regimen is not preferred because of potential adverse reactions in the gastrointestinal tract and vestibular system. If chosen, a combination of sulbactam with minocycline should be considered, with a recommended dose of 200 mg administered every 12 h.[29]

Tigecycline

Tigecycline is a glycyl tetracycline-based antibiotic that, as a derivative of minocycline, has activity against CRAB. It can achieve high concentrations in several tissues of the body. For example, the drug's concentration in the lungs is two times higher than that in the serum.[36] To enhance the curative effect in infected patients, therapy should be started with a 200 mg loading dose followed by 100 mg every 12 h. A high-dose regimen safely increases plasma and pulmonary concentrations rather than conventional dosing.[57]

Carbapenems

Carbapenem antibiotics have the broadest antibacterial spectrum among β-lactam antibiotics. They inhibit PBP, thus hindering the synthesis of cell wall mucopeptide and causing bacterial cell wall defects and bacterial plasma osmotic pressure changes, dissolution, and killing. Currently, carbapenem antibiotics, including imipenem and meropenem, are primarily used in clinical practice.[29] Meropenem is the most intensively evaluated antibiotic for combination with colistin. Two large randomised controlled trials (RCTs) revealed no significant differences in clinical outcomes between colistin monotherapy and colistin plus meropenem combination therapy. In the OVERCOME trial conducted from October 2012 to August 2020, hospitals in seven countries (the US, Thailand, Taiwan, Israel, Greece, Italy, and Bulgaria) recruited 329 patients with pneumonia or bacteremia caused by carbapenem-resistant Gram-negative bacteria (GNB). The primary outcome was all-cause 28-day mortality, and secondary outcomes included clinical and microbiological failure. Subgroup analysis for CRAB infections showed that there was no difference between colistin monotherapy and colistin plus meropenem combination therapy in 28-day mortality (76/165 vs. 69/164; 95% CI, −6.7–14.7), clinical failure (95/140 vs. 88/146; 95% CI, −35–18.7), and microbiological failure (76/121 vs. 74/130; 95% CI, −7.2–25.3).[58] In the AIDA trial conducted from October 2013 to December 2016, six hospitals in Israel, Greece, and Italy recruited 406 patients with invasive carbapenem-resistant GNB infections, 76.8% (312/406) of whom were infected with CRAB. 96.9% (281/290) of clinical isolates exhibited a meropenem MIC over eight μg/mL. The sites of infection were bacteremia (42.6%, 173/406), pneumonia (51.0%, 207/406), and urinary tract infections (6.4%, 26/406). The primary outcome was clinical success 14 days after randomization, defined as a composite of improved or stable PaO_2 (for pneumonia only) and microbiological cure (for bacteremia only). Secondary outcomes included 14- and 28-day mortality rates. No significant difference was observed between colistin monotherapy and combination therapy for clinical failure (125/151 vs. 130/161; relative risk [RR], 0.97; 95% CI, 0.87–1.09), 14-day mortality (54/151 vs. 62/161; RR, 1.11; 95% CI, 0.82–1.52), and 28-day mortality (70/151 vs. 84/161; RR, 1.11; 95% CI, 0.87–1.41).[8] Based on these two large-scale RCTs, the Infectious Diseases Society of America and the European Society of Clinical Microbiology and Infectious Diseases guidelines do not recommend colistin and meropenem combination therapy for CRAB infections.[59,60] However, three-drug combinations with other potentially active antibiotics,

such as ampicillin/sulbactam or tigecycline, plus colistin and meropenem, could be considered a treatment option for CRAB infections. Three-drug combination therapy has been studied in *in-vitro* infection models[46,61] and in limited clinical studies.[62,63] Further research on the three-drug combination therapy is necessary to establish robust evidence.

Aminoglycosides

Aminoglycosides such as amikacin exhibit *in vitro* antibacterial activity against CRAB and are another choice to treat CRAB infections. However, because of their high resistance rate and side effects, such as renal toxicity, their clinical use is limited, and they are not the preferred treatment option.[64] In a multicenter study conducted in a highly endemic area of South Korea, the related clinical response was increased in patients with CRAB infections treated with amikacin.[44] In addition, patients with pneumonia caused by CRAB strains received inhaled aminoglycosides and colistin treatment, which cleared specific pathogens; however, whether this could improve clinical prognosis remains unknown.[65,66]

Rifamycins

Rifamycin antibiotics include rifampin, rifabutin, and rifapentine, which inhibit bacterial ribonucleic acid RNA polymerase. There are data suggesting synergy between rifamycins and polymyxins that may also reduce the emergence of resistance; however, toxicities and drug-drug interactions limit the use of rifamycin for CRAB infections.[67] As mentioned, rifampin combined with polymyxins has a significant effect on VAP-related mortality or microbiological responses compared to that of colistin monotherapy; however, the safety of the drug needs to be considered.[49,68] It is not recommended for routine clinical use. Still, according to its demonstrated effect on CRAB infections in combination with colistin, this combination could be tried when other treatment options don't respond.

Fosfomycin

Fosfomycin, as a phosphonic antibiotic, combines with bacterial cell wall synthetase to prevent bacteria from using related substances to synthesize their cell wall and has a bactericidal role. It is usually used to treat uncomplicated urinary tract infections but may also have other uses.[69] Fosfomycin alone can quickly induce drug resistance; therefore, it is often used in combination with other drugs. Recently, intravenous fosfomycin combined with CRAB infection treatments has attracted increasing attention.[70] A study of 180 patients with hospital-acquired pneumonia due to CRAB demonstrated the superiority of Fosfomycin regimens.[71] A study including 94 patients with VAP, primary bacteremia, urinary tract infection, skin, and soft tissue infection, and intra-abdominal or gastrointestinal infection due to CRAB revealed that patients treated with fosfomycin plus colistin had higher pathogen clearance rates, better clinical outcomes, and lower mortality rates than those treated with colistin monotherapy.[72] A case series investigated the efficacy of fosfomycin-containing regimens such as "colistin + trimethoprim/sulfamethoxaz ole + fosfomycin" or "colistin + fosfomycin" or "a mpicillin/sulbactam + amikacin + colistin + fosfomycin" or "colistin + tigecycline + fosfomyci n) or (ampicillin/ sulbactam + amikacin + tigecycline + fosfomycin" or "colistin + trimethoprim/sulfam ethoxazole + fosfomycin + meropenem + gentamicin" or "colistin + tigecycline + fosfomycin + amik acin + trimethoprim/sulfamethoxazole" in patients with bacteremia caused by pan-drug-resistant *A. baumannii*. Patients who received the fosfomycin regimens had significantly better survival rates than those who did not, and lower doses of fosfomycin improved bacterial clearance in combination therapy.[73] However, there is not enough data to endorse using this drug for the treatment of life-threatening infections unless there are no other options.

Conclusion

CRAB is a major MDR organism responsible for nosocomial infections with high mortality rates and challenging antibiotic selection, thus posing a global threat.

In this review, we discussed epidemiology, risk factors, and currently available treatments for VAP caused by CRAB and suggest that because this patient population is usually very ill and suffers from severe comorbidities and antibiotics may initially appear active and then develop resistance, combination therapy is the best option for treatment.

Although numerous studies have reported on the drug treatment of CRAB, clinical evidence is essential to confirm the effectiveness and safety of current clinical drugs for CRAB. No single treatment option with an absolute advantage currently exists, and no consensus has emerged on the established therapeutic regimen for CRAB infections. Ampicillin/sulbactam and colistin, used in combination with each other or other antimicrobials such as tigecycline, meropenem, or fosfomycin, are among the effective agents. It is worth considering that further studies with other drugs, such as rifampin, are needed to evaluate and demonstrate their effectiveness as an alternative regimen for treating VAP caused by CRAB.

In summary, it is hoped that through a rational combination of drugs and the exploration of new

therapeutic regimens, the effects of alleviating or preventing CRAB infections, reducing the length of hospital stays and mortality rates of patients, and reducing side effects of drug regimens can be achieved.

Authors' Contribution

All authors contributed to the conceptualization, searching databases, drafting, and editing of the manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Wang T, Costa V, Jenkins SG, Hartman BJ, Westblade LF. *Acinetobacter radioresistens* infection with bacteremia and pneumonia. IDCases 2019;15:e00495.
2. Kyriakidis I, Vasileiou E, Pana ZD, Tragiannidis A. *Acinetobacter baumannii* antibiotic resistance mechanisms. Pathogens 2021;10:373.
3. Ibrahim S, Al-Saryi N, Al-Kadmy IM, Aziz SN. Multidrug-resistant *Acinetobacter baumannii* as an emerging concern in hospitals. Mol Biol Rep 2021;48:6987-98.
4. Medioli F, Bacca E, Faltoni M, Burastero GJ, Volpi S, Menozzi M, *et al.* Is it possible to eradicate carbapenem-resistant *Acinetobacter baumannii* (CRAB) from endemic hospitals? Antibiotics (Basel) 2022;11:1015.
5. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, *et al.* Discovery, research, and development of new antibiotics: The WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis 2018;18:318-27.
6. Vazquez Guillamet C, Kollef MH. *Acinetobacter* pneumonia: Improving outcomes with early identification and appropriate therapy. Clin Infect Dis 2018;67:1455-62.
7. Bassetti M, Echols R, Matsunaga Y, Ariyasu M, Doi Y, Ferrer R, *et al.* Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): A randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. Lancet Infect Dis 2021;21:226-40.
8. Paul M, Daikos GL, Durante-Mangoni E, Yahav D, Carmeli Y, Benattar YD, *et al.* Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: An open-label, randomised controlled trial. Lancet Infect Dis 2018;18:391-400.
9. Berditsch M, Jäger T, Strempel N, Schwartz T, Overhage J, Ulrich AS. Synergistic effect of membrane-active peptides polymyxin B and gramicidin S on multidrug-resistant strains and biofilms of *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 2015;59:5288-96.
10. Wan G, Ruan L, Yin Y, Yang T, Ge M, Cheng X. Effects of silver nanoparticles in combination with antibiotics on the resistant bacteria *Acinetobacter baumannii*. Int J Nanomedicine 2016;11:3789-800.
11. Manchanda V, Sanchaita S, Singh N. Multidrug resistant *Acinetobacter*. J Glob Infect Dis 2010;2:291-304.
12. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, *et al.* International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009;302:2323-9.
13. Lee CR, Lee JH, Park M, Park KS, Bae IK, Kim YB, *et al.* Biology of *Acinetobacter baumannii*: Pathogenesis, antibiotic resistance mechanisms, and prospective treatment options. Front Cell Infect Microbiol 2017;7:55.
14. Antunes LC, Visca P, Towner KJ. *Acinetobacter baumannii*: Evolution of a global pathogen. Pathog Dis 2014;71:292-301.
15. Kao HH, Peng CK, Sheu CC, Lin YC, Chan MC, Wang SH, *et al.* Mortality and ventilator dependence in critically ill patients with ventilator-associated pneumonia caused by carbapenem-resistant *Acinetobacter baumannii*. J Microbiol Immunol Infect 2023;56:822-32.
16. Liu C, Chen K, Wu Y, Huang L, Fang Y, Lu J, *et al.* Epidemiological and genetic characteristics of clinical carbapenem-resistant *Acinetobacter baumannii* strains collected countrywide from hospital intensive care units (ICUs) in China. Emerg Microbes Infect 2022;11:1730-41.
17. Koulenti D, Tsigou E, Rello J. Nosocomial pneumonia in 27 ICUs in Europe: Perspectives from the EU-VAP/CAP study. Eur J Clin Microbiol Infect Dis 2017;36:1999-2006.
18. Lambiase A, Piazza O, Rossano F, Del Pezzo M, Tufano R, Catania MR. Persistence of carbapenem-resistant *Acinetobacter baumannii* strains in an Italian intensive care unit during a forty-six month study period. New Microbiol 2012;35:199-206.
19. He S, Li Z, Yang Q, Quan M, Zhao L, Hong Z. Resistance trends among 1,294 nosocomial *Acinetobacter baumannii* strains from a tertiary general hospital in China, 2014-2017. Clin Lab 2020;66.
20. Lăzureanu V, Porosnicu M, Gândac C, Moisil T, Bădițoiu L, Laza R, *et al.* Infection with *Acinetobacter baumannii* in an intensive care unit in the Western part of Romania. BMC Infect Dis 2016;16 Suppl 1:95.
21. Mammina C, Palma DM, Bonura C, Aleo A, Fasciana T, Sodano C, *et al.* Epidemiology and clonality of carbapenem-resistant *Acinetobacter baumannii* from an intensive care unit in Palermo, Italy. BMC Res Notes 2012;5:365.
22. Mohd Sazlly Lim S, Zainal Abidin A, Liew SM, Roberts JA, Sime FB. The global prevalence of multidrug-resistance among *Acinetobacter baumannii* causing hospital-acquired and ventilator-associated pneumonia and its associated mortality: A systematic review and meta-analysis. J Infect 2019;79:593-600.
23. Moghnieh RA, Kanafani ZA, Tabaja HZ, Sharara SL, Awad LS, Kanj SS. Epidemiology of common resistant bacterial pathogens in the countries of the Arab League. Lancet Infect Dis 2018;18:e379-94.
24. van Duin D, Kaye KS, Neuner EA, Bonomo RA. Carbapenem-resistant *Enterobacteriaceae*: A review of treatment and outcomes. Diagn Microbiol Infect Dis 2013;75:115-20.
25. Asif M, Alvi IA, Rehman SU. Insight into *Acinetobacter baumannii*: Pathogenesis, global resistance, mechanisms of resistance, treatment options, and alternative modalities. Infect Drug Resist 2018;11:1249-60.
26. Li YJ, Pan CZ, Fang CQ, Zhao ZX, Chen HL, Guo PH, *et al.* Pneumonia caused by extensive drug-resistant *Acinetobacter baumannii* among hospitalized patients: Genetic relationships, risk factors and mortality. BMC Infect Dis 2017;17:371.
27. Henig O, Kaye KS. Bacterial pneumonia in older adults. Infect Dis Clin North Am 2017;31:689-713.
28. Zaragoza R, Vidal-Cortés P, Aguilar G, Borges M, Diaz E, Ferrer R, *et al.* Update of the treatment of nosocomial pneumonia in the ICU. Crit Care 2020;24:383.
29. Zhang S, Di L, Qi Y, Qian X, Wang S. Treatment of infections caused by carbapenem-resistant *Acinetobacter baumannii*. Front Cell Infect Microbiol 2024;14:1395260.
30. Gordon NC, Wareham DW. Multidrug-resistant *Acinetobacter*

baumannii: Mechanisms of virulence and resistance. Int J Antimicrob Agents 2010;35:219-26.

31. Rodríguez-Baño J, Paño-Pardo JR, Alvarez-Rocha L, Asensio A, Calbo E, Cercenado E, *et al.* Programs for optimizing the use of antibiotics (PROA) in Spanish hospitals: GEIH-SEIMC, SEFH and SEMPSPH consensus document. Enferm Infecc Microbiol Clin 2012;30:22.e1-23.
32. Bartal C, Rolston KV, Nesher L. Carbapenem-resistant *Acinetobacter baumannii*: Colonization, infection and current treatment options. Infect Dis Ther 2022;11:683-94.
33. Penwell WF, Shapiro AB, Giacobbe RA, Gu RF, Gao N, Thresher J, *et al.* Molecular mechanisms of sulbactam antibacterial activity and resistance determinants in *Acinetobacter baumannii*. Antimicrob Agents Chemother 2015;59:1680-9.
34. Betrosian AP, Frantzeskaki F, Xanthaki A, Douzinas EE. Efficacy and safety of high-dose ampicillin/sulbactam versus. colistin as monotherapy for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. J Infect 2008;56:432-6.
35. Jones RN, Flonta M, Gurler N, Cepparulo M, Mendes RE, Castanheira M. Resistance surveillance program report for selected European nations (2011). Diagn Microbiol Infect Dis 2014;78:429-36.
36. Zeng M, Xia J, Zong Z, Shi Y, Ni Y, Hu F, *et al.* Guidelines for the diagnosis, treatment, prevention and control of infections caused by carbapenem-resistant gram-negative bacilli. J Microbiol Immunol Infect 2023;56:653-71.
37. Santimaleeworagun W, Wongpoowarak P, Chayakul P, Pattharachayakul S, Tansakul P, Garey KW. *In vitro* activity of colistin or sulbactam in combination with fosfomycin or imipenem against clinical isolates of carbapenem-resistant *Acinetobacter baumannii* producing OXA-23 carbapenemases. Southeast Asian J Trop Med Public Health 2011;42:890-900.
38. Pei G, Mao Y, Sun Y. *In vitro* activity of minocycline alone and in combination with cefoperazone-sulbactam against carbapenem-resistant *Acinetobacter baumannii*. Microb Drug Resist 2012;18:574-7.
39. Poulikakos P, Tansarli GS, Falagas ME. Combination antibiotic treatment versus monotherapy for multidrug-resistant, extensively drug-resistant, and pandrug-resistant *Acinetobacter* infections: A systematic review. Eur J Clin Microbiol Infect Dis 2014;33:1675-85.
40. Kalin G, Alp E, Akin A, Coskun R, Doganay M. Comparison of colistin and colistin/sulbactam for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. Infection 2014;42:37-42.
41. Khalili H, Shojaei L, Mohammadi M, Beigmohammadi MT, Abdollahi A, Doomanlou M. Meropenem/colistin versus meropenem/ampicillin-sulbactam in the treatment of carbapenem-resistant pneumonia. J Comp Eff Res 2018;7:901-11.
42. Liu J, Shu Y, Zhu F, Feng B, Zhang Z, Liu L, *et al.* Comparative efficacy and safety of combination therapy with high-dose sulbactam or colistin with additional antibacterial agents for multiple drug-resistant and extensively drug-resistant *Acinetobacter baumannii* infections: A systematic review and network meta-analysis. J Glob Antimicrob Resist 2021;24:136-47.
43. Makris D, Petinaki E, Tsolaki V, Manoulakas E, Mantzarlis K, Apostolopoulou O, *et al.* Colistin versus colistin combined with ampicillin-sulbactam for multiresistant *Acinetobacter baumannii* ventilator-associated pneumonia treatment: An open-label prospective study. Indian J Crit Care Med 2018;22:67-77.
44. Seok H, Choi WS, Lee S, Moon C, Park DW, Song JY, *et al.* What is the optimal antibiotic treatment strategy for carbapenem-resistant *Acinetobacter baumannii* (CRAB)? A multicentre study in Korea. J Glob Antimicrob Resist 2021;24:429-39.
45. Kempf M, Djouhri-Bouktab L, Brunel JM, Raoult D, Rolain JM. Synergistic activity of sulbactam combined with colistin against colistin-resistant *Acinetobacter baumannii*. Int J Antimicrob Agents 2012;39:180-1.
46. Lenhard JR, Smith NM, Bulman ZP, Tao X, Thamlikitkul V, Shin BS, *et al.* High-dose ampicillin-sulbactam combinations combat polymyxin-resistant *Acinetobacter baumannii* in a hollow-fiber infection model. Antimicrob Agents Chemother 2017;61:e01268-16.
47. Kengkla K, Kongpakwattana K, Saokaew S, Apisarnthanarak A, Chaiyakunapruk N. Comparative efficacy and safety of treatment options for MDR and XDR *Acinetobacter baumannii* infections: A systematic review and network meta-analysis. J Antimicrob Chemother 2018;73:22-32.
48. Park HJ, Cho JH, Kim HJ, Han SH, Jeong SH, Byun MK. Colistin monotherapy versus colistin/rifampicin combination therapy in pneumonia caused by colistin-resistant *Acinetobacter baumannii*: A randomised controlled trial. J Glob Antimicrob Resist 2019;17:66-71.
49. Aydemir H, Akduman D, Piskin N, Comert F, Horuz E, Terzi A, *et al.* Colistin versus. the combination of colistin and rifampicin for the treatment of carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia. Epidemiol Infect 2013;141:1214-22.
50. Liang CA, Lin YC, Lu PL, Chen HC, Chang HL, Sheu CC. Antibiotic strategies and clinical outcomes in critically ill patients with pneumonia caused by carbapenem-resistant *Acinetobacter baumannii*. Clin Microbiol Infect 2018;24:908.e1-7.
51. Assimakopoulos SF, Karamouzos V, Lefkaditi A, Sklavou C, Kolonitsiou F, Christofidou M, *et al.* Triple combination therapy with high-dose ampicillin/sulbactam, high-dose tigecycline and colistin in the treatment of ventilator-associated pneumonia caused by pan-drug resistant *Acinetobacter baumannii*: A case series study. Infez Med 2019;27:11-6.
52. Noel AR, Attwood M, Bowker KE, MacGowan AP. *In vitro* pharmacodynamics of omadacycline against *Escherichia coli* and *Acinetobacter baumannii*. J Antimicrob Chemother 2021;76:667-70.
53. Greig SL, Scott LJ. Intravenous minocycline: A review in *Acinetobacter* infections. Drugs 2016;76:1467-76.
54. Ritchie DJ, Garavaglia-Wilson A. A review of intravenous minocycline for treatment of multidrug-resistant *Acinetobacter* infections. Clin Infect Dis 2014;59 Suppl 6:S374-80.
55. Goff DA, Bauer KA, Mangino JE. Bad bugs need old drugs: A stewardship program's evaluation of minocycline for multidrug-resistant *Acinetobacter baumannii* infections. Clin Infect Dis 2014;59 Suppl 6:S381-7.
56. Beganovic M, Daffinee KE, Luther MK, LaPlante KL. Minocycline alone and in combination with polymyxin B, meropenem, and sulbactam against carbapenem-susceptible and -resistant *Acinetobacter baumannii* in an *in vitro* pharmacodynamic model. Antimicrob Agents Chemother 2021;65:e01680-20.
57. Zha L, Pan L, Guo J, French N, Villanueva EV, Tefsen B. Effectiveness and safety of high dose tigecycline for the treatment of severe infections: A systematic review and meta-analysis. Adv Ther 2020;37:1049-64.
58. Kaye KS, Marchaim D, Thamlikitkul V, Carmeli Y, Chiu CH, Daikos G, *et al.* Colistin monotherapy versus combination therapy for carbapenem-resistant organisms. NEJM Evid 2023;2.

59. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious diseases society of America 2023 guidance on the treatment of antimicrobial resistant gram-negative infections. Clin Infect Dis 2023:ciad428.
60. Paul M, Carrara E, Retamar P, Tängdén T, Bitterman R, Bonomo RA, *et al.* 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). Clin Microbiol Infect 2022;28:521-47.
61. Lenhard JR, Thamlikitkul V, Silveira FP, Garonzik SM, Tao X, Forrest A, *et al.* Polymyxin-resistant, carbapenem-resistant *Acinetobacter baumannii* is eradicated by a triple combination of agents that lack individual activity. J Antimicrob Chemother 2017;72:1415-20.
62. Heil EL, Claeys KC, Kline EG, Rogers TM, Squires KM, Iovleva A, *et al.* Early initiation of three-drug combinations for the treatment of carbapenem-resistant *A. baumannii* among COVID-19 patients. J Antimicrob Chemother 2023;78:1034-40.
63. Qureshi ZA, Hittle LE, O'Hara JA, Rivera JI, Syed A, Shields RK, *et al.* Colistin-resistant *Acinetobacter baumannii*: Beyond carbapenem resistance. Clin Infect Dis 2015;60:1295-303.
64. Isler B, Doi Y, Bonomo RA, Paterson DL. New treatment options against carbapenem-resistant *Acinetobacter baumannii* infections. Antimicrob Agents Chemother 2019;63:e01110-18.
65. Vardakas KZ, Voulgaris GL, Samonis G, Falagas ME. Inhaled colistin monotherapy for respiratory tract infections in adults without cystic fibrosis: A systematic review and meta-analysis. Int J Antimicrob Agents 2018;51:1-9.
66. Niederman MS, Alder J, Bassetti M, Boateng F, Cao B, Corkery K, *et al.* Inhaled amikacin adjunctive to intravenous standard-of-care antibiotics in mechanically ventilated patients with Gram-negative pneumonia (INHALE): A double-blind, randomised, placebo-controlled, phase 3, superiority trial. Lancet Infect Dis 2020;20:330-40.
67. Cheng J, Yan J, Reyna Z, Slarve M, Lu P, Spellberg B, *et al.* Synergistic rifabutin and colistin reduce emergence of resistance when treating *Acinetobacter baumannii*. Antimicrob Agents Chemother 2021;65:e02204-20.
68. Durante-Mangoni E, Signoriello G, Andini R, Mattei A, De Cristoforo M, Murino P, *et al.* Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant *Acinetobacter baumannii*: A multicenter, randomized clinical trial. Clin Infect Dis 2013;57:349-58.
69. Falagas ME, Giannopoulou KP, Kokolakis GN, Rafailidis PI. Fosfomycin: Use beyond urinary tract and gastrointestinal infections. Clin Infect Dis 2008;46:1069-77.
70. Marino A, Stracquadanio S, Campanella E, Munafò A, Gussio M, Ceccarelli M, *et al.* Intravenous fosfomycin: A potential good partner for cefiderocol. Clinical experience and considerations. Antibiotics (Basel) 2022;12:49.
71. Russo A, Bassetti M, Bellelli V, Bianchi L, Marincola Cattaneo F, Mazzocchetti S, *et al.* Efficacy of a fosfomycin-containing regimen for treatment of severe pneumonia caused by multidrug-resistant *Acinetobacter baumannii*: A prospective, observational study. Infect Dis Ther 2021;10:187-200.
72. Sirijatuphat R, Thamlikitkul V. Preliminary study of colistin versus colistin plus fosfomycin for treatment of carbapenem-resistant *Acinetobacter baumannii* infections. Antimicrob Agents Chemother 2014;58:5598-601.
73. Assimakopoulos SF, Karamouzos V, Eleftheriotis G, Lagadinou M, Bartzavali C, Kolonitsiou F, *et al.* Efficacy of fosfomycin-containing regimens for treatment of bacteremia due to pan-drug resistant *Acinetobacter baumannii* in critically Ill patients: A case series study. Pathogens 2023;12:286.