Original paper • 10.2478/pneum-2024-0020 • 72 • 2023 • 140-147

Pneumologia

Exploring the ESKAPE maze: Pneumonias, resistance and therapeutic perspectives

Ioana Adelina Stoian[1,2], Andreea Zabară Antal[1,2,*], Paula Vasilache Antohi[1], Victoria Țău[1], Adriana Loredana Pintilie[1], Antigona Carmen Trofor[1,3], Radu Adrian Crișan-Dabija[1,3]

[1]*Clinical Hospital of Pulmonary Diseases, 700116 Iasi, Romania*
[2]*Doctoral School, Faculty of Medicine, University of Medicine and Pharmacy "Grigore T. Popa", 700115 Iași, Romania*
[3]*Pulmonary Department, Faculty of General Medicine, University of Medicine and Pharmacy "Grigore T. Popa", 700115 Iași, Romania*

Abstract

English:

The article explores drug-resistant bacteria within the ESKAPE group, commonly associated with nosocomial infections, focusing on the resistance mechanisms of Acinetobacter baumannii and Klebsiella pneumoniae. The study delves into various β-lactamase enzymes and resistance mechanisms exhibited by ESKAPE bacteria, shedding light on the challenges posed by carbapenem-resistant infections. Notably, the article underscores the ongoing need for research to develop more effective treatments and address the persistent challenges associated with drug resistance in the context of nosocomial infections. The examination of this subset of bacteria aims to contribute to a comprehensive understanding of their resistance mechanisms and provides insights into the difficulties encountered in treating infections with carbapenem-resistant pathogens. The article serves as a valuable resource for clinicians, researchers and policymakers, offering a detailed perspective on the current state of drug resistance among nosocomial pathogens and advocating for continuous research to enhance treatment efficacy in the face of evolving challenges.

Keywords

ESKAPE pathogens • drug-resistant bacteria • carbapenem resistance

Explorarea labirintului ESKAPE: pneumonie, rezistență, și perspective terapeutice

Rezumat

Romanian:

Articolul explorează asocierea bacteriilor chimiorezistente din cadrul grupului ESKAPE cu infecțiile nosocomiale, concentrându-se pe mecanismele de rezistență ale A. baumannii și K. pneumoniae. Studiul investighează diverse enzime β-lactamază și mecanisme de rezistență expuse de bacteriile ESKAPE, evidențiind provocările generate de infecțiile rezistente la carbapeneme. Deosebit de important, articolul subliniază necesitatea continuă de cercetare pentru dezvoltarea unor tratamente mai eficiente și abordarea provocărilor persistente ale rezistenței la medicamente în infecțiile nosocomiale. Examinarea acestei subcategorii de bacterii are ca scop contribuția la o înțelegere cuprinzătoare a mecanismelor lor de rezistență. Oferă perspective asupra dificultăților întâmpinate în tratarea infecțiilor cu agenți patogeni rezistenți la carbapeneme. Articolul reprezintă o resursă valoroasă pentru clinicieni, cercetători și factori de decizie, oferind o perspectivă detaliată asupra stării actuale a rezistenței la medicamente în rândul patogenilor nosocomiali și pledând pentru continuarea cercetărilor în vederea îmbunătățirii eficacității tratamentului în fața provocărilor în evoluție.

Cuvinte-cheie

patogeni ESKAPE • bacterii rezistente la medicamente • rezistență la carbapeneme

*Corresponding author: Andreea Zabară Antal
E-mail: zabara-antal_andreea@d.umfiasi.ro

Introduction

ESKAPE represents an acronym for a group of bacteria, including both Gram-positive and Gram-negative species: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter*. These bacteria are common causes of nosocomial infections in critical and immunocompromised individuals, characterised by potential drug resistance mechanisms. These mechanisms include drug inactivation/alteration, modification of binding sites, changes in cellular permeability and biofilm formation (1,2).

Drug resistance, a major threat to global health, primarily results from the overuse and inadequate prescription of drugs, as well as the non-compliant use of antimicrobials and substandard medications. Many bacteria produce enzymes, such as β-lactamases, which irreversibly modify and inactivate antibiotics. β-Lactamases are classified into two main systems: the Ambler scheme (molecular classification) and the Bush–Jacoby–Medeiros system. Class A Ambler enzymes, such as penicillinase, cephalosporinase, broad-spectrum β-lactamases and carbapenemases, can inactivate various antibiotics, including penicillins and cephalosporins. Class B Ambler enzymes include metallo-β-lactamases (MBL), conferring resistance to all β-lactams. MBL genes are transmissible, facilitating resistance spread. Class C Ambler confers resistance to cephalosporins. Class D Ambler includes enzymes, such as OXA, involved in oxacillin hydrolysis (1).

Gram-negative bacteria have porins in their outer membranes that allow antibiotic passage, and their loss in *A. baumannii* confers insensitivity to imipenem and meropenem. Multidrug-resistant *K. pneumoniae* loses porins OmpK35 and OmpK36, while also having resistance enzymes such as AmpC β-lactamase and carbapenemase KPC. These bacteria are common pathogens in medical infections. *K. pneumoniae* strains have developed resistance to β-lactam antibiotics, including carbapenems, posing a challenge in treating infections. Outbreaks of carbapenem-resistant strains cannot be completely eradicated, necessitating effective treatments. *A. baumannii*, a significant nosocomial pathogen, exhibits antibiotic resistance and can survive on human surfaces, contributing to nosocomial infections. *A. baumannii* strains producing MBL and oxacillinase β-lactamases show resistance to colistin and imipenem, representing a significant threat (1).

Materials and methods

In the process of developing this review article, we adopted a multidimensional approach to analyse the complexity of issues related to pneumonia and bacterial resistance, focusing specifically on two of the six bacteria within the ESKAPE group of pathogens. We conducted a comprehensive literature review, examining both retrospective and prospective cohort studies, clinical cases and available meta-analyses in the field. Our analysis encompassed data derived from studies investigating therapeutic perspectives in the management of respiratory infections caused by ESKAPE pathogens, with a specific focus on current and future treatments. By integrating these sources, the objective was to provide a comprehensive insight into the intricate labyrinth of pneumonias and to highlight challenges in addressing bacterial resistance, while simultaneously exploring emerging therapeutic options.

Results

Hospital-acquired pneumonia (HAP) is one of the most common health care-associated infections (HAIs) contributing to mortality, and it is estimated to prolong hospitalisation up to 12 days and mechanical ventilation duration up to 10 days (2). *K. pneumoniae* is one of the rare Gram-negative bacteria capable of causing primary pneumonia and is a significant cause of nosocomial pneumonia. Although common in community-acquired infections, there is an increasing number of reports on hypervirulent isolates causing health care-associated diseases, including pulmonary and ventilator-associated infections, as well as bacteraemia. The increased circulation of these strains in the hospital environment can contribute to an elevated burden of this pathogen (3).

K. pneumoniae was first identified in 1882 by Carl Friedlander in the lungs of patients who died from pneumonia. In the United States, *Klebsiella* species rank third in the causes of HAIs, following *Clostridium difficile* and *S. aureus*, with a prevalence of 9.9%. These species are also the third leading cause of hospital-associated pneumonia and account for the majority of HAPs, with a reported mortality rate of up to 50% (4).

Diverse strains within the *Klebsiella* genus have evolved into a significant threat to global health. *Klebsiella* spp., opportunistic pathogens normally present in the human flora, can cause various infections, including pneumonia, soft tissue infections, surgical site infections, urinary tract infections, bloodstream infections and septicaemia (5).

MDR *K. pneumoniae* is closely associated with plasmid-encoded antibiotic resistance genes (ARGs). Through plasmids and transferable genetic elements, *K. pneumoniae* accumulates ARGs, resulting in the emergence of extensively drug-resistant (XDR) strains with a ‘super resistome’ (6).

A. baumannii is a nosocomial bacterium characterised by catalase-positive, oxidase-negative, non-fermentative and non-pigmented. Infections with this bacterium are

predominantly nosocomial, with pneumonia being the most frequent clinical manifestation, associated with a significant increase in mortality, especially in mechanically ventilated patients in intensive care units (ICUs). Virulence factors include a polysaccharide capsule and a lipooligosaccharide which contribute to resistance to complement and colistin, respectively. Capsular polysaccharide synthesis is regulated in specific pathways that influence biofilm development. Membrane-associated protein O-glycosylation is associated with virulence and biofilm formation. Risk factors for *A. baumannii* infection include diabetes, cancer, lung diseases, immunocompromised status and chronic alcoholism. Alcohol abuse contributes to community-acquired pneumonia (CAP) and affects the immune response. The effect of ethanol on virulence includes multiple aspects, such as increased lipid and carbohydrate anabolism, enhanced biofilm formation and reduced motility. Regarding resistance to β-lactam antibiotics, enzymatic hydrolysis mediated by β-lactamases is a common mechanism, which is divided into four molecular classes (A, B, C and D), catalysing the hydrolysis of β-lactam substrates (7).

Since the reporting of the first case of carbapenem-resistant *A. baumannii* in 1991, there has been a significant increase in these resistant strains globally. In Greece (in 2015), 94.5% of *A. baumannii* isolates were resistant to imipenem, and in North American hospitals (in 2008), 58% were identified as carbapenem-resistant *A. baumannii* (CRAB) (8).

A study conducted this year explores the complex interactions between fungi and bacteria in the body, highlighting their coevolution and reciprocal influence on virulence. The inoculation of the respiratory tract with *Candida albicans*, simulating colonisation, favoured the subsequent development of *A. baumannii* infection by reducing the interleukin 17A (IL-17A) levels. This decrease was associated with an increase in the incidence of *A. baumannii* pneumonia in the context of previous colonisation with *C. albicans*. This was confirmed through the subsequent administration of IL-17A to infected mice, which had a protective effect demonstrated by a decrease in the incidence of pneumonia and bacterial load. The cytokine IL-17A induces inflammatory responses and plays a crucial protective role in host defence against lung infections. The importance of this cytokine varies depending on the type of fungus or bacterium, such as *Candida*, *Cryptococcus*, *Klebsiella* and *Staphylococcus*. The study highlights that IL-17A promotes the production of chemokines, enhances neutrophil migration, and contributes to maintaining epithelial homeostasis. In *A. baumannii* infection, an excess of neutrophils can cause severe tissue damage. IL-17A administration reduced the number of neutrophils, levels of inflammatory markers and tissue damage. Furthermore, IL-17A influenced neutrophil apoptosis, reducing their lysis and limiting inflammatory responses and tissue damage. The conclusions suggest that IL-17A may be a potential therapeutic target for controlling *A. baumannii* infection in the context of colonisation with *C. albicans* (9).

Another study highlighted a diminished immune response to *A. baumannii* instillation in mice with compromised immune function compared to those with normal immunity. Immunosuppression induced by intraperitoneal cyclophosphamide (CTX) administration led to more severe lung injuries and pronounced deterioration in *A. baumannii* pneumonia. CTX negatively affected rapidly cycling immune cells, including granulocytes, lymphocytes and dendritic cells (DC), specialised in activating adaptive immune responses. Under normal conditions, DC plays a crucial role in the defensive immune response to bacterial infections. In *A. baumannii* infection, a rapid accumulation of DC was observed in mice with normal immunity, but significant inhibition in immunocompromised mice, possibly due to bacterial virulence. Adaptive immunity, especially T cells and Th1/Th2 polarisation, was affected following *A. baumannii* instillation, with a decrease in lymphocyte numbers. In conclusion, *A. baumannii* infection induces an inhibited immune response under compromised immunity conditions associated with severe lung injuries. Further studies are needed to better understand the specific interactions between *A. baumannii* and different immune cells, as well as the underlying mechanisms (10).

A study conducted last year evaluated the effectiveness of the Toll-like receptor agonist, 3-deacyl phosphorylated hexa-acyl disaccharide (3D PHAD), in a murine model of *K. pneumoniae*-induced pneumonia. Mice received a dose of 20 μg of 3D PHAD 48 hr and 24 hr before infection. The treatment effects, including survival, lung *K. pneumoniae* load, pulmonary leucocyte profile, phagocytic capacity and cytokine production, were monitored for 14 days. Histopathological examination showed that mice treated with 3D PHAD exhibited mild to moderate neutrophilic alveolitis, while the *K. pneumoniae*-infected control group developed bronchopneumonia and lung consolidation. Treatment with 3D PHAD led to improved phagocytosis by lung cells and a significant increase in pulmonary and plasma cytokines. 3D PHAD enhanced resistance to *K. pneumoniae*, reducing bronchopneumonia severity and improving survival. However, 3D PHAD administration induced a decrease in systemic inflammation, suggesting a potential advantage in treating critically ill patients with ventilator-associated pneumonia (VAP). Intrapulmonary instillation of 3D PHAD improved immunity against *K. pneumoniae*, justifying further investigations for its development as antibiotic-independent antimicrobial immunotherapy (11,33).

The global drug resistance rate of *K. pneumoniae* has reached up to 70%, and the infection-related mortality rate has also reached 40%–70% (12).

The addition of carbapenems to the treatment did not bring survival benefits for CRKP pneumonia, in contrast to previous findings. Host factors, especially malignancy, significantly influenced the outcomes of patients with appropriate treatment (13).

It has been demonstrated that the accumulation of M2 macrophages, caused by factors such as alcoholism or trauma, promotes *K. pneumoniae* infections. The absence of STAT6 in M2 macrophages led to an increased capacity for bacterial clearance. Inhibiting STAT6 resulted in improved clearance of *K. pneumoniae* in *in vivo* experiments (14,34).

There are significant associations between *A. baumannii* infections and the characteristics of patients with chronic obstructive pulmonary disease (COPD). Specifically, the presence of *A. baumannii* in sputum cultures has been associated with low body mass index (BMI) and impaired lung function. The detection of *A. baumannii* complex (ABC) and the presence of ABC or *P. aeruginosa* in sputum cultures were associated with lower levels of serum albumin. Patients with *A. baumannii* isolates had higher chances of extubation failure and death compared to those without *A. baumannii* isolates. The tested antimicrobials showed effective activity against *A. baumannii*, noting that only tigecycline had a consistent therapeutic response. The study also highlighted an association between *A. baumannii* isolation and critically ill patients with COPD and CAP who had a low BMI. The results aligned with previous research, indicating a close connection between *A. baumannii* and COPD, underscoring the importance of early diagnosis and appropriate treatment in these critical cases (15).

In a multicentre study on prescribing patterns for CRAB in real-world settings and their associations with clinical outcomes, tigecycline was the most frequently prescribed antibiotic for CRAB pneumonia. However, tigecycline-based therapy was associated with higher rates of mortality and treatment failure compared to non-tigecycline therapy. In contrast, colistin therapy had a similar mortality rate compared to non-colistin therapy. The study indicated that colistin monotherapy and sulbactam-based therapy were associated with better clinical outcomes than tigecycline monotherapy. Recent analyses, including a meta-analysis and a cohort study, supported that colistin-based therapy had a better microbiological response, with no significant differences in mortality. Additionally, combination therapy with colistin showed a higher clinical response compared to colistin monotherapy, without a significant impact on mortality. The effectiveness of sulbactam was also highlighted in several studies, suggesting that it is a rational option for treating CRAB infections. However, it is noted that further comprehensive studies are needed to confirm these conclusions (16).

The effectiveness of tigecycline in the treatment of HAP caused by multidrug-resistant *A. baumannii* (MDRAB) has been analysed. Following the American Thoracic Society guidelines (2005) for defining HAP, a study focused on patients treated with tigecycline and explored factors associated with clinical success and 30-day mortality. The results showed clinical resolution and 30-day survival rates of 70%, with microbiological eradication recorded at 48%. Factors such as prolonged use of tigecycline, higher CURB65 scores, mechanical ventilation and tigecycline resistance of MDRAB were significantly associated with outcomes. Tigecycline sensitivity, especially for minimum inhibitory concentrations (MIC) >2 mg/L, was highlighted as a crucial aspect in choosing the regimen against MDRAB. However, the study also discussed the increased resistance to tigecycline, as well as limitations related to the retrospective nature of data collection (17).

It was found that the 90-day mortality for HAP and VAP caused by *A. baumannii* in high-risk ICU patients was 56.7%. This figure aligns with previous results that reported mortality for *A. baumannii*-associated infections in ICUs ranging from 28.3% to 84.3%. Prolonged ICU stay was significantly associated with higher 90-day mortality in *A. baumannii*-caused HAP and VAP. Infections with *A. baumannii*, especially the carbapenem-resistant form (CRAB), presented a high rate of 84.8%, reflecting a global trend of severe drug resistance. The study emphasises the importance of proper management of infections caused by *A. baumannii*, highlighting the need for identifying risk factors and effective antimicrobial therapy in managing these critical infections (18).

The treatment of severe pneumonia caused by MDRAB poses significant challenges, and the selection of an appropriate antibiotic regimen is a matter of debate, given the limitations in the penetration of many antibiotics into the lung parenchyma. The elevated mortality associated with these infections can be attributed, in part, to false sensitivity to colistin. Recent studies have explored various antibiotic combinations, such as the addition of rifampicin to colistin or the combined therapy of colistin and meropenem. Fosfomycin has been identified as an effective adjuvant option, exhibiting synergy with colistin and presenting significant benefits compared to other treatments, including improved microbiological responses and reduced mortality rates (9).

The incidence of nephrotoxicity associated with colistin in the treatment of patients with pneumonia caused by CRAB was examined using the RIFLE criteria. Nephrotoxicity was observed in 28% of the studied patient cohort, with rates of 20% on day 7 and 28% at the end of treatment. The maximum concentrations of colistin and colistin methanesulphonate were higher in the nephrotoxicity group, and the minimum concentration of colistin was also higher, although without reaching statistical significance. However, further studies are required to establish optimal colistin levels associated with minimising nephrotoxicity and maximising clinical success (20).

A. baumannii utilises outer membrane vesicles (OMVs), containing lipopolysaccharides and membrane proteins, to modify cellular balance and induce cytopathic effects. The IL-17 pathway is crucial in stimulating granulopoiesis and the synthesis of proinflammatory cytokines such as GM-CSF, IL-8 and IL-37. It is also noted that IL-17, together with IL-22, stimulates the expression of antimicrobial peptides, such as β-defensins, S100A8 and lipocalin 2, with extended antimicrobial activity. An important aspect is that the immune response to *A. baumannii* may vary depending on individual characteristics and the nature of the infection. Additionally, it is highlighted that the TLR4 receptor recognises Gram-negative bacteria, including *A. baumannii*, and activates the innate immune response, contributing to bacterial elimination. The interaction of *A. baumannii* with mast cells and the release of TNF-α are also emphasised, underscoring the need for further research on this interaction (21).

A retrospective study on 86 elderly patients with acute pneumonia caused by *K. pneumoniae* investigated radiological patterns and their association with mortality. Computer tomogram (CT) results showed that 81% of patients exhibited a bronchopneumonia pattern, while 19% had lobar pneumonia. The analysis revealed that patients with lobar pneumonia had a significantly higher in-hospital mortality rate (40% compared to 10% in those with bronchopneumonia). Factors such as low albumin levels, elevated aspartate aminotransferase levels and C-reactive protein were also associated with an increased mortality rate. Even after adjusting for other risk factors, the lobar pneumonia pattern remained an independent predictor of an unfavourable prognosis. The study underscores the importance of assessing radiological patterns in managing elderly patients with severe pneumonia caused by *K. pneumoniae* and associating these patterns with clinical prognosis (22).

Another study conducted at the All India Institute of Medical Sciences on patients with severe SARS-CoV-2 infection reveals that 46.5% of them presented coinfections with various bacterial pathogens. Among these pathogens are *S. aureus*, *Streptococcus pneumoniae*, *K. pneumoniae*, *Legionella pneumophila*, *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*. Coinfections with *A. baumannii* and *K. pneumoniae*, both exhibiting antibiotic resistance, were also identified. Specifically, *K. pneumoniae* was associated with the risk of hospital-acquired infections in cases of severe COVID-19 respiratory infections. Infections with *K. pneumoniae*, especially those caused by hypervirulent strains, have been noted to potentially complicate the course of COVID-19. Risk factors for such coinfections include chronic diseases, endotracheal intubation and previous antibiotic use. The study emphasises the importance of evaluating and appropriately treating bacterial coinfections in patients with COVID-19 (23).

The prescription of antibiotics to patients with COVID-19 was initially driven by concerns about bacterial superinfections or secondary bacterial pneumonia. However, since COVID-19 is a viral illness, bacterial coinfections are rare, making antibiotic use not always necessary. The pandemic has led to a global increase in antibiotic use, negatively impacting antibiotic resistance worldwide, with significant consequences for critically ill and ventilated patients. Antibiotic resistance remains a heightened concern in low- and middle-income countries, and coinfections with Gram-negative bacteria, such as *K. pneumoniae* and *A. baumannii*, are more common in severe cases of COVID-19. These pathogens are considered major global threats, and resistance to antibiotics, including colistin, tigecycline and carbapenems, poses a public health emergency. The development of new antibiotics and non-antibiotic strategies, such as *A. baumannii* vaccines, is essential to address the challenges of drug-resistant infections. Coinfections with *K. pneumoniae* and *A. baumannii* in SARS-CoV-2 infection present complex interactions, and the implementation of effective antimicrobial stewardship programmes is crucial to limit secondary infections in COVID-19 patients (24).

A 55-year-old patient with hypoxic respiratory failure due to COVID-19, previously intubated for acute respiratory distress syndrome and right pneumothorax, is noteworthy. Initially treated with remdesivir and dexamethasone, the patient showed initial clinical improvement but experienced a rapid relapse, necessitating reintubation and vasopressor support. Cultures identified pan-resistant *A. baumannii*. Initial therapy with vancomycin and meropenem was unsuccessful, and the introduction of sulbactam-durlobactam (SUL-DUR), a drug in phase 3 of clinical trials for severe *A. baumannii* infections, in combination with imipenem-cilastatin, led to significant improvement within 72 hr. Subsequently, cefiderocol was introduced. The patient had a steady recovery and was discharged after 38 days with physical therapy and reconditioning. This treatment combination shows promise in treating severe infections with MDRAB, offering an optimised option in the context of increasing antimicrobial resistance (24).

A retrospective study at the University Hospital of Pisa, conducted between January 2020 and August 2021, evaluated the effectiveness of cefiderocol compared to colistin in treating CRAB infections. Of the 124 patients, 37.9% received cefiderocol, and 62.1% received colistin. The 30-day mortality was lower in the cefiderocol group (34% vs 55.8%), and multivariable analysis identified septic shock, SOFA score and age as factors associated with mortality. Cefiderocol was associated with protection against mortality in the analysis but had a higher frequency of nephrotoxicity. Microbiological failure was more common in the cefiderocol group, and among these cases, half developed resistance

to cefiderocol. The conclusion is that cefiderocol represents a promising therapeutic option for severe CRAB infections, with the need for a randomised clinical trial to confirm the results (25).

Discussions

Treatment options for CRAB are limited due to multiple resistance mechanisms, including reduced membrane permeability, increased efflux and carbapenemase production. New β-lactam-β-lactamase inhibitors such as meropenem/vaborbactam, imipenem/relebactam and others are not effective against these strains. Current options include minocycline, eravacycline and cefiderocol. However, there are reports of resistance to cefiderocol. Synergistic combinations, particularly those based on polymyxins, represent a potential option. However, their clinical benefits are unclear, and differences between laboratory studies and real-world situations may influence outcomes. Polymyxin-based combinations may be beneficial, with the caveat that polymyxin B may require clinical assessments. Other options include combining colistin with rifampin, high-dose ampicillin/sulbactam or sulbactam/avibactam. Tigecycline-based combinations have been proposed, but their effectiveness is still unclear. Older agents such as minocycline, ampicillin/sulbactam and trimethoprim/sulphamethoxazole may be considered in combination. Eravacycline and cefiderocol are alternatives, and in their absence, polymyxin-based, tigecycline and sulbactam combinations may be considered, noting that their effectiveness against carbapenem-resistant strains is still unexplored (26,35).

In recent years, several new antibiotics against Gram-negative pathogens have been approved, but there is variability in the spectrum of activity, indications and clinical experience. Careful selection of the optimal option for each patient is essential, and further new agents are in clinical development, offering exciting prospects for the future treatment of Gram-negative pneumonia (27).

Combination therapy with tigecycline and sulbactam has demonstrated a significant reduction in mortality rates, suggesting that these treatments could be beneficial in cases of severe hospital-acquired MDRAB pneumonia, with particular attention to the doses of sulbactam used (28).

Efforts to develop newer antibacterial agents have shifted towards using natural or synthetic antimicrobial peptides as a model, given the potential of these groups of molecules as effective antibacterial agents (29).

Resistance to polymyxins, although increasing, still keeps them among the most active agents against CRAB, with rapid bactericidal activity and concentration-dependent *in vitro* activity. However, the clinical performance of polymyxins is limited due to suboptimal pharmacokinetic/pharmacodynamic profiles. For instance, colistin has a slow rate of achieving effective concentrations at the onset of infection and can cause nephrotoxicity. Polymyxin B has pharmacological advantages, such as independent administration of renal function, but it is also associated with nephrotoxicity. In murine models of *A. baumannii* pulmonary infection, both colistin and polymyxin B struggled to reach adequate concentrations in the epithelial lining fluid, limiting their effectiveness. Tigecycline, used in drug-resistant *A. baumannii* infections, is debated due to its unfavourable pharmacokinetics. Sulbactam, with its activity against *Acinetobacter*, is limited by resistance. Development of new compounds, such as cefiderocol and eravacycline, is in progress to provide therapeutic alternatives against CRAB. Cefiderocol, an innovative cephalosporin, and eravacycline, a synthetic tetracycline, show potential in treating carbapenem-resistant infections, but phase III clinical studies are still ongoing to evaluate their effectiveness (30).

Glycoconjugate vaccines are recognised tools for preventing bacterial infections, generating effective antibodies against ESKAPE pathogens. This class of vaccines influences bacterial transport and prevents invasive infections such as pneumonia. Emerging technologies, such as chemically synthesised carbohydrates, bioconjugation, glyconanoparticles/GMMA and MAPS, provide new approaches for the development of innovative glycoconjugate vaccines (31,32).

Conclusions

The article examines a subset of the ESKAPE group of bacteria, commonly associated with nosocomial infections, and analyses their mechanisms of drug resistance. The importance of issues related to drug resistance, such as excessive use and inappropriate prescription of antibiotics, is emphasised. The article provides a detailed perspective on various β-lactamase enzymes and resistance mechanisms of ESKAPE bacteria, with a focus on *A. baumannii* and *K. pneumoniae*. The challenges in treating carbapenem-resistant pathogenic infections are highlighted, and available therapeutic options, including new compounds under development, are discussed. However, the ongoing need for research to develop more effective treatments and address challenges associated with drug resistance in the context of nosocomial infections is underscored.

Author contributions

This research received no external funding.

Institutional review board statement

Not applicable.

Informed consent statement

This study did not involve humans. It is a narrative review of published literature in the field.

Data availability statement

The data published in this research are available on request from the first author and the corresponding author. All information provided in this review is documented by relevant references.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Santajit, Sirijan, and Nitaya Indrawattana. "Mechanisms of Antimicrobial Resistance in ESKAPE Pathogens." *BioMed research international* vol. 2016 (2016): 2475067. doi:10.1155/2016/2475067
2. Ablakimova, Nurgul, et al. "Microbial Landscape and Antibiotic-Susceptibility Profiles of Microorganisms in Patients with Bacterial Pneumonia: A Comparative Cross-Sectional Study of COVID-19 and Non-COVID-19 Cases in Aktobe, Kazakhstan." *Antibiotics (Basel, Switzerland)* vol. 12,8 1297. 8 Aug. 2023, doi:10.3390/antibiotics12081297
3. Choby, J E et al. "Hypervirulent Klebsiella pneumoniae - clinical and molecular perspectives." *Journal of Internal Medicine* vol. 287,3 (2020): 283-300. doi:10.1111/joim.13007
4. Martin, Rebekah M, and Michael A Bachman. "Colonization, Infection, and the Accessory Genome of *Klebsiella pneumoniae*." *Frontiers in cellular and infection microbiology* vol. 8 4. 22 Jan. 2018, doi:10.3389/fcimb.2018.00004
5. Dong, Ning, et al. "Klebsiella species: Taxonomy, hypervirulence, and multidrug resistance." *EBioMedicine* vol. 79 (2022): 103998. doi:10.1016/j.ebiom.2022.103998
6. Wang, Guoying et al. "The Characteristic of Virulence, Biofilm and Antibiotic Resistance of *Klebsiella pneumoniae*." *International journal of environmental research and public health* vol. 17,17 6278. 28 Aug. 2020, doi:10.3390/ijerph17176278
7. Ramirez, Maria Soledad et al. "Carbapenemases: Transforming *Acinetobacter baumannii* into a Yet More Dangerous Menace." *Biomolecules* vol. 10,5 720. 6 May. 2020, doi:10.3390/biom10050720
8. Ramirez, Maria Soledad et al. "Carbapenemases: Transforming *Acinetobacter baumannii* into a Yet More Dangerous Menace." *Biomolecules* vol. 10,5 720. 6 May. 2020, doi:10.3390/biom10050720
9. Tang, Jiaxin, et al. "The Protective Role of Interleukin 17A in Acinetobacter baumannii Pneumonia Is Associated with Candida albicans in the Airway." *Infection and immunity* vol. 91,1 (2023): e0037822. doi:10.1128/iai.00378-22
10. Liu, Ai-Ran, et al. "Role of immunodeficiency in Acinetobacter baumannii associated pneumonia in mice." *Chinese Medical Journal* vol. 133,18 (2020): 2161-2169. doi:10.1097/CM9.0000000000001027
11. Hernandez, Antonio, et al. "INTRAPULMONARY TREATMENT WITH A NOVEL TLR4 AGONIST CONFERS PROTECTION AGAINST KLEBSIELLA PNEUMONIA." *Shock (Augusta, Ga.)* vol. 58,4 (2022): 295-303. doi:10.1097/SHK.0000000000001977
12. Li, Yanping et al. "*Klebsiella pneumonia* and Its Antibiotic Resistance: A Bibliometric Analysis." *BioMed research international* vol. 2022 1668789. 6 Jun. 2022, doi:10.1155/2022/1668789
13. Chen, I-Ren, et al. "Clinical characteristics and outcomes of 56 patients with pneumonia caused by carbapenem-resistant Klebsiella pneumonia." *Journal of Global Antimicrobial Resistance* vol. 25 (2021): 326-330. doi:10.1016/j.jgar.2021.03.028
14. De Oliveira DMP, Forde BM, Kidd TJ, Harris PNA, Schembri MA, Beatson SA, Paterson DL, Walker MJ. Antimicrobial Resistance in ESKAPE Pathogens. Clin Microbiol Rev. 2020 May 13;33(3):e00181-19. Doi: 10.1128/CMR.00181-19. PMID: 32404435; PMCID: PMC7227449.
15. Chang, Ko-Yun, et al. "Clinical Features and Antimicrobial Susceptibility of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* Complex Isolates in Intensive Care Patients with Chronic Obstructive Pulmonary Disease and Community-Acquired Pneumonia in Taiwan." *International journal of chronic obstructive pulmonary disease* vol. 16 1801-1811. 17 Jun. 2021, doi:10.2147/COPD.S311714
16. Liang, C-A et al. "Antibiotic strategies and clinical outcomes in critically ill patients with pneumonia caused by carbapenem-resistant Acinetobacter baumannii." *Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases* vol. 24,8 (2018): 908.e1-908.e7. doi:10.1016/j.cmi.2017.10.033
17. Zhou, Yangang, et al. "Clinical experience with tigecycline in treating hospital-acquired pneumonia caused by multidrug-resistant Acinetobacter baumannii." *BMC pharmacology & toxicology* vol. 20,1 19. 25 Apr. 2019, doi:10.1186/s40360-019-0300-3
18. Pei, Yongjian, et al. "Nomogram for predicting 90-day mortality in patients with *Acinetobacter baumannii*-caused hospital-acquired and ventilator-associated pneumonia in the respiratory intensive

care unit." *The Journal of International Medical Research* vol. 51,3 (2023): 3000605231161481. doi:10.1177/03000605231161481

19. Russo, Alessandro, et al. "Efficacy of a Fosfomycin-Containing Regimen for Treatment of Severe Pneumonia Caused by Multidrug-Resistant Acinetobacter baumannii: A Prospective, Observational Study." *Infectious diseases and therapy* vol. 10,1 (2021): 187-200. doi:10.1007/s40121-020-00357-8
20. Jeong, Yun-Jeong, et al. "Prospective observational study of the impact of plasma colistin levels in patients with carbapenem-resistant Acinetobacter baumannii pneumonia." *Journal of Global Antimicrobial Resistance* vol. 27 (2021): 315-323. doi:10.1016/j.jgar.2021.10.017
21. Manfi Ahmed, S et al. "Immunological Evaluation of Individuals Infected with *Acinetobacter baumannii*." *Archives of Razi Institute* vol. 77,5 1813-1819. 31 Oct. 2022, doi:10.22092/ARI.2022.357980.2126
22. Komiya, Kosaku, et al. "Radiological patterns and prognosis in elderly patients with acute Klebsiella pneumoniae pneumonia: A retrospective study." *Medicine* vol. 101,32 (2022): e29734. doi:10.1097/MD.0000000000029734
23. Sreenath, K et al. "Coinfections with Other Respiratory Pathogens among Patients with COVID-19." *Microbiology spectrum* vol. 9,1 (2021): e0016321. doi:10.1128/Spectrum.00163-21
24. Zaidan, Noor et al. "Extensively Drug-Resistant Acinetobacter baumannii Nosocomial Pneumonia Successfully Treated with a Novel Antibiotic Combination." *Antimicrobial agents and chemotherapy* vol. 65,11 (2021): e0092421. doi:10.1128/AAC.00924-21
25. Falcone, Marco, et al. "Cefiderocol- Compared to Colistin-Based Regimens for the Treatment of Severe Infections Caused by Carbapenem-Resistant Acinetobacter baumannii." *Antimicrobial agents and chemotherapy* vol. 66,5 (2022): e0214221. doi:10.1128/aac.02142-21
26. Karakonstantis, Stamatis, et al. "Treatment options for K. pneumoniae, P. aeruginosa, and A. baumannii co-resistant to carbapenems, aminoglycosides, polymyxins, and tigecycline: an approach based on the mechanisms of resistance to carbapenems." *Infection* vol. 48,6 (2020): 835-851. doi:10.1007/s15010-020-01520-6
27. Bassetti, Matteo, et al. "New antibiotics for Gram-negative pneumonia." *European Respiratory Review: An Official Journal of the European Respiratory Society* vol. 31,166 220119. 21 Dec. 2022, doi:10.1183/16000617.0119-2022
28. Deng, Yanling, et al. "Sulbactam combined with tigecycline improves outcomes in patients with severe multidrug-resistant Acinetobacter baumannii pneumonia." *BMC Infectious Diseases* vol. 22,1 795. 21 Oct. 2022, doi:10.1186/s12879-022-07778-5
29. Pulingam, Thiruchelvi, et al. "Antimicrobial resistance: Prevalence, economic burden, mechanisms of resistance and strategies to overcome." *European Journal of pharmaceutical sciences: official journal of the European Federation for Pharmaceutical Sciences* vol. 170 (2022): 106103. doi:10.1016/j.ejps.2021.106103
30. Piperaki ET, Tzouvelekis LS, Miriagou V, Daikos GL. Carbapenem-resistant *Acinetobacter baumannii*: in pursuit of an effective treatment. Clin Microbiol Infect. 2019 Aug;25(8):951-957. doi: 10.1016/j.cmi.2019.03.014. Epub 2019 Mar 23. PMID: 30914347.)
31. Sorieul, Charlotte, et al. "Glycoconjugate vaccines against antimicrobial-resistant pathogens." *Expert review of vaccines* vol. 22,1 (2023): 1055-1078. doi:10.1080/14760584.2023.2274955
32. Semenec, Lucie et al. "Cross-protection and cross-feeding between Klebsiella pneumoniae and Acinetobacter baumannii promotes their co-existence." *Nature communications* vol. 14,1 702. 9 Feb. 2023, doi:10.1038/s41467-023-36252-2
33. Ahn, Danielle et al. "Acquired resistance to innate immune clearance promotes *Klebsiella pneumoniae* ST258 pulmonary infection." *JCI insight* vol. 1,17 e89704. 20 Oct. 2016, doi:10.1172/jci.insight.89704
34. Dumigan, Amy et al. "In vivo single-cell transcriptomics reveal Klebsiella pneumoniae skews lung macrophages to promote infection." *EMBO molecular medicine* vol. 14,12 (2022): e16888. doi:10.15252/emmm.202216888
35. Catalano, Alessia et al. "Antibiotic-Resistant ESKAPE Pathogens and COVID-19: The Pandemic beyond the Pandemic." *Viruses* vol. 15,9 1843. 30 Aug. 2023, doi:10.3390/v15091843