Biomolecules and Biomedicine
ISSN: 2831-0896 (Print) | ISSN: 2831-090X (Online)
Journal Impact Factor® (2024): 2.2
CiteScore® (2024): 5.2
www.biomolbiomed.com | blog.bjbms.org

The BiomolBiomed publishes an “Advanced Online” manuscript format as a free service to authors in order to expedite the dissemination of scientific findings to the research community as soon as possible after acceptance following peer review and corresponding modification (where appropriate). An “Advanced Online” manuscript is published online prior to copyediting, formatting for publication and author proofreading, but is nonetheless fully citable through its Digital Object Identifier (doi®). Nevertheless, this “Advanced Online” version is NOT the final version of the manuscript. When the final version of this paper is published within a definitive issue of the journal with copyediting, full pagination, etc., the new final version will be accessible through the same doi and this "Advanced Online" version of the paper will disappear.

REVIEW

Halabi et al: Pandoraea infections: Treatment gaps

Multidrug resistance, diagnostic challenges, and treatment gaps in *Pandoraea* infections: A review

Waiel S. Halabi[1], Sulaiman Bani Abdel-Rahman[2], Hala Altarawneh[2], Rawan Altalhi[3], Loui A. Ismaeel[4], Khulud A. Alhazmi[5], Ohood S. Alharbi[5], Malaz Gazzaz[6], Sarah Almuhayya[7], Turki M. Alharthi[8], Bandar Hasan Saleh[9,10], Nabeel Hussain Alhussainy[9], Abdulaziz Alsaedi[9], Hatoon A. Niyazi[9,10], Hanouf A. Niyazi[9], Noha A. Juma[9], Mona Abdulrahman[9], Karem Ibrahem[9,10]*

[1]Department of Optometry, Faculty of Applied Medical Sciences, University of Jeddah, Jeddah, Saudi Arabia;

[2]Department of Microbiology and Pathology, Faculty of Medicine, Mutah University, Al-Karak, Jordan;

[3]Department of Biological Sciences, College of Science, University of Jeddah, Jeddah, Saudi Arabia;

[4]Department of Nursing, School of Applied Medical Sciences, University of Jeddah, Jeddah, Saudi Arabia;

[5]Department of Microbiology and Parasitology, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia;

[6]Pharmaceutical Practices Department, College of Pharmacy, Umm Al-Qura University, Makkah, Saudi Arabia;

EARLY ACCESS

[7]Department of Clinical Laboratory Science, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia;

[8]Department of Clinical Laboratory Sciences, Faculty of Applied Medical Sciences, Umm Al-Qura University, Makkah, Saudi Arabia;

[9]Department of Clinical Microbiology and Immunology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia;

[10]Department of Clinical Microbiology Laboratory, King Abdulaziz University Hospital, Jeddah, Saudi Arabia.

*Correspondence to Karem Ibrahem: kaibrahem@kau.edu.sa

DOI: https://doi.org/10.17305/bb.2025.13126

EARLY ACCEPTED

ABSTRACT

Pandoraea species are emerging multidrug-resistant pathogens increasingly associated with respiratory tract infections, particularly in cystic fibrosis patients. Despite their growing clinical relevance, these bacteria are underrepresented in the scientific literature. This review aims to consolidate existing evidence regarding *Pandoraea* species as emerging multidrug-resistant pathogens, with a focus on their taxonomy, diagnostic methodologies, antimicrobial resistance mechanisms, and treatment challenges. By identifying gaps in current therapeutic strategies and the limited clinical outcome data, this review underscores the necessity of advancing research into innovative interventions, such as bacteriophages, antimicrobial peptides, and combination therapies, to enhance patient management and infection control. A comprehensive literature search was conducted using PubMed and Google Scholar, employing relevant keywords to identify case reports, clinical studies, and *in vitro* research related to *Pandoraea* infections, resistance mechanisms, and therapeutic strategies. Our findings reveal a significant lack of comprehensive data on therapeutic approaches, particularly concerning bacteriophages, antimicrobial peptides, and combination antibiotic therapies. Furthermore, clinical data on treatment efficacy remain sparse, with the majority of evidence stemming from *in vitro* studies rather than real-world clinical settings. This review emphasizes the urgent need for further research to address these knowledge deficits and to develop effective therapeutic interventions against *Pandoraea* infections.

Keywords: *Pandoraea* spp, multidrug-resistant pathogens, bacteriophages, antimicrobial peptides, combination antibiotic therapies.

EARLY ACCESS

INTRODUCTION

The *Pandoraea* genus comprises emerging Gram-negative, rod-shaped, obligately aerobic bacteria belonging to the Burkholderiaceae family. First identified in 2000, it was established to reclassify certain species formerly grouped under Pseudomonas rRNA homology group II [1]. As of now, a total of eleven *Pandoraea* species have been identified and described, including *P. apista, P. pnomenusa, P. pulmonicola, P. sputorum, P. thiooxydans, P. norimbergensis, and P. oxalalivorans*, along with additional provisional species identified via molecular analyses [2], [3]. These organisms are phylogenetically related to Ralstonia and Burkholderia spp. However, they are differentiated using 16S rRNA gene sequencing and multilocus sequence analysis [2]. *Pandoraea* spp. are ubiquitous in soil, water, and plant rhizospheres [4]; nonetheless, clinical isolates have increasingly been reported from respiratory secretions, blood cultures, and wound specimens [5]. The unique genomic features of *Pandoraea*, including specific efflux pump families and β-lactamase genes, underlie their environmental persistence and virulence potential [6].

Clinically, *Pandoraea* infections are most often associated with patients with cystic fibrosis (CF), where they can colonize the respiratory tract and contribute to chronic lung disease. Beyond CF, cases have also been reported in immunocompromised and non-CF patients, including bloodstream infections, pneumonia, and bacteremia, highlighting their broader clinical relevance. These bacteria are of particular concern due to their distinctive multidrug-resistant (MDR) profiles, frequently demonstrating resistance to β-lactams, aminoglycosides, and carbapenems, with variable susceptibility to agents such as imipenem, trimethoprim-sulfamethoxazole, and tetracyclines [5].

Despite their growing importance, knowledge about *Pandoraea* remains limited, with most data derived from isolated case reports or small series. Studying these pathogens is crucial for improving clinical recognition, guiding infection control measures, and identifying novel therapeutic options. This review aims to provide a comprehensive overview of *Pandoraea* infections, with a focus on their taxonomy, diagnostic challenges, antimicrobial resistance patterns, and current therapeutic options. In doing so, it seeks to highlight existing knowledge gaps, particularly the scarcity of clinical data on treatment efficacy, and to emphasize the urgent need for research into novel strategies such as bacteriophages, antimicrobial peptides, and combination antibiotic

EARLY ACCESS

therapies to improve the management of these emerging multidrug-resistant pathogens.

METHODS

A structured literature search was conducted to identify publications on *Pandoraea* species. The search was performed in PubMed and Google Scholar using keywords including "*Pandoraea*," "virulence," "pathogenesis," "epidemiology," "antimicrobial resistance," "treatment," "phage therapy," "antimicrobial peptides," "combination therapy," and "novel therapy." No restrictions were applied regarding publication date or study type due to the very limited literature available on *Pandoraea* infections. Inclusion criteria encompassed case reports, clinical studies, and *in vitro* research addressing taxonomy, identification, resistance mechanisms, and therapeutic strategies. Studies lacking primary data or relevance to human infections were excluded. Articles were screened by title and abstract, followed by full-text review to extract key findings, and quality was assessed based on study type and methodological clarity. This approach ensured a comprehensive synthesis of the scarce existing evidence on *Pandoraea* infections.

EARLY ACCESS

EPIDEMIOLOGY

Considering the scarcity of reported *Pandoraea* species infections in the literature, accurately defining their epidemiological profile remains difficult [7]. The majority of instances included male patients, with a mean age of 42.08 years. Notably, most reported cases originated from European countries, while only 27.58% were documented in Asia and the Americas, and just 10.34% in Oceania. The observable dominance in Europe may indicate more effective surveillance systems or a greater incidence of cystic fibrosis (CF) throughout the population [8]. Conversely, the low number of cases in Asia (in China and India) and the absence of reports from Africa suggest that *Pandoraea* infections may not be strongly linked to socioeconomic or environmental conditions [5] [9]. Nonetheless, the overall limited data and the high potential for misdiagnosis hinder the ability to draw firm epidemiological conclusions about the global distribution and burden of *Pandoraea* infections. The predominant risk factor is CF, where *Pandoraea* colonization occurs in up to 5% of patients, often co-colonizing with Pseudomonas aeruginosa and Candida spp [5]. Additional at-risk categories comprise those with chronic pulmonary conditions, hematologic cancers, organ transplant recipients, and patients with implanted medical devices [5]. Outbreaks associated with contaminated hospital water sources and bronchoscopes have been described, highlighting nosocomial transmission potential [5]. An outbreak of *Pandoraea pulmonicola* was reported in a cystic fibrosis center, affecting 6 out of 243 patients. Identification techniques comprised ARDRA, MALDI-TOF MS, and 16S rDNA sequencing, whereas PFGE validated clonal dissemination. Presumably transferred through droplets owing to deficiencies in infection management, the bacteria exhibited resistance to multiple antibiotics while remaining sensitive to trimethoprim-sulfamethoxazole. All patients were co-colonized with *Pseudomonas aeruginosa*, and *P. pulmonicola* colonization became chronic. Three patients died, highlighting the organism's transmissibility and the importance of strict infection control measures [10]. A 46-year-old non-cystic fibrosis female with injuries and burns developed sepsis caused by P. sputorum, verified using 16S rRNA PCR and MALDI-TOF MS. The isolate exhibited resistance to meropenem but was susceptible to imipenem and other specific antibiotics. Following targeted therapy and supportive care, the patient achieved recovery. This case underscores the emerging virulence and resistance profile of *Pandoraea* species, with imipenem as a potential early treatment option [11]. The report holds importance for clinicians managing rare multidrug-resistant Gram-negative infections, particularly in trauma and non-cystic fibrosis (non-CF) patients. However, this study highlights that *Pandoraea sputorum* infections are exceptionally uncommon in non-CF individuals. Furthermore, the absence of comparisons with other reported cases or control groups limits the ability to determine whether the clinical presentation and treatment response observed here are unique or representative. Finally, the focus is restricted to the short-term outcome—patient discharge after two months—without long-term follow-up data to evaluate recurrence or delayed complications [11].

Despite the presence of *Pandoraea* species. An epidemic involving 24 non-cystic fibrosis (CF) patients occurred in two German hospitals between July 2019 and December 2021. Most patients were critically ill and had undergone surgery or received prior antibiotics. Genomic analysis identified a clonal strain, *Pandoraea commovens* LB-19-202-79, which was resistant to many antibiotics but susceptible to ampicillin/sulbactam, imipenem, and trimethoprim/sulfamethoxazole. This outbreak

EARLY ACCESS

highlights the potential for *Pandoraea* to spread in non-CF settings, emphasizing the need for heightened clinical and microbiological awareness [12].

Pandoraea infections remain few; nevertheless, specific variables appear to elevate the risk. Individuals with cystic fibrosis are predominantly impacted, as the bacteria are frequently located in their lungs. However, infections have also been seen in individuals without cystic fibrosis, particularly among those who are very ill or hospitalized for extended durations [13]. Patients in the ICU, those on ventilators, or anyone who has recently had surgery or major trauma—like burns—appear to be more vulnerable [1], [5]. The use of broad-spectrum antibiotics can also make things worse by wiping out normal bacteria and giving *Pandoraea* a chance to grow. In several instances, infections have been associated with hospital outbreaks, presumably due to deficiencies in infection control measures [14]. Individuals with significant underlying health issues, particularly those with chronic pulmonary disorders or who have received lung transplants, may be at an elevated risk for *Pandoraea* infections.

A 30-year-old man developed sepsis caused by *Pandoraea pnomenusa* following a lung transplant and ultimately succumbed, underscoring the high risk this pathogen poses to immunocompromised individuals. *P. pnomenusa*, a rare multidrug-resistant Gram-negative bacterium, is typically resistant to most β-lactams and aminoglycosides, with imipenem often remaining effective, though resistance patterns vary and necessitate *in vitro* testing. Treatment is particularly challenging due to its resistance profile and the absence of standardized guidelines, with empirical therapy often involving carbapenems (especially imipenem), cephalosporins, and trimethoprim/sulfamethoxazole [15]. Outcomes are frequently poor, with high mortality seen in sepsis and multi-organ failure post-transplantation. However, available data are limited to case reports and small series, making generalization difficult, and misidentification is common without advanced diagnostic tools. This case highlights the urgent need for rapid and accurate identification of *Pandoraea* species and tailored therapeutic strategies in transplant and other immunocompromised patients [15].

PATHOGENESIS

The pathogenesis of *Pandoraea* infections is not yet fully understood, but it has been suggested that these bacteria act as opportunistic pathogens [5], [10], mainly

EARLY ACCESS

affecting people who are already vulnerable—such as those with cystic fibrosis, weakened immune systems, or serious illnesses requiring ICU care [12], [13], [16]. They can be difficult to identify correctly, often mistaken for other bacteria like *Burkholderia* or *Ralstonia*, which can delay diagnosis and treatment [17]. *Pandoraea* are recognized for their ability to build biofilms, particularly on medical devices such as catheters and ventilators, facilitating their evasion of the immune system and resistance to antibiotics [8], [18]. It has been demonstrated that the genome of *Pandoraea* sp. XY-2 contains genes that are likely involved in producing exopolysaccharides, including proteins like PelF and PelG, which help the bacteria stick together and form protective layers. It also carries genes like CdgC and LeuO, which are believed to play a role in helping the bacteria build biofilms—slimy structures that allow them to survive harsh conditions and resist antibiotics [18]. On top of that, they are often resistant to multiple antibiotics, including meropenem, making infections hard to treat [19]. In more severe cases, especially in patients with weakened defenses, the bacteria can spread into the bloodstream and trigger a strong inflammatory response, sometimes leading to sepsis or organ failure [10], [11], [20]. Overall, these infections tend to occur in people who are already compromised, and their ability to resist treatment and go undetected makes them particularly challenging in hospital settings [21].

Pandoraea infections are usually acquired in hospital settings, especially among patients who are critically ill or undergoing intensive treatment [5], [12]. They often affect people who have had recent surgeries, are on ventilators, or have medical devices like catheters or central lines, which can provide a pathway for the bacteria to enter the body [5], [22]. Infections may disseminate amongst patients if infection control protocols, such as adequate hand hygiene or equipment sterilization, are not rigorously adhered to [5], [23]. In some cases, patients may first become colonized with *Pandoraea*, especially in the lungs, and later develop an infection if their immune system is weakened or they are treated with broad-spectrum antibiotics [5], [16], [22].

A 44-year-old male patient with a history of multiple trauma underwent evacuation of traumatic intracranial hematomas followed by decompressive craniectomy. During his hospital stay, *Pandoraea apista* was isolated from sputum samples and identified by MALDI-TOF MS. Antimicrobial susceptibility testing revealed a multidrug-resistant

EARLY ACCESS

pattern, with resistance to meropenem and variable susceptibility to other agents.. The patient was treated with meropenem and vancomycin, but despite therapy, his clinical status worsened, and he ultimately died. This case underscores the challenges of managing severe infections caused by *Pandoraea apista* in critically ill patients, particularly given its unpredictable and resistant susceptibility profile [23]. This study is limited by its focus on a single patient, which restricts the ability to generalize the findings or draw firm conclusions about *Pandoraea apista* infections in non-cystic fibrosis (non-CF) patients. The pathogenic role and clinical importance of *Pandoraea* species in non-CF settings remain unclear, as the authors acknowledge. Moreover, the absence of comparative analysis with other reported cases or organisms, coupled with the lack of long-term follow-up, reduces the value of the report for understanding patient outcomes and guiding management strategies. While the study highlights the highly variable and multidrug-resistant susceptibility profiles of *Pandoraea*, it does not provide systematic data on treatment effectiveness [23].

Lower respiratory tract involvement is predominant in respiratory infections, especially among cystic fibrosis patients, manifesting as heightened cough, sputum production, and deterioration in lung function [24]. Radiographically, *Pandoraea* infections may mimic Pseudomonas pneumonia, with infiltrates and bronchiectasis [25], [26]. Acute exacerbations often require hospitalization and intravenous antibiotics [27]. Bacteraemia and sepsis *Pandoraea* bloodstream infections, though infrequent, have been documented in patients with central venous catheters, malignancy, or post-surgical infections [11]. Clinical features include fever, hypotension, and elevated inflammatory markers [28]. Other Manifestations Reports of infective endocarditis, osteomyelitis, urinary tract infections, and wound infections exist, albeit in limited numbers [5]. These infections often involve implanted devices or surgical wounds and require combined medical and surgical management [29]. Moreover, *Pandoraea* expresses lipopolysaccharides (LPS), which activate host immune responses. This response largely depends on the specific structure of the lipid A component of LPS. A recent analysis of a chronic strain of *P. pulmonicola* (RL 8228), known for its high virulence, revealed a smooth-type LPS with hypoacylated lipid A variants. These include rare features such as 2-hydroxylation of acyl chains and additional glucosamine substitutions on phosphate groups, offering new insight into the inflammation-inducing properties of this pathogen [30].

EARLY ACCESS

ANTIMICROBIAL RESISTANCE

Currently, there are no standardized antibiotic susceptibility breakpoints defined for *Pandoraea* species. These bacteria are generally classified as multidrug-resistant, often showing strong resistance to β-lactams and aminoglycosides. Recognizing their distinctive resistance profiles is crucial for timely and effective infection control measures [1], [5]. It has been shown that *Pandoraea sputorum*, often found in cystic fibrosis patients, was isolated for the first time in Japan from an elderly male. Whole-genome sequencing of this strain THI4931 revealed resistance to multiple antibiotics, including β-lactams, aminoglycosides, colistin, and polymyxin B, while remaining susceptible to aztreonam, imipenem, and minocycline. The genome carried *AmpC* and *OXA-62* β-lactamase genes. This highlights the potential risk posed by *P. sputorum* in vulnerable hospitalized patients [31]. A different study showed that the complete sequences of eight *Pandoraea* plasmids for the first time, revealing unique features not found in public databases. Some plasmids lacked common replication and segregation genes, suggesting they may rely on host interactions for maintenance. Interestingly, several carried toxin-antitoxin systems and conjugation genes, which could help them persist and spread. These plasmids also contained virulence and antibiotic resistance genes, highlighting the potential of *Pandoraea* spp. as emerging opportunistic pathogens [32]. *A* case with no history of CF who developed *P. sputorum* sepsis following multiple traumatic injuries and burns sustained from a brick kiln collapse. The strain was resistant to many antibiotics, including meropenem, quinolones, and aminoglycosides, but remained sensitive to imipenem, tetracyclines, and ampicillin/sulbactam. This may be linked to their ability to form biofilms and produce carbapenemases. The case underlines the importance of early identification and targeted therapy, as *P. sputorum* can pose a serious threat even in patients without underlying conditions [11]. Although the study focused on *Pseudomonas aeruginosa*, similar resistance mechanisms may be at play in *Pandoraea* species. These include the production of extended-spectrum beta-lactamases, enzymes that modify aminoglycosides, mutations in DNA gyrase and topoisomerase, loss of the OprD2 porin protein, and overactive efflux pumps. Together, these factors likely contribute to the high level of multidrug resistance seen in *Pandoraea* [33]. Notably, *Pandoraea* species, have been found to produce novel siderophores—pandorabactin A and B—through a conserved NRPS gene cluster (pan). These molecules, identified via

EARLY ACCESS

genome mining and metabolite analysis, exhibit iron-chelating. Functional assays demonstrated that pandorabactins deplete iron and exhibit antibacterial activity against CF-associated pathogens lung pathogens such as *Pseudomonas*, *Mycobacterium*, and *Stenotrophomonas*. Metagenomic analysis further links the pan gene's presence to microbial patterns in CF lung samples. These findings shed light on *Pandoraea's* virulence mechanisms and its role in shaping lung microbiota through iron competition [34]. (Table 1).

MICROBIOLOGY AND IDENTIFICATION

The precise identification of *Pandoraea* species is a significant difficulty in clinical microbiology, mainly because to the diagnostic limits of several regular hospital laboratories. Many clinical environments continue to depend on traditional biochemical techniques or commercial identification technologies, which may not possess the requisite sensitivity or specificity to accurately distinguish rare or emerging infections. Advanced molecular techniques, such as 16S rRNA gene sequencing, whole-genome sequencing, or matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS), have proven essential in accurately classifying non-fermentative Gram-negative bacilli like *Pandoraea* [35]. However, these tools are often unavailable in resource-limited environments due to their cost, the need for technical expertise, and infrastructure demands. Compounding the issue, many commercial identification databases used in automated systems either exclude *Pandoraea* species altogether or contain incomplete reference profiles, leading to misidentification or ambiguous results [35]. This highlights the critical need for broader implementation of molecular diagnostics and continuous updates of microbial databases to improve the detection and characterization of rare pathogens like *Pandoraea* in clinical settings [35]. Advancements in genetic techniques, have significantly increased the identification of previously unrecognized microorganisms. These modern tools enhance diagnostic accuracy, particularly for infections caused by organisms that are often missed by conventional microbiological methods [5], [36]. Conventional systems misidentify *Pandoraea* as *Burkholderia* or *Ralstonia* in many cases [15]. Precise identification of microorganisms often depends on advanced microbiological methods, with 16S rRNA gene sequencing being one of the most reliable tools available [37]. Pandoraea spp. can be readily grown on conventional

EARLY ACCESS

bacteriological media, including tryptic soy agar, they typically form cream-colored, circular, convex colonies with smooth, entire margins measuring approximately 1–2 mm in diameter [38].

A 9-year-old boy with cystic fibrosis, chronically colonized by *Pseudomonas aeruginosa* and *Staphylococcus aureus*, was diagnosed with *Pandoraea sputorum* infection, initially misidentified but later confirmed using 16S rRNA sequencing and MALDI-TOF MS. The isolate exhibited a multidrug-resistant profile, showing susceptibility only to imipenem and trimethoprim-sulfamethoxazole (TMS). The patient was treated with both agents; however, *P. sputorum* was not eradicated, and chronic colonization persisted, contributing to progressive lung function decline. Despite this, his clinical condition improved after adjustment of therapy of combination therapy of imipenem, amikacin and colistin [37]. This report, the first documented Argentinian case, underscores the diagnostic challenges posed by *Pandoraea* species, the limited treatment options available, and the difficulty in attributing outcomes due to co-infection with other pathogens. While the single-case nature restricts generalizability, the case highlights the importance of accurate identification and the urgent need for further studies to clarify the pathogenic role and management strategies for *P. sputorum* in cystic fibrosis patients [37]. (Table 2).

Timely identification of *Pandoraea* infections requires heightened clinical awareness and microbiological vigilance, particularly given the organism's rarity and diagnostic challenges [15]. One of the most notable features aiding in its detection is its unique antimicrobial resistance profile, especially in relation to carbapenems. *Pandoraea* species often exhibit a distinctive pattern of resistance characterized by susceptibility to imipenem while demonstrating resistance to meropenem—a trait not commonly observed in other non-fermenting Gram-negative bacilli. This unusual carbapenem (meropenem) susceptibility pattern, combined with broader multidrug resistance, serves as a critical diagnostic clue and underscores the need for accurate antimicrobial susceptibility testing to guide appropriate therapy [15], [39]. Precise identification of *Pandoraea* species often requires the use of advanced microbiological techniques, particularly due to the limitations of conventional diagnostic tools. Among these, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) and 16S rRNA gene sequencing are the most reliable. In this review, MALDI-TOF emerged as the most frequently employed technique, followed closely

EARLY ACCESS

by 16S rRNA sequencing [37]. In numerous cases, both methods were used in tandem to confirm the diagnosis. For instance, a study conducted by Martina et al. highlighted the effectiveness of combining 16S rRNA sequencing with mass spectrometry in accurately identifying *P. sputorum*, a pathogen that had previously been misdiagnosed using standard laboratory methods [37], [40]. This underscores the importance of integrating multiple advanced technologies for the accurate detection of rare or atypical pathogens. Despite the accuracy of advanced molecular tools, their high cost and limited accessibility in many clinical laboratories necessitate reliance on distinctive biochemical and cultural characteristics for identifying *Pandoraea* species. Supporting this approach, Jorgensen et al. employed pulsed-field gel electrophoresis (PFGE) to perform an epidemiological investigation of *P. apista* isolates, demonstrating the value of conventional yet powerful techniques in the absence of high-end molecular diagnostics [37], [40].

To evaluate the possibility of differentiating among *Pandoraea* species, restriction fragment length polymorphism (RFLP) analysis and direct sequencing of the gyrB gene were performed on 67 isolates. Distinct RFLP patterns specific to each species were observed after digesting the PCR-amplified *gyrB* gene with MspI, and these groupings were validated through sequencing of selected representative strains. The findings highlight the effectiveness of *gyrB*-based RFLP and sequencing as reliable tools for species-level identification of *Pandoraea* [41]. Additionally, the study suggests that improved primer sets could enhance the amplification and use of the *gyrB* gene in broader β-Proteobacteria taxonomy. Importantly, the classification of *Pandoraea* genomospecies 2 may warrant reevaluation based on genetic data [42]. Recently, a study has been reported the isolation of *Ralstonia* and *Pandoraea* species from the respiratory cultures of cystic fibrosis (CF) patients [41]. It has been used the ribosomal DNA restriction analysis (ARDRA) for species differentiation within *Ralstonia* and *Pandoraea*, researchers compared restriction profiles of reference strains using six enzymes previously validated for *Burkholderia* identification. ARDRA successfully differentiated all tested *Ralstonia* species and *Pandoraea norimbergensis*, but it was less effective at distinguishing *P. pnomenusa*, *P. sputorum*, *P. pulmonicola*, and *P. apista* at the species level [41]. Early diagnosis is crucial to prevent delays in commencing suitable therapy, which can greatly affect patient outcomes and avert problems.

EARLY ACCESS

TREATMENT

At present, there are no established treatment methods for *Pandoraea* infections, and therapy is frequently commenced experimentally while awaiting susceptibility test outcomes. The absence of explicit instructions is probably attributable to the limited availability of public data globally. Treatment outcomes vary, with higher mortality rates observed, often depending on factors such as the site of infection and the patient's overall health status [5]. The treatment of the *Pandoraea* genus remain largely unclear, contributing to diagnostic and therapeutic challenges. Infections caused by *Pandoraea* in non-cystic fibrosis (non-CF) patients may be underreported or misidentified, highlighting the need for improved detection and a deeper understanding of these emerging pathogens [22]. Moreover, The treatment of infections caused by *Pandoraea* species is particularly challenging due to their resistance to multiple antibiotics [22]. Carbapenems, especially imipenem, seem to be a viable treatment for severe *Pandoraea* infections, as the majority of isolates demonstrate resistance to this antibiotic. Imipenem may give a more effective therapeutic alternative compared to other antimicrobials, especially in the absence of established treatment guidelines. Trimethoprim/sulfamethoxazole has also been frequently used in the management of *Pandoraea* infections, with aminoglycosides and quinolones being considered in some cases [5]. However, due to the variable and often multidrug-resistant nature of *Pandoraea* species, antibiotic selection should be guided by *in vitro* susceptibility testing to ensure effective and targeted therapy [5]. It has been shown that the antibiotic susceptibility profile of *Pandoraea* species isolated from blood and wound secretion samples in our case highlights a pattern of multidrug resistance. Across all samples, the isolates demonstrated resistance to a wide range of β-lactam antibiotics, including piperacillin, piperacillin/tazobactam, cefazolin, cefuroxime (both sodium and axetil forms), cefotetan, ceftazidime, cefepime, and aztreonam. Resistance was also observed to aminoglycosides (amikacin, gentamicin, and tobramycin) and fluoroquinolones (ciprofloxacin and levofloxacin), with only intermediate susceptibility to ceftriaxone and levofloxacin in two samples [11]. Notably, the isolates were uniformly susceptible to trimethoprim/sulfamethoxazole and imipenem, while showing resistance to meropenem, a finding consistent with the known unique resistance profile of *Pandoraea* species. Additionally, ampicillin/sulbactam and minocycline showed favorable activity, indicating their

EARLY ACCESS

potential as alternative treatment options. This susceptibility pattern emphasizes the importance of accurate and timely antimicrobial susceptibility testing to guide effective therapy for *Pandoraea* infections [11].

A study demonstrated the *in vitro* efficacy of various β-lactam–β-lactamase inhibitor combinations, including ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, and piperacillin-tazobactam, as well as 11 additional antibiotics against 420 clinical isolates of *Burkholderia*, *Achromobacter*, Stenotrophomonas, and *Pandoraea* species [43]. 89% of these isolates were recovered from respiratory samples of individuals with cystic fibrosis. Among the newer combination therapies, meropenem-vaborbactam exhibited the strongest activity, particularly against *Burkholderia* and *Achromobacter* strains, including those with multidrug-resistant (MDR) and extensively drug-resistant (XDR) profiles [43]. However, none of the newer β-lactam–β-lactamase inhibitor combinations offered improved efficacy over older agents when tested against *Stenotrophomonas maltophilia* and *Pandoraea* species, highlighting the persistent challenge of treating infections caused by these organisms [43].

There is currently a lack of detailed clinical data on how effective these antimicrobial agents truly are against *Pandoraea* infections. While some *in vitro* studies may suggest potential activity, real-world evidence from clinical cases remains scarce. As a result, it is hard to make confident therapy recommendations for *Pandoraea* infections depending on solely on existing data. More targeted research, including clinical trials and case studies, is immediate needed to better understand the therapeutic possible and limitations of these antibiotics when dealing with *Pandoraea* species [5], [11], [22], [42]. (Table 3).

DISCUSSION

Future approaches

The current study highlights a critical gap in the scientific literature regarding effective strategies to combat *Pandoraea* infections. None of the available reviews have addressed the isolation, characterization, or therapeutic application of bacteriophages specific to *Pandoraea* spp., representing a promising but unexplored area. Similarly, there is a noticeable lack of studies evaluating the efficacy of antimicrobial peptides or combination antibiotic therapies against this emerging

EARLY ACCESS

pathogen. This limited evidence base underscores the urgent need for targeted research to develop innovative and effective treatment strategies.

In particular, phage therapy should be investigated not only for its therapeutic potential but also for its role in reducing biofilm-associated resistance, which is a hallmark of *Pandoraea* spp. Similarly, antimicrobial peptides warrant further attention because of their unique mechanisms of disrupting bacterial membranes and their reduced likelihood of inducing resistance compared to conventional drugs [44], [45]. Exploring rationally designed combination therapies could provide a dual benefit—enhancing antimicrobial efficacy while simultaneously limiting resistance development. Moreover, integrating genomic and transcriptomic studies could help uncover potential molecular targets and resistance mechanisms, thereby guiding the design of novel interventions. Finally, establishing international collaborative networks and multicenter studies will be essential to generate robust clinical evidence and translate these experimental strategies into viable therapeutic options [44], [45].

Notably, bacteriophages and their derivatives, such as endolysins, play a crucial role in combating biofilms by degrading the extracellular matrix and directly killing embedded bacteria. These phages produce enzymes like depolymerases and endolysins that break down biofilm polysaccharides and peptidoglycan, thereby enhancing biofilm penetration and bacterial eradication [44], [45]. Moreover, phage-antibiotic combinations and phage cocktails have shown superior efficacy, as they not only synergistically disrupt biofilms but also help prevent or delay the development of resistance [44], [45]. For instance, phage vB_C4, which targets *Aeromonas veronii*, demonstrated remarkable effectiveness when combined with antibiotics, leading to significant removal of mature biofilms while simultaneously reducing the emergence of phage-resistant bacterial populations [44]. These studies highlight the potential of exploring bacteriophage therapy against *Pandoraea* spp., either as a standalone approach or in combination with antibiotics.

Antimicrobial peptides (AMPs), such as SAAP-148, LI14, CIT-8, and TM18, exert their activity primarily by permeabilizing and disrupting bacterial membranes, resulting in rapid cell death and effective biofilm eradication. They act by targeting key membrane components, including phosphatidylglycerol, cardiolipin, and lipopolysaccharides (LPS), which leads to dissipation of the proton motive force and

EARLY ACCESS

leakage of vital cellular contents. Importantly, many AMPs not only inhibit biofilm formation but also eradicate mature biofilms, even in multidrug-resistant strains, highlighting their therapeutic promise. Furthermore, their unique membrane-targeting mechanism makes them less likely to induce bacterial resistance, as circumventing this activity would compromise cell viability [46]–[50]. Collectively, these findings underscore the significance of AMPs in addressing antimicrobial resistance (AMR) and biofilm-associated infections, while also encouraging further research into novel peptide-based therapeutics targeting challenging pathogens such as *Pandoraea* spp.

On the other hand, efflux pumps play a central role in both drug extrusion and biofilm development, making them attractive targets for efflux pump inhibitors (EPIs), which show promise in restoring antibiotic efficacy against bacteria [51]. Notably, *Staphylococcus aureus* uses the NorA efflux pump to resist multiple antibiotics and biocides, and although several efflux pump inhibitors have been identified, none are clinically approved due to toxicity concerns [52]. It has been shown that screening of ~1200 approved drugs identified nilotinib, a tyrosine kinase inhibitor, as a potent NorA EPI that synergizes with ciprofloxacin and effectively reduces both biofilm formation and mature biofilms at clinically achievable concentrations [52]. Moreover, another study demonstrated that boeravinone B acts as a potent NorA efflux pump inhibitor, enhancing ciprofloxacin activity against *Staphylococcus aureus*, including methicillin-resistant strains, while significantly reducing biofilm formation and bacterial invasion into macrophages. Mechanistic assays affirmed its efflux inhibition and accumulation effects, and boeravinone B also inhibited human P-glycoprotein, highlighting its dual role in reversing bacterial resistance and modulating drug transport [53]. Surprisingly, Carbonyl cyanide p-nitrophenylhydrazone (2e) exhibited synergistic antibiofilm activity with ofloxacin against MRSA, significantly lowering Minimum Biofilm Eradication Concentration values and more effectively reducing bacterial load *in vivo* than 2e alone. This synergy works by 2e inhibiting the NorA efflux pump and down-regulating quorum-sensing and virulence genes, including agrA, sarA, icaA, and hla, enhancing the bactericidal effect of the antibiotic [54].

On the other hand, Metallic nanoparticles offer a promising strategy to inhibit these pumps, potentially restoring antibiotic activity and reducing microbial biofilm formation when used in combination with conventional drugs [55]. Moreover, Metal-based nanoparticles, in particular, show promising potential to disrupt efflux activity,

EARLY ACCESS

reduce biofilm formation, and enhance antimicrobial efficacy, though further mechanistic studies are needed to fully exploit this approach [56]. Based on the literature, future research should focus on identifying and optimizing safe and effective efflux pump inhibitors, including repurposed drugs like nilotinib and natural compounds such as boeravinone B, to restore antibiotic activity and reduce biofilm formation, particularly against challenging pathogens like *Pandoraea* spp. Additionally, exploring metal-based nanoparticles as novel efflux pump-targeting agents could provide a promising complementary strategy to enhance antimicrobial efficacy, though detailed mechanistic studies are still needed.

Most clinically important antibiotic resistance genes in Gram-negative bacteria are located in the accessory genome, particularly on mobile genetic elements such as plasmids, integrons, and transposons, rather than in the core genome. These elements facilitate horizontal gene transfer and accelerate the dissemination of resistance traits in clinical environments [57]–[60].. Resistance genes are often mobilized by insertion sequences such as IS26, integrons, and transposons, enabling their movement between plasmids and chromosomes—a major driver of multidrug resistance. In contrast, some mechanisms like efflux pumps and reduced outer membrane permeability are encoded by core genome genes and are universally present across bacterial species. While these core determinants contribute to intrinsic resistance, they are generally less associated with high-level acquired resistance compared to genes carried on plasmids and other accessory elements [57]–[60].

Future efforts should prioritize experimental studies, *in vivo* models, and clinical trials to explore phage therapy, antimicrobial peptides, and synergistic drug regimens. Such investigations would not only fill the existing knowledge gaps but also pave the way toward more effective management of *Pandoraea* infections. The scarcity of comprehensive literature on this subject should inspire researchers to explore this neglected area and contribute meaningful insights to the scientific community.

CONCLUSION

Pandoraea infections represent a significant but overlooked threat in the landscape of multidrug-resistant pathogens. This review reveals a substantial gap in the available clinical and experimental data, especially concerning targeted therapeutic approaches such as phage therapy, antimicrobial peptides, and antibiotic combinations. The

EARLY ACCESS

scarcity of real-world evidence limits the development of confident treatment recommendations. Therefore, future studies must focus on the isolation and characterization of *Pandoraea*-specific bacteriophages, evaluation of novel antimicrobial agents, and robust clinical investigations. Addressing these challenges is crucial not only to improving patient outcomes but also to expanding the scientific understanding of this emerging pathogen.

Conflicts of interest: Authors declare no conflicts of interest.

Funding: Authors received no specific funding for this work.

Submitted: August 14, 2025

Accepted: October 4, 2025

Published online: October 23, 2025

EARLY ACCESS

REFERENCES

1- Goris J, De Vos P, Coenye T, et al. Description of Pandoraea gen. nov. with Pandoraea apista sp. nov., Pandoraea pulmonicola sp. nov., Pandoraea pnomenusa sp. nov., Pandoraea sputorum sp. nov. and Pandoraea norimbergensis comb. nov. Int J Syst Evol Microbiol. 2000;50(2):887–99.

2- See-Too WS, Ee R, Lim YL, et al. Pandoraea fibrosis sp. nov., a novel Pandoraea species isolated from clinical respiratory samples. Int J Syst Evol Microbiol. 2019;69(3):645–51.

3- Green H, Jones AM. Emerging Gram-negative bacteria: Pathogenic or innocent bystanders. Curr Opin Pulm Med. 2018;24(6):592–8.

4- Anandham R, Indiragandhi P, Madhaiyan M, et al. Pandoraea thiooxydans sp. nov., a facultatively chemolithotrophic, thiosulfate-oxidizing bacterium isolated from rhizosphere soils of sesame (Sesamum indicum L.). Int J Syst Evol Microbiol. 2010;60(1):21–6.

5- Ziogou A, Giannakodimos A, Giannakodimos I, Tsantes AG, Ioannou P. Pandoraea infections in humans—A systematic review. J Clin Med. 2024;13(22):1–15.

6- Gao W, Zhao Q, Chen J, et al. An efflux pump in genomic island GI-M202a mediates the transfer of polymyxin B resistance in Pandoraea pnomenusa M202. Int Microbiol. 2024;27(1):277–90.

7- Pugès M, Debelleix S, Fayon M, Mégraud F, Lehours P. Persistent infection due to Pandoraea sputorum in a young cystic fibrosis patient resistant to antimicrobial treatment. Pediatr Infect Dis J. 2015;34(10):1135–7.

8- Tabatabaei M, Dastbarsar M, Moslehi MA. Isolation and identification of Pandoraea spp. from bronchoalveolar lavage of cystic fibrosis patients in Iran. Ital J Pediatr. 2019;45(1):1–8.

9- Singh S, Sahu C, Patel SS, Garg A, Ghoshal U. Pandoraea apista bacteremia in a COVID-positive man: A rare coinfection case report from North India. J Lab Physicians. 2021;13(2):192–4.

EARLY ACCESS

10- Degand N, Marchandin H, Fertin A, et al. Epidemic spread of Pandoraea pulmonicola in a cystic fibrosis center. BMC Infect Dis. 2015;15(1):1–7.

11- Ma Z, Zou X, Lin J, Zhang C, Xiao S. Sepsis due to Pandoraea sputorum infection after multiple trauma in a non-cystic fibrosis patient: A case report from Southeast China. Infect Drug Resist. 2022;15:7043–52.

12- Kruis T, Kaase M, Wichelhaus TA, et al. Outbreak of Pandoraea commovens infections among non–cystic fibrosis intensive care patients, Germany, 2019–2021. Emerg Infect Dis. 2023;29(11):2229–37.

13- Pimentel JD, MacLeod C. Misidentification of Pandoraea sputorum isolated from sputum of a patient with cystic fibrosis and review of Pandoraea species infections in transplant patients. J Clin Microbiol. 2008;46(9):3165–8.

14- Monzón T, Valga F, Reichert J, López C. Hemodialysis catheter colonised by Pandoraea spotorum. Nefrologia. 2018;38(6):662–4.

15- Stryjewski ME, LiPuma JJ, Messier RH, Reller LB, Alexander BD. Sepsis, multiple organ failure, and death due to Pandoraea pnomenusa infection after lung transplantation. J Clin Microbiol. 2003;41(5):2255–7.

16- Caraher E, Collins J, Herbert G, et al. Evaluation of in vitro virulence characteristics of the genus Pandoraea in lung epithelial cells. J Med Microbiol. 2008;57(1):15–20.

17- Chen H, Yin Y, Gao H, et al. Identification of pathogen(s) in infectious diseases using shotgun metagenomic sequencing and conventional culture: A comparative study. PeerJ. 2021;9:1–20.

18- Wu X, Zhang C, Xu H, et al. The roles of extracellular polymeric substances of Pandoraea sp. XY-2 in the removal of tetracycline. Bioprocess Biosyst Eng. 2020;43(11):1951–60.

19- Dlewati MM, Aung PP, Park K, Rodriguez JA, Poon KK. Meropenem-resistant Pandoraea pneumonia in a critically ill patient with COVID-19. Cureus. 2021;13(11):10–4.

EARLY ACCESS

20- Kokcha S, Bittar F, Richet H, et al. Pandoraea pulmonicola chronic colonization in a cystic fibrosis patient, France. New Microbes New Infect. 2013;1(2):27–9.

21- J. A. Johnson, L. N. Lindsey, J.-Y. Han, S. M. Moskowitz, J. L. Burns, and X. Qin, “Pandoraea bacteremia in a cystic fibrosis patient with associated systemic illness,” Pediatr. Infect. Dis. J. 2004; 23 (9): 881–882.

22- C. Lin et al., “Pneumonia due to Pandoraea apista after evacuation of traumatic intracranial hematomas: a case report and literature review,” BMC Infect. Dis. 2019; 19 (1): 1–9.

23- A. M. Jones, and A. K. Webb. “Recent advances in cross-infection in cystic fibrosis: Burkholderia cepacia complex, Pseudomonas aeruginosa, MRSA and Pandoraea spp.,” J. R. Soc. Med. Suppl. 2003; 96 (43): 66–72.

24- E. Chiappini, G. Taccetti, and M. De Martino. “Bacterial lung infections in cystic fibrosis patients: an update,” Pediatr. Infect. Dis. J. 2014; 33 (6): 653–654.

25- T. C. Mcloud, and P. M. Boiselle. “Pulmonary infections in the normal host,” Thorac. Radiol. 2020; ch. 3, Jan.

26- J. J. Lipuma, B. J. Currie, S. J. Peacock, and P. A. R. Vandamme. “Burkholderia, Stenotrophomonas, Ralstonia, Cupriavidus, Pandoraea, Brevundimonas, Comamonas, Delftia, and Acidovorax,” Man. Clin. Microbiol. 2015; 791–812.

27- N. Itoh, N. Akazawa, Y. Ishibana, T. Masuishi, A. Nakata, and H. Murakami. “Clinical and microbiological features of obstructive cholangitis with bloodstream infection caused by Pandoraea apista identified by MALDI-TOF mass spectrometry and ribosomal RNA sequencing in a cancer patient,” BMC Infect. Dis. 2022; 22 (1): 1–7.

28- R. Gauer, D. Forbes, and N. Boyer. “Sepsis: diagnosis and management,” Am. Fam. Physician. 2020; 101 (7): 409–418.

EARLY ACCESS

29- 29- S. R. Oliveira, I. C. Monteiro, C. Rodrigues, and M. J. Soares. “Fever in a patient with a central venous catheter colonized by Pandoraea pnomenusa,” Acta Med. Port. 2023; 36 (2): 127–130.

30- M. D. Pither, S. McClean, A. Silipo, A. Molinaro, and F. Di Lorenzo. “A chronic strain of the cystic fibrosis pathogen Pandoraea pulmonicola expresses a heterogenous hypo-acylated lipid A,” Glycoconj. J. 2021; 38 (2): 135–144.

31- J. Koizumi, Y. Nasu, Y. Hirai, and H. Nakaminami. “Emergence of multidrug-resistant Pandoraea sputorum in Japan,” Microbiol. Resour. Announc. 2024; 13 (4): 2–4.

32- D. Yong, K. K. Tee, W. F. Yin, and K. G. Chan. “Characterization and comparative overview of complete sequences of the first plasmids of Pandoraea across clinical and non-clinical strains,” Front. Microbiol. 2016; 7 (Oct): 1–11.

33- M. G. Shen, J. L. Zhu, D. M. Zhu, and J. Wang. “Mechanisms of pandrug-resistance of Pseudomonas aeruginosa,” Zhonghua Yi Xue Za Zhi. 2008; 88: 1859–1862.

34- E. Herzog, et al. “Antibacterial siderophores of Pandoraea pathogens and their impact on the diseased lung microbiota,” Angew. Chemie. 2025; 137 (24).

35- A. Pagé, M. K. Tivey, D. S. Stakes, and A. L. Reysenbach. “Temporal and spatial archaeal colonization of hydrothermal vent deposits,” Environ. Microbiol. 2008; 10 (4): 874–884.

36- T. Coenye, L. Liu, P. Vandamme, and J. J. Lipuma. “Identification of Pandoraea species by 16S ribosomal DNA-based PCR assays,” J. Clin. Microbiol. 2001; 39 (12): 4452–4455.

37- P. F. Martina, et al. “First time identification of Pandoraea sputorum from a patient with cystic fibrosis in Argentina: A case report,” BMC Pulm. Med. 2017; 17 (1): 1–5.

EARLY ACCESS

38- N. Sahin, et al. “Pandoraea oxalativorans sp. nov., Pandoraea faecigallinarum sp. nov. and Pandoraea vervacti sp. nov., isolated from oxalate-enriched culture,” Int. J. Syst. Evol. Microbiol. 2011; 61 (9): 2247–2253.

39- M. I. Daneshvar, et al. “Assignment of CDC weak oxidizer group 2 (WO-2) to the genus Pandoraea and characterization of three new Pandoraea genomospecies,” J. Clin. Microbiol. 2001; 39 (5): 1819–1826.

40- I. M. Jørgensen, et al. “Epidemic spread of Pandoraea apista, a new pathogen causing severe lung disease in cystic fibrosis patients,” Pediatr. Pulmonol. 2003; 36 (5): 439–446.

41- 42-C. Segonds, S. Paute, and G. Chabanon. “Use of amplified ribosomal DNA restriction analysis for identification of Ralstonia and Pandoraea species: Interest in determination of the respiratory bacterial flora in patients with cystic fibrosis,” J. Clin. Microbiol. 2003; 41 (7): 3415–3418.

42- T. Coenye, J. J. Lipuma, and P. Vandamme. “Use of the gyrB gene for the identification of Pandoraea species,” FEMS Microbiol. Lett. 2002; 208 (1): 15–19.

43- L. J. Caverly, et al. “In vitro activities of β-lactam–β-lactamase inhibitor antimicrobial agents against cystic fibrosis respiratory pathogens,” Antimicrob. Agents Chemother. 2019; 64 (1): 1–4.

44- X. Cao, et al. “Enhanced bacteriostatic effects of phage vB_C4 and cell wall-targeting antibiotic combinations against drug-resistant Aeromonas veronii,” Microbiol. Spectr. 2025; 13 (2): 1–15.

45- S. Liu, H. Lu, S. Zhang, Y. Shi, Q. Chen. “Phages against pathogenic bacterial biofilms and biofilm-based infections: A review,” Pharmaceutics 2022; 14 (2).

46- J. Shi, C. Chen, D. Wang, Z. Wang, Y. Liu. “The antimicrobial peptide LI14 combats multidrug-resistant bacterial infections,” Commun. Biol. 2022; 5 (1): 1–14.

EARLY ACCESS

47- P. H. De Breij, A. Riool, M. Cordfunke, R. A. Malanovic, N. de Boer, L. Koning, R. I. … & Nibbering. “The antimicrobial peptide SAAP-148 combats drug-resistant bacteria and biofilms,” Sci. Transl. Med. 2018; 10 (423): 3044.

48- S. J. T. Wardell, et al. “A biofilm-targeting lipo-peptoid to treat Pseudomonas aeruginosa and Staphylococcus aureus co-infections,” Biofilm 2025; 9.

49- J. S. Khara, et al. “Disruption of drug-resistant biofilms using de novo designed short α-helical antimicrobial peptides with idealized facial amphiphilicity,” Acta Biomater. 2017; 57: 103–114.

50- A. Di Somma, A. Moretta, C. Canè, A. Cirillo, A. Duilio. “Antimicrobial and antibiofilm peptides,” Biomolecules 2020; 10 (4): 1–15.

51- A. Reza, J. Mark Sutton, K. M. Rahman. “Effectiveness of efflux pump inhibitors as biofilm disruptors and resistance breakers in gram-negative (ESKAPEE) bacteria,” Antibiotics 2019; 8 (4).

52- S. Zimmermann, et al. “Clinically approved drugs inhibit the Staphylococcus aureus multidrug NorA efflux pump and reduce biofilm formation,” Front. Microbiol. 2019; 10: 1–13.

53- S. Singh, et al. “Boeravinone B, a novel dual inhibitor of NorA bacterial efflux pump of Staphylococcus aureus and human P-glycoprotein, reduces biofilm formation and intracellular invasion of bacteria,” Front. Microbiol. 2017; 8: 1–12.

54- X. Lu, G. Wang, Y. Xie, W. Tang, B. Liu, J. Zhang. “Efflux pump inhibitor combined with ofloxacin decreases MRSA biofilm formation by regulating the gene expression of NorA and quorum sensing,” RSC Adv. 2023; 13 (4): 2707–2717.

55- D. Gupta, A. Singh, A. U. Khan. “Nanoparticles as efflux pump and biofilm inhibitor to rejuvenate bactericidal effect of conventional antibiotics,” Nanoscale Res. Lett. 2017; 12: 9–11.

EARLY ACCESS

56- R. Musiol. “Efflux systems as a target for anti-biofilm nanoparticles: perspectives on emerging applications,” Expert Opin. Ther. Targets 2023; 27 (10): 953–963.

57- X. Wang, et al. Inter-plasmid transfer of antibiotic resistance genes accelerates antibiotic resistance in bacterial pathogens. *ISME J.* 2024; 18 (1).

58- T. Kjaergaard Nielsen, P. Denis Browne, L. H. Hansen. Mobilization of antibiotic resistance genes differ by resistance mechanism. *bioRxiv* 2021; p. 2021.01.10.426126.

59- D. Debroas. Global analysis of the metaplasmidome: ecological drivers and spread of antibiotic resistance genes across ecosystems. *Microbiome* 2025; 13 (1).

60- Y. Wang, A. Batra, H. Schulenburg, T. Dagan. Gene sharing among plasmids and chromosomes reveals barriers for antibiotic resistance gene transfer. *Philos. Trans. R. Soc. B Biol. Sci.* 2022; 377 (1842).

EARLY ACCESS

TABLES WITH LEGENDS

Table 1. Key resistance features of *Pandoraea* spp.

Aspect	**Key findings**	**References**
Breakpoints	No defined standards; MDR common	[1], [5]
Resistance	Resistant to β-lactams, aminoglycosides, colistin; susceptible to imipenem, TMS, minocycline, aztreonam	[11], [31]
Resistance genes	*ampC*, *OXA-62*; plasmid-borne genes	[31], [32]
Plasmids	Unique, with toxin–antitoxin and conjugation genes	[32]
Mechanisms	Biofilm, carbapenemases, efflux, porin loss	[11], [33]
Metabolites	Pandorabactin siderophores (iron competition)	[34]

Abbreviations: MDR: Multidrug-resistant; TMS: Trimethoprim–sulfamethoxazole; β-lactams: Beta-lactam antibiotics; *ampC*: AmpC β-lactamase gene; OXA-62: Oxacillinase-62.

Table 2. Summary of reported clinical cases of *Pandoraea* infections, including treatment approaches, outcomes, and key clinical points

Case	**Treatment**	**Outcome**	**Key point**	**Ref.**
46F, non-CF, burns (*P. sputorum*)	Targeted therapy + supportive care	Recovered, discharged after 2 months	Rare non-CF case; imipenem effective	[11]
30M, lung transplant (*P. pnomenusa*)	Empirical carbapenems, cephalosporins, TMS	Died (sepsis, multi-organ failure)	High mortality in transplant pts; rapid ID crucial	[15]
44M, trauma (*P.*	Meropenem +	Died (clinical	Poor prognosis; MDR, variable	[23]

EARLY ACCESS

Case	Treatment	Outcome	Key point	Ref.
apista)	vancomycin	deterioration)	susceptibility	
9M, CF (*P. sputorum*)	Imipenem + TMS (later with amikacin, colistin)	Colonization persisted; clinical improvement	Diagnostic challenge; first Argentinian CF case	[37]

These reports highlight the emerging clinical significance of multidrug-resistant *Pandoraea* species, their variable susceptibility profiles, and challenges in management. Abbreviations: CF: Cystic fibrosis; F: Female; M: Male; MDR: Multidrug-resistant; TMS: Trimethoprim-sulfamethoxazole; pts: Patients; ID: Identification.

Table 3. Summary of treatment and antimicrobial susceptibility in *Pandoraea* infections

Aspect	Key findings	References
Treatment guidelines	No standard therapy; empirical use common; outcomes vary	[5], [22]
Main effective agents	Imipenem, trimethoprim/sulfamethoxazole (TMS) most reliable	[5], [11], [22]
Alternative agents	Ampicillin/sulbactam, minocycline sometimes active	[11]
Ineffective agents	Resistance to most β-lactams, aminoglycosides, fluoroquinolones, meropenem	[11]
Challenges	MDR patterns, frequent misidentification, lack of clinical data	[5], [11], [22], [42]

Abbreviations: TMS: Trimethoprim/sulfamethoxazole; MDR: Multidrug-resistant.

EARLY ACCESS