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Managing Multidrug-Resistant *Pandoraea* spp.: current evidence and knowledge gaps

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SUMMARY

Pandoraea species are emerging Gram-negative non-fermenting pathogens increasingly associated with human infections, particularly in patients with cystic fibrosis, immunocompromised hosts, and critically ill individuals. These bacteria exhibit intrinsic multi-drug resistance (MDR), complicating treatment and management. A comprehensive literature search was conducted to identify relevant studies concerning *Pandoraea* infections on PubMed/MEDLINE/Google Scholar and books written by experts in microbiology and infectious diseases. *Pandoraea* isolates frequently demonstrate resistance to the most common antimicrobials, such as β-lactams, aminoglycosides, fluoroquinolones, and polymyxins. Interestingly, many strains retain susceptibility to imipenem (IMP) despite resistance to meropenem due to the production of specific oxacillinase-type β-lactamases (OXA) called OXA-1152. Although robust clinical data are lacking, IMP and trimethoprim-sulfamethoxazole (SXT) are the most active agents and may be considered for empirical or combination therapy. Data on the efficacy of newer antibiotics against *Pandoraea* spp. are extremely limited and often inconsistent. This lack of strong evidence highlights a significant knowledge gap. A few antibiotic options are appropriate for treating *Pandoraea* spp. with IMP and SXT, which remains the treatment of choice, as well as in combination in the case of severe infections. This review focuses on a niche topic to support clinicians in selecting appropriate therapeutic decisions without precise evidence-based medicine.

Keywords: Pandoraea, antibiotic treatment, non-fermenter bacteria, Gram-negative non-fermenting bacteria, Multi-drug resistance Gram-negative bacteria, cystic fibrosis.

INTRODUCTION

The *Pandoraea* genus is an emerging Gram-negative non-fermenting, obligately aerobic, rod-shaped bacterium first described by Coenye *et al.* in 2000. It was initially misclassified within the *Burkholderia cepacia* complex or the genera *Ralstonia paucula* and *R. pickettii* [1, 2]. *Pandoraea* includes several human-pathogenic species, such as *P. apista, P. pnomenusa, P. sputorum, P. pulmonicola, P. norimbergensis, P. commovens, P. vervacti, P. oxalalivorans* and *P. fibrosis* [1-6]. Infections in humans are considered rare and are predominantly reported in individuals with predisposing conditions such as cystic fibrosis (CF) [7]. Still, cases have also been reported in individuals with other comorbidities or immunocompromised states. A systematic review identified 43 documented cases of *Pandoraea* infections in the literature and among these cases, 39.5% of patients had CF [8]. The most frequently reported infections related to this bacteria were respiratory tract infections, bacteremia, infective endocarditis, pancreatitis, skin and soft tissue infections and osteomyelitis. Figure 1 summarizes the principal infections caused by *Pandoraea* spp alongside a pro-

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posal of antimicrobials for empirical therapy (of course, therapy should be optimized with antimicrobial susceptibility testing (AST) results). The overall mortality rate attributed specifically to *Pandoraea* depends on the type of infection; however, bacteremia can reach 30.23% [8].

Although the prevalence of *Pandoraea* infections in the general population is not well defined, these pathogens represent a significant threat to vulnerable patient populations. The difficulty in accurately identifying *Pandoraea* spp. using routine diagnostic methods may contribute to underestimating their true incidence [9]. Commonly used tests, such as conventional phenotypic methods and the VITEK 2 (bioMérieux, Marcy-l'Étoile, France), often misdiagnose this pathogen as *Ralstonia*, *Stenotrophomonas*, or *Burkholderia* spp. [9, 10]. Additionally, 16S rRNA analysis and gyrB gene sequences are possible options but have some limitations for the identification of *Pandoraea* spp. [11]. Recently, it has been reported that Matrix Assisted Laser Desorption/Ionisation Time-Of-Flight Mass Spectrometry (MALDI-TOF MS) shows promising results in the identification of many bacterial species. However, a lack of discriminatory power was noted with *Pandoraea*, which can be incorrectly identified as *Achromobacter* or other non-fermenters that are close phylogenetic relative [12].

Intrinsic resistance mechanisms play a central role in the pathogenicity and treatment resistance among *Pandoraea* spp., posing a significant challenge in clinical settings. These bacteria are often resistant to multiple antibiotic classes, including β-lactams, aminoglycosides, fluoroquinolones, and polymyxins [7, 8]. Notably, many *Pandoraea* isolates demonstrate resistance to meropenem (MEM) while retaining susceptibility to imipenem (IMP), suggesting distinct resistance mechanisms, such as the production of OXA-type β-lactamases [13]. Another critical challenge is the absence of species-specific susceptibility breakpoints for *Pandoraea* spp. established by EUCAST (European Committee on Antimicrobial Susceptibility Testing) or CLSI (Clinical and Laboratory Standards Institute). Without standardized interpretive criteria, clinicians and microbiologists are left without reliable guidance to interpret in vitro AST, potentially leading to critical therapeutic dilemmas and possible suboptimal treatment outcomes [14].

This article aims to review the antibiotic resistance profiles of *Pandoraea* spp., evaluate currently available treatment options, and discuss emerging antimicrobial agents.

MATERIAL AND METHODS

A comprehensive literature search was conducted to identify relevant studies concerning *Pandoraea* infections. The search strategy was implemented using

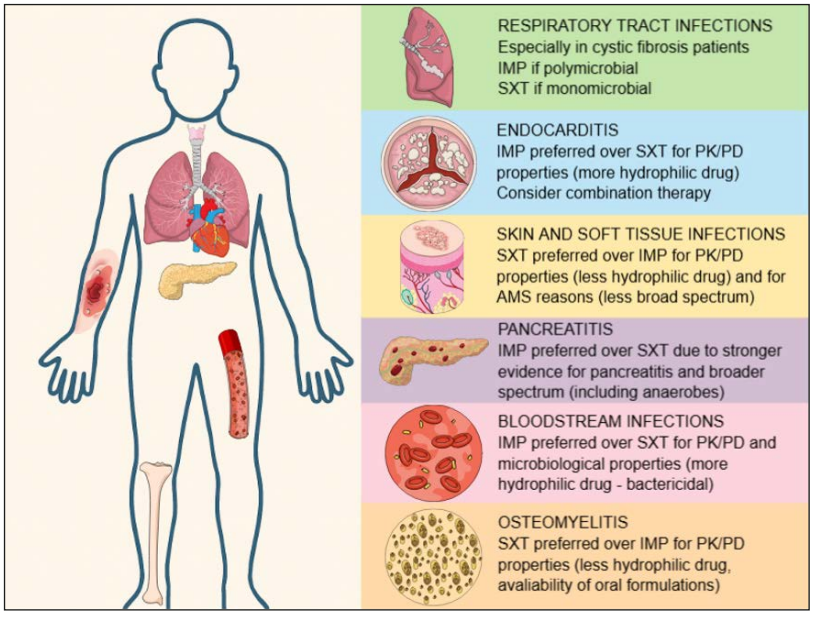

Figure 1
Infections caused by *Pandoraea* spp. and empirical therapy considerations.

online databases (PubMed/MEDLINE/Google Scholar) and books written by experts in microbiology and infectious diseases. The search was not restricted by language, region, study type or publication date and covered articles up to the cutoff date of March 2025. The following keywords and MeSH were used: "*Pandoraea* AND human infections", "*Pandoraea* AND treatment", "*Pandoraea* AND antibiotic resistance", "*Pandoraea* AND ceftolozane-tazobactam", "*Pandoraea* AND ceftazidime-avibactam", "*Pandoraea* AND meropenem-vaborabactam", "*Pandoraea* AND imipenem-relebactam", "*Pandoraea* AND cefiderocol", "*Pandoraea* AND aztreonam-avibactam", "Rare Gram-negative non-fermenting bacteria AND treatment". We screened the articles by title, abstract and full text. After an initial screening of titles and abstracts of the published articles, the reviewers evaluated the full articles to assess the eligibility for each study's inclusion in this narrative review. A study was included to determine if it was likely to provide valid and valuable information according to their view's objective.

The interpretation of minimum inhibitory concentration (MIC), without any species-specific breakpoints, relies on the reference antimicrobial susceptibility testing method and the interpretive criteria established by the CLSI for other non-Enterobacterales which include *Pseudomonas aeruginosa* and other non-fermenting Gram-negative bacteria [15, 16].

Epidemiology

Infections due to *Pandoraea* spp. are rare events. According to the literature, the most frequently observed site of *Pandoraea* infection is the lower respiratory tract, followed by bloodstream infections [8]. However, this microorganism can be associated with outbreaks, especially in fragile populations or intensive care units, representing an essential issue in therapeutic and clinical management [5]. Patients with underlying lung diseases, such as cystic fibrosis, or those who are immunocompromised are particularly susceptible to these types of infections. However, they may also occur in critically ill patients, especially those receiving mechanical ventilation or with a history of prolonged antibiotic use or prior surgeries [5, 17].

Mechanisms of antibiotic resistance

Pandoraea spp. have developed multiple antibiotic resistance mechanisms, making infections difficult or, in some cases, impossible to treat. One of the primary resistance strategies involves the production of β-lactamases, particularly oxacillinases (OXA), which degrade β-lactam antibiotics such as penicillins, cephalosporins, and carbapenems [18]. Of particular interest is that *P. sputorum* can produce a variant known as OXA-1152, which demonstrates stronger binding and hydrolytic activity against MEM than IMP. The combination of avibactam with carbapenems has been shown to restore susceptibility to MEM and significantly reduce IMP MIC, by 64- and 4-fold, respectively [19]. However, it is essential to clarify that the combination of MEM-avibactam is exclusively experimental and not available as a commercial combination. Moreover, *P. pnomenusa* can produce different OXA-like carbapenemases, including OXA-33 and OXA-62. Notably, OXA-62 can hydrolyze penicillins, oxacillin, and carbapenems (including both IMP and MEM), but not expanded-spectrum cephalosporins [20]. Other chromosomally encoded OXA-like genes identified in *Pandoraea* range from OXA-151 to OXA-159, exhibiting varying activity against penicillins, cephalosporins, and carbapenems. In addition to OXA-type β-lactamases, other β-lactamases have been described in *Pandoraea*, such as the FEZ-1 β-lactamase and the AQU-1-type AmpC β-lactamase [21].

These bacteria also utilize efflux pumps, notably resistance-nodulation-cell division (RND) and ATP-binding cassette (ABC) transporters, which actively expel antibiotics from the cell, thereby reducing intracellular concentrations of drugs such as fluoroquinolones, aminoglycosides, and β-lactams [8]. Efflux pumps are particularly problematic in MDR *Pandoraea* strains. In some cases, resistance to polymyxin B is associated with an efflux pump encoded within the genomic island GI-M202a in *P. pnomenusa* [22]. Resistance to tetracyclines has been variably reported among *Pandoraea* species. While minocycline often shows the most consistent in vitro activity, resistance to tigecycline and doxycycline has also been observed [23]. The mechanisms underlying this resistance are not yet fully known. Efflux pumps, particularly of the RND family, are believed to contribute significantly [8].

Another essential resistance mechanism is the modification or loss of outer membrane porins. These structural alterations reduce the permeability to hydrophilic antibiotics, such as carbapenems, limiting their efficacy [24].

Table 1 - Principal resistance mechanisms and their antibiotic target.

Resistance Mechanisms	*Affected Antibiotics*	*References*
Enzymes: OXA-type β-lactamases (e.g., OXA-1152, OXA-33, OXA-62, OXA-151–159)	Penicillins, cephalosporins, carbapenems (especially meropenem and imipenem)	[15-17]
Other β-lactamases (e.g., FEZ-1, AQU-1-type AmpC)	Broad-spectrum β-lactams	[18]
Efflux pumps	Fluoroquinolones, aminoglycosides, β-lactams, Polymyxin B	[8, 19]
Outer membrane porin modification or loss	Carbapenems	[21]
AMEs	Aminoglycosides	[20]
DNA gyrase and topoisomerase IV	Fluoroquinolones	[14]
Not fully understood mechanisms	Tetracyclines (tigecycline, doxycycline), minocycline, trimethoprim-sulfamethoxazole	[8, 20]

AMEs= aminoglycoside-modifying enzymes.

Additionally, *Pandoraea* species can enzymatically inactivate aminoglycosides via aminoglycoside-modifying enzymes (AMEs), further contributing to treatment failure [23].
Resistance to fluoroquinolones in *Pandoraea* is primarily associated with mutations in DNA gyrase and topoisomerase IV, which alter the antibiotic target sites and reduce drug-binding affinity [14]. Although trimethoprim-sulfamethoxazole (SXT) is sometimes considered a therapeutic option, resistance to this combination has been reported in several *Pandoraea* isolates, further limiting treatment alternatives. However, the underlying resistance mechanism in *Pandoraea* remains not fully understood [23].
High-level antibiotic resistance has previously been linked to fitness costs, affecting various phenotypic traits such as growth rate and virulence and contributing to the emergence of bacterial diversity [3]. The combination of these resistance mechanisms, often acting synergistically, severely limits the efficacy of conventional antibiotic therapy and highlights the urgent need for novel therapeutic strategies to manage *Pandoraea* infections effectively. Table 1 shows the principal resistance mechanism and their antibiotic target in *Pandoraea* spp.

Current therapeutic options and resistance rates
The treatment of infections caused by *Pandoraea* spp. is challenging due to their demonstrated resistance to a broad range of antibiotics, including ampicillin, cefazolin, piperacillin, azithromycin, broad-spectrum cephalosporins, and aminoglycosides. Moreover, there could be susceptibility to fluoroquinolones, SXT, macrolide, tetracycline and carbapenems [8, 25]. The main issue regarding susceptibility data in humans is the scarcity of available bibliographic sources. Recently, a systematic review attempted to highlight the main resistance patterns observed in Pandoraea. The review considered 29 studies, including a total of 43 patients [8]. Among β-lactams, IMP remains a valid option, with approximately 85.7% of isolates reported as susceptible; instead, MEM-resistant isolates are prevalent [8, 26]. In contrast, resistance rates to piperacillin-tazobactam and cephalosporins are high, reaching 69.2% and 76.5%, respectively [8].
Aminoglycosides, including gentamicin and tobramycin, show high resistance rates of 96-100% [8, 25]. Fluoroquinolones, such as ciprofloxacin and levofloxacin, also display high resistance, with rates around 78.8%. However, the susceptibility can depend on the species with significant variability [8, 27]. SXT has been among the more effective options, with resistance reported in only 8.8% of cases [8].
Pandoraea spp. exhibit marked macrolide resistance, with susceptibility observed in only 8.33% of tested isolates. In contrast, susceptibility to tetracyclines is more variable, with minocycline showing the highest activity, with 41.67% of isolates reported susceptible [8].
In some studies, colistin and polymyxin B demonstrate variable efficacy, with resistance ranging from 73% to 90% [8, 23]. Given these high resistance rates, AST is essential to guide treatment decisions. However, susceptibility breakpoints for *Pandoraea* are currently lacking in EUCAST and CLSI guidelines. In severe cases or where an antibiogram is unknown, combination therapy may be required [7].

New therapeutic options

Ceftolozane–tazobactam combines an advanced cephalosporin and a β-lactamase inhibitor, primarily designed to target MDR Gram-negative bacteria, including *P. aeruginosa* [14]. In vitro AST has shown that ceftolozane-tazobactam exhibits poor activity against *Pandoraea* isolates, with MICs ranging from 16 to 256 mg/L [5, 14, 28].

Ceftazidime-avibactam is another β-lactam/β-lactamase inhibitor combination that has demonstrated efficacy against various multidrug-resistant Gram-negative pathogens [14]. Data on its activity against *Pandoraea* spp. are limited; however, some studies have reported MIC values of ≥16–32 mg/L [5, 14]. Caverly *et al*., when comparing the MIC values of ceftazidime–avibactam with those of ceftazidime alone, observed no restorative effect of avibactam, as both agents exhibited MICs >32 mg/L [14].

Meropenem–vaborbactam and imipenem–relebactam are two β-lactam/β-lactamase inhibitor combinations developed to treat carbapenem-resistant Gram-negative infections. Meropenem–vaborbactam showed low activity against *Pandoraea* spp., with MIC_{50} values >32 mg/L [14, 29].

Data on imipenem–relebactam are more variable. Since IMP is often considered the drug of choice for treating *Pandoraea* infections, the combination with relebactam has demonstrated promising in vitro activity, with MICs <1 mg/L [5]. However, data on the specific contribution of relebactam to this activity are scarce and not yet fully understood.

Cefiderocol is a novel siderophore cephalosporin designed to overcome resistance in Gram-negative bacteria [30]. However, in vitro, data regarding its activity against *Pandoraea* spp. are highly inconsistent. Kruis *et al*. reported very high MIC values (>256 mg/L) in 24 isolates of *P. commovens* collected during an outbreak among non–CF intensive care unit patients in Germany between 2019 and 2021 [5].

Aztreonam–avibactam is a β-lactam/β-lactamase inhibitor combination specifically designed to target metallo-β-lactamase (MBL)-producing Gram-negative bacteria [31]. As with other agents, data on its activity against *Pandoraea* spp. are limited. Unfortunately, findings from Kruis *et al*. also indicate high MIC values for this compound [5]. Figure 2 reported the usual phenotype of *Pandoraea* spp.

DISCUSSION

The clinical management of *Pandoraea* infections is particularly challenging due to their intrinsic and acquired resistance mechanisms and the lack of standardized antimicrobial susceptibility breakpoints. While initially associated with CF patients, *Pandoraea* spp. are increasingly reported in non-CF individuals, often with underlying comorbidities

Antibiotic		Comment
Imipenem		Susceptible in the majority of the isolates ↘
Meropenem		Resistant in the majority of isolates
Piperacillin-tazobactam		Resistance medium-high (65-80% of the isolates)
Cephalosporins		Resistance medium-high (65-80% of the isolates)
Aminoglycosides		Resistant in the majority of isolates
Fluoroquinolones		Resistance medium-high (65-80% of the isolates)
Trimethoprim-sulfamethoxazole		Susceptible in the majority of the isolates ↘
Azithromycin		Resistant in the majority of isolates
Minocycline		Half of the isolates are resistant
Tigecycline/Doxycycline		Resistance medium-high (65-80% of the isolates)
Colistin		Resistant in the majority of isolates
Ceftolozane-tazobactam		Resistant in the majority of isolates
Ceftazidime-avibactam		Resistant in the majority of isolates
Meropenem-vaborbactam		Resistant in the majority of isolates
Imipenem-relebactam		Susceptible in the majority of the isolates
Cefiderocol		Resistant in the majority of isolates
Aztreonam-avibactam		Resistant in the majority of isolates
↘ Treatment of choice		

Figure 2
Graphical representation of usual phenotype and antimicrobial resistance pattern in *Pandoraea* spp. ↘ = antibiotic that should be prescribed.

or immunosuppression [24]. These pathogens are capable of causing severe infections and exhibit resistance to commonly used antibiotic classes, including β-lactams, fluoroquinolones, aminoglycosides, and polymyxins [8, 23].

Among available antibiotics, IMP and SXT currently represent the most reliable therapeutic options [7]. IMP often retains in vitro activity even when resistance to MEM is present, and SXT shows relatively low resistance rates in tested isolates [8, 19]. These agents may also be considered part of combination regimens, especially in severe infections, although clinical data supporting such strategies are currently lacking [7].

Several novel β-lactam/β-lactamase inhibitor combinations, including ceftolozane–tazobactam, ceftazidime–avibactam, meropenem–vaborbactam, and aztreonam–avibactam, have demonstrated limited efficacy against *Pandoraea* spp., with high MIC values in many studies [5, 14, 32]. Similarly, the activity of cefiderocol appears highly inconsistent, particularly in outbreak-derived isolates *of P. commovens* [5]. Unfortunately, available data on the efficacy of these newer agents remain scarce and often of limited quality, with most evidence deriving from small case series or isolated in vitro observations. There is a clear need for systematic AST and well-designed experimental and clinical studies to assess the real therapeutic potential of these drugs in *Pandoraea* infections. Moreover, in vitro studies on potential therapeutic combinations could be extremely useful in the case of *Pandoraea* infections, given their intrinsic ability to develop multiple resistance mechanisms.

The absence of EUCAST and CLSI breakpoints for *Pandoraea* spp. remains a significant obstacle to consistently interpreting AST and appropriate antibiotic selection [14]. This highlights the importance of individualized, MIC-guided therapy and the need for collaborative clinical decision-making in complex cases.

CONCLUSION

Pandoraea species are emerging MDR pathogens associated with severe infections in CF and non-CF patients. Treatment is challenging due to intrinsic resistance and the absence of species-specific breakpoints. Although clinical evidence is limited, IMP and SXT currently represent the most reliable options and may be used as part of combination therapy. Data supporting the use of newer antibiotics are currently lacking, with few studies available and inconsistent in vitro results. There is a clear need for standardized susceptibility testing, experimental research, and clinical studies to define effective therapeutic strategies.

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