



The Epidemiology and Pathogenesis and Treatment of *Pseudomonas aeruginosa* Infections: An Update

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Abstract

Pseudomonas aeruginosa is a Gram-negative bacterial pathogen that is a common cause of nosocomial infections, particularly pneumonia, infection in immunocompromised hosts, and in those with structural lung disease such as cystic fibrosis. Epidemiological studies have identified increasing trends of antimicrobial resistance, including multi-drug resistant (MDR) isolates in recent years. *P. aeruginosa* has several virulence mechanisms that increase its ability to cause severe infections, such as secreted toxins, quorum sensing and biofilm formation. Management of *P. aeruginosa* infections focuses on prevention when possible, obtaining cultures, and prompt initiation of antimicrobial therapy, occasionally with combination therapy depending on the clinical scenario to ensure activity against *P. aeruginosa*. Newer anti-pseudomonal antibiotics are available and are increasingly being used in the management of MDR *P. aeruginosa*.

Key Points

Pseudomonas aeruginosa is an important Gram-negative organism that is implicated in nosocomial infections, and in patients with structural lung disease, such as in cystic fibrosis.

P. aeruginosa attacks respiratory epithelial cells via its pili and flagellum, and utilizes biofilm formation, quorum sensing, and a type III secretion system to increase its virulence.

Newer antimicrobials that have activity against MDR *P. aeruginosa* have been shown to be efficacious in the treatment of MDR *Pseudomonas*.

1 Introduction

Pseudomonas aeruginosa is a Gram-negative pathogen that is commonly associated with hospital-acquired infections, infections in immunocompromised hosts, and chronic infections in patients with structural lung disease such as cystic fibrosis (CF). For this review, we sought to update the readers with regard to the epidemiology of *P. aeruginosa* infections, mechanisms of virulence of *P. aeruginosa*, which aid in its ability to cause severe infection, and advancements in the diagnosis and management of *P. aeruginosa*. The authors conducted an extensive literature review utilizing the MEDLINE/Pubmed and Cochrane library databases, aiming to find relevant articles on *P. aeruginosa* epidemiology, pathogenesis, treatment, nosocomial infections, hospital-acquired and ventilator associated pneumonias, as well as CF.

2 Epidemiology

2.1 *Pseudomonas aeruginosa* and Nosocomial Infections

P. aeruginosa is a common cause of nosocomial infections, manifesting as pneumonia, surgical site infections, urinary tract infections and bacteremia. It is estimated that *P. aeruginosa* has a prevalence of 7.1%–7.3% amongst all healthcare-associated infections [1, 2]. The most common site of *P.*

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aeruginosa infection is pneumonia, and it is the most common Gram-negative organism identified in nosocomial pneumonia. Prevalence has been increasing over the past decade [3, 4]. In intensive care unit (ICU) patients, *P. aeruginosa* is responsible for an even higher percentage of healthcare-associated infections. A large international observational point-prevalence study of infections in ICU patients found that *P. aeruginosa* represented 16.2% of patient infections and was the cause of 23% of all ICU-acquired infections, with a respiratory source being the most common site of *P. aeruginosa* infection [5].

Healthcare-associated pneumonia (HAP) and ventilator-associated pneumonia (VAP) are a significant source of stress on the healthcare system, and they account for up to 22% of all healthcare-acquired infections [1, 6]. *P. aeruginosa* accounts for 10%–20% of isolates in cases of VAP, second only to *Staphylococcus aureus* [2]. Nosocomial pneumonia secondary to *P. aeruginosa* is associated with worse outcomes than other typical organisms [7–9]. Mortality from VAP secondary to *P. aeruginosa* is estimated to be as high as 32%–42.8% [7, 10, 11]. One multicenter observational study estimated the global prevalence of VAP due to *P. aeruginosa* as 4.1%, and *P. aeruginosa* was the most common cause of VAP globally, accounting for 26% of cases, with the most common risk factors for *P. aeruginosa* VAP being prior colonization with *P. aeruginosa* and prolonged hospitalization [12]. A prospective observational study of 28 ICUs in the USA estimated that *P. aeruginosa* was the cause of 11% of all HAP/VAP in ICU patients deemed to be at risk for developing nosocomial pneumonia, second only to *S. aureus* [13].

P. aeruginosa is a common cause of nosocomial urinary tract infections (UTI), particularly catheter-associated UTI (CAUTI). *P. aeruginosa* accounts for approximately 10% of all CAUTIs, and up to 16% of UTIs in ICU patients [14, 15]. Nosocomial UTI secondary to *P. aeruginosa* is associated with high morbidity and mortality and bacteremia is a potential complication [16–18]. Additionally, *P. aeruginosa* CAUTI is associated with high rates of antimicrobial resistance, depending on local antimicrobial resistance patterns. Data from the International Nosocomial Infection Control Consortium report found resistance rates of > 40% for antibiotics such as fluoroquinolones, piperacillin-tazobactam, and meropenem in ICU patients, although the report notes these resistance rates are higher than are reported elsewhere [14].

Amongst healthcare-associated infections reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention (CDC) from 2011–2014, 5.7% of surgical site infections were found to be secondary to *P. aeruginosa*, with breast and cardiac surgeries being the type of surgery most associated with *P. aeruginosa* [2]. Data from England from 2000–2013 showed that *Pseudomonas* species

accounted for 4.3%–6.5% of all surgical site infection (SSI) annually [19]. Additionally, *P. aeruginosa* infection after surgery is associated with worse outcomes, with a retrospective study of cardiac surgeries performed at a university hospital over a 7-year period showing that *P. aeruginosa* infection was associated with increased mortality [20].

P. aeruginosa is a known complication of and important pathogen in burn patients, with the moist environment of burn-wound patients believed to contribute to its predilection for burn patients [21]. *P. aeruginosa* is the most common Gram-negative organism leading to infection in burn-wound patients, and it is associated with sepsis and death [21–24]. Multi-drug resistant (MDR) *P. aeruginosa* is an increasingly common cause of death in burn patients, with 86% of sepsis deaths in a pediatric burn ICUs due to MDR organisms, with *P. aeruginosa* as the responsible organism 64% of the time from 1999–2009 [22].

Bloodstream infections (BSIs) due to *P. aeruginosa* are associated with high rates of morbidity and mortality, with estimated mortality rates of 43.2%–58.8% [25–27]. Additionally, MDR BSIs of *P. aeruginosa* are estimated to complicate 16.7%–28% of *P. aeruginosa* BSIs, with increased mortality associated with the presence of MDR *P. aeruginosa* [26, 27]. Furthermore, *P. aeruginosa* BSI was more likely to be a hospital-acquired bacteremia compared to all other Gram-negative BSIs (51% vs 27%) in a 13-year study of all BSIs in a large university medical center [27]. *P. aeruginosa* is estimated to represent 4.0% of all central line-associated BSIs [2].

2.2 Cystic Fibrosis and *P. aeruginosa*

In patients with cystic fibrosis (CF), *P. aeruginosa* is a critically important pathogen, and is a predominant cause of morbidity and mortality [28]. Complications of CF include chronic respiratory infections, structural lung disease and bronchiectasis, airflow obstruction, and death. Chronic infection with *P. aeruginosa* is associated with worsening lung function and guidelines recommend aggressive early therapy to treat *P. aeruginosa* in CF patients in order to preserve lung function [29–35]. *P. aeruginosa* may thrive in the CF lung due to its ability to undergo mutations and genetic changes that allow it to survive in the typically anaerobic environment of the CF lung [36]. Chronic infection with *P. aeruginosa* typically leads to production of a biofilm, and this conversion to a mucoid phenotype is associated with the production of the polysaccharide alginate [3, 36, 37]. The development of a mucoid phenotype of *P. aeruginosa* is associated with a decline in lung function and is associated with increased mortality, which has led to early treatment of *P. aeruginosa* in CF patients becoming the standard of care [34–36, 38].

Aggressive treatment regimens for *P. aeruginosa* has been associated with a decrease in the prevalence of *P. aeruginosa* in CF patients over recent years; however, data from the Cystic Fibrosis Foundation Patient Registry from 2006 to 2012 showed that *P. aeruginosa* still had a prevalence of 49.6%, with increasing prevalence in older patients, as 74.1% of cultures were positive in patients aged > 26 years [39]. Data from the European Cystic Fibrosis Society registry showed *P. aeruginosa* had a prevalence of 29.8% with over half of patients aged > 40 years having a positive culture for *P. aeruginosa* [40].

2.3 Non-cystic Fibrosis Bronchiectasis and *P. aeruginosa*

Bronchiectasis is characterized by the dilation and thickening of airways, which leads to chronic infection and airway inflammation. Non-CF bronchiectasis is more common than CF and has a variety of causes such as post-infectious, primary ciliary dyskinesia, immunodeficiency, and idiopathic bronchiectasis [41]. *P. aeruginosa* is one of the most frequently isolated organisms in patients with non-CF bronchiectasis and is associated with worsening lung function and increased mortality [42–44]. Management of *P. aeruginosa* in non-CF bronchiectasis typically consists of treating exacerbations to prevent decline in lung function [44].

2.4 Immunocompromised Hosts

P. aeruginosa is an especially important pathogen in immunocompromised patients, particularly patients with neutropenia. It is a critically important pathogen in patients with hematological malignancies [45, 46]. In one multicenter study, *P. aeruginosa* was found to cause 17% of all Gram-negative BSI in patients with hematological malignancies, with risk factors for *P. aeruginosa* being prior surgery, neutropenia, use of steroids, and severity of underlying disease [45]. Another study found that of all BSIs in patients with hematological malignancies, *P. aeruginosa* was responsible for 12.1% of all Gram-negative BSI, while also showing an increasing trend of MDR isolates in patients with hematological malignancies [47].

Patients who have undergone transplantation are also at high risk of *P. aeruginosa* infection and are at increased risk of adverse outcomes. Previous mortality estimates of BSI with *P. aeruginosa* in patients with a history of stem cell, liver, or lung transplant have been as high as 50% [48]. In a large study of over 500 patients with *P. aeruginosa* BSI at a single center, mortality was found to be 42%, with resistance to all antibiotic classes being higher in the transplant patients compared to nontransplant patients. The risk for *P. aeruginosa* is highest

immediately after transplantation, with over half (52%) of *P. aeruginosa* occurring within 3 months of transplant [48].

2.5 Emerging Resistance Profiles

Antimicrobial resistance to *P. aeruginosa* remains a serious health threat and is a major source of morbidity and mortality, especially in ICUs and long-term care hospitals (LTACHs). MDR *P. aeruginosa* is found in isolates from CAUTIs, BSI, and VAPs. Data from the CDC show that 9% of *P. aeruginosa* isolates were MDR in 2018, down from 15.7% in 2011 [49]. Data from the National Healthcare Safety Network from 2015 to 2017 show that antimicrobial resistance to *P. aeruginosa* remains a serious concern. Amongst *P. aeruginosa* isolates in ICU patients, 26.3% of isolates were resistant to carbapenems, 26.5% were resistant to extended-spectrum cephalosporins, and 27.1% were resistant to fluoroquinolones. Additionally, 18.6% of isolates from ICU patients were classified as MDR, resistant to 3 or more antimicrobials [50]. LTACHs reported 29.9% of *P. aeruginosa* isolates were MDR, while 11.6% of isolates from hospital oncology units were MDR [50].

Carbapenem resistance in *P. aeruginosa* can complicate treatment regimens, given how often *P. aeruginosa* is resistant to other antimicrobials. In a study that investigated the prevalence of carbapenem-resistant *P. aeruginosa* isolates over a 4-month period at multiple centers in the USA, 9% of *P. aeruginosa* isolates were found to be carbapenem resistant. Over 90% of the patients who had carbapenem-resistant isolates had healthcare exposures prior to their positive culture, emphasizing the relevance of nosocomial infections in *P. aeruginosa* [51].

Antimicrobial resistance in *P. aeruginosa* BSI is especially relevant, given the increased mortality associated with *P. aeruginosa* BSI [26, 27]. One study found that resistance to one antimicrobial for a *P. aeruginosa* BSI was highly correlated with other antimicrobial resistance. For example, 83% of *P. aeruginosa* BSI isolates that were resistant to piperacillin-tazobactam were also resistant to ceftazidime, and 67% were resistant to ciprofloxacin [52]. Another study that investigated all *P. aeruginosa* BSI at a single center over a 13-year period found that 28% of isolates were MDR, and 15% were extensively drug resistant [27]. Nosocomial pneumonia due to *P. aeruginosa* has a high incidence of MDR strains, with an international multicenter retrospective study showing that 30.5% of nosocomial pneumonia secondary to *P. aeruginosa* were MDR-strains, and this was associated with increased in-hospital mortality [53].

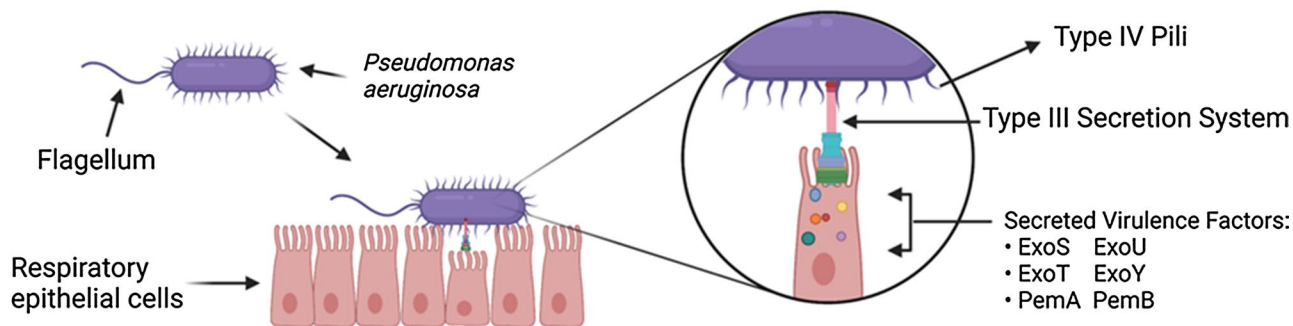
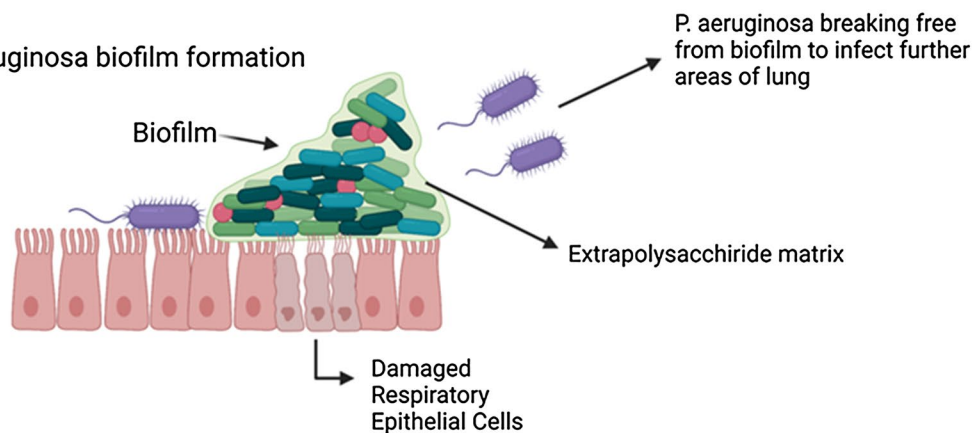
(A) *Pseudomonas aeruginosa* attacking respiratory epithelial cells**(B) *Pseudomonas aeruginosa* biofilm formation**

Fig. 1 Mechanisms of virulence and biofilm formation in *Pseudomonas aeruginosa* infections. Figure Created with BioRender.com

3 Mechanisms of Infection, Virulence and Resistance

3.1 Motility and Attachment

P. aeruginosa has flagella and pili that are necessary for motility and respiratory infection, as they enable attachment to respiratory epithelium via respiratory mucins and the glycolipid asialoGM1 [54, 55]. Bacterial adhesion to the respiratory epithelium is an essential step for infection and is accomplished by interactions between bacterial adhesins and host receptors. For *P. aeruginosa* infection, the main adhesins are the single flagellum, which is necessary for motility, adhesion to cells and formation of a biofilm, and the type IV pili, which are appendages composed of pilin polymers, which allow the bacteria to move over surfaces in addition to serving relevant roles in biofilm formation and respiratory epithelial cell attachment [56]. Figure 1 outlines the relevant virulent mechanisms used by *P. aeruginosa* to attack respiratory epithelial cells.

3.2 Biofilm Formation, Alginate Secretion, and Quorum Sensing

Infection with *P. aeruginosa* can occur in an acute phase in patients with abnormal respiratory epithelium from patients with chronic lung disease or who have an acute illness that has led to respiratory failure and mechanical ventilation. A more chronic form of infection can occur in patients with underlying lung disease, such as CF. In the acute phase, *P. aeruginosa* is able to attach to respiratory epithelium using its type IV pili and flagellum, and toxins secreted by the bacterium damage the host cell lung. *P. aeruginosa* then begins to secrete an extracellular matrix, forming a biofilm, which is a structural matrix of bacterial cells encased within an extracellular matrix that adheres to the respiratory epithelium [54, 57]. The matrix is largely made up of polysaccharides, proteins, extracellular DNA, and lipids. As a result of biofilm formation, bacteria are able to act synergistically while also providing protection from phagocytosis by neutrophils and antibiotics [54, 55, 57]. After the initial biofilm is formed, some bacteria may break free and progress to infect other areas of the lung (Fig. 1). Biofilm formation can also occur in the lungs of patients with chronic lung disease,

such as in CF or chronic bronchiectasis, where *P. aeruginosa* organisms form a biofilm in thickened airway mucous and rarely need to travel to cell surfaces. In this model of chronic infection, *P. aeruginosa* bacteria lose their appendages and mutate into a mucoid phenotype with production of alginate, allowing for chronic infection [54].

Alginate is an exopolysaccharide composed of D-mannuronic acid and L-guluronic acid, and its production, induced by expression from *P. aeruginosa*, is essential for forming the mucoid phenotype of *P. aeruginosa* seen in CF. Typically, production of alginate is limited by an anti-sigma factor, MucA, which binds AlgT, preventing it from inducing expression of alginate at the *algD* promoter region. In the CF airway, *P. aeruginosa* acquires mutations in the *mucA* gene, which leads to uninhibited production of alginate due to unsuppressed activity of *algT* and conversion to a mucoid colony of *P. aeruginosa* [54, 58]. Alginate overproduction in *P. aeruginosa* is beneficial for the microbe for a variety of reasons including formation of biofilm, preventing bacterial clearance by host immune cells, and antimicrobial therapy, as well as immunomodulatory effects that may impair host immune response to infection [58].

Quorum sensing is a form of bacterial communication that enables *P. aeruginosa* to regulate gene expression allowing the microbes to coordinate activity against the host in the setting of infection. *P. aeruginosa* has several well-defined quorum sensing pathways, such as *Las*, *Rhl*, and *Pqs* that all generate autoinducers, which diffuse into bacterial and host cells leading to transcriptional regulation that benefits continued bacterial survival and decreased immune response to infection [55, 59].

3.3 Type III Secretions System

Amongst the most powerful mechanisms for increasing the virulence and morbidity from a *P. aeruginosa* infection is the type III secretion system which enables the bacterium to inject effector proteins into host cells, such as the respiratory epithelium. The effector cells are able to alter host cell functions, such as disrupting innate immune response and altering host actin cytoskeleton [60]. Four effector proteins, ExoS, ExoT, ExoU, and ExoY have been typically described as the effector proteins used by the *P. aeruginosa* type III secretion system [61]; however, two additional effectors, PemA and PemB, have recently been described [62]. The most clinically relevant effectors may be ExoS and ExoU, which are thought to be mutually exclusive when found in *P. aeruginosa* strains [63]. ExoS impairs cell-to-cell adhesion through disruption of the actin cytoskeleton of host respiratory epithelial cells [63], while also inducing apoptosis of host cells [64]. ExoU is thought to be responsible for the greatest virulence due to its cytotoxic activity that induces

host cell death and is more often found in patients in ICUs or burn units [63, 65, 66].

Previous studies have demonstrated that the presence of a type III secretion system in *P. aeruginosa* is associated with poor outcomes including a larger burden of bacteria, persistence of infection and increased mortality [61, 63, 67–70]. Chronic infection with *P. aeruginosa*, such as in patients with CF, may select against type III secretion system, as many CF patients have antibodies directed against effector proteins and the conversion to a mucoid phenotype leading to downregulation of type III secretion proteins [61, 71, 72]. Given the relevance of the type III secretion system in acute infection, it is the subject of significant research to find targets for treatment to prevent or treat *P. aeruginosa* infection. PcrV is a part of the translocation apparatus and is necessary for injection of effector proteins into host cells, and immunization against PcrV has been shown to be protective against infection in animal studies [61]. *P. aeruginosa* isolates with PcrV have been associated with higher mortality, and clinical studies are ongoing to assess response to PcrV-specific antibodies [61, 68].

3.4 Diagnosis of *P. aeruginosa* Infection

The diagnosis of *P. aeruginosa* infection is dependent on timely and appropriate cultures obtained from an appropriate site. For critically ill patients with suspected *P. aeruginosa* infection, blood cultures should be obtained prior to starting antibiotics, ideally within one hour of identification of a critically ill patient [73]. Urine cultures should be obtained for patients with suspected UTI or CAUTI. For patients with suspected pneumonia, sputum cultures should be obtained when sputum is able to be produced. For patients with CF, sputum culture should be directed to look for CF-associated organisms, such as *P. aeruginosa*. The presence of *P. aeruginosa* on a sputum culture in a child can be an early clue to a diagnosis of CF [74].

Typical methods to identify *P. aeruginosa* in the laboratory include recognizing morphology and microbial colonies that have grown on media [75]. Selective media, such as that with cetrimide, is available and can be useful for identifying *P. aeruginosa* in polymicrobial samples [76]. Once identification of *P. aeruginosa* is made on culture, antimicrobial susceptibility testing is an essential next step in order to identify resistance and guide appropriate antibiotic therapy. Most labs use commercially available automated antimicrobial susceptibility kits that allow for identification of antimicrobial resistance as well as measurement of minimum inhibitory concentrations [75]. Identification of carbapenem-resistant strains of *P. aeruginosa* is essential, especially when identifying potential outbreaks.

Diagnosis of *P. aeruginosa* in nosocomial pneumonia presents more diagnostic challenge in terms of how to sample

for the infection. In ventilated patients with suspected VAP or HAP that has subsequently led to mechanical ventilation, guidelines from the American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) recommend endotracheal aspiration for semiquantitative cultures, although quality evidence comparing endotracheal aspiration to more invasive sampling via a bronchoscopy with bronchoalveolar lavage (BAL) is lacking [6]. Guidelines from the European Respiratory Society (ERS) recommend obtaining more distal samples, such as via BAL in order to reduce unnecessary antibiotic exposure [77]. Proponents of invasive sampling via bronchoscopy with quantitative culture argue that more invasive sampling can lead to more precise therapy that targets the known pathogen and earlier narrowing of antibiotics. A study of 413 patients with VAP found that an invasive strategy was associated with more antibiotic-free days [78], whereas a subsequent study of 740 patients found no difference in antibiotic use between an invasive and non-invasive strategy [79]. Neither study showed a difference in 28-day mortality [78, 79].

Rapid diagnostic testing is also available for diagnosis of *P. aeruginosa* nosocomial pneumonia. Tests for lower respiratory tract infections that utilize multiplex real-time polymerase-chain reaction to test for a variety of pathogens known to cause pneumonia have demonstrated good sensitivity and specificity for *P. aeruginosa*, including BAL samples [80, 81]. There are multiple advantages to utilizing a rapid diagnostic test for *P. aeruginosa* infection, including a diagnosis within 2 h, as opposed to standard culture which can take 48–72 h, identification of concomitant viral or bacterial infection, and early identification of some antimicrobial resistance genes that are able to be identified in PCR-tests that can lead to initial appropriate antibiotic therapy, as well as timely de-escalation of antibiotics [81]. An important caveat with rapid diagnostic testing is that, while it is able to assist in determining that the organism is present, it does not assist in determining if this is due to infection or colonization. Therefore, it is essential that it be ordered when there is concern for infection and results taken into clinical context.

4 Treatment of *P. aeruginosa* Infections

4.1 Infection Control and Prevention

One of the most important aspects of management of *P. aeruginosa* infections is preventing new infections whenever possible, especially in the setting of MDR organisms. There are a range of practices and guidelines available for preventing the spread of MDR pathogens like *P. aeruginosa* and other Gram-negative bacilli (GNB), including standard care such as hand hygiene and contact precautions for patients with MDR organisms [82–85]. Other relevant measures that

may reduce the incidence of MDR *P. aeruginosa* include antimicrobial stewardship programs, environmental cleaning, and decolonization procedures [82]. Prevention of VAP, which is frequently due to *P. aeruginosa*, can be achieved with avoidance of intubation, when possible, daily assessments for extubation, minimizing sedation, elevating the head of the bed, and minimizing secretions. Furthermore, prevention of healthcare-associated infections such as CLABSI and CAUTI, as well as surgical site infections, can be achieved with strict sterile technique, frequent reassessments for the need of a central line or urinary catheter and removal of nonessential lines and catheter [86]. A large systematic review and meta-analysis previously found that the most effective measures for preventing the development of an MDR GNB infection in the ICU was a combination of standard care (hand hygiene and contact precautions), antimicrobial stewardship, environmental cleaning, and source control [82].

Given the prevalence of MDR *P. aeruginosa* organisms, overtreatment is a concern. Antibiotic de-escalation is an essential strategy when treating *P. aeruginosa* infections, and antibiotics should be narrowed once culture sensitivities have returned. Moreover, initial antimicrobial therapy directed against *P. aeruginosa* should only be done when there is a risk for *P. aeruginosa* infection. Additionally, certain antimicrobials that are available for MDR *P. aeruginosa* are often restricted by hospitals for use in known MDR *P. aeruginosa* and consultation with infectious disease department may be recommended in order to prescribe newer antimicrobials with MDR activity.

4.2 Prompt and Appropriate Antibiotic Administration

The initial management of a patient with a suspected *P. aeruginosa* infection, especially in those critically ill in the ICU, involves obtaining cultures and the administration of appropriate antibiotics. For patients who are ill with suspected sepsis, guidelines recommend administration of antibiotics within 1 h [87]. Additionally, source control is an essential part of treatment of any infection, and any abscesses should be drained while any indwelling devices such as urinary catheters or vascular catheters should be removed if thought to be the source of *P. aeruginosa* infection.

Appropriate initial antibiotic choice is essential in the management of *P. aeruginosa* infection, as inappropriate initial choice of antimicrobial regimen has previously been shown to be associated with increased mortality [9, 11, 88, 89]. A previous retrospective study found that initial inappropriate antimicrobial therapy in septic shock resulted in a 5-fold reduction in survival [90]. A large meta-analysis of patients with severe bacterial infections showed that patients who received appropriate initial antibiotic therapy had lower

rates of treatment failure, shorter hospital length of stay and cost, as well as reduced mortality rates compared to patients who received inappropriate initial antibiotic therapy [91]. Additional evidence for the benefits of appropriate initial therapy is seen in the MERINO trial, a prospective randomized trial that compared piperacillin-tazobactam to meropenem in patients with Gram-negative bacteremia that was ceftriaxone-resistant, which is typically treated with a carbapenem. In this noninferiority study, noninferiority could not be established for piperacillin-tazobactam compared to meropenem, with 12.3% of subjects randomized to piperacillin-tazobactam dying within 30 days, compared to (3.7%) randomized to meropenem (risk difference, 8.6% [1-sided 97.5% CI, $-\infty$ to 14.5%]; $p = 0.90$ for noninferiority) [92]. While the MERINO study was looking specifically into *Klebsiella* and *E. coli* organisms that were ceftriaxone-resistant, the trial demonstrates the importance of early appropriate antimicrobial therapy in severe bacterial infections, which also applies to *P. aeruginosa* infections.

Initial therapy with broad-spectrum antibiotics is often indicated, especially in critically ill patients while awaiting culture results [73]. Patients with known colonization or risk factors for MDR pathogens, should receive an initial antibiotic regimen that would be active against the MDR pathogen based on previous culture results or broad-spectrum antibiotics while awaiting culture results. Previous retrospective analyses have shown that initial antibiotics aimed at *P. aeruginosa* improve outcomes in healthcare-associated pneumonia and in nosocomial sepsis secondary to GNB [9, 93].

4.3 Combination versus Monotherapy for Treatment of *P. aeruginosa*

The management of *P. aeruginosa* infection with combination or monotherapy remains an area of debate. Given that inappropriate initial empiric therapy is a risk factor for mortality in *P. aeruginosa* infection, empiric therapy with a combination of antipseudomonal therapy is often given to severely ill patients [6, 73, 75]. Additionally, synergistic activity of a combination of antibiotics active against *P. aeruginosa* has been suggested to be beneficial in *P. aeruginosa* infection, although definitive evidence showing a clear benefit to synergistic activity is lacking [94–96].

Data regarding the benefits of combination therapy have been contradictory. In a retrospective single-center study of 100 patients with Pseudomonal bacteremia, inadequate initial antibiotics therapy was associated with increased mortality, and adequate combination therapy was associated with decreased mortality [97]. Additional observational and retrospective studies have suggested a potential benefit to combination therapy in patients with septic shock or VAP secondary to *P. aeruginosa* [98, 99]. Conversely, a post hoc analysis of 593 patients with *P. aeruginosa* found

no association with 30-day mortality in combination versus single drug therapy [100]. A meta-analysis comparing beta-lactam plus aminoglycoside or fluoroquinolone compared to beta-lactam monotherapy in *P. aeruginosa* infections also found no mortality benefit to using two active antipseudomonal agents over a single antibiotic as treatment [95]. Current guidelines for management of sepsis and septic shock recommend combination or multidrug therapy in critically ill patients with shock at risk of an organism that is associated with high rates of antimicrobial resistance, such as *P. aeruginosa*, in order to increase the likelihood that at least one active drug is being given [73]. A Cochrane review from 2016 found no difference in outcomes for CF patients treated with combination therapy compared to monotherapy in *P. aeruginosa* infections, although the studies included were at high risk of bias and combination therapy is still frequently used in CF exacerbations [96].

Management of VAP caused by *P. aeruginosa* also remains an area of contention, as guidelines state that there have been no randomized controlled trials which compare antibiotic regimens in patients with VAP caused by *P. aeruginosa* [6]. It is important to note that trials of HAP/VAP are difficult to complete for a variety of reasons including ensuring that patients enrolled have a nosocomial pneumonia, long time to completion of the study, and complexity surrounding novel antimicrobials being evaluated for both safety and efficacy in ill patients with a variety of pathogens [101]. Previous studies in HAP/VAP may have failed to show benefit due to inadequate dosing of antimicrobials in VAP in the setting of normal creatinine clearance and augmented renal clearance [101, 102].

4.4 Treatment Recommendations for *P. aeruginosa* Nosocomial Pneumonia

The most recent recommendations for treatment of *P. aeruginosa* in hospitalized patients make a distinction in the management of VAP versus hospital-acquired pneumonia (HAP). In the case of suspected VAP, joint recommendations from the IDSA and ATS state that empiric coverage including MRSA and anti-pseudomonal coverage is recommended in addition to coverage against other Gram-negative bacilli. Two antipseudomonal antibiotics, typically a beta-lactam and an aminoglycoside, are recommended in the management of VAP when the patient is at risk of multidrug resistance, patients in ICUs where >10% of Gram-negative isolates are resistant to an agent being considered for monotherapy of a patient in an ICU where antimicrobial susceptibility rates are not known [6]. In the absence of these risk factors, a single antipseudomonal can be utilized in the treatment of VAP in addition to MRSA coverage.

Table 1 Initial treatment of *Pseudomonas aeruginosa* pneumonia^a

One of the following	
Ceftazidime	IV 2 g Q8–12 h
Cefepime	IV 1–2 g Q8 h
Piperacillin-tazobactam	IV 4.5 g Q6 h
Meropenem	IV 2 g Q8 h
Imipenem	IV 500 mg Q6 h or 1 g Q8 h
Aztreonam ^b	IV 2 g every 8 h
Plus one of the following if treating with combination therapy	
Tobramycin	IV 7 mg/kg od ^c
Gentamicin	IV 7 mg/kg od ^c
Levofloxacin	IV or PO 750 mg od
Ciprofloxacin	IV or PO 400 mg od
Amikacin	IV 20 mg/kg od ^d
Antimicrobial options for MDR- <i>P. aeruginosa</i> pneumonia	
Ceftolozane-tazobactam	IV 3 g Q8 h
Ceftazidime-avibactam	IV 2.5 g Q8 h
Imipenem-cilastatin-relebactam	IV 1.25 g Q6 h
Cefiderocol	IV 2 g Q6–8 h

IV intravenous, MDR multi-drug resistant, od once daily, PO oral, Q every

^aDosages recommended based on normal renal and hepatic function

^bTypically reserved for patients with beta-lactam allergy

^cDose should be adjusted for serum trough concentration < 1 µg/mL

^dDose should be adjusted for serum trough concentration < 5 µg/mL

Table 2 Risk factors for *Pseudomonas aeruginosa* infection

Prior <i>P. aeruginosa</i> colonization
Structural lung disease (CF, bronchiectasis)
Hematological malignancy/neutropenia
Transplantation
Skin burns
Antimicrobial therapy within 90 days
Presence of indwelling catheter (vascular catheter, urinary catheter)
Prolonged hospitalization
Mechanical ventilation
<i>CF</i> cystic fibrosis

In the case of HAP, similar antibiotic recommendations exist (see Table 1); however, combination therapy is only recommended in the setting of those at high risk for mortality (such as ventilated or those in septic shock) or those at high risk for drug resistance [6]. See Table 1 for specific antibiotic and dosing recommendations. Risk factors for *P. aeruginosa* infection, which may guide when to start broad-spectrum antibiotics or cover for MDR isolates, are outlined in Table 2.

Guidelines from European Societies differ from the ATS and IDSA. The European Respiratory Society (ERS) guidelines for the management of HAP/VAP recommend monotherapy with a narrow-spectrum antibiotic, such as ceftriaxone, ertapenem or levofloxacin for patients with suspected HAP/VAP deemed to be at low risk of MDR pathogens and low mortality risk. However, they recommend dual antipseudomonal coverage for patients with HAP/VAP with a high MDR risk and septic shock [77].

As mentioned, no specific RCTs have been conducted that specifically compared antimicrobial regimens for *P. aeruginosa* HAP/VAP. A meta-analysis that included 41 randomized trials with over 7000 patients found no specific antibiotic regimen was superior in reducing mortality and treatment failure in patients with VAP [103]. However, current guidelines do recommend against aminoglycosides as monotherapy in *P. aeruginosa* pneumonia due to poor lung penetration by aminoglycosides as well as lack of studies specifically investigating aminoglycosides in *P. aeruginosa* pneumonia. Furthermore, doripenem is not recommended in treatment of pneumonia as it currently holds a black-box warning [6] due to a clinical trial that found increased mortality and lower clinical cure rate than standard therapy in patients with VAP [102]. It is important to note that specific doses for nosocomial pneumonia secondary to *P. aeruginosa* may be higher than used in other circumstances. Poor penetration of antibiotics into alveolar space may contribute to the need for higher doses of antibiotics in order to penetrate epithelial lining fluid in the lung [101]. From a practical standpoint, antibiotics frequently used for the treatment of nosocomial pneumonia secondary to *P. aeruginosa* without evidence of MDR organisms typically include either cefepime, meropenem, piperacillin-tazobactam or imipenem. Specific reasons to include one antimicrobial over another may be dependent on patient factors such as allergies, renal function, as well as institutional factors such as which antibiotics are locally available as well as local antibiograms and resistance patterns.

4.5 Other Treatment Options

Ceftolozane-tazobactam is a novel combination antimicrobial and antipseudomonal activity. It has been approved for complicated UTIs and intraabdominal infections [6] with in vitro activity against *P. aeruginosa* isolates including drug-resistant and multi-drug resistant isolates [104]. A multi-center, non-inferiority RCT of ceftolozane-tazobactam in ventilated patients with nosocomial pneumonia demonstrated that ceftolozane-tazobactam was non-inferior to meropenem in 28-day mortality and clinical cure with an acceptable safety profile [105]. In this study, subjects received 3 g of IV ceftolozane-tazobactam, whereas the usual dose in UTI and intraabdominal infection is 1.5

grams. Ceftolozane-tazobactam is now often used as monotherapy in *P. aeruginosa* infections known to be resistant to other beta-lactams, but is also increasingly being used in critically ill patients who have a high likelihood of having an MDR isolate of *P. aeruginosa*, as well as in high-risk patients who are known to be at risk for MDR *P. aeruginosa*, such as CF patients or lung transplant recipients [106]. Additionally, ceftolozane-tazobactam is increasingly recommended as empiric therapy in combination with an aminoglycoside in the management of nosocomial pneumonia in the ICU when there are risk factors for *P. aeruginosa*, known *P. aeruginosa* colonization, or high local incidence of *P. aeruginosa*. When *P. aeruginosa* is found to have caused pneumonia or bacteremia, ceftolozane-tazobactam monotherapy is recommended by some as targeted antimicrobial therapy due to risks of failure from MDR pathogens [107].

Ceftazidime-avibactam is another novel combination antimicrobial with antipseudomonal activity, combining the anti-pseudomonal cephalosporin ceftazidime with the non-beta-lactam beta-lactamase inhibitor avibactam, extending the antipseudomonal activity of ceftazidime. In a multicenter, non-inferiority RCT, ceftazidime-avibactam was found to be non-inferior to meropenem in the treatment of nosocomial pneumonia for the outcome of clinical cure [108]. In this study, the dose administered was 2 g of ceftazidime with 500 mg of avibactam, administered intravenously. The addition of ceftolozane-tazobactam and ceftazidime-avibactam has increased the number of available drugs for the management of pneumonia due to *P. aeruginosa*, especially in drug-resistant isolates.

Another new antimicrobial available for use in MDR *P. aeruginosa* is imipenem-cilastatin-relebactam, which is a combination of carbapenem with relebactam, which is a beta-lactamase inhibitor that inhibits class A carbapenemases and class C cephalosporinases [109–111]. A recent randomized multicenter trial compared imipenem-cilastatin-relebactam to piperacillin-tazobactam I adults with HAP or VAP and it was found to be noninferior [109]. Meropenem-vaborbactam is an additional combination carbapenem-beta-lactamase inhibitor, with activity against MDR *P. aeruginosa* [110, 111]. Data for the use of meropenem-vaborbactam in pneumonia are lacking at this time, although it was found to be noninferior to piperacillin-tazobactam in a randomized study of complicated UTIs and acute pyelonephritis [112].

A newer antibiotic, cefiderocol, which is a novel siderophore cephalosporin, was recently studied in a multicenter randomized noninferiority study of 148 subjects, which compared cefiderocol to extended-infusion high-dose meropenem for subjects with hospital-acquired pneumonia or VAP due to GNB, and found that cefiderocol was non-inferior to meropenem for the primary outcome of 14-day

mortality, adding another potential choice for treatment of MDR pseudomonas in nosocomial pneumonia [113].

Infrequently used antimicrobials for MDR *P. aeruginosa* include plazomicin and colistin. Plazomicin is a synthetic derivative of sisomicin, and has activity against *P. aeruginosa* to a degree similar to that of other aminoglycosides, although data for its use in pneumonia due to *P. aeruginosa* are limited [111]. Colistin, or polymyxin B, is an older antimicrobial with antipseudomonal activity in addition to good coverage against other MDR Gram-negative pathogens. While colistin is not used as frequently as other antimicrobials, it has been shown to be as efficacious as others in the management of VAP [114], although it does have a high incidence of nephrotoxicity, estimated at 18%–43% [115]. Colistin is also available as an inhaled antibiotic, and current guidelines recommend its use as an adjunctive therapy (in addition to IV therapy) in *P. aeruginosa* VAP when the isolate is only susceptible to aminoglycosides or polymyxins [6]. With the development of newer antimicrobials with strong activity against MDR *P. aeruginosa*, the use of colistin is not typically recommended as initial therapy in MDR *P. aeruginosa*.

As previously mentioned, use of newer antimicrobials with activity against MDR isolates of MDR *P. aeruginosa* are often restricted by hospitals and can only be prescribed in certain circumstances, typically the presence of MDR *P. aeruginosa*. The decision of what newer antimicrobial to use in the presence of an MDR organism depends on sensitivities from *P. aeruginosa* culture results as well as which antimicrobials are available to prescribe at a specific institution. Ceftolozane-tazobactam and ceftazidime-avibactam, as previously mentioned, are more commonly being used for treatment of MDR *P. aeruginosa* pneumonia, with options such as colistin rarely being used.

4.6 Treatment of *P. aeruginosa* in Cystic Fibrosis Patients

As previously mentioned, *P. aeruginosa* is the most important pathogen in patients with CF and up to 70% of CF patients will eventually develop chronic *P. aeruginosa* infection [116]. Chronic infection with *P. aeruginosa* in CF also frequently leads to conversion of *P. aeruginosa* to a mucoid phenotype [36, 37], and has been associated with worsening lung function and increased morbidity and mortality [116, 117]. Routine cultures are recommended in CF patients in order to identify early infection with *P. aeruginosa* [28].

New infection with *P. aeruginosa* that is identified in a CF patient should be treated in order to eradicate *P. aeruginosa* from the airways of patients with CF, regardless of the presence of symptoms [28, 117, 118]. In an observational study of children with CF who developed a new *P. aeruginosa* infection, 69% were able to successfully achieve eradication

of *P. aeruginosa* with antibiotic therapy, and those subjects who did achieve eradication had significantly lower risk of developing chronic *P. aeruginosa* infection and mucoid conversion over a 5-year follow-up period [118]. Eradication of *P. aeruginosa* has also been described to be successful in adults [119]. The Cystic Fibrosis Foundation guidelines strongly recommend eradication of initial *P. aeruginosa* infection [28].

The most typical regimen for treatment of initial *P. aeruginosa* in CF is inhaled tobramycin 300 mg twice per day for 28 days, which has been shown to achieve eradication of *P. aeruginosa* in more than 70% of patients with associated improvements in lung function and reduced CF exacerbations [28, 32, 117–120]. Inhaled aztreonam has also been studied in new-onset *P. aeruginosa* infections, with eradication rates similar to inhaled tobramycin [121]. Furthermore, treatment with oral antibiotics such as ciprofloxacin in addition to inhaled antipseudomonas have not been more effective than inhaled tobramycin monotherapy [33, 122].

In addition to proper timing of antimicrobial therapy in *P. aeruginosa* infections, appropriate dosing of antibiotics is essential. Typical regimens used for the treatment of *P. aeruginosa* in the setting of normal renal function would include cefepime 2 g intravenously every 8 h, meropenem 2 g intravenously every 8 hours, and piperacillin-tazobactam 4.5 g intravenously every 6 hours. It is important to note that antimicrobials used for *P. aeruginosa* are often used at higher doses and at increased frequency when compared to doses and frequencies used for same drug for other infectious organisms. Moreover, it is essential to monitor patient's renal function prior to and during use of antibiotics for *P. aeruginosa* infection, as dose adjustments are often necessary, and consultation with a pharmacist may be necessary.

Chronic infection with *P. aeruginosa* in CF patients is typically also managed with aerosolized antibiotics due to the progressive decline in lung function and increased mortality associated with chronic infection [117]. The most common regimen used in chronic *P. aeruginosa* infection in CF is a rotating 28 days of inhaled tobramycin followed by 28 days of no treatment. Inhaled tobramycin has been extensively studied in this setting and is associated with improvements in lung function and decreased CF exacerbations [120, 123–126]. Inhaled aztreonam, prescribed on a similar 28-days-on, 28-days-off regimen, is another treatment option for CF patients with chronic *P. aeruginosa*, and it has been shown to be efficacious in improving lung function, quality of life and time to further antibiotic therapy [127, 128], although it is not as extensively studied as tobramycin. Many patients who received inhaled aztreonam were previously treated with inhaled tobramycin [120]. Inhaled colistin is another aerosolized antipseudomonal that is an option for chronic infection, with studies demonstrating conflicting results regarding the superiority of tobramycin compared to

Table 3 Typical antibiotic regimen for acute cystic fibrosis exacerbation

Antibiotic	Dose
Cefepime	IV 2 g Q8h
Ceftazidime	IV 2 g Q8h
Meropenem	IV 1 g Q8h
Piperacillin-tazobactam	IV 4.5 g Q6h
Plus	
Tobramycin	IV 10 mg/kg od ^a

IV intravenous, od once daily, Q6h every 6 h, Q8h every 8 h

^aDose should be adjusted to a serum peak concentration of 20–30 mg/L and a trough concentration of < 1 mg/L

colistin, and current guidelines do not recommend inhaled colistin [124, 129, 130].

Acute exacerbations of CF are defined by clinical changes of a CF patient including changes in sputum, hemoptysis, worsening cough or dyspnea, fever, decrements in lung function, and radiographic changes, amongst other possible symptoms [131]. CF exacerbations are especially relevant in the management of CF patients, as they decrease lung function, worsen quality of life, and are associated with significant costs due to hospitalization [131]. The management of acute bronchiectasis exacerbations in non-CF patients is often similar and understanding the treatment of a CF exacerbation is important for physicians in multiple specialties. Most CF exacerbations are thought to be due to bacteria, with pseudomonas being the most important pathogen in CF. Therefore, management of a CF exacerbation involves intravenous antibiotics with antipseudomonal activity, and current guidelines recommend combination therapy with two intravenous antibiotics with activity against pseudomonas for moderate-to-severe exacerbations [94]. These recommendations are largely based on expert opinion and quality evidence comparing outcomes for single therapy versus combination therapy in CF exacerbations is lacking [96].

Specific antibiotic recommendations that are typically used at Barnes-Jewish Hospital are outlined in Table 3. Aminoglycosides, such as tobramycin, are commonly used for management of CF exacerbations and current recommendations are for once-daily dosing of aminoglycosides, which may reduce nephrotoxicity [94, 132]. Beta-lactam antibiotics such as piperacillin-tazobactam, cefepime, ceftazidime, or meropenem, are typical antibiotics used in addition to an aminoglycoside. It is important to note specific dose recommendations for *P. aeruginosa* in Table 3, as CF patients are known to have altered pharmacokinetics, due to alterations in volume of distribution of certain antibiotics in nutritionally deficient CF patients, metabolism and clearance, while also facing challenges in lung penetration of intravenous antibiotics due to altered lung architecture [133]. Optimal

duration of antimicrobial therapy in a CF exacerbation remains an area of debate, and while current guidelines do not recommend a specific time frame, treatment often ranges from as few as 10 days to up to 3 weeks [94].

5 Conclusion

P. aeruginosa is an important Gram-negative pathogen, particularly in patients with chronic lung disease and in patients at risk for nosocomial infections. It is a particularly important pathogen in hospital-acquired and ventilator-associated nosocomial pneumonias. *P. aeruginosa* possesses a number of virulence factors that enable it to attack respiratory epithelial cells and is adept at developing mechanisms for antimicrobial resistance. Treatment of *P. aeruginosa* will often involve combination therapy with two antibiotics which are known to have activity against pseudomonas; this appropriate early antibiotic therapy in *P. aeruginosa* infections is associated with improved outcomes. Exacerbations of CF will also typically be treated with antimicrobials with activity against *P. aeruginosa*, due to the high rates of chronic infection with *P. aeruginosa* in patients with CF. Newer antibiotics have been developed for treatment of MDR *P. aeruginosa*, such as ceftolozane-tazobactam, which is increasingly being used as therapy for patients with suspected MDR *P. aeruginosa*.

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