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The Epidemiology, Pathogenesis and Treatment of *Pseudomonas aeruginosa* Infections

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Abstract

Pseudomonas aeruginosa is an important bacterial pathogen, particularly as a cause of infections in hospitalised patients, immunocompromised hosts and patients with cystic fibrosis. Surveillance of nosocomial *P. aeruginosa* infections has revealed trends of increasing antimicrobial resistance, including carbapenem resistance and multidrug resistance. Mechanisms of antimicrobial resistance

include multidrug efflux pumps, β-lactamases and downregulation of outer membrane porins. Mechanisms of virulence include secreted toxins and the ability to form biofilms. The effective treatment of infections caused by *P. aeruginosa* includes prevention when possible, source control measures as necessary and prompt administration of appropriate antibacterial agents. Antibacterial de-escalation should be pursued in patients with an appropriate clinical response, especially when antibacterial susceptibilities are known. Multidrug-resistant *P. aeruginosa* may require treatment with less commonly used antibacterials (e.g. colistin), but newer anti-pseudomonal antibacterials are expected to be available in the near future.

Pseudomonas aeruginosa is an aerobic Gram-negative bacterium that is an important cause of both community-acquired and hospital-acquired infections. Community-acquired infections include, but are not limited to, ulcerative keratitis (usually associated with contact lens use), otitis externa (typically in immunocompromised hosts such as those with diabetes mellitus), and skin and soft tissue infections (including diabetic foot infections). Hospitalised patients may be colonised with *P. aeruginosa* on admission or may acquire *P. aeruginosa* during their hospital stay, and *P. aeruginosa* can be isolated from nearly any conceivable source within hospitals.[1,2] Nosocomial infections caused by *P. aeruginosa* include pneumonias, urinary tract infections (UTIs), bloodstream infections, surgical site infections and skin infections in the setting of burn injuries. Chronic sinopulmonary colonisation and recurrent infections from *P. aeruginosa* are seen in patients with cystic fibrosis (CF). Infections caused by *P. aeruginosa* are not only common,[3,4] but they have also been associated with high morbidity and mortality when compared with other bacterial pathogens.[5,6] Of additional concern are the antimicrobial resistance trends that have been noted in large databases of nosocomial *P. aeruginosa* isolates.[7-9]

The purpose of this review is to discuss the epidemiology, pathogenesis and treatment of *P. aeruginosa* infections. Emphasis is placed on nosocomial infections and infections arising in patients with CF.

1. Epidemiology

1.1 *Pseudomonas aeruginosa* and Nosocomial Infections

P. aeruginosa is a common cause of nosocomial infections, accounting for 11–13.8% of all nosocomial infections when a microbiological isolate is identifiable.[10-12] In intensive care units (ICUs), *P. aeruginosa* is typically responsible for an even higher percentage of nosocomial infections, with rates of 13.2–22.6% reported.[9,11-13]

Although patterns may vary among institutions, *P. aeruginosa* has been identified as the second most common cause of hospital-acquired pneumonia (HAP), healthcare-associated pneumonia (HCAP) and ventilator-associated pneumonia (VAP), exceeded in frequency only by *Staphylococcus aureus*.[4,9] *P. aeruginosa* has been identified as the most common infectious isolate in HAP arising after 4 days in an ICU, in VAP after 4 days of mechanical ventilation, or in VAP after percutaneous tracheostomy.[3,14,15] In paediatric ICUs, *P. aeruginosa* is reported as the most common cause of nosocomial pneumonia.[16]

Numerous studies have identified *P. aeruginosa* to be an important pathogen in burn patients. Microbiological surveillance has shown that the frequency of burn wound colonisation with *P. aeruginosa* increases significantly during the first week of hospitalisation.[17,18] Although patterns vary between centres, *P. aeruginosa* is often identified as the most frequent infectious isolate in burn units, and it accounts for a large percentage of documented wound

infections, bacteraemia and VAP in these units.[17,19,20]

In large series of hospital-wide surgical site infections, *P. aeruginosa* was believed to be responsible for approximately 6% of all cases. Among surgical site infections affecting patients in ICUs and reported to the National Nosocomial Infections Surveillance (NNIS) System from 1986 to 2003, 9.5% were the result of *P. aeruginosa*.[9,21,22] In data collected from paediatric ICUs, *P. aeruginosa* was reported to be responsible for around 16% of surgical site infections and was the most common cause of surgical site infections after gastrointestinal surgery.[16]

P. aeruginosa is a common cause of nosocomial UTIs, accounting for approximately 9% of UTIs hospital wide and up to 16.3% of UTIs in ICU patients.[9,11,23,24] *P. aeruginosa* is more frequently responsible for nosocomial UTIs in patients with indwelling urinary catheters than in those without these devices (10.5% vs 4.1%).[25]

Nosocomial bloodstream infections have been reported to be due to *P. aeruginosa* in 4–6% of cases in published series,[6,9,12] but higher rates (14–20%) are reported by burn ICUs.[19,26] Although a less common cause of bloodstream infections than Gram-positive organisms, *P. aeruginosa* has been associated with higher mortality rates in some series.[5,6]

1.2 Immunocompromised Hosts

P. aeruginosa is an important pathogen in patients with both primary and acquired immunodeficiencies. For example, *P. aeruginosa* was the most commonly identified cause of septicaemia in a cohort of patients with primary immunodeficiencies.[27] *P. aeruginosa* is also an important cause of bacteraemia in patients with acute leukaemia, accounting for 14–21% of bacteraemic episodes in this patient population.[28,29]

In one study of patients infected with HIV, the incidence of *P. aeruginosa* bacteraemia was approximately 10 times the rate of that seen in the general population of the participating hospitals. Neutropenia and CD4+ lymphocyte counts <50 cells/mm^3 were among the identified independent risk factors for *P. aeruginosa* bacteraemia in the study population.[30] In a study of 111 patients with pneumonia in hospitalised adults with HIV, *P. aeruginosa* was the most commonly isolated bacterial pathogen.[31] In a review of 233 autopsies of patients infected with HIV-1, *P. aeruginosa* was identified as the most common cause of bacterial bronchopneumonia, accounting for 16 of 98 cases.[32]

Solid organ transplant and bone marrow transplant patients have increased rates of *P. aeruginosa* bacteraemia compared with the general hospital population.[30] In series of bone marrow transplant patients and heart-lung transplant patients, *P. aeruginosa* was identified as a common cause of nosocomial infection.[33,34] When lung transplant recipients develop bronchiolitis obliterans, *P. aeruginosa* becomes an important cause of late-onset pneumonia.[34]

P. aeruginosa is an important source of infection when the barrier function of the skin is compromised, as mentioned previously in burn patients and found similarly in patients with toxic epidermal necrolysis.[35] In addition, *P. aeruginosa* is commonly isolated from diabetic foot infections, rivalling *S. aureus* as the most common isolate from these wounds.[36,37]

1.3 Cystic Fibrosis and *P. aeruginosa*

P. aeruginosa plays a particularly important role in patients with CF, in whom chronic and recurrent infections of the sinopulmonary tract by *P. aeruginosa* are common. In the 2004 US Cystic Fibrosis Foundation Patient Registry, 57.3% of all reported respiratory cultures contained *P. aeruginosa*. In one longitudinal study that combined the culture of respiratory samples with serological screening for *P. aeruginosa* infection, up to 97.5% of CF patients were found to be infected with *P. aeruginosa* by the age of 3 years.[38] When chronically infected with *P. aeruginosa*, CF patients may carry more than one genotypic strain, and both non-mucoid and mucoid (alginate-producing) morphotypes may be cultured from a single respiratory sample.[39,40]

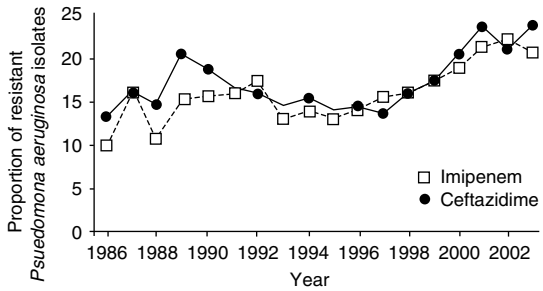

Fig. 1. Proportions of intensive care unit isolates resistant to imipenem and ceftazidime (National Nosocomial Infections Surveillance System, 1986–2003) [reproduced from Gaynes and Edwards,[9] with permission].

Pediatric CF patients with respiratory cultures positive for *P. aeruginosa* experience higher mortality, increased frequency of hospitalisation, decreased lung function and lower weight when compared with those without *P. aeruginosa*.[41] Even after lung transplantation, *P. aeruginosa* remains important for CF patients, in whom the sinuses often serve as a reservoir for recurrent lung infection.[42]

1.4 Emerging Resistance Profiles

Surveillance of *P. aeruginosa* isolated from hospitalised patients has revealed disturbing antimicrobial resistance trends in recent years (figure 1). Data published by the NNIS revealed that *P. aeruginosa* isolated from ICUs in 2003 exhibited resistance rates to imipenem, fluoroquinolones and third-generation cephalosporins of 21.1%, 29.5% and 31.9%, respectively, all of which were increased compared with mean resistance rates to these antibacterials between 1998 and 2002.[7] Multidrug-resistant (MDR) *P. aeruginosa* has become relatively common in ICUs. Data published by the SENTRY antimicrobial surveillance programme revealed that, between 1997 and 2002, 10.4% of ICU bloodstream *P. aeruginosa* isolates were MDR, as defined by resistance to ceftazidime, piperacillin, gentamicin and ciprofloxacin.[8] This phenomenon exhibited geographical variability, as demonstrated by significantly higher rates of MDR *P. aeruginosa* in Europe and Latin America compared with North America.[8] However, MDR *P. aeruginosa* is also a growing problem in the US. For example, a 9-year surveillance study from 1994 to 2002 in a single US hospital noted an increase from 1% to 16% in the number of nosocomial *P. aeruginosa* isolates that were resistant to three or more antimicrobial classes.[43]

Of additional concern is the frequent isolation of *P. aeruginosa* resistant to carbapenems, a class of antibacterials often prescribed when bacterial isolates are resistant to cephalosporins and fluoroquinolones. Among all bloodstream isolates from North American centres reported by the SENTRY programme, between 1997 and 2002, the percentage that were sensitive to meropenem fell from 95% to 91.3% (imipenem sensitivity was stable over the same period).[8] Carbapenem resistance rates are highest in ICUs, where, between 1998 and 2004, 19.1% of *P. aeruginosa* isolates were resistant to imipenem, compared with 12.3% and 7% of *P. aeruginosa* isolates from non-ICU inpatient areas and outpatient areas, respectively (according to NNIS data).[7] Multiple mechanisms of carbapenem resistance have been described and will be discussed in greater detail in section 2.

2. Mechanisms of Infection, Virulence and Resistance

2.1 Motility and Attachment

P. aeruginosa possesses a single flagellum that enables motility and may mediate initial surface interactions.[44] *P. aeruginosa* also has multiple cell surface pili (type IV) that are responsible for adherence to cell membranes and other surfaces. In the respiratory tract, glycolipid asialo-ganglioside M1

(aG_{M1}) is one target for binding to the epithelial cell surface.[45,46] aG_{M1} is maximally expressed during the epithelial cell repair process (and possibly not expressed in intact/uninjured epithelium), which may account for the observation that *P. aeruginosa* has only been shown to adhere to injured respiratory epithelium.[47] Upon cell surface attachment, a number of pathogenic mechanisms may be exhibited (figure 2).

2.2 Alginate Secretion, Quorum Sensing and Biofilm Formation

Some isolates of *P. aeruginosa* overproduce the extracellular polysaccharide alginate (a condition termed 'mucoidy'), with an associated mucoid morphology apparent on culture. Mucoid isolates typically express mutations in the *mucA* gene. In the absence of MucA, alginate biosynthesis genes are activated under the influence of AlgU (also called 'AlgT' or 'σ^{22}').[46] Alginate has been noted to have a number of effects that may impede bacterial clearance by the infected host, including scavenging of free radicals released by macrophages, providing a physical barrier that impairs phagocytosis, and inhibiting neutrophil chemotaxis and complement activation.[48] In addition, alginate appears to be important for the formation of *P. aeruginosa* biofilms.

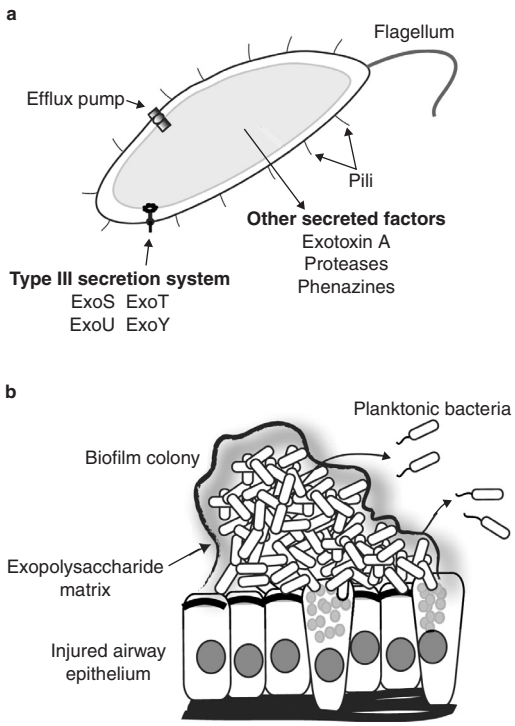

Fig. 2. (**a**) Mechanisms of virulence and antibacterial resistance in *Pseudomonas aeruginosa*; (**b**) biofilm growth mode.

The term 'biofilm' refers to a growth mode of bacteria that results in a cluster of microcolonies that are encased in a biopolymer matrix and attached to a surface. Bacterial biofilms are known to form on indwelling medical devices, and *P. aeruginosa* biofilms are present in the airways of patients with CF.[49] *P. aeruginosa* biofilms are believed to arise in the respiratory tract of CF patients through a series of steps beginning with the attachment of planktonic (i.e. free swimming) *P. aeruginosa* to epithelial cells or debris within the airway.[48] Groups of these planktonic bacteria are able to communicate via intercellular signals (e.g. acylated homoserine lactones) in a process termed 'quorum sensing', which allows collective regulation of gene transcription with subsequent effects on metabolism, protein synthesis and virulence.[50] In the process of biofilm formation, colonies of *P. aeruginosa* will secrete exopolysaccharides (including alginate), resulting in the production of a matrix that is characterised by a complex architecture of bacterial microcolonies separated by water channels.[48] Individual bacteria may periodically detach or be sheared from the biofilm and spread in the planktonic state. *P. aeruginosa* biofilm formation has been specifically studied in the context of CF airway infections, but bacterial biofilms are considered an important component in the pathogenesis of diverse disease states, including urinary and vascular catheter-related infections, infection-related (or struvite) kidney stones, infective endocarditis and chronic osteomyelitis.[51,52] In addition, quorum-sensing deficient *P. aeruginosa* strains have been shown to be less virulent in mouse models of acute pneumonia and burn wound infection, suggesting that quorum sensing is also an important determinant of acute infection.[53-55]

2.3 Type III Secretion System

When *P. aeruginosa* binds to an epithelial cell, the type III secretion system may be activated.[56] This contact-dependent system enables *P. aeruginosa* to inject certain effector proteins directly into the epithelial cell, which results in altered immune responses, cell injury and cell death. The four known exoenzymes (ExoS, ExoT, ExoU and ExoY) are variably expressed in different strains and have different activities. Among these exoenzymes, ExoU may be responsible for the greatest virulence.[57,58]

Secretion of exoenzymes via the type III secretion system is thought to be associated with more acute or invasive infection, as compared with the chronic infection states often seen in CF patients.[59] The expression of the type III secretion system in *P. aeruginosa* isolates has been associated with increased mortality in patients with pneumonia, sepsis and respiratory failure, and with more severe disease (defined as death or relapse of infection) in VAP.[57,59] In mouse, rabbit and rat *in vivo* models of *P. aeruginosa* pneumonia, blocking the type III secretion system by the administration of antibody products targeting PcrV (an integral component of the type III system) resulted in decreased lung injury, shock and death compared with controls.[60,61]

2.4 Other Secreted Virulence Factors

Brief mention is made here of other virulence factors produced by *P. aeruginosa*, but a complete discussion is beyond the scope of this review. The reader is referred to two excellent recent articles for further information.[46,56] Exotoxin A inhibits eukaryotic elongation factor 2, thereby halting protein synthesis and contributing to host cell death.[46] Alkaline proteases, elastases and protease IV are secreted enzymes capable of degrading multiple host immunoregulatory proteins, including surfactant proteins A and D, complement, immunoglobulin and antibacterial peptides.[62-65] The phenazines (e.g. pyocyanin) are secreted metabolites that cause ciliary dysfunction in the respiratory tract and exert proinflammatory and oxidative effects that damage host cells.[46]

2.5 Mechanisms of Antimicrobial Resistance

P. aeruginosa is intrinsically resistant to many antibacterials, including many β-lactams, the macrolides, the tetracyclines, co-trimoxazole (trimethoprim/sulfamethoxazole) and most fluoroquinolones. *P. aeruginosa* is not intrinsically resistant to the carboxypenicillins (ticarcillin), ureidopenicillins (piperacillin), β-lactam/β-lactamase inhibitor combinations (piperacillin/tazobactam and ticarcillin/clavulanic acid), fourth-generation and some third-generation cephalosporins (cefepime, ceftazidime and cefoperazone), aminoglycosides (gentamicin, tobramycin and amikacin), monobactams (aztreonam), some fluoroquinolones (levofloxacin and ciprofloxacin), carbapenems (imipenem/cilastatin, meropenem and ertapenem) and the polymyxins (colistin). However, *P. aeruginosa* is capable of developing resistance to any of these agents, often under the influence of previous antibacterial exposure. The risk of emergence of antibacterial resistance as a consequence of antibacterial exposure varies by the drug used, but has been particularly associated with ciprofloxacin and imipenem/cilastatin.[66]

General mechanisms of antibacterial resistance include blockade of entry, active efflux from the cell, enzymatic degradation and target structure alteration.[67] *P. aeruginosa* is capable of effecting any of these mechanisms in the development of resistance.

Like all Gram-negative bacteria, *P. aeruginosa* possesses an outer membrane composed of an asymmetric bilayer of lipopolysaccharide and phospholipids traversed by protein channels termed 'porins'.[68] The permeability of the outer membrane of *P. aeruginosa* is limited (even compared with other Gram-negative bacteria such as *Escherichia coli*), and this limitation (coupled with efflux mechanisms) accounts largely for the broad intrinsic resistance to antibacterials.[69] OprD is a carbapenem-specific outer membrane porin. Decreased or absent expression of OprD has been shown to be a primary mechanism of carbapenem resistance in both clinical and laboratory isolates of *P. aeruginosa*.[70-72]

Table I. *Pseudomonas aeruginosa* multidrug efflux pumps with antibacterial substrates (reproduced from Aeschlimann,[73] with permission)

MexA-MexB-OprM	MexC-MexD-OprJ	MexE-MexF-OprN	MexX-MexY-OprM
Aztreonam	Cefepime	Chloramphenicol	Amikacin
Carbenicillin	Cefuroxime	Ciprofloxacin	Cefepime
Cefotaxime	Chloramphenicol	Clavulanic acid	Cefotaxime
Ceftazidime	Ciprofloxacin	Levofloxacin	Ciprofloxacin
Cefuroxime	Erythromycin	Norfloxacin	Erythromycin
Chloramphenicol	Levofloxacin	Sulbactam	Gentamicin
Ciprofloxacin	Nafcillin	Trimethoprim	Levofloxacin
Clavulanic acid	Norfloxacin		Tetracycline
Faropenem	Tetracycline		Tobramycin
Levofloxacin	Trovafloxacin		
Meropenem			
Nafcillin			
Norfloxacin			
Piperacillin			
Sulbactam			
Tetracycline			
Trimethoprim			

Antibacterials may be extruded from within *P. aeruginosa* via multidrug efflux pumps. Functional efflux pump systems are thought to be tripartite structures (containing three individual proteins) that span both the inner and outer membranes, as well as the periplasmic space between the membranes. These multidrug efflux pumps are named for their protein components, and four have been well characterised (MexA-MexB-OprM, MexC-MexD-OprJ, MexE-MexF-OprN and MexX-MexY-OprM), although the *P. aeruginosa* genome contains at least 10 distinct efflux pump system operons.[67,73] These efflux pumps may be constitutively expressed at low levels or overexpressed in the setting of repressor gene mutations. Expression may be upregulated in response to certain environmental factors, including subinhibitory concentrations of antibacterials or high concentrations of acylated serine lactones (the signalling molecules implicated in quorum sensing).[73] Overexpression of a multidrug efflux pump raises the mean inhibitory concentration (MIC) of any drug susceptible to the pump, and each pump is able to handle multiple antibacterial substrates (table I). Antibacterial therapy exerts an additional pressure by selecting *P. aeruginosa* strains that overexpress these efflux pumps, a phenomenon that can be a particular problem with fluoroquinolones, which are recognised substrates of all four of the efflux pumps mentioned.[73,74]

β-Lactamases are enzymes capable of degrading β-lactams by hydrolysis and are a prominent mechanism of β-lactam resistance among gram-negative bacteria. *P. aeruginosa* possesses a chromosomal AmpC (or Class C) β-lactamase, and its expression can be induced by exposure to a β-lactam. Induction of AmpC β-lactamase may result in resistance to both the inducing antibacterial and other β-lactams.[69] Not all β-lactams are equally effective inducers of chromosomal AmpC β-lactamase. For instance, imipenem is a known inducer, whereas third- and fourth-generation cephalosporins are typically poor inducers.[75] In addition, the horizontal transfer of integron-encoded extended-spectrum β-lactamases (e.g. VEB and GES types), which are resistant to β-lactamase inhibitors such as clavulanic acid, is a well described phenomenon among *P. aeruginosa* and other Gram-negative bacteria.[76,77] Similarly, acquired metallo-β-lactamases (e.g. VIM and IMP types), which possess carbapenemase activity, are a growing problem worldwide. Prevalence rates for these metallo-β-lactamases can be quite high among carbapenem-resistant isolates of *P. aeruginosa*, with rates of 11.1% reported by a nationwide surveillance network in South Korea and

70% reported in a single university hospital in Italy.[78,79]

MDR strains of *P. aeruginosa* typically exhibit several resistance mechanisms simultaneously,[80,81] although resistance to specific antibacterials may be mediated by different combinations of these mechanisms. Acquired β-lactam resistance is often the result of derepression of chromosomal AmpC or acquisition of a plasmid-encoded β-lactamase.[82] Fluoroquinolone resistance is typically caused by active efflux and mutations in the antibacterial targets (primarily DNA gyrase and also topoisomerase IV).[83] Carbapenem resistance is primarily related to decreased expression of the OprD porin, with efflux pumps and β-lactamases often playing important secondary roles, especially in mediating meropenem resistance.[70]

3. Treatment of *P. aeruginosa* Infections

3.1 Infection Control Practices and Preventive Measures

Imperative to controlling *P. aeruginosa* infections is to prevent them when possible. The medical literature abounds with reports of outbreaks of nosocomially acquired *P. aeruginosa* infections, and some cases can be traced to chronic carriage states by hospital personnel.[84,85] Best-practice guidelines for the prevention of nosocomial infections that are generally accepted include surveillance of ICU and hospital-wide infections to identify endemic and new MDR pathogens, contact isolation precautions for patients carrying MDR bacterial species, hand washing or alcohol-based disinfection before and after every patient contact, strict sterile technique and maximal sterile barrier precautions when placing central venous catheters, discontinuation of central venous and urinary tract catheters when not needed, avoidance of intubation and reintubation whenever possible, semirecumbent positioning of patients receiving mechanical ventilation, and the avoidance of nasotracheal intubation and nasogastric feeding tubes in favour of orotracheal intubation and orogastric tubes in mechanically ventilated patients whenever possible. Further detailed discussions of nosocomial prevention strategies are available elsewhere.[86-89]

3.2 Identifying At-Risk Individuals and Collecting Cultures

Patients presenting with suspected acute infections or sepsis states are prescribed antibacterials empirically based on pathogens likely to be responsible, and inappropriate initial empirical therapy in the acutely ill is known to adversely affect outcomes.[90,91] Indications for empirical antipseudomonal antibacterial therapy include HAP, HCAP or VAP; ICU (and particularly burn ICU)-acquired infections; neutropenic sepsis as a result of chemotherapy, acute leukaemia or AIDS; and CF with acute exacerbation of bronchiectasis (particularly when the patient is known to be colonised with *P. aeruginosa*). Antibacterial regimens are often adjusted when an offending microbe is isolated, underscoring the importance of collecting cultures (blood, respiratory tract secretions, urine, cerebrospinal fluid or other sources as appropriate), ideally prior to antibacterial administration if this can be done in a timely manner.

3.3 Prompt Administration of Antibacterials and Source Control

Antibacterial therapy should not be delayed, particularly in the severely ill, with a goal of administering appropriate antibacterials within an hour in the most ill patients (i.e. those with severe sepsis and septic shock) advocated by expert consensus.[92] In addition, effective treatment of any infection typically mandates source control. Patients should be evaluated carefully for sources of initial or ongoing infection that are amenable to drainage, debridement or removal.[92] Abscesses and empyemas should be drained, infected indwelling devices (including vascular catheters) removed, and other sources of sepsis (e.g. ischaemic colon, undrained cholangitis or obstructive pyelonephritis) addressed with the assistance of the appropriate specialists after initial stabilisation and administration of antibacterials.

3.4 The Importance of Appropriate Initial Therapy

Inappropriate initial empirical antibacterial therapy is known to adversely affect patient outcomes.[90,91] The importance of appropriate therapy for *P. aeruginosa* bloodstream infections was specifically addressed in a recent retrospective study.[93] Significantly higher mortality rates (30.7% vs 17.8%) were observed in patients who had not received appropriate initial antibacterial therapy (i.e. at least one antibacterial to which a bloodstream *P. aeruginosa* isolate was sensitive at the time sensitivities were known). Initial treatment with a combination of agents active against *P. aeruginosa* was more likely to provide appropriate initial therapy compared with monotherapy in this study, probably reflecting the prevalence of MDR *P. aeruginosa* that has been noted in large series of nosocomial infections.

3.5 Combination versus Monotherapy for the Treatment of *P. aeruginosa*

Although the simultaneous use of two anti-pseudomonal antibacterials decreases the rate of inappropriate initial antibacterial therapy, a separate question is whether combination therapy with more than one agent active against *P. aeruginosa* has an advantage over monotherapy when sensitivities of the offending isolate are known. Synergy of certain antibacterial combinations against *P. aeruginosa* can be demonstrated *in vitro*. However, the clinical relevance of this finding is unclear. A meta-analysis of β-lactam monotherapy versus β-lactam plus aminoglycoside combination therapy for sepsis in immunocompetent patients failed to show a difference in all cause mortality.[94] By contrast, a meta-analysis of treatment outcomes in Gram-negative bacteraemia showed a survival advantage with combination therapy (most often using a β-lactam and an aminoglycoside) only in the subgroup analysis of *P. aeruginosa* bacteraemia.[95] The authors of this meta-analysis cautioned that considerable heterogeneity existed in the studies included in the subgroup analysis, and in the largest of these (which independently showed a survival difference favouring combination therapy) most patients treated with monotherapy had received an aminoglycoside as a single agent.[95,96] The lack of efficacy of aminoglycoside monotherapy for the treatment of *P. aeruginosa* has been noted in other studies.[28,97] For example, in a study of *P. aeruginosa* bacteraemia among cancer patients, a lower cure rate was seen with aminoglycoside monotherapy when compared with other regimens, including β-lactam monotherapy, β-lactam plus aminoglycoside combination therapy, and ciprofloxacin monotherapy (although these other regimens showed similar cure rates compared with each other).[28] Another study of *P. aeruginosa* bloodstream infections noted that mortality was similar among patients receiving appropriate initial therapy with either a single β-lactam, single aminoglycoside, β-lactam plus aminoglycoside combination or ciprofloxacin alone.[93]

In a study of *P. aeruginosa* bacteraemia in which therapy was characterised as empirical (i.e. before antibiogram results were available) and definitive (i.e. after antibiogram results were available), adequate empirical combination anti-pseudomonal therapy was associated with lower mortality at one month than adequate empirical anti-pseudomonal monotherapy. However, mortality rates did not differ between adequate definitive combination therapy and adequate definitive monotherapy. The authors of this study concluded that in patients with suspected *P. aeruginosa* bacteraemia, two anti-pseudomonal antibacterials should be prescribed empirically, but combination therapy could be changed to monotherapy on the basis of antibacterial susceptibilities when available.[98] In this study, aminoglycoside monotherapy was excluded from analysis based on the results of the previous studies showing poor clinical outcomes when aminoglycosides were used alone.[28,96,97]

Therefore, based on the available data discussed in this section, an appropriate approach to treating infections suspected to be caused by *P. aeruginosa* would be to begin therapy with two anti-pseudomonal agents (to minimise the risk of inappropriate initial therapy) and to subsequently de-escalate to a single agent when a bacterial isolate is

available and drug sensitivities are known. Important caveats to this approach are as follows: (i) aminoglycosides should not be used as monotherapy to treat *P. aeruginosa* when alternative agents are available; and (ii) consensus statements on the treatment of CF recommend combination anti-pseudomonal therapy for the treatment of moderate to severe CF pulmonary exacerbations.[99,100] Specific treatment recommendations are included in subsequent sections of this review.

3.6 The Concept of Antibacterial De-escalation

It is clear that antibacterial usage promotes subsequent emergence of antibacterial-resistant bacteria.[101,102] In addition, the prolonged administration of antibacterials appears to increase the likelihood that subsequent infections will be due to MDR bacteria.[103] As discussed previously, the available data suggest no clinical benefit from the treatment of sepsis or bacteraemia caused by *P. aeruginosa* with a combination of agents once antibacterial susceptibilities are available,[28,93,98] and treatment with combination therapy has not been shown to prevent the emergence of resistant *P. aeruginosa*.[104] These observations, coupled with several recent studies that have established the efficacy of antibacterial courses shorter than those historically prescribed,[103,105,106] help to emphasise the importance of antibacterial de-escalation when possible.

Of primary importance in treating infections caused by *P. aeruginosa* (or any other pathogen) is providing appropriate coverage of the microbe(s) responsible. Initial empirical antibacterial choices are made based on the knowledge of pathogens likely to cause a particular infection, local pathogen profiles and various host risk factors for infection. After an initial regimen is prescribed, modification of the antibacterial regimen should occur based on the patient's clinical response and the available microbiological data. The de-escalation strategy of antibacterial therapy should include decreasing the number and/or spectrum of antibacterials prescribed and shortening the duration of therapy in patients with uncomplicated infections who are demonstrating signs of clinical improvement.

In regard to this strategy as it applies to *P. aeruginosa*, mention should be made of a recent prospective study of treatment duration for VAP, which found no difference in clinical outcomes among patients treated with 8 days of appropriate initial antibacterial therapy compared with 15 days of appropriate initial therapy.[103] However, the subgroup of patients in the study with VAP caused by nonfermenting Gram-negative bacilli (including *P. aeruginosa*) experienced a higher pulmonary infection recurrence rate with the 8-day treatment regimen (40.6% vs 25.4%). However, these patients showed no difference in any other clinical outcome (including mortality, ventilator-free days, organ-failure-free days or ICU length of stay) with an 8 versus 15-day regimen. In addition, among patients with recurrent infections, those previously treated with 15 days of antibacterials were more likely to subsequently harbour multiresistant pathogens. The authors of the study concluded (reasonably) that an 8-day course of antibacterial therapy could be safely used to treat patients with VAP caused by *P. aeruginosa*, provided extreme vigilance was maintained to monitor for recurrent infection.

3.7 Specific Dose Administration Recommendations for *P. aeruginosa* Pneumonia

Comparative studies of different dose administration regimens of the same antibacterial are infrequently available, and many dose administration recommendations are based on *in vitro* efficacy and pharmacokinetic/pharmacodynamic profiles of the antibacterials used. These profiles differ among different classes of antibacterials. For example, bacterial eradication is enhanced by maximising the time the serum drug concentration of β-lactams, carbapenems and monobactams remains above the mean inhibitory concentration (MIC).[107] In contrast, the bactericidal effects of aminoglycosides are maximised by optimising the ratio of the maximum drug concentration (C_{max}) to MIC. Fluoroquinolone efficacy has been correlated with the 24-hour area

Table II. Treatment of *Pseudomonas aeruginosa* pneumonia: initial empirical antibacterial options[a]

Antibacterial	Dosage
One of the following:	
Piperacillin/tazobactam	IV 4.5g every 6 hours
Cefepime	IV 1–2g every 8–12 hours
Ceftazidime	IV 2g every 8 hours
Imipenem cilastatin	IV 500mg every 6 hours or 1g every 8 hours
Meropenem	IV 1g every 8 hours
Aztreonam[b]	IV 2g every 8 hours
Plus one of the following:	
Gentamicin	IV 7 mg/kg once daily[c]
Tobramycin	IV 7 mg/kg once daily[c]
Amikacin	IV 20 mg/kg once daily[d]
Levofloxacin	IV or PO 750mg once daily
Ciprofloxacin	IV or PO 400mg every 8 hours

a Dosages for adults with normal renal and hepatic function.

b Typically reserved for penicillin-allergic patients.

c Dosage should be adjusted to serum trough concentration <1 μg/mL.

d Dosage should be adjusted to serum trough concentration <4–5 μg/mL.

IV = intravenous; **PO** = orally.

under the antimicrobial concentration curve (AUC_{24}) to MIC ratio.[107]

For nosocomial pneumonias (including HAP, HCAP and VAP) of late onset in which *P. aeruginosa* is a common pathogen, consensus guidelines for treatment have been formulated by the American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA).[86] Empirical antibacterial regimens should include two anti-pseudomonal agents from different classes (as well as either vancomycin or linezolid to cover meticillin-resistant *S. aureus* [MRSA] if the cause of the pneumonia is unknown). Acceptable anti-pseudomonal agents with dose administration recommendations are included in table II. Duration of therapy should generally be limited to 7–8 days of appropriate therapy (i.e. at least one antibacterial active against any identified isolate), assuming an appropriate clinical response and normal lung architecture.

Inhaled anti-pseudomonal antibacterials have been used in the treatment of acute respiratory infections in non-CF patients, but there is currently inadequate evidence of efficacy to recommend their routine use. Nevertheless, inhaled antibacterials may be used adjunctively to treat pneumonia caused by MDR pathogens, particularly when intravenous alternatives are lacking.[108,109] Tobramycin and colistin are the most commonly used agents for this purpose.

3.8 Other Antimicrobial Options

3.8.1 Colistin

Polymyxin B and polymyxin E (colistin) are older antibacterials with anti-pseudomonal activity that are not commonly prescribed. The infrequent use of these antibacterials likely reflects a lack of familiarity with their dose administration, and concerns about neurotoxicity and nephrotoxicity. Use of colistin has increased in recent years as a consequence of the increasing problem of MDR Gram-negative bacteria, which may remain susceptible only to this drug while expressing multiple resistance mechanisms that preclude the use of other agents.[81] The efficacy of intravenous colistin for treating serious infections caused by MDR organisms appears to be acceptable, considering especially that its use is often driven by a lack of alternatives.[110-112] Recent studies of the use of intravenous colistin have reported rates of nephrotoxicity ranging from 8% to 14.3%.[113-115] Nephrotoxicity was a rare occurrence in a series of patients receiving

prolonged (>4 week) courses of colistin,[116] and in one study comparing the treatment of VAP with colistin to imipenem/cilastatin, nephrotoxicity was significantly less common in the colistin-treated group (24% vs 42%).[112] Changes in serum creatinine may be related to the cumulative dose of colistin given,[113] and increased rates of nephrotoxicity have been noted in patients with abnormal baseline renal function.[110] Neurotoxicity from colistin (historically to include weakness, paresthesias, neuromuscular blockade and apnoea) has been reported to be infrequent in recent studies, with occasional cases of reversible weakness and polyneuropathy described.[111,116]

The discrepancy between the rates of nephrotoxicity and neurotoxicity in recent studies compared with older studies of colistin may be the result of the different formulations of colistin used currently, as well as the high doses of colistin administered in the past, with some historical adverse events occurring in the setting of colistin overdose.[117] Despite the superior safety profile recently reported, certain precautions should be taken when administering intravenous colistin, including dose reduction in the setting of renal insufficiency and avoidance of concomitant nephrotoxins. In addition, potential neurotoxins (including neuromuscular blocking agents and aminoglycosides) should be avoided when using colistin.[117] Multiple formulations of intravenous colistin are available worldwide, and the use of international units (IUs) when prescribing the drug has been advocated to avoid confusion with the dosage when comparing regimens used by different centres.[118] Centres experienced with the use of intravenous colistin for the treatment of serious infections have reported average and maximum daily dosages of 4.5 million IU and 9 million IUs, respectively, with dosages decreased in the setting of renal dysfunction.[118] At our hospital, we use colistimethate sodium (X-Gen Pharmaceuticals, Big Flats, NY, USA) administered at 2.5–5 mg/kg/day intravenously divided into two to four doses in the setting of normal renal function. With renal insufficiency, the dose is adjusted as per the package insert for the drug. Support from a clinical pharmacist is encouraged in the setting of dose administration uncertainty.

3.8.2 Doripenem

Doripenem is a new 1-β-methyl-carbapenem with a structure that confers β-lactamase stability and resists inactivation by renal dihydropeptidases.[119] Doripenem is effective *in vitro* against both Gram-positive bacteria (except *Enterococcus* species and MRSA) and a broad spectrum of Gram-negative species, including *P. aeruginosa*. Comparative studies of doripenem have shown greater *in vitro* anti-pseudomonal activity than meropenem or imipenem,[119,120] and in studies including carbapenem-resistant *P. aeruginosa* it was reported as the most active agent tested against these strains.[121-123] Murine *in vivo* studies have shown similar results, with doripenem shown to be as effective or slightly better than meropenem or imipenem cilastatin, depending on the *P. aeruginosa* strain used.[121] Doripenem has a serum elimination half-life, post-antibiotic effect against Gram-negative bacteria, and a seizure risk similar to that seen with meropenem.[122] A number of phase III clinical trials of doripenem (for the treatment of intra-abdominal and UTIs) have completed enrolment. Phase III trials in the treatment of HAP and VAP are still enrolling patients. It is expected that in the near future doripenem will be available for use in treating infections caused by MDR strains of *P. aeruginosa*.

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

The long-term care of CF patients is best provided by specialised care centres,[124,125] and the approach to treating *P. aeruginosa* at these centres typically involves routine follow-up and monitoring of sputum cultures. The purpose of this section is to introduce the non-CF specialist to the therapeutic approach to chronic CF airway infection employed at these centres and to provide some direction to non-CF specialists (e.g. internists, pulmonologists and intensivists) who may occasionally provide care to CF patients when they are acutely ill.

3.9.1 Treatment of Initial Colonisation

Chronic infection of the respiratory tract by *P. aeruginosa* will eventually occur in most patients with CF, and once it occurs eradication is considered to be nearly impossible.[99] During the chronic infection state, mucoid phenotypes of *P. aeruginosa* predominate. However, the chronic infection state is thought to be preceded by a period of intermittent colonisation by non-mucoid strains of *P. aeruginosa*.[126] This observation has prompted trials of aggressive antibacterial therapy targeting *P. aeruginosa* when it is first identified on surveillance sputum or throat swab cultures. These trials have shown that such an approach reduces the risk of developing a chronic infection state, and also improves lung function and decreases hospitalisation days when compared with non-treated controls.[126,127] Treatment may have to be repeated in patients who become recurrently infected, and the long-term benefit of this approach is not known.[99,127]

3.9.2 Chronic Suppressive Therapy

The chronic *P. aeruginosa* infection state in CF is typically defined by recurrent culture of *P. aeruginosa* from sputum for 6 months (often in the presence of detectable specific antibodies). Trials of scheduled intermittent antibacterial therapy (including intravenous, oral and nebulised antibacterials) have been undertaken to determine whether this strategy will alter the clinical course of the disease once chronic infection is established. The use of intermittent nebulised tobramycin has been shown to improve lung function, decrease the frequency of acute pulmonary exacerbations and increase weight gain in CF patients.[128,129] As such, consensus statements from CF experts recommend the use of inhaled anti-pseudomonal antibacterials in patients chronically infected with *P. aeruginosa*.[99,100] Inhaled antibacterials are usually given in 28-day cycles (i.e. 28 days 'on', followed by 28 days 'off' when the drug is not taken) and include tobramycin (300mg nebulised twice daily) and colistin (500 000–1 million IU nebulised twice daily). The nebulised antibacterials are given via jet nebulisers that generate particle sizes around 2–5μm, resulting in drug deposition in the endobronchial tree (rather than the alveolar space), thus limiting systemic exposure and the associated risks of ototoxicity and nephrotoxicity.[99,129,130]

3.9.3 Treatment of Acute Respiratory Exacerbations

Perhaps most relevant to the practice of non-CF specialists is the treatment of acute respiratory exacerbations of CF-related bronchiectasis. Many of these principles of therapy apply to non-CF patients with bronchiectasis from other causes, when they are known to be chronically infected with *P. aeruginosa* (in particular with mucoid strains). Virtually all CF patients experiencing acute pulmonary exacerbations are prescribed bronchodilators, chest physiotherapy with postural drainage and often nebulised DNAse to help mobilise respiratory secretions for expectoration. Antibacterials are typically prescribed to treat *P. aeruginosa*, as well as any other pathogens (e.g. *S. aureus*) that are known to be present in the patient's respiratory tract.

On the basis of pharmacokinetic studies showing increased drug clearance and decreased elimination half-life in CF patients (coupled with the poor penetrance of antibacterials into mucoid plugs of *P. aeruginosa* in the CF airway), higher doses of antibacterials and/or decreased dose administration intervals have been used to treat acute CF respiratory exacerbations compared with pulmonary infections in non-CF patients.[99,131,132] Duration of antibacterial therapy typically ranges from 2 to 3 weeks, depending on the severity of symptoms and the clinical response to therapy. For mild pulmonary symptoms, oral ciprofloxacin is often prescribed, usually at a dosage of 30 mg/kg per day, divided into bid or tid dose administration intervals. More severe disease is treated with intravenous antibacterials.

Although inhaled anti-pseudomonal agents are an important component of the maintenance regimen of patients with CF, there is inadequate evidence supporting their routine use in the treatment of acute pulmonary exacerbations.[99] Studies using nebulised agents in addition to intravenous therapy for acute pulmonary exacerbations have typically revealed decreases in *P. aeruginosa* colony counts in the sputum of treated patients without any dis-

Table III. Anti-pseudomonal regimens used to treat acute pulmonary exacerbations of cystic fibrosis at Washington University in Saint Louis/Barnes-Jewish Hospital[a]

Antibacterial	Dosage
One of the following:	
Ceftazidime	IV 2g every 8 hours
Cefepime	IV 2g every 8 hours
Meropenem	IV 1g every 8 hours
Plus:	
Tobramycin	IV 3 mg/kg every 8 hours[b]

a Dosages for adults with normal renal function.

b Dosage adjusted to peak serum concentration 8–12 μg/mL, trough level <2 μg/mL.

IV = intravenous.

cernible difference in clinical outcomes.[133,134] However, patients who are treated as outpatients with oral ciprofloxacin for mild exacerbations often continue their maintenance inhaled anti-pseudomonal therapy.

Although compelling data in support of the practice are lacking, most CF experts recommend using two intravenous anti-pseudomonal agents simultaneously to treat moderate to severe acute pulmonary exacerbations of CF.[99,100] Regimens typically used to treat adult CF patients at Washington University in Saint Louis are displayed in table III. The initial antibacterials are often chosen based on the most recent sputum culture data available and may be adjusted based on newly acquired sputum culture findings. Known carriers of other bacterial pathogens (e.g. *S. aureus*) receive therapy targeting those species as well.

4. Conclusions

P. aeruginosa is an important bacterial pathogen, particularly as a cause of nosocomial infections, infections in immunocompromised hosts, and sinopulmonary infections in patients with CF. *P. aeruginosa* exhibits a number of virulence factors, as well as multiple antibacterial resistance mechanisms that have contributed to increasing rates of antibacterial resistance in recent years. Strategies important in the treatment of *P. aeruginosa* infections include prevention when possible, appropriate initial antibacterial therapy (usually with two anti-pseudomonal agents to ensure adequate coverage) in patients at high risk of infection, and appropriate dose administration of antibacterials. De-escalation of antibacterials to a single agent (other than an aminoglycoside) should be employed for uncomplicated acute infections in the setting of an appropriate clinical response when the offending isolate (with known sensitivities) is available. The treatment of *P. aeruginosa* in CF patients is typically provided by dedicated CF physicians, although non-CF specialists may encounter these patients when they are acutely ill. Effective therapies in the setting of MDR *P. aeruginosa* may be limited, requiring physicians to be familiar with older antibacterials (i.e. colistin), inhaled antibacterials (for respiratory tract infections) and antibacterials expected to be released for general use in the near future (e.g. doripenem).

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