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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]

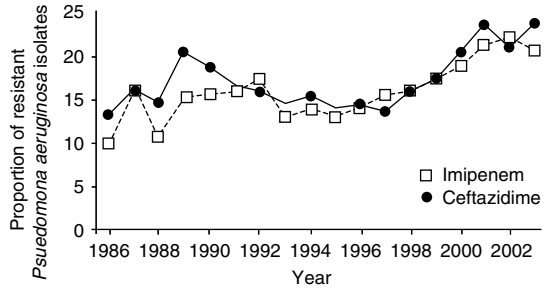

Fig. 1. Proportions of intensive care unit isolates resistant to imipenem and ceftazidime (National Nosocomial Infections Surveillance System, 1986–2003) [reproduced from Gaynes and Edwards,[9] with permission].

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

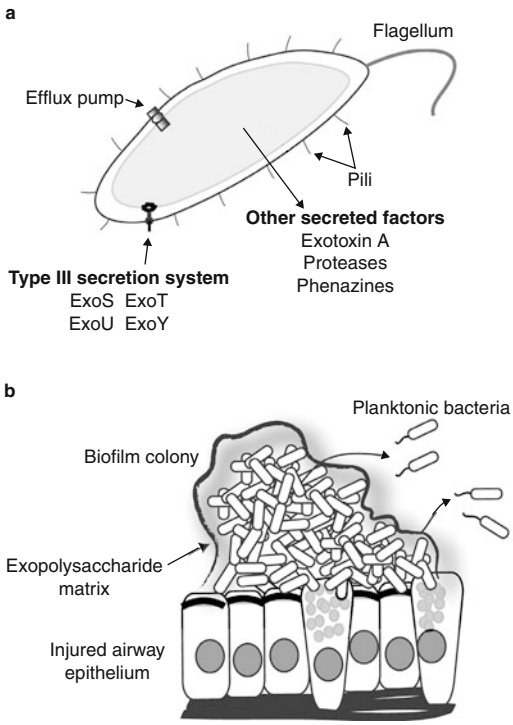

Fig. 2. (**a**) Mechanisms of virulence and antibacterial resistance in *Pseudomonas aeruginosa*; (**b**) biofilm growth mode.

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.

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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References

1. Bonten MJ, Bergmans DC, Speijer H, et al. Characteristics of polyclonal endemicity of *P. aeruginosa* aeruginosa colonization in intensive care units: implications for infection control. Am J Respir Crit Care Med 1999; 160: 1212-9
2. Pirnay JP, De Vos D, Cochez C, et al. Molecular epidemiology of *Pseudomonas aeruginosa* colonization in a burn unit: persistence of a multidrug-resistant clone and a silver sulfadiazine-resistant clone. J Clin Microbiol 2003; 41: 1192-202
3. Rello J, Ollendorf DA, Oster G, et al. Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. Chest 2002; 122: 2115-21
4. Kollef MH, Shorr A, Tabak YP, et al. Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. Chest 2005; 128: 3854-62
5. Osmon S, Ward S, Fraser VJ, et al. Hospital mortality for patients with bacteremia due to *Staphylococcus aureus* or *Pseudomonas aeruginosa*. Chest 2004; 125: 607-16
6. Harbarth S, Ferrière K, Hugonnet S, et al. Epidemiology and prognostic determinants of bloodstream infections in surgical intensive care. Arch Surg 2002; 137: 1353-9
7. National Nosocomial Infections Surveillance System Report. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control 2004; 32: 470-85
8. Biedenbach DJ, Moet GJ, Jones RN. Occurrence and antimicrobial resistance pattern comparisons among bloodstream infection isolates from the SENTRY Antimicrobial Surveillance Program (1997-2002). Diagn Microbiol Infect Dis 2004; 50: 59-69

9. Gaynes R, Edwards JR, National Nosocomial Infections Surveillance System. Overview of nosocomial infections caused by gram-negative bacilli. Clin Infect Dis 2005; 41: 848-54
10. Pittet D, Harbarth S, Ruef C, et al. Prevalence and risk factors for nosocomial infections in four university hospitals in Switzerland. Infect Control Hosp Epidemiol 1999; 20: 37-42
11. Lizioli A, Privitera G, Alliata E, et al. Prevalence of nosocomial infections in Italy: result from the Lombardy survey in 2000. J Hosp Infect 2003; 54: 141-8
12. Kim JM, Park ES, Jeong JS, et al. Multicenter surveillance study for nosocomial infections in major hospitals in Korea. Nosocomial Infection Surveillance Committee of the Korean Society for Nosocomial Infection Control. Am J Infect Control 2000; 28: 454-8
13. Erbay H, Yalcin AN, Serin S, et al. Nosocomial infections in intensive care unit in a Turkish university hospital: a 2-year survey. Intensive Care Med 2003; 29: 1482-8
14. Rello J, Lorente C, Diaz E, et al. Incidence, etiology, and outcome of nosocomial pneumonia in ICU patients requiring percutaneous tracheotomy for mechanical ventilation. Chest 2003; 124: 2239-43
15. Ibrahim EH, Ward S, Sherman G, et al. A comparative analysis of patients with early-onset vs late-onset nosocomial pneumonia in the ICU setting. Chest 2000; 117: 1434-42
16. Richards MJ, Edwards JR, Culver DH, et al. Nosocomial infections in pediatric intensive care units in the United States. National Nosocomial Infections Surveillance System. Pediatrics 1999; 103: e39
17. Lari AR, Alaghehbandan R. Nosocomial infections in an Iranian burn care center. Burns 2000; 26: 737-40
18. Erol S, Altoparlak U, Akcay MN, et al. Changes of microbial flora and wound colonization in burned patients. Burns 2004; 30: 357-61
19. Song W, Lee KM, Kang HJ, et al. Microbiologic aspects of predominant bacteria isolated from the burn patients in Korea. Burns 2001; 27: 136-9
20. Yildirim S, Nursal TZ, Tarim A, et al. Bacteriological profile and antibiotic resistance: comparison of findings in a burn intensive care unit, other intensive care units, and the hospital services unit of a single center. J Burn Care Rehabil 2005; 26: 488-92
21. Weiss CA, Statz CL, Dahms RA, et al. Six years of surgical wound infection surveillance at a tertiary care center: review of the microbiologic and epidemiological aspects of 20,007 wounds. Arch Surg 1999; 134: 1041-8
22. Arias CA, Quintero G, Vanegas BE, et al. Surveillance of surgical site infections: decade of experience at a Colombian tertiary care center. World J Surg 2003; 27: 529-33
23. Chan RK, Lye WC, Lee EJ, et al. Nosocomial urinary tract infection: a microbiological study. Ann Acad Med Singapore 1993; 22: 873-7
24. Jodrá VM, Díaz-Agero Pérez C, Sainz de Los Terreros Soler L, et al. Results of the Spanish national nosocomial infection surveillance network (VICONOS) for surgery patients from January 1997 through December 2003. Am J Infect Control 2006; 34: 134-41
25. Bouza E, San Juan R, Muñoz P, et al. A European perspective on nosocomial urinary tract infections. I: report on the microbiology workload, etiology and antimicrobial susceptibility (ESGNI-003 study). European Study Group on Nosocomial Infections. Clin Microbiol Infect 2001; 7: 523-31
26. Taneja N, Emmanuel R, Chari PS, et al. A prospective study of hospital-acquired infections in burn patients at a tertiary care referral centre in North India. Burns 2004; 30: 665-9
27. Lee WI, Jaing TH, Hsieh MY, et al. Distribution, infections, treatments and molecular analysis in a large cohort of patients with primary immunodeficiency diseases (PIDs) in Taiwan. J Clin Immunol 2006; 26: 274-83
28. Chatzinikolaou I, Abi-Said D, Bodey GP, et al. Recent experience with *Pseudomonas aeruginosa* bacteremia in patients with cancer: retrospective analysis of 245 episodes. Arch Intern Med 2000; 160: 501-9
29. Funada H, Matsuda T. Changes in the incidence and etiological patterns of bacteremia associated with acute leukemia over a 25-year period. Intern Med 1998; 37: 1014-8
30. Vidal F, Mensa J, Martínez JA, et al. *Pseudomonas aeruginosa* bacteremia in patients infected with human immunodeficiency virus type 1. Eur J Clin Microbiol Infect Dis 1999; 18: 473-7
31. Afessa B, Green B. Bacterial pneumonia in hospitalized patients with HIV infection: the Pulmonary Complications, ICU Support, and Prognostic Factors of Hospitalized Patients with HIV (PIP) Study. Chest 2000; 117: 1017-22
32. Afessa B, Green W, Chiao J, et al. Pulmonary complications of HIV infection: autopsy findings. Chest 1998; 113: 1225-9
33. Lossos IS, Breuer R, Or R, et al. Bacterial pneumonia in recipients of bone marrow transplantation: a five-year prospective study. Transplantation 1995; 60: 672-8
34. Kramer MR, Marshall SE, Starnes VA, et al. Infectious complications in heart-lung transplantation: analysis of 200 episodes. Arch Intern Med 1993; 153: 2010-6
35. Revuz J, Penso D, Roujeau JC, et al. Toxic epidermal necrolysis: clinical findings and prognosis factors in 87 patients. Arch Dermatol 1987; 123: 1160-5
36. Shankar EM, Mohan V, Premalatha G, et al. Bacterial etiology of diabetic foot infections in South India. Eur J Intern Med 2005; 16: 567-70
37. Abdulrazak A, Bitar ZI, Al-Shamali AA, et al. Bacteriological study of diabetic foot infections. J Diabetes Complications 2005; 19: 138-41
38. Burns JL, Gibson RL, McNamara S, et al. Longitudinal assessment of *Pseudomonas aeruginosa* in young children with cystic fibrosis. J Infect Dis 2001; 183: 444-52
39. Van Daele S, Vaneechoutte M, De Boeck K, et al. Survey of *Pseudomonas aeruginosa* genotypes in colonised cystic fibrosis patients. Eur Respir J 2006; 28: 740-7
40. Lee B, Haagensen JA, Ciofu O, et al. Heterogeneity of biofilms formed by nonmucoid *Pseudomonas aeruginosa* isolates from patients with cystic fibrosis. J Clin Microbiol 2005; 43: 5247-55
41. Emerson J, Rosenfeld M, McNamara S, et al. *Pseudomonas aeruginosa* and other predictors of mortality and morbidity in young children with cystic fibrosis. Pediatr Pulmonol 2002; 34: 91-100
42. Holzmann D, Speich R, Kaufmann T, et al. Effects of sinus surgery in patients with cystic fibrosis after lung transplantation: a 10-year experience. Transplantation 2004; 77: 134-6
43. D'Agata EM. Rapidly rising prevalence of nosocomial multidrug-resistant, gram-negative bacilli: a 9-year surveillance study. Infect Control Hosp Epidemiol 2004; 25: 842-6
44. O'Toole GA, Kolter R. Flagellar and twitching motility are necessary for *Pseudomonas aeruginosa* biofilm development. Mol Microbiol 1998; 30: 295-304

45. Kipnis E, Sawa T, Wiener-Kronish J. Targeting mechanisms of *Pseudomonas aeruginosa* pathogenesis. Med Mal Infect 2006; 36: 78-91
46. Lau GW, Hassett DJ, Britigan BE. Modulation of lung epithelial functions by *Pseudomonas aeruginosa*. Trends Microbiol 2005; 13: 389-97
47. de Bentzmann S, Roger P, Puchelle E. *Pseudomonas aeruginosa* adherence to remodelling respiratory epithelium. Eur Respir J 1996; 9: 2145-50
48. Ramsey DM, Wozniak DJ. Understanding the control of *Pseudomonas aeruginosa* alginate synthesis and the prospects for management of chronic infections in cystic fibrosis. Mol Microbiol 2005; 56: 309-22
49. Singh PK, Schaefer AL, Parsek MR, et al. Quorum-sensing signals indicate that cystic fibrosis lungs are infected with bacterial biofilms. Nature 2000; 407: 762-4
50. Smith RS, Iglewski BH. *P. aeruginosa* quorum-sensing systems and virulence. Curr Opin Microbiol 2003; 6: 56-60
51. Parsek MR, Singh PK. Bacterial biofilms: an emerging link to disease pathogenesis. Annu Rev Microbiol 2003; 57: 677-701
52. Trautner BW, Darouiche RO. Catheter-associated infections: pathogenesis affects prevention. Arch Intern Med 2004; 164: 842-50
53. Smith RS, Harris SG, Phipps R, et al. The *Pseudomonas aeruginosa* quorum-sensing molecule N-(3-oxododecanoyl)homoserine lactone contributes to virulence and induces inflammation in vivo. J Bacteriol 2002; 184: 1132-9
54. Rumbaugh KP, Griswold JA, Iglewski BH, et al. Contribution of quorum sensing to the virulence of *Pseudomonas aeruginosa* in burn wound infections. Infect Immun 1999; 67: 5854-62
55. Pearson JP, Feldman M, Iglewski BH, et al. *Pseudomonas aeruginosa* cell-to-cell signaling is required for virulence in a model of acute pulmonary infection. Infect Immun 2000; 68: 4331-4
56. Sadikot RT, Blackwell TS, Christman JW, et al. Pathogen-host interactions in *Pseudomonas aeruginosa* pneumonia. Am J Respir Crit Care Med 2005; 171: 1209-23
57. Hauser AR, Cobb E, Bodi M, et al. Type III protein secretion is associated with poor clinical outcomes in patients with ventilator-associated pneumonia caused by *Pseudomonas aeruginosa*. Crit Care Med 2002; 30: 521-8
58. Schulert GS, Feltman H, Rabin SD, et al. Secretion of the toxin ExoU is a marker for highly virulent *Pseudomonas aeruginosa* isolates obtained from patients with hospital-acquired pneumonia. J Infect Dis 2003; 188: 1695-706
59. Roy-Burman A, Savel RH, Racine S, et al. Type III protein secretion is associated with death in lower respiratory and systemic *Pseudomonas aeruginosa* infections. J Infect Dis 2001; 183: 1767-74
60. Shime N, Sawa T, Fujimoto J, et al. Therapeutic administration of anti-PcrV F(ab')(2) in sepsis associated with *Pseudomonas aeruginosa*. J Immunol 2001; 167: 5880-6
61. Faure K, Fujimoto J, Shimabukuro DW, et al. Effects of monoclonal anti-PcrV antibody on *Pseudomonas aeruginosa*-induced acute lung injury in a rat model. J Immune Based Ther Vaccines 2003; 1: 2
62. Mariencheck WI, Alcorn JF, Palmer SM, et al. *Pseudomonas aeruginosa* elastase degrades surfactant proteins A and D. Am J Respir Cell Mol Biol 2003; 28: 528-37
63. Schmidtchen A, Holst E, Tapper H, et al. Elastase-producing *Pseudomonas aeruginosa* degrade plasma proteins and extracellular products of human skin and fibroblasts, and inhibit fibroblast growth. Microb Pathog 2003; 34: 47-55
64. Schmidtchen A, Frick IM, Andersson E, et al. Proteinases of common pathogenic bacteria degrade and inactivate the antibacterial peptide LL-37. Mol Microbiol 2002; 46: 157-68
65. Engel LS, Hill JM, Caballero AR, et al. Protease IV, a unique extracellular protease and virulence factor from *Pseudomonas aeruginosa*. J Biol Chem 1998; 273: 16792-7
66. Carmeli Y, Troillet N, Eliopoulos GM, et al. Emergence of antibiotic-resistant *Pseudomonas aeruginosa*: comparison of risks associated with different antipseudomonal agents. Antimicrob Agents Chemother 1999; 43: 1379-82
67. Schweizer HP. Efflux as a mechanism of resistance to antimicrobials in *Pseudomonas aeruginosa* and related bacteria: unanswered questions. Genet Mol Res 2003; 2: 48-62
68. Tamber S, Hancock RE. On the mechanism of solute uptake in Pseudomonas. Front Biosci 2003; 8: s472-83
69. Hancock RE, Speert DP. Antibiotic resistance in *Pseudomonas aeruginosa*: mechanisms and impact on treatment. Drug Resist Updat 2000; 3: 247-55
70. Pai H, Kim J, Lee JH, et al. Carbapenem resistance mechanisms in *Pseudomonas aeruginosa* clinical isolates. Antimicrob Agents Chemother 2001; 45: 480-4
71. Köhler T, Michea-Hamzehpour M, Epp SF, et al. Carbapenem activities against *Pseudomonas aeruginosa*: respective contributions of OprD and efflux systems. Antimicrob Agents Chemother 1999; 43: 424-7
72. Sasaki M, Hiyama E, Takesue Y, et al. Clinical surveillance of surgical imipenem-resistant *Pseudomonas aeruginosa* infection in a Japanese hospital. J Hosp Infect 2004; 56: 111-8
73. Aeschlimann JR. The role of multidrug efflux pumps in the antibiotic resistance of *Pseudomonas aeruginosa* and other gram-negative bacteria: insights from the Society of Infectious Diseases Pharmacists. Pharmacotherapy 2003; 23: 916-24
74. Jalal S, Ciofu O, Hoiby N, et al. Molecular mechanisms of fluoroquinolone resistance in *Pseudomonas aeruginosa* isolates from cystic fibrosis patients. Antimicrob Agents Chemother 2000; 44: 710-2
75. Hanson ND. AmpC beta-lactamases: what do we need to know for the future? J Antimicrob Chemother 2003; 52: 2-4
76. Weldhagen GF, Poirel L, Nordmann P. Ambler class A extended-spectrum beta-lactamases in *Pseudomonas aeruginosa*: novel developments and clinical impact. Antimicrob Agents Chemother 2003; 47: 2385-92
77. Weldhagen GF. Integrons and beta-lactamases: a novel perspective on resistance. Int J Antimicrob Agents 2004; 23: 556-62
78. Lee K, Ha GY, Shin BM, et al. Metallo-beta-lactamase-producing gram-negative bacilli in Korean Nationwide Surveillance of Antimicrobial Resistance group hospitals in 2003: continued prevalence of VIM-producing Pseudomonas spp. and increase of IMP-producing Acinetobacter spp. Diagn Microbiol Infect Dis 2004; 50: 51-8
79. Lagatolla C, Tonin EA, Monti-Bragadin C, et al. Endemic carbapenem-resistant *Pseudomonas aeruginosa* with acquired metallo-beta-lactamase determinants in European hospital. Emerg Infect Dis 2004; 10: 535-8
80. Dubois V, Arpin C, Melon M, et al. Nosocomial outbreak due to a multiresistant strain of *Pseudomonas aeruginosa* P12: efficacy of cefepime-amikacin therapy and analysis of beta-lactam resistance. J Clin Microbiol 2001; 39: 2072-8
81. Deplano A, Denis O, Poirel L, et al. Molecular characterization of an epidemic clone of panantibiotic-resistant *Pseudomonas aeruginosa*. J Clin Microbiol 2005; 43: 1198-204

82. Chen HY, Yuan M, Livermore DM. Mechanisms of resistance to beta-lactam antibiotics amongst *Pseudomonas aeruginosa* isolates collected in the UK in 1993. J Med Microbiol 1995; 43: 300-9
83. Mouneimné H, Robert J, Jarlier V, et al. Type II topoisomerase mutations in ciprofloxacin-resistant strains of *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 1999; 43: 62-6
84. Zawacki A, O'Rourke E, Potter-Bynoe G, et al. An outbreak of *Pseudomonas aeruginosa* pneumonia and bloodstream infection associated with intermittent otitis externa in a healthcare worker. Infect Control Hosp Epidemiol 2004; 25: 1083-9
85. McNeil SA, Nordstrom-Lerner L, Malani PN, et al. Outbreak of sternal surgical site infections due to *Pseudomonas aeruginosa* traced to a scrub nurse with onychomycosis. Clin Infect Dis 2001; 33: 317-23
86. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005; 171: 388-416
87. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. Am J Infect Control 2002; 30: 476-89
88. Mangram AJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. Am J Infect Control 1999; 27: 97-132
89. Bearman GM, Munro C, Sessler CN, et al. Infection control and the prevention of nosocomial infections in the intensive care unit. Semin Respir Crit Care Med 2006; 27: 310-24
90. Kollef MH, Sherman G, Ward S, et al. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 1999; 115: 462-74
91. Leibovici L, Shraga I, Drucker M, et al. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. J Intern Med 1998; 244: 379-86
92. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004; 32: 858-73
93. Micek ST, Lloyd AE, Ritchie DJ, et al. *Pseudomonas aeruginosa* bloodstream infection: importance of appropriate initial antimicrobial treatment. Antimicrob Agents Chemother 2005; 49: 1306-11
94. Paul M, Benuri-Silbiger I, Soares-Weiser K, et al. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials. BMJ 2004; 328: 668
95. Safdar N, Handelsman J, Maki DG. Does combination antimicrobial therapy reduce mortality in gram-negative bacteraemia? A meta-analysis. Lancet Infect Dis 2004; 4: 519-27
96. Hilf M, Yu VL, Sharp J, et al. Antibiotic therapy for *Pseudomonas aeruginosa* bacteremia: outcome correlations in a prospective study of 200 patients. Am J Med 1989; 87: 540-6
97. Kuikka A, Valtonen VV. Factors associated with improved outcome of *Pseudomonas aeruginosa* bacteremia in a Finnish university hospital. Eur J Clin Microbiol Infect Dis 1998; 17: 701-8
98. Chamot E, Boffi El Amari E, Rohner P, et al. Effectiveness of combination antimicrobial therapy for *Pseudomonas aeruginosa* bacteremia. Antimicrob Agents Chemother 2003; 47: 2756-64
99. Döring G, Conway SP, Heijerman HG, et al. Antibiotic therapy against *Pseudomonas aeruginosa* in cystic fibrosis: a European consensus. Eur Respir J 2000; 16: 749-67
100. Yankaskas JR, Marshall BC, Sufian B, et al. Cystic fibrosis adult care: consensus conference report. Chest 2004; 125: 1-39S
101. Zaoutis TE, Goyal M, Chu JH, et al. Risk factors for and outcomes of bloodstream infection caused by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella* species in children. Pediatrics 2005; 115: 942-9
102. del Mar Tomas M, Cartelle M, Pertega S, et al. Hospital outbreak caused by a carbapenem-resistant strain of *Acinetobacter baumannii*: patient prognosis and risk-factors for colonisation and infection. Clin Microbiol Infect 2005; 11: 540-6
103. Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 2003; 290: 2588-98
104. Cometta A, Baumgartner JD, Lew D, et al. Prospective randomized comparison of imipenem monotherapy with imipenem plus netilmicin for treatment of severe infections in nonneutropenic patients. Antimicrob Agents Chemother 1994; 38: 1309-13
105. Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis pyelonephritis in women: a randomized trial. JAMA 2000; 283: 1583-90
106. Dunbar LM, Wunderink RG, Habib MP, et al. High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. Clin Infect Dis 2003; 37: 752-60
107. Kollef MH, Micek ST. Strategies to prevent antimicrobial resistance in the intensive care unit. Crit Care Med 2005; 33: 1845-53
108. Kwa AL, Loh C, Low JG, et al. Nebulized colistin in the treatment of pneumonia due to multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Clin Infect Dis 2005; 41: 754-7
109. Hamer DH. Treatment of nosocomial pneumonia and tracheobronchitis caused by multidrug-resistant *Pseudomonas aeruginosa* with aerosolized colistin. Am J Respir Crit Care Med 2000; 162: 328-30
110. Levin AS, Barone AA, Penço J, et al. Intravenous colistin as therapy for nosocomial infections caused by multidrug-resistant *Pseudomonas aeruginosa* and Acinetobacter baumannii. Clin Infect Dis 1999; 28: 1008-11
111. Linden PK, Kusne S, Coley K, et al. Use of parenteral colistin for the treatment of serious infection due to antimicrobial-resistant *Pseudomonas aeruginosa*. Clin Infect Dis 2003; 37: e154-60
112. Garnacho-Montero J, Ortiz-Leyba C, Jiménez-Jiménez FJ, et al. Treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia (VAP) with intravenous colistin: a comparison with imipenem-susceptible VAP. Clin Infect Dis 2003; 36: 1111-8
113. Falagas ME, Fragoulis KN, Kasiakou SK, et al. Nephrotoxicity of intravenous colistin: a prospective evaluation. Int J Antimicrob Agents 2005; 26: 504-7
114. Kasiakou SK, Michalopoulos A, Soteriades ES, et al. Combination therapy with intravenous colistin for management of infections due to multidrug-resistant gram-negative bacteria in patients without cystic fibrosis. Antimicrob Agents Chemother 2005; 49: 3136-46
115. Conway SP, Etherington C, Munday J, et al. Safety and tolerability of bolus intravenous colistin in acute respiratory exacer-

bations in adults with cystic fibrosis. Ann Pharmacother 2000; 34: 1238-42

116. Falagas ME, Rizos M, Bliziotis IA, et al. Toxicity after prolonged (more than four weeks) administration of intravenous colistin. BMC Infect Dis 2005; 5: 1
117. Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. Crit Care 2006; 10: R27
118. Falagas ME, Kasiakou SK. Use of international units when dosing colistin will help decrease confusion related to various formulations of the drug around the world. Antimicrob Agents Chemother 2006; 50: 2274-5
119. Jones RN, Huynh HK, Biedenbach DJ, et al. Doripenem (S-4661), a novel carbapenem: comparative activity against contemporary pathogens including bactericidal action and preliminary in vitro methods evaluations. J Antimicrob Chemother 2004; 54: 144-54
120. Fritsche TR, Stilwell MG, Jones RN. Antimicrobial activity of doripenem (S-4661): a global surveillance report (2003). Clin Microbiol Infect 2005; 11: 974-84
121. Tsuji M, Ishii Y, Ohno A, et al. In vitro and in vivo antibacterial activities of S-4661, a new carbapenem. Antimicrob Agents Chemother 1998; 42: 94-9
122. Jones RN, Huynh HK, Biedenbach DJ. Activities of doripenem (S-4661) against drug-resistant clinical pathogens. Antimicrob Agents Chemother 2004; 48: 3136-40
123. Traczewski MM, Brown SD. In vitro activity of doripenem against *Pseudomonas aeruginosa* and Burkholderia cepacia isolates from both cystic fibrosis and non-cystic fibrosis patients. Antimicrob Agents Chemother 2006; 50: 819-21
124. Mahadeva R, Webb K, Westerbeek RC, et al. Clinical outcome in relation to care in centres specialising in cystic fibrosis: cross sectional study. BMJ 1998; 316: 1771-5
125. Kerem E, Conway S, Elborn S, et al. Standards of care for patients with cystic fibrosis: a European consensus. J Cyst Fibros 2005; 4: 7-26
126. Wiesemann HG, Steinkamp G, Ratjen F, et al. Placebo-controlled, double-blind, randomized study of aerosolized tobramycin for early treatment of *Pseudomonas aeruginosa* colonization in cystic fibrosis. Pediatr Pulmonol 1998; 25: 88-92
127. Frederiksen B, Koch C, Høiby N. Antibiotic treatment of initial colonization with *Pseudomonas aeruginosa* postpones chronic infection and prevents deterioration of pulmonary function in cystic fibrosis. Pediatr Pulmonol 1997; 23: 330-5
128. Moss RB. Long-term benefits of inhaled tobramycin in adolescent patients with cystic fibrosis. Chest 2002; 121: 55-63
129. Ramsey BW, Pepe MS, Quan JM, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. N Engl J Med 1999; 340: 23-30
130. Moss RB. Administration of aerosolized antibiotics in cystic fibrosis patients. Chest 2001; 120: 107-3S
131. Levy J, Smith AL, Koup JR, et al. Disposition of tobramycin in patients with cystic fibrosis: a prospective controlled study. J Pediatr 1984; 105: 117-24
132. de Groot R, Hack BD, Weber A, et al. Pharmacokinetics of ticarcillin in patients with cystic fibrosis: a controlled prospective study. Clin Pharmacol Ther 1990; 47: 73-8
133. Stephens D, Garey N, Isles A, et al. Efficacy of inhaled tobramycin in the treatment of pulmonary exacerbations in children with cystic fibrosis. Pediatr Infect Dis 1983; 2: 209-11
134. Schaad UB, Wedgwood-Krucko J, Suter S, et al. Efficacy of inhaled amikacin as adjunct to intravenous combination therapy (ceftazidime and amikacin) in cystic fibrosis. J Pediatr 1987; 111: 599-605

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