A clinical approach to managing *Pseudomonas aeruginosa* infections

The *Pseudomonas* genus is a group of more than 140 bacterial species, all strictly aerobic Gram-negative rods, widely found in the environment, including in and around water sources. The most common species in the context of human health is *Pseudomonas aeruginosa*, where estimates of colonization vary from 3–5% in healthy individuals up to 20% among inpatients. However, colonization does not equate to infection, and despite these high rates of colonization and the potential for virulence, it is thought that fewer than 10% of inpatient infections are caused by *P. aeruginosa*.

Specific bacterial virulence factors have been identified, the presence of which is associated with altered clinical outcomes. These virulence factors include the ability of *P. aeruginosa* to form biofilms (facilitating adherence to host epithelia and immunological evasion), produce extracellular proteases (to aid invasion), and directly deliver effector proteins (ExoY, ExoS, ExoT and, particularly relevant to pulmonary infections, ExoU) into the cytosol of host cells via a type III section system (Sawa et al, 2014). Yet with an inability to quickly and confidently discern virulence among *P. aeruginosa* in clinical laboratories, the dichotomy between colonization and infection can cause confusion in clinical practice, with potential for both under- and overtreating clinical conditions involving this bacteria. Clinical management of patients with *P. aeruginosa* is further complicated by the complex antimicrobial resistance of this organism. This article reviews the most common presentations associated with *P. aeruginosa*, appropriate investigations and their interpretation, management options, and implications for infection control and public health.

Clinical spectrum of disease

**Pulmonary**

Acute health-care-associated infections

*P. aeruginosa* is a prominent cause of health-care-associated pneumonia and ventilator-acquired pneumonia (*Table 1*), particularly in critical care areas. Risk factors include exposure to reservoirs within the institutional environment, but also selective antimicrobial pressure and compromise of the respiratory tract (for example following endotracheal intubation). Mortality rates from health-care-associated pneumonia and ventilator-acquired pneumonia can be significant (ranging from 7% to 62%), but vary dependent upon host factors (pre-existing comorbidities, including alterations to normal physical barriers of the lung, and the presence of immunosuppression – both neutropaenia and T-cell) and bacterial factors (both degree of antimicrobial resistance and presence of virulence factors).

Pre-existing lung pathology

Respiratory tract colonization with *P. aeruginosa* is not uncommon among patients with certain chronic pulmonary diseases. In patients with cystic fibrosis, frequent and often early colonization with this organism occurs. The cause is multifactorial, but includes aberrant inflammatory responses, increased pathogen adhesion to the endothelium and altered host response to biofilm production. Carriage of the organism is often not a cause for clinical concern until adolescent and early adult years when, at the level of the organism, there is a shift from a non-mucoid to mucoid phenotype which coincides with worsening respiratory function (Hewitt et al, 2005).

### Table 1. Classification of acute respiratory tract infections

<table>
<thead>
<tr>
<th>Type of Acute Pneumonia</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Hospital-acquired pneumonia</td>
<td>Pneumonia occurring &gt;48 hours after hospital admission and not incubating at the time of admission</td>
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<tr>
<td>Ventilator-acquired pneumonia</td>
<td>Pneumonia occurring &gt;48 hours following endotracheal intubation</td>
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<tr>
<td>Early hospital-acquired pneumonia or ventilator-acquired pneumonia</td>
<td>&lt;5 days following admission or intubation. Causative organisms are usually common pathogens, e.g., <em>Streptococcus pneumoniae</em>, <em>Haemophilus influenzae</em>, methicillin-susceptible <em>Staphylococcus aureus</em>, drug-susceptible Gram-negative bacteria. Low mortality</td>
</tr>
<tr>
<td>Late hospital-acquired pneumonia or ventilator-acquired pneumonia</td>
<td>≥5 days following admission or intubation. Causative organisms are frequently drug resistant, including <em>Pseudomonas aeruginosa</em>, <em>Acinetobacter</em> species, methicillin-resistant <em>Staphylococcus aureus</em>, multidrug-resistant Gram-negative bacteria. Significant mortality</td>
</tr>
</tbody>
</table>

Modified from Napolitano (2010). Although the ‘CURB65’ score is useful in defining severity of community-acquired pneumonias, there is little evidence for robust prognostic scoring tools in hospital-acquired pneumonia or ventilator-acquired pneumonia.
The other group particularly at risk of *P. aeruginosa* colonization are patients with bronchiectasis. The characteristic airway dilation and thickening with chronic sputum production predisposes to chronic and recurrent bacterial infection. There is a general progression during the disease course from typical respiratory pathogens towards more resilient microbes such as *P. aeruginosa*, with colonization rates of between 12% and 31% (Pappalettera et al, 2009). Similar to patients with cystic fibrosis, it is difficult to eradicate *P. aeruginosa* once established, and colonization is associated with a decline in respiratory function.

There is also increasing evidence to suggest that *P. aeruginosa* colonization has a pathological role in a subset of patients with chronic obstructive pulmonary disease, where chronic biofilm persistence is thought to predispose to ‘acute exacerbations’ with this organism. There is a correlation between colonization and deterioration of lung function, although attribution of causality is confounded by general disease progression (Holm et al, 2013).

### Non-pulmonary

**Prosthetic material infections**

The ability of *P. aeruginosa* to form biofilms extends to abiotic material and is a key virulence factor; colonization of and subsequent infection around prosthetic devices is a not infrequent complication. This ranges from intravascular device-associated bacteraemia (cannulae and central lines; particularly in critical care and among immunocompromised patients, such as those undergoing chemotherapy or dialysis), to prosthetic joint infections, through to indwelling intrathecal or intracranial devices in neurology and neurosurgical patients associated with CNS infections. All patients with a prosthetic device who develop a fever, or in whom local clinical signs of infection develop around the device (erythema, pain, pustular discharge), should have samples taken for culture and a risk–benefit analysis regarding device exchange or removal.

**Burns**

Infection with *P. aeruginosa* can be a serious complication of burns. In these patients the disruption of the tegument, combined with the local immunosuppression that comes with burnt tissue (reduced T-cell activity, inflammatory cytokines and complement), means colonization frequently progresses to infection. Furthermore, non-*P. aeruginosa* species of *Pseudomonas* may also be considered as pathogens, unlike in other patient cohorts. Where there is delayed grafting of a burn, biofilms may develop in the burn site, and *P. aeruginosa* is a particular problem in these cases; difficulty in clearing the infection can make subsequent grafting considerably more difficult. Early grafting of burns and early antimicrobial therapy where *P. aeruginosa* is isolated is advocated.

**Diabetic feet and soft tissue wounds**

The predilection of *P. aeruginosa* for moist areas means wounds, including foot wounds among patients with diabetes, are frequently colonized with this organism and swab results commonly report its presence. However, the contribution of this organism to wound infections here is less clear; while *P. aeruginosa* has the potential to cause wound infections (including calcaneal osteomyelitis in diabetic foot infections), non-pathological colonization is more commonplace.

Other clinical manifestations of *P. aeruginosa* infection can be seen less frequently. These are usually associated with particular settings or interventions, but must be considered in specific patients (Table 2).

### Investigations

Investigations of pulmonary infections should begin with sputum samples (or in the case of ventilator-acquired pneumonia, endotracheal aspirates or bronchoalveolar lavage). In cases of chronic colonization, sputum samples should be sought with each new exacerbation to detect development of new resistance.

Where medical device infections are suspected, and removal is possible, the device should be sent for culture (e.g. the

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**Table 2. *Pseudomonas aeruginosa* infections in special settings**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Considerations</th>
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<tbody>
<tr>
<td>Endocarditis</td>
<td>Consider <em>Pseudomonas aeruginosa</em> as a potential cause in patients with a history of intravenous drug use, or those with prosthetic heart valves or pacemakers</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>In neutropaenic patients (particularly where this is secondary to haematological malignancy or chemotherapy), and in neonatology among low birth weight infants, presentation with abdominal pain, tenderness and fever should raise concerns over necrotizing enterocolitis associated with <em>P. aeruginosa</em> sepsis</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>An infrequent complication following urinary tract instrumentation or urethral catheterization is <em>P. aeruginosa</em> infection of the urinary tract. However, care must be taken when interpreting <em>P. aeruginosa</em> culture results from long-term catheter urine samples, as this may represent colonization of the distal end of the catheter</td>
</tr>
<tr>
<td>Keratitis</td>
<td>Contact lens wearers presenting with keratitis must have <em>P. aeruginosa</em> considered as a possible microbiological cause</td>
</tr>
<tr>
<td>Otitis externa</td>
<td>Inflammation of the outer ear is most frequently associated with <em>Staphylococcus aureus</em> or <em>Aspergillus</em> spp. However, necrotizing- (or malignant-) otitis externa can develop as a life-threatening complication (particularly among elderly patients or those with diabetes mellitus) where it presents with pain, exudate and often cranial nerve palsies – in these cases there is a frequent association with <em>P. aeruginosa</em></td>
</tr>
<tr>
<td>Folliculitis</td>
<td><em>P. aeruginosa</em> has been described as a cause of peri-folliculitis – classically reported after sauna and ‘hot tub’ use and associated with contaminated water</td>
</tr>
<tr>
<td>Superficial skin infections</td>
<td>Superficial cutaneous infections, particularly occurring in the feet and paronychia, can both be caused by <em>P. aeruginosa</em></td>
</tr>
<tr>
<td>Ecthyma gangrenosum</td>
<td>This cutaneous manifestation of <em>P. aeruginosa</em> bacteraemia typically occurs in immunocompromised patients, where the lesions are most frequently described as haemorrhagic pustules which evolve into necrotic ulcers</td>
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</tbody>
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cannula tip in cases of suspected central line infection). Supporting samples are also useful (blood culture where central line infections are considered; CSF or spinal fluid where intrathecal or intracranial devices are implicated). Exit site swabs for intravascular lines are poorly correlated with infecting organisms and should be interpreted with care. Where prosthetic joint infections are considered, multiple samples for culture (four or five, using separate instruments) should be taken from around the prosthesis. Burns should be swabbed promptly and acted upon rapidly. In contrast, in diabetic foot infections superficial swabs can be misleading (as above) – guidelines advocate deep tissue samples in preference (Lipsky et al., 2012; National Institute for Health and Care Excellence, 2015). Where there is a suspicion of underlying osteomyelitis, deep tissue or bone sampling rather than superficial swabbing is key to effective therapy.

In the laboratory, culture using standard methods is usually undertaken on agar-based culture media (Figure 1). Presumptive identification of a Gram-negative organism as a Pseudomonas spp. after 24 hours is based upon it being an oxidase-positive non-lactose fermenter with typical colony morphology. Formal identification to the species level can take several more hours depending upon laboratory practice. Susceptibility testing usually then follows the next day, being available 48 hours after the sample was received in the laboratory. While rapid genotypic-based diagnostic tests may become available in the future, currently clinical use is rare. There are no serological tests available.

Because of its ubiquitous nature, P. aeruginosa is frequently isolated with other organisms. In these cases, a clinical decision must be made as to whether the other organism(s) are causing the disease process (and P. aeruginosa represents colonization), P. aeruginosa is the pathogen, or it is a true polymicrobial infection (unusual).

Management
Antimicrobials
Antimicrobial effectiveness against P. aeruginosa is limited by the pathogen’s broad range of intrinsic and adaptive antimicrobial resistance mechanisms. Chromosomally, P. aeruginosa encodes an AmpC beta-lactamase (granting resistance to many penicillins and cephalosporins), has an OprD outer membrane porin which can be variably expressed (loss of which confers resistance to carbapenems), and harbours several drug efflux pumps such as MexAB-OprM (which export antimicrobials from several classes out of the cytosol); these are all inducible and regulation is dependent upon the environment encountered by the organism.

In addition P. aeruginosa can import further resistance mechanisms, predominantly via plasmids, which grant resistance to several drugs including carbapenems (through IMP and VIM metallo-beta-lactamas). These intrinsic and adaptive resistance mechanisms can be coregulated, which clinically translates to P. aeruginosa frequently being multi-drug resistant. Classically the carbapenem and polymyxin classes have been the least affected by resistance, although resistance to carbapenems has been increasing more recently (Moore et al., 2014). Table 3 lists the commonly used anti-pseudomonal agents; many are often restricted in hospital formularies, necessitating discussion with infection specialists.

Acute pulmonary infections
Acutely unwell patients with confirmed or suspected P. aeruginosa infection should be treated with appropriate intravenous agents. There is ongoing debate as to whether mono- or dual-antimicrobial therapy should be used in acute P. aeruginosa pulmonary infections. Dual therapy minimizes the potential for failure to cover resistant isolates (Micke et al., 2005) yet well-chosen monotherapy reduces side effects without impacting mortality (Damas et al., 2006). Furthermore, optimal duration of antimicrobial therapy is contentious, with a shorter course (8 days) producing fewer side effects and less ecological microbial selectivity, but at the cost of marginally worse clinical outcomes compared to longer courses (15 days) (Chastre et al., 2003). This lack of decisive evidence to guide treatment reinforces the importance of early discussion with infection specialists to personalize management strategies.

Chronic pulmonary colonization
The role of antimicrobials in eradication or suppression of P. aeruginosa to reduce lung damage is established in patients with cystic fibrosis (Haiby, 2011). However, there is less evidence for the role of maintenance therapy in patients with bronchiectasis, although many clinicians do support its use to reduce the frequency of exacerbations (Pappalegata et al., 2009). Patients with bronchiectasis or cystic fibrosis should be managed by a respiratory physician in close liaison with an infection specialist, but several concepts are clear. First, initial acquisition of P. aeruginosa should be actively treated. Combination therapy with inhaled or nebulized polymyxins (e.g. colistin or colistimethate) or aminoglycosides (e.g. tobramycin) in conjunction with oral ciprofloxacin for up to 3 months can be used to reduce pathogen load in the respiratory tract. While this regimen allows patients to be treated at home, there is insufficient evidence to set this strategy apart from an initial 2-week intravenous course of antimicrobials (Haiby, 2011).

Figure 1. Presumptive laboratory identification of Pseudomonas aeruginosa. a. Laboratory identification of P. aeruginosa is typically through use of agar-based culture media, where bacterial production of pyocyanin typically produces a green tint to colonies. Identification is further confirmed through simple bench top biochemistry in a few seconds (b) where pseudomonads are oxidase positive (c) negative control. Determination of drug resistance for pseudomonads is commonly performed using disc susceptibility testing, but few agents warrant testing given the intrinsic resistance to many agents harboured by P. aeruginosa (as shown). CIP = ciprofloxacin, CAZ = ceftazidime, MEM = meropenem, CN = gentamicin, TZP = piperacillin-tazobactam, AZ = aztreonam.
Second, acute respiratory exacerbations with suspected or confirmed \textit{P. aeruginosa} should be treated with intravenous antimicrobials based on up-to-date culture and susceptibility testing. Duration of treatment is typically 10–14 days, although evidence for this is not robust. Ambulatory care may facilitate receipt of intravenous antimicrobials at home. Oral ciprofloxacin can be used for acute infective exacerbations of cystic fibrosis, but a Cochrane review failed to definitively show that oral agents are more or less effective than intravenous agents (Remington et al, 2013). The role of nebulized therapy in acute infections is highly contentious with little evidence to inform its role and efficacy (El Solh and Alhajhusain, 2009).

Third, macrolides such as azithromycin are often used as long-term therapy in chronic lung pathology patients with \textit{P. aeruginosa} colonization, likely acting as anti-inflammatories given the intrinsic resistance of this organism to this antimicrobial class. A meta-analysis focussing on patients with cystic fibrosis suggested long-term azithromycin may improve lung function without significant side effects, although evidence of their effect on frequency of infective exacerbations is less clear (Cai et al, 2011).

**Soft tissue infection**

Treatment for diabetic foot infections should in the first instance be targeted against Gram-positive organisms and anaerobes, with specific anti-pseudomonal therapy only instigated where standard therapy is clinically failing and \textit{P. aeruginosa} has been isolated (Lipsky et al, 2012). Anti-pseudomonal therapy should not be instigated solely on isolation of \textit{P. aeruginosa} from a wound swab.

**Future**

Ongoing research into anti-pseudomonal agents aims to overcome the growing drug-resistance. Areas of development include next generation carbapenems and cephalosporins, and more definitive investigation of aerosolized agents to maximize delivery in pulmonary infections. Monoclonal antibodies targeted against pseudomonal virulence mechanisms are also in early stage exploration (El Solh and Alhajhusain, 2009).

**Infection control and public health**

\textit{P. aeruginosa} has been of particular concern in relation to clinical sink units in augmented care (adult, neonatal, and paediatric intensive care units), with proven transmission from these environmental sources to patients (Witney et al, 2014). While regulations minimizing the risk from the built environment apply at the institutional level, at the clinical level some units may advocate applying alcohol gel after hand washing to minimize onwards transmission. Where multi-drug resistant \textit{P. aeruginosa} is confirmed, additional precautions may be instigated including isolation and gloving. \textit{P. aeruginosa} is not a notifiable disease, but outbreaks (particularly of resistant strains) often necessitate public health investigation.

**Conclusions**

\textit{P. aeruginosa}, a ubiquitous environmental organism, is frequently seen in clinical practice and commonly reported in culture results. However, this frequently represents colonization and targeted therapy is not indicated. Where specific treatment is necessary choice is limited, and with antimicrobial resistance increasing at local, national and international levels, careful consideration and liaison with infection specialists is key.

**What You Need To Know About**

**Table 3. Antimicrobials most commonly used to treat \textit{Pseudomonas aeruginosa} infections**

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Antimicrobial</th>
<th>Prescribing notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>Piperacillin- tazobactam</td>
<td>As this is a penicillin, any history of previous allergy to this class of antimicrobials should be clearly elucidated before prescription</td>
</tr>
<tr>
<td></td>
<td>Cefazidime or cefepime</td>
<td>Increased risk of development of \textit{Clostridium difficile} infection in the &gt;65-year-old population; cross-allergy in those with penicillin allergy can occur, but is infrequent</td>
</tr>
<tr>
<td></td>
<td>Gentamicin, amikacin or tobramycin</td>
<td>Narrow therapeutic window – plasma trough level monitoring essential. Has the potential for oto- and nephrotoxicity with prolonged use</td>
</tr>
<tr>
<td></td>
<td>Meropenem, imipenem or doripenem</td>
<td>Cross-allergy in those with penicillin allergy can occur but is rare; imipenem-cilastatin has been associated with neurological adverse events</td>
</tr>
<tr>
<td></td>
<td>Aztreonam</td>
<td>Resistance to this agent among \textit{P. aeruginosa} is common</td>
</tr>
<tr>
<td>Oral</td>
<td>Colistimethate sodium (Polymixin E)</td>
<td>Nephro- and neuro-toxicity may occur and should be actively monitored for</td>
</tr>
<tr>
<td>Inhaled or nebulized</td>
<td>Colistimethate sodium (Polymixin E) Gentamicin or tobramycin</td>
<td>Bronchospasm may occur on inhalation of antimicrobials, but may be ameliorated through use of inhaled beta2-agonists; sore throat may be reported, and may be the result of either local drug hypersensitivity reactions or \textit{Candida} spp. infection</td>
</tr>
</tbody>
</table>

Listed agents can be used empirically where there is clinical suspicion of \textit{P. aeruginosa} as a causative organism, or where culture and susceptibility testing indicate activity against the organism. Choice of therapy depends upon the individual patient and clinical presentation, and discussion with infection specialists is advocated.

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The ability of Pseudomonas aeruginosa to form biofilms, on both biotic and abiotic surfaces, is a key virulence factor. Investigation of patients with suspected P. aeruginosa infections should be through culture of appropriate (and often invasive) specimens, with susceptibility testing playing a key role in determination of appropriate therapy.

Treatment of patients with P. aeruginosa is complex as a result of inherent resistance to many antimicrobials and, increasingly, acquired resistance to the remainder.

therapy versus monotherapy; a randomised pilot study on the evolution of inflammatory parameters after ventilator associated pneumonia [ISRCTN31976779]. Crit Care 10(2): R52 (doi: 10.1186/cc8479)


