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8.6.8 Pseudomonas aeruginosa 1041 8.6.8 Pseudomonas aeruginosa G.C.K.W. Koh and Sharon J. Peacock ESSENTIALS Pseudomonas aeruginosa is a highly versatile environmental Gram- negative bacterium that can be isolated from a wide range of habi- tats, including soil, marshes, and the ocean, as well as from plant and animal tissues. It is resistant to many disinfectants and antibiotics, giving it a selective advantage in hospitals. It rarely causes infection in the healthy host but is a major opportunistic pathogen. Clinical features—(1) Hospitals—causes a range of infections, including bacteraemia (often in association with neutropenia), ventilator-associated pneumonia, urinary tract infection, skin and soft tissue infections, and bacteraemia associated with burns. (2) Community—the largest group of people affected by P. aeruginosa are those with cystic fibrosis, who develop long-term colonization of the airways, punctuated by episodes of clinical infection. Diagnosis—Diagnosis is usually straightforward when the or- ganism is cultured from samples collected from normally sterile sites, but is often challenging when infection is suspected in non- sterile sites such as a catheterized urinary tract, burns, or skin ulcers, because P. aeruginosa may be either a pathogen or an innocent bystander. Treatment—P. aeruginosa is intrinsically resistant to a broad range of antimicrobials. Appropriate and effective prescribing requires (1) awareness of risk factors for P. aeruginosa, combined with know- ledge of the spectrum of diseases it causes; (2) carefully considered empirical regimens based on local antimicrobial susceptibility data— typically a β-lactam (e.g. ceftazidime, meropenem, or piperacillin); and (3) attention to susceptibility profiles once the causative strain has been isolated and tested. Genetics and pathogenesis The Pseudomonas aeruginosa genome is composed of a single chromosome of 6.3 Mbp containing around 5700 predicted open reading frames. This is markedly larger than most other sequenced bacterial genomes (for comparison, the genome of the simple eu- karyote Saccharomyces cerevisiae encodes around 6200 proteins). The P. aeruginosa genome contains a high proportion of regulatory genes and many genes involved in catabolism, transport, and efflux of organic chemicals. The size and complexity of the genome under- pins its ability to thrive in diverse environments. P. aeruginosa produces a single polar flagellum (which makes it motile) and type IV pili (which allow it to adhere to the respiratory epithelium). More than half of all clinical isolates produce pyocyanin (a blue pigment) and pyoverdin (a green pigment),

which are re- sponsible for the characteristic blue-green colour of P. aeruginosa colonies growing on solid media. Pyocyanin is an exotoxin that has immunomodulatory effects on respiratory epithelial cells, is toxic to neutrophils, and is involved in iron acquisition. P. aeruginosa is able to produce an alginate-containing biofilm that increases its resistance to antimicrobials and protects it from the host immune response. P. aeruginosa in the environment P. aeruginosa is ubiquitous in the environment. In homes, it is often found in the aerators and traps of sinks, shower heads, water coolers, contact lens solutions, and cosmetics, as well as in swimming pools, whirlpool baths, and jacuzzis. It may also be cultured from a wide variety of raw fruit and vegetables. It is difficult to eradicate from the hospital environment, where it has been found in soap dishes, dia- lysis fluid, irrigation fluids, eye drops, disinfectants, ointments, and mechanical ventilators. P. aeruginosa is resistant to several commonly used disinfectants: ammonium acetate-buffered benzalkonium chloride solution will support the growth and division of P. aerugi- nosa, and the organism readily develops resistance to chlorhexidine. P. aeruginosa is killed by povidone-iodine, glutaraldehyde, bleach, and alcohol, but may be relatively resistant to these when present in a biofilm or embedded within proteinaceous material. Human colonization and disease Colonization P. aeruginosa is probably consumed regularly and is capable of col- onizing the human gastrointestinal tract. It is rarely present on the intact skin or mucous membranes of healthy individuals but often colonizes severely ill patients, particularly those on broad-spectrum antibiotics. P. aeruginosa often colonizes broken skin (e.g. ulcers) and medical devices in contact with the environment, such as long- term urinary catheters. The organism may cause a broad range of infections, most commonly in patients with one or more risk factors. Bacteraemia Bacteraemia occurs primarily in immunocompromised patients, particularly those with haematological malignancies, neutropenia, or severe burns. P. aeruginosa accounts for approximately one- quarter of all hospital-acquired bacteraemias, and has a mortality of c.20%. In 2017, the incidence of Pseudomonas aeruginosa bacter- aemia in England, Wales and Northen Ireland was 8.1 per 100 000 population. The highest rates were in children less than 1 year of age (8.8 per 100 000) and those aged more than 85 years (73.5 per 100 000). In the elderly, males were three-times more commonly affected than females. The clinical features of sepsis associated with P. aeruginosa infection do not differ from those associated with other bacterial infections, and empirical antimicrobial prescribing for high-risk patients should include cover for P. aeruginosa. A pri- mary source of infection (e.g. a chronic ulcer in a diabetic patient, a urinary catheter, and so on) should be sought and removed wher- ever possible. In rare cases of P. aeruginosa infection, patients may develop a skin lesion called ecthyma gangrenosum (Fig. 8.6.8.1) which, although not pathognomonic for P. aeruginosa, is rarely a feature of infection by any other organism. This presents as a painful, well-circumscribed, erythematous lesion anywhere on the body that progresses to necrosis within hours or days. Ecthyma rarely appears in a nonneutropenic host, and its appearance marks the failure of the host immune response to control the infection. In these patients, P. aeruginosa may often be cultured both from blood and from the lesion, but not every patient with ecthyma is detect- ably bacteraemic.

 Pulmonary infection P. aeruginosa consistently ranks as the most common cause of ven- tilator-associated pneumonia in the USA and Europe (National Healthcare Safety Network). Diagnosis is complicated by the fact that severely ill patients commonly become colonized by P. aeruginosa, and appropriate sampling of patients with suspected ventilator-associated pneumonia requires the use of bronchoalveolar lavage or protected- specimen brush sampling of the distal airways. Tracheal aspirates are easier to obtain

but less helpful (positive cultures are suggestive but not diagnostic). The diagnosis and treatment of ventilator-associated pneumonia is described in Section 18 and Chapter 18.4.3. P. aeruginosa commonly colonizes the respiratory tract of people with cystic fibrosis and is the leading cause of respiratory infection in this group. Asymptomatic P. aeruginosa colonization is associ- ated with a more rapid decline in lung function and increased mor- tality from respiratory failure in this patient group. Bronchoscopy is sometimes the only available diagnostic technique in children: some clinicians have attempted to avoid invasive sampling by using sero- logical tests, but the results are unreliable. Early treatment with nebulized tobramycin, inhaled colistin or oral ciprofloxacin is cap- able of eradicating P. aeruginosa from cystic fibrosis patients, but the impact of P. aeruginosa eradication on mortality and morbidity is unclear. Cystic fibrosis is discussed in Chapter 18.10. P. aeruginosa may cause a fulminant necrotizing pneumonia in neutropenic patients as part of a syndrome of disseminated infection. Skin and soft tissue infection P. aeruginosa rarely invades healthy skin and a breach of the in- tegument (e.g. skin maceration from chronic immersion in water, a burn, a cut, or nick from a razor blade or rose thorn, a surgical wound, and so on) is usually required for infection to become established. 'Hot tub' dermatitis is a self-limiting skin infection in healthy people caused by exposure to water contaminated with P. aeruginosa and manifests as folliculitis or vesicular lesions. Outbreaks have been associated with jacuzzis, spas, and swimming pools. P. aeruginosa can cause surgical wound infections but is far less common than Staphylococcus aureus or Escherichia coli. P. aeruginosa colonization of chronic leg ulcers is common, but it is rarely the only organism found from superficial swabs taken from this type of lesion and is usually a colonizer rather than an invader. Superficial swabs of ulcers are best avoided in the absence of clinical signs of active infection, since the results are difficult to interpret. When infection is present (e.g. cellulitis, associated osteomyelitis, bacteraemia), cultures from deep tissue that does not communi- cate with the ulcer or wound surface should be obtained. Ecthyma gangrenosum is described under the section on bacteraemia (see earlier). P. aeruginosa is an important cause of infection in patients with burns, the other important pathogen being S. aureus. Urinary tract The initiating event in P. aeruginosa urinary tract infection is usually urinary catheterization or instrumentation of the urinary tract, al- though infection may occasionally occur by haematogenous spread to the kidneys. Patients with long-term indwelling urinary catheters are at particular risk (a combined effect of the presence of prosthetic material that provides a nidus for infection and because frequent antimicrobial therapy for recurrent urinary infection selects for re- sistant organisms such as P. aeruginosa). No specific clinical features distinguish P. aeruginosa urinary infections from infection caused by other pathogens. The diagnosis is made on urine culture in the presence of appropriate clinical features, predominant of which is fever. P. aeruginosa infection in this patient group is rarely cured without removal/replacement of the urinary catheter on which or- ganisms persist within a biofilm. Catheter change should be per- formed towards the end of therapy once the burden of planktonic bacteria (bacteria free in urine) is much reduced. Routine urine cul- ture of patients with long-term urinary catheters provides no useful information in the absence of clinical features of active infection. Renal imaging may be useful to exclude renal abscesses or calculi if the reason for the infection is not obvious. The most commonly identified source of P. aeruginosa blood stream infections is compli- cated urinary tract infections (30%). Ear infection P. aeruginosa is a leading cause of otitis externa, an infection of the external auditory canal that causes inflammation, pain (exacerbated by traction on the pinna), and, if severe, a purulent discharge. It is common to find lymphadenopathy just anterior to the tragus. The disease is usually seen in children and the source of infection in- cludes underchlorinated swimming pools or fresh water lakes and rivers. The diagnosis is based on signs and symptoms, and empiric

treatment with eardrops is usually effective. Malignant otitis externa is rare but much more serious. It is not a neoplastic process, but is so called because of the risk of localized destructive spread to the central nervous system. It most commonly occurs in elderly patients with diabetes and people with HIV infection, and is essentially an osteomyelitis of the mastoid and petrous temporal bone. Affected patients present with an erythematous, oedematous, and inflamed external auditory canal, and the tympanic membrane is often hidden by oedema. Otoscopy is necessary to make the diagnosis, but is often poorly tolerated because of pain. Lymphadenopathy of the ipsilat- eral cervical lymph nodes may be present; facial nerve involvement produces an ipsilateral lower motor neuron seventh nerve palsy. Spread to the temporomandibular joint causes pain on mastica- tion, and spread to the apex of the petrous temporal nerve produces Gradenigo's syndrome (trigeminal and trochlear nerve palsies). Features of malignant otitis externa should prompt immediate re- ferral to an ear, nose, and throat surgeon for assessment and de- bridement of the ear canal and adjacent bone. The diagnosis is made by demonstrating osteomyelitis of the skull base on a technetium-99 bone scintigram or on MRI, along with P. aeruginosa cultured from the discharge or from a bone biopsy. Fig. 8.6.8.1 Ecthyma gangrenosum lesion in a patient with Pseudomonas aeruginosa septicaemia. Courtesy of the late Dr BE Juel-Jensen.

8.6.8 Pseudomonas aeruginosa 1043 Eye infection The most common manifestation of P. aeruginosa eye infection is keratitis, which occurs following direct inoculation from trauma (e.g. contact sports, industrial accidents) or minor abrasions (e.g. contact lens use). Contact lens keratitis has been associated with contamin- ated contact lens disinfectant solutions. P. aeruginosa keratitis requires prompt ophthalmological referral and treatment since infection may be rapidly progressive and can result in corneal opacification and even perforation within 48 h. Pseudomonal endophthalmitis most com- monly occurs as a consequence of penetrating injury or surgery, but there is also a rare syndrome of neonatal endophthalmitis that may be bilateral, the main risk factor for which is prematurity. Clinical fea- tures include severe pain, chemosis, loss of the red reflex, hypopyon, and corneal clouding. Neonatal pseudomonal endophthalmitis most commonly arises from haematogenous spread, frequently in associ- ation with a syndrome of disseminated disease that includes men- ingitis and pneumonia, and is commonly fatal. Endophthalmitis is diagnosed by culture of vitreous humour. Endocarditis P. aeruginosa endocarditis is a disease confined almost exclu- sively to injecting drug users, in whom it is usually right-sided. Extended intravenous combination therapy with a β-lactam and an aminoglycoside is required, and valve replacement is often neces- sary. In the case of left-sided endocarditis, antibiotic therapy alone is rarely sufficient and valve replacement is mandatory. Bone and joint infection Patients with diabetes may develop osteomyelitis of the foot fol- lowing penetrating injury or local extension of an untreated chronic ulcer. Results from superficial swabs are of minimal clinical rele- vance, and diagnosis should be based on the results of bone bi- opsy which should be processed for culture and histopathology. Parenteral antimicrobials are not always successful and radical de- bridement or amputation may be necessary to clear the infection. Intravenous drug users are susceptible to P. aeruginosa septic arth- ritis and osteomyelitis of the axial skeleton. HIV infection Patients with HIV infection are more susceptible to P. aeruginosa infection when the CD4 count is below 100 cells/μl. The incidence has fallen since the advent of highly active antiretroviral therapy (HAART). The presentation of P. aeruginosa infection in HIV pa- tients is more indolent than that in neutropenic patients, but mor- tality is 22–34%. The fever is frequently low grade and ecthyma gangrenosum is rare. It is most commonly intravenous device re- lated. Pneumonia is the most common community-acquired pres- entation, followed by sinusitis, and infections of the urinary tract, all of which may be associated with bacteraemia. Antimicrobial therapy P. aeruginosa

elaborates a range of β-lactamases (penicillinases and cephalosporinases) and has a relatively impermeable outer membrane which makes it intrinsically resistant to a wide variety of antimicrobials, including all first-generation and second-gen- eration cephalosporins, most penicillins, and all macrolides. The antipseudomonal cephalosporins ceftazidime and cefepime are effective; of the carbapenems imipenem and meropenem are ef- fective. The antipseudomonal penicillins are piperacillin and ticarcillin (commonly available in combined preparations with tazobactam or clavulanate). The β-lactams are bactericidal and there is good clinical evidence for their efficacy and safety. However, cefepime monotherapy is associated with a high all-cause mortality and cannot be recommended. There is evidence from animal studies that continuous infusions of β-lactams are superior to intermittent dosing. Aztreonam, has not found widespread use, because isolates that are resistant to ceftazidime or piperacillin are generally also resistant to aztreonam. There are rare metallo-β-lactamase-produ- cing strains of P. aeruginosa that can be resistant to carbapenems but sensitive to aztreonam. Therapeutic combinations which con- tain beta-lactamase inhibitors, such as ceftazidime-avibactam, ceftolozone-tazobactam and meropenem-vaborbactam have re- cently become available. The aminoglycosides (gentamicin, amikacin, kanamycin, tobra- mycin, and so on) are effective in vitro, but their use in combin- ation with β-lactam drugs in patients with febrile neutropenia has been called into question by a Cochrane review (2013). This con- cluded that β-lactam monotherapy was advantageous compared with β-lactam-aminoglycoside combination therapy with regard to survival, adverse events, and fungal super-infections. Some clinicians may choose instead to use β-lactam-fluoroquinolone combinations, although there is currently little evidence to support this. β-lactams and aminoglycosides are commonly used in com- bination when treating serious infections such as P. aeruginosa ventilator-associated pneumonia. The toxicity of systemic aminoglycosides means inhaled or top- ical aminoglycosides may be preferred, depending on the site of infection (e.g. inhaled tobramycin for cystic fibrosis patients, or topical gentamicin for otitis externa and superficial eye infections). Ciprofloxacin is active when administered orally, an attribute that makes it almost unique among the therapeutic options available for P. aeruginosa treatment. Acquired drug resistance is a problem in patients who are anti- biotic experienced (an important example being patients with cystic fibrosis), but resistance to commonly used antibiotics is a problem even outside this patient group. The Public Health England re- ported that of the P. aeruginosa strains isolated from blood in 2016, 8% were not susceptible to ciprofloxacin, 3% to gentamicin, 2% to amikacin, 7% to piperacillin-tazobactam, 6% to ceftazidime, and 5% to meropenem. It is not uncommon for resistance to develop during the course of treatment, an event that is associated with excess mor- tality. Gentamicin-resistant strains are usually also resistant to tobra- mycin, but may remain susceptible to amikacin. Plazomicin is a new aminoglycoside that is resistant to inactivation by aminoglycoside- modifying enzymes, and may be useful in gentamicin-or amikacin-resistant strains. Strains that colonize patients with cystic fibrosis frequently become multiply resistant: older antimicrobial agents such as colistin and polymyxin B may then be required. The antimicrobial treatment and management of P. aeruginosa infection is complex because the infections are often system- or patient-group specific: a single guideline is not appropriate. For patients with serious suspected P. aeruginosa infection, increasing resistance rates mean first line therapy should include a β-lactam (e.g. piperacillin–tazobactam or meropenem) in combination with a second agent in order to achieve adequate coverage. Therapy should be reviewed when culture and susceptibility results are known.

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