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MICROBIOLOGY

Pseudomonas aeruginosa

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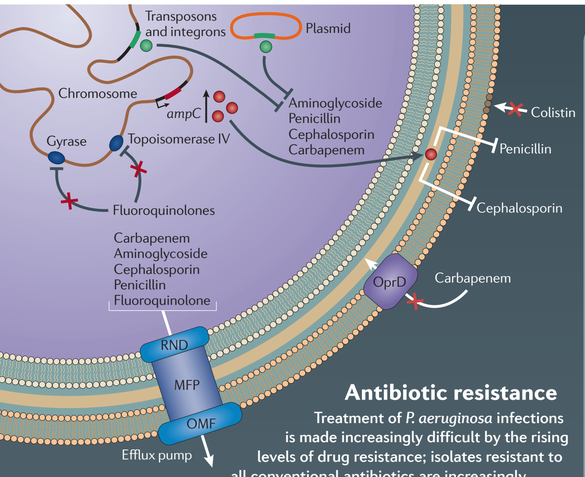
Pseudomonas aeruginosa is an opportunistic pathogen that infects humans with compromised natural defences. Predisposing conditions include a disrupted epithelial barrier (as found in a patient with a burn wound), a depletion of neutrophils (for example, in a cancer patient receiving chemotherapy), the presence of a foreign body (a patient with a central venous catheter) and altered mucociliary clearance (in an individual with cystic fibrosis). Many *P. aeruginosa* infections occur after patients have been hospitalized. Several factors account for the success of *P. aeruginosa*. It can utilize a broad spectrum of nutrients and can thus grow in hospital drains, sinks and even disinfectant solutions. *P. aeruginosa* is intrinsically resistant to a large number of antibiotics and can acquire resistance to many others, making treatment difficult. The propensity of *P. aeruginosa* to form biofilms further protects it from antibiotics and from the host immune system. In addition, a large arsenal of pathogenicity factors is used to interfere with host defences.



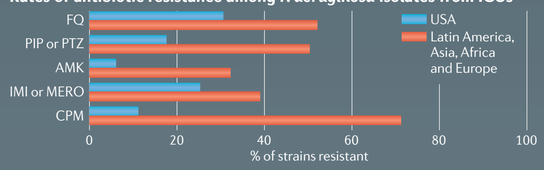
Antibiotic resistance

Treatment of *P. aeruginosa* infections is made increasingly difficult by the rising levels of drug resistance; isolates resistant to all conventional antibiotics are increasingly common. The mechanisms of drug resistance can be specific for a particular drug class or general, affecting many different types of antibiotics. Specific mechanisms include alteration of antibiotic targets (such as topoisomerase IV and gyrase, which are targeted by fluoroquinolones; and LPS, which is targeted by colistin), uptake channels (such as OprD, which mediates influx of carbapenems) or regulatory systems (such as AmpD, which indirectly represses the gene encoding AmpC β-lactamase). General mechanisms include drug efflux pumps, which remove a variety of antibiotics from the bacterium (see below). Efflux pumps consist of outer membrane channel-forming proteins (OMFs), a cytoplasmic membrane-associated antiporter (RND) and a periplasmic membrane fusion protein (MFP). Plasmids, transposons and integrons can encode additional antibiotic resistance factors, including metallo-β-lactamases, which are active against nearly all β-lactams, and enzymes that inactivate aminoglycosides.

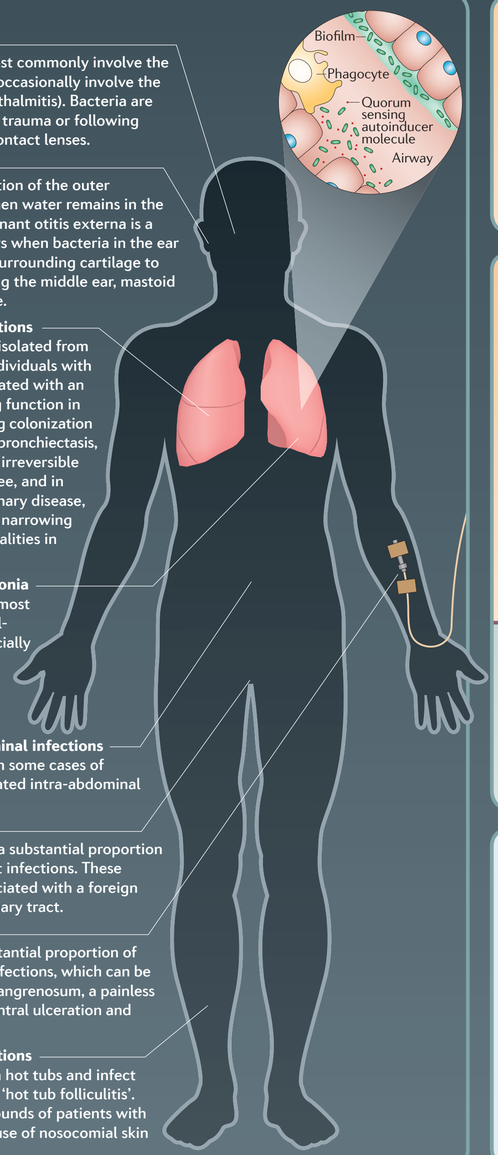
Antibiotic efflux pumps[1]

RND efflux pump	Substrates
MexA–MexB–OprM	FQ, β-lactams (except IMI), tetracyclines, chloramphenicol, macrolides, trimethoprim, sulphonamides
MexC–MexD–OprJ	FQ, Anti-PA PCN, CPM, MERO, tetracycline, chloramphenicol, macrolides, trimethoprim
MexE–MexF–OprN	FQ, carbapenems, chloramphenicol, trimethoprim
MexX–MexY	FQ, Anti-PA PCN, CPM, MERO, tetracyline, AG, macrolides, chloramphenicol
MexJ–MexK	Tetracycline, erythromycin
MexG–MexH–MexI–OpmD	FQ
MexV–MexW	FQ, tetracycline, chloramphenicol, erythromycin
MexP–MexQ–OpmE	FQ, tetracycline, chloramphenicol, macrolides
MexM–MexN	Chloramphenicol

Rates of antibiotic resistance among *P. aeruginosa* isolates from ICUs[2,3]



Clinical disease



Eye infections
P. aeruginosa infections most commonly involve the cornea (keratitis) but may occasionally involve the intraocular cavity (endophthalmitis). Bacteria are introduced into the eye by trauma or following corneal injury caused by contact lenses.

Ear infections
'Swimmer's ear' is an infection of the outer ear canal that develops when water remains in the ear after swimming. Malignant otitis externa is a severe infection that occurs when bacteria in the ear canal invade through the surrounding cartilage to deeper structures, including the middle ear, mastoid air cells and temporal bone.

Chronic respiratory infections
P. aeruginosa is commonly isolated from the respiratory tracts of individuals with cystic fibrosis and is associated with an accelerated decline in lung function in these patients. Chronic lung colonization and infection also occur in bronchiectasis, a disease characterized by irreversible dilation of the bronchial tree, and in chronic obstructive pulmonary disease, a disease characterized by narrowing of the airways and abnormalities in air flow.

Hospital-acquired pneumonia
P. aeruginosa is one of the most common causes of hospital-acquired pneumonia, especially in mechanically ventilated patients; it is associated with a particularly high mortality rate.

Complicated intra-abdominal infections
P. aeruginosa is identified in some cases of hospital-acquired complicated intra-abdominal infections.

Urinary tract infections
P. aeruginosa accounts for a substantial proportion of nosocomial urinary tract infections. These infections are usually associated with a foreign body or surgery of the urinary tract.

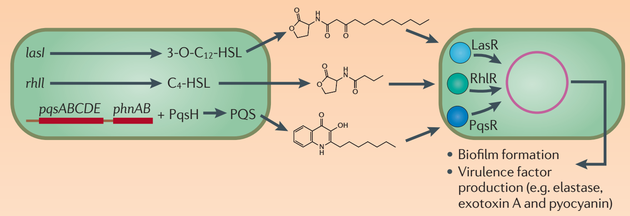
Bloodstream infections
P. aeruginosa causes a substantial proportion of nosocomial bloodstream infections, which can be associated with ecthyma gangrenosum, a painless nodular skin lesion with central ulceration and haemorrhage.

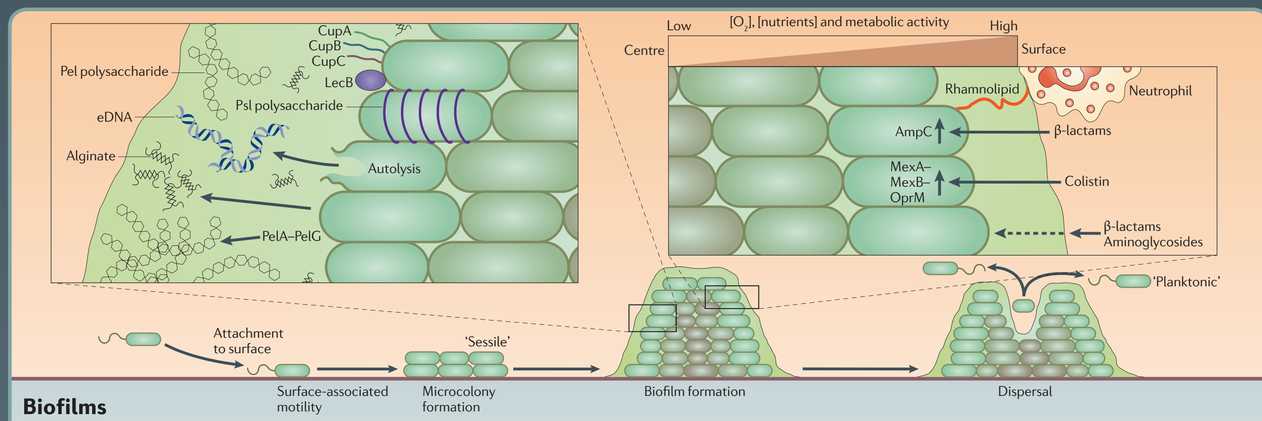
Skin and soft tissue infections
P. aeruginosa can survive in hot tubs and infect macerated skin, leading to 'hot tub folliculitis'. *P. eruginosa* also infects wounds of patients with burns and is a common cause of nosocomial skin and soft tissue infections.

Quorum sensing

Three quorum sensing systems in *P. aeruginosa* regulate biofilm architecture and a large number of virulence determinants. Cross regulation of the three systems provides an additional level of complexity.

- *N*-(3-oxododecanoyl)-L-homoserine lactone (3-O-C_{12}-HSL) production is controlled by LasI. The molecule is detected by LasR.
- *N*-butanoyl-L-homoserine lactone (C_4-HSL) is produced by RhlI and detected by RhlR
- 2-heptyl-3-hydroxy-4-quinolone (PQS) is synthesized by the products of the *pqsABCDE* and *phnAB* operons along with PqsH. PQS is detected by PqsR.



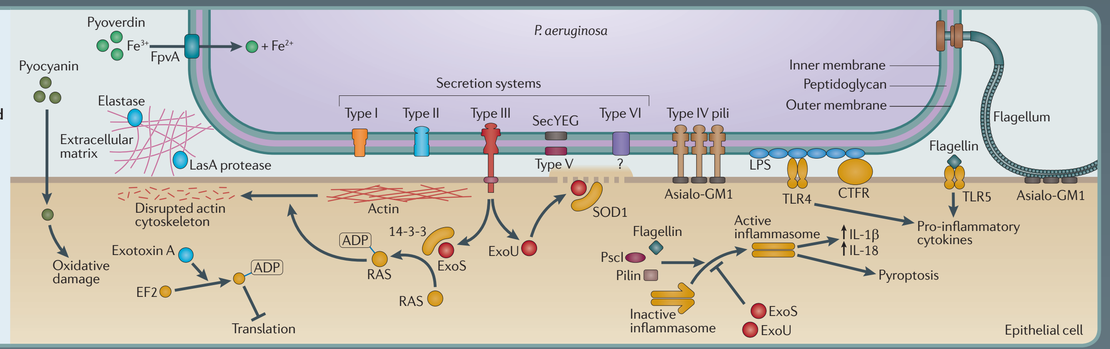


Biofilms

Biofilm formation starts with the attachment of bacteria to a surface, followed by twitching motility and the formation of microcolonies, which evolve into mature biofilms. Biofilm architecture depends on the production of the biofilm matrix, which consists of the polysaccharides Pel (synthesized by PelA–PelG), Psl (arranged in a helical pattern around cells) and alginate, extracellular DNA (eDNA), and proteins, including the CupA, CupB and CupC fimbriae, which mediate bacterial attachment during initial biofilm formation, and the lectin LecB. The extracellular polymeric matrix delays diffusion of some antibiotics into the biofilm. A gradient of oxygen and nutrients induces the formation of distinct bacterial subpopulations that vary in their susceptibility to antibiotics; exposure to β-lactams or colistin can induce the production of resistance factors (AmpC β-lactamase and MexA–MexB–OprM efflux pumps). Rhamnolipids on bacteria at the surface induce necrosis of neutrophils. Finally, planktonic bacteria are released from parts of the mature biofilm. The steps of biofilm maturation shown here are based on *in vitro* studies; the corresponding steps and biofilms structures that occur during *in vivo* infections are less clear.

Pathogenesis

Pathogenesis in *P. aeruginosa* is mediated by various adhesins and secreted toxins, proteases, effector proteins and pigments that facilitate adhesion, modulate or disrupt host cell pathways and target the extracellular matrix.



Cubist Pharmaceuticals
Headquartered in Lexington, Massachusetts, USA, Cubist Pharmaceuticals is unique in its focus on the development of badly needed antibiotics for serious, often life-threatening infections. In addition to its first-in-class I.V. antibiotic CUBICIN® (daptomycin for injection), used in the treatment of serious skin and bloodstream infections caused by methicillin-resistant *Staphylococcus aureus* (the super bug also known as MRSA), Cubist is currently building a pipeline of new therapies to treat infections caused by other multi-drug resistant pathogens — such as *Pseudomonas aeruginosa*.
More at www.cubist.com

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Abbreviations
AG, aminoglycosides; AMK, amikacin; Anti-PA PCN, anti-pseudomonal penicillin; Asialo-GM1, asialo-gangliotetraocyl ceramide 1; CPM, cefepime; CTFR, cystic fibrosis transmembrane conductance receptor; EF2, elongation factor 2; FQ, fluoroquinolones; ICU, intensive-care unit; IL, interleukin; IMI, imipenem; LPS, lipopolysaccharide; MERO, meropenem; PIP, piperacillin; PTZ, piperacillin–tazobactam; TLR, Toll-like receptor; SOD1, superoxide dismutase 1.

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Further reading:
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