

**Review Article**

An Overview of Different Mechanisms of Resistance, Immune Response & Clinical Variation in *Pseudomonas aeruginosa*: A Guide for Physicians

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Abstract: *Pseudomonas aeruginosa* is a globally recognised nosocomial and opportunistic pathogen which is one of the main cause of morbidity and mortality in hospitalized patients, patients having cystic fibrosis (CF) and immunosuppression. *Pseudomonas aeruginosa* is the species most commonly associated with human disease, particularly nosocomial infections. Other opportunistic species of *Pseudomonas* include *Pseudomonas putida*, *Pseudomonas fluorescens* (associated with blood transfusions), and *Pseudomonas stutzeri*. Hospitalized patients may be colonized with *Pseudomonas aeruginosa* at moist sites such as perineum, ear & axilla. It is the most commonest opportunistic pathogen, especially in the hospital setting mainly due to its resistance to many antibiotics, ability to adapt to a wide range of physical conditions and minimal nutritional requirements. Eradication of *Pseudomonas aeruginosa* is highly challenging due to its versatile capability to resist different antibiotic classes through various mechanisms (Intrinsic, extrinsic & adaptive) of resistance. Tremendous rampant usage of antibiotics in clinical practice across the globe nourished the path of *Pseudomonas aeruginosa* for development of varied resistance mechanisms. Moreover, adaptive antibiotic resistance mechanism of *Pseudomonas aeruginosa* leads to biofilm-mediated resistance by forming multidrug-tolerant persister cells, which can cause relapse of infection. This review attempts to highlight different resistance mechanisms, variable host immune response & clinical variation in *Pseudomonas aeruginosa* infections.

Keywords: *Pseudomonas aeruginosa*, Antibiotics, Resistance Mechanisms

1. Introduction

Pseudomonas aeruginosa is strict aerobic but can grow anaerobically in the presence of nitrate, oxidative, gram negative opportunistic pathogen found almost anywhere in the environment, including surface waters, vegetation, and soil. It usually colonizes hospital and domestic sink traps, taps, and drains. It also colonizes moist areas of human skin, leading to 'toe web rot' in soldiers stationed in swampy areas, and otitis externa in divers in saturation chambers. It is a highly successful opportunistic pathogen, especially in the hospital setting largely due to its resistance to many antibiotics, ability to adapt to a wide range of physical conditions and minimal

nutritional requirements. [1]. Serious *Pseudomonas aeruginosa* infections are often nosocomial, and nearly all are associated with compromised host defenses such as in neutropenia, severe burns, or cystic fibrosis. [2]. Therapeutic options are increasingly limited due to the continued emergence and spread of antimicrobial resistant strains; as a result, *Pseudomonas aeruginosa* infections demonstrate high morbidity and mortality. *Pseudomonas aeruginosa* presents a serious therapeutic challenge for treatment of both community-acquired and nosocomial infections, and selection of the appropriate antibiotic to initiate therapy is essential to optimizing the clinical outcome. [3-5]. Epidemiological outcome studies have shown that infections caused by drug-resistant *Pseudomonas aeruginosa* are associated with

significant increases in morbidity, mortality, need for surgical intervention, length of hospital stay and chronic care and overall cost of treating the infection. [3, 6-8]

2. Main Body

2.1. Different Mechanisms of Resistance

Pseudomonas aeruginosa has a very high capacity for antibiotic resistance, utilizing combination of intrinsic, acquired and adaptive mechanisms to persist in host despite antibiotic treatment. Intrinsic mechanisms refer to innate bacterial properties that diminish effectiveness of particular types of antibiotics. Acquired mechanisms include mutations and horizontal transfer of genes leading to antibiotic resistance. Adaptive mechanisms are transient gene expression or protein alterations produced in response to environmental stimuli.

2.2. Intrinsic Resistance Mechanisms

Include outer membrane permeability (OMP). The outer membrane acts as selective barrier preventing antibiotic penetration through porin channels. The membrane is extremely restrictive with permeability 12- to 100-folds less than that of *Escherichia coli*. The structure is asymmetric bilayer composed of phospholipid and lipopolysaccharide (LPS) with embedded porins forming beta-barrel protein channels. *Pseudomonas aeruginosa* can produce alterations in cell wall permeability that deny access to antimicrobials during the course of therapy. [9]. Major nonspecific outer membrane porin F (OprF) mainly exists in closed conformation, decreasing outer membrane permeability. Decreased expression of specific porin associated with antibiotic uptake (OprD) increases resistance to carbapenem antibiotics. Overexpression of smallest porin (OprH) associated with Mg²⁺ starvation can cause increased resistance to polymyxin B and aminoglycosides like gentamicin. Efflux pumps are able to pump antibiotic components out of *Pseudomonas aeruginosa* cells, including beta-lactams, quinolones & aminoglycosides. Overexpression of multiple efflux pumps in some strains is associated with wider resistance and leads to development of multidrug resistance (MDR) strains. Antibiotic-inactivating enzymes (primarily beta-lactamase) break down or modify antibiotics & may hydrolyse antibiotics (e.g., beta-lactams & aminoglycosides) possessing susceptible chemical bonds, such as, amides and esters. *Pseudomonas aeruginosa* possesses inducible AmpC gene, which encodes hydrolytic enzyme beta-lactamase which can break amide bonds of beta-lactam ring & lead to beta-lactam antibiotic inactivation. AmpC induction requires binding of an inducing β -lactam or β -lactamase inhibitor (e.g., cefoxitin, imipenem, or clavulanate) to penicillin binding proteins (PBPs). [10-12]. Some *Pseudomonas aeruginosa* strains can produce extended-spectrum beta-lactamases (ESBLs) resulting in increased resistance to penicillins, cephalosporins & aztreonam. *Pseudomonas aeruginosa* produces 3 types of aminoglycoside-modifying enzymes (AMEs), viz.,

aminoglycoside phosphotransferases (APH) can inactivate kanamycin, neomycin & streptomycin, aminoglycoside acetyltransferases (AAC) can inactivate gentamicin, tobramycin, netilmicin, kanamycin & amikacin and aminoglycoside nucleotidyltransferases (ANT) can inactivate gentamicin, amikacin & tobramycin.

2.3. Acquired Resistance Mechanisms

Include mutations. Spontaneous mutations may influence expression or function of specific porins, efflux pumps, or antibiotic-inactivating enzymes increasing antibiotic resistance through intrinsic mechanisms. Mutations may interfere with antibacterial targets to avoid antimicrobial action & it can be acquired through protection of antibacterial targets and modifications of target sites. Quinolone target sites (DNA gyrase and topoisomerase IV) are often mutated. Ribosomal mutations can cause HLR (high levels of resistance) to aminoglycosides (e.g. Amikacin, Gentamicin, etc.). Modification of PBPs (Penicillin-binding proteins) confers increased resistance to beta-lactams. Polymyxin resistance may be achieved through mutations modifying outer membrane reducing polymyxin ability to bind to LPS. Acquisition of resistance genes means resistance genes can be acquired through horizontal transfer from same or different bacterial species & these genes may be carried on plasmids, transposons, integrons and prophages. [1] Acquired resistance to all antibiotic classes in *Pseudomonas aeruginosa* is due to low outer membrane permeability (OMP). [13]. Ceftolozane-tazobactam usually retains susceptibility against *Pseudomonas aeruginosa* isolates, which have become resistant to ceftazidime, piperacillin-tazobactam and meropenem acquired through different mechanisms. However, some *Pseudomonas aeruginosa* strains have acquired extended-spectrum beta-lactamases, which are usually VEB (Vietnam extended - spectrum β - lactamase) rather than CTX-M, TEM- or SHV- ESBLs. These VEB ESBL *Pseudomonas aeruginosa* isolates, and those which have acquired a metallo-beta-lactamase, are almost universally resistant to ceftolozane-tazobactam.

2.4. Adaptive Resistance Mechanisms

Include biofilm formation which increases protection of bacteria against antibiotics and host immune response compared to free bacterium. Bacteria with less intrinsic resistance or protective mutations may be less susceptible to antibiotics when grown in biofilm. [2]. Antibiotic sensitivity gets restored, when bacteria lose protection of biofilm, i.e., Reversible type. Mechanisms of biofilm-mediated antibiotic resistance involve prevention of antibiotic penetration, alteration of microenvironment to promote slow growth of biofilm cells, induction of adaptive stress response and persister cell differentiation. [3]. *Pseudomonas aeruginosa* permanently colonizes cystic fibrosis lungs and probably exists as biofilms coordinated by quorum sensing – structured communities of bacteria encased in a self-produced polymeric matrix. *Pseudomonas aeruginosa*

converts to a mucoid phenotype which up regulates alginate production allowing formation of biofilm colonies. Swarming colony phenotypes utilize flagellum to initiate biofilm formation after attachment. Flagellum expression is down regulated (or flagellum removed) causing reduction in activation of host immune response. Persister cells are about 1% biofilm cells & slow growing metabolically inactive persister cells do not reproduce in presence of antibiotics, but resume growth once antibiotics stopped, resulting in chronic infections. [2]. Toxin-antitoxin (TA) pairs are primarily responsible for formation of persister cells & these TA systems are involved in regulation of DNA replication, protein translation, plasmid maintenance and cell wall synthesis. [2]. Patients with cystic fibrosis typically have high levels of persister cells. Nutrient deficiencies can enhance persister cell formation. [14].

2.5. Immune Response

It differs by site of infection and clinical presentation. Chronic inflammation as a result of airway infections involves damage or dysregulation to epithelial cells and neutrophils. Epithelial cells of patients with cystic fibrosis may become dehydrated with thickening of airway surface liquid (ASL) due to dysregulation caused by cystic fibrosis transmembrane regulator (CFTR) gene mutations. Dehydrated ciliated epithelial cells have reduced ability to clear bacterial infections. Thickened ASL severely impairs immune response which may cause chronic lung inflammation. Excessive neutrophil production may cause local inflammation and tissue damage. Short lifespan of neutrophils helps to minimize damage in acute infection. Chronic infections with persistent neutrophil response cause more damage to host tissues. Neutrophils in patients with cystic fibrosis tend to have reduced ability to clear infection. Other cells involved in immune response include dendritic cells, T cells and macrophages. [15].

2.6. Overview of Clinical Variation

Pseudomonas aeruginosa may be the causative infectious organism in any body system or organ with presentation varying by site and severity, several well described infections include those associated with chronic colonization in patients with cystic fibrosis, hospital-acquired pneumonia & ventilator-associated pneumonia, intra-abdominal infections, such as, SBP (spontaneous bacterial peritonitis), secondary bacterial peritonitis and neutropenic enterocolitis. It can cause septicemia, bacteremia related to catheter-related bloodstream infections (CRBSI), a variety of skin and soft tissue infections including ecthyma gangrenosum, necrotizing fasciitis, gangrenous cellulitis, green nail syndrome, interdigital infections, etc.

3. Conclusions

In spite of our understanding of *Pseudomonas aeruginosa* has advanced a lot over the last decade, this versatile bacteria

still remains one of the commonest organism causing HAIs (Hospital acquired infections). Given its ubiquitous habitat & metabolic versatility, it's practically impossible to completely eliminate *Pseudomonas aeruginosa* from hospital settings. Hence, prevention & control and early intervention are likely to remain the most effective methods of treatment. For epidemiological studies, serotyping may be useful; four 'O serotypes' account for approximately 50% of clinical and environmental isolates. PFGE (Pulse-field gel electrophoresis) may help discriminate between serotypes. VNTR (Variable-Number Tandem Repeat) typing is useful for cross-infection and outbreak investigations, and for surveillance among CF patients.

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