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Epidemiology, Virulence Factors and Antibiotic Therapy of Pseudomonas Aeruginosa Infections

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ABSTRACT: Pseudomonas aeruginosa has been known as an aerobic rod bacterium, with negative response to Gram staining, does not form spores. It is able to cause many types of infectious diseases human. Because of its tendency to cause infections in people with weakened immune systems, its adaptability, resistance to antibiotics, and the wide range of dynamic defense mechanisms it possesses, this organism is a very difficult thing to treat in modern medicine. This bacterial species is accountable for both hospital and community-acquired infections. They frequently cause hospital pneumonia and urinary tract infections. Pseudomonas aeruginosa contain various virulence factors like lipopolysaccharide (LPS), exoenzyme S and exotoxin a. aminoglycosides, cephalosporins and carbapenems are the first line of antibiotic therapy for P. aeruginosa infection. This article highlights the epidemiology, virulence factors, diagnosis and management of Pseudomonas aeruginosa.

1. INTRODUCTION

Pseudomonas aeruginosa is a rod-shaped bacterium that responds negatively to Gram staining and thrives in various environments, from mammalian tissues down to plants and even soil. It has anchoring factors (like biofilms, pili and flagella) that enable it to live on or in water, surfaces, and medical implements. Therefore, it is environmentally widespread because of its prevalence in both natural and artificial settings; for example, household sink drains and hospitals as well as lake water. (Remold et al., 2011).

Pseudomonas aeruginosa is an ubiquitous bacterium in freshwater environments and can also be isolated from various man-made reservoirs within urban communities, including swimming pools, jacuzzis, and hot tubs. This opportunistic pathogen causes a large set of infections in humans, ranging from folliculitis, puncture wounds of otitis externa, pneumonia, to osteomyelitis. It is notorious for being opportunistic and a major contributor to both community-acquired and hospital infections, in addition to antibiotic resistance. Pseudomonas aeruginosa has been detected from the hospital environment in sources such as endoscope washers, endoscopes, respiratory therapy equipment, soap bars, sanitizers, disinfecting solutions, icemakers, toothbrushes, sinks, taps potable water. Important infections associated with this bacterium are ventilator-associated pneumonia, catheter-associated urinary tract infections, surgical site infections, burn wound infections and keratitis (Figure 1). (Mulcahy et al., 2014; Subhi et al., 2017).

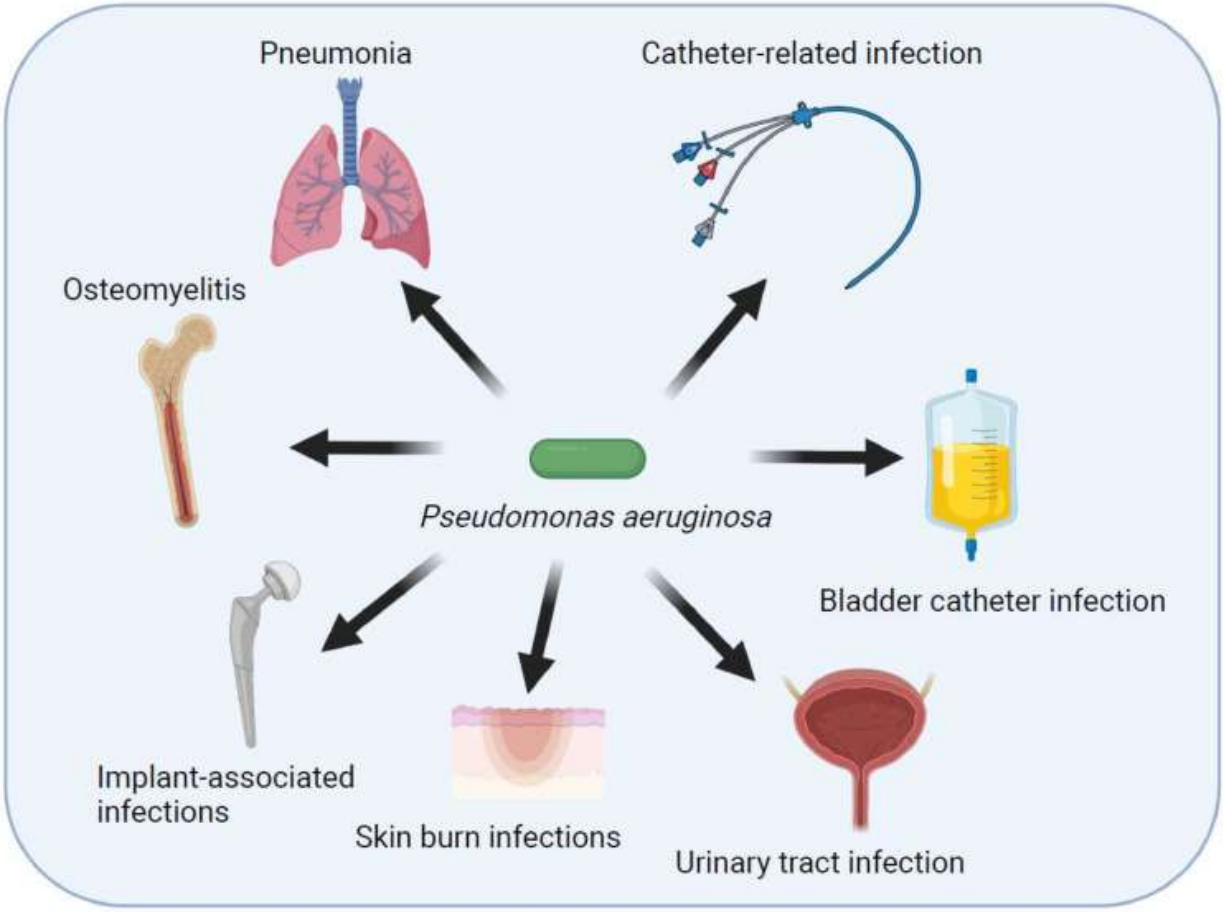

Figure 1. Infections associated with Pseudomonas aeruginosa (Tuon et al., 2022)

EPIDEMIOLOGY

In a previous multinational point prevalence research conducted in Europe until 2017, Pseudomonas aeruginosa was the fifth most common nosocomial infection isolated, with a prevalence rate of 7.11%. Overall, nosocomial infections were found in 6.8% of the surveyed patients, and 33.1% of them were due to extensively drug-resistant (XDR) and\or multidrug-resistant (MDR) pathogenic bacteria. The potential prevalence of acquired P. aeruginosa infections could reach 23% among ICU patients; the incidence of resistant P. aeruginosa in ICUs might go up to 48.7%. After 2016, more than 30,000 patients in the United States contracted MDR P. aeruginosa during their stay in hospital wards alone, according to the Centers for Disease Control and Prevention (Ribeiro et al., 2019).

In cases of nosocomial pneumonia, *P. aeruginosa* is the most frequently isolated bacillus that respond negatively to Gram staining, and it remains the leading cause of mortality and morbidity among infections caused by non-fermenting Gram-negative bacilli. Its frequency has increased in recent years. Among nosocomial infectious disease in the intensive care unit, P. aeruginosa is the most frequent gram-negative bacillus. Results from a large international study of infections in ICU patients indicated that *P. aeruginosa* represented 16.20% of isolates from ICU-acquired infections; thus, it is an important pathogen in ICUs worldwide. Reservoirs in the respiratory tract were the most frequent sources of isolation of *P. aeruginosa* (Reynolds & Kollef, 2021).

Pseudomonas aeruginosa is one of the major causes of nosocomial urinary tract infections (UTIs), especially catheter-associated ones. It causes about 10% of all catheter-associated UTIs and as many as 16% of UTIs occurring in the ICU. P. aeruginosa UTIs related to healthcare-associated transmission are highly morbid, potentially leading to bacteremia. Catheter-associated UTIs with P. aeruginosa have some of the highest rates of antibiotic resistance reported, which varies based on local patterns of resistance. According to data from the International Nosocomial Infection Control Consortium, resistance levels can surpass 40% in drugs like meropenem, tazobactam-piperacillin, and fluoroquinolones among others for ICU patients. These rates are higher than those published in most other parts of the world. (Rosenthal et al., 2016).

PATHOGENESIS

Pseudomonas aeruginosa is one of the most frequent opportunistic pathogenic bacteria accountable for a wide spectrum of infections. It has developed numerous mechanisms of antibiotic resistance and possesses various virulence factors. These factors collectively contribute to the challenges in treating such infections after the development of antibiotic resistance. Several mechanisms have been

identified to be responsible for Pseudomonas' antimicrobial resistance; production of enzymes that degrade antibiotics, efflux systems that expel antibiotics from the cell, and limiting membrane permeability to antimicrobials as a result of low intrinsic impermeability. Moreover, many strains of Pseudomonas aeruginosa produce extended-spectrum beta-lactamases (ESBLs) and beta-lactamases. In addition to its antibiotic resistance mechanisms, Pseudomonas aeruginosa possesses several virulence factors that allow it to cause disease conditions more effectively. Pseudomonas aeruginosa contain various virulence factors like lipopolysaccharide (LPS), exoenzyme S and exotoxin a (Wilson and Pandey, 2013; Subhi, 2022).

The motility and respiratory infection of P. aeruginosa is enabled by its flagella and pili, which play a critical role in attaching to respiratory epithelial tissue through respiratory mucins and the glycolipid receptor asialoGM1. The first step in infection is bacterial adhesion to the respiratory epithelial surface, which occurs due to interactions between bacterial adhesins and host receptors. In the case of P. aeruginosa, major adhesins are one flagellum that is also essential for type IV pili formation in addition to biofilm development, cell adhesion, and motility. These appendages consist of pilin polymers that make bacteria not only to transport across surfaces but also to attach greatly to respiratory epithelial cells and biofilm formation (Mobley et al., 2019).

Patients with abnormal respiratory epithelium, whether as a consequence of chronic lung disease or acute respiratory failure with mechanical ventilation, are at risk for an acute phase infection with P. aeruginosa. Those with underlying lung disease may present more commonly with a chronic form of infection. During the acute phase, P. aeruginosa uses its type IV pili and flagellum for attachment to respiratory epithelium while its toxins cause damage to host lung cells. Subsequently, P. aeruginosa forms biofilms and secretes an extracellular matrix that is lipid-rich in composition along with extracellular DNA, proteins, and polysaccharides; this matrix adheres to the respiratory epithelium. This provides both synergism among the bacteria and protection against neutrophil phagocytosis and antibiotics (Rosenthal et al., 2015).

Mucoid phenotype development in P. aeruginosa, which is observed in lung disease, relies on alginate production. Alginate is an exopolysaccharide that comprises residues of D-mannuronic acid and L-guluronic acid. Induction of alginate expression by P. aeruginosa is therefore necessary for the development of mucoid phenotypes. Normally, an anti-sigma factor called MucA regulates the production of alginate. This anti-sigma factor binds to AlgT and thereby prevents it from activating the expression of alginate at the algD promoter region. However, in airways with lung disease, there are mucA mutations in P. aeruginosa. As a result, activity at AlgT is not suppressed, and this leads to uncontrolled production of alginate. As a consequence, P. aeruginosa forms a mucoid colony. Overproduction of alginate by P. aeruginosa has some benefits to the microbe. It promotes biofilm formation, aiding bacteria in evading clearance by host immune cells and antibiotic treatment. It also has immunomodulatory impacts that might compromise the host immune response to infectious diseases such as high expression of CD4 (Hauser et al., 2011; Hassan et al., 2023).

Quorum sensing is the process through which bacteria communicate, allowing them to coordinate gene expression and, consequently, effectively control their actions against the host during an infection. Quorum sensing in P. aeruginosa involves several well-established pathways: Pqs, Rhl, and Ls synthesis different types of autoinducers that diffuse away to both bacterial and host cells, leading to the regulation of gene transcription. This benefits the bacteria in promoting their continued survival and propagation because the immune response to the infection is dampened (Curran et al., 2023).

The severity and outcome of infection with P. aeruginosa are dependent on the type III secretory system. This system allows *P.* aeruginosa to inject effector proteins into host cells, including those of the respiratory epithelial tissue. These proteins can then modulate the host cells' function; they may act innately immunosuppressive actions and may also have effects on the actin cytoskeleton. ExoY, ExoU, ExoT, and ExoS have long been known as the effector proteins of the P. aeruginosa type III secretion system, but recent research has identified two more: PemA and PemB. Of clinical importance among these effectors, ExoS and ExoU are found to be mutually exclusive in most strains isolated from human infections. While ExoS acts as a potent cytotoxin unrelated to respiratory epithelial cells' actin cytoskeleton, ExoU does. On the other hand, ExoU is known for its highly cytotoxic activity, causing host cell death and is found more often among clinical isolates from patients in ICUs or burn units (Horna & Ruiz, 2021).

DIAGNOSIS

To detect P. aeruginosa infection, cultures must be drawn from the appropriate site and at the appropriate time. Before initiating antibiotic therapy, blood cultures should be drawn in all intensively ill patients suspected of having P. aeruginosa infection and ideally within one hour of identifying the patient as critically ill. Urine cultures have to be done for those patients with suspected urinary tract infection or catheter-associated UTI. Whenever possible, sputum cultures should be collected for the microbiologic diagnosis of pneumonia. Sputum cultures in subjects with cystic fibrosis (CF) should be targeted specifically to identify CF pathogens, including P. aeruginosa. The isolation of Pseudomonas from a single sputum culture specimen in a pediatric patient can be a primary indicator of infection of CF (Rhodes et al., 2017).

In the laboratory, there are conventional techniques used to detect the growth of P. aeruginosa such as observing the appearance of microbial colonies on culture media. To specifically identify P. aeruginosa in mixed samples, selective media containing cetrimide can be employed. Once a patient has been recognized to have P. aeruginosa infection, it is essential to carry out antimicrobial susceptibility testing so as to obtain resistance patterns for guidance in selecting appropriate antibiotic treatment. Automated

antimicrobial susceptibility kits are used by many laboratories; they do not only give resistance but also minimum inhibitory concentrations. The diagnosis of carbapenem-resistant strains of P. aeruginosa may be very important especially in the context of potential outbreaks (Bassetti et al., 2018).

Nosocomial pneumonia caused by P. aeruginosa can be diagnosed using a rapid diagnostic test. These tests have the highest sensitivity and specificity for the identification of P. aeruginosa from lower respiratory tract infections, including bronchoalveolar lavage samples, among other methods, using multiplex real-time polymerase chain reaction. The advantages of this rapid diagnostic test include the ability to provide a diagnosis within 2 hours compared to 48-72 hours for standard culture methods. They also have the ability to detect co-infections with certain viruses or bacteria and to identify some antimicrobial resistance genes; thus, they allow appropriate initial antibiotic therapy and timely de-escalation of antibiotics (Kollef et al., 2017).

MANAGEMENT

To reduce costs and the risk of developing antibiotic resistance, it is recommended that antibiotics be prescribed only when necessary. This applies to all multidrug-resistant bacteria, including Pseudomonas. The need for infection control measures targeting the prevention of pseudomonal infections in hospitals is gaining recognition. A comparison of various antibiotic resistance mechanisms would be very useful in understanding the epidemiology of these infections and improving strategies for preventing them (Angeletti et al., 2018).

When managing high-risk patients, it is very important for clinicians to always have Pseudomonas infections in their differential diagnosis hat and be suspicious. If severe infections lead to septic shock, respiratory failure, or the need for ICU admission, then consider it. Hot tub folliculitis is usually self-limited and does not require therapy; however, systemic antipseudomonal antimicrobials may be indicated. For puncture wounds, in addition to routine staphylococcal and streptococcal coverage, pseudomonal coverage should be considered particularly when these infections appear deep. Prolonged intravenous antibiotic therapy and surgical debridement may be necessary. When a patient presents with respiratory failure as a consequence of another underlying process (e.g., pneumonia) or with sepsis or septic shock due to any other systemic infection that would ultimately require ICU admission, the possibility of Pseudomonas infections should be considered early (Slattery et al., 1996).

When sensitivity results are not yet available, the local antibiogram is very important in guiding empiric therapy. In cases where a patient has septic shock or respiratory failure needing mechanical ventilation or if they need to be admitted to the ICU and have one or more risk factors for multi-drug resistant organisms, it might be essential to initiate double pseudomonal coverage in addition to broad-spectrum antibiotics. There are several groups of antibiotics that have activity against Pseudomonas, including Fluoroquinolones (e.g., levofloxacin and ciprofloxacin), aminoglycosides (e.g., amikacin, tobramycin and gentamicin), cephalosporins (e.g., ceftazidime and cefepime), and carbapenems (e.g., meropenem). These agents are commonly utilized as empirical first-line treatment until sensitivity and culture outcomes are present (Makhnevich et al., 2019).

Regarding herbal therapy, a previous study has shown that the extract of black tea may have inhibitory effect on growth of P. aeruginosa (Flayyih et al., 2013).

CONCLUSION

Pseudomonas aeruginosa has been known as an aerobic rod bacterium, with negative response to Gram staining, does not form spores. It is able to cause many types of infectious diseases human. Because of its tendency to cause infections in people with weakened immune systems, its adaptability, resistance to antibiotics, and the wide range of dynamic defense mechanisms it possesses, this organism is a very difficult thing to treat in modern medicine. This bacterial species is responsible for both community and hospital-acquired infections. They frequently cause hospital pneumonia and urinary tract infections. *Pseudomonas aeruginosa* contain various virulence factors like lipopolysaccharide (LPS), exoenzyme S and exotoxin a. aminoglycosides, cephalosporins and carbapenems are the first line of antibiotic therapy for *P. aeruginosa* infection. This review highlights the epidemiology, virulence factors, diagnosis and management of *Pseudomonas aeruginosa*.

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