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Pseudomonas aeruginosa Infection in Humans and Antibiotic Resistance

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Authors' contributions

This work was carried out in collaboration between all authors. Author OA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors YK and EI managed the analyses of the study. Author EI managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

In addition to other gram-negative bacteria identified as agents at high rates in hospital infections, *P. aeruginosa* is particularly important with its epidemiological and microbiological characteristics. In this study, infections developing due to *Pseudomonas aeruginosa* were discussed and increased antibiotic resistance in these bacterial infections and new therapeutic approaches were investigated.

Keywords: Pseudomonas aeruginosa; hospital infection; antibiotic resistance.

1. INTRODUCTION

Pseudomonas aeruginosa is one of the leading agents of hospital infections [1,2]. Hospital infections are an important health problem in our country as in the whole world due to their high economic cost, morbidity and mortality rates. *Pseudomonas aeruginosa* is responsible for 10-25% of hospital infections. *P.aeruginosa* is a very important bacterium due to its natural and developed resistance mechanisms, in addition to its ability to reproduce under minimal

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reproduction conditions, being widely available in nature, and its various virulence factors [3,4]. *P. aeruginosa* is found as a saprophyte in healthy humans and rarely causes disease. It colonizes more in patients in intensive care units, burn units, and units where mechanical ventilators and cancer chemotherapy are applied, or broad-spectrum antibiotics are administered, and this predisposes to invasive infections [1,5].

2. GENERAL FEATURES

Pseudomonas aeruginosa is an asporous, polar flagellated, motile, Gram-negative, and usually non-capsulate microorganism. It is fine, flat rod-shaped bacterium sometimes observed in pairs, but mostly observed individually in cultures. *P. aeruginosa* easily reproduces in any medium. It produces beta hemolysis on sheep"s blood-agar. When the Petri dish is opened, grape or viola is smelled. Two types of colonies form at 37°C after 24 hours. The first type of colonies is large, smooth, bright, moist, and widespread. The second type of colonies is formed mainly from the strains isolated from natural sources. These are small, convex, and irregularly shaped. *P. aeruginosa* does not ferment carbohydrates. In an oxidation-fermentation medium, acid is formed from glucose by oxidation. Oxidase and catalase are positive. In TSI agar (Merck 1.03915), an alkali reacts but does not form a gas. Most of the strains form nitrogen gas from nitrates and nitrites on the Fluorescence Denitrification (FN) medium. Gelatin, urease, and citrate are positive, while lysine decarboxylase, indole, MR, and VP are negative. It produces bacteriocin (Pyocin). It has lytic phages. It has 17 somatic and 6 flagellar (H) antigens; they produce exotoxins [6,7,8].

3. PATHOGENESIS

P. aeruginosa require oxygen to grow. *Pseudomonas* produces endotoxin and enterotoxin. *Pseudomonas* endotoxin causes diarrhea syndrome. The role of enterotoxin in the etiology of diarrhea is not well known. *Pseudomonas* also produces extracellular enzymes such as lecithinase, collagenase, lipase, elastase, caseinase, gelatinase, fibrinolysin, hemolysin, exotoxin A. Proteolytic enzymes cause localized necrosis on the skin or lungs and ulceration in the cornea. The solubilization and destruction of lecithin (surfactant) lead to the formation of atelectasis in lung infections due to *Pseudomonas*. The hemolysis caused by *P. aeruginosa* depends on the heat-stable phospholipase C and heat-stable component. Furthermore, exotoxin S has been identified. This is also considered as a virulence factor. The pigments of *P. aeruginosa* are not toxic [8,9,10].

Glycocalyx in surface structures helps the adhesion of *Pseudomonas* to mucosal surfaces. *P. aeruginosa* is preferably attached to the normal respiratory mucin [11]. The pathogenesis of *P. aeruginosa* is associated with the degree of phagocytosis resistance. In cystic fibrosis patients, the opsonic antibody function is decreased as a result of the molecular change in the Fc part of the IgG molecule. Bacterial proteases break the IgG and disrupt the opsonic activity. The settlement of *Pseudomonas* in the lungs of patients particularly with cystic fibrosis depends on one or more factors that interfere with the bactericidal activity in the normal fresh human serum for *P. aeruginosa* present in the sputum of these patients [12]. These blocking factors are in the class of IgG antibodies and block the normal bactericidal IgM activity in the normal human serum. The role of lipopolysaccharides in the virulence of *P. aeruginosa* has also been investigated. The virulence of many strains of *P. aeruginosa* is due to the lipopolysaccharide integrity in the mouse with burns. The insufficiency in the O-side chain of lipopolysaccharide provides less virulence [9,10].

4. CLINICAL FEATURES

Pseudomonas can also infect normal healthy individuals. The agent can enter the body even from a small wound and followingly, it can turn into a green or bluish pyogenic abscess. Skin lesions may develop directly due to inoculation or secondarily due to septicemia. It initially occurs in the form of pink spots, then, leads to the formation of necrosis and scar and this region is surrounded by a red ring (ecthyma gangrenosum). The bacterium multiplie locally and may rarely lead to septicemia, pneumonia, and urinary tract infection in normal children. *Pseudomonas* osteomyelitis can develop in injuries caused by puncture, especially in the foot [6,13].

Pseudomonas can cause dermatitis and urinary tract infections in normal children by being transmitted from swimming pools. Skin lesions may develop in a period from a few hours to two days following the contact with water sources. They can be erythematous, macular, or pustulous. Sometimes the nodule can be

observed. The severity of the disease may vary from person to person. Fatigue, fever, vomiting, sore throat, conjunctivitis, rhinitis, and swelling of the chest may coexist in some children. Several serotypes of *P. aeruginosa* have been found in secretions. The overhydration of the skin in hot tubs and the presence of *P. aeruginosa* lead to a primary *Pseudomonas* infection. The water in hot tubs is heated to 37.8°C, and *P. aeruginosa* very easily since there is usually not any filter. Otitis externa is common in swimmers swimming in contaminated waters. Rather than the high fever form that courses with necrosis in the external auditory canal, facial palsy, and mastoiditis, it is more observed in malnutrition, leukopenia, leukocyte dysfunction, or diabetes mellitus. *P. aeruginosa* is causing sepsis at an increasing frequency in neonates. It has high mortality and morbidity [9,13,14,15].

4.1 Burn and Wound Infection

Pseudomonas and other Gram-negative microorganisms are found on the wound and burn surfaces. Colonization does not necessarily mean the formation of an infection. *P. aeruginosa* septicemia is a major problem in a burned patient. Infarct tissue, lasting intravenous or urinary catheterization facilitate the formation of an infection. The use of antibiotics reduces the microbiological flora but does not prevent the development of some specific *Pseudomonas*. In burned cases, neutrophil dysfunctions are detected just before septicemia. The killing of *Pseudomonas* by neutrophils is impaired. In burns, the response to antigens is impaired, the removal of homograft is delayed, the vascular response is impaired, hypersensitivity responses and the capture of the particles of the reticuloendothelial system are impaired [14,16].

4.2 Cystic Fibrosis

One of the most lethal hereditary diseases of childhood is cystic fibrosis. Death is usually from chronic obstructive pulmonary disease. *Pseudomonas* is reproduced in the majority of children with cystic fibrosis. The presence of *Pseudomonas* in the sputum of children with cystic fibrosis does not always indicate an infection. Colonization is related to the continuous use of steam and broad-spectrum antibiotics. Recent studies have shown that there is a more specific relationship between *Pseudomonas* and cystic fibrosis [9,17].

The sputum of patients with cystic fibrosis almost always contains mucoid *P. aeruginosa*. The tracheobronchial tree is colonized chronically. The microorganism can be eradicated spontaneously or with antibiotic treatment. Different serotypes were found in patients with cystic fibrosis. Homma type 8 strains were obtained at the rate of 50-93%. The alveolar macrophages obtained from the rabbit cannot phagocytose *Pseudomonas* against the serum of patients with cystic fibrosis and kill it. This suggests a local defect in the lung resistance to *Pseudomonas* in patients with cystic fibrosis. Septicemia is rare. The lung infection is chronic. Bronchitis, bronchiolitis, and bronchiectasis can be observed. Local necrotizing pneumonia may develop [9,17,18].

4.3 Malignant Diseases

Children with leukemia, and especially those receiving immunosuppressive treatment, and neutropenic patients are susceptible to *Pseudomonas* septicemia. Infection develops in cases when *Pseudomonas* has been colonized previously, for example passing from the gastrointestinal tract into the blood circulation. The loss of appetite, fatigue, nausea, vomiting, diarrhea, and fever draw attention.

Generalized vasculitis develops, and all organs have hemorrhagic necrotic lesions, purpuric nodules or ecchymotic areas occur on the skin and become gangrenous. Hemorrhagic or gangrenous perirectal cellulitis or abscess may occur, Ileus and deep hypotension may develop. Granulocytopenia is the most important factor predisposing cancer children to infection. In patients with leukemia and other neoplasms, the bactericidal capacity is impaired. In patients with an intensive chemotherapy combination, specific opsonins that develop against the heat-stable *P. aeruginosa* decrease. Fatal infections due to *Pseudomonas* are partly due to the lack of specific opsonin [14].

4.4 Immunosuppression

Immunosuppressive agents are used in malignant diseases, transplantation or in collagen-vascular diseases. *P. aeruginosa* infection is observed in individuals receiving immunosuppressive treatment, especially in the form of pneumonia and septicemia [15].

5. DIAGNOSIS OF *Pseudomonas aeruginosa* INFECTION

The diagnosis of *Pseudomonas aeruginosa* infection is possible by obtainment from the

blood, cerebrospinal fluid, urine, cellulite or abscess areas. In diabetic foot infections, the most reliable method for the determination of the infection agent is to culture deep tissues. While *Pseudomonas* pneumonia is diagnosed using the material taken from the lungs by needle biopsy, it can be determined with the sputum taken after postural drainage in children with cystic fibrosis. Microorganisms obtained from the skin, throat, tracheal aspiration, and bronchial secretions may suggest colonization but do not always lead to infection. These findings should be accepted as an indication of *Pseudomonas* infection in bluish nodular skin lesions and ulcers with ecchymotic and gangrenous centers and in ecthyma gangrenosum. Skin lesions rarely may not be clinically distinguished from *Aeromonas hydrophila* septicemia [9,13,16].

6. PROGNOSIS

The prognosis depends on the underlying cause of the infection. In children with leukemia, *Pseudomonas aeruginosa* septicemia is an important condition leading to death. The main cause of death in children with cystic fibrosis is lung failure, and thus, in the majority of patients who died, *Pseudomonas* could be shown in lungs. Situations such as the misuse of antibiotics, the length of hospital or intensive care stay, and need for prolonged ventilation are among the most important factors affecting the prognosis. While amputation can be prevented up to 85% with the early and appropriate treatment of diabetic foot ulcers, it is known that approximately 15-20% of patients without early and appropriate treatment undergo amputation [2,9,13,16].

7. PREVENTION OF *Pseudomonas aeruginosa* INFECTION

Prevention of *Pseudomonas aeruginosa* infection is only possible by constantly controlling the hospital and its surroundings. The proliferation of *Pseudomonas* can be prevented by keeping the water pH between 7.2 and 7.8 and the chlorine concentration at 70.5 mg/l. Proliferation occurs in infected hands, disinfectant solutions, and solutions in which aspiration catheters are washed in neonatal units. It is necessary to wash hands with plenty of water and soap before and after examining neonates. Liquid iodoform handwash solutions prevent the spread of disease. It is necessary to take great care, especially when placing catheters during parenteral nutrition. *Pseudomonas* septicemia can frequently occurs in burn cases. The topical use of 0.5% silver nitrate and 10% mafenide acetate cream minimizes the risk of infection in burns. Debridement is applied. If the urinary tract has obstructive lesions, surgical procedure can be protective against *Pseudomonas* infection [16,19,20].

8. TREATMENT

Due to its structural properties, *P. aeruginosa* is a bacterium that can develop resistance very quickly. It is an opportunistic pathogen with gradually increasing resistant strains that causes infections such as bacteremia, meningitis, brain abscess, pneumonia, otitis, septic arthritis, osteomyelitis, skin and soft tissue infections, endocarditis, and diarrhea, especially in the hospital environment [6]. Due to the increased resistance to antibiotics used in the treatment, the number of antibiotics to be used in the treatment is increasingly limited [21]. The incorrect and inappropriate use of antibiotics increases the resistance development, and intensive antibiotic pressure in hospitals leads to the selection of these resistant resources.

The increased number of *P.aeruginosa* strains with multiple antibiotic resistance in recent years has led to experiencing problems in the treatment of these bacterial infections. In the treatment of infections caused by *P. aeruginosa*, the combination treatment is recommended for the purpose of preventing the resistance development during treatment and providing a broad-spectrum effect and mostly, an antipseudomonal beta-lactam and aminoglycoside or quinolone combination is used [22].

In their study conducted between 1995-1999, Cesur et al. showed that ceftazidime and imipenem resistance increased [23]. In a study conducted between 2000 and 2004, it was reported that aztreonam, ceftazidime, and piperacillin/tazobactam resistances increased and amikacin, ciprofloxacin, imipenem, and meropenem resistances decreased [24]. In fact, in a study by Allegranzi et al., it was reported that with the use of imipenem instead of piperacillin/tazobactam in the empirical treatment, piperacillin/tazobactam resistance decreased significantly and imipenem resistance increased [25]. In a study conducted between 2005 and 2007, Dündar and Tamer revealed that there were significant increases in piperacillin, piperacillin/tazobactam, and cefoperazone/

sulbactam resistance within three years. This is thought to be due to the widespread use of these antibiotics. Within three years, gentamicin and tobramycin resistance decreased significantly. The researchers revealed that this may be associated with the preference of mostly amikacin for combination therapy in *P.aeruginosa* infections [1]. In their studies conducted between 2011 and 2013, Durmaz and Toka Özer found out that the highest resistance rates in *P.aeruginosa* strains were against cefepime and ceftazidime and the most effective antibiotics were amikacin and piperacillin-tazobactam with 93% and 92% susceptibility rates, respectively [26].

9. CONCLUSION

Consequently, upon examining the resistance rates reported in various studies conducted in Turkey and in the world, antibiotic resistance is within quite broad limits. Studies have shown that resistance rates are quite dynamic. It is important to remember that antibiotic susceptibility may vary from region to region, hospital to hospital, service to service, even from year to year in the same unit, and resistance development should be monitored constantly. These data should be used in the selection of empirical treatment, the treatment initiated as empirical should be guided according to the antibiogram result, and cultures and antibiograms should be repeated during the treatment considering that resistance may develop during treatment in infections developing due to *P.aeruginosa*.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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