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Review

Upper aero-digestive contamination by *Pseudomonas aeruginosa* and implications in Cystic Fibrosis

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Abstract

Background: Cystic Fibrosis (CF) is a severe genetic disorder that is common among the Caucasian population. Bacterial respiratory infections are the main cause of morbidity and mortality in CF patients. *Pseudomonas aeruginosa* is the main pathogen of lower airways (LAW) decline.
Method: To understand chronic broncho-pulmonary colonization, a systematic review is conducted. The aim of our article is to identify the pathways of contamination in the upper aero-digestive tract.
Results: A large number of articles report that *P. aeruginosa* is established first at nasopharyngeal sites. The vast majority of authors agree that the upper aero-digestive tract is the first location of colonization by *P. aeruginosa* and its presence appears to be predictive of subsequent broncho-pulmonary colonization.
Conclusion: This review supports the possible involvement of the nasal and paranasal sinuses and oral cavity as means of contamination.

Keywords: Pseudomonas aeruginosa; Cystic Fibrosis; Mouth; Paranasal sinuses; Nasal cavity

Contents

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1. Introduction

Cystic Fibrosis is one of the most common autosomal recessive lethal disorders affecting the Caucasian population. The rate in Brittany, France is 1/3300 births [1]. In 1974, the average age of death was 8 years due to a lack of appropriate treatment. The disease is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene on the long arm of chromosome 7, which codes for a transmembrane regulator protein. More than 1500 mutations have been reported to date [2]. *CFTR* mutations result in an abnormal performance of the cAMP-dependent chloride channel on the apical membrane of epithelial cells, manifested as dehydrated airway mucus, disordered cilia-motility and impaired mucociliary clearance [2–4]. The main clinical manifestations are characterized by malabsorption, chronic rhinosinusitis and LAW infections. The natural history of this disease includes acquisition through time of bacterial species. During early childhood, the broncho-pulmonary infections are due to *Haemophilus influenzae* and *Staphylococcus aureus*. As the patient grows older, pathogenic Gram-negative bacteria like *Achromobacter xylosoxidans*, *Burkholderia cepacia* complex and especially *Pseudomonas aeruginosa* are more frequently seen. *P. aeruginosa* is a turning point in the respiratory disease and its prevalence increases with age [5]. Before arriving to the lungs, these respiratory pathogens cross different anatomical areas like the nose and paranasal sinuses on the one hand, and the oral cavity on the other converging in the oropharynx. The pharynx is a transition zone and an intersection between the respiratory tract and digestive tract.

Initially, *P. aeruginosa* colonizes the lungs intermittently, and after rapid adaptation, it turns into chronic infection [2,6]. Chronic airway infection with *P. aeruginosa* and bronchiectasis are the major causes of morbidity and subsequent mortality in CF patients [7,8]. Once established in the lungs, this organism is extremely difficult to eradicate.

P. aeruginosa and especially the mucoid strains are responsible for lung decline in CF patients. There is a vicious circle due to local inflammation caused by this bacterium that causes lesions in CF patients generating a loss of respiratory function [9].

This ubiquitous aerobic bacterium is noted for its environmental versatility. In contrast to many environmental bacteria, *P. aeruginosa* rarely causes infection in healthy individuals but it has a remarkable capacity to cause disease in susceptible hosts. This bacterium is an opportunistic pathogen associated with respiratory tract infections, causing nosocomial infections in hospitalized and immunocompromised patients who are mechanically ventilated [6].

P. aeruginosa possesses several factors that contribute to colonization and chronic infections, in particular the capacity to form biofilm composed of exopolysaccharides as well as host mucin and water up to 97%. The initial step is the biofilm adhesion to a surface. In CF, epithelial mucus accumulation facilitates this process. This biofilm is found in different parts of the body. Colonized lungs with presence of biofilm confer to this bacterium a large resistance to antibiotics and reduce the immune response of patients. Bacteria populations organized in biofilm are more difficult to eradicate [6].

Often, this bacterium changes its morphology. It becomes immobile, decreases the production of virulent factors, changes its lipopolysaccharide (LPS) structure [3] and becomes a mucoid strain [6,10]. In addition, *P. aeruginosa* isolates in chronically infected patients are phenotypically different from those isolates in other patients (in ventilator-associated pneumonia patients and patients with acute respiratory failure) or from those in the environment. It can produce several pigments, a blue-green pigment pyocyanin, a fluorescent yellow-green pigment and a brown-red pigment pyomelanin.

Others factors implicated in colonization are surface components, the polar pili for eukaryotic cell attachment; flagella expression in initial stages; and the type III secretion system, the major virulence factor that allows bacteria to inject toxins into host cells. One of the secreted proteins is ExoU that causes damage to cellular membranes and rapid necrotic death. Another factor is *P. aeruginosa* Quorum Sensing (cell-to-cell signaling), a density-dependent system that coordinates gene expression by the production of small diffusible molecules such as acyl homoserine lactones (AHL). Some of interconnecting genes are implicated in biofilm formation, making conditions favorable for bacterial multiplication and survival and formation of structured communities.

Persistence of *P. aeruginosa* colonization is due to the genetic flexibility provided by its large genome [6]. The large proportion of hypermutable strains favors adaptation. This hypermutable character is generated when the rate of spontaneous mutation is 100–1000 times higher than usual.

Mutation development favors bacterial persistence with a higher resistance to antibiotics because of the large amount of antimicrobial treatments in CF patients. The presence of 43% hypermutable *P. aeruginosa* in CF patients has been demonstrated [10].

In VAP, *P. aeruginosa* causes a mortality rate of 34–48%, due to damage of the epithelium associated with endotracheal intubation that favors bacterial colonization of the endotracheal tube and upper respiratory tract. In immunosuppressed patients, transplant recipients, cancer and neutropenia, the risk of acquiring *P. aeruginosa* is increased, with a mortality rate of 40% in *P. aeruginosa* associated pneumonia.

The aim of our study is to systematically review the different pathways of *P. aeruginosa* in the upper aero-digestive tract implicated in chronic LAW colonization to better understand the stages of colonization.

2. Methods

2.1. Search strategy

In November 2013, we conducted a literature review searching in electronic databases and scanning reference lists in PubMed to identify studies with *P. aeruginosa* human colonization data. We searched in English, Spanish and French languages. We used the keywords, Mesh terms, synonyms: *P. aeruginosa*, CF, nose, paranasal sinus, oral cavity, saliva, upper airways (UAW) and LAW to find studies, case reports relating association of these search terms.