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Review

Serum antibodies to *Pseudomonas aeruginosa* in cystic fibrosis as a diagnostic tool: A systematic review

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Abstract

Background: A systematic literature review of the last 40 years on the research of serum antibodies to *Pseudomonas aeruginosa* in cystic fibrosis and its utility as a diagnostic tool.
Methods: Research papers in English, Portuguese, and Spanish were accessed through electronic databases (PubMed, Medline, LILACS, and SciELO).
Results: 26 studies were assessed. ELISA technique was the most commonly used technique to detect serum *P. aeruginosa* antibodies. The most consistent results were those in which the response against the antigen St-Ag:1–17 was evaluated. The accuracy levels of the ELISA technique remain controversial, but most studies showed a good correlation between antibody titers and microbiological culture.
Conclusions: The detection of serum antibodies to *P. aeruginosa* shows capacity for early detection of this pathogen and potential utility and viability of incorporation in the diagnostic routine of patients with cystic fibrosis.

Keywords: *Pseudomonas aeruginosa*; Cystic fibrosis; Serum antibodies; Review

Contents

Abbreviations: CF, Cystic fibrosis; BAL, Bronchoalveolar lavage; ELISA, Enzyme-linked immunosorbent assay; CIE, Crossed immune electrophoresis; RIA, Radioimmunoassay; ExoA, Exotoxin A; ELA, Elastase; AP, Alkaline protease; TTSS, Type three secretion system; PCR, Polymerase chain reaction; PPV, Positive predictive value; NPV, Negative predictive value

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1. Introduction

Pseudomonas aeruginosa pulmonary infection is responsible for elevated morbidity and mortality among cystic fibrosis (CF) patients [1,2]. In childhood, 10 to 30% of these patients are colonized and in adulthood, 80 to 90% are infected with this bacterium. Patients infected with *P. aeruginosa* generally present a reduction of about 10 years in life expectancy when compared with the non-infected ones [3].

When chronic infection [4] is established, *P. aeruginosa* is practically impossible to be eradicated [1,2], although, its clearance from the respiratory tract is possible through early intervention with antibiotic therapy, as soon as the pathogen settles in the organism. Thus, early aggressive treatment is recommended, being possible to delay the chronic colonization and progression of the pulmonary disease [5].

Detection of *P. aeruginosa* in the diagnostic routine is made mostly through sputum culture — spontaneously expectorated or induced by inhalation of hypertonic saline (3–7%); however, many patients – especially children under 7 years – are incapable of producing an expectorated sputum specimen. BAL, the gold standard, is an option, but it is invasive and usually employed only when there is a compelling reason to obtain a respiratory sample and other approaches have failed. For this reason, oropharyngeal (OP) swabs are used as a surrogate for sputum or BAL fluid specimens in these individuals, sampling the microbial flora of the upper respiratory tract, which is assumed to reflect that of the lower respiratory tract [6]. Despite the good specificity reported for this method, in comparison to BAL culture, it is known that a negative culture from the upper airways does not exclude the presence of *P. aeruginosa* in the lower airways [7,8]. Sampling errors during the BAL and the frequent insufficient sample obtained through oropharyngeal swab can lead to false negative results [7]. The difficulty in obtaining representative respiratory specimens from the airways of infants and children indicates the need for the use of methods that can complement or be an alternative to microbiological culture [9].

The detection of serum antibodies against *P. aeruginosa* has emerged as a possible auxiliary method to assess the early eradication therapy [10,11]. Highly sensitive methods for detection of antibodies against several *P. aeruginosa* antigens may complement the monitoring methods currently used [11]. Positive antibody titer results and culture-negative samples of respiratory secretion should alert health professionals to perform a more thorough search for a probable infection, by repeating the test or by using more sensitive and specific methods. In contrast, increasing antibody levels are associated with a greater likelihood of persistent *P. aeruginosa* chronic infection [9]. Elevated antibody titers at the time of initial OP culture may be a useful tool for CF clinicians and researchers monitoring patients at risk for subsequent infection. However, their use in routine practice remains controversial [9].

Thus, the aim of this systematic review was to collect studies published in the last 40 years addressing the detection of serum antibodies to *P. aeruginosa* and to evaluate its utility for early detection of this bacterium and the diagnostic and prognostic value in CF patients.

2. Methods

Research papers in English, Portuguese, and Spanish in the period from 1973 to 2013 were reviewed. The search for references was made through electronic database exploration (PubMed, Medline, LILACS and SciELO), using the keywords "Cystic Fibrosis", "*Pseudomonas aeruginosa*", "serology", and "serum antibodies", and their correspondent translations in varied combinations, from November to August of 2013. In addition, the references of all papers were consulted in the search of new papers to include.

Then, we began the paper selection process, by reviewing titles and abstracts. The first inclusion criterion was the identification of potentially relevant papers, considering those in which the study assessed the utility of serum antibody detection in the diagnostic routine of pulmonary disease. The recuperation criteria for complete papers were the following types of study: cohort, longitudinal, case–control, descriptive, experimental and cross-sectional, whose results addressed such subject. The selection was based on the limits of the compliance of issues in relation to objectives, excluding those in which, despite appearing in the search results, did not address the issue from the diagnostic point of view of serum antibody detection. We also excluded review articles, studies addressing the immune response to *P. aeruginosa* but not related to CF, or related to CF but without clinical application or applied to the diagnosis and studies not related to the CF pulmonary disease.

3. Data synthesis

3.1. Studies addressed, casuistries and methods used

In the first search, a total of 29 research papers were found, being submitted to a filter process, from which only the papers that could be fully accessed were selected. The review was finished by reading the complete papers and, in the final text, 25 papers were included. The studies were mostly longitudinal [13,14,19,21,28,30,35,37] and experimental [16,18,23,26,32–34], and there were also prospective [12,15,16], case–control [27], cohort [20,23,29] and cross-sectional studies [21,30,36]; all of them were in English (Table 1).

In the last 40 years, a total of 3148 patients were evaluated, aged from 0 to 65 years of age, and seven of the studies did not specify their age range (Table 2). With regard to the diagnostic method (Table 3), the ELISA technique was the most commonly used method (22 studies), followed by CIE (5 studies), Western blot (5 studies), and RIA (one study). Five studies used more than one method. Different antigens were used, being Exotoxin A (ExoA) the most used (13 studies), followed by Elastase (ELA) (10 studies), St-Ag:1–17 (Statens Serum Institute®) (8 studies), Alkaline protease (AP) (8 studies), Lipopolysaccharides (LPS) (3 studies), and other antigens in 8 studies (Table 2). Six studies used the M-15 kit (Mediagnost®) — ExoA, ELA, and AP.

3.2. Diagnostic and prognostic value

The pioneer studies on serological diagnosis of *P. aeruginosa* infection in CF patients date from the 70s by Høiby et al. [12],