Microbial Pathogenesis 125 (2018) 122–128

Contents lists available at ScienceDirect

Microbial Pathogenesis

journal homepage: www.elsevier.com/locate/micpath

The co-colonization prevalence of *Pseudomonas aeruginosa* and *Aspergillus fumigatus* in cystic fibrosis: A systematic review and meta-analysis☆

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ARTICLE INFO

Keywords:
Meta-analysis
Prevalence
Pseudomonas aeruginosa
Aspergillus fumigatus
Cystic fibrosis

ABSTRACT

Purpose: The co-colonization prevalence of *P. aeruginosa* and *A. fumigatus* in cystic fibrosis (CF) has been inconsistently reported. The purpose of this systematic review and meta-analysis was to estimate the overall co-colonization prevalence of *P. aeruginosa* and *A. fumigatus* in CF.

Methods: The Embase, PubMed and Web of Science databases were systematically searched for studies reporting the co-colonization prevalence of *P. aeruginosa* and *A. fumigatus* in CF. The co-colonization prevalence of two pathogenic microorganisms in the individual studies was assessed by calculating the proportion and 95% confidence interval (CI). The random effects model was used to calculate the pooled prevalence. The I^2 test was used to assess statistical heterogeneity. The funnel plot and two statistical methods were used to assess publication bias.

Results: Twenty-three eligible studies were included in this analysis. The pooled co-colonization prevalence of *P. aeruginosa* and *A. fumigatus* in CF patients was 15.8% (95% CI: 9.9–21.8). The co-colonization prevalence of *P. aeruginosa* and *A. fumigatus* chronic colonization was lower than that of intermittent colonization, higher in sputum cultures than in bronchoalveolar lavage (BAL) cultures, and lower in children than in adults. There was a statistically significant difference in co-colonization prevalence among studies from different decades, but the prevalence was similar in different geographical regions and with different study types.

Conclusions: The co-colonization prevalence of *P. aeruginosa* and *A. fumigatus* in the lower respiratory tract of CF patients was high. The anti-infective treatment in exacerbation of CF should be considered to cover the two pathogenic microorganisms simultaneously. Large-scale research is still needed to obtain more accurate co-colonization data.

1. Introduction

Cystic fibrosis (CF) is the most commonly inherited lung disease. It is estimated that more than 70,000 people worldwide suffer from CF [1]. CF is a syndrome that accumulates within multiple organs. Most morbidity and mortality cases are caused by airway infections and their associated inflammation [2]. The transmembrane conductance regulator (CFTR) gene mutation causes dysfunctional or absent CFTR protein, resulting in impaired mucociliary clearance in CF patients. The lung function of CF patients begins to deteriorate at the age of 6 [3].

P. aeruginosa and *A. fumigatus* are common pathogenic microorganisms in lung infections. In CF patients, the isolation rate of these two pathogenic microorganisms is higher. Previous studies have reported that the sputum of CF patients contains both *P. aeruginosa* and *A. fumigatus*, with *A. fumigatus* having been isolated in up to 60% of CF patients who exhibit a *P. aeruginosa* infection and *P. aeruginosa* having been isolated in up to 64.2% of CF patients exhibiting an *A. fumigatus* infection [4–6]. These data suggest a high frequency of *P. aeruginosa* and *A. fumigatus* co-infection in CF patients.

The co-colonization of *P. aeruginosa* and *A. fumigatus* causes worsened disease conditions in CF patients [7–9]. The results from an Irish registry analysis showed that co-colonization with both *P. aeruginosa* and *A. fumigatus* was associated with reduction in FEV1, more frequent hospitalizations, more respiratory exacerbations and higher use of antimicrobials compared to non-coinfected patients [10]. The analysis also showed that the cytotoxic elastase in supernatants from *P. aeruginosa* and *A. fumigatus* co-cultures were higher than that from cultures containing only *P. aeruginosa* [11]. Increased cytotoxic elastase caused

☆ This systematic review and meta-analysis has been registered on PROSPERO under registration number CRD42018089824.

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https://doi.org/10.1016/j.micpath.2018.09.010
Received 27 March 2018; Received in revised form 26 July 2018; Accepted 5 September 2018
Available online 11 September 2018
0882-4010/

damage to human lung epithelial cells, decreased lung function and progression of the disease.

The importance of *P. aeruginosa* and *A. fumigatus* co-infection in the development of CF aroused the attention of many scholars. Many studies investigated co-colonization prevalence of the two pathogenic microorganisms in CF patients. However, there are some differences in the data obtained from the research. At present, there are only a few large-scale clinical investigations and studies. These accurate data of co-colonization prevalence data required further summary and analyses for better accuracy. We have performed a systematic review and meta-analysis and calculated the pooled prevalence of *P. aeruginosa* and *A. fumigatus* in patients with CF. The systematic measurements of the prevalence of these two pathogenic microorganisms from CF patients will show the magnitude of this problem to clinicians and further strengthen the management practices for infection. The purpose of this study is to generate a large database and enhance the sample size to determine the prevalence of *P. aeruginosa* and *A. fumigatus* in CF patients by using a systematic review. These prevalence values can be further used for CF disease burden estimation and can also contribute in estimating the sample size required to explore future epidemiological studies.

2. Methods

2.1. Search strategy

The Embase, PubMed and Web of Science databases were searched for studies published prior to January 2018 using the following free text terms:('*Pseudomonas aeruginosa*' OR '*P. aeruginosa*' OR 'PA') AND ('*Aspergillus fumigatus*' OR '*A. fumigatus*' OR 'AF') AND ('cystic fibrosis' OR 'CF'). We reviewed the references from the primary studies identified from the search, as well as reference lists from editorials and reviews on this topic. There were no language restrictions.

2.2. Inclusion and exclusion criteria

We included studies reporting the co-colonization prevalence of *P. aeruginosa* and *A. fumigatus* in CF. Diagnostic criteria for CF included positive sweat tests and/or molecular genetic identification of two disease-causing CFTR mutations. Colonization is defined as the presence of microorganisms as detected by isolation of the *P. aeruginosa* and *A. fumigatus* in culture. The co-colonization of *P. aeruginosa* and *A. fumigatus* was confirmed by sputum culture or BAL. Chronic colonization was defined as positivity of > 50% of respiratory cultures in a given year [12]. We excluded the following literature: (a) abstracts, editorials, case reports and studies that included fewer than 10 patients; (b) studies describing the co-colonization prevalence of *P. aeruginosa* and *A. fumigatus* in diseases other than CF; (c) studies in which the number of patients with CF screened (i.e., the denominator) was not reported; (d) studies involving lung transplant patients; (e) studies involving patients with acute exacerbation; and (f) studies about patients receiving special treatment (e.g., being treated with antibiotics).

2.3. Data extraction

We compiled a database created from the electronic searches in a reference manager package and eliminated all duplicate citations. The citations were first screened by the authors and then the relevant studies were captured. The full text of each citation was obtained and reviewed in detail. Data were recorded on the standard data extraction sheet. The following items were extracted: (a) details of publication (e.g., authors, title and other citation details including geographical region); (b) age group of the study subjects; (c) type of study (i.e., retrospective or prospective); (d) details of the criteria used for CF diagnosis; (e) methods used for respiratory specimen acquisition or culture; and (f) co-colonization prevalence of *P. aeruginosa* and *A. fumigatus* in CF. Two of our researchers independently screened and extracted the same data. Any contradictions that arose between these researchers' findings were resolved by consensus.

2.4. Meta-analysis

All statistical analyses were performed by a statistical software package (STATA, version 14.0). The prevalence was assessed by calculating the proportion with 95% CI for each study, and then, the summary proportion with 95% CI was derived by pooling the data. In the presence of significant heterogeneity, DerSimonian weights were used for the random effects model [13]. The I^2 test was used to assess the impact of heterogeneity on the pooled estimates of the individual outcomes in the meta-analysis. Significant heterogeneity was indicated with an I^2 value of more than 50%. The funnel plot and two statistical methods (Egger's and Begg's tests) were used to assess publication bias. Our study did not need institutional review board clearance because it was based on the systematic review and meta-analysis of previously published research.

3. Results

A total of 1710 studies were retrieved in our initial database search, of which 23 were included in the final systematic review and meta-analysis (Fig. 1). A total of 2114 CF patients were investigated for the prevalence of *P. aeruginosa* and *A. fumigatus*. We explored the co-colonization prevalence of *P. aeruginosa* and *A. fumigatus* within the lower respiratory tract of patients with CF, and the articles exploring prevalence of the upper respiratory infection were excluded from our current study. CF patients in these studies were diagnosed by positive sweat tests and/or molecular genetic identification of CFTR mutations.

Most of the studies on the prevalence of co-colonization were conducted after 2000, and there were only 3 studies conducted before 2000. Fifteen studies were from Europe, 4 from the Americas, 3 from Oceania and only 1 from Asia. Eighteen studies obtained data on the prevalence of co-colonization by the result of sputum culture, and 3 studies obtained data based on the results of BAL. In the studies included in this meta-analysis, sputum retention and cultures were conducted according to national recommendations, which reduced the contamination of pathogenic microorganisms in the upper respiratory tract. Doctors instructed patients to provide sputum samples in all studies. At least three sputum samples were taken from each patient, and the results of the three sputum cultures were all positively judged as exhibiting co-colonization of *P. aeruginosa* and A. fumigatus. Six studies explored the co-colonization prevalence in children with CF, 9 studies investigated the prevalence in adults, and 8 studies investigated the prevalence in both children and adults. The prevalence of chronic co-colonization was performed in 5 studies, and the remaining 18 studies explored the prevalence of intermittent co-colonization. Thirteen of the studies were prospective, while 10 were retrospective. The characteristics of these studies and the types of patients are detailed in Table 1.

3.1. The co-colonization prevalence of P. aeruginosa and A. fumigatus in CF patients

The pooled colonization prevalence of *P. aeruginosa* was 48.2% (95% CI: 37.6–58.8), while the pooled colonization prevalence of *A. fumigatus* was 24.1% (95% CI: 17.7–30.4). The pooled co-colonization prevalence of *P. aeruginosa* and *A. fumigatus* was 15.8% (95% CI: 9.9–21.8) with variation ranging between 2.3% and 44.8%. There was statistical heterogeneity (I^2 = 93.5%) (Fig. 2). The statistical heterogeneity was calculated via STATA statistical software. There was significant evidence of publication bias (Egger's test P = 0.012), which was also detectable by visual examination of the funnel plot (Fig. 3). Some points are not within the 95% confidence interval, and the points