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Original Article

Association between *Staphylococcus aureus* alone or combined with *Pseudomonas aeruginosa* and the clinical condition of patients with cystic fibrosis

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Abstract

Background: The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in cystic fibrosis (CF) patients has increased and MRSA seems to be associated with a poorer prognosis. The aim of this study was to assess the prevalence and clinical consequences of MRSA and methicillin-susceptible *Staphylococcus aureus* (MSSA), associated or not associated with *Pseudomonas aeruginosa* (PA).
Methods: In a retrospective study on 419 sputum producer patients (293 adults and 126 children >7 years of age), we recorded patient characteristics, lung function, nutritional status, IV antibiotics and hospitalisations, the presence of SA and/or PA and FEV1 decline over 2 years.
Results: SA was found in 72% of the patients: MSSA in 68.2% of children and 48.8% of adults; MRSA in 17.5% of children and 17.8% of adults. Sixty percent of MRSA patients and 60.4% of MSSA patients also harboured PA. The rate of deterioration of clinical status of the various groups, as assessed from respiratory function, IV antibiotic courses and hospitalisations, increased in the order: no SA/no PA, MSSA alone, MRSA alone, MSSA/PA, MRSA/PA, and PA alone. Nutritional status did not differ between groups. Results were roughly similar for children and adults. The yearly FEV1 decline was significantly higher only for MRSA/PA patients ($p=0.03$) compared to no SA/no PA patients.
Conclusion: Clinical condition of CF patients with MSSA only or MRSA only appeared similar, whereas MRSA/PA patients had more severe respiratory function than MSSA/PA patients. In CF patients, MRSA might be more deleterious than MSSA only when associated with PA.

Keywords: Cystic fibrosis; *Staphylococcus aureus*; MRSA; *Pseudomonas aeruginosa*; Lung function

1. Introduction

Staphylococcus aureus (SA) is one of the bacteria most frequently isolated from the airways of patients with cystic fibrosis (CF) and one of the first microbes to infect the lungs of patients with CF [1–4]. It is the most prevalent pathogen in CF children and adolescents and in many cases is later replaced by

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Pseudomonas aeruginosa (PA). However, still 40% of adults remain infected by SA. The prevalence of methicillin-susceptible *Staphylococcus aureus* (MSSA) has remained stable, whereas methicillin-resistant *Staphylococcus aureus* (MRSA) strains have become more prevalent, reaching 25.7% in US patients in 2010 [5].

Chronic bronchial colonisation by PA in children [6] and adults with CF [7] is associated with a worse prognosis. By contrast, the consequences of SA colonisation on CF outcomes have been controversial [8]. However, several recent studies have suggested that MRSA is associated with increased antibiotic use [9], greater decline in lung function [10] and increased mortality [11]. Very few studies have assessed the clinical impact of SA and PA, each one or together [12], and rarely differentiated between MSSA and MRSA. Nevertheless, Dasenbrook et al. suggested that MRSA when not co-cultured with PA may be associated with worse outcomes [10,11].

The aim of our study was to determine the prevalence and clinical consequences of MSSA and MRSA bronchial colonisation, alone or associated with PA, in a large paediatric and adult CF cohort.

2. Patients and methods

2.1. Patients

We report a retrospective cohort study performed from January 1st, 2005 to December 31st, 2006 at two large CF centres affiliated with Paris Descartes University (Cochin University Hospital for adults and Necker University Hospital for children). This study was conducted in accordance with the Declaration of Helsinki and French law and was approved by the Institutional Review Board for Medical Research (CCTIRS # 08-370).

Criteria for inclusion were diagnosis of CF (positive sweat test and/or two *CFTR* disease-causing mutations), age above 7 years old and capacity of producing sputum. Criteria for non-inclusion were lung transplanted patients, patients younger than 7 years old and patients unable to produce sputum.

2.2. Microbiological methods

Identification of SA was confirmed with the Pastorex Staph-Plus® slide test (Biorad, France) and antimicrobial susceptibility testing was performed by disc diffusion assay on Mueller-Hinton agar plates or by VITEK® 2 (bioMérieux, France) and interpreted according to CSLI and French guidelines [13,14].

2.3. Clinical data

Clinical data were extracted from patient files. Demographic data included sex and age at the beginning of the study. Genotypes were classified according to the probable effect of their mutations on CFTR function [15], regardless of clinical severity as follows: severe genotype (two severe mutations), mild genotype (at least one mild mutation), or undetermined genotype (at least one unidentified mutation and no mild mutation). Patients were classified as having pancreatic insufficiency if faecal elastase was <200 μg/g or faecal fat was >6 g/day. We also collected data about diabetes and liver cirrhosis.

At visits at the beginning of the study (in the beginning of 2005), body mass index (BMI) (weight/height^2) was calculated and pulmonary function tests were performed. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) are expressed as percentages of the predicted value (% pred.). We also recorded data concerning IV antibiotic courses and hospitalisations during the year 2005. This allowed a cross sectional study, looking for differences in clinical variables associated with the presence of MRSA, MSSA or PA colonisation alone, or in combination.

We also computed the yearly change in FEV1 (delta FEV1) as the difference between the value at the index visit and that at the end of each year (from the beginning of 2005 to the end of 2006). We compared the decline in FEV1 over a 2-year period in patients colonised with MRSA or MSSA, alone or in combination with PA to patients not colonised with SA nor PA.

Results of sputum samples were available one year previous the beginning of the study and during the two years of the study. Patients were considered to be chronically colonised with SA or PA when these organisms were detected in at least three sputum samples during the previous year. Patients harbouring both MSSA and MRSA were classified in the MRSA group. MRSA was considered to be persistent if detected in more than one year.

2.4. Statistical analysis

Data are reported as means ± 1 standard deviation or percentages, as appropriate. Baseline characteristics were compared between groups using χ^2 or Fisher's exact tests for categorical variables and analysis of variance or Kruskal–Wallis tests for continuous variables, as appropriate. Variables which were available for each year of the follow-up, whether recorded (colonisation) or computed (delta FEV1 or absolute difference in FEV1), were analysed using linear or logistic regressions as appropriate, and multilevel modelling to account for the clustering effect of subjects (two measures by subject). Linear regression models with delta FEV1 as the outcome variable were adjusted for gender, age at baseline, age at diagnosis of CF, genotype, and pancreatic insufficiency. Residuals were checked for normality and found to be reasonably satisfactory. Statistical analyses were 2-sided and $p<0.05$ was considered to have statistical significance. Since missing data were very few (always $<2\%$) no additional procedure was necessary for correcting their effect on the analysis.

3. Results

3.1. Clinical characteristics of the patients

A total of 419 CF patients were included in the study. Their clinical characteristics at baseline are reported in Table 1. All the adult patients were sputum producers and only 14 lung transplanted adult patients could not be included. Among the children with CF, 72 were not included in the study as they