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

Dominique Hubert\(^a\), Hélène Réglier-Poupet\(^b\), Isabelle Sermet-Gaudelus\(^c\), Agnès Ferroni\(^d\), Muriel Le Bourgeois\(^c\), Pierre-Régis Burgel\(^a\), Raphaël Serreau\(^c\), Daniel Dusser\(^a\), Claire Poyart\(^b\), Joël Coste\(^f\)

\(^a\) Service de Pneumologie, Hôpital Cochin, AP-HP, Paris, France
\(^b\) Service de Microbiologie, Hôpital Cochin, AP-HP, Paris, France
\(^c\) Service de Pédiatrie, Hôpital Necker, AP-HP, Paris, France
\(^d\) Service de Microbiologie, Hôpital Necker, AP-HP, Paris, France
\(^e\) Unité de Recherche Clinique Cochin-Necker, AP-HP, Paris, France
\(^f\) Service de Statistiques Médicales, Hôpital Cochin, AP-HP, Paris, France

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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.

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**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
**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/height²) 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 χ² 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...
were younger than 7 or non-sputum producers. The cohort included 70% adults and 30% children, with a mean age of 23.1 years (range 7–65); 75% of the patients had a severe CFTR genotype with 42% (n = 177) being F508del homozygous. Their mean FEV1 at inclusion was 58.5% of the predicted value. The mean number of IV antibiotic courses per year was 1.5 (range 0–15) and the mean number of hospitalisations per year was 0.3 (range 0–7).

### 3.2. Microbiological characteristics of the patients

Bacteriological analysis of sputum was available for 413 patients at the beginning of the study (Table 2): 72% (299 patients) had SA, MRSA was present in 73 patients (24% of the patients with SA), and the prevalence of MRSA was similar in adults and children; MSSA was more prevalent in children and PA in adults. PA associated with SA was observed in 146 patients, i.e. in 60% of the patients colonised with SA (107 of 177 patients with MSSA and 39 of 65 patients with MRSA). Twenty-three patients harboured both MSSA and MRSA.

A large majority of patients with MRSA (77%) had persistent colonisation with MSSA only, MRSA only, MSSA/PA, MRSA/PA, and was worst in patients with PA alone. The number of IV antibiotic courses per year significantly increased between the groups in the same order. Indeed, no statistically significant difference for any of these clinical variables was observed between patients with MRSA only and patients with MSSA only, as well as between patients with MRSA/PA and PA only. However, patients with MRSA/PA had poorer clinical condition than patients with MRSA only (p = 0.001 for FEV1 and 0.0004 for yearly IV antibiotic courses) or patients with MSSA/PA (p = 0.005 for FEV1 and 0.003 for yearly IV antibiotic courses). Patients with MRSA/PA had more hospitalisations than patients with MRSA only (p < 0.04). No difference was observed between groups for nutritional status.

Results for adults and children were roughly similar (Fig. 1). Children only tended to have less IV antibiotics than adults when they were colonised with SA (especially with MRSA) and/or PA. In adults, FEV1 (% pred.) values were: 74.9 ± 22.6 for the no PA and no SA group, 69.1 ± 24.2 for MSSA alone, 63.2 ± 20.9 for MRSA alone, 55.2 ± 21.8 for MSSA/PA, 44.6 ± 22.3 for MRSA/PA, and 41.7 ± 10.4 for the PA alone group (p < 0.0001 for trend). A similar trend was observed for FEV1 values for children in the different groups: 99.2 ± 15.8 for the no PA and no SA group, 85.2 ± 18.8 for MSSA alone, 93.6 ± 30.5 for MRSA alone, 74.3 ± 22.8 for MSSA/PA, 63.3 ± 25.0 for MRSA/PA, and 60.6 ± 22.4 for PA alone (p < 0.0001).

We also compared the percentage of severe CFTR genotype patients between the different groups of bacterial colonisation; it was 48% in the no SA/no PA group, 68% in the MSSA alone group, 81% in the MRSA alone group, 75% in the MSSA/PA group, 83% in the MRSA/PA group and 82% in the PA alone group. These differences between groups were not statistically significant when the no SA/no PA group was excluded.

The yearly decline in FEV1 was statistically significant only in the MRSA/PA group (Table 4) in comparison with the no SA/no PA patients. Patients infected with MRSA/PA experienced a decline in FEV1 per year of 0.1% more than that of non-colonised patients. Patients with persistent MRSA did not experienced higher decline in FEV1 (p = 0.68).

### 4. Discussion

In our 419 patients with CF, 53.9% had chronic bronchial colonisation with MSSA, 17.4% with MRSA and 66.3% with PA. MSSA was more prevalent in children and PA in adults, and the prevalence of MRSA was similar in adults and children. In France, the prevalence of MRSA increased until the year 2005 (16.2% in the adult population and 11.8% in the paediatric population) [16], corresponding to our study timeframe. Since this peak, the prevalence of MRSA has gradually declined (in 2010, 8% in the whole population, 9.7% in adults and 6% in children) [17]. The increase in the annual prevalence of MRSA has become a matter of concern in the USA, reaching 25.3% in the 2010 CFF Patient Registry [5]. Rates of MRSA are much lower in most European CF centres [1] but have been increasing over the last 10 years in many groups.
There are very few data on the prevalence of associated SA and PA bronchial colonisation, as this information is not available from the publications of national CF registries. Among patients with CF participating in a phase 3 clinical trial of aerosolised tobramycin who had PA at entry, 43.2% were also culture positive for SA [18]; 36 of 191 SA isolates (18.8%) were found to be MRSA. In comparison, in our study which took place 10 years later, 58.6% of the patients with PA also harboured SA (43.0% MSSA and 15.6% MRSA). In an American CF centre, among 82 patients with MRSA between 2005 and 2007, only 12.2% were never colonised by PA [19].

The long-term consequences of infection with SA in CF patients have generally been considered less severe than those of more aggressive pathogens such as PA [12,20–22], but no distinction has been made between MSSA and MRSA. A growing concern has emerged in recent years for CF patients harbouring MRSA, who had lower lung function, higher rates of hospitalisation and antibiotic treatment than patients with MSSA only [9]. In our study, we found that patients with MSSA or MRSA not associated with PA were similar for respiratory function, rate of infection, use of hospitalisation, and antibiotic courses.

Table 3
Clinical characteristics of study cohort according to respiratory colonisation with Staphylococcus aureus and Pseudomonas aeruginosa.
(Authority conducted on 362 patients, excluding those with Achromobacter xylosoxidans, Burkholderia cepacia complex and nontuberculous mycobacteria).

<table>
<thead>
<tr>
<th></th>
<th>No SA/no PA</th>
<th>MSSA alone</th>
<th>MRSA alone</th>
<th>MRSA/PA</th>
<th>MSSA/PA</th>
<th>PA alone</th>
<th>p * value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (percentage)</td>
<td>17 (4.7)</td>
<td>70 (19.3)</td>
<td>26 (7.2)</td>
<td>107 (29.6)</td>
<td>39 (10.8)</td>
<td>103 (28.4)</td>
<td></td>
</tr>
<tr>
<td>Number of adults/children</td>
<td>10/7</td>
<td>35/35</td>
<td>17/9</td>
<td>66/41</td>
<td>29/10</td>
<td>93/10</td>
<td>NS</td>
</tr>
<tr>
<td>Respiratory function and nutritional status b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1, % predicted (mean±SD)</td>
<td>81.9±23.3</td>
<td>76.3±23.2</td>
<td>72.0±27.3</td>
<td>61.9±23.9</td>
<td>49.2±24.1</td>
<td>43.6±20.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FVC, % predicted (mean±SD)</td>
<td>87.8±20.8</td>
<td>83.5±20.5</td>
<td>82.6±21.2</td>
<td>74.0±22.1</td>
<td>63.8±20.7</td>
<td>59.3±22.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI, kg/m² (mean±SD)</td>
<td>20.5±4.6</td>
<td>19.2±3.6</td>
<td>19.3±3.0</td>
<td>18.9±3.0</td>
<td>18.8±2.3</td>
<td>19.1±2.9</td>
<td>NS</td>
</tr>
<tr>
<td>IV antibiotic courses and hospitalisations b</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of antibiotic IV courses/year</td>
<td>0.2±0.6</td>
<td>0.5±1.0</td>
<td>0.8±1.9</td>
<td>1.4±2.3</td>
<td>2.5±2.6</td>
<td>2.3±1.7</td>
<td>&lt;0.0001</td>
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<tr>
<td>(mean±SD)</td>
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</tr>
<tr>
<td>Number of days of antibiotic IV courses/year</td>
<td>3.9±8.9</td>
<td>9.2±22.0</td>
<td>12.5±33.6</td>
<td>23.3±43.1</td>
<td>38.1±42.5</td>
<td>36.4±30.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(mean±SD)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td>Number of hospitalisations/year</td>
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<td>0.2±0.4</td>
<td>0.1±0.3</td>
<td>0.3±0.5</td>
<td>0.8±1.5</td>
<td>0.3±0.6</td>
<td>0.03</td>
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<tr>
<td>(mean±SD)</td>
<td></td>
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<td></td>
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<tr>
<td>Number of days of hospitalisation/year</td>
<td>0.7±1.3</td>
<td>1.1±2.9</td>
<td>1.1±1.5</td>
<td>3.8±10.0</td>
<td>8.6±22.0</td>
<td>3.1±10.3</td>
<td>NS</td>
</tr>
<tr>
<td>(mean±SD)</td>
<td></td>
<td></td>
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</table>

P values for comparisons between groups (post hoc Wilcoxon Rank-Sum test)

<table>
<thead>
<tr>
<th></th>
<th>MRSA vs MSSA</th>
<th>MRSA vs MSSA/PA</th>
<th>MRSA vs PA</th>
<th>MRSA/PA vs PA</th>
<th>MSSA/PA vs PA</th>
<th>MSSA vs PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.0001</td>
<td>0.005</td>
<td>NS</td>
<td>0.0004</td>
</tr>
<tr>
<td>FVC</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.0001</td>
<td>0.02</td>
<td>NS</td>
<td>0.0182</td>
</tr>
<tr>
<td>BMI</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Number of antibiotic IV courses/year</td>
<td>NS</td>
<td>NS</td>
<td>0.0004</td>
<td>&lt;0.0001</td>
<td>NS</td>
<td>0.004</td>
</tr>
<tr>
<td>Number of days of antibiotic IV courses/year</td>
<td>NS</td>
<td>NS</td>
<td>0.0008</td>
<td>&lt;0.0001</td>
<td>NS</td>
<td>0.003</td>
</tr>
<tr>
<td>Number of hospitalisations/year</td>
<td>NS</td>
<td>NS</td>
<td>0.037</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Number of days of hospitalisation/year</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>


* Kruskal–Wallis non-parametric test for comparison of the six groups.

b Values of respiratory function and nutritional status were collected at the beginning of the year 2005; IV antibiotic courses and hospitalisations were collected during the year 2005.
antibiotic courses and hospitalisation. In a single centre study in which MRSA and MSSA patients were matched on PA status, age and gender, nutritional outcomes and FEV1 percent predicted did not differ in patients with MRSA compared to those with MSSA, but patients with chronic MRSA were treated more intensely [19]. In a Belgian retrospective case–control study, the MRSA positive group had more frequent hospitalisations than age- and sex-matched controls chronically colonised with SA [23].

However, our patients with MRSA/PA appeared more severely affected than those with MSSA/PA; they had lower respiratory function (FEV1 49.2% pred. vs 61.9% pred.) and more IV antibiotic courses. Indeed, patients with MRSA/PA were similar to those with PA for respiratory function and rate of antibiotic courses.

In our study, the yearly decline in FEV1 was significantly larger in MRSA/PA patients than in the comparator group with no SA/no PA, but this was not the case for patients with MRSA alone or PA alone. Dasenbrook et al. found that the rate of FEV1 decline was greater in patients with MRSA than in patients who were culture-negative for MRSA [10]; however, the association of MRSA and FEV1 decline was not clinically significant in adults. On another hand, Sawicki et al. showed that patients with MRSA displayed a faster decline in lung function prior to MRSA acquisition and noted that MRSA did not affect lung function decline [24]; this led the authors to suggest that MRSA in CF might reflect, rather than cause, greater disease severity. However, we were not able to demonstrate a higher prevalence of severe CFTR genotypes in patients colonised with

![Fig. 1. Clinical characteristics of adults and children of the study cohort according to respiratory colonisation with Staphylococcus aureus and Pseudomonas aeruginosa. * Interaction (Friedman test) across age subgroups was only significant for the number of IV antibiotic courses/year (p=0.02) and the number of days of IV antibiotic courses/year (p=0.01). Note that black bars represent the same data reported in Table 3.](image-url)

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Yearly decline in FEV1 according to the type of colonisation adjusted for potential confounders a in reference to patients with neither SA nor PA.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression coefficient (%) b</td>
<td>95% CI</td>
</tr>
<tr>
<td>No SA no PA</td>
<td>–</td>
</tr>
<tr>
<td>MSSA alone</td>
<td>–0.08</td>
</tr>
<tr>
<td>MRSA alone</td>
<td>–0.08</td>
</tr>
<tr>
<td>PA alone</td>
<td>–0.07</td>
</tr>
<tr>
<td>PA/MSSA</td>
<td>–0.05</td>
</tr>
<tr>
<td>PA/MRSA</td>
<td>–0.11</td>
</tr>
</tbody>
</table>

SA Staphylococcus aureus
PA Pseudomonas aeruginosa
MSSA methicillin-resistant Staphylococcus aureus
MRSA methicillin-resistant Staphylococcus aureus
PA Pseudomonas aeruginosa

*a Age, sex, age at diagnosis, severe genotype (yes/no), and pancreatic insufficiency (yes/no).

b The regression coefficient represents the change in deltaFEV1 (% pred.) relative to that for subjects with no PA or SA colonisation. The analysis was conducted on 658 patient-years excluding those with Achromobacter xylosoxidans, Burkholderia cepacia complex and nontuberculous mycobacteria infection.
MRSA than in patients colonised with MSSA, alone or combined with PA. Finally, in another single centre study, the FEV1 declines over 2- and 6-year periods were significantly greater in the chronic MRSA group than in the controls; note that these patients were not matched for PA status [23].

In most of the studies assessing the consequences of infection with MRSA and/or MSSA in CF patients, there was no separate analysis of SA-positive patients according to the presence or absence of PA, although PA, as well as *Burkholderia cepacia complex*, was taken into account in multivariate regression models [24], FEV1 decline [10] or estimates of survival [11]. We wanted to test whether, in patients with CF, concurrent colonisation with both SA and PA might have a specific impact. Consequently, we compared patients with SA only and patients with both SA and PA, considering MRSA as well as MSSA. We found that patients with MRSA/PA and PA alone were the most severe cases, according to their respiratory function, need for IV antibiotic courses and hospitalisation. FEV1 and FVC were lower in patients with SA who co-cultured PA than in patients with SA alone, and this was more marked for MRSA-positive patients than MSSA-positive patients. Our MSSA/PA patients were in better clinical condition than PA patients, but this was not true for MRSA/PA patients. The MRSA/PA patients also showed the largest yearly decline in FEV1.

Rosenbluth et al. [25] studied the effects of concurrent infection with both PA and SA (but without differentiating MSSA from MRSA) in a cohort of 153 adults with CF. They showed that such double infections were a significant risk factor for rapidly declining lung function, although infection either with PA or with MRSA was not. In infants and young children, Hudson et al. reported that patients with PA or SA/PA in their sputa had worse lung function than patients with SA alone [26]; although SA alone did not affect survival, patients with SA/PA had a significantly lower 10-year survival rate than those with either SA alone or PA alone. The authors concluded that SA and PA contributed independently and additively to poorer outcomes in CF. This notion is supported by the analysis of bronchoalveolar lavage in infants and young children with CF: subjects infected with SA and PA tend to have more airway inflammation than subjects infected with PA or SA alone [27]. The independent and additive effects described for SA on inflammation support the significance of polymicrobial infection in CF lung disease, but no information was given about MRSA vs MSSA.

Our study is the first to assess the association of combined MSSA/PA or MRSA/PA colonisation and the clinical status of patients with CF including their yearly decline in FEV1. It includes a large cohort of children and adults and differentiates SA between MRSA and MSSA. One limitation of our study is that the data were collected retrospectively. To determine more clearly the impact of MRSA colonisation on lung function, larger prospective longitudinal studies are needed, which investigate possible links between MRSA and PA co-colonisation and clinical outcomes.

In conclusion, the prevalence of MRSA colonisation in our cohort of CF patients was 17% and corresponds to the peak in the prevalence in France. The respiratory function of our patients with MRSA alone was similar to that of children and adults with MSSA alone. The association of PA and SA worsened the respiratory status of the patients, mainly for patients with MRSA/PA. These patients co-colonised with MRSA and PA had the greatest decline in FEV1. Our data suggest that MRSA in patients with CF may be more deleterious than MSSA only when associated with PA.

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Transparency declaration

The authors declare no conflict of interest of any nature.

References


