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Original article

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Achromobacter xylosoxidans airway infection is associated with lung disease severity in children with cystic fibrosis

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Take home message: The prevalence of the opportunistic pathogen *Achromobacter xylosoxidans* increases in patients with cystic fibrosis. This study shows an association between airway infection with this bacterium and a more severe lung disease in children with cystic fibrosis.

Abstract

Background: Despite the increasing prevalence of *Achromobacter xylosoxidans* (*A. xylosoxidans)* lung infection in patients with cystic fibrosis (CF), its clinical pathogenicity remains controversial. The objective of this study was to evaluate the effects of this emerging bacterium on lung disease severity in CF children.

Methods: This case-control retrospective study took place in two French paediatric CF centres. Forty-five cases infected by *A. xylosoxidans* were matched for age, sex, *CFTR* genotypes and pancreatic status, to 45 never infected controls. Clinical data were retrieved from clinical records over the 2 years before and after *A. xylosoxidans* initial infection.

Results: At infection onset, lung function was lower in the cases compared to controls (p=0.006). Over the 2 years prior *A. xylosoxidans* acquisition, compared to controls, cases had more frequent pulmonary exacerbations (P=0.02), hospitalisations (P=0.05), as well as intravenous (P=0.03) and oral (P=0.001) antibiotic courses. In the 2 years following *A. xylosoxidans* infection, the cases remained more severe with more frequent pulmonary exacerbations (P=0.0001), hospitalisations (P=0.0001), as well as intravenous (P=0.0001) and oral antibiotic courses (P=0.0001). Lung function decline tended to be faster in the cases (-5.5 %/year) compared to controls (-0.5 %/year).

Conclusions: This case-control study demonstrates that *A. xylosoxidans* occurs more frequently in the patients with the worse lung disease. Further studies assessing the pathogenicity of this emerging pathogen and international treatment recommendations are warranted.

Introduction

Cystic fibrosis (CF) is a severe autosomal recessive genetic disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene [1]. Lung disease remains the major cause of morbidity and mortality in CF, with progressive decline of the lung function due to excessive airway inflammation associated with recurrent bacterial infections [2, 3]. While *Staphylococcus aureus* and *Haemophilus influenzae* are the most prevalent bacteria in the airways of young patients with CF, *Pseudomonas aeruginosa* (*P. aeruginosa*) predominates in later decades [4, 5]. Other opportunistic pathogens, including *Achromobacter xylosoxidans* (*A. xylosoxidans*), *Burkholderia cepacia* and *Stenotrophomonas maltophilia*, are increasingly detected in patients with CF [4-6].

A. xylosoxidans is a strict aerobic Gram-negative bacillus with broad natural resistance

and frequent acquired resistance to antibiotics [7]. Although prevalence of *A. xylosoxidans* in the CF airways varies worldwide, it has increased over the last few decades. In 2017, the prevalence was recognized to reach 5.8% in the US and 6.7% in France [4, 5]. The pathogenicity of *A. xylosoxidans* lung infection remains controversial [8-14] and there is no international recommendation concerning its management. Indeed, it is actually unclear whether antimicrobial treatments directed against this emerging pathogen alter the severity of CF lung disease [8-11]. Therefore, we conducted a retrospective study to evaluate the effects of *A. xylosoxidans* airway infection on lung disease severity in CF children.

Methods

Patients

This case-control retrospective study took place in two French paediatric CF centres, where 480 patients are registered. The cases were defined as CF patients with at least one positive sputum culture with *A. xylosoxidans* during their clinical follow-up. *A. xylosoxidans* was identified in sputum cultures by MALDI-TOF (matrix-assisted laser desorption-ionization-time-of-flight) mass spectrometry analysis.

These cases were matched for age, sex and *CFTR* genotypes and pancreatic status with CF controls, for whom *A. xylosoxidans* had never been identified. Clinical data were retrieved from electronic patient records, supplemented when necessary with data from paper patient records. The database and data collection were approved by French national data protection authorities (CNIL n°908324 and CCTIRS n°08.015bis) and each patient and/or his legal guardians were informed prior to entering their data into the database.

For each case, the date of initial infection by *A. xylosoxidans* defined time T0. Clinical data were subsequently collected over 2 years before and after T0, defining time T-24, T-12, T+12 and T+24. Lung function was evaluated by measurements of the forced expiratory volume measured in 1 second (FEV_1), expressed as percent-predicted values (FEV_{1pp}) using the Global Lung Function Initiative (GLI) equations [15]. Rates of pulmonary exacerbations, of hospitalisations for pulmonary exacerbations, and of intravenous and oral antibiotic courses were obtained, as well as changes in airway bacterial colonisation.

Statistical analysis

Data were expressed as means ± SD for continuous variables and numbers (%) for categorical variables. The Student's t test was used to compare quantitative data and

Fisher's exact test for categorical data comparisons. The differences were considered significant for P-values less than 0.05.

Results

Case analysis: CF children infected by *A. xylosoxidans*

Among the 480 patients followed in the 2 paediatric CF centres, 45 CF children (28 girls and 17 boys) had been infected by *A. xylosoxidans* at a median age of 11.5 ± 4.9 years old. Eighteen (40 %) patients were homozygotes for the *CFTR* F508del mutation and 42 (93%) were exocrine pancreatic insufficient. None of these patients were under CFTR modulator at the time of the data collection.

Over the 2 years before and after *A. xylosoxidans* initial infection (from T-24 to T24), annual lung function decline reached 2.4 %/year, FEV_{1pp} decreasing from 88 ± 18 % to 78.4 ± 16 % (p=0.04). In comparison with the year before *A. xylosoxidans* infection, during the year after infection, the following rates increased: annual rate of respiratory exacerbations (+1.8/year, p=0.001); hospitalisations (+0.3/year, p=0.006); and oral antibiotic courses (+1.7/year, p=0.001). Although following the same trend, the increase in intra venous antibiotic courses was not significant (+0.4/year, p=0.08).

Case-control comparison analyses

Each of the 45 cases was matched (age, sex, *CFTR* genotypes and pancreatic status) to 45 controls. Similarly to the cases, none of these controls were under CFTR modulator at the time of the data collection. Cases and controls were compared in the 2 years before (**Table 1**) and 2 years after (**Table 2**) *A. xylosoxidans* acquisition. At infection onset, lung function was lower in the cases compared to controls (FEV_{1pp} 81.3 ± 18 % *vs* 94.2 ± 16 % respectively, p=0.006, **Figure 1**).

Over the 2 years prior *A. xylosoxidans* acquisition, the cases had more frequent pulmonary exacerbations (p=0.02), hospitalisations (p=0.05), oral (p=0.001) and intravenous

(p=0.03) antibiotic courses, and were more frequently colonised by *P. aeruginosa* (p=0.0002) (**Table 1**). No difference was observed for colonisation with methicillin-resistant *Staphyloccocus aureus* (MRSA) before *A. xylosoxidans* acquisition.

In the 2 years following *A. xylosoxidans* initial infection, FEV_{1pp} values were systematically lower in the cases compared to controls (FEV_{1pp} 78.4 ± 16 % *vs* 93.2 ± 17 % respectively, p=0.003 after 2 years, **Table 2**). The FEV_{1pp} rate of decline between T-12 and T+12 was faster in the cases, although not significantly (-5.5 %/year in the cases *vs* -0.5 %/ year in the controls, p=0.14, **Figure 1**). The cases remained more severe, with more frequent pulmonary exacerbations (p=0.0001), hospitalisations (p=0.0001), intravenous (p=0.0001) and oral (p=0.0001) antibiotic courses **(Table 2)**. Colonisation with *P. aeruginosa* was more frequent in the cases (incidence 51 % in the cases *vs* 29 % in the controls, p=0.04), as was colonisation with MRSA (incidence 16 % in the cases *vs* 2 % in the controls, p=0.05) **(Table 2).**

Discussion

This case-control study demonstrates that *A. xylosoxidans* occurs more frequently in the patients with the worse lung disease. Indeed, before the initial infection and in comparison with age, sex and *CFTR* mutations matched CF controls, these children had a lower lung function, experienced more frequent respiratory exacerbations and required more frequent hospitalisations and antibiotic courses (oral and intravenous).

We observed a higher prevalence of airway infections by *A. xylosoxidans* than that reported in the registries worldwide [4, 5]. Besides, we found a prevalence of 10.6 % in children with CF, while the French CF Registry reports in 2018 a prevalence of 6.7 % in the overall cohort [5]. Although the prevalence showed in this study is higher than these reported in the French and US registries [4, 5], it is comparable to that found in recent studies realized in France [11], Italy [9], and Spain [10], suggesting a recent increasing prevalence worldwide, or at least in Europe. This increase may also be secondary to the improvement of bacteria detection in CF sputum. Besides, in 1998, Burns et al. used standardized techniques for identification and susceptibility testing of CF specimens, and observed in 595 American CF patients a prevalence of 8.7 % of *A. xylosoxidans* lung infection, whereas the same year the US CF Registry reported a prevalence of only 0.5 % [16]. In this study, *A. xylosoxidans* was identified in sputum cultures by MALDI-TOF mass spectrometry analysis, a method applied routinely in microbiology laboratories since a decade. MALDI-TOF mass spectrometry is recognized to allow identification of rare pathogen in CF, and might be involved in the increasing identification of *A. xylosoxidans* [17].

We observed that the children with CF infected by *A. xylosoxidans* had a more severe lung disease with worse lung function, more frequent respiratory exacerbations,

hospitalisations and antibiotic courses before and after *A. xylosoxidans* acquisition. These results are in accordance to several studies such as De Baets *et al.* in 2007 [8], Recio *et al.* in 2018 [10] and Tetart *et al.* in 2019 [11]. A Brazilian retrospective case-control study also showed that the infected cases were more frequently hospitalised in the 2 years following primary infection with *A. xylosoxidans* compared to non-infected controls [13]. The hypothesis could be that *A. xylosoxidans* acquisition is more frequent in CF patients who already have a severe lung disease, which severity further increases after infection with this deleterious bacterium. This hypothesis is also supported by the more frequent *P. aeruginosa* airway colonisation in the cases, a pathogen well known to be associated with an accelerated lung function decline in CF patients [18]. Tétart *et al.* have underlined that co-isolation of *P. aeruginosa* with *A. xylosoxidans* was associated with a significantly faster annual decrease in FEV_1 compared to patients colonised with *A. xylosoxidans* only [11]. However, it is difficult to differentiate the specific influence of either bacterium, i.e. *A. xylosoxidans* and *P. aeruginosa*, as also highlighted by Hansen et al. [19]. Moreover, this team has shown that chronic pulmonary inflammation, measured by cytokine production, was comparable in patients infected with *A. xylosoxidans* and patients infected with *P. aeruginosa,* underlying the deleterious pathogenicity of this pathogen [19].

These observations show the importance of *A. xylosoxidans* for the patient's prognosis. Besides, a 5-years modelling study showed that each respiratory exacerbation had a detrimental effect on the lung function, equivalent to a loss of 12% of FEV_1 [20]. As such, the increasing frequency of exacerbations observed in our study after *A. xylosoxidans* acquisition is of great importance. In the same way, a Canadian cohort of 1,103 CF patients followed during 18 years observed that patients chronically infected with *Achromobacter spp.* had higher risks of death or transplantation than uninfected patients [14]. In our study,

the FEV_{1pp} of the cases also continued to be lower in the 2 years following the primary infection, compared to that of controls. Nevertheless, the real causal link between the decline in respiratory function and the presence of *A. xylosoxidans* in the airways is difficult to establish. Indeed, in our study, the cases being already more severe before the primary infection, their lung function did not seem to decrease significantly after, compared to that of the controls. Case-control studies have shown that *A. xylosoxidans* infection was associated with a significantly higher FEV_1 annual rate of decline in the 3 years following primary infection [10, 11]. Another Danish study found the same tendency of worsen respiratory function with a faster decline in FEV_1 for patients infected with *A. xylosoxidans*, with high levels of specific anti-*A. xylosoxidans* antibodies [21].

Efficacy of antibiotic treatments for this multi-drug resistant organism is still unclear, and there are no treatment recommendations so far, in particular on the need to systematically prescribe an antibiotic therapy at the time of discovery. According to several studies, the most active antibiotics against *A. xylosoxidans* would be piperacillin-tazobactam, meropenem, and trimethoprim-sulfamethoxazole [22-25]. It was also shown that early treatment with inhaled antibiotics such as ceftazidime, colistin or tobramycin, could prevent or at least postpone chronic *A. xylosoxidans* airway colonisation in patients with CF [24]. However, some studies have underlined high rate of acquired resistance to many of these antibiotics [7, 26]. Thus, management recommendations for this multidrug-resistant organism appear crucial.

Our study has several limitations. First, it is a retrospective study and, despite the rigorous analysis of the medical files, some data were missing that could have resulted in recruitment bias. To limit this bias, we chose to conduct an observational study as well as a case-control analysis to increase the power of the analyses. Moreover, our study only

involved 2 paediatric CF centres, which led to a selection bias with the impossibility of having a very large sample size. There is therefore a risk of loss of statistical power. Nevertheless, we were able to observe significant results.

To conclude, we have shown that *A. xylosoxidans* lung infection is associated with increased lung disease severity in children with CF. While this pathogen was considered as an infrequent bacterium infecting the airways of CF patients until recently, its incidence appears to be increasing. Larger prospective studies assessing the pathogenicity of this emerging pathogen, as well as international treatment recommendations are urgently warranted.

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Conflict of interest

None of the authors have any commercial or other associations that might pose a conflict of interest.

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Tables

Table 1. **Case-control comparison over the two years prior *A. xylosoxidans* initial infection for the cases**

	Cases (n = 45)	**Controls (n = 45)**	**P-value[$]**
FEV_{1pp}, mean (SD)	88.0 (18)	92.7 (17)	0.3
BMI (Z-score), mean (SD)	0.03 (0.9)	-0.03 (0.9)	0.8
Annual rates of respiratory exacerbations, mean (SD)	2.8 (1.7)	2.0 (1.3)	0.02*
Annual rates of hospitalisations, mean (SD)	0.1 (0.4)	0	0.05*
Annual rates of oral antibiotic courses, mean (SD)	3.7 (1.8)	2.4 (1.6)	0.001*
Annual rates of intravenous antibiotic courses, mean (SD)	0.4 (0.9)	0.12 (0.4)	0.03*
P. aeruginosa colonisation, % (n)	64 % (29)	24 % (11)	0.0002*
MRSA colonisation, % (n)	9 % (4)	9 % (4)	0.9

Abbreviations: FEV_{1pp}: forced expiratory volume in one second percent predicted; BMI: body mass index, *P. aeruginosa*: *Pseudomonas aeruginosa*; MRSA: methicillin-resistant S*taphylococcus aureus*.

The data are the means (SD) or % (numbers) over the 2 years prior *A. xylosoxidans* initial infection for the cases (between T-24 and T0). [$]For the comparison of sex, age and *CFTR* genotypes and pancreatic status matched cases and controls. *p<0.05

Table 2. **Case-control comparison over the two years following *A. xylosoxidans* initial infection for the cases**

	Cases (n = 45)	**Controls (n = 45)**	**P-value[$]**
FEV_{1pp}, mean (SD)	78.4 (16)	93.2 (17)	0.003*
BMI (Z-score), mean (SD)	-0.1 (1)	-0.01 (0.8)	0.7
Annual rates of respiratory exacerbations, mean (SD)	4.7 (2.3)	1.9 (1.1)	0.0001*
Annual rates of hospitalisations, mean (SD)	0.5 (0.7)	0 (0.0)	0.0001*
Annual rates of oral antibiotic courses, mean (SD)	5.3 (2.4)	2.2 (1.4)	0.0001*
Annual rates of intravenous antibiotic courses, mean (SD)	1.3 (1.6)	0.2 (0.5)	0.0001*
P. aeruginosa colonisation, % (n)	51 % (23)	29 % (13)	0.04*
MRSA colonisation, % (n)	16 % (7)	2 % (1)	0.05*

Abbreviations: FEV_{1pp}: forced expiratory volume in one second percent predicted; BMI: body mass index, *P. aeruginosa*: *Pseudomonas aeruginosa*; MRSA: methicillin-resistant S*taphylococcus aureus*.

The data are the means (SD) or % (numbers) over the 2 years following *A. xylosoxidans* initial infection for the cases (between T0 and T+24). [$]For the comparison of sex, age, *CFTR* genotypes and pancreatic status matched cases and controls. *p<0.05

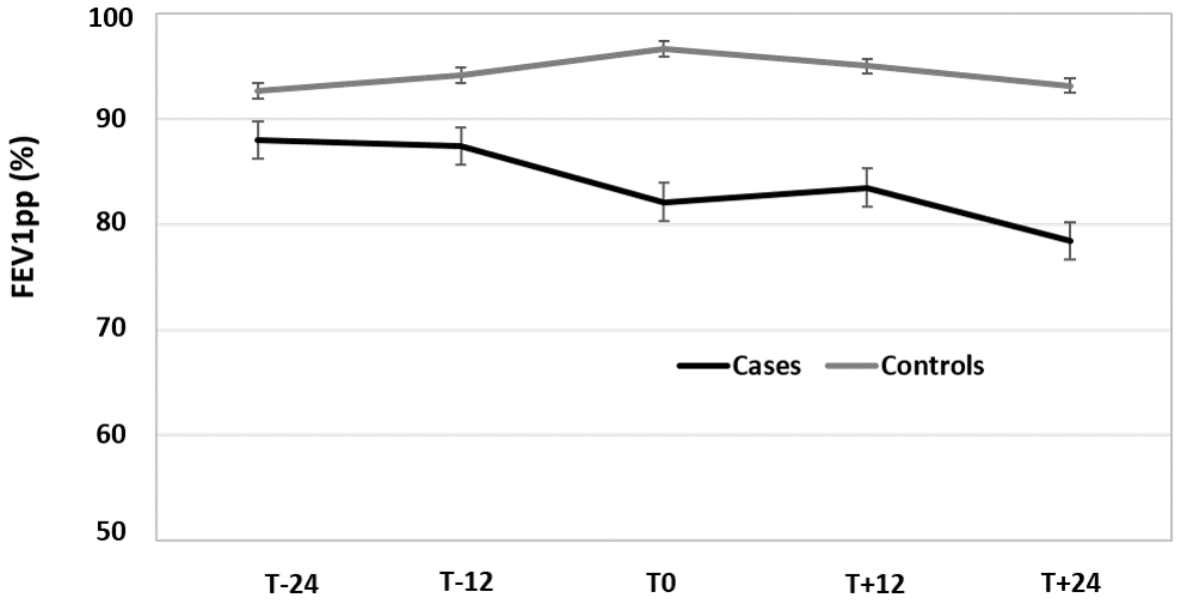

Figure 1. Trajectories of the forced expiratory volume in one second percent predicted (FEV1pp) for the cases (black curve) and the matched controls (grey curve) over 2 years before (T-24) and after (T+24) initial infection by A. xylosoxidans (T0).