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## ► To cite this version:

Charlotte Marsac, Laura Berdah, Guillaume Thouvenin, Isabelle Sermet-Gaudelus, Harriet Corvol. Achromobacter xylosoxidans airway infection is associated with lung disease severity in children with cystic fibrosis. ERJ Open Research, 2021, 7 (2), pp.00076-2021. 10.1183/23120541.00076-2021]. hal-03251638

**HAL Id: hal-03251638**

**<https://hal.sorbonne-universite.fr/hal-03251638>**



Submitted on 7 Jun 2021

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

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## ABSTRACT

**Background:** Despite the increasing prevalence of *Achromobacter 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. 45 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 cases compared with controls ( $p=0.006$ ). Over the 2 years prior to *A. xylosoxidans* acquisition, compared with controls, cases had more frequent pulmonary exacerbations ( $p=0.02$ ), hospitalisations ( $p=0.05$ ), and intravenous ( $p=0.03$ ) and oral ( $p=0.001$ ) antibiotic courses. In the 2 years following *A. xylosoxidans* infection, cases remained more severe with more frequent pulmonary exacerbations ( $p=0.0001$ ), hospitalisations ( $p=0.0001$ ), and intravenous ( $p=0.0001$ ) and oral antibiotic courses ( $p=0.0001$ ). Lung function decline tended to be faster in cases ( $-5.5\%$  per year) compared with controls ( $-0.5\%$  per 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.



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The prevalence of the opportunistic pathogen *Achromobacter xylosoxidans* increases in patients with CF. This study shows an association between airway infection with this bacterium and more severe lung disease in children with CF. <https://bit.ly/3a7ioSi>

**Cite this article as:** Marsac C, Berdah L, Thouvenin G, et al. *Achromobacter xylosoxidans* airway infection is associated with lung disease severity in children with cystic fibrosis. *ERJ Open Res* 2021; 7: 00076-2021 [<https://doi.org/10.1183/23120541.00076-2021>].



## Introduction

Cystic fibrosis (CF) is a severe autosomal recessive genetic disease caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene [1]. Lung disease remains the major cause of morbidity and mortality in CF, with progressive decline of 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* predominates in later decades [4, 5]. Other opportunistic pathogens, including *Achromobacter 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 recognised to reach 5.8% in the USA 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 were registered: Hôpital Trousseau and Hôpital Necker Enfants Malades (Paris, France). 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/ionisation time-of-flight) mass spectrometry analysis.

These cases were matched for age, sex, *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 the French national data protection authorities (CNIL 908324 and CCTIRS 08.015bis) and each patient and/or their 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 forced expiratory volume in 1 s (FEV<sub>1</sub>), expressed as percent predicted values using the Global Lung Function Initiative 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 mean±SD for continuous variables and number (percentage) for categorical variables. The *t*-test was used to compare quantitative data and Fisher's exact test was used for categorical data comparisons. The differences were considered significant for *p*-values <0.05.

## Results

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

Among the 480 patients followed in the two 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. 18 (40%) patients were homozygous for the *CFTR* F508del mutation and 42 (93%) were exocrine pancreatic insufficient. None of these patients were under a *CFTR* modulator at the time of data collection.

Over the 2 years before and after *A. xylosoxidans* initial infection (from T–24 to T+24), annual lung function decline reached 2.4% per year, with FEV<sub>1</sub> % pred 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 per year; *p*=0.001), hospitalisations (+0.3 per year; *p*=0.006) and oral antibiotic courses (+1.7 per year; *p*=0.001). Although following the same trend, the increase in intravenous antibiotic courses was not significant (+0.4 per 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. Similar to the cases, none of these controls were under a *CFTR* modulator at the time of data collection. Cases and controls were compared in the 2 years before (table 1) and 2 years after (table 2) *A. xylosoxidans*

TABLE 1 Case-control comparison over the 2 years prior to *Achromobacter xylosoxidans* initial infection

	Cases	Controls	p-value <sup>#</sup>
<b>Subjects</b>	45	45	
<b>FEV<sub>1</sub> % pred</b>	88.0±18	92.7±17	0.3
<b>BMI z-score</b>	0.03±0.9	-0.03±0.9	0.8
<b>Annual rate of respiratory exacerbations</b>	2.8±1.7	2.0±1.3	0.02*
<b>Annual rate of hospitalisations</b>	0.1±0.4	0	0.05*
<b>Annual rate of oral antibiotic courses</b>	3.7±1.8	2.4±1.6	0.001*
<b>Annual rate of intravenous antibiotic courses</b>	0.4±0.9	0.12±0.4	0.03*
<b><i>Pseudomonas aeruginosa</i> colonisation</b>	64 [29]	24 [11]	0.0002*
<b>MRSA colonisation</b>	9 [4]	9 [4]	0.9

Data are presented as mean±SD or % (n) over the 2 years prior to *A. xylosoxidans* initial infection for the cases (between T-24 and T0). FEV<sub>1</sub>: forced expiratory volume in 1 s; BMI: body mass index; MRSA: methicillin-resistant *Staphylococcus aureus*. <sup>#</sup>: for the comparison of sex, age, *CFTR* genotypes and pancreatic status matched cases and controls. \*: p<0.05.

acquisition. At infection onset, lung function was lower in cases compared with controls (FEV<sub>1</sub> % pred 81.3±18% versus 94.2±16%, respectively; p=0.006) (figure 1).

Over the 2 years prior to *A. xylosoxidans* acquisition, the cases had more frequent pulmonary exacerbations (p=0.02), hospitalisations (p=0.05), and 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 *S. aureus* (MRSA) before *A. xylosoxidans* acquisition.

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

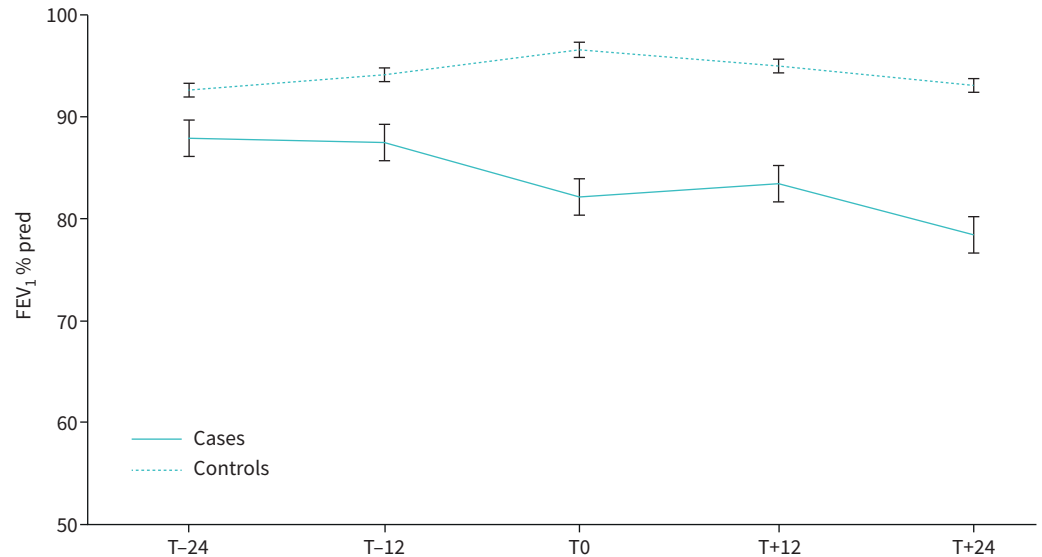
## Discussion

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 CF controls matched on age, sex and *CFTR* mutations, these children had a lower lung function, experienced more frequent

TABLE 2 Case-control comparison over the 2 years following *Achromobacter xylosoxidans* initial infection

	Cases	Controls	p-value <sup>#</sup>
<b>Subjects</b>	45	45	
<b>FEV<sub>1</sub> % pred</b>	78.4±16	93.2±17	0.003*
<b>BMI z-score</b>	-0.1±1	-0.01±0.8	0.7
<b>Annual rate of respiratory exacerbations</b>	4.7±2.3	1.9±1.1	0.0001*
<b>Annual rate of hospitalisations</b>	0.5±0.7	0	0.0001*
<b>Annual rate of oral antibiotic courses</b>	5.3±2.4	2.2±1.4	0.0001*
<b>Annual rate of intravenous antibiotic courses</b>	1.3±1.6	0.2±0.5	0.0001*
<b><i>Pseudomonas aeruginosa</i> colonisation</b>	51 [23]	29 [13]	0.04*
<b>MRSA colonisation</b>	16 [7]	2 [1]	0.05*

Data are presented as mean±SD or % (n) over the 2 years following *A. xylosoxidans* initial infection for the cases (between T0 and T+24). FEV<sub>1</sub>: forced expiratory volume in 1 s; BMI: body mass index; MRSA: methicillin-resistant *Staphylococcus aureus*. <sup>#</sup>: for the comparison of sex, age, *CFTR* genotypes and pancreatic status matched cases and controls. \*: p<0.05.



**FIGURE 1** Trajectories of forced expiratory volume in 1 s (FEV<sub>1</sub>) for cases and matched controls over 2 years before (T-24) and after (T+24) initial infection by *Achromobacter xylosoxidans* (T0).

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]. We also found a prevalence of 10.6% in children with CF, whereas the French CF Registry reported a prevalence of 6.7% in the overall cohort in 2018 [5]. Although the prevalence shown in this study is higher than those reported in the French and US CF registries [4, 5], it is comparable to that found in recent studies realised 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. In 1998, BURNS *et al.* [16] used standardised techniques for identification and susceptibility testing of CF specimens, and observed a prevalence of 8.7% of *A. xylosoxidans* lung infection in 595 American CF patients, whereas in the same year the US CF Registry reported a prevalence of only 0.5%. In our study, *A. xylosoxidans* was identified in sputum cultures by MALDI-TOF mass spectrometry analysis, a method applied routinely in microbiology laboratories for a decade. MALDI-TOF mass spectrometry is recognised to allow identification of rare pathogens 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, and more frequent respiratory exacerbations, hospitalisations and antibiotic courses before and after *A. xylosoxidans* acquisition. These results are in accordance with several other studies, such as DE BAETS *et al.* [8] in 2007, RECIO *et al.* [10] in 2018 and TETART *et al.* [11] in 2019. A Brazilian retrospective case-control study also showed that infected cases were more frequently hospitalised in the 2 years following primary infection with *A. xylosoxidans* compared with non-infected controls [13]. The hypothesis could be that *A. xylosoxidans* acquisition is more frequent in CF patients who already have severe lung disease, the severity of which further increases after infection with this deleterious bacterium. This hypothesis is also supported by the more frequent *P. aeruginosa* airway colonisation in cases; *P. aeruginosa* is well known to be associated with accelerated lung function decline in CF patients [18]. TETART *et al.* [11] underlined that co-isolation of *P. aeruginosa* with *A. xylosoxidans* is associated with a significantly faster annual decrease in FEV<sub>1</sub> compared with patients colonised with *A. xylosoxidans* only. 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, HANSEN *et al.* [19] showed 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.

These observations show the importance of *A. xylosoxidans* for the patient's prognosis. A 5-year modelling study has shown that each respiratory exacerbation had a detrimental effect on lung function, equivalent to a loss of 12% of FEV<sub>1</sub> [20]. As such, the increasing frequency of exacerbations observed in our study after *A. xylosoxidans* acquisition is of great importance. In the same way, in a Canadian cohort of 1103 CF

patients followed during 18 years it was observed that patients chronically infected with *Achromobacter* spp. had higher risk of death or transplantation than uninfected patients [14]. In our study, FEV<sub>1</sub> % pred of cases also continued to be lower in the 2 years following the primary infection, compared with 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, with the cases being already more severe before the primary infection, their lung function did not seem to decrease significantly after, compared with that of controls. Case-control studies have shown that *A. xylosoxidans* infection was associated with a significantly higher FEV<sub>1</sub> annual rate of decline in the 3 years following primary infection [10, 11]. Another Danish study found the same tendency of worsened respiratory function with a faster decline in FEV<sub>1</sub> for patients infected with *A. xylosoxidans*, with high levels of specific anti-*A. xylosoxidans* antibodies [21].

Efficacy of antibiotic treatments for this multidrug-resistant organism is still unclear and there are no treatment recommendations so far, in particular on the need to systematically prescribe 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 a 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 two 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.

**Acknowledgements:** The authors would like to thank Thibaut Degorre (Institut Mines-Télécom Lille Douai, University of Lille, France) for his help in the realisation of the statistical analyses, and the nurses from the Trousseau and Necker Paediatric CF Centres for their help with data collection.

**Author contributions:** H. Corvol and C. Marsac conceptualised and designed the study, collected the data, drafted the initial manuscript, and reviewed and revised the manuscript. L. Berdah, G. Thouvenin and I. Sermet-Gaudelus participated in the study conceptualisation and data collection, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

**Conflict of interest:** None declared.

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