**Achromobacter xylosoxidans** in cystic fibrosis:
Prevalence and clinical relevance

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**Abstract**

**Background:** *Achromobacter xylosoxidans* is increasingly cultured in sputum from cystic fibrosis (CF) patients; nevertheless, there are few published data on the clinical impact of this infection or chronic colonisation.

**Methods:** Relying on DNA fingerprinting techniques we studied the prevalence of *A. xylosoxidans* in our CF population. In a retrospective case control study the clinical status of patients with at least 3 sputum cultures positive for *A. xylosoxidans* over at least 9 months, at the moment of the first positive culture and during the period of colonisation were compared to age (±1 year), gender and to *Pseudomonas aeruginosa* colonisation controlled CF patients who had never *A. xylosoxidans* positive sputum cultures.

**Results:** The prevalence of patients with at least one positive *A. xylosoxidans* culture was 17.9%. 5.3% of the patients fulfilled the criteria of our definition of colonisation.

Colonised patients had a median age of 20 years (range 11–27 years) and a mean colonisation period of 1.5 (±0.9) years.

At the moment of the first positive culture we found significantly lower Bhalla scores on HRCT scans of the lungs (11±3 versus 16±3, p<0.002), lower Brasfield chest X-ray scores (14±3 versus 18±3, p<0.019), lower FVC values (70%±22 versus 94%±12, p<0.017) and lower FEV₁ values (55%±32 versus 78%±23, p=0.123), although the latter did not reach significance. There was no significant difference in body mass index (BMI) (18.7±3 kg/m² versus 19.6±3 kg/m², p=0.8).

Over the study period *A. xylosoxidans*-colonised patients did have more need for intravenous antibiotic treatment courses (19 versus 5, p<0.001); nevertheless, there was no significant difference in lung function decline over the study period (FVC: −6.25±12.34% versus −5.62±8.30%, p=0.77, FEV₁: −5.62±8.30% versus −1.87±11.58%, p<0.47).

**Conclusions:** The prevalence of *A. xylosoxidans* infection or colonisation is probably underestimated. Colonised patients are mostly older, with more pronounced lung damage and lower lung function values. Although there was more need for intravenous antibiotic treatment courses, no faster decline in lung function was observed in *A. xylosoxidans* positive patients.

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**Keywords:** Cystic fibrosis; *Achromobacter xylosoxidans*; *Pseudomonas aeruginosa*; Lung function; Morbidity

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**1. Introduction**

Although *Pseudomonas aeruginosa* is the main Gram-negative pathogen found in the sputum of cystic fibrosis (CF) patients, recently other Gram-negative bacilli emerge. Among these emerging pathogens has been *Achromobacter xylosoxidans*. The clinical significance of this micro-organism is unclear and there is limited evidence to direct treatment.

*A. xylosoxidans* is increasingly cultured in CF sputum; nevertheless, there are few published data on the clinical impact of this infection or chronic colonisation.

In a group of 557 CF patients, Tan et al. [1] reported a prevalence of 2.3%, considering patients with at least three positive cultures over a period of 6 months. In a prospective multi-centre German study Steinkamp et al. [2] reported a prevalence of 1.1% among 1419 CF patients. In the Belgian CF Register 2002 [3], gathering 826 patients, a prevalence of...
1.9% is mentioned, collecting all patients with at least one positive culture over the year 2002. The U.S. Cystic Fibrosis Foundation’s National Patient Registry, however, reported over the last 10 years an increase in prevalence of patients harbouring *A. xylosoxidans*: 0.5%, 1.9%, 2.7%, 3.8% and 5.2% in 1995, 1996, 1997, 1999 and 2002, respectively [4].

In order to study the relative risk of cross infection of *P. aeruginosa* in our CF population DNA fingerprinting techniques were carried out on multiple *Pseudomonas* and/or Gram-negative non-fermenting bacilli.

Relying on these DNA techniques we studied the prevalence of *A. xylosoxidans* in our CF population. We evaluated the clinical history of CF patients with at least 3 positive sputum cultures for *A. xylosoxidans* over at least 9 months. In a retrospective case control study we evaluated the clinical status of the patients at the moment of the first positive culture and during the period of colonisation.

2. Materials and methods

*A. xylosoxidans* is a motile Gram-negative, oxidase-positive rod. The morphology of *A. xylosoxidans* colonies is not that different from that of *P. aeruginosa* colonies.

In our CF centre, taking care of 140 CF patients, *P. aeruginosa* strains and strains of morphologically different looking Gram-negative, non-fermenting bacilli were sent to the DNA laboratory for further identification using DNA fingerprinting techniques.

2.1. Isolation and identification

Lactose negative colonies on McConkey agar were isolated on Mueller Hinton Agar containing 5% sheep blood, and subsequently tested for oxidase activity. Oxidase positive isolates were further identified using tDNA-PCR in combination with fluorescent capillary electrophoresis [5]. This approach enables us to distinguish between Gram-negative non-fermenters like *P. aeruginosa*, *Burkholderia* species and *Achromobacter* species (unpublished data), by comparing the tDNA-PCR fingerprints of unknowns with those of reference strains in a library (available at http://usersallserv.ugent.be/~mvaneech/LBR.html). Identification of isolates as *A. xylosoxidans* was confirmed by using API20 NE (bioMérieux, Marcy l’Etoile, France).

2.2. Patients

A retrospective case control study design was used. In our CF centre each patient is seen on a three monthly basis, when a clinical history is taken, a sputum culture and a lung function measurement are done. In young children or none sputum producers, a pharyngeal swab alternating with a nasopharyngeal aspirate is taken. Patients with at least 3 positive cultures for *A. xylosoxidans* over at least 9 months were compared to subjects who had never grown *A. xylosoxidans*, matched for age (±1 year), gender and *P. aeruginosa* colonisation. Our CF group of 140 patients did not allow to match each colonized patient with 2 control patients, unless we enlarged the age limits to ±2 years which would have weakened our findings because of the large age range (4 years). Comparison was done for chest X-rays and high-resolution CT scans, relying on the Brasfield [6] and Bhalla [7] scores, respectively. Lung function measurements, forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) and body mass index (BMI, kg/m²) were compared. Over the study period the need for intravenous antibiotic courses and the decline in lung function were evaluated.

Data were compared for the period from the first positive culture for *A. xylosoxidans* until 31 December 2004, giving a mean colonisation period of 1.5 (±0.9) years.

Respiratory function tests were performed on a Masterlab® (Jaeger®).

Respiratory infections in *P. aeruginosa* colonised patients are treated for 2–3 weeks with intravenous antibiotics: an aminoglycoside and a betalactam penicillin. When there was coexistent *A. xylosoxidans* infection antibiotics were chosen, where possible, according to their in vitro activity against both micro-organisms. Elective three monthly intravenous antibiotic treatment policy for chronic *P. aeruginosa* infection is not practised in our CF clinic. Symptomatic patients with positive sputum cultures only for *A. xylosoxidans* were treated, relying to severity, with two intravenous antibiotics chosen according to in vitro sensitivity or with an oral antibiotic (cotrimoxazol or tetracycline) for 2–3 weeks.

Statistical analysis was done using the chi-square test and the unpaired Student’s *t*-test for normally distributed data.

3. Results

17.9% of our patient population did have at least one positive culture for *A. xylosoxidans*.

According to our criteria, the prevalence of *A. xylosoxidans* colonisation in our CF-centre was 5.3%. All patients remained colonised with *A. xylosoxidans* throughout the study period.

Eight patients out of 140 at our CF centre were found to be colonised by *A. xylosoxidans*. They had a median age of 20 years (range 11–27 years) and a mean colonisation period of 1.5 (±0.9) years. They were compared to 8 control CF patients, who have never grown *A. xylosoxidans*, matched for age (±1 year), gender and *P. aeruginosa* colonisation.

Seven patients were co-colonised with *P. Aeruginosa*, four by *Staphylococcus aureus* and *Stenotrophomonas maltophilia* was cultured intermittently in 2 patients.

At the moment of the first positive culture we found significantly lower Bhalla-scores on HRCT scans of the lungs (11±3 versus 16±3, *p*<0.002), lower Brasfield chest X-ray scores (14±3 versus 18±3, *p<0.019), lower FVC values (70±22% versus 94±12%, *p<0.017) and lower FEV1 values (55±32% versus 78±23%, *p=0.123*), although the latter did not reach significance. There was no significant
difference in BMI (18.7 kg/m² ± 3 versus 19.6 kg/m² ± 3, p = 0.8) (Table 1).

Over the study period, A. xylosoxidans-colonised patients needed more intravenous antibiotic treatment courses (19 versus 5, p < 0.001); nevertheless, there was no significant difference in lung function decline over the study period (FVC: −6.25 ± 12.34% versus −5.62 ± 8.30%, p = 0.77, FEV₁: −5.62 ± 8.30% versus −1.87 ± 11.58%, p < 0.47) (Table 2).

4. Discussion

17.9% of our patient population did have at least one positive culture for A. xylosoxidans. The prevalence in our centre was significantly higher than that reported in the literature [1–4]. However, the prevalence measured in our population is cumulative and not annual; moreover, because of an ongoing National Pseudomonas study we relied on DNA fingerprinting techniques for species identification. Indeed, some of the isolates, identified genotypically as A. xylosoxidans, were initially considered as atypical P. aeruginosa in our routine laboratory, using standard phenotypic identification. It is well known that, due to the diversity of colony morphology and biochemical reactivity, misidentification of Gram-negative non-fermenters cultured from CF sputum may occur. In one study, misidentification of 11% of A. xylosoxidans strains was reported [8].

The morphology of Achromobacter colonies is not that different from the appearance of P. aeruginosa colonies. In the routine laboratory where specific mediums or DNA techniques are not available, the true prevalence is probably underestimated.

The prevalence of A. xylosoxidans colonisation in our CF-centre was 5.3%.

This is comparable with the findings of Burns et al. [9] who found as part of the pre-enrolment visits for a study on the use of the aerosolised tobramycine, over a period of 6 months, a positive culture for A. xylosoxidans on three different occasions in 7% of the 427 screened patients.

As no consensus definition of colonisation is available, we are aware that our definition of colonisation is debatable.

At the moment of the first positive culture we found significantly lower Bhalla scores on HRCT scans of the lungs, lower Brasfield chest X-ray scores, lower FVC values and lower FEV₁ values, although the latter did not reach significance. There was no significant difference in BMI. These findings suggest that particularly patients with more lung damage are prone to infection or colonisation with A. xylosoxidans. This could explain the older age at which a first infection is found.

Tan et al. [1] studied 13 patients colonized with A. xylosoxidans, with a median age of 17.2 years (range 6.5–32.8). They were compared to 26 control CF-patients matched for gender, age (±2 years), body weight (±10%), FEV₁ (±10%) and bacterial colonisation. Over a period of 4 years they did not find either a significant difference in decrease of lung function parameters, neither significant differences in the use of antibiotics, inhaled antibiotics or oral or inhaled corticosteroids.

As in their study patients were matched for FEV₁, Tan et al. [1] did not look for lung function differences; unfortunately, they neither evaluated HRCT-scan scores, although discrepancy between lung function measurements and morphologic damage, evaluated by HRCT scan scores has been reported [10]. Because they had the opportunity to study a large group of patients, their study would probably have been more informative if they had included all age-matched controls irrespective of their FEV₁.

We chose in our case control study not to stratify for lung function.

This study has the weaknesses of all case control studies. If one matches the control group for lung function, no conclusions can be made for this parameter as a possible determinant for A. xylosoxidans colonisation.

Ideally each colonised patient should be compared with as many controls, matched for age, gender and P. aeruginosa colonisation as possible, regardless of their lung function. This would strengthen the findings concerning the possible role of lung destruction as a permissive factor for colonisation and the decline in lung function after colonisation.

A prospective study would of course be more informative; however, it is difficult to predict who will remain culture positive and negative over a certain period, and therefore, large numbers of patients would be required.

Over the study period, A. xylosoxidans-colonised patients needed more intravenous antibiotic treatment courses. This finding is not confirmed by the study of Tan et al. [1]. Since in their CF centre patients with chronic P. aeruginosa infection received elective three monthly intravenous antibiotic treatment courses, differences between both groups possibly have been attenuated. Whether the higher need for IV antibiotics, as observed in our study, depends on

Table 1
Comparison of morphologic and functional parameters at the moment of the first isolation of A. xylosoxidans (mean ± standard deviation)

<table>
<thead>
<tr>
<th></th>
<th>A. xylosoxidans +</th>
<th>A. xylosoxidans −</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>BHALLA scores</td>
<td>11 ± 3</td>
<td>16 ± 3</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Brasfield scores</td>
<td>14 ± 3</td>
<td>18 ± 3</td>
<td>&lt;0.019</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>70 ± 22</td>
<td>94 ± 12</td>
<td>&lt;0.017</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>55 ± 32</td>
<td>78 ± 23</td>
<td>0.139</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>18.7 ± 3</td>
<td>19.6 ± 3</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Table 2
The number of IV AB treatment courses and decline in lung function parameters (mean ± standard deviation) over the study period (1.5 ± 0.9 years)

<table>
<thead>
<tr>
<th></th>
<th>A. xylosoxidans +</th>
<th>A. xylosoxidans −</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV AB treatment courses</td>
<td>19</td>
<td>5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lung function decline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>6.25 ± 12.34</td>
<td>4.5 ± 11.9</td>
<td>=0.77</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>5.62 ± 8.30</td>
<td>1.87 ± 11.58</td>
<td>=0.47</td>
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</table>
the colonisation by A. xylosoxidans or on the more pronounced lung damage remains an unanswered question.

Although there seems to be a tendency, there was no significant difference in lung function decline over the study period. Probably such differences may become evident after a longer follow-up period in a larger group of patients. Until now, a low transmissibility of A. xylosoxidans was reported. However, recently we reported [11] that out of 13 patients colonised with A. xylosoxidans, staying in a CF-revalidation centre, 9 patients shared one genotype, three shared another genotype and one patient had both genotypes, suggestive for patient-to-patient spread. According Kanellopoulou et al. [12] reported 9 colonised patients, 5 of them sharing the same genotype.

Considering the results of Tan et al. [1], who could not detect a need for more intravenous antibiotic treatment courses in A. xylosoxidans-colonised patients and our finding that colonised patients have more damaged lungs, it is tempting to hypothesize that A. xylosoxidans is a coloniser of more damaged lungs rather than a destructive infectious organism; however, it is obvious that more, especially prospective, studies on the clinical relevance of A. xylosoxidans infection or colonisation are warranted.

5. Conclusions

Relying on routine laboratory analysis, the prevalence of A. xylosoxidans infection or colonisation is probably underestimated. Mostly older patients, with more pronounced lung damage and lower lung function values have positive cultures. Data on the post-acquisition morbidity showed a higher need for intravenous antibiotic treatment courses. No significantly faster decline in lung function was observed in A. xylosoxidans positive patients; however, observations were done retrospectively in a small number of patients over a short period; therefore, one should be cautious interpreting these results. In view of the possibility of patient to patient spread further longitudinal studies are warranted to elucidate the clinical impact of A. xylosoxidans infection in CF patients.

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References