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Original article

Achromobacter xylosoxidans infection in an adult cystic fibrosis unit in Madrid

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ABSTRACT

Background: *Achromobacter xylosoxidans* is an emerging pathogen in cystic fibrosis (CF). Although the rate of colonization by this microorganism is variable, prevalence is increasing in CF units.
Methods: A microbiological/clinical study was conducted on of adult CF patients harboring *A. xylosoxidans*. Identification and susceptibility testing were performed using MicroScan (Siemens). Decline in lung function was assessed using the variable, annual percentage loss of FEV1 (forced expiratory volume in 1 s).
Results: *A. xylosoxidans* was isolated in 18 (19.8%) of 91 patients over a 14-year period. Mean age was 26.6 years (18–39 years). Nine patients (9.8%) were chronically colonized. Piperacillin/tazobactam and imipenem were the most active antibiotics. Mean annual decline in lung function in chronically colonized patients was 2.49%.
Conclusions: *A. xylosoxidans* is a major pathogen in CF. A decreased lung function was observed among patients who were chronically colonized by *A. xylosoxidans*. Antibiotic therapy should be started early in order to prevent chronic colonization by this microorganism.

Infección por *Achromobacter xylosoxidans* en una unidad adulta de fibrosis quística en Madrid

Palabras clave:
Achromobacter xylosoxidans
Fibrosis quística
Función pulmonar

RESUMEN

Introducción: *Achromobacter xylosoxidans* es un patógeno emergente en fibrosis quística (FQ). Aunque la tasa de colonización por este microorganismo es variable, la prevalencia está aumentando en las unidades de FQ.
Métodos: Llevamos a cabo un estudio clínico-microbiológico de los pacientes adultos con FQ portadores de *A. xylosoxidans*. La identificación y sensibilidad fueron realizadas usando MicroScan (Siemens). La pérdida de función pulmonar fue evaluada por la variable porcentaje anual de perdida de FEV1.
Resultados: *A. xylosoxidans* fue aislado en 18 (19.8%) de 91 pacientes, en un periodo de 14 años. La edad media fue 26.6 años (18-39 años). Nueve pacientes (9.8%) presentaban colonización crónica. Piperacilina/tazobactam e imipenem fueron los antibióticos más activos. La media anual de pérdida de función pulmonar en los pacientes colonizados de forma crónica fue 2.6%.
Conclusiones: *A. xylosoxidans* es un importante patógeno en FQ. Observamos pérdida de la función pulmonar en los pacientes colonizados de forma crónica por *A. xylosoxidans*. El tratamiento antibiótico debe iniciarse lo más rápido posible para prevenir la colonización crónica por este microorganismo.

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Introduction

Cystic fibrosis (CF) is the most frequent fatal genetic disorder in Caucasians. The main cause of morbidity and mortality in patients with CF is chronic lung infection by *Pseudomonas aeruginosa*.[1] Other respiratory pathogens that can cause lung infection in CF patients include *Staphylococcus aureus* and *Haemophilus influenzae* in infants and children and *Burkholderia cepacia* complex, *Achromobacter xylosoxidans*, *Stenotrophomonas maltophilia*, and non-tuberculous mycobacteria in adults.

A. xylosoxidans is an aerobic, non-fermenting, motile, Gram-negative rod that was previously known as *Alcaligenes xylosoxidans*. Since this entity is frequently misidentified as *P. aeruginosa*, its prevalence is likely to be underestimated in CF patients with lung colonization/infection.[2–4] *A. xylosoxidans* is widely distributed in the environment[5,6] and has been isolated from a wide variety of clinical samples such as blood, vascular catheters, cerebrospinal fluid, sputum, and wounds.[7,8]

According to the U.S. Cystic Fibrosis Foundation National Patient Registry, the prevalence of patients harboring *A. xylosoxidans* has increased over the last few years from 0.5% in 1995 to 6.2% in 2011.[9]

The higher prevalence of *A. xylosoxidans* in the lungs of CF patients could be the result of an increase in patient life expectancy.[10–12] In addition, the microbiological techniques used to identify *A. xylosoxidans* and other emerging Gram-negative pathogens in the lungs of CF patients have improved.[4,11]

The clinical significance of *A. xylosoxidans* in the sputum of CF patients and the role of the microorganism in declining lung function in this group remain unclear.[13] There are few published data on the clinical impact of *A. xylosoxidans* infection. Colonization has been associated with exacerbation of pulmonary symptoms,[14] and strains are often highly resistant to many of the antibiotics commonly used to treat lung infection in CF patients (e.g., β-lactams, aminoglycosides, quinolones, carbapenems, and colistin).

The goal of this study was to assess the isolates and susceptibility of *A. xylosoxidans* and to analyze the clinical progress of CF patients with *A. xylosoxidans*.

Materials and methods

Patients

We performed a retrospective microbiological and clinical study of patients with CF harboring *A. xylosoxidans* treated in our adult CF Unit (Hospital La Princesa, Madrid, Spain) from January 1999 to December 2013. In total, 91 patients received care in the unit, which works in collaboration with the pediatric unit of Hospital Universitario Niño Jesús (Madrid, Spain). Patients are referred to the unit at 18 years of age. Most patients attend the center every 2 months.

We recorded the following variables: age, sex, weight, mutations in the *CFTR* gene, presence of diabetes mellitus, pancreatic insufficiency, and lung function parameters such as forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), FVC%, and FEV_1%. Respiratory function tests were performed on a Datospir 120® Silbelmed® spirometer. We define the decline in lung function as follows: annual percentage loss of $FEV_1\% = [\text{initial}FEV_1\% - \text{actual}FEV_1\%)/\text{initial}FEV_1\% \times 100]/\text{follow-up}$ in years]. FEV_1 is reported as the percentage of the theoretical value.

Lower respiratory tract secretions for sputum microbiology testing were obtained by coughing. Co-colonization with other microorganisms, allergic bronchopulmonary aspergillosis (ABPA), and the number of annual exacerbations.

Patients were considered chronically colonized according to the criteria of Pereira et al.,[15] namely at least 3 positive cultures obtained in 1 year, with a minimum 1-month interval between them, for at least 2 years.

Processing of sputum samples

Sputum samples were pretreated (vol/vol) with N-acetylcysteine to decrease viscosity and then mixed vigorously to obtain a homogenous sample. As many pathogens are present in the respiratory tract of CF patients; selective media are required to identify specific pathogens. We inoculated the following plates: blood agar, bacitracin chocolate agar, mannitol-salt agar, MacConkey agar, Sabouraud agar with chloramphenicol, and *B. cepacia* selective agar (bioMérieux, Marcy l'Etoile, France). The incubation time was 3 to 5 days at 35 °C. Bacitracin chocolate agar was incubated in CO_2 increased atmosphere. We used a quantitative 3 mcl loop to measure bacterial counts.

Isolation and identification

All bacteriological analyses were performed in our microbiology laboratory. Lactose-negative colonies isolated on McConkey agar were re-isolated on blood agar and subsequently tested for oxidase activity.

Isolates were identified as *A. xylosoxidans* by conventional methods including MicroScan WalkAway (Siemens Healthcare Diagnostics Inc., West Sacramento, California, USA), API 20NE (bioMérieux, Marcy l'Etoile, France) and matrix-assisted laser-desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS; MALDI Biotyper, Bruker). MALDI-TOF MS was used only during the last year of the study. Six patients have at least one strain in which the identification of the organism is confirmed by sequencing at the Microbiology Reference Center (Majadahonda). In the rest of the patients it was not possible to perform the confirmation by sequencing.

These procedures were performed according to the manufacturer's recommendations.[16]

Susceptibility testing

Susceptibility testing was performed using broth microdilution (MicroScan WalkAway, Siemens Healthcare Diagnostics Inc., West Sacramento, California, USA).

As there are currently no specific standardized sensitivities for *A. xylosoxidans*, we used minimal inhibitory concentration (MIC) interpretive criteria for "Other Non-*Enterobacteriaceae*" from the Clinical Laboratory Standards Institute (CLSI).[17]

We studied the following antibiotics: piperacillin/tazobactam, ceftazidime, cotrimoxazole, minocycline, imipenem, and meropenem.

Results

A. xylosoxidans was isolated in 18 (19.8%) of 91 adult CF patients during the study period. The mean age was 26.6 years (range, 18–39 years). As for mutations in the *CFTR* gene, 61.1% of the patients had F508del/other, 22.2% had F508del/F508del, and 16.7% had other/other. Table 1 shows the clinical characteristics of CF patients harboring *A. xylosoxidans*. According to the criteria defined by Pereira et al.,[15] 9 patients (9.8%) were chronically colonized with *A. xylosoxidans* and the mean colonization period was 3.9 (±0.8) years. The most frequent concomitant species were *S. aureus*, *Haemophilus* spp., and *P. aeruginosa*. Most chronically infected patients (8/9) were concomitantly colonized by *S. aureus*. Two strains were methicillin-resistant.