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Sepsis Caused by *Achromobacter xylosoxidans* in a Child with Cystic Fibrosis and Severe Lung Disease

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Study Design A
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Statistical Analysis C
Data Interpretation D
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Patient: Female, 10
Final Diagnosis: Sepsis
Symptoms: Fever • hypotension • not tolerating enteral feeds • respiratory deterioration
Medication: —
Clinical Procedure: IV antibiotics • lungtransplantation
Specialty: Pediatrics and Neonatology

Objective: Unusual clinical course





Background: *Achromobacter xylosoxidans* is an aerobic, motile, Gram-negative, opportunistic pathogen that can be responsible for various severe nosocomial and community-acquired infections. It has been found in immunocompromised patients and patients with several other underlying conditions, but the clinical role of this microorganism in cystic fibrosis is unclear.

Case Report: We describe a case of septic shock caused by *A. xylosoxidans* in a 10-year-old child with cystic fibrosis and severe lung disease.

Conclusions: As the prevalence of *A. xylosoxidans* in cystic fibrosis patients is rising and patient-to-patient transmission is highly probable, further studies are warranted to determine its role and to document the appropriate treatment strategy for eradication and long-term treatment of this organism.

MeSH Keywords: *Achromobacter denitrificans* • Cystic Fibrosis • Sepsis

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/896577>

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Background

Over the last two decades, the epidemiology of acute bacterial infections in patients with cystic fibrosis has evolved and has become increasingly complex. *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* have been the main pathogens in the respiratory tracts of cystic fibrosis patients, but recently other potentially pathogenic bacteria, such as *Achromobacter xylosoxidans*, have emerged [1]. *A. xylosoxidans* is an aerobic, motile, Gram-negative rod that can be found in aquatic environments, as well as in the human respiratory and gastro-intestinal tract and the ear canal. It was previously known as *Alcaligenes dentrificans subspecies xylosoxidans* and *Alcaligenes xylosoxidans subspecies xylosoxidans*, and was first described in 1971 by Yabuuchi and Ohyama, who discovered it in patients with chronic, purulent otitis media [2].

A. xylosoxidans is an opportunistic pathogen that can cause severe infections, especially in immunocompromised patients [3]. It has been found in neonates and in patients with cancer, neutropenia, diabetes mellitus, renal failure, HIV infection, IgM deficiency, and in bone marrow or liver transplant patients. A number of case reports have described infections with *A. xylosoxidans* in patients with non-CF-bronchiectasis [4]. Clinical syndromes, such as bacteremia, meningitis, pneumonia, osteomyelitis, urinary tract infections, prosthetic valve endocarditis, and peritonitis have been described in infected patients, the most common symptoms of which are primary bacteremia and bacteremia related to an intravenous catheter [1,2]. Malignancies, central venous catheter implants, and previous major surgery are the most common predisposing conditions. Patients with *A. xylosoxidans* bacteremia frequently present with fever, sepsis syndrome, respiratory complaints, hypotension, and altered consciousness. Abdominal pain, oliguria, and diarrhea can also be found. In a study with neonates, thrombocytopenia, neutropenia, abdominal distension, and apnea were the most common clinical features [3,5].

We describe a case of septic shock caused by *A. xylosoxidans* in a 10-year-old child with cystic fibrosis and severe lung disease.

Case Report

A 10-year-old girl was diagnosed with cystic fibrosis in the neonatal period after presenting with meconium ileus. She was homozygous for F508del mutation and had severe lung disease. Her current “forced expiratory volume in 1 second” (FEV1) ranged between 33–38% predicted, and her lung function further showed severe obstruction with increased airway resistance and hyperinflation. A recent CT scan revealed cystic bronchiectasis in the apical and basal regions and a persistent atelectasis of the right middle lobe.

In March 2010, a multi-resistant *A. xylosoxidans* (with multi-resistance defined as resistance against all agents in at least two of the following antibiotic classes: β -lactams, quinolones, or aminoglycosides) was cultured for the first time from her sputum. Since April 2013 she had been chronically colonized with this pathogen. In addition, *Staphylococcus aureus* grew intermittently from her sputum samples. Her maintenance therapy included azithromycin, nebulized hypertonic saline, dornase alfa, pancreatic enzyme replacement therapy, and fat-soluble vitamins. Nebulized ceftazidime twice daily was used as suppressive antibiotic therapy for the airway colonization with *A. xylosoxidans*. Cyclic intravenous antibiotic therapy with combinations of amikacin and either meropenem and piperacillin-tazobactam was administered approximately every eight weeks to maintain a stable clinical situation. During several months per year, she was admitted to an inpatient rehabilitation center to maximize therapeutic possibilities. She was on chronic oxygen therapy because of episodes of desaturation at minimal exercise, and required non-invasive ventilation (NIV) during sleep. She received enteral tube feeding because of chronic anorexia and feeding difficulties. She remained in a relatively stable condition with regular admissions to the rehabilitation center and regular intravenous (IV) treatment courses.

In April 2014, she was admitted to our hospital a few days prior to her scheduled IV treatment because of malaise, not tolerating enteral feeding, vomiting, and a deteriorated respiratory condition. Spirometry showed a FEV1 of 28% predicted. Her oxygen need increased, as well as the need for NIV. IV treatment with meropenem and colistin was started. Total parenteral nutrition was temporarily initiated. She developed refeeding syndrome with hypophosphatemia and mild hypocalcemia, which resolved after adequate supplementation. Two days after her admission to the hospital, she developed a fever and her levels of C-reactive protein (CRP) increased to a maximum of 60 mg/L. Multi-resistant *A. xylosoxidans* was cultured from her sputum sample. Cultures for viruses, *Mycoplasma spp.* and *Mycobacteria spp.* were negative. Because of her persistent fever, flucloxacillin was added to her therapy, although a culture at time of admission for *S. aureus* was negative. She improved clinically, and enteral feeding was gradually reintroduced. Erythromycin was added because of delayed gastric emptying. She was discharged from the hospital after two weeks, with IV treatment continuing at home.

However, only a few days after discharge, she was readmitted because of fever, severe respiratory deterioration, and hypotension, a picture consistent with septic shock. Admission to the pediatric intensive care unit (PICU) was necessary because of the need for fluid resuscitation and continuous NIV. Antibiotics were switched to high-dose piperacillin-tazobactam, based on a recent sputum culture displaying intermediate sensitivity of *A. xylosoxidans* to this antibiotic (Table 1). After consulting the infectious

Table 1. Antibiotic susceptibility of *A. xylosoxidans* at time of admission to the PICU.

Antibiotic	Sensitivity	MIC (µg/mL)
Piperacillin-tazobactam	I	>256
Ceftazidime	R	>256
Meropenem	R	>32
Ciprofloxacin	R	>32
Polymyxins	R	12
Ticarillin	R	Not available*
Aztreonam	R	Not available*
Fosfomycin	R	Not available*
Trimethoprim-sulfamethoxazole	R	Not available*

* MIC values could not be calculated for all antibiotics.

diseases specialist, high-dose trimethoprim-sulfamethoxazole was added, while high-dose colistin was continued. Her initial fever persisted and CRP levels continued to rise, but both started to recover after two days. At that time, blood cultures taken at time of admission were reported to be positive for *A. xylosoxidans*. Antibiotic treatment remained unchanged because of clinical and biochemical improvement. Consecutive blood cultures taken after initiation of the antibiotic therapy were negative.

The patient was transferred to the pediatric ward, and after two weeks she again experienced intermittent fever with increasing CRP levels and an increased need for oxygen and NIV. *A. xylosoxidans* was the only microorganism cultured from her sputum sample, and her blood cultures remained negative. Eventually readmission to the PICU was necessary, where antibiotic treatment was switched to a combination of thiamfenicol, imipenem, and colistin, because of *in vitro* susceptibility for imipenem, and because thiamfenicol had been used with success in a similar case in another hospital. This resulted in a gradual clinical improvement with decreased oxygen need, weaning of NIV, and increasing FEV1 values up to 34%. Several repeat blood cultures remained sterile. She received this combination of antibiotics for four weeks and was then discharged home in combination with intensive rehabilitation at a specialized treatment center. Several weeks after discharge, she was readmitted to the PICU because of vomiting, intolerance to enteral feeding (again), and a subsequent worsening respiratory condition. Because of this and the need of repetitive hospital admissions with minimal improvement, she was referred for a lung transplant to another care center.

Discussion

Knowledge about infections caused by *A. xylosoxidans* in patients with cystic fibrosis is relatively scarce. As far as we

know, this case is the first case of a proven bloodstream infection caused by *A. xylosoxidans* in a cystic fibrosis patient. *A. xylosoxidans* is being isolated with increasing frequency in the sputum of cystic fibrosis patients all over the world [6]. The US Cystic Fibrosis Foundation Patient Registry reported an increased prevalence, with a rate of 6.2% in 2011 [7]. The Belgium Cystic Fibrosis Registry of 2013 reported a prevalence as high as 10.5%, which was significantly higher than the 7.5% reported in 2010. The prevalence of chronic colonization with *A. xylosoxidans* has increased as well, from 2.9% in 2010 to 6.3% in 2013 [8]. This prevalence may be underestimated, as the micro-organism is sometimes difficult to identify. Bacterial misidentification as atypical *P. aeruginosa* has occurred with standard phenotypic identification methods; misidentification presents a challenge to effective infection control, to antimicrobial therapy, and to prognosis in cystic fibrosis patients [6].

The clinical relevance of *A. xylosoxidans* in cystic fibrosis patients remains uncertain. De Baets et al. found that patients with a first positive sputum culture for *A. xylosoxidans* had significantly lower Bhalla scores [9] on HRCT, lower Brasfield scores [10] on chest x-rays, and lower, although not significant, forced vital capacity (FVC) and FEV1 values. These findings, combined with the results of Tan et al., who could not detect a need for more intravenous antibiotic treatment courses, led to the hypothesis that *A. xylosoxidans* is a colonizer of severely damaged lungs [11,12]. In their study, Tan et al. also reported no significant difference in the change in lung function over four years, Northern chest x-ray score [13], Schachman-Kulczycki score [14], or nutritional status. However, Hansen et al. reported a significant difference in FEV1 and FVC values in patients before and after chronic infection. Furthermore, they reported a significantly faster deterioration in FEV1 and FVC values in patients with rapidly increasing antibody levels [6]. Another study reported a higher prevalence of *A. xylosoxidans* in patients awaiting lung transplantation than in

the general cystic fibrosis population [15]. Our case study could be another illustration of a clear pathogenic role of this organism in cystic fibrosis patients. Although the lungs were the probable source of the septicemia in our case study, our patient also had an implanted venous access device present. Repeated cultures from this port, however, remained negative.

Patient-to-patient transmission has been described by others and is another reason why *A. xylosoxidans* infection should be feared. Vu-thien et al. and Tan et al. excluded the possibility of interpatient transmission, whereas several other authors found that some of their patients harbored the same strain, indicating cross-infection or infection through a common source [1,6,11,12,16].

Finally, because of its inherent and acquired resistance to several antibiotics, there is a lack of good therapeutic options to eradicate *A. xylosoxidans*. In one study, Lambiase et al. found that 20% of *A. xylosoxidans* isolates showed a multidrug-resistant profile, with resistance to aztreonam, cephalosporins (including cefepime, ceftazidime, and cefotaxime), carbapenems, aminoglycosides, quinolones, and trimethoprim-sulfamethoxazole. These same isolates were sensitive to piperacillin and piperacillin-tazobactam. Moreover, the study indicated that *A. xylosoxidans* isolates could be resistant to many antibiotics, regardless of the study population, as isolates that were recovered from non-cystic-fibrosis patients also showed resistance to ceftazidime, carbapenems, and levofloxacin. Trancassini et al. also discovered a high frequency of resistance to aztreonam, gentamicin, amikacin, tobramycin, cefepime, and ciprofloxacin in their study population [1]. Saiman et al. found that minocycline, imipenem, meropenem, and piperacillin with or without tazobactam showed the highest antibacterial activity. They also discovered that a minority of their *A. xylosoxidans*

strains was resistant to higher concentrations of tobramycin and colistin. Furthermore, synergistic activity was noted for combinations of chloramphenicol with minocycline, for ciprofloxacin with imipenem, and for ciprofloxacin with meropenem [17]. Increasing evidence of resistance to aminoglycosides, cephalosporins and most of the β -lactam antibiotics, and the variable susceptibility to fluoroquinolones, makes antipseudomonal penicillins and trimethoprim-sulfamethoxazole the preferred agents in treatment. In our case study, the isolate recovered from sputum samples was multi-resistant, showing resistance to piperacillin/tazobactam, ceftazidime, meropenem, ciprofloxacin, and polymyxins on multiple occasions. Our patient received nebulized ceftazidime twice daily as a maintenance therapy, although resistance to this antimicrobial agent had already been documented. The therapeutic combination strategy with imipenem, thiamfenicol, and high-dose colistin eventually lead to a clinical improvement.

Conclusions

To our knowledge, the case we presented is the first case of a proven *A. xylosoxidans* septicemia in a cystic fibrosis patient with severe lung disease. This case supports the clinical importance of *A. xylosoxidans* infection in cystic fibrosis patients. As its prevalence is rising and patient-to-patient transmission is highly probable, further studies are warranted to determine its role and to document the appropriate treatment strategy for eradication and long-term treatment strategies of this organism.

Conflict of interests

None.

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