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# The Brazilian Journal of INFECTIOUS DISEASES

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## Original article

# Bacteremia due to *Achromobacter xylosoxidans* in neonates: clinical features and outcome

Ozden Turel<sup>a,\*</sup>, Sultan Kavuncuoglu<sup>b</sup>, Emine Hosaf<sup>c</sup>, Sibel Ozbek<sup>b</sup>, Esin Aldemir<sup>b</sup>, Turkan Uygur<sup>b</sup>, Nevin Hatipoglu<sup>b</sup>, Rengin Siraneci<sup>a</sup>

<sup>a</sup> Department of Pediatrics, Bezmialem Vakif University, Adnan Menderes Bulvarı Vatan Caddesi 34093, Fatih, İstanbul, Turkey

<sup>b</sup> Department of Pediatrics, Kanuni Sultan Süleyman Research Hospital, İstanbul, Turkey

<sup>c</sup> Department of Microbiology, Kanuni Sultan Süleyman Research Hospital, İstanbul, Turkey

## ARTICLE INFO

### Article history:

Received 17 November 2012

Accepted 6 January 2013

Available online 3 June 2013

### Keywords:

*Achromobacter xylosoxidans*

Bloodstream infection

Neonate

## ABSTRACT

**Objective:** We report an outbreak of *Achromobacter xylosoxidans* at a neonatal intensive care unit. We aimed to present clinical, laboratory and treatment data of the patients.

**Materials and methods:** All consecutive episodes of bacteremia due to *A. xylosoxidans* at our neonatal intensive care unit, beginning with the index case detected at November 2009 until cessation of the outbreak in April 2010, were evaluated retrospectively.

**Results:** Thirty-four episodes of bacteremia occurred in 22 neonates during a 6-month period. Among the affected, 90% were preterm newborns with gestational age of 32 weeks or less and 60% had birth weight of 1000 g or less. Endotracheal intubation, intravenous catheter use, total parenteral nutrition and prolonged antibiotic therapy were the predisposing conditions. Presenting features were abdominal distention, thrombocytopenia and neutropenia. The mortality rate was 13.6% and the majority of isolates were susceptible to piperacillin-tazobactam, carbapenems and trimethoprim-sulfamethoxazole, and resistant to gentamycin. More than half were breakthrough infections. Despite intensive efforts to control the outbreak by standard methods of hand hygiene, patient screening and isolation, containment could be achieved only after the neonatal intensive care unit was relocated. The investigation was not able to single out the source of the outbreak.

**Conclusion:** *A. xylosoxidans* has the potential to cause serious infections in premature babies. More studies are needed to determine the importance of different sources of infection in hospital units.

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## Introduction

*Achromobacter xylosoxidans* is a nonfermentative Gram-negative bacillus which is widely distributed in nature,

especially in aquatic environments.<sup>1,2</sup> It was first described by Yabuuchi and Ohyama in 1971 from purulent ear discharge of patients with chronic otitis media.<sup>3</sup> Since it is an opportunistic pathogen it usually affects patients with underlying illnesses and immunosuppression.<sup>4,5</sup> Infections such as bacteremia,

\* Corresponding author at: Department of Pediatrics and Pediatric Infectious Diseases, Bezmialem Vakif University, Adnan Menderes Bulvarı Vatan Caddesi 34093, Fatih, İstanbul.

E-mail address: barisbulent98@yahoo.com (O. Turel).

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<http://dx.doi.org/10.1016/j.bjid.2013.01.008>

pneumonia, meningitis, urinary tract infections, abscesses, osteomyelitis, corneal ulcers, prosthetic valve endocarditis and peritonitis have been reported.<sup>1,4-11</sup> Treatment of *Achromobacter* infections is difficult since the bacterium may be resistant to several antibiotics.<sup>2</sup>

Because of limited data and lack of large series of infections caused by *Achromobacter* in children, especially in newborns, we aimed to present an outbreak of *A. xylosoxidans* bacteremia that took place at our neonatal intensive care unit (NICU).

## Methods

The study was performed in a level III neonatal reference unit of a tertiary care hospital where a mean of 400 newborns are admitted annually. All consecutive episodes of bacteremia due to *A. xylosoxidans*, beginning with the index case detected in November 2009 until cessation of the outbreak in April 2010 were evaluated retrospectively. A case of *A. xylosoxidans* bacteremia was defined as one or more blood cultures positive for *A. xylosoxidans* when clinical signs of sepsis were present.<sup>12</sup> Blood samples were incubated into Bactec 9240 system (Becton Dickinson, USA) for up to seven days. A sample from the blood culture bottle with positive bacterial growth was inoculated into 5% sheep blood agar and EMB (eosin methylene blue) agar (Oxoid, England), and incubated at 36.5 °C for 18–20 h. Gram negative bacilli with positive reaction for oxidase were detected in Gram-stained smears prepared from colonies. Identification of the microorganisms was done by API 20 NE system (bioMerieux, France). Susceptibility of the organisms to antimicrobial agents was performed by using (Kirby-Bauer) disk-diffusion method on Mueller-Hinton agar, according to the Clinical Laboratory Standards Institute (CLSI) Guidelines. Multiple episodes were indicated by the finding of *A. xylosoxidans* isolates in blood cultures obtained >four weeks apart, or >two weeks apart if the blood cultures became sterile and/or there was evidence of clinical resolution of the infection.<sup>4</sup>

Data recorded included sex, gestational age, birth weight, date of admission, underlying diseases, presence of intravascular catheters, administration of broad-spectrum antibiotics and total parenteral nutrition, number of positive blood cultures and sites of other cultures from which *A. xylosoxidans* was isolated. Neutropenia was defined as a count less than  $1.5 \times 10^9$ /L cells/mm<sup>3</sup>, thrombocytopenia was defined as a platelet count of  $<80 \times 10^9$ /L.<sup>13</sup> Infections that occurred more than 72 h after admission were defined as nosocomial.<sup>14</sup> A breakthrough infection was indicated by the isolation of bacteria from blood cultures obtained while the patient was receiving systemic antibiotics to which the bacteria was later confirmed to be susceptible.<sup>4</sup>

For the investigation of outbreak, bacteriological cultures of environmental samples were taken including antiseptic solutions (chlorhexidine digluconate, aqueous and alcoholic), wash basins, incubator surfaces, liquid soaps, faucets, nebulizers and tap water. Hands of health care workers were sampled by direct fingerprinting in Petri dishes. Fluids were filtered through 0.45 µm membranes (Millipore, Bedford, MA, USA) and cultivated on sheep blood agar (SLB, Turkey), EMB agar. Swabs were plated on EMB agar and 5% sheep blood agar.

Plates were incubated for 24 h at 36 °C. Environmental cultures were taken following detection of first four bacteremia cases in November 2009 and discontinued after April 2010.

## Results

### Index case

The index case was a 25-week gestational age male (birth weight 660 g) baby born to a G1P0A0 mother. After birth he was intubated and transferred to the NICU with a diagnosis of respiratory distress syndrome (RDS). He received ampicillin-sulbactam and gentamycin since congenital pneumonia could not be excluded. On the 7th day of life, minimal enteral feeding was initiated but in the next day abdominal distension developed and antibiotics were switched to vancomycin and meropenem with a diagnosis of necrotizing enterocolitis (NEC). Blood cultures remained sterile and vancomycin was discontinued after 14 days. On 21st day of meropenem therapy, he developed apnea, leukopenia and thrombocytopenia. He was reintubated and meropenem was switched to sulbactam-cefoperazone and fluconazole pending culture results. His clinical condition deteriorated and he developed acidosis, hypotension and bradycardia necessitating a short duration of adrenalin infusion. Two sets of blood cultures yielded *A. xylosoxidans* susceptible to ciprofloxacin, meropenem and trimethoprim-sulfamethoxazole (TMP-SXM). Sulbactam-cefoperazone and fluconazole were discontinued and meropenem plus ciprofloxacin were given. Blood cultures became sterile after five days. The patient's clinical condition resolved gradually and he was extubated after seven days. He was discharged from the NICU when at the age of two months.

### Epidemiologic investigation

Following the index case, four additional cases were diagnosed within the same week. An outbreak was suspected and cohorting and contact precautions with gown and glove use on entry to rooms of patients infected with *A. xylosoxidans* and enhanced environmental cleaning were instituted. An investigation for determination of source of infection was started. Standard infection control practices such as hand hygiene (hand washing upon unit entry before and after patient contact and use of alcohol hand sanitizer between patient contacts), aseptic technique for all invasive procedures, sterile procedures requiring gown, mask, and gloves and environmental cleaning were overviewed. Education of healthcare staff was repeated but no flaw was found. Environmental vectors were suspected and bacteriological cultures of environmental samples were taken but the source could not be identified. Twelve patients were determined to be infected during November and December. A second attack affecting 10 patients was observed in March. Patients were transferred to an other part of the hospital prepared as NICU in April. No further cases were detected during the following 12 months.

### Clinical features and treatment of affected neonates

A total of 22 neonates, 12 (54.5%) male, were diagnosed with *A. xylosoxidans* bacteremia. All infecting strains were

**Table 1 – Characteristics of 22 newborns infected with *Achromobacter xylosoxidans*.**

Characteristic	Value
Birth weight, mean $\pm$ SD	1197 $\pm$ 799 g
Gestational age, mean (range)	27.8 (23–37) weeks
Male/female	12/10
Age (days) at the time of diagnosis, mean (range)	21 (6–45)
Mortality, no. (%)	3 (13.6)
<b>Predisposing factors (%)</b>	
Prematurity	100
Catheter	100
TPN	100
Previous broad spectrum antibiotic administration	100
<b>Diagnosis at admission (%)</b>	
Prematurity	13.6
Prematurity + respiratory distress syndrome (RDS)	72.7
Prematurity + RDS + digestive disorders	4.5
Other (chylothorax, hydrops fetalis, etc.)	9.1
<b>Clinical findings at the time of diagnosis (%)</b>	
Fever	4.5
Abdominal distension	68.2
Apnea	45
Neutropenia	63.6
Thrombocytopenia	100
Breakthrough infection (%)	63.6

considered nosocomially acquired. All patients were preterm and 60% were under 1000 g birth weight. Prematurity and respiratory distress syndrome (RDS) were the most common diagnosis at admission. Most common presenting features of infection were abdominal distention, apnea, thrombocytopenia and leukopenia (Table 1). Three out of 22 patients had cerebrospinal fluid (CSF) abnormalities suggestive of bacterial meningitis and *A. xylosoxidans* growth was detected in CSF in addition to blood culture. 84% of patients recovered with antibiotic therapy while three patients died due to *Achromobacter* sepsis. Two patients had multiple growths of *A. xylosoxidans*. *In vitro* susceptibility profile of *A. xylosoxidans* isolates to antimicrobial agents is given in Table 2. Breakthrough infection was observed in 14 patients (63.6%). Patients received 10–21 day course of meropenem alone (9.7%), meropenem in combination with other antibiotics (meropenem plus ciprofloxacin, meropenem plus ceftazidime and meropenem plus piperacillin-tazobactam in 50%, 22.7%,

and 13.6% of patients, respectively) or ciprofloxacin plus ceftazidime (4.5%).

## Discussion

*A. xylosoxidans* is an emerging nosocomial pathogen. It represented 12.5% of nonfermenting Gram negative bacilli isolated in Latin America medical centers during SENTRY program 1997–2002.<sup>15</sup> Respiratory tract colonization in cystic fibrosis patients has also been recognized during the last decade.<sup>16</sup> Case reports due to *A. xylosoxidans* infection in Turkey are increasingly reported.<sup>17–19</sup> Nevertheless, knowledge about neonatal infections caused by *A. xylosoxidans* is relatively scarce. It was reported as a contaminant leading to pseudobacteremia outbreak at NICU but serious infections such as meningitis and fatal sepsis in prematures were also described.<sup>6,20–22</sup>

*A. xylosoxidans* bacteremia is almost always a nosocomial infection.<sup>23</sup> Bacteremia due to *A. xylosoxidans* is usually related to intravascular catheters and is frequently polymicrobial in patients with underlying malignancies.<sup>4,24</sup> Shie et al. evaluated characteristics of *A. xylosoxidans* bacteremia in Taiwan and reported that malignancies, central venous catheter implants and previous major surgery were the most common underlying conditions.<sup>25</sup> Another study in a tertiary care hospital in India identified 20 strains of *A. xylosoxidans* isolated from 15 patients during one year period.<sup>26</sup> Seventeen isolates were from blood, two from CSF and one from pleural fluid; 30% of patients were premature neonates. We identified low birth weight, prematurity, total parenteral nutrition (TPN) and previous broad spectrum antibiotic therapy as the major predisposing conditions for *Achromobacter* bacteremia in our study. 4.5% of patients had undergone surgical interventions. The mean interval from hospital admission to isolation of a positive culture was 21 days. All affected neonates had umbilical catheter insertion and in all bacteremia episodes *A. xylosoxidans* was isolated as the sole pathogen.

Aisenberg et al. reported that *Achromobacter* bacteremia presented with fever (52%), sepsis syndrome (22%) and respiratory complaints (17%).<sup>4</sup> In another report of 40 cases of *A. xylosoxidans* bacteremia, the most common manifestations were fever (82%), chills (37.5%), hypotension (32.5%) and altered consciousness.<sup>25</sup> Dyspnea, abdominal pain, oliguria and diarrhea were also noted. In our study, thrombocytopenia (100%), neutropenia (63.6), abdominal distension (69%) and apnea (45%) were the most common clinical features. These

**Table 2 – *In vitro* susceptibility profile of 34 *Achromobacter xylosoxidans* isolates to antimicrobial agents.**

Antimicrobial agent	Number of isolates (n = 34)		
	Susceptible (%)	Intermediately susceptible (%)	Resistant (%)
Trimethoprim-sulfametoxazole (TMP-SXM)	100	0	0
Meropenem	100	0	0
Piperacillin-tazobactam	91	3	6
Ciprofloxacin	82	15	3
Ceftazidime	82	3	15
Cefepime	15	9	76
Gentamycin	0	0	100

findings are common with other Gram negative bacilli and fungi septicemia which makes the diagnosis rather difficult unless proven by culture. Fever was reported less frequently (4.5%) probably because of insufficient immune response of premature neonates. Three deaths were attributable to *A. xylosoxidans* sepsis with a fatality rate lower than previous reports (15–47.5%).<sup>4,23,25</sup>

There have been many reports of *A. xylosoxidans* isolation from environmental sources in hospital acquired infections.<sup>23</sup> *A. xylosoxidans* was detected in deionized water in an intensive care unit and tap water and on the hands of two health care workers in a hemodialysis unit.<sup>1,23</sup> We checked environmental samples and hands of healthcare personnel for colonization but were unable to determine the source. In a similar report from India, Kumar et al. were also unable to determine the source.<sup>26</sup> Since there was similarity of antibiotic susceptibility pattern of isolates, probable clonality of the isolates could be predicted but we were unable to perform testing for molecular epidemiology. In addition to enhanced infection control measures and increased awareness of health care staff, decreased patient capacity during the first days following relocation of NICU may have prevented development of additional cases of *A. xylosoxidans* bacteremia.

*A. xylosoxidans* has an unusual susceptibility pattern with resistance to aminoglycosides and to the majority of  $\beta$ -lactam antibiotics. Anti-pseudomonal penicillins, TMP-SMZ and carbapenems are the preferred agents in treatment.<sup>2,27</sup> All of our isolates were sensitive to TMP-SXM and meropenem and the majority were sensitive to piperacillin-tazobactam similar to previous reports. Susceptibility to the fluoroquinolones is variable.<sup>28</sup> Gomez et al. and Almuzara et al. have reported that quinolones have poor activity against *Achromobacter* spp.<sup>23,29</sup> In contrast 82% of our isolates were susceptible to ciprofloxacin. For infections caused by multidrug-resistant *A. xylosoxidans*, antimicrobial combinations such as piperacillin plus gentamycin, azitromycin plus doxycycline, and azitromycin plus TMP-SXM have been tested with favorable results.<sup>24</sup> Since 63% of infections were definite breakthrough infections and the patients were severely ill we used combination therapy in most patients.

## Conclusion

*A. xylosoxidans* has the potential to cause serious infections in hospitalized neonates. Antimicrobial susceptibility profile for each case should be taken into account for determining the therapy. More studies are needed to assess the importance of different sources of contamination in hospital units.

## Conflict of interest

The authors declare no conflicts of interest.

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