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# Characteristics of *Achromobacter xylosoxidans* bacteremia in northern Taiwan

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There were 40 cases of *Achromobacter xylosoxidans* bacteremia during a 6-year period in a medical center in northern Taiwan. Males outnumbered females (72.5% vs 27.5%). Common underlying diseases and conditions in these 40 bacteremic patients were malignancies (57.5%), central venous catheter implants (55%), surgery (35%), neutropenia (30%) and use of steroids (25%). Recurrent bacteremia occurred in 4 patients (10%), all of whom had a central venous catheter implant which was considered the most probable source of infection. More than one-quarter (27.5%) of the cases were community acquired. The mortality rate due to *A. xylosoxidans* bacteremia was 47.5%. Risk factors significantly associated with mortality were nosocomial acquisition and polymicrobial bacteremia. Disk susceptibility testing showed that these isolates were resistant to aminoglycosides and most cephalosporins but were susceptible to piperacillin, imipenem, ceftazidime and trimethoprim-sulfamethoxazole.

**Key words:** *Achromobacter xylosoxidans*, bacteremia, malignancy, microbial sensitivity tests, mortality

*Achromobacter xylosoxidans*, also known as *Alcaligenes xylosoxidans*, is an aerobic, oxidase-positive, non-fermentative, Gram-negative peritrichous rod which is a rare pathogen in humans. It was isolated and named in 1971 by Yabuuchi and Oyama from ear discharges of 7 patients with chronic otitis media [1]. *A. xylosoxidans* distributes widely in nature and is frequently found in aqueous environments. It has been isolated occasionally from the normal flora of the ear and gastrointestinal tract in humans. Sporadic cases of *A. xylosoxidans* infection have been reported with bacteremia, meningitis, pneumonia, empyema, pulmonary abscess, peritonitis, urinary tract infection, prosthetic valve endocarditis, septic arthritis, prosthetic joint infection, osteomyelitis, chronic otitis media, endophthalmitis, and keratitis [2-15]. Bacteremia with this organism occurs mostly in immunocompromised or debilitated patients. Although it is an uncommon human pathogen, it can cause invasive infections with high mortality. Nosocomial outbreaks have occasionally been reported and attributed to contaminated saline, intravenous catheter, intravascular pressure transducer, disinfectant, contrast solution, topical aqueous eosin, deionized water and chlorhexidine [16-21].

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Because of the very limited data available on this pathogen [2,3,22,23], we analyzed the clinical manifestations, underlying conditions and risk factors for mortality from the 40 cases of *A. xylosoxidans* bacteremia at Chang Gung Memorial Hospital-Linkou Medical Center in northern Taiwan over a period of 6 years, and studied the antimicrobial susceptibility of the 45 isolates from these 40 bacteremic patients.

## Materials and Methods

Medical records of 40 consecutive cases of *A. xylosoxidans* bacteremia treated during the period from July 1998 to March 2004 at Chang Gung Memorial Hospital-Linkou Medical Center (Taiwan) were reviewed. The criteria for diagnosis of *A. xylosoxidans* bacteremia was isolation of the pathogen from at least 1 blood specimen in a patient with clinical symptoms or signs of infection. Infections that occurred more than 72 h after admission in patients who had no evident infection on admission were categorized as nosocomial. Clinical isolates were identified with the API ID 32 GN kit (bioMérieux, Marcy-l'Etoile, France).

Disk susceptibility testing of the organisms to antimicrobial agents was performed using the (Kirby-Bauer) disk-diffusion method on Meüller-Hinton agar, according to the guidelines of the National Committee for Clinical Laboratory Standards. Antibiotics tested

included ampicillin, aztreonam, cefazolin, cefuroxime, ceftriaxone, ceftizoxime, cefepime, amikacin, gentamicin, ciprofloxacin, imipenem, piperacillin and trimethoprim-sulfamethoxazole.

Cases of *A. xylosoxidans* bacteremia included in this study were categorized as either fatal or nonfatal. Mortality was attributed to *A. xylosoxidans* bacteremia if the patient died within 14 days after a blood culture was positive and had signs of sepsis at the time of death.

The relationship between possible risk factors and mortality was evaluated. Possible risk factors studied included age, gender, coexisting conditions (such as diabetes mellitus, cardiovascular disease, hepatic disease, pulmonary disease, renal disease, old cerebral vascular accident and malignancy), and hospital events (surgery, hospital stay, central venous catheter insertion, use of steroids and neutropenia). We used case numbers as denominators to calculate percentiles for variables. Statistical data were analyzed using chi-squared test. A 2-tailed $p$ value $<0.05$ was considered significant.

## Results

### Demographic data

During the 6-year study period, 45 episodes of *A. xylosoxidans* bacteremia were diagnosed in 40 patients. There was a predominance of male patients (72.5%). The mean age was 58.5 ± 19.9 years (range, 18 days to 93 years). Twenty two patients (55%) were older than 60 years. Only 2 patients were not adults, including 1 neonate and 1 infant. Episodes occurred year round without a seasonal distribution. Sixteen episodes (27.5%) of *A. xylosoxidans* bacteremia were community acquired and 29 (72.5%) were nosocomial; the mean hospital stay before acquiring bacteremia was 24 days (range, 6-96 days).

### Clinical features

Fever (82.5%), chills (37.5%), hypotension (32.5%), and altered consciousness (27.5%) were the most common manifestations of *A. xylosoxidans* bacteremia (Table 1). Other symptoms and signs included dyspnea, abdominal pain, diarrhea, headache, anorexia and weakness. The most common complication was acute renal failure.

### Underlying diseases and conditions

The underlying conditions in the 40 patients are listed in Table 2. All bacteremic patients had at least 1 underlying comorbidity and most of them were considered immunocompromised. Malignancy (57.5%) was the most common underlying disease. Fifteen patients (37.5%) had solid tumors, including: nasopharyngeal cancer (3 patients), esophageal cancer (3), tongue cancer (1), lung cancer (1), hepatoma (1), breast cancer (1), pancreatic cancer (1), retroperitoneal leiomyosarcoma (1), ureter cancer (1), colon cancer (1) and 1 patient had cancer of both the ureter and the biliary tract. Eight patients (20%) had hematologic malignancy including lymphoma (2), multiple myeloma (2), acute leukemia (2), myelodysplastic syndrome (1) and aplastic anemia (1). Twenty two patients (55%) had central venous catheter (Port-A-Cath) implants (55%). Major surgery (35%), neutropenia postchemotherapy (30%), use of steroids (25%) and chronic renal insufficiency (22.5%) were other conditions commonly found in these bacteremic patients.

**Table 1.** Clinical manifestations of 40 patients with *Achromobacter xylosoxidans* bacteremia

| Symptom/sign | No. of cases (%) |
|---|---|
| Fever | 33 (82.5) |
| Chills | 15 (37.5) |
| Hypotension | 13 (32.5) |
| Altered consciousness | 11 (27.5) |
| Dyspnea | 6 (15) |
| Abdominal pain | 5 (12.5) |
| Oliguria | 4 (10) |
| Diarrhea | 3 (7.5) |
| Headache | 2 (5) |

### Source of infection

*A. xylosoxidans* was isolated only from the blood and no coexisting isolate was found from other body sites in any of the bacteremic patients. However, 22 (55%) of these patients had Port-A-Cath implants. Four of the 40 bacteremic patients had recurrent episodes of bacteremia. Three of them had a second episode of bacteremia within 3 months, 2 months and 1 week, respectively, and the other 1 had 3 episodes of bacteremia within 3 months. All patients with recurrent bacteremia also had a Port-A-Cath implant. Three of them had no further episodes of bacteremia after the removal of the implant, and the other died without removal of the implant. These findings suggest that the central venous catheter implant was a likely source of *A. xylosoxidans* infection.

### Polymicrobial bacteremia

Seven patients (17.5%) had polymicrobial bacteremia. The concomitant organisms isolated were *Staphylococcus*

**Table 2.** Underlying conditions of 40 patients with *Achromobacter xylosoxidans* bacteremia

| Underlying conditions | No. of patients (%) |
|---|---|
| Malignancy | 23 (57.5) |
| Solid tumor | 15 (37.5) |
| Hematologic malignancy | 8 (20) |
| Major surgery | 14 (35) |
| Head and neck surgery | 3 (7.5) |
| Intrathoracic surgery | 1 (2.5) |
| Intra-abdominal surgery | 10 (25) |
| Neutropenia postchemotherapy | 12 (30) |
| Use of steroids | 10 (25) |
| Chronic renal insufficiency | 9 (22.5) |
| Diabetes mellitus | 6 (15) |
| Liver cirrhosis | 6 (15) |
| Chronic obstructive lung disease | 5 (12.5) |
| Cardiovascular disease | 4 (10) |
| Old cerebral vascular accident | 4 (10) |
| Collagen vascular disease | 2 (5) |

*aureus* (2 patients), *Klebsiella pneumoniae* (1), *Klebsiella oxytoca* (1), Viridans streptococci (1), *Acinetobacter* spp. (1), *Bacteroides* spp. (1) and *Candida tropicalis* (1).

### Mortality

Nineteen bacteremic patients (47.5%) died within 2 weeks after isolation of this organism from blood, and mortality was considered to be related to *A. xylosoxidans* sepsis. Nosocomial infection [62.1% vs 9.1%; odds ratio (OR), 16.4; 95% confidence interval (CI), 1.8-146.0; $p$=0.003] and polymicrobial infection (85.7% vs 39.4%; OR, 9.2; 95% CI, 1.0-85.8; $p$=0.04) were the only 2 factors significantly associated with mortality (Table 3). There was also a trend suggesting a possible association of mortality with old age (≥60 years), chronic renal insufficiency, liver cirrhosis, cardiovascular disease, use of steroids and neutropenia. Although these associations were not significant, the sample size was too small to have adequate statistical power.

### Disk susceptibility testing

This organism had a peculiar susceptibility pattern to antimicrobial agents (Table 4). Ceftazidime (91.1%), imipenem (97.2%), piperacillin (95.6%) and trimethoprim-sulfamethoxazole (78.6%) were usually active against *A. xylosoxidans* in vitro. Only 20-25% of the isolates were susceptible to ciprofloxacin and cefepime. Most of the isolates were resistant to ampicillin, aztreonam, aminoglycosides and most cephalosporins including cefazolin, cefuroxime and ceftriaxone.

## Discussion

*A. xylosoxidans* is often encountered in aqueous environments but is rarely recognized as a human pathogen. However, it can cause serious infections in humans. Our data suggest that *A. xylosoxidans* is a significant opportunistic pathogen in immunocompromised hosts.

**Table 3.** Factors related to mortality in 40 cases of *Achromobacter xylosoxidans* bacteremia

| Factor | No. of deaths/ no. of cases (%) | Odds ratio of deaths within each category (95% confidence interval) | $p$ value |
|---|---|---|---|
| Gender | | | 0.873 |
| Male | 14/29 (48.3) | 1 | |
| Female | 5/11 (45.5) | 1.12 (0.278-4.508) | |
| Age | | | 0.105 |
| <60 years | 6/18 (33.3) | 1 | |
| ≤60 years | 13/22 (59.1) | 2.889 (0.79-10.57) | |
| Acquisition | | | 0.003 |
| Community | 1/11 (9.1) | 1 | |
| Hospital | 18/29 (62.1) | 16.364 (1.835-145.95) | |
| Polymicrobial bacteremia | 6/7 (85.7) | 9.231 (0.993-85.775) | 0.04 |
| Diabetes mellitus | 2/6 (33.3) | 0.5 (0.081-3.103) | 0.664 |
| Chronic renal insufficiency | 5/9 (55.6) | 1.518 (0.341-6.755) | 0.712 |
| Liver cirrhosis | 4/6 (66.7) | 2.533 (0.407-15.751) | 0.398 |
| Malignancy | 11/23 (69.6) | 1.031 (0.294-3.619) | 0.962 |
| Cardiovascular disease | 3/4 (75) | 3.75 (0.355-39.586) | 0.331 |
| Major surgery | 6/14 (42.9) | 0.75 (0.203-2.775) | 0.666 |
| Use of steroids | 7/10 (70) | 3.5 (0.752-16.279) | 0.148 |
| Neutropenia | 7/12 (58.3) | 1.867 (0.474-7.347) | 0.369 |

**Table 4.** Activity of antimicrobial agents against 45 isolates of *Achromobacter xylosoxidans* by disk susceptibility testing

| Antibiotic | Total no. of isolates tested | Sensitive (%) | Intermediate (%) | Resistant (%) |
|---|---|---|---|---|
| Ampicillin | 22 | 4.5 | 54.5 | 40.9 |
| Aztreonam | 30 | 0 | 0 | 100 |
| Cefazolin | 22 | 0 | 4.5 | 95.5 |
| Cefuroxime | 14 | 0 | 0 | 100 |
| Ceftriaxone | 14 | 0 | 16.7 | 83.3 |
| Ceftizoxime | 16 | 0 | 0 | 100 |
| Ceftazidime | 45 | 91.1 | 6.7 | 2.2 |
| Cefepime | 35 | 22.9 | 25.7 | 51.4 |
| Amikacin | 45 | 4.4 | 8.9 | 86.7 |
| Gentamicin | 45 | 0 | 6.7 | 93.3 |
| Ciprofloxacin | 43 | 18.6 | 28 | 53.5 |
| Imipenem | 36 | 97.2 | 0 | 2.8 |
| Piperacillin | 45 | 95.6 | 0 | 4.4 |
| TMP-SMZ | 14 | 78.6 | 0 | 21.4 |

Abbreviation: TMP-SMZ = trimethoprim-sulfamethoxazole

It caused bacteremia with substantial mortality (47.5%). Review of our medical records revealed serious infections other than bacteremia, such as peritonitis, empyema, meningitis, ocular infection, pneumonia and chronic otitis media. These results are similar to previous reports [2,3,24,25]. The clinical manifestations in our bacteremic patients were similar to those in other types of Gram-negative bacilli septicemia including fever (82.5%), chills (37.5%), hypotension (32.5%) and altered consciousness (27.5%).

Among the 40 bacteremic patients, *A. xylosoxidans* was not isolated concomitantly from other body sites. However, Port-A-Cath implants (55%) and surgery (35%), especially intra-abdominal surgery (25%), were frequent among these bacteremic patients. The finding of recurrent positive blood cultures suggests the foci of infection were in the colonized central venous catheters. Removal of the Port-A-Cath prevented further bacteremia in 3 out 4 patients with recurrent *A. xylosoxidans* bacteremia. This suggests central venous catheters are the common sources of infection. These findings are consistent with previous reports [2,3,24-26].

Nosocomial infection and outbreaks caused by *A. xylosoxidans* have been reported with contaminated intravascular catheters and fluids (saline, disinfectants, chlorhexidine and deionized water in hemodialysis systems) [16-19,21]. However, the source of contamination in our patients could not be demonstrated because environmental factors could not be investigated in this retrospective study. A previous report suggested that health care workers contaminated the intravenous catheters by not wearing gloves [3].

The fatality rate due to *A. xylosoxidans* bacteremia was 47.5% in this series, which is much higher than that reported previously (15-30%) [2,3]. The only risk factors significantly associated with mortality in this series were nosocomial acquisition and polymicrobial bacteremia ($p<0.05$). A previous report suggested that age over 65 years and neutropenia were also risk factors [3]. Our data could not confirm these factors as associated with mortality. The significance of diabetes mellitus, chronic renal insufficiency, liver cirrhosis, cardiovascular disease, and use of steroids were not demonstrated in this study.

*A. xylosoxidans* bacteremia was always a nosocomial infection in previous studies [2,20,24]. However, more than one-quarter (27.5%) of the bacteremic episodes in this series were community acquired. The mortality rate was lower in community-acquired (9.1%) than in nosocomial bacteremia (62.1%). The results of disk susceptibility testing of hospital acquired and community-acquired isolates were not different. One of the reasons other than antimicrobial sensitivity that might have accounted for a higher mortality in nosocomial bacteremia was delayed or inappropriate antimicrobial treatment.

*Achromobacter* spp. are identified by recovery of oxidase-positive, catalase-positive, indole-negative, and urease-negative organisms with flat, spreading edges on blood agar plates. Because of the lack of reactivity in many biochemical or assimilation tests, *A. xylosoxidans* can be mistaken for other non-fermentative, Gram-negative rods, such as *Pseudomonas* spp. [27]. This fact leads to underestimation and misdiagnosis of *A. xylosoxidans* infection resulting in inappropriate

treatment. To prevent *A. xylosoxidans* nosocomial infections, it is important to promptly identify the sources of contamination and to distinguish *A. xylosoxidans* from related strains, especially *Pseudomonas* spp.

The in vitro antimicrobial susceptibility of *A. xylosoxidans* in this series demonstrates a characteristic susceptibility profile. Our bacteremic isolates were susceptible to piperacillin (95.6%), ceftazidime (91.1%), imipenem (97.2%) and trimethoprim-sulfamethoxazole (78.6%) and resistant to aminoglycosides, ampicillin, aztreonam and most cephalosporins. The susceptibility to cefepime and ciprofloxacin varied. These results are in agreement with previous reports [2,3,24,25]. Plasmid-mediated β-lactamases might contribute to the resistance of these organisms to most β-lactam antibiotics [28]. Optimal treatment for *A. xylosoxidans* infection remains to be established but the use of susceptible antibiotics as monotherapy or in combination may be adequate.

In conclusion, *A. xylosoxidans* is a rare human pathogen which can cause invasive infections in immunocompromised or debilitated patients. In this series, bacteremia resulted in high mortality and was usually associated with central venous catheter infection. Nosocomial bacteremia and polymicrobial bacteremia were risk factors for fatal outcome. Once an *A. xylosoxidans* infection is confirmed, investigation of potential environmental factors is critical. Materials related to intravascular intervention such as saline, disinfectants, iodine, and intravascular catheters should be examined for the presence of this organism. Intensive hygienic measures are important to eliminate colonization and transmission to prevent nosocomial spread. In patients with recurrent infection, removal of catheter implants should be considered. Empiric antimicrobial therapy with piperacillin, imipenem, ceftazidime or trimethoprim-sulfamethoxazole, or a combination of these agents may be appropriate before the susceptibility profile is available.

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