

Achromobacter xylosoxidans Bacteremia: Report of Four Cases and Review of the Literature

Joan M. Duggan,* Steven J. Goldstein,*
Carol E. Chenoweth, Carol A. Kauffman,
and Suzanne F. Bradley

From the Divisions of Infectious Diseases and Geriatric Medicine,
Department of Internal Medicine, Department of Veterans Affairs
Medical Center and University of Michigan Medical School,
Ann Arbor, Michigan

Seventy-seven cases of bacteremia due to *Achromobacter xylosoxidans* were reviewed, and susceptibility studies were performed on 11 clinical isolates of *A. xylosoxidans*. Nosocomial bacteremia was noted in 54 of 77 patients (70%), and 28 (36%) had infection associated with an outbreak or acquired from a discrete point source. The most common underlying illnesses were malignancies (30%) and cardiac disease (21%); immunosuppression affected 27%. The most common clinical syndromes were primary and catheter-associated bacteremia (19% each) and pneumonia (16%). The case-fatality rate was 30%; only 3% of patients with primary or catheter-associated bacteremia died, but 65% of patients with meningitis, endocarditis, and pneumonia died. The case-fatality rate in neonates was 80%. Susceptibility studies showed that all strains were resistant to aminoglycosides, most were resistant to quinolones, and all were susceptible to broad-spectrum penicillins, imipenem, ceftazidime, and trimethoprim-sulfamethoxazole. Two-disk approximation and time-kill studies showed synergy or additive effects for the combination of gentamicin and piperacillin against most strains.

Achromobacter xylosoxidans is an aerobic, motile, gram-negative rod first described in 1971 by Yabuuchi and Ohyama, who discovered it in patients with chronic, purulent otitis media [1]. It is a member of a heterogeneous group of oxidase-positive, nonfermentative gram-negative bacilli previously classified as CDC group Vd, which includes other related but taxonomically distinct organisms such as *Ochrobactrum anthropi*, *Agrobacterium tumefaciens* (*radiobacter*), and *Achromobacter* group b [2–4]. Previously this organism was named *Alcaligenes denitrificans* subspecies *xylosoxidans* and *Alcaligenes xylosoxidans* subspecies *xylosoxidans*, but clinically it is more widely recognized as *Achromobacter xylosoxidans*.

While *Achromobacter* species have been isolated occasionally from the human gastrointestinal tract and ear canal, it is unclear whether the organisms are a usual component of human endogenous flora [5]. *Achromobacter* species inhabit aquatic environments, including well water, intravenous fluids, and water in humidifiers [6–8]. Infections with *A. xylosoxidans* have included bacteremia, meningitis, urinary tract infections, abscesses, osteomyelitis, corneal ulcers, prosthetic valve endocarditis, peritonitis, and pneumonia in both immunocompetent and immunocompromised hosts [5–40]. Bacteremic infection with this organism is thought to occur mostly nosocomially in immunocompromised patients and to be associated with a high mortality. Treatment of *A. xylosoxidans* infections is often dif-

ficult, and an optimal antimicrobial regimen has not been determined [28].

We present four cases of *A. xylosoxidans* bacteremia and review another 73 cases in the English-language literature in regard to risk factors, clinical presentation, sequelae, and optimal therapeutic modalities for this unusual infection. We also present our results of antimicrobial susceptibility testing and synergy studies of 11 clinical isolates of *A. xylosoxidans*.

Methods

Case reports of *A. xylosoxidans* bacteremia in the English-language literature were identified through a computer-generated search and the subsequent review of noted references. A case was defined as one in which at least one blood culture was positive for *A. xylosoxidans* or *A. denitrificans* subspecies *xylosoxidans* in the setting of clinical illness or, with regard to cases described before 1977, one in which at least one blood culture was positive for an *Achromobacter* species that was retrospectively considered to be *A. xylosoxidans*. Cases were included for analysis if enough demographic information was available to allow identification of individual patients.

Isolates of *A. xylosoxidans* were obtained from 1991 to 1992 from 11 patients seen at the University of Michigan Hospitals. Four patients (described in this report) had bacteremia, six had pneumonia or tracheitis, and one had a wound infection. Isolates were identified as *A. xylosoxidans* by the MicroID system (Organon Teknika, Raleigh, NC) and API 20E system (Analytab Products, Plainview, NY).

Antibiotic susceptibility studies were performed by both standard Kirby-Bauer methods and microtiter broth dilution assays, according to guidelines of the National Committee for Clinical Laboratory Standards [41, 42]. Two-disk approxima-

Received 13 December 1995; revised 13 May 1996.

* Current addresses: Dr. Duggan, Medical College of Ohio, Toledo, Ohio 43699; Dr. Goldstein, 2201 Greentree, Clarksville, Indiana 47129.

Reprints or correspondence: Dr. Suzanne F. Bradley, GRECC IIG, V.A. Medical Center, 2215 Fuller Road, Ann Arbor, Michigan 48105.

Clinical Infectious Diseases 1996;23:569–76

This article is in the public domain.

tion studies were performed with pairs of antibiotic disks (BBL—Becton Dickinson Microbiology Systems, Cockeysville, MD) placed at distances equal to or slightly greater than the sum of the individual radii of their zones of inhibition. Synergy was defined as an increased and convex inhibition of growth between two disks. Antagonism was defined as growth between the two disks. If the zones were unchanged, this was considered as no effect [43].

Time-kill-curve studies were performed with selected combinations of antibiotics that appeared to be synergistic by two-disk diffusion studies. Each isolate was subcultured onto a trypticase soy agar plate, and 3–5 colonies were picked and grown overnight in supplemented Mueller-Hinton broth. After standardization to 10^8 cfu/mL with use of a 0.5 McFarland standard (Remel, Lenexa, KS), each organism was diluted to 10^5 cfu/mL in Mueller-Hinton broth. The actual inoculum present was verified by standard spread-plate methods.

The three antibiotics studied (piperacillin, gentamicin, and trimethoprim-sulfamethoxazole [TMP-SMZ]) were added alone or in combination to tubes containing the standardized inocula for each organism [44]. Synergy and antagonism were defined as a 3-log decrease or increase, respectively, in bacterial growth when tubes with a combination of antibiotics were compared with tubes with a single antibiotic. An additive, but not synergistic, effect was defined as a decrease in bacterial growth that was less than 3 logs.

Case Reports

Case 1. A 21-year-old man with no medical history was admitted to the hospital following 3 days of vomiting, diarrhea, headache, fevers, chills, chest tenderness, and cough. He was noted to be lethargic and had a temperature of 38.8°C , a pulse of 110/min, and respirations of 24/min. There were decreased breath sounds in the left lung. The WBC count was $8,000/\text{mm}^3$ and the platelet count was $4,000/\text{mm}^3$. The blood urea nitrogen concentration was 27 mg/dL, and that of serum creatinine was 1.4 mg/dL. A chest roentgenogram revealed diffuse interstitial markings with a nodular pattern, and adult respiratory distress syndrome later developed. He required vasopressor support for hypotension and hemodialysis for worsening renal failure.

On hospital day 6, culture of an endotracheal aspirate yielded *A. xylosoxidans* and *Stenotrophomonas maltophilia*. On hospital day 10, blood cultures yielded *A. xylosoxidans*. Therapy with intravenous ceftazidime was initiated on day 8, and administration of tobramycin was started 2 days later. His antimicrobial therapy was eventually changed to administration of intravenous TMP-SMZ with tobramycin. Despite antimicrobial therapy, sputum cultures performed on day 23 yielded *A. xylosoxidans*. Thirty days after admission the patient died of hypotension, persistent sepsis, and adult respiratory distress syndrome. The etiology of his presenting illness was never identified.

Case 2. An 18-year-old boy with a history of cerebral palsy and congenital ichthyosis was admitted to the hospital for his

second course of chemotherapy for acute lymphocytic leukemia. On hospital day 3 a subclavian venous access port was placed, and 2 days later cytosine arabinoside, daunorubicin, and 6-thioguanine were administered. On hospital day 8 his temperature rose to 38.8°C . Two sets of blood cultures yielded methicillin-susceptible *Staphylococcus aureus*, and treatment with intravenous vancomycin was initiated.

On hospital day 10 the venous access port site became erythematous, and blood culture specimens drawn through the port yielded *A. xylosoxidans* and *Serratia marcescens*. His WBC count was $4,000$ cells/ mm^3 . Antibiotics were changed to ticarcillin/clavulanic acid and tobramycin, and the patient defervesced. On hospital day 21 fever again developed, and repeated blood cultures yielded methicillin-resistant *S. aureus*. Therapy with vancomycin was restarted, and the venous access port was removed on hospital day 22. Culture of the catheter tip yielded methicillin-resistant *S. aureus*; *A. xylosoxidans* was not found. Antibiotics were withdrawn after 20 days of therapy, and the remainder of his hospitalization was uneventful.

Case 3. A 12-year-old girl receiving maintenance chemotherapy for relapsed acute lymphocytic leukemia was admitted to the hospital because of a 1-day history of headache and chills. Eleven days before admission she had received chemotherapy with adriamycin, cytosine arabinoside, and 6-thioguanine through an indwelling Broviac catheter. Upon admission she had a temperature of 39.8°C , blood pressure of 70/50 mm Hg, and pulse of 115/min. No tenderness, erythema, or drainage was noted at the Broviac catheter site. Her WBC count was $5,200/\text{mm}^3$. Blood culture specimens drawn from the Broviac catheter and from a peripheral site yielded *A. xylosoxidans*. The blood from the catheter also yielded a methicillin-susceptible coagulase-negative *Staphylococcus* species and *Acinetobacter baumannii*.

Administration of intravenous ticarcillin, tobramycin, and vancomycin was initiated. On the fifth hospital day the antibiotics were changed to ticarcillin/clavulanic acid and gentamicin, and this therapy continued through day 14. She quickly became afebrile, although cultures of blood drawn from the Broviac catheter were repeated on days 2 and 5 and yielded a coagulase-negative *Staphylococcus* species. She was discharged on hospital day 15 with the catheter in place and had no recurrence of bacteremia.

Case 4. A 36-year-old woman was admitted to the hospital following 2–3 days of fevers, chills, myalgia, nausea, vomiting, cough productive of clear sputum, headache, and somnolence. Her medical history was significant for renal failure due to congenital renal hypoplasia, bilateral nephrectomy, a failed cadaveric renal transplantation, and peritoneal dialysis complicated by *Aspergillus fumigatus* peritonitis and a perisplenic abscess. She was undergoing hemodialysis through a subclavian access catheter. On physical examination she appeared ill and lethargic but was arousable, and she had a temperature of 38.9°C , blood pressure of 150/92 mm Hg, and pulse of 112/min. She had maxillary sinus tenderness and a II/VI systolic murmur at the left-upper-sternal border. Her previous

Table 1. Underlying conditions of 77 patients with *Achromobacter xylosoxidans* bacteremia.

Condition or risk-associated status	No. (%) of patients*
Malignancy	23 (30)
Hematologic	10
Solid organ	13
Cardiovascular disease	16 (21)
Neonate or premature infant	10 (13)
Renal failure	6 (8)
Transplant recipient	3 (4)
Diabetes mellitus	3 (4)
Other†	13 (17)
Unknown/none	4 (5)

* Some patients had more than one underlying condition.

† Gastrointestinal disease (3), prior pneumonia (3), neurological disorder (2), collagen vascular disease (2), cirrhosis (1), HIV infection (1), or injection drug use (1).

abdominal wound sites were well-healed. Purulent drainage from the catheter site was noted.

Treatment with vancomycin and tobramycin began on hospital day 1. Two blood specimens, one from the subclavian access catheter and another from a peripheral site, yielded a coagulase-negative *Staphylococcus* species and *A. xylosoxidans* when cultured. Culture of drainage from the subclavian access catheter site yielded a coagulase-negative *Staphylococcus* species. On hospital day 4 ceftazidime was added to the treatment regimen. She became afebrile on hospital day 5; however, cultures of blood drawn on days 5, 7, and 9 yielded *A. xylosoxidans*.

The patient initially declined to have her subclavian access catheter removed and was discharged on hospital day 10 during therapy with oral ciprofloxacin and intravenous ceftazidime (given post-dialysis). Two more sets of blood cultures performed the following day were positive for *A. xylosoxidans*, and the catheter was subsequently removed. She did well and had no further recurrence of bacteremia.

Results

Demographics. A total of 77 cases of *A. xylosoxidans* bacteremia were reported between 1960 and 1993 [5, 6, 8, 17, 19–40], comprising 42 men (55%) and 35 women (45%). Twenty-one patients (27%) were <18 years of age; 14 of the 21 were ≤12 months of age. The mean age of all patients (± SD) was 38 ± 28.1 years (range, 2 days to 83 years). Fifty-four patients (70%) had nosocomial bacteremia, and 28 (36%) of these had infection associated with an outbreak or an isolated point source. Twelve patients (16%) had community-acquired infection, and for 11 patients (14%) sufficient demographic information was not available.

Underlying diseases. The majority of patients had significant underlying illnesses (table 1). The most commonly seen underlying illnesses were malignancies and cardiovascular dis-

eases. Ten patients (13%) were neonates or premature infants, and 21 (27%) were considered to be immunosuppressed.

Polymicrobial infection. Eight patients, five of whom were immunocompromised, had polymicrobial bacteremia ([19, 34, 40] and cases 2 and 3). Four patients had three or four organisms recovered concurrently from blood cultures. Concomitant infecting organisms were most often *Acinetobacter*, *Pseudomonas*, and *Staphylococcus* species. Three of 12 patients with *A. xylosoxidans* pneumonia ([5, 28] and case 1) had other organisms recovered concurrently from sputum.

Source of infection. An exogenous source was determined for 27 patients (35%) who had infection associated with an outbreak or an isolated point source. The source of one patient’s achromobacter bacteremia appeared to be well water [6]; for the other 26 [5, 8, 20, 35, 38, 39], the source was a contaminated solution or contaminated equipment used in the hospital. Thus, in ~50% of nosocomial cases a discrete point source was identified. One patient had bacteremia secondary to use of a contaminated hemodialysis system [5]. For two patients, endocarditis was related to a contaminated cardiovascular bypass machine used during surgery [20]. Contaminated aqueous eosin solution applied to an area of dermatitis led to another case of bacteremia [35].

Most of the cases were associated with the use of contaminated solutions. In the largest outbreak, nonbacteriostatic saline used to dilute radionuclide tracers became contaminated, and bacteremia subsequently occurred in 10 patients [38]. Another eight patients were infected when arterial pressure transducers were reused after presumed “sterilization” in a contaminated quaternary ammonium solution [39]. An outbreak involving four infants was traced back to contaminated eye wash and incubator-humidification equipment in a neonatal nursery [8]. In all of these point-source infections, adherence to appropriate infection-control practices stopped the outbreak.

Clinical syndromes. The most common clinical syndromes associated with *A. xylosoxidans* bacteremia were primary bacteremia (in which no source was identified), occurring in 15 patients (19%), and bacteremia related to an intravenous catheter, which occurred in another 15 patients (19%) (table 2). With regard to 17 patients there were too few data to establish

Table 2. Clinical syndromes associated with *Achromobacter xylosoxidans* bacteremia in 77 patients.

Syndrome	No. (%) of patients
Primary bacteremia	15 (19)
Intravascular catheter-associated bacteremia	15 (19)
Pneumonia	12 (16)
Gastrointestinal or biliary tract infection	5 (6)
Endocarditis	4 (5)
Meningitis	4 (5)
Urinary tract infection	3 (4)
Septic arthritis	1 (1)
Soft-tissue infection	1 (1)
Unknown	17 (22)

whether focal infection or primary bacteremia was present. Eight of the 12 patients (67%) with community-acquired infection had a specific focus of infection rather than primary bacteremia. Of the 10 neonates, 4 had pneumonia [8], 3 had meningitis [21, 30, 35], 1 had primary bacteremia in utero [32], and 2 had an unknown site of infection [40].

There were 12 patients with pneumonia; 2 had community-acquired infection [23, 28], and 4 of the 12 patients were immunocompromised [5, 23, 34]. Intraabdominal infection occurred in five patients, four of whom had cholecystitis [22, 29, 31, 34, 37]. Three patients had proven or presumed urinary tract infection [19, 31, 32]; in two of these patients, urinary tract instrumentation preceded bacteremia. Four patients had endocarditis [20, 24, 25]. Two patients with congenital cardiac anomalies acquired infection from a contaminated cardiovascular bypass machine, and the onset of bacteremia occurred within 72 hours of operation [20]. Two other patients had prosthetic valve endocarditis within 6 months of cardiac surgery [24, 25]. Four infants had bacteremic achromobacter meningitis [17, 21, 30, 35]. All had significant underlying illnesses or were born after a complicated pregnancy.

Symptoms and signs. Fifty-seven cases involved documented signs and symptoms at initial presentation or during the patient's hospital stay. Forty-nine patients (86%) were febrile. Five of the eight patients who were afebrile were newborns [5, 8, 22, 32]. Fifteen patients (26%) reported chills, while 17 patients (30%) had constitutional complaints, including arthralgias, myalgias, anorexia, lethargy, and weakness.

Eleven patients (19%) had skin manifestations ([6, 8, 33–35] and case 2). Seven patients had erythematous, nodular, or plaquelike lesions without eschars or ulcerations [6, 8, 35]. In three other patients, erythema or purulence at an intravascular catheter site was thought to be due to *A. xylosoxidans* ([34] and case 2). One patient had cellulitis in several different anatomic areas and a joint effusion that subsequently yielded *A. xylosoxidans* [33]. Only two patients' lesions were biopsied for culture, and in both cases cultures subsequently yielded *A. xylosoxidans* [6, 34]. Six of the seven patients with metastatic skin lesions died.

The few patients who had initial complaints pertaining to the pulmonary, genitourinary, or central nervous system were found to have infection involving these organs. On the other hand, 10 patients (17%), only three of whom were thought to have infection from a gastrointestinal source, reported epigastric or generalized abdominal pain, nausea, vomiting, or diarrhea.

Patients with community-acquired pneumonia presented following the acute onset of cough that was productive of purulent sputum, pleuritic chest pain, hypoxemia, and lobar infiltrates [23, 28]. Cases of hospital-acquired pneumonia had variable manifestations, but generally the symptoms and signs were less dramatic than those in the cases of community-acquired pneumonia.

Three neonates and one 2-month-old infant had meningitis [17, 21, 30, 35]. All were febrile, and two of the four were irritable. No other specific signs of CNS infection were present.

WBC counts in the CSF ranged from 210/mm³ to 9,200/mm³, with a predominance of either neutrophils (63% in one infant) or mononuclear cells (86% in another). Three children's CSF, as well as blood, yielded *A. xylosoxidans*.

For two of the four patients with endocarditis, few clinical data were provided [20], but both had infection within 3 days of surgery and one died 5 days later. The other two patients, in whom endocarditis developed 4–6 months after valve replacement, manifested a subacute course with fever, malaise, and myalgias [24, 25]. Embolic events occurred in both patients. Blood cultures remained persistently positive in spite of antibiotic therapy, and both patients died.

Treatment. For 38 of the 77 patients, no information about treatment was reported. Of the remaining 39 patients, one patient received no treatment [8] and another was treated only by removal of an infected intravascular catheter [34]. Ten patients (26%) underwent either a surgical procedure or removal of an intravascular catheter, in addition to antibiotic therapy. Five of these 10 patients received monotherapy with TMP-SMZ, an extended-spectrum penicillin, or a third-generation cephalosporin, and the other five patients received combination therapy, generally with an aminoglycoside and one of the antibiotics listed above.

Twenty-seven patients (69%) were treated with antibiotics alone, including two ([36] and case 3) who were subsequently cured of infection despite the fact that an infected intravascular catheter was left in place. Five of these 27 received monotherapy and the remaining 22 received combination therapy. Eleven patients treated with combination antibiotic therapy received an aminoglycoside and a β -lactam antibiotic. The duration of 24 patients' antibiotic therapy was specified: 10 received it for >21 days, 2 for 14–21 days, 5 for 7–14 days, and 7 for <7 days.

Susceptibility data were available for isolates from 73 of 77 patients. In general, most isolates were resistant to all aminoglycosides, narrow-spectrum penicillins, and first- and second-generation cephalosporins and were susceptible to extended-spectrum penicillins, third-generation cephalosporins, TMP-SMZ, and imipenem. Eleven of 20 isolates were resistant to ciprofloxacin.

Complications. Complications and long-term sequelae were reported to occur in only 13 patients. However, 10 of the 12 patients with pneumonia had complications, including empyema, adult respiratory distress syndrome, chronic scarring, and secondary and recurrent pneumonia. Three of four infants with meningitis had hydrocephalus, seizures, intraventricular hemorrhage, or developmental delays [17, 21, 30, 35]. One patient experienced acute renal failure [26], and another had recurrent septic arthritis [33].

Mortality. A total of 23 patients (30%) died. There were no deaths from intravascular catheter-associated bacteremia, and only one death (that of a neonate) occurred among patients with primary bacteremia. However, 8 of 12 patients with pneumonia died ([5, 8, 27, 28] and case 1), as did 3 of 4 patients with endocarditis [20, 24, 25]. The highest case-fatality rate

was among neonates, of whom eight of 10 died [8, 21, 32, 35, 40]. Immunosuppressed patients had a lower case-fatality rate (24%) than patients who did not have underlying immunosuppression (32%). Fifteen (65%) of the 23 deaths occurred as a consequence of nosocomial infection, and 9 (60%) of these 15 deaths were associated with outbreaks.

In vitro susceptibility studies. In Kirby-Bauer disk-diffusion studies, our 11 isolates were susceptible to piperacillin, imipenem, ticarcillin/clavulanic acid, ceftazidime, and TMP-SMZ. Only two isolates were susceptible to ofloxacin and ciprofloxacin, and another was susceptible to ofloxacin alone. All 11 isolates were resistant to gentamicin (MIC₉₀, >500 µg/mL). The MIC₉₀ and MBC₉₀ of piperacillin were each 0.5 µg/mL; the MIC₉₀ of TMP-SMZ was 2/38 µg/mL, and the MBC₉₀ was 16/304 µg/mL.

Further studies by a two-disk approximation method showed that β-lactam drugs were synergistic with gentamicin, but few isolates showed synergy when a β-lactam drug, imipenem, or gentamicin was combined with ciprofloxacin (table 3). Synergy was demonstrated when TMP-SMZ and gentamicin were used in combination, but the combination of TMP-SMZ and ciprofloxacin was rarely synergistic. Antagonism was noted when TMP-SMZ was combined with β-lactam antibiotics.

For the combination of piperacillin and gentamicin, the two-disk approximation studies predicted a synergistic effect in nine isolates and no effect in two. Time-kill studies on 10 of the 11 isolates showed synergy for only 1 isolate, an additive effect for 5 isolates, and no effect for 4 isolates (figure 1). When

Table 3. Results of two-disk diffusion assays for 11 isolates of *Achromobacter xylosoxidans*.

Antibiotic combination	No. of isolates for which assays indicated:		
	Synergy	Antagonism	No effect
Gentamicin plus			
Piperacillin	9	0	2
Ticarcillin/clavulanate	10	0	1
Ceftazidime	9	0	2
Imipenem	8	1	2
TMP-SMZ	7	0	4
Ciprofloxacin	2	0	9
Ciprofloxacin plus			
Piperacillin	2	0	9
Ticarcillin/clavulanate	1	0	10
Ceftazidime	1	0	10
Imipenem	1	0	10
TMP-SMZ	1	0	10
Gentamicin	2	0	9
TMP-SMZ plus			
Piperacillin	0	11	0
Ticarcillin/clavulanate	0	10	1
Ceftazidime	0	10	1
Imipenem	0	4	7
Gentamicin	7	0	4
Ciprofloxacin	1	0	10

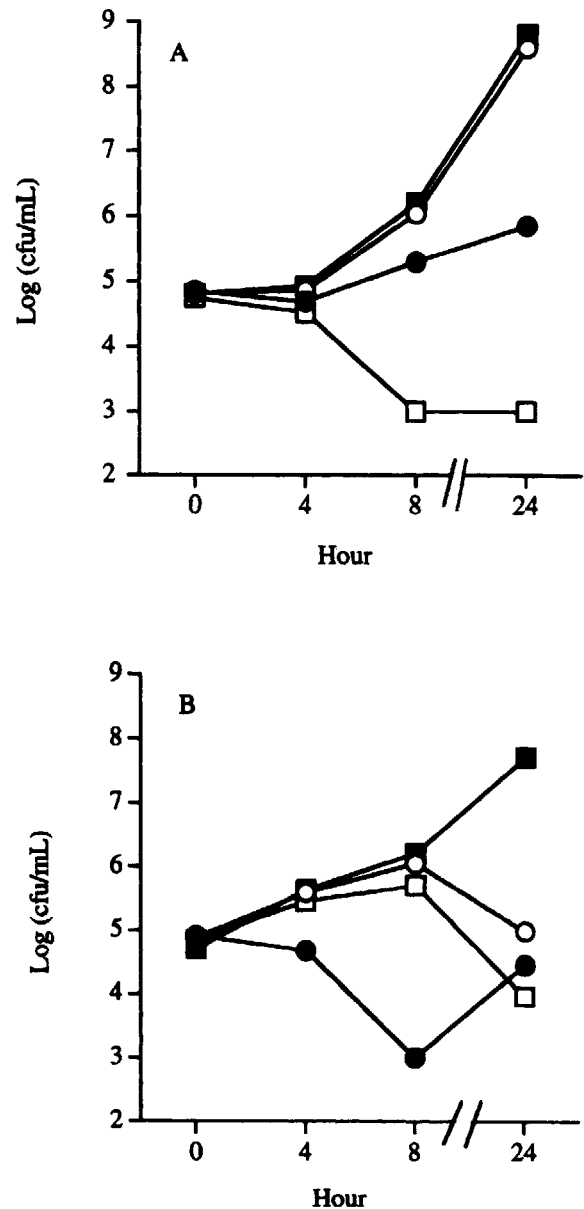


Figure 1. A, results of time-kill assays for a representative isolate of *A. xylosoxidans* that showed synergy with the combination of piperacillin and gentamicin. Of the 10 isolates studied, the combination (□) resulted in a ≥3-log decrease in bacterial growth (synergy) for only this one isolate at 24 hours, a <3-log decrease (additive effect) for 5 isolates, and no effect for 4 isolates, as compared with the effect of piperacillin alone (○), as compared with the growth control (■). B, results for a representative isolate of *A. xylosoxidans* that showed indifference with the combination of piperacillin and TMP-SMZ. Of the 10 isolates studied, the combination (□) resulted in a <3-log decrease in bacterial growth (additive effect) for 2 isolates and an increase for 8 isolates, as compared with the effect of piperacillin alone (●). A decline in bacterial growth was seen only at 24 hours with TMP-SMZ alone (○), as compared with the growth control (■).

piperacillin and TMP-SMZ were combined, the two-disk diffusion studies predicted antagonism for all 11 isolates. However, in time-kill studies, 8 of the 10 isolates studied showed increased growth but not true antagonism, and 2 showed an

additive effect when TMP-SMZ was added to piperacillin, as compared with the effect of piperacillin alone (figure 1).

Discussion

A. xylosoxidans is an aerobic, catalase-positive, oxidase-positive, gram-negative bacillus that inhabits a variety of aqueous environments. Most descriptions of small outbreaks and individual case reports have emphasized the propensity of *Achromobacter* species to cause bacteremia in immunosuppressed hosts. In fact, only 27% of patients were immunosuppressed, although many had other underlying illnesses. Most cases of bacteremia involved hospitalized patients who had bacteremia secondary to a diagnostic or therapeutic procedure.

In cases in which verification was feasible, the source was usually found to be a contaminated solution. *A. xylosoxidans* is not found as a typical component of the normal human flora, but it does have the ability to survive in aqueous environments with minimal nutrients [28, 45, 46] and thus is likely to cause nosocomial infection when there is a breakdown of infection control techniques.

A. xylosoxidans is a very uncommon cause of bacteremia. In several large reviews of gram-negative bacteremia, no cases were due to *A. xylosoxidans* [47, 48], and in others this organism and other species of *Achromobacter* or *Alcaligenes* accounted for <2% of cases [49, 50]. This circumstance is most likely a reflection of the fact that the organism is not usually found as part of normal human flora, and thus many patients—such as neutropenic hosts, who are prone to bacteremia that develops from their own flora—are less likely to have infection with *A. xylosoxidans* than infection with other gram-negative bacilli [34, 51, 52]. In addition, the small number of cases may be due to the relative nonpathogenicity of *A. xylosoxidans* [46].

The urinary tract is not a common site for the subsequent development of bacteremia with *A. xylosoxidans*, unlike that with other gram-negative bacilli. Only three patients' bacteremia had a urinary tract source. Since urine is the most common site from which *Achromobacter* is isolated in clinical microbiology laboratories [46], this low number of cases of bacteremia is consistent with the low pathogenicity of this organism.

It is noteworthy that almost 20% of patients had metastatic skin lesions during the acute illness. The features of these lesions were similar to those described in patients with infection with other gram-negative bacilli, such as *S. maltophilia* [52]. However, they differed from the classic ecthyma gangrenosum seen with *Pseudomonas aeruginosa* in that they did not progress to central ulceration and eschar formation [53, 54].

Pneumonia was associated with a high case-fatality rate, regardless of whether infection was nosocomial or community-acquired. The case-fatality rate of 67% is not unlike that associated with other bacteremic pneumonias due to gram-negative bacilli, such as *P. aeruginosa* and *S. maltophilia* [55–57]. In our patients, as well as those described with other bacteremic gram-negative pneumonias, pulmonary infection was associ-

ated with underlying illnesses, intubation, and treatment in an intensive care unit.

A. xylosoxidans bacteremia was associated with a case-fatality rate of 80% among neonates, regardless of the site of infection. The majority of neonates had pneumonia or meningitis, which probably contributed to the high mortality rate. Mortality rates among neonates with gram-negative bacteremia and/or meningitis are generally high [58], but neonates with *Achromobacter* bacteremia appeared to do even more poorly. It should be noted that four neonates who died were involved in an outbreak in a nursery, in which it seemed probable that a large number of organisms were aerosolized into the environment and caused pneumonia and subsequent bacteremia [8].

Although the majority of patients who acquired primary or intravascular catheter-associated *Achromobacter* bacteremia in the hospital had some underlying illness, only one death, that of a neonate, was reported in this group. Other investigators have also noted that, with the exception of the rate in cases from a urinary tract source, catheter-associated gram-negative bacteremia is associated with the lowest mortality rate [55, 59, 60]. The majority of intravascular catheter-associated infections were treated initially with removal of the catheter. However, for several patients, therapy was attempted without catheter removal. Bacteremia recurred in most of these patients if the catheter remained in place, as has been noted with regard to catheter-associated infections due to other, similar gram-negative bacilli [59–61]. A surprising finding was that two patients, one of whom we described herein, appeared to be cured by antibiotic therapy alone.

Most *Achromobacter* species isolates have been found to be resistant to first- and second-generation cephalosporins, aminoglycosides, and narrow-spectrum penicillins; susceptible to sulfonamides, carbapenems, broad-spectrum penicillins, and third-generation cephalosporins; and variably susceptible to fluoroquinolones [28, 62, 63]. Our Kirby-Bauer disk susceptibility tests confirmed uniform susceptibility to ceftazidime, piperacillin, imipenem, ticarcillin/clavulanic acid, and TMP-SMZ; resistance to all aminoglycosides; and varying degrees of resistance to ciprofloxacin and ofloxacin.

In addition, the MICs and MBCs of piperacillin and gentamicin and the MIC of TMP-SMZ were comparable to the findings of other investigators [5, 10, 15, 16, 26, 28, 34, 62, 63]. MBCs have been determined infrequently, generally in studies of single isolates [10, 25, 26, 28]. While some investigators found that TMP-SMZ effectively killed *Achromobacter* species organisms, we and others found that TMP-SMZ was bacteriostatic and not bactericidal at concentrations achievable in serum [10, 25].

In two-disk approximation studies, the combination of a β -lactam drug or TMP-SMZ with gentamicin was synergistic. For most isolates, the results of the two-disk approximation studies were predictive of additive or synergistic effects demonstrated by time-kill curves when piperacillin and gentamicin were combined. Although all isolates were resistant to gentamicin, the lower the MIC of gentamicin, the more likely the

piperacillin/gentamicin combination was synergistic or additive. It is possible that a synergistic effect of piperacillin and gentamicin might have been demonstrated in more of our isolates if higher concentrations of piperacillin or gentamicin had been used.

The combination of carbenicillin and TMP-SMZ has been shown to be effective in the empirical treatment of the febrile neutropenic patient [64]. Chandrasekar et al. found that the combination of piperacillin and TMP-SMZ was effective in the treatment of a woman with *A. xylosoxidans* pneumonia, and they demonstrated enhanced killing in vitro [26]. We found by two-disk diffusion studies that combinations of a β -lactam drug and TMP-SMZ were uniformly antagonistic. In time-kill studies the combination of TMP-SMZ and piperacillin demonstrated enhanced growth, but not true antagonism, in nine of 11 isolates. For the majority of isolates, the time-kill curve for TMP-SMZ and piperacillin most closely resembled the time-kill curve for TMP-SMZ alone, rather than that of piperacillin alone.

Despite nearly uniform resistance to aminoglycosides, many patients were treated with an aminoglycoside and a β -lactam drug. Although time-kill techniques have not been well-standardized for gram-negative bacilli, our studies suggest that the addition of gentamicin to piperacillin enhances killing of *A. xylosoxidans*. Thus, a combination of piperacillin and gentamicin might be more effective than a single agent in treating patients with serious *A. xylosoxidans* infection, even if isolates do not appear to be susceptible to aminoglycosides by routine susceptibility testing methods.

Acknowledgment

The authors thank Dr. Carl Pierson for his advice regarding time-kill and two-disk approximation studies.

References

1. Yabuuchi E, Ohyama A. *Achromobacter xylosoxidans* n. sp. from human ear discharge. *Jpn J Microbiol* 1971;15:477-81.
2. Cieslak TJ, Robb ML, Drabick CJ, Fischer GW. Catheter-associated sepsis caused by *Ochrobactrum anthropi*: report of a case and review of related nonfermentative bacteria. *Clin Infect Dis* 1992;14:902-7.
3. Kern WV, Oethinger M, Kaufhold A, Rozdzinski E, Marre R. *Ochrobactrum anthropi* bacteremia: report of four cases and short review. *Infection* 1993;21:306-10.
4. Pickett MJ, Hollis DG, Bottone EJ. Miscellaneous gram-negative bacteria. In: Balows A, Hausler WJ Jr, Herrmann KL, Isenberg HD, Shadomy HJ, eds. *Manual of clinical microbiology*. 5th ed. Washington, DC: American Society for Microbiology, 1991:410-28.
5. Reverdy ME, Freney J, Fleurette J, et al. Nosocomial colonization and infection by *Achromobacter xylosoxidans*. *J Clin Microbiol* 1984;19:140-3.
6. Spear JB, Fuhrer J, Kirby BD. *Achromobacter xylosoxidans* (*Alcaligenes xylosoxidans* subsp. *xylosoxidans*) bacteremia associated with a well-water source: case report and review of the literature. *J Clin Microbiol* 1988;26:598-9.
7. Reina J, Antich M, Siquier B, Alomar P. Nosocomial outbreak of *Achromobacter xylosoxidans* associated with a diagnostic contrast solution [letter]. *J Clin Pathol* 1988;41:920-1.

8. Foley JF, Gravelle CR, Englehard WE, Chin TDY. *Achromobacter* septicemia—fatalities in prematures. I. Clinical and epidemiological study. *Am J Dis Child* 1961;101:279-88.
9. Appelbaum PC, Campbell DB. Pancreatic abscess associated with *Achromobacter* group Vd biovar 1. *J Clin Microbiol* 1980;12:282-3.
10. D'Amato RF, Salemi M, Mathews A, Cleri DJ, Reddy G. *Achromobacter xylosoxidans* (*Alcaligenes xylosoxidans* subsp. *xylosoxidans*) meningitis associated with a gunshot wound. *J Clin Microbiol* 1988;26:2425-6.
11. Morrison AJ Jr, Boyce K IV. Peritonitis caused by *Alcaligenes denitrificans* subsp. *xylosoxydans*: case report and review of the literature. *J Clin Microbiol* 1986;24:879-81.
12. Namnyak SS, Holmes B, Fathalla SE. Neonatal meningitis caused by *Achromobacter xylosoxidans*. *J Clin Microbiol* 1985;22:470-1.
13. Barson WJ, Cromer BA, Marcon MJ. Puncture wound osteochondritis of the foot caused by CDC group Vd. *J Clin Microbiol* 1987;25:2014-6.
14. Gradon JD, Mayrer AR, Hayes J. Pulmonary abscess associated with *Alcaligenes xylosoxidans* in a patient with AIDS [letter]. *Clin Infect Dis* 1993;17:1071-2.
15. Newman PE, Ilider P, Waring GO III, Ilill EO, Wilson LA, Harbin TS. Corneal ulcer due to *Achromobacter xylosoxidans*. *Br J Ophthalmol* 1984;68:472-4.
16. Shigeta S, Yasunaga Y, Honzumi K, Okamura H, Kumata R, Endo S. Cerebral ventriculitis associated with *Achromobacter xylosoxidans*. *J Clin Pathol* 1978;31:156-61.
17. Sepkowitz DV, Bostic DE, Maslow MJ. *Achromobacter xylosoxidans* meningitis: case report and review of the literature. *Clin Pediatr* 1987;26:483-5.
18. Taylor P, Fischbein L. Prosthetic knee infection due to *Achromobacter xylosoxidans*. *J Rheumatol* 1992;19:992-3.
19. Van Horn KG, Gedris CA, Ahmed T, Wormser GP. Bacteremia and urinary tract infection associated with CDC Group Vd biovar 2. *J Clin Microbiol* 1989;27:201-2.
20. Linde LM, Heins HL. Bacterial endocarditis following surgery for congenital heart disease. *N Engl J Med* 1960;263:65-9.
21. Lee SL, Tan KL. *Achromobacter* meningitis in the newborn. *Singapore Med J* 1972;13:261-5.
22. Holmes B, Snell JJS, Lapage SP. Strains of *Achromobacter xylosoxidans* from clinical material. *J Clin Pathol* 1977;30:595-601.
23. Dworzack DL, Murray CM, Hodges GR, Barnes WG. Community-acquired bacteremic *Achromobacter xylosoxidans* type IIIa pneumonia in a patient with idiopathic IgM deficiency. *Am J Clin Pathol* 1978;70:712-7.
24. Lofgren RP, Nelson AE, Crossley KB. Prosthetic valve endocarditis due to *Achromobacter xylosoxidans*. *Am Heart J* 1981;101:502.
25. Olson DA, Hoepflich PD. Postoperative infection of an aortic prosthesis with *Achromobacter xylosoxidans*. *West J Med* 1982;136:153-7.
26. Chandrasekar PH, Arathoon E, Levine DP. Infections due to *Achromobacter xylosoxidans*: case report and review of the literature. *Infection* 1986;14:279-82.
27. Arroyo JC, Jordan W, Lema MW, Brown A. Diversity of plasmids in *Achromobacter xylosoxidans* isolates responsible for a seemingly common-source nosocomial outbreak. *J Clin Microbiol* 1987;25:1952-5.
28. Mandell WF, Garvey GJ, Neu HC. *Achromobacter xylosoxidans* bacteremia. *Rev Infect Dis* 1987;9:1001-5.
29. Manzella JP. *Achromobacter xylosoxidans* bacteremia [letter]. *Dig Dis Sci* 1987;32:781-2.
30. Sindhu SS. *Achromobacter* meningitis in the newborn. *J Singapore Paediatr Soc* 1971;13:31-6.
31. McGann KA, Provencher M, Hoegg C, Talbot GH. *Achromobacter xylosoxidans* bacteremia. *Infect Control Hosp Epidemiol* 1990;11:539-41.
32. Hearn YR, Gander RM. *Achromobacter xylosoxidans*: an unusual neonatal pathogen. *Am J Clin Pathol* 1991;96:211-4.
33. San Miguel VV, Lavery JP, York JC, Lisse JR. *Achromobacter xylosoxidans* septic arthritis in a patient with systemic lupus erythematosus. *Arthritis Rheum* 1991;34:1484-5.

34. Legrand C, Anaissie E. Bacteremia due to *Achromobacter xylosoxidans* in patients with cancer. *Clin Infect Dis* 1992;14:479-84.
35. Boukadida J, Monastiri K, Snoussi N, Jeddi M, Berche P. Nosocomial neonatal meningitis by *Alcaligenes xylosoxidans* transmitted by aqueous eosin. *Pediatr Infect Dis J* 1993;12:696-7.
36. Cieslak TJ, Raszka WV. Catheter-associated sepsis due to *Alcaligenes xylosoxidans* in a child with AIDS [letter]. *Clin Infect Dis* 1993;16:592-3.
37. Dupon M, Winnock S, Rogues AM, Janvier G, de Barbeyrac G, Saric J. *Achromobacter xylosoxidans* (*Alcaligenes xylosoxidans* subspecies *xylosoxidans*) bacteremia after liver transplantation [letter]. *Intensive Care Med* 1993;19:480.
38. McGuckin MB, Thorpe RJ, Koch KM, Alavi A, Staum M, Abrutyn E. An outbreak of *Achromobacter xylosoxidans* related to diagnostic tracer procedures. *Am J Epidemiol* 1982;115:785-93.
39. Gahrn-Hansen B, Alstrup P, Dessau R, et al. Outbreak of infection with *Achromobacter xylosoxidans* from contaminated intravascular pressure transducers. *J Hosp Infect* 1988;12:1-6.
40. Puthucheary SD, Ngew YF. Infections with *Achromobacter xylosoxidans*. *Singapore Med J* 1986;27:58-62.
41. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial disk susceptibility tests. 4th ed. NCCLS document M2-A4. Villanova, Pennsylvania: National Committee for Clinical Laboratory Standards, 1990.
42. National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. 2nd ed. NCCLS document M7-A2. Villanova, Pennsylvania: National Committee for Clinical Laboratory Standards, 1990.
43. Moody JA. Synergism testing. Broth microdilution, checkerboard, and broth macrodilution methods. In: Isenberg HD, ed. *Clinical microbiology procedures handbook*. Washington, DC: American Society for Microbiology 1992;5:18.22.
44. Knapp C, Moody JA. Tests to assess bactericidal activity. In: Isenberg HD, ed. *Clinical microbiology procedures handbook*. Washington, DC: American Society for Microbiology, 1992;5:16.1-5.16.32.
45. Schoch PE, Cunha BA. Nosocomial *Achromobacter xylosoxidans* infections. *Infect Control Hosp Epidemiol* 1988;9:84-7.
46. Igra-Siegman Y, Chmel H, Cobbs C. Clinical and laboratory characteristics of *Achromobacter xylosoxidans* infection. *J Clin Microbiol* 1980;11:141-5.
47. Weinstein MP, Reller LB, Murphy JR, Lichtenstein KA. The clinical significance of positive blood cultures: a comprehensive analysis of 500 episodes of bacteremia and fungemia in adults. I. Laboratory and epidemiologic observations. *Rev Infect Dis* 1983;5:35-53.
48. Arpi M, Renneberg J, Andersen H-K, Nielsen B, Larsen SO. Bacteremia at a Danish university hospital during a twenty-five-year period (1968-1992). *Scand J Infect Dis* 1995;27:245-251.
49. Haug JB, Harthug S, Kalager T, Digranes A, Solberg CO. Bloodstream infections at a Norwegian university hospital, 1974-1979 and 1988-1989: changing etiology, clinical features, and outcome. *Clin Infect Dis* 1994;19:246-56.
50. Kreger BE, Craven DE, Carling PC, McCabe WR. Gram-negative bacteremia. III. Reassessment of etiology, epidemiology, and ecology in 612 patients. *Am J Med* 1980;68:332-43.
51. Johansson PJH, Sternby E, Ursing B. Septicemia in granulocytopenic patients: a shift in bacterial etiology. *Scand J Infect Dis* 1992;24:357-60.
52. Vartivarian SE, Papadakis KA, Palacios JA, Manning JT Jr, Anaissie EJ. Mucocutaneous and soft tissue infections caused by *Xanthomonas maltophilia*: a new spectrum. *Ann Intern Med* 1994;121:969-73.
53. Dorff GJ, Geimer NF, Rosenthal DR, Rytel MW. *Pseudomonas* septicemia: illustrated evolution of its skin lesion. *Arch Intern Med* 1971;128:591-5.
54. Bodey GP, Bolivar R, Fainstein V, Jadeja L. Infections caused by *Pseudomonas aeruginosa*. *Rev Infect Dis* 1983;5:279-313.
55. Bisbe J, Gatell JM, Puig J, et al. *Pseudomonas aeruginosa* bacteremia: univariate and multivariate analyses of factors influencing the prognosis in 133 episodes. *Rev Infect Dis* 1988;10:629-35.
56. Gallagher PG, Watanakunakorn C. *Pseudomonas* bacteremia in a community teaching hospital, 1980-1984. *Rev Infect Dis* 1989;6:846-52.
57. Morrison AJ Jr, Hoffmann KK, Wenzel RP. Associated mortality and clinical characteristics of nosocomial *Pseudomonas maltophilia* in a university hospital. *J Clin Microbiol* 1986;24:52-5.
58. Gladstone JM, Ehrenkranz RA, Edberg SC, Baltimore RS. A ten-year review of neonatal sepsis and comparison with the previous fifty-year experience. *Pediatr Infect Dis J* 1990;9:819-25.
59. Elting LS, Bodey GP. Septicemia due to *Xanthomonas* species and non-*aeruginosa Pseudomonas* species: increasing incidence of catheter-related infections. *Medicine (Baltimore)* 1990;69:296-306.
60. Seifert H, Strate A, Schulze A, Pulverer G. Vascular catheter-related bloodstream infection due to *Acinetobacter johnsonii* (formerly *Acinetobacter calcoaceticus* var. *lwoffii*): report of 13 cases. *Clin Infect Dis* 1993;17:632-6.
61. Alnor D, Frimodt-Møller N, Espersen F, Frederiksen W. Infections with the unusual human pathogens *Agrobacterium* species and *Ochrobactrum anthropi*. *Clin Infect Dis* 1994;18:914-20.
62. Glupczynski Y, Hansen W, Freney J, Yourassowsky E. *In vitro* susceptibility of *Alcaligenes denitrificans* subsp. *xylosoxidans* to 24 antimicrobial agents. *Antimicrob Agents Chemother* 1988;32:276-8.
63. Rolston KVI, Messer M. The *in-vitro* susceptibility of *Alcaligenes denitrificans* subsp. *xylosoxidans* to 40 antimicrobial agents [letter]. *J Antimicrob Chemother* 1990;26:857-60.
64. Braine HG, Stuart RK, Saral R, Lietman PS. Parenteral trimethoprim-sulfamethoxazole and carbenicillin as empiric therapy for neutropenic patients with cancer. *Rev Infect Dis* 1982;4:586-92.