

Brief report

Edgar Pérez Barragán¹
Justo Sandino Pérez²
Laura Corbella¹
María Ángeles Orellana³
Mario Fernández-Ruiz¹

Achromobacter xylosoxidans bacteremia: clinical and microbiological features in a 10-year case series

¹Unidad de Enfermedades Infecciosas, Hospital Universitario "12 de Octubre". Instituto de Investigación Sanitaria Hospital "12 de Octubre" (imas12). Facultad de Medicina, Universidad Complutense. Madrid, Spain

²Servicio de Nefrología, Hospital Universitario "12 de Octubre". Instituto de Investigación Sanitaria Hospital "12 de Octubre" (imas12). Facultad de Medicina, Universidad Complutense. Madrid, Spain

³Servicio de Microbiología. Hospital Universitario "12 de Octubre". Instituto de Investigación Sanitaria Hospital "12 de Octubre" (imas12). Facultad de Medicina, Universidad Complutense. Madrid, Spain

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ABSTRACT

Objective. The treatment of *Achromobacter xylosoxidans* bacteremia is challenged by antimicrobial resistance and the paucity of data. We aimed at offering a contemporary description of this uncommon entity.

Patients and methods. Retrospective case series of 13 episodes of *A. xylosoxidans* bacteremia diagnosed over a 10-year period (November 2007 to May 2017) in our tertiary care center.

Results. Solid organ cancer and heart failure were the most common comorbidities (4/13 [30.7%]). All but one episodes were hospital-acquired. Most patients had received previous antibiotic therapy (7/13 [53.8%]) and had a central venous catheter in place (6/13 [46.1%]). Primary and intravascular catheter were the most common sources (4/13 [30.7%] each). Meropenem was the agent with best *in vitro* activity (92.3% [12/13] of susceptible isolates). All-cause 30-day mortality (overall 23.1%) was higher in patients with primary bacteremia (50.0% vs. 11.1%; P -value=0.203) and prior chemotherapy (66.7% vs. 10.0%; P -value=0.108).

Conclusions. Bacteremia due to *A. xylosoxidans* constitutes a serious infection among immunocompromised hosts. Carbapenem-based therapy may be appropriate in most cases.

Keywords: *Achromobacter xylosoxidans*; *Alcaligenes xylosoxidans*; bacteremia; therapy; antimicrobial susceptibility

Bacteriemia por *Achromobacter xylosoxidans*: características clínicas y microbiológicas a lo largo de 10 años

RESUMEN

Objetivo. El abordaje de la bacteriemia por *Achromobacter xylosoxidans* se ve dificultado por la presencia de resistencias y la escasez de estudios en la literatura. Pretendemos ofrecer una descripción contemporánea de esta infrecuente entidad.

Pacientes y métodos. Serie retrospectiva de 13 episodios de bacteriemia por *A. xylosoxidans* diagnosticados en un centro de tercer nivel a lo largo de 10 años (noviembre de 2007 a mayo de 2017).

Resultados. La neoplasia de órgano sólido y la insuficiencia cardíaca fueron las comorbilidades más frecuentes (4/13 [30,7%]). Todos los episodios (excepto uno) fueron nosocomiales. La mayor parte de los pacientes había recibido tratamiento antibiótico (7/13 [53,8%]) y eran portadores de un catéter venoso central (6/13 [46,1%]). Predominaron las bacteriemias primarias y las asociadas a catéter intravascular (4/13 [30,7%]). Meropenem fue el agente con mejor actividad (92,3% [12/13] de aislados susceptibles). La mortalidad a los 30 días (23,1% globalmente) fue mayor en pacientes con bacteriemia primaria (50,0% vs. 11,1%; $P=0,203$) y quimioterapia previa (66,7% vs. 10,0%; $P=0,108$).

Conclusiones. La bacteriemia por *A. xylosoxidans* constituye una complicación grave en pacientes inmunodeprimidos. Las pautas basadas en carbapenémicos pueden ser eficaces en la mayor parte de los casos.

Palabras clave: *Achromobacter xylosoxidans*; *Alcaligenes xylosoxidans*; bacteriemia; tratamiento; susceptibilidad a antibióticos.

Correspondence:
Mario Fernández Ruiz.
Unidad de Enfermedades Infecciosas. Hospital Universitario "12 de Octubre". Centro de Actividades Ambulatorias, planta 2ª, bloque D. Avda. de Córdoba, s/n. 28041 (Madrid).
Teléfono: +34 913908000.
Fax: +34 914695775.
E-mail: mario_fdezruiz@yahoo.es

INTRODUCTION

Achromobacter xylosoxidans is an aerobic, motile, oxidase-positive, non-fermenting Gram-negative rod widely distributed in the environment that mainly causes health-care-associated infection [1,2]. Previously termed *Alcaligenes xylosoxidans*, the name *A. xylosoxidans* (which had been originally proposed in 1971 by Yabuuchi and Ohyama) was formalized since 1998 and now encompasses two different subspecies (*A. xylosoxidans* subsp. *xylosoxidans* and *A. xylosoxidans* subsp. *denitrificans*) [3,4]. Most cases in the literature are described in patients with some form of immunosuppression, usually haematological malignancies. Primary bacteraemia represents the most common clinical presentation [5-8]. Other reported infection sites of infection include meningitis, urinary tract infection, abscesses, osteomyelitis, corneal ulcers, prosthetic valve endocarditis, peritonitis and pneumonia [2,9-12].

The treatment of patients with *A. xylosoxidans* bacteraemia is challenging due to the fact that this microorganism carries both intrinsic and acquired mechanisms of resistance, often conferring a phenotype of multidrug resistance (MDR) [13,14]. In addition, current data on this uncommon entity is mostly limited to very small series or single case reports. With the aim of gaining further insight into the clinical characteristics and optimal therapeutic approach of *A. xylosoxidans* bacteraemia, we present a retrospective review of 13 cases occurring in our institution over a 10-year period.

PATIENTS AND METHODS

We retrospectively analysed all consecutive episodes of bacteraemia due to *A. xylosoxidans* diagnosed between November 2007 and May 2017 at the University Hospital "12 de Octubre" (Madrid, Spain), a 1,300-bed tertiary care centre with a reference population of 431,325 inhabitants in 2015. It has five different adult intensive care units (medical, trauma, coronary, general surgery, and cardiac surgery) and an active program of solid organ and hematopoietic stem-cell transplantation. No age restriction was applied. Study protocol was approved by the local Clinical Ethics Committee (number 17014). Informed consent was waived due to the retrospective nature of the research.

Cases were identified through a search of the computerized database of the Department of Microbiology and defined by the isolation of *A. xylosoxidans* in one or more blood cultures in the presence of clinical signs compatible with systemic infection. Blood samples were inoculated in the BacT/ALERT® FA aerobic and FN anaerobic bottles and incubated in an automated system (BacT/ALERT 3D, Biomerieux, France) for 5 days. Bacterial identification and antimicrobial susceptibility testing were performed by the Wider® system (Soria Melguizo, Madrid, Spain), MicroScan WalkAway® system (Siemens Healthcare Diagnostics, Deerfield, IL, USA) and, since 2014, MALDI-TOF mass spectrometry (Bruker Daltonics, Bremen, Germany). Until 2014 isolates were categorized according to the Clinical Laboratory Standards Institute (CLSI) susceptibility breakpoints for

Table 1 Demographics and clinical characteristics of included patients (n = 13).

Variable	
Age, years [mean ± SD]	52.1 ± 32
Gender (male) [n (%)]	5 (38.5)
Pitt score [median (IQR)]	2 (0-5.5)
Comorbidities [n (%)]	
Solid organ malignancy	4 (30.7)
Heart failure	4 (30.7)
Hematologic malignancy	2 (15.3)
Diabetes mellitus	2 (15.3)
Chronic liver disease	3 (23.1)
Solid organ transplantation	1 (7.7)
Predisposing conditions [n (%)]	
Prior systemic antibiotic therapy ^a	7 (53.8)
Recent surgery ^a	4 (30.7)
Chemotherapy	3 (23.1)
Recent ICU admission ^a	1 (7.7)
CVC in place at diagnosis ^b	6 (46.1)
Duration of CVC placement [median (IQR)]	17 (1-17)
Source of bacteraemia [n (%)]	
Primary	4 (30.7)
Catheter-related	4 (30.7)
Intraabdominal infection	2 (15.3)
Pneumonia	1 (7.7)
Urinary tract infection	1 (7.7)
SSTI	1 (7.7)
Polimicrobial bacteraemia [n (%)] ^c	2 (15.3)
Empirical antibiotic therapy [n (%)]	
Monotherapy ^d	10 (76.9)
Combination therapy ^d	3 (23.1)
Regimen containing	
Carbapenem	5 (38.5)
Third-generation cephalosporin	3 (23.1)
Beta-lactam/beta-lactamase inhibitor	2 (15.3)
Aminoglycoside	2 (15.3)
Vancomycin	2 (15.3)
Others	2 (15.3)
30-day all-cause mortality [n (%)]	3 (23.1)

CVC: central venous catheter; ICU: intensive care unit; SSTI: skin and soft-tissue infection.

^aWithin the previous 30 days.

^bIncludes non-tunneled temporary catheters (n = 3), skin-tunneled catheters (n = 2) and peripherally inserted central catheters (n = 1).

^cConcomitant bacteraemia by *Bacillus* spp. and *Streptococcus sanguinis*.

^dCombination therapy included meropenem plus vancomycin, ceftriaxone plus amikacin, and gentamicin plus aztreonam.

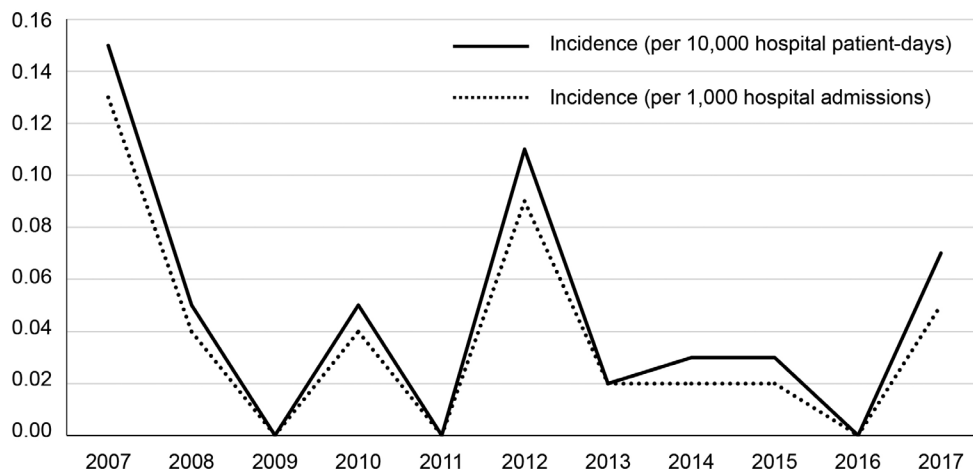


Figure 1 Incidence rates of *Achromobacter xylosoxidans* at our centre across the 10 years encompassed by the study period.

non-fermenting gram-negative bacteria and, thereafter, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for *Pseudomonas aeruginosa*. The MDR phenotype was defined by demonstrated non-susceptibility to one agent belonging to ≥ 3 different antimicrobial categories [15].

Clinical charts were reviewed by means of a standardized case report form to obtain data on demographics, comorbidities, predisposing factors (i.e., surgical intervention within the previous 30 days, stay in the intensive care unit [ICU] or presence of intravascular catheters), use of systemic antibiotics within the previous 30 days, source of bacteraemia, severity of infection, antibiotic susceptibility of the isolate, antibiotics employed to treat the episode of bacteraemia, and 30-day all-cause mortality.

For the purposes of the present study, the diagnosis of intravascular catheter-related bacteraemia was considered when the criteria proposed by the Infectious Diseases Society of America were met [16] or in the presence of local signs of infection (erythema, swelling, tenderness or purulent discharge) at the site of insertion or along the subcutaneous tunnel tract and no alternative source. Other sources of bacteraemia such as pneumonia, urinary tract infection or skin and soft-tissue infection (SSTI) were considered in the presence of consistent clinical, radiological and laboratory data. The diagnosis of primary bacteraemia was reserved for cases with no identifiable source of infection. Severity of illness at time of bacteraemia onset was assessed according to the Pitt score [17]. Adequate therapy required the administration within the first 48 hours after the sampling of index blood cultures of the recommended dose of an antibiotic agent with *in vitro* activity according to the reported susceptibility testing.

Quantitative data were shown as the mean \pm standard deviation or the median with interquartile ranges. Qualitative variables were expressed as absolute and relative frequencies.

Categorical variables were compared using the Fisher's exact test. All the significance tests were two-tailed. Statistical analysis was performed using SPSS, version 15.0 (Statistical Package for Social Sciences Inc., Chicago, IL).

RESULTS

We identified 13 patients with *A. xylosoxidans* bacteraemia whose demographics and clinical characteristics are detailed in table 1. The incidence rates across the years encompassed by the study period were overall very low (<0.2 cases per 1,000 hospital admissions or per 10,000 hospital patient-days) and no clear trend could be identified (figure 1). Solid organ malignancy and heart failure were the most common comorbidities (4 cases each [30.7%]). Most patients (7 [53.8%]) had received antibiotic therapy (mainly beta-lactams) within the previous 30 days and had a central venous catheter (CVC) in place at the onset of bacteraemia (6 [46.1%]). Recent surgery and chemotherapy were also common. Primary and catheter-related sources were equally represented (4 cases each [30.7%]). One patient developed bacteraemia during the first hours of hospital admission due to community-acquired SSTI, with no evidence of an alternative source. The remaining episodes occurred after 72 hours of hospitalization.

The susceptibility profile of *A. xylosoxidans* isolates is shown in table 2. Meropenem was the agent with the best *in vitro* activity (92.3% [12/13] of isolates were susceptible), followed by imipenem and piperacillin/tazobactam (76.9% [10/13] of isolates). On the other hand, resistance to aminoglycosides was common (69.2% [9/13] for gentamicin and 38.4% [5/13] for amikacin). The criteria for MDR phenotype [15] were fulfilled in 38.4% (5/13) of isolates.

Empirical antibiotic therapy was mostly based on carbapenems (5 cases [38.5%]), whereas combination therapy was used in 3 patients (23.1%). In most cases (8 [61.5%]) empirical

Table 2 Results of *in vitro* susceptibility testing of *A. xylosoxidans* isolates (n = 13) and clinical breakpoints used for categorization.

Agent	Susceptible (%)	Intermediate (%)	Resistant (%)	Clinical breakpoints (mg/L) ^a	
				Until 2014 ^b	2014 onwards ^b
Amikacin	61.5	0.0	38.4	S: ≤16, R: >32	S: ≤8, R: >16
Aztreonam	0.0	0.0	100.0	S: ≤8, R: >16	S: ≤1, R: >16
Cefepime	46.1	0.0	53.8	S: ≤8, R: >16	S: ≤8, R: >8
Ceftazidime	69.2	0.0	30.7	S: ≤8, R: >16	S: ≤8, R: >8
Ceftriaxone	28.5	0.0	71.4	S: ≤8, R: >16	S: ≤8, R: >8
Ciprofloxacin	36.3	27.2	36.3	S: ≤1, R: >2	S: ≤0.5, R: >0.5
Fosfomycin	0.0	20.0	80.0	NA	S: ≤32, R: >32
Gentamicin	30.7	0.0	69.2	S: ≤4, R: >8	S: ≤4, R: >4
Imipenem	76.9	7.6	15.3	S: ≤2, R: >4	S: ≤4, R: >8
Meropenem	92.3	0.0	7.6	S: ≤2, R: >4	S: ≤2, R: >8
Piperacillin/tazobactam	76.9	7.6	15.3	S: ≤16/4, R: >64/4	S: ≤16/4, R: >16/4
Trimethoprim/sulfamethoxazole	53.8	0.0	43.1	S: ≤2/38, R: >4/76	NA

NA: not available; R: resistant; S: susceptible.

^aThe intermediate should be interpreted as values between the S and the R breakpoints.

^bClinical Laboratory Standards Institute (CLSI) susceptibility breakpoints for non-fermenting gram-negative bacteria and European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for *Pseudomonas aeruginosa* were applied until 2014 and thereafter, respectively.

therapy was adequate according to *in vitro* susceptibility tests and did not require further modification. None of the patients had persistent bacteraemia. The all-cause 30-day mortality rate was 23.1%, with the 3 observed deaths deemed attributable to infection due to multiple organ failure (table 1). Patients with primary bacteraemia had higher 30-day mortality than those with other sources (2/4 [50.0%] versus 1/9 [11.1%]; *P*-value = 0.203), as well as those who had received prior chemotherapy (2/3 [66.7%] versus 1/10 [10.0%]; *P*-value = 0.108), although such differences were not statistically significant. There were no apparent differences in mortality according to the appropriateness or not of empirical therapy (2/8 [25.0%] versus 1/4 [25.0%], respectively; *P*-value = 1.000).

DISCUSSION

In our single-centre experience, approximately half of the cases of *A. xylosoxidans* bacteraemia occurred in patients with underlying malignancies that had received previous antibiotic therapy. Catheter-related bacteraemia was predominant among those episodes with a documented source of infection, whereas patients with primary bacteraemia (which accounted for one third of the overall cohort) had higher 30-day mortality, as well as those who had received prior chemotherapy. For both associations, nevertheless, it is likely that the low sample size precluded statistical significance.

In the few existing reports on this entity, *A. xylosoxidans* bacteraemia has been mainly observed in patients with malig-

nant diseases, especially haematological. In one of the largest series published to date, Aisenberg et al. included 52 episodes diagnosed during a 14-year period in 46 patients with cancer [5]. In a previous Spanish single-centre study, 39% of episodes of *A. xylosoxidans* bacteraemia occurred in patients with cancer, whereas prior chemotherapy and neutropenia were also common (35% and 30% of cases, respectively) [6]. In addition, we found that more than half of the patients had received antibiotic therapy within the previous 30 days. This predisposing factor has been also described by Ozden et al [18] in the setting of a neonatal outbreak, in which 100% of patients had been treated with broad-spectrum antibiotics.

In line with some previous reports [5-7], catheter-related infection was the main source of bacteraemia in the present cohort. Infection due to *A. xylosoxidans* is usually regarded as healthcare-associated, as supported by our experience (in which 92.3% of cases were hospital-acquired). However, we also observed a case of bacteraemia associated to a community-acquired SSTI, which is very infrequent. There is only one previous report in the literature of community-acquired SSTI due to *A. xylosoxidans* [19], although the microorganism was not isolated in blood samples in any of the 9 cases.

Most of our isolates showed *in vitro* sensitivity to carbapenems and piperacillin/tazobactam, in agreement with other authors [18,20]. However, we also found a notable rate of resistance to aminoglycosides, ciprofloxacin, ceftazidime or trimethoprim/sulfamethoxazole, to which *A. xylosoxidans* has been previously reported to remain sensitive [5,8]. Such infor-

mation is important when making therapeutic decisions, especially among immunocompromised and critically ill patients, since the emergence of MDR strains has been reported [21]. In that sense, it should be highlighted that almost 40% of the isolates in the present study exhibited MDR phenotypes.

All cases of death at 30 days from diagnosis in our series were ultimately related to infection. This figure yielded a 30-day attributable mortality (23.1%) slightly higher than that previously reported, which ranged from 0.0% to about 15.0% [5-7]. In a case series restricted to patients with cancer, the presence of sepsis and high APACHE II scores at infection onset were independent predictors of 30-day mortality [5]. We were unable to identify significant differences in outcome across different subgroups of patients, although those who had primary bacteraemia and previous chemotherapy suffered from higher mortality. This possible association has not been previously described, although the number of patients analysed was too small to draw definitive conclusions.

In conclusion, bacteraemia due to *A. xylosoxidans* can be a serious complication among hospitalized patients, mainly those with cancer-related immunosuppression. Empirical antibiotic therapy including a carbapenem agent appears to be appropriate in most cases, although further adjustment should be performed according to the result of *in vitro* susceptibility testing. The potential impact on the outcome of different sources of infection, underlying conditions and appropriateness of initial therapy should be evaluated in future studies on this uncommon entity.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest

FUNDING

None to declare

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