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Case Report

Case of recurrent *Achromobacter xylosoxidans* bacteraemia and PICC (peripherally-inserted central catheter) line infection in an immunocompromised patient

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SUMMARY

Background: This report describes recurrent *A. xylosoxidans* bloodstream and PICC (peripherally-inserted central catheter) line infection in an immunocompromised patient.

Presentation of Case: A 64-year-old female with acute promyelocytic leukaemia presented during a non-neutropenic febrile episode, and *A. xylosoxidans* was isolated from multiple PICC and peripheral blood cultures, and from the tip of the line on removal. The patient was treated with meropenem and a new PICC line was inserted after sterile blood cultures. Six weeks later, she represented with *A. xylosoxidans* from multiple cultures from the line. She was treated with piperacillin-tazobactam and the line was removed. There was no evidence of deep-seated infection. Further discussion revealed that the patient was using a sponge to clean, and a sleeve to cover her PICC-line while bathing. *A. xylosoxidans* was cultured from both the sponge and the swab. Whole Genome Sequencing performed on two blood culture isolated and both environmental isolates confirmed all four isolates were indistinguishable. The patient was advised not to use the sponge/sleeve in future and we have incorporated specific advice in this regard into our patient information.

Discussion: *Achromobacter xylosoxidans* is an aerobic, non-lactose fermenting gram-negative bacillus usually considered an opportunistic pathogen. It is associated with infection in immunocompromised patients, and is an emerging pathogen in catheter-related infections, sometimes associated with contaminated water.

Abbreviations: PICC, Peripherally-inserted central catheter; APLM, Acute promyelocytic leukaemia; ATRA, All-trans-retinoic acid; WCC, white cell count; ANC, absolute neutrophil count; CRP, C-reactive protein; CLED, cystine-lactose-electrolyte deficient; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight; MIC, minimum inhibitory concentration; EUCAST, European Committee on Antimicrobial Susceptibility Testing; CLSI, Clinical Laboratory Standards Institute; WGS, Whole genome sequencing; rMLST, Ribosomal multi-locus sequence typing; SNP, single nucleotide polymorphisms; CF, cystic fibrosis; AIDS, acquired immune deficiency syndrome; rRNA, ribosomal ribonucleic acid; MLST, multilocus sequence typing; ESBL, extended-spectrum beta-lactamase.

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Conclusion: This case of recurrent *A. xylosoxidans* line infection highlights diagnostic and management challenges associated with catheter-related infections. Treatment is challenging because of intrinsic and acquired resistance mechanisms. Empiric treatment with anti-pseudomonal penicillins or carbapenems with line removal is typically required.

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Introduction

Achromobacter xylosoxidans is an aerobic, non-lactose fermenting gram-negative bacillus that is considered to be an opportunistic pathogen and has been associated with healthcare-associated infections including bacteraemia in immunocompromised patients, and respiratory tract infections in patients with cystic fibrosis. It is an emerging pathogen in catheter-related infections, and is often associated with contaminated water supply. Treatment is challenging because of increasing resistance to many antibiotic agents. Empiric treatment with anti-pseudomonal penicillins or carbapenems with line removal is typically required.

Presentation of Case

A 64-year-old female was diagnosed with acute promyelocytic leukemia (APML) in September 2020. After diagnosis, a PICC (peripherally-inserted central catheter) line was inserted, and a chemotherapy treatment regimen of ATRA (all-trans-retinoic acid) and arsenic trioxide was commenced. She had a relatively uncomplicated treatment course for the first four chemotherapy cycles requiring both inpatient stays and outpatient visits. She had periods of neutropenia during this time, however she remained clinically well with sterile blood cultures, and no concerns with the PICC line were reported.

The patient was electively admitted for cycle five of chemotherapy and was noted to be febrile on admission. She was haemodynamically stable with no symptoms/signs of note, and her physical examination revealed no source of infection. The PICC line was examined, and objectively there were no concerns of infection such as erythema, tenderness or discharge at the exit site. As per local hospital protocol, a full septic screen was taken including blood cultures and she was commenced empirically on piperacillin-tazobactam 4.5g TDS. Initial bloods revealed a white cell count (WCC) of $3.6 \times 10^9/L$ (4–11), absolute neutrophil count (ANC) of $2.42 \times 10^9/L$ (2–7.5) and an elevated C-reactive protein (CRP) of 57mg/L (0–5). The blood culture system in use in the microbiology laboratory is the Bactec FX Blood Culture System, and a typical blood culture set consists of two blood culture bottles. Gram-negative bacilli were identified in both aerobic and anaerobic blood culture bottles. Colonies grew on blood, chocolate and CLED (cystine-lactose-electrolyte deficient) agar on the patient's admission blood cultures. The white PICC lumen was positive first at 10 hours incubation, the purple PICC lumen at 15 hours incubation, and the peripheral blood cultures at 20 hours incubation. *Achromobacter spp.* was identified via MALDI-TOF (matrix-assisted laser desorption/ionization time-of-flight) mass spectrometry. The MALDI-TOF identification system is unable to identify the species in the *Achromobacter* genus and so is reported as *Achromobacter spp.* Repeat blood cultures taken on day two of

admission (following commencement of antibiotic therapy) also grew *Achromobacter spp.* Again, the white PICC lumen flagged positive first, followed by the purple lumen and the peripheral set. A total of six blood culture sets (eight bottles) cultured *Achromobacter spp.* during this admission. The patient's PICC line was removed, and the tip of the PICC line grew <15 colonies of *Achromobacter spp.* on culture. The patient was treated with meropenem with good clinical response, and a new PICC line was inserted after sterile blood cultures.

Susceptibility testing was performed using the minimum inhibitory concentration (MIC) disk diffusion method and interpreted using both EUCAST (European Committee on Antimicrobial Susceptibility Testing) (Version 10.0, 2020) and CLSI (Clinical Laboratory Standards Institute) (30th edition, CLSI supplement M100, 2020) interpretive criteria. Non-species (EUCAST) and Non-*Enterobacterales* (CLSI) breakpoints were used to interpret the susceptibility testing, as organism specific for *A. xylosoxidans* breakpoints were not available. The organism tested resistant to ciprofloxacin and gentamicin, and susceptible to meropenem, piperacillin-tazobactam and cotrimoxazole. Susceptibility results are outlined in Table 1. To note, updated EUCAST guidelines (Version 11.0 2021) provide interpretive criteria for *A. xylosoxidans* including breakpoints for piperacillin-tazobactam, meropenem and trimethoprim-sulfamethoxazole. Our interpreted results would be unchanged if the new breakpoints were used.

Six weeks later, the patient was electively admitted for cycle six of chemotherapy. Again, she was febrile on day one of this admission, and admission bloods revealed inflammatory markers within normal range (WCC $3.2 \times 10^9/L$, ANC $1.74 \times 10^9/L$, CRP 2.8mg/L). *Achromobacter spp.* was cultured again from a total of five PICC-line blood culture bottles incubated aerobically and anaerobically. The patient was treated with a course of piperacillin-tazobactam and the PICC line was removed. Infective endocarditis was ruled out on echocardiogram, and there was no evidence of deep-seated infection.

Following two distinct episodes of PICC-line associated *Achromobacter spp.* bacteraemia, further discussion with the patient revealed that she was using a sponge (Figure 1) to clean and a sleeve (Figure 2) to cover her PICC line while bathing, both purchased in a local pharmacy. *Achromobacter spp.* was cultured from both the sponge and the sleeve. Sterile conditions were unlikely achieved with repeated use of the sponge, and it is very likely that this covering was not adequately waterproof, specifically because there were no seals at either end of the dressing to prevent introduction of water. Susceptibility testing was comparable between all isolates (Table 1).

Whole genome sequencing (WGS) performed on two blood culture isolates and both environmental swabs confirmed that all four isolates were indistinguishable. Extraction was

Table 1
Susceptibility testing of *Achromobacter* spp. using MIC (Minimum inhibitory concentration) disk diffusion method

	Blood culture (peripheral) Admission #1	Blood culture (PICC) Admission #2	Culture of sleeve Admission #2	Culture of sponge Admission #2
Ciprofloxacin EUCAST MIC S (Susceptible) ≤ 0.25 R (Resistant) > 0.5	2 = Resistant	3 = Resistant	4 = Resistant	3 = Resistant
Gentamicin EUCAST MIC S ≤ 0.5 R > 0.5	> 256 = Resistant	96 = Resistant	> 256 = Resistant	> 256 = Resistant
Amikacin EUCAST MIC S ≤ 1 R > 1	Test not performed	> 256 = Resistant	> 256 = Resistant	> 256 = Resistant
Meropenem EUCAST MIC S < 2 R > 8	0.94 = Susceptible	0.94 = Susceptible	0.125 = Susceptible	0.94 = Susceptible
Piperacillin-Tazobactam CLSI MIC S ≤ 16 R ≥ 128	0.5 = Susceptible	0.38 = Susceptible	0.5 = Susceptible	0.5 = Susceptible
Co-trimoxazole CLSI MIC S ≤ 2 R ≥ 4	0.006 = Susceptible	0.008 = Susceptible	0.008 = Susceptible	0.008 = Susceptible

performed using Qiagen EZ1 tissue extraction kit, library preparation was via Nextera DNA Prep kit. Sequencing was performed on MiSeq V3 kit, and bioinformatics analysis was performed using BioNumerics software. Ribosomal multi-locus sequence typing (rMLST) (<https://pubmlst.org/species-id>) confirmed a 100% identification of *Achromobacter xylosoxidans*. All four isolates encoded blaOXA-114c gene, which is a chromosomally-encoded class D beta-lactamase; possibly

naturally occurring in this species. All isolates clustered (0–1 SNPs (single nucleotide polymorphisms)).

The patient improved with appropriate antibiotic therapy and line removal, and suffered no further complications. The patient was advised not to use the sponge/sleeve in future and we have incorporated specific advice in this regard into our patient information. This advice highlights the importance of hand hygiene prior to handling the line, and instructions to ensure that the dressing covering the line, and thus the PICC line, remains clean, dry and neatly secured to the skin at all times. A waterproof barrier should be used when the patient is bathing, but the PICC line must remain dry and moisture-free to reduce the risk of infection. Changing the dressing should be performed in clean, dry and sterile conditions.

Written informed consent has been given and retained by authors.

Discussion

Achromobacter is one of 19 genera belonging to the *Alcaligenaceae* family. There are 16 species of *Achromobacter*, with *A. xylosoxidans* the most common [1]. *Achromobacter xylosoxidans* has undergone a number of name changes, and was previously classified as *Alcaligenes xylosoxidans*, *Alcaligenes denitrificans* subsp. *xylosoxidans*, and *Alcaligenes xylosoxidans* subsp. *xylosoxidans*. It has most recently been reclassified as *Achromobacter xylosoxidans* [2,3].

Achromobacter xylosoxidans is an aerobic, oxidase- and catalase-positive [4], non-lactose fermenting gram-negative bacillus [5]. It is a motile, water-borne organism which may



Figure 1. Sponge used to clean the PICC line.



Figure 2. Sleeve covering PICC line.

be confused with *Pseudomonas* spp. except for the presence of peritrichous flagella [6]. It is also frequently misidentified as other non-lactose fermenting Gram-negative bacilli such as *Stenotrophomonas maltophilia*, *Burkholderia cepacia* complex and *Acinetobacter* spp. [7]. This environmental organism is typically found in aqueous settings such as well-water, tap-water, swimming pools [2], and bloodstream infections have been linked to contaminated water supply and medical devices.

Notably, *A. xylosoxidans* is recoverable from the respiratory tracts of patients with cystic fibrosis (CF) [8,3,7], and reportedly infects up to 9% of patients in this cohort. Aside from this population, *A. xylosoxidans* is considered to be a weakly-virulent pathogen, and infections are predominantly observed in immunocompromised hosts. Specific at-risk populations for *A. xylosoxidans* infections include those with haematological diagnoses such as hypogammaglobulinemia, AIDS (acquired immune deficiency syndrome), solid-organ transplant recipients [9], and chronic heart and renal disease [7]. Neutropenia in isolation is not considered to be a major risk factor [8].

The clinical manifestation of *A. xylosoxidans* infection is variable, and bloodstream infections generally produce an illness indistinguishable from other Gram-negative bacilli sepsis [8]. The most common clinical presentations of infection are pneumonia and bacteraemia [7], and less frequently can present as otitis media, skin and soft tissue infections and surgical site infections [4,10,9]. The organism has been isolated from many body sites including blood, cerebrospinal fluid, stool, urine, joints, skin and wounds [2]. It is an emerging pathogen in catheter-related infections [5] including central venous catheters and peritoneal dialysis catheters. Eradication of the organism is difficult due to biofilm formation [11].

A small number of case reports have been published on *Achromobacter* spp. bloodstream and line infections in the immunocompromised [4] and in 2003 the European Journal of Clinical Microbiology and Infectious Diseases published a ten-year review of a total of 54 cases of *Achromobacter*

xylosoxidans bacteraemia. In this case review, 60% (n=35) were associated with contaminated intravenous catheters and the most frequent underlying condition was malignancy, either solid-organ or haematological. Specific risk factors mentioned included age over 65 years and neutropenia. A 15% death rate (n=8) was reported and the review of in vitro susceptibility tests concluded that empiric treatment with anti-pseudomonal penicillin carbapenems is recommended [12]. Another review published in 1996 reported on 77 published cases of *A. xylosoxidans* bacteraemia in paediatric and adult patients between 1960 and 1993. 35% (n=27) were associated with an exogenous source including haemodialysis systems and contaminated water and 27% (n=21) were reportedly immunocompromised. 30% (n=23) of patients died, the highest case-fatality rate being in the neonatal group and those with complicated pneumonia, and there were no deaths reported in those with intravascular catheter-associated bacteraemia [13]. A fatal case of *A. xylosoxidans* infective endocarditis has been reported [5]. Reported case fatality rates of *Achromobacter* spp. bacteraemia varies from 3% for catheter-associated bacteraemia to 80% for neonatal infections [2].

Identification of *A. xylosoxidans* and management of *A. xylosoxidans* infection in immunocompromised patients is challenging.

The correct identification of *Achromobacter* spp is important, particularly in CF patients, because of both therapy and infection control implications [3]. Research on the development of alternative methods to reliably identify *A. xylosoxidans* is promising with the aim to improve clinical outcomes and infection control management [3]. Both MALDI-TOF and amplification and sequencing of the 16S rRNA (ribosomal ribonucleic acid) coding gene are not able to discriminate between species of *Achromobacter* [14]. The detection of blaOXA-114c beta-lactamase gene has been proposed for rapid and accurate *A. xylosoxidans* identification [15], as it has been recognized as a naturally occurring chromosomal gene in non-epidemiological-related clinical isolates of *A. xylosoxidans* [16]. Current reference methods for identification [1] include MLST (multilocus sequence typing), and the amplification and sequencing of an inner fragment of the *nrdA* gene. MLST is a complex diagnostic method, and may not be considered cost- or time-efficient when compared to other laboratory investigations (in particular rapid laboratory tests).

Treatment of *A. xylosoxidans* is challenging because of both intrinsic and acquired resistant mechanisms. Acquired resistance mechanisms include extended-spectrum beta-lactamases (ESBLs), *AmpC*-beta-lactamases, efflux pumps and metallo-beta-lactamases [7], the latter resulting in carbapenem resistance [14,7]. The organism is frequently resistant to many antibiotics including amoxicillin, first and second-generation cephalosporins, fluoroquinolones but is usually susceptible to anti-*Pseudomonas* beta-lactams (such as piperacillin-tazobactam and ceftazidime), carbapenems and cotrimoxazole [2,8,7]. Appropriate source control, i.e., removal of infected catheters (i.e. central venous catheters, peritoneal dialysis catheters), is recommended in addition to antibiotic therapy. Monotherapy is suitable for clinical resolution unless there is concern for severe, deep-seated infections [8]. Inhaled agents such as ceftazidime, colistin and tobramycin have been used as adjunct to systemic therapy for treatment of *Achromobacter* infections in CF patients [7]. Carbapenems should be spared as reserve agents where possible.

Conclusion

This is a unique case of recurrent *Achromobacter xylosoxidans* bloodstream and PICC line infection. Although the patient was receiving chemotherapy for underlying leukaemia, she was not neutropenic at the time of either bloodstream infection. The patient improved with appropriate antibiotic therapy and line removal, and suffered no further complications. She was advised not to use the sponge/sleeve in future and we have incorporated specific advice in this regard into our patient information.

A. xylosoxidans is a rare but important cause of bacteraemia in immunocompromised patients. The most common presentation reported in literature is an uncomplicated bacteraemia with low mortality rate, especially when associated with line infection, however it has been associated with deep-seated infections. It is an important pathogen in the cystic fibrosis population. Identification and treatment of *A. xylosoxidans* pose a clinical challenge. Empiric treatment pending susceptibility testing includes anti-pseudomonal penicillins or carbapenems, and removal of intravenous catheters should be considered promptly at the time of diagnosis because of risk of life-threatening complications.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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