**Case Report**

*Achromobacter xylosoxidans* endocarditis and septic arthritis in an infant affected by generalized arterial calcification of infancy

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**Introduction:** *Achromobacter xylosoxidans* is a non-fermentative aerobic Gram-negative bacillus, which most frequently causes nosocomial infections. Endocarditis from the pathogen has only rarely been reported and has a near-fatal outcome without surgical intervention.

**Case Presentation:** We present a case of *A. xylosoxidans* endocarditis and septic arthritis in an infant affected by generalized arterial calcification of infancy. The patient was successfully treated with 6 weeks of intravenous colistin, meropenem and trimethoprim/sulfamethoxazole.

**Conclusion:** This is the first reported case of colistin used to treat *A. xylosoxidans* endocarditis. We discuss the antibiotic challenges of treating multidrug-resistant *A. xylosoxidans* endocarditis in a patient who is not a surgical candidate.

**Keywords:** *Achromobacter xylosoxidans*; colistin; endocarditis; generalized arterial calcification of infancy; septic arthritis.

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**Introduction**

*Achromobacter xylosoxidans* is a non-fermentative aerobic Gram-negative bacillus, which most frequently causes nosocomial infections. Taxonomy has changed several times since its original description in 1971, including the nomenclature *Alcaligenes xylosoxidans*, but most recent studies have classified the bacterium as *Achromobacter xylosoxidans* (Yabuuchi & Ohyama, 1971; Yabuuchi et al., 1998). Infections with the pathogen vary and are traditionally noted in immunocompromised patients. *A. xylosoxidans* is well-described amongst cystic fibrosis patients, presenting as an opportunistic lung infection that readily acquires drug resistance (Jeukens et al., 2015; Tokuyasu et al., 2012). *A. xylosoxidans* endocarditis has only rarely been described in the literature and has a near-fatality without surgical intervention (Derber et al., 2011).

Generalized arterial calcification of infancy (GACI; OMIM: 208000) is a rare autosomal recessive disorder, most attributed to mutations of the ENPP1 gene, characterized by calcification of the internal elastic lamina of muscular arteries (Chong & Hutchins, 2008; Edouard et al., 2011; Farquhar et al., 2005; Kalal et al., 012; Ramjan et al., 2009; Rutsch et al., 2003, 2008; Shaireen et al., 2013; van der Sluis et al., 2006). GACI is often fatal within the first 6 months of life, usually secondary to myocardial ischaemia resulting in refractory heart failure (Chong & Hutchins, 2008; Rutsch et al., 2003, 2008). Recent studies, however, have demonstrated survival of patients with GACI beyond the infancy period when treated with bisphosphate therapy (Edouard et al., 2011; Ramjan et al., 2009; Rutsch et al., 2008; van der Sluis et al., 2006). No formalized treatment plan exists in the literature for patients affected by GACI. Drug choice, dosing, duration and route remain controversial (Ramjan et al., 2009).

Colistin, also known as polymyxin E, is an antibiotic that has been used in the cystic fibrosis population as a drug of ‘last resort’ for multidrug-resistant (MDR) Gram-negative bacterial pneumonia (Biswas et al., 2013). A recent study demonstrated that intravenous colistin was safe and effective in the treatment of severe nosocomial infections caused by...
MDR Gram-negative bacteria in the paediatric population (Karli et al., 2013).

Our case describes a 6-month-old Hispanic male with GACI, found to have MDR A. xylosoxidans endocarditis and septic arthritis/myositis, who was successfully treated with 6 weeks of intravenous colistin, meropenem, and trimethoprim/sulfamethoxazole.

**Case report**

A 6-month-old Hispanic male with a medical history of GACI presented with fever and a 2-day history of right hip pain with decreased range of motion. The patient was receiving long-term weekly intravenous bisphosphonate therapy via a tunnelled central venous catheter for treatment of his GACI. The patient had a rectal temperature of 38.6 °C on presentation. There was no cardiac murmur on the initial physical examination. His right hip was held in a flexed position and he cried with passive hip movement. Magnetic resonance imaging of the right hip demonstrated a small right joint effusion with synovial and adjacent muscle enhancement. The patient subsequently underwent incision and drainage of the right hip. Culture of the hip joint aspirate, as well as blood cultures from peripheral and central venous line sites, ultimately grew A. xylosoxidans. Identification of the organism was accomplished using a MicroScan Walk-Away combo identification and MIC panel (Beckman). The initial isolate was susceptible to ceftazidime, levofloxacin, meropenem, piperacillin/tazobactam, imipenem/cilastatin, trimethoprim/sulfamethoxazole and ticarcillin/clavulanate; intermediate to ceftriaxone; and resistant to amikacin, aztreonam, cefepime, ciprofloxacin, gentamicin and tobramycin. Antimicrobial susceptibility testing to these antibiotics was performed using both MicroScan Walk-Away and Etest (bioMérieux) with Clinical and Laboratory Standards Institute interpretation. The patient’s tunnelled central line was removed and he was started on intravenous piperacillin/tazobactam (300 mg kg⁻¹ day⁻¹).

Despite central line removal, the patient remained persistently bacteraemic and ultimately a systolic murmur was auscultated on physical exam. A transthoracic echocardiogram revealed a hyperechoic lesion on the anterior mitral valve leaflet with a hypermobile vegetation measuring 7 mm × 8 mm prolapsing into the left atrium during ventricular systole. Surgical intervention was considered. Specialist consultation and paediatric team meetings, however, determined that cardiothoracic surgery posed too high of a risk of mortality given the patient’s underlying GACI.

The patient was therefore continued on intravenous meropenem, trimethoprim/sulfamethoxazole and colistin for a total of 6 weeks after the first set of negative blood cultures were obtained. Subsequent blood cultures over the 6 weeks showed no bacterial growth. Towards the latter part of the hospital course, one blood culture from a peripherally inserted central catheter (PICC) grew Candida parapsilosis. The PICC line was immediately removed and the patient was treated with intravenous fluconazole (12 mg kg⁻¹ day⁻¹), with repeat peripheral blood cultures demonstrating no growth.

To avoid the need for placement of a new central venous line, the patient was transitioned to oral bisphosphonate therapy (risedronate 5 mg once per week) for treatment of his GACI. Six months following hospital discharge, the patient remained afebrile with negative blood cultures. Outpatient follow-up transthoracic echocardiogram showed no significant change. The patient did not develop any neurotoxic or nephrotoxic side-effects as a result of colistin therapy.

**Discussion**

To the best of our knowledge, this is the only paediatric case report of a patient with GACI diagnosed with left-sided native valve A. xylosoxidans endocarditis and right hip septic arthritis/myositis. This is also the only report of a patient with A. xylosoxidans endocarditis treated, successfully or otherwise, with colistin as part of the antibiotic regimen.
No formalized therapeutic plan exists in the literature for patients affected by GACI. In our case, the patient presented with a treatment regimen consisting of long-term weekly low-dose (0.1 mg kg \(^{-1}\)) intravenous pamidronate. The probable source of infection in our patient was the indwelling tunnelled central venous line. The patient’s pre-existing mitral valve calcification secondary to his underlying GACI likely acted as a nidus for the opportunistic \textit{A. xylosoxidans} bacterium. Using the Modified Duke criteria for infective endocarditis, the patient met two major (positive blood culture and evidence of endocardial involvement) and two minor criteria (predisposing heart condition and fever > 38 °C) (Li et al., 2000).

A MEDLINE search of the English language literature resulted in only two case reports of \textit{A. xylosoxidans} septic arthritis (San Miguel et al., 1991; Suryavanshi & Lalwani 2015). Broadening the search to include cases of osteomyelitis resulted in a total of seven reported cases (Dubey et al., 1988; Fort et al., 2014; Hoddy & Barton, 1991; Pamuk et al., 2015; Ozer et al., 2012; Stark, 2007; Walsh et al., 1993).

A MEDLINE search of the English language literature for infective endocarditis secondary to \textit{A. xylosoxidans} resulted in only 14 reported cases (Ahn et al., 2004; Davis et al., 1982; Derber et al., 2011; Lofgren et al., 1981; Malek-Marin et al., 2009; Martino et al., 1990; McKinley et al., 1990; Nanuashvili et al., 2007; Olson & Hoeprich, 1982; Rafael et al., 2014; Sasaki et al., 1993; Storey et al., 2010; Tokuyasu et al., 2012; van Hal et al., 2008). A review of those cases demonstrated a >50% mortality rate (Derber et al., 2011; Tokuyasu et al., 2012). Of the surviving patients, only one case series reported survival in a patient who did not undergo surgical intervention (McKinley et al., 1990).

Based on expert medical opinion, our patient was not a surgical candidate. Additionally, resistance to antibiotic therapy developed during treatment. Given the near certain risk of fatality without surgical intervention, we explored additional antibiotic options.

Little is known about optimal antibiotic therapy for \textit{A. xylosoxidans} infections. Neither the Clinical and Laboratory Standards Institute nor the European Committee on Antimicrobial Susceptibility Testing provide specific guidance beyond non-species-related breakpoints. Intrinsic antibiotic resistance patterns and acquired resistance has been widely reported (Abbott & Peleg 2015). It has been suggested that the most active antibiotic agents against \textit{A. xylosoxidans} are Piperacillin/tazobactam, meropenem, and trimethoprim/sulfamethoxazole, with tetracyclines having variable activity (Abbott & Peleg, 2015). In the cystic fibrosis patient population, the use of concurrent inhaled colistin has been reported as effective (Abbott & Peleg, 2015; Jacquier et al., 2012; Biswas et al., 2013; Karli et al., 2013). The use of intravenous colistin, in conjunction with meropenem and trimethoprim/sulfamethoxazole, led to resolution of bacteremia in our patient. This case demonstrates two important, but separate, findings: the first specifically for patients affected by GACI and the second for patients with difficult-to-clear \textit{A. xylosoxidans} infections. First, while inherently limited, the current literature on GACI treatment has demonstrated similar efficacy of short-term intravenous bisphosphonate therapy followed by transition to oral bisphosphonate therapy when compared with long-term intravenous bisphosphonate therapy alone (Ramjan et al., 2009). Our case highlights the importance of the former approach over the latter, secondary to the risk of line infection associated with long-term intravenous therapy. Second, this is the first known case report of \textit{A. xylosoxidans} infective endocarditis treated with intravenous colistin. Clearance of the bacteria was noted within 3 days of starting colistin therapy. Our case is one of only two known reports of survival in a patient with \textit{A. xylosoxidans} endocarditis who did not undergo surgical intervention. In cases of non-operative MDR \textit{A. xylosoxidans} endocarditis, we propose the consideration of colistin as part of an extended intravenous antibiotic regimen.

**References**


