

Tsukamurella catheter-related bloodstream infection in a pediatric patient with pulmonary hypertension

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Abstract

Catheter-related bloodstream infections (CR-BSI) are important complications in patients with long-term indwelling central venous catheters. In this report, we present the case of a 14-year-old male with pulmonary hypertension treated with continuous treprostinil infusion, who presented with a CR-BSI caused by a *Tsukamurella* species. This case highlights the potential for this unusual organism to cause infection in immunocompetent patients.

Introduction

Intravascular catheters have become an integral component of contemporary medical treatment for various diseases, and they are used commonly for infusions of chemotherapeutics and antibiotics. Complications including catheter-related bloodstream infections (CR-BSI) can be a significant source of morbidity and mortality for patients with indwelling central venous catheters.¹ Patients with pulmonary hypertension require long-term central venous catheters for the continuous infusion of prostanoids, which help to reduce pulmonary artery pressure.² Therefore, these patients are at risk for CR-BSI. While CR-BSI are frequently caused by *Staphylococcus* species,³ many other pathogens have been identified as causes of CR-BSI. In this report, we describe a pediatric patient with pulmonary hypertension who had a CR-BSI caused by a *Tsukamurella* species, which is an unusual pathogen to cause infection in an otherwise immunocompetent patient.

Case Report

A 14-year-old male with a history of idiopathic pulmonary hypertension treated with intravenous treprostinil presented to the emergency room with a three-day history of fever to 103.2°F along with leakage from his Broviac central venous catheter. The catheter, which had been in place for three years, was found to have an external break and subsequently was repaired. There was no evidence of infection at the insertion site. Blood cultures obtained from the catheter grew coagulase-negative staphylococci and a gram-positive bacillus. The patient was admitted to the hospital and treated with intravenous vancomycin run through the catheter. Vancomycin locks were used in the catheter between antibiotic doses.

The patient remained afebrile after admission, but a second blood culture obtained on hospital day number 2 (to determine whether the line had been sterilized) again grew a gram-positive bacillus. Catalase-positive, beaded gram-positive bacilli were isolated from subcultures to solid media. Based on these initial characteristics, a preliminary identification of a possible rapid-growing mycobacterium was considered. The patient's antibiotic regimen was changed to a combination of amikacin, clarithromycin, and linezolid on hospital day number 6. Line removal was recommended, but the procedure was delayed until anticoagulation from the patient's long-term coumadin therapy could be reversed. On hospital day 9, the patient became febrile for the first time after admission, although the most recent set of cultures from the line obtained from hospital days 3-8 had been negative. A transthoracic echocardiogram showed no evidence of valvular vegetations. A chest CT scan performed without contrast revealed a small left pleural effusion, scattered areas of atelectasis, and enlargement of pulmonary arteries compatible with the patient's pulmonary hypertension.

Modified acid-fast stains performed on the isolate from the first positive blood culture were negative, and the isolate was referred to the Bureau of Laboratories, at the Michigan Department of Community Health (Lansing, Michigan) for further identification. By hospital day 10, the reference laboratory had determined that the organism was not a mycobacterium species. At that point, amikacin, clarithromycin, and linezolid were discontinued and vancomycin was started. The central venous catheter was removed on hospital day number 11. A culture of the catheter tip remained negative, but a peripheral blood culture obtained after removal of the catheter again grew a gram-positive rod. The patient remained febrile following removal of the

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catheter. No venous thrombus was identified by Doppler ultrasound evaluation of the site of his previous catheter.

Using high-performance liquid chromatography (HPLC) and other conventional biochemical tests,⁴ the isolate was identified as a *Tsukamurella* species. Based on this information, levofloxacin was added to the vancomycin therapy on hospital day 13. The patient's fever subsided quickly after this change. Multiple blood cultures (eight in total) obtained over the next 10 days remained negative. Vancomycin was discontinued on hospital day 18. A new indwelling central venous catheter was inserted on hospital day 25. The patient remained afebrile and was discharged from the hospital shortly thereafter. Although there had been no overt evidence of endocarditis by echocardiogram or thrombus by Doppler ultrasound, the decision was made to treat the patient with an extended course of antibiotics owing to the prolonged bacteremia and the patient's underlying disease. He finished a six-week course of oral levofloxacin with no further complications related to this infection.

The *Tsukamurella* isolate was sent to a second reference laboratory at National Jewish Health (Denver, Colorado) for susceptibility testing. The results (Table 1) demonstrate low minimum inhibitory concentration (MIC) values (<1 µg/mL) for minocycline, ciprofloxacin, and trimethoprim/sulfamethoxazole. In addition, MIC values were low (<8 µg/mL) for amikacin, kanamycin, ceftriaxone, cefepime, imipenem, clarithromycin, and linezolid. MIC values were

higher for tobramycin and gentamicin (>4 µg/mL), azithromycin (>32/16 µg/mL), and amoxicillin/clavulanate (128 µg/mL).

Discussion

CR-BSI remains a medically important problem in patients who require long-term intravenous access. The reported incidence of CR-BSI in patients with long-term indwelling central venous catheters varies from 0.3 to 9.1 infections per 1000 patient days,^{5,6} although higher rates have been documented in intensive care unit settings (7.7 per 1000 patient days⁶) compared to outpatient settings (0.45 per 1000 patient days⁵). The risk of infection also appears to increase over time, with more infections occurring after at least 30 days of catheter use.⁵

Patients receiving continuous prostanoid infusions to treat pulmonary hypertension are at risk for CR-BSI. The rate of CR-BSI in patients with pulmonary hypertension and an indwelling central venous catheter has ranged from 0.1 per 1000 patient days to 0.89 per 1000 patient days/catheter days.⁷⁻¹⁰ These rates are comparable to rates seen in other patient populations in outpatient settings.^{11,12} The majority of reported cases in patients with pulmonary hypertension has been caused by gram-positive organisms, especially *Staphylococcus* species.^{7-10,13} Interestingly, both an overall increased incidence of CR-BSI and an increased proportion of CR-BSI caused by gram-negative pathogens have been reported in patients receiving treprostinil compared to patients receiving epoprostenol.^{8,9,14} While the presence of an indwelling central venous catheter is likely the biggest risk factor for CR-BSI in this patient population, there has been some speculation that potential immunomodulatory activities of the prostanoids may increase the risk of infection.⁹ For instance, synthetic prostacylin analogs have been shown to inhibit bacterial phagocytosis and killing by macrophages *in vitro*.¹⁵

In this report, we describe a case of CR-BSI caused by a *Tsukamurella* species. *Tsukamurella* species are aerobic gram-positive organisms from the order Actinomycetales. Other genera of this order, including *Nocardia*, *Gordonia*, *Streptomyces*, *Rhodococcus*, *Mycobacterium*, and *Corynebacterium*, are closely related to *Tsukamurella* species; this may explain the easy misidentification of *Tsukamurella* in the literature.¹⁶ *Tsukamurella* species typically are found primarily in soil and sludge.¹⁷ *Tsukamurella* was first isolated in humans from the sputum of patients with chronic lung disease in 1971 by Tsukamura and Mizuno.¹⁸ The organism was known as *Gordona aurantiaca*¹⁶ until 1988,

Table 1. Susceptibility testing of *Tsukamurella* sp. isolate.

Antibiotic	Minimum inhibitory concentration (µg/mL)
Amikacin	<8.0
Kanamycin	<8.0
Tobramycin	4.0
Gentamicin	8.0
Ceftriaxone	<8.0
Cefepime	8.0
Cefotaxime	16.0
Imipenem	4.0
Minocycline	<1.0
Ciprofloxacin	<1.0
Clarithromycin	2.0
Azithromycin	128.0
Trimethoprim/Sulfamethoxazole	<0.5/9.5
Amoxicillin/Clavulanate	>32/16
Linezolid	4.0

when it was first proposed as a genus based on gene sequence analysis.¹⁹ Seven *Tsukamurella* species have been identified, but only five have been reported to cause infections in humans, including *T. inchonensis*, *T. paurometabola*, *T. pulmonis*, *T. strandjordae*, and *T. tyrosinosolvens*. The first case of bacteremia caused by *T. pulmonis* was reported in 1998 in an immunosuppressed patient.²⁰ *T. pulmonis* was identified subsequently as a cause of cavitory pneumonia and CR-BSI in immunocompromised patients.²¹ *T. tyrosinosolvens* has been identified in a patient with gastric carcinoma who developed hemoptysis²² and in immunocompromised patients with CR-BSI,²³ as well as in an immunocompetent patient with a brain abscess.²⁴ *T. pulmonis* and *T. tyrosinosolvens* have also been implicated in conjunctivitis in immunocompetent patients.²⁵ Finally, *T. paurometabola* has been isolated in immunosuppressed patients with CR-BSI.²⁶

Tsukamurella species are infrequent causes of CR-BSI. In a recent review, Bouza and colleagues noted that 12 of 14 reported patients with CR-BSI caused by *Tsukamurella* species were being treated for an underlying malignancy.²⁷ The remaining patients had chronic renal failure and required long-term intravenous access for hemodialysis. In general, underlying conditions in patients presenting with *Tsukamurella* CR-BSI have included primary immunodeficiencies, a variety of malignancies, and chronic renal failure.^{16,23,26-29} One case of *Tsukamurella* CR-BSI in a patient receiving intravenous epoprostenol for pulmonary hypertension was included in a recent series of CR-BSI in patients with pulmonary hypertension,⁸ although no details of the case presentation are included in the report. Although it is possible that our patient's treprostinil therapy and underlying lung disease

increased his risk for CR-BSI, the break in his central venous catheter was the most likely risk factor for developing CR-BSI caused by both the *Tsukamurella* species and the coagulase-negative staphylococcus.

Tsukamurella species may be misidentified as atypical *Mycobacterium* species when conventional mycobacterial testing is used initially in the identification of a gram-positive bacillus.^{30,31} Given the difficulty of identifying *Tsukamurella* isolates using routine laboratory techniques, it is likely that some cases of *Tsukamurella* CR-BSI have been incorrectly attributed to other pathogens. Of the *Tsukamurella* species associated with CR-BSI reviewed here, five were first identified as *Corynebacterium*,^{16,23,27-29} four as *Nocardia*,^{26,27,29} two as *Rhodococcus*,^{23,26} one as *Bacillus*,²⁹ and one as a nontuberculous mycobacterium.¹⁶ Final identification as *Tsukamurella* species often depended on the use of techniques that are not readily available in most clinical microbiology laboratories, such as HPLC^{16,26} or 16S rRNA sequencing.^{16,23,26,27}

In vitro testing suggests that *Tsukamurella* isolates may be susceptible to quinolones, macrolids, carbapenams, trimethoprim/sulfamethoxazole, and aminoglycosides.^{16,23,27,28} Low MIC values for ciprofloxacin, imipenem, and trimethoprim/sulfamethoxazole (Table 1) suggest that this was true for the isolate that we describe in this report. The activity of other classes of antibiotics varies in other reports. Susceptibilities may vary even within a class of antibiotics, as with the aminoglycosides for the isolate described here (Table 1). Importantly, antibiotics that are common empiric choices when a gram-positive rod is isolated may not have sufficient activity against *Tsukamurella* species. For instance, although MIC values for vancomycin were not

available for the isolate obtained from our patient, other reports have documented MIC values for vancomycin between 2 and 8 µg/mL.²⁷ Many antibiotics have been used to treat *Tsukamurella* CR-BSI, particularly trimethoprim/sulfamethoxazole and quinolones by themselves or in combination with other antibiotics.^{16,27} Because of the varying susceptibilities of *Tsukamurella* species and the relative lack of clinical experience with *Tsukamurella* CR-BSI, appropriate identification of a *Tsukamurella* species and subsequent susceptibility testing are therefore essential to facilitate appropriate antimicrobial therapy. In the setting of CR-BSI caused by a *Tsukamurella* species, treatment in our patient and in all other previously reported cases^{16,20,23,27,28} ultimately required the removal of the infected catheter in addition to antimicrobial therapy.

In summary, it is important to consider *Tsukamurella* species in cases of CR-BSI, particularly when specific identification of a gram-positive bacillus is difficult or delayed or when a patient fails to respond promptly to empiric antibiotic therapy. Our report highlights the potential for *Tsukamurella* species, while most often associated with CR-BSI in immunocompromised patients, to cause disease in other patient populations including otherwise immunocompetent patients treated with intravenous prostanoids for pulmonary hypertension.

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