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CASE REPORT

Chryseomonas luteola bloodstream infection in a pediatric patient with pulmonary arterial hypertension receiving intravenous treprostinil therapy

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Abstract Treprostinil is a prostacyclin analogue approved for the treatment of pulmonary arterial hypertension (PAH). It is commonly administered through a central venous catheter (CVC). Treprostinil is associated with the incidence of Gram-negative bacterial bloodstream infections (BSI), a susceptibility that has been associated with a diluent used for treprostinil. We report the case of a 14-year-old boy with idiopathic PAH on continuous intravenous treprostinil therapy who presented with fever and fatigue. A blood culture drawn from his CVC was positive for the rare Gram-negative organism *Chryseomonas luteola*. The patient made a complete recovery with antibacterial treatment. This is the only documented case of a *C. luteola* BSI in a PAH patient receiving continuous intravenous treprostinil. We recommend maintaining a high index of suspicion for both common and rare Gram-negative pathogens and the early administration of appropriate antibiotic therapy in this population. The use of an alternate diluent solution, such as Sterile Diluent for Flolan, further decreases the infection risk.

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Introduction

The efficacy of prostanoid therapy in the setting of pulmonary arterial hypertension (PAH) is well supported by clinical trials. Treprostinil is a modified prostacyclin analogue which is commonly administered by continuous infusion through a central venous catheter (CVC). Five years after its market introduction, the Centers for Disease Control and Prevention (CDC) reported in the Morbidity and Mortality Weekly Report that treprostinil use is associated with a higher incidence of Gram-negative bacterial bloodstream infections (BSI) (1 per 2.5 patient-years of use) compared with epoprostenol [1]. The mechanism for the increased incidence of BSI is unknown and is likely multi-factorial. To our knowledge, we present the only documented case of a *Chryseomonas luteola* BSI in a pediatric PAH patient receiving continuous intravenous (IV) treprostinil therapy. Although there is growing familiarity with emerging guidelines for the prevention of CVC-associated BSI, we present this case to emphasize the need for a high index-of-suspicion for Gram-negative bacterial BSI when treating sepsis in patients with PAH on treprostinil therapy. Significant efforts are being made within hospital systems to decrease the incidence of CVC-related BSI, but less attention has been paid to potential infectious risks associated with the medications administered through these catheters. There is evidence that the recent use of an alternate diluent decreases this risk among patients receiving treprostinil by altering the pH of the resultant solution.

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Case report

The patient is a 14-year-old boy diagnosed with World Health Organization Group I idiopathic PAH. He originally presented at 12 years of age with a 6-month history of chest pain, shortness of breath, and dyspnea on exertion. Echocardiography at that time revealed a poorly contractile right ventricle, with an estimated ejection fraction of 30 % (normal 45–55 %) and an estimated right ventricular pressure of approximately 93 mm Hg (normal <25 mm Hg). Serum brain natriuretic peptide was measured at 1,403 pg/mL (normal <100 pg/mL). An extensive evaluation for rheumatologic disease, including collagen vascular disease, was negative. The patient was treated aggressively with bosentan and furosemide. Following CVC placement, IV treprostinil was started and administered as a continuous infusion. On this regimen, his exercise tolerance gradually improved. Over the course of several months, he regained the ability to walk up one flight of stairs without symptoms. Later, routine surveillance echocardiography revealed improvement in his PAH.

Two years after his initial presentation, the patient had been at his baseline state of health when he began to experience fatigue, episodes of quadriceps muscle cramping, and fevers as high as 102 °F. He presented to the emergency department with no other signs of illness, such as cough, shortness of breath, rash, vomiting, or diarrhea. He was subsequently admitted to the pediatric intensive care unit out of concern for emerging CVC sepsis. Admission laboratory values, including white blood cell count and electrolyte levels, were within normal limits. A chest radiograph revealed increased pulmonary vascular markings associated with pulmonary hypertension. This was unchanged in comparison to previous radiographs. A CVC blood culture was drawn. Blood was cultured in a BacT/Alert system in standard aerobic bottles (Biomérieux, Marcy-l'Étoile, France) and grew Gram-negative bacilli, which were identified as *C. luteola* by the API 20NE microorganism identification test kit (Biomérieux). Identification was confirmed by the appearance of characteristic wrinkled yellow colonies on sheep's blood agar (BD, Sparks, MD), negative oxidase reaction, positive adenylate dehydrogenase, and positive esculin reactions. Antimicrobial susceptibility testing was performed using in-house prepared, reference broth microdilution, and the resutls were interpreted using the Clinical and Laboratory Standards Institute M100 document (CLSI, Wayne, PA). The isolate was found to be susceptible to ceftriaxone [minimum inhibitory concentration (MIC) 1 mcg/mL], gentamicin (MIC ≤0.5 mcg/mL), piperacillin/tazobactam (MIC ≤8 mcg/mL), and trimethoprim/sulfamethoxazole (MIC ≤1/20 mcg/mL). Antibiotic therapy at presentation consisted of vancomycin and pipercillin/tazobactam. Meropenem, amikacin, and ceftrixone were also used to treat this infection. The patient was ultimately discharged home with ceftriaxone to complete a total of approximately 14 days of antibiotic therapy as he unintentionally received 1 day of partial dosing during his infection. Two additional blood samples (one more than 4 days after the *C. luteola* culture) were drawn for culture after the patient had been started on antibiotic therapy, but no further organisms were grown. The patient ultimately made a full recovery and was seen during a clinic appointment more than 2 weeks after initial presentation.

Discussion

The efficacy of prostanoid therapy in the setting of PAH is well supported by several clinical trials [2, 3]. Currently, four agents, namely, epoprostenol, treprostinil, beraprost, and iloprost, are approved by the U.S. Food and Drug Administration (FDA) for use. These agents are, in essence, stable structural analogues of prostacyclin. They exert their effects by agonizing the G-protein-coupled prostacyclin (PGI_2) receptor, which then modulates the transcriptional activity of a family of transcription factors known as peroxisome proliferator-activated receptors [4]. Epoprostenol, the best studied agent, has been demonstrated to improve exercise capacity and a number of hemodynamic indices in those with PAH. Importantly, in clinical trials, this drug significantly prolonged patient survival in those with PAH and New York Heart Association stage III–IV heart failure [5].

Empiric evidence suggests that in addition to inducing tonic vasodilation of pulmonary arterioles and, thus, directly reducing pulmonary resistance, extended prostanoid therapy elicits therapeutic remodeling of the pulmonary vascular architecture, leading to a reduction in the proliferative vasculopathy characteristic of PAH [6]. PGI_2 is known to play a critical role in regulating smooth muscle differentiation and inhibits vascular smooth muscle cell proliferation and migration in vitro [7].

In 2002, treprostinil, a modified prostacyclin analogue, was approved by the FDA for use in the treatment of PAH. One of treprostinil's advantages includes its longer half-life, thus reducing the risk of cardiorespiratory compromise in the case of infusion interruptions [8].

Five years after its market introduction, however, a CDC Morbidity and Mortality Weekly Report was released which noted that treprostinil use is associated with a higher incidence of Gram-negative bacterial BSI, with an incidence of one per 2.5 patient-years of use for treprostinil

versus one per 6.4 patient-years in those receiving epoprostenol [1]. The reason for this disparity remains unclear, but a number of hypotheses have been proposed to explain these observations. Treprostinil is typically supplied in multi-dose, multi-use vials. These can become contaminated with bacteria through repeated accessing, and this has been known to predispose patients to BSI. In contrast, epoprostenol is not supplied in multi-use vials. Alternatively, these two drugs may have different immuno-modulating effects. The complex in vitro effects of treprostinil on chemokines have recently been reported [9]. Therefore, treprostinil may induce a relative susceptibility to Gram-negative bacteria through an immunologic mechanism. Adding to the risks, treprostinil vials could become contaminated during the manufacturing or packaging processes, and inappropriate CVC care could lead to CVC-associated microbial infection.

However, compelling evidence presented in two recent studies raises the question of whether the diluent used for treprostinil may contribute to the higher incidence of BSI than that used for epoprostenol. Zaccardelli and colleagues found that treprostinil diluted in the relatively alkaline Sterile Diluent for Flolan (SDF) (GlaxoSmithKline, Research Triangle Park, NC) demonstrated substantially greater antimicrobial activity than treprostinil in sterile saline, which has a neutral pH [10]. SDF was particularly more effective against Gram-negative bacterial organisms, with a >4 $\log_{10}$ reduction in Gram-negative bacterial growth. Thus, the relatively higher risk of Gram-negative BSI for patients receiving treprostinil compared to epoprostenol may reflect differences in the antimicrobial activity of each of their usual diluents. A subsequent study has shown that the use of epoprostenol diluent in patients receiving treprostinil is associated with a decrease in the incidence of Gram-negative BSI [8]. Our patient's diluent was subsequently changed to this more alkaline diluent.

Our patient was found to have *C. luteola* from a CVC blood culture. A CVC skin culture taken the day after this culture identified two oxacillin-sensitive *Staphylococcus aureus* organisms. In addition, 7 months earlier, a CVC skin culture identified an oxacillin-sensitive *S. aureus* organism. The only previously documented positive CVC blood culture at our hospital identified a *Corynebacterium* species 17 months earlier. Given that the treprostinil reservoir changes and that CVC care is typically provided in a home setting, infection control education is imperative. Although we cannot identify the exact cause of this patient's infection with complete certainty, the patient's low rate of infection despite the numerous CVC dressing and treprostinil reservoir changes likely performed during this time makes CVC care and medication administration technique less likely to be causative.

On a population level, *C. luteola* is an infrequent cause of bacteremia. First described in 1985, this motile, aerobic Gram-negative rod has since been classified as a pseudomonad, given its genomic and metabolic similarity to other members of this family [11]. *C. luteola* had been given the CDC group Ve-1 designation, which denotes its close similarity to CDC group Ve-2, later termed *Flavimonas oryzihabitans* [12].

The *C. luteola* organism can cause a variety of infections and has been identified as a cause of bacterial infections in patients with a catheter or graft material [12, 13]. Unlike other *Pseudomonas* species, this pathogen has not been reported to cause disease in children with chronic lung disease, such as cystic fibrosis. Cell-wall synthesis inhibitors are generally chosen as therapeutic agents in cases of infection, and the length of treatment has been reported to vary from 2 to 6 weeks, with longer treatment courses chosen for cases of hardware infection. This organism has been reported to be resistant to amoxicillin, trimethoprim/sulfamethoxazole, and some cephalosporins [14, 15]. Ceftriaxone and ceftazidime have been used, however, to treat *C. luteola* infections [13, 16]. The organism described in our patient was susceptible to ceftriaxone.

This case illustrates one of the risks associated with treprostinil, namely, Gram-negative bacterial BSI, and represents the first case report of *C. luteola* in a pediatric patient with PAH receiving continuous IV treprostinil through a CVC. As evidence accumulates, clearer host and drug factors which may predispose patients receiving treprostinil to Gram-negative bacterial BSI may be identified. For example, there is evidence that the recent use of an alternate diluent decreases this risk among patients by altering the pH of the resultant solution.

In summary, there is an association between treprostinil therapy and Gram-negative BSI. *C. luteola* is a rare pathogen which has been identified as a cause of bacterial infections in patients with a catheter or graft material. Although we cannot identify the exact cause of this patient's infection with complete certainty, our case documents the risk of Gram-negative bacterial BSI to patients on treprostinil. To date, it is the only published case report of *C. luteola* bacteremia in a pediatric patient with PAH receiving continuous IV treprostinil. We encourage the use of an alternate diluent solution, such as SDF, to decrease this risk.

Conflict of interest None.

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