Micrococcus-Associated Central Venous Catheter Infection in Patients With Pulmonary Arterial Hypertension*

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Study objectives: **To determine the incidence of catheter-related infection in patients with pulmonary arterial hypertension (PAH) receiving epoprostenol (EPO), and to note an etiologic role for Micrococcus spp, which is rarely reported as a pathogen in the medical literature.**
Design: **Observational study.**
Setting: **Two PAH specialty treatment centers, Harbor-UCLA Medical Center (Torrance, CA), and the College of Physicians and Surgeons, Columbia University (New York, NY).**
Patients: **A total of 192 patients with PAH receiving continuous therapy with IV EPO.**
Interventions: **From 1987 to 2000, 192 patients with PAH received infusions of EPO via central venous catheter. Catheter care included regular dressing changes with dry gauze using a sterile procedure, without the use of flushes. Patients were asked to report on known infections and treatments, and symptoms. All infections were verified by a telephone call to the patient, care provider, and microbiology laboratory whenever possible.**
Measurements and results: **There were 335,285 catheter days (mean ± SD, 1,325 ± 974 catheter days). There were 88 clinical catheter infections with 51 blood culture-positive infections, necessitating catheter removal in 38 instances. The following pathogens were isolated: *Staphylococcus aureus* (25); Micrococcus spp (14); mixed flora (3); coagulase-negative Staphylococcus spp (2); Corynebacterium spp (2); *Serratia marcessens* (1); Enterobacter spp (1); *Pseudomonas aeruginosa* (1); enterococci (1); and unidentified Gram-positive cocci (1). The catheter infection rate was 0.26 per 1,000 catheter days.**
Conclusions: **The use of long-term therapy with continuous EPO appears to be associated with a low incidence of catheter-related infections. Micrococcus spp were the second most common etiologic agent. Caregivers managing patients with PAH must be aware of the risk of catheter infection, as it may contribute to the morbidity and mortality associated with the use of EPO. When isolated, Micrococcus spp should not be viewed as a contaminant, but rather as a true pathogen that may require therapeutic intervention.** ***(CHEST 2004; 126:90–94)***

Key words: catheter infection; epoprostenol; Micrococcus; pulmonary arterial hypertension

Abbreviations: EPO = epoprostenol; PAH = pulmonary arterial hypertension

Bacteremia and sepsis are common and often life-threatening complications of permanent central venous catheters. In patients with long-term, indwelling central venous catheters, the incidence of catheter infection varies from 0.3 to 9.1 infections per 1,000 patient-days,[1–3] with the majority of etiologic organisms being coagulase-negative Staphylococci and Streptococcus spp.

The use of central venous catheters in patients with pulmonary arterial hypertension (PAH) is a known contributor to the morbidity and mortality associated with the use of long-term therapy with epoprostenol (EPO) [Flolan; GlaxoSmithKline; Middlesex, UK] in these patients.[4] Catheter infection data are limited in patients with PAH, in part

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because the disease is rare, and few centers are able to track PAH patients for long periods of time. We report an observational study of all catheter-related infections in patients with PAH who were receiving continuous therapy with EPO who were seen at two large referral centers for PAH. We also note a possible etiologic role for Micrococcus spp, which are only rarely reported as pathogens in the medical literature.[5–7]

Materials and Methods

From January 1987 to August 2000, 192 patients were referred to two PAH specialty treatment centers, Harbor-UCLA Medical Center (Torrance, CA) and the College of Physicians and Surgeons at Columbia University (New York, NY). Outcome data from subgroups of patients at both centers have been reported previously.[4,8] Patients had to have a diagnosis of PAH according to the following criteria: (1) PAH that was idiopathic, was related to connective tissue disease, HIV, and portal hypertension, or was related to congenital systemic-to-pulmonary shunts (repaired or unrepaired); and (2) mean pulmonary artery pressure of > 25 mm Hg at rest, pulmonary capillary wedge pressure or left ventricular end-diastolic pressure of < 15 mm Hg, and pulmonary vascular resistance of ≥ 240 dyne $\cdot$ s $\cdot$ cm^{-5}.[9,10] Table 1 lists the baseline demographics of the patients in this study. Initially, all patients underwent infusion of EPO via a peripheral vein, with a right heart catheter in place. A central venous catheter (Hickman, Groshong, or Broviac; CR Bard, Inc; Murray Hill, NJ) was later inserted into the superior vena cava, and EPO infusion was subsequently transferred from the peripheral to central venous catheter. Patients were then discharged from the hospital after they and their supporting caregiver were instructed on the care and maintenance of the catheter.

Catheter care included regular dressing changes with dry gauze or semi-permeable dressings using sterile procedures, without the use of saline solution or heparin flushes. Patients were instructed to seek nurse and/or physician evaluation immediately if they noted redness or a persistent discharge at the catheter site. The administration of EPO required daily mixing of the drug and filling of a backup infusion pump reservoir using a sterile procedure, followed by disconnection of the infusing pump from the catheter, and rapid connection to the newly filled pump.

A direct follow-up of this group of patients was possible approximately every 3 to 6 months in most patients. Some patients returned for follow-up on a less-frequent basis. Others were managed by their private physician; however, regular contact from one of our centers by a PAH nurse coordinator for the dosing of EPO was maintained. Patients were asked to report on known infections, symptoms, treatments, and, if known, outcomes. In addition, patients were asked to provide the names and addresses of physicians involved in the treatment of infections, if treated at a facility other than our 2 specialty centers. All possible and documented catheter infections were verified by a telephone call to the patient, care provider, and microbiology laboratory whenever possible.

Statistical Analysis

Infection rates are reported per 1,000 patient days. Where known, positive blood culture identification is reported. Values are reported as the mean ± SD.

Results

The total number of catheter days was 335,285. The range of catheter duration was 30 to 4,887 days, with a mean of 1,325 ± 974 days (or 3.6 ± 2.7 years). During the study period, 52 patients (27%) had a total of 88 catheter infections. Nearly all 52 patients had symptoms of redness and/or discharge, and warmth and/or pain at the catheter entrance site at some time during their EPO treatment; however, many instances were reportedly self-limited. Thirty-eight episodes of clinical catheter infection required the removal of the catheter as part of the treatment (according to the discretion of the treating physician), corresponding to 43% of all infections and 73% of all patients with catheter infections. All episodes were treated with a minimum of 2 weeks of IV antibiotic therapy (range, 2 to 6 weeks). The etiologic organism was cultured in at least one specimen from the blood or catheter tip in 51 of the 88 clinical infections. The organisms cultured are listed in Table 2. In 37 infections, the diagnosis of catheter infection was presumptive, and was based on the resolution of symptoms and signs after antibiotic treatment alone (3 patients) or antibiotic treatment plus catheter removal (34 patients).

Of note was the presence of catheter-related infection with Micrococcus spp, occurring in 14 patients (27% of all blood culture-positive catheter infections). In three of these cases, the treating physician initially considered the Micrococcus spp to be a contaminant and initiated antibiotic treatment only after there was no response to conventional management of the patient. In one of these cases, the catheter was removed twice before the Micrococcus spp infection was recognized and treated. The distribution of Micrococcus spp infection was similar in both of our centers (West Coast center, 26%; East Coast center, 28%).

The overall catheter infection rate for our patients

Table 1—*Patient Demographics

Variables	Values
Age, yr	40 ± 22
Female, %	79
Diagnoses	
Idiopathic PPH	65
CHD	19
CTD	12
Porto	2
HIV	2

*Values given as mean ± SD or %. PPH = primary pulmonary hypertension; CHD = congenital heart disease; CTD = connective tissue disease; Porto = portopulmonary-associated PAH; HIV = HIV-associated PAH.

Table 2—*Bacterial Species Recovered From Blood Cultures of 192 PAH Patients With Central Venous Catheters

Organism	Instances
Staphylococcus aureus	25 (49)
Micrococcus spp	14 (27)
Mixed flora	3 (6)
Coagulase-negative Staphylococcus spp	2 (4)
Corynebacterium spp	2 (4)
Serratia marcessens	1 (2)
Enterobacter spp	1 (2)
Pseudomonas aeruginosa	1 (2)
Enterococcus spp	1 (2)
Unidentified Gram-positive cocci	1 (2)
Total	51 (100)

*Values given as No. (%).

was 0.26 per 1,000 catheter days. This compares favorably to reports of catheter infection rates between 0.3 and 9.1 per 1,000 catheter days in patients with Hickman, Groshong, or Broviac catheters placed for other reasons, such as for the long-term administration of chemotherapy.[1,2]

Morbidity and Mortality

Two patients died as a direct complication of their catheter infection, and at least 15% of patients were hospitalized for prolonged periods. One of the deaths was related to the reinsertion of a replacement catheter, after removal of an infected catheter. A third patient died of a catheter-related infection; however, this patient's death occurred after the study period. At least 10% of the patients in this study required admission to critical care wards, some requiring IV pressor support. In addition, outside the study period, several additional deaths related to catheter infections have been observed at both PAH specialty centers.

Discussion

In this study, the incidence of overall catheter-related infection was relatively low in comparison to other studies of nonpulmonary hypertensive patients with central venous access devices. This may be due to the fact that many patients with PAH are often very motivated to learn about their disease, participate in their treatment, and take extra precautions in order to improve their quality of life and survival. Nevertheless, a systemic infection in PAH patients can be catastrophic because of their degree of physiologic impairment. This is especially true for patients who are debilitated enough to warrant therapy with EPO, such as those in the present study.

Significant morbidity and mortality associated with the use of EPO in patients with PAH occurs because of the necessity for long-term central venous catheter use. Relatively few data have been published in this patient population, probably because of the very low incidence of this disease, which is estimated to be about 1 to 2 per million population per year in the United States for primary idiopathic PAH. In addition, the association of Micrococcus spp with a clinical syndrome of catheter infection has only rarely been demonstrated.[11–13]

One of the difficulties in managing patients with PAH receiving EPO is the challenge of early detection and intervention for infections related to their central venous catheter. Based on the experiences of our centers, the clinical syndrome of micrococcal catheter infection often presents as generalized weakness and fatigue, with or without fever. Often, patients with PAH complain of lethargy and other constitutive symptoms that may represent the waxing and waning physical well-being in these patients or worsening PAH and/or medication overdose, or may represent an undiagnosed catheter infection. Patients with infection due to Micrococcus spp also may develop unexplained pulmonary "infiltrates" on chest radiographs, which do not resolve until the infection is treated. Finally, even when symptoms such as fever and malaise may suggest an infectious etiology, the catheter entrance sight may appear to be normal, and blood culture results may be negative or may yield apparently "contaminant" organisms, such as Micrococcus spp. Thus, it is important that clinicians have a low threshold for aggressively searching for infection when a patient receiving EPO starts to complain of constitutional symptoms for no apparent reason.

Because HIV-associated pulmonary hypertension is an increasingly recognized clinical entity, this patient population presents a particular concern with regard to catheter infections.[14,15] These patients derive benefit from EPO therapy[15]; however, their immunodeficiency places them at increased risk of catheter infection.

Our population of patients is unique because of the rare disease that they share in common (*ie*, PAH), and the opportunity for long-term follow-up that is available in this relatively large group of patients. The relatively high number of Micrococcus spp infections is also unique to this group of patients and has not been reported previously. The etiologic factors responsible for this association are not known; however, one possibility is self-contamination/poor catheter hygiene.

A report demonstrating the facile transfer of Micrococcus spp from stethoscope to skin[16] has suggested that inoculation by the caregiver has a possi-

ble etiologic role. This has particular implications in patients with PAH, since the clinical follow-up visits of most patients occur in PAH centers. Thus, it is possible that the transmission of Micrococcus spp might have occurred during routine visits to the PAH center, where several PAH patients were examined on the same day, sometimes in the same place, and with the same stethoscope. That the frequency of Micrococcus spp as the etiologic agent was similar between PAH centers in the western and eastern United States in this study supports this possibility. However, there are several other explanations that could have accounted for the Micrococcus spp infections, including mouth-hand–wound or mouth-hand–drug contamination.

In 1995, Jones et al[17] surveyed 150 health-care providers, which included 50 emergency medicine housestaff and attending physicians, 50 emergency department nurses, and 50 prehospital personnel, and found that only 48% cleaned their stethoscopes daily or weekly, 37% cleaned them monthly, and 7% cleaned them annually. In fact, 7% of stethoscope users had never cleaned their stethoscopes at all.[17]

It has been shown that the Micrococcus spp can be an opportunistic pathogen in an immunocompromised patient.[11–13] While immunodeficiency has not been documented in patients with PAH, the chronicity of their debilitating disease and the chronic right ventricular failure that accompanies their disease may place them at increased risk for opportunistic infections.

Simple measures, such as improved clinician hygiene might help to decrease the contamination and transmission of microorganisms via stethoscopes. A more thorough approach to this problem might be to implement the use of disposable stethoscope diaphragms, which can significantly reduce bacterial counts on stethoscope surfaces.[18] Yet another approach to decreasing catheter-related infections would be to use antiseptic-impregnated catheters.[19]

Limitations

This observational study has several limitations. The incidence of catheter infection was determined based on information reported by the patient and the treating clinician, and may have underestimated the true incidence of infection. In contrast, several catheter infections in this study were based on clinical findings that prompted intervention despite the lack of identification of a specific etiologic agent. This practice may have overestimated the already low incidence of catheter-related infection. That these patients improved after intervention, however, argues against this possibility. Nevertheless, our study may have had a significant bias on the real incidence of catheter infection and on the microbiological diagnostic sensitivity. In addition, the lack of a definite control group using central venous catheters placed for other reasons prevents definitive conclusions about the catheter infection rate seen in our study.

We were not able to determine the cause of death in many of the patients, as they were sometimes at a great distance from the study centers. This information could yield additional insight into catheter-related complications, since some of the patient deaths could have been related to bacteremia and/or sepsis. Finally, we were unable to determine the independent clinical variables that were responsible for the catheter infection rate and/or clinical outcome in our patients because these data were not collected prospectively in all patients. Such variables may indeed be revealing in their association with catheter infections.

Conclusion

Based on the information presented from this study of PAH patients with long-term, indwelling central venous catheters, it is important that clinicians caring for this patient group are aware of the incidence of catheter-related infections in PAH patients, as well as the potential for Micrococcus spp to cause clinical infection. If a patient with PAH experiences symptoms that vaguely suggest infection, clinicians should have a lower threshold for conducting a thorough investigation into catheter infection, including obtaining multiple blood cultures (including blood cultures obtained from the catheter itself and from both lumens if a double-lumen catheter is used), the close measurement of temperature curves, and more frequent follow-up.

Because of the new available alternatives to EPO therapy, many patients with PAH often have several therapeutic options to choose from. Such alternatives to EPO therapy may come in the form of inhaled therapies,[20,21] subcutaneous therapy,[22] or oral therapy.[23] It is important for physicians to be aware that catheter-related infections in patients with PAH may contribute to significant morbidity and mortality, and that these infections may be difficult to document. In addition, the Micrococcus spp, previously thought to not be a pathogen, appears to be capable of producing a systemic syndrome that is identical to that seen with more common bacteriologic pathogens. Thus, the decision to initiate IV EPO therapy for the treatment of PAH should include careful consideration of the potential for catheter-related infections.

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