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Closed-Hub Systems with Protected Connections and the Reduction of Risk of Catheter-Related Bloodstream Infection in Pediatric Patients Receiving Intravenous Prostanoid Therapy for Pulmonary Hypertension

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Abstract

BACKGROUND—Intravenous prostanoids (epoprostenol and treprostinil) are effective therapies for pulmonary arterial hypertension but carry a risk of catheter-related bloodstream infection (CR-BSI). Prevention of CR-BSI during long-term use of indwelling central venous catheters is important.

OBJECTIVE—To evaluate whether using a closed-hub system and waterproofing catheter hub connections reduces the rate of CR-BSI per 1,000 catheter-days.

DESIGN—Single-center open observational study (January 2003–December 2008).

PATIENTS—Pediatric patients with pulmonary arterial hypertension who received intravenous prostanoids.

METHODS—In July 2007, CR-BSI preventive measures were implemented, including the use of a closed-hub system and the waterproofing of catheter hub connections during showering. Rates of CR-BSI before and after implementing preventive measures were compared with respect to medication administered and type of bacterial infection.

RESULTS—Fifty patients received intravenous prostanoid therapy for a total of 41,840 catheter-days. The rate of CR-BSI during the study period was 0.51 infections per 1,000 catheter-days for epoprostenol and 1.38 infections per 1,000 catheter-days for treprostinil, which differed significantly ($P < .01$). CR-BSIs caused by gram-negative pathogens occurred more frequently with treprostinil than with epoprostenol (0.91 infections per 1,000 catheter-days vs 0.08 infections

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per 1,000 catheter-days; $P < .01$). Patients treated with treprostinil after the implemented changes had a significant decrease in CR-BSI rate (1.95 infections per 1,000 catheter-days vs 0.19 infections per 1,000 catheter-days; $P < .01$).

CONCLUSION—The closed-hub system and the maintenance of dry catheter hub connections significantly reduced the incidence of CR-BSI (particularly infections caused by gram-negative pathogens) in patients receiving intravenous treprostinil.

Treatment with continuous intravenous (IV) prostanoids (ie, epoprostenol and treprostinil) has been shown to improve exercise capacity,[1-3] hemodynamics,[1-3] and survival rates[1,2] in patients with pulmonary arterial hypertension (PAH). Administration of IV formulations of prostanoids involves continuous infusion of medication through a central venous catheter (CVC).[4] Although CVCs are common vehicles for drug delivery (an estimated 5 million CVCs are implanted annually in the United States), they are associated with a risk of complications.[5] Indeed, more than 15% of patients with CVCs develop catheter-related complications, including mechanical, thrombotic, and infectious complications.[5]

Catheter-related bloodstream infections (CR-BSIs) are caused by a wide range of opportunistic pathogens, including gram-negative and gram-positive bacterial species.[4,6] The mean rate of CR-BSI in medical intensive care units is 2.9 infections per 1,000 catheter-days,[7] and the reported incidence of CR-BSI among patients with long-term, indwelling CVCs for various diseases and conditions ranges from 0.3 infections per 1,000 catheter-days to 9.1 infections per 1,000 catheter-days.[6,8-10] The use of CVCs in patients with PAH has been associated with CR-BSI rates reportedly ranging from 0.1 infections per 1,000 catheter-days to 1.1 infections per 1,000 catheter-days.[6,11,12] In the largest review of patients with PAH and CR-BSI, the Centers for Disease Control and Prevention conducted a retrospective evaluation of CR-BSIs in patients who had received IV prostanoids from 7 major PAH centers.[12] A total of 57 CR-BSIs were identified during 51,183 catheter-days among patients receiving IV treprostinil, and 87 CR-BSIs were noted during 201,158 catheter-days among patients receiving IV epoprostenol. Thus, CR-BSI rates were found to be higher among patients receiving treprostinil than among patients receiving epoprostenol (1.11 infections per 1,000 catheter-days vs 0.43 infections per 1,000 catheter-days; pooled incidence rate ratio [IRR], 2.57; 95% confidence interval [CI], 1.81–3.64). However, the incidence of CR-BSI at individual centers varied widely; reported CR-BSI rates ranged from 0.28 to 2.10 infections per 1,000 catheter-days for treprostinil and from 0.23 to 1.02 infections per 1,000 catheter-days for epoprostenol, reflecting an approximate 2-fold difference between centers.

The increased incidence of CR-BSI with treprostinil may be associated with higher rates of infection caused by gram-negative pathogens.[4,12] The Centers for Disease Control and Prevention report identified a significantly higher pooled mean rate of CR-BSI caused by gram-negative pathogens among patients who received treprostinil than among patients who received epoprostenol (0.76 infections per 1,000 catheter-days vs 0.06 infections per 1,000 catheter-days; pooled IRR, 12.77; 95% CI, 6.55–26.80).[12] Higher rates of CR-BSI and the increased frequency of infection caused by gram-negative pathogens associated with treprostinil, compared with epoprostenol, were also reported in a separate publication detailing CR-BSI rates at 2 of the 7 PAH centers and that retrospectively evaluated a total of 224 patients during 146,093 catheter-days.[4] Thus, CR-BSIs are rare but significant events in PAH, and infections caused by gram-negative pathogens are more commonly associated with IV treprostinil.

The catheter hub is generally the suspected point of entry for pathogens causing CR-BSI in patients receiving long-term treatment.[13,14] Akagi et al[11] evaluated the effect of adopting a closed-hub system on CR-BSI rates among 20 patients with PAH who were receiving

continuous IV epoprostenol. Eleven patients started to receive epoprostenol therapy before introduction of the closed-hub system. During the 6.5-year study period, a total of 7 CR-BSIs occurred in 6 patients, resulting in a CR-BSI rate of 1.2 infections per 1,000 catheter-days in the non–closed-hub system group. Thirteen patients received IV epoprostenol via a closed-hub system, including 4 patients who were switched from the non–closed-hub system. Catheter-related BSIs in the closed-hub system group included 2 infections that occurred in 1 patient, and the CR-BSI rate in this patient population was 0.23 infections per 1,000 catheter-days. Thus, the closed-hub system significantly reduced the risk for CR-BSI among patients with PAH who were receiving IV epoprostenol ($P = .04$). The infusion line connections also may represent a point of entry for bacterial pathogens present in tap water or transferred from the shower head. Therefore, interventions designed to prevent the exposure of infusion system connections to tap water, such as during bathing, may further reduce the risk of CR-BSI.

In this context, the objective of the current study was to evaluate whether the incidence of CR-BSI among patients with PAH receiving IV prostanoids could be reduced through the introduction of 2 new preventive measures: the introduction of a closed-hub system and the waterproofing of catheter hub connections during showering.

METHODS

Study Design and Population

We conducted a single-center observational study involving all pediatric patients with PAH who received IV prostanoids from January 2003 through December 2008. All patients were enrolled in an institutional review board–approved protocol, A Prospective Evaluation of Adolescents and Children with Pulmonary Arterial Hypertension. IV epoprostenol exclusively was administered before July 2004, when treprostinil first became available at our institution. Beginning in July 2004, patients received either IV epoprostenol or IV treprostinil. In June 2006, an apparent spike in the incidence of CR-BSI caused by gram-negative pathogens was observed, which led our center to reassess the approach to prevention of CR-BSI. Rates of CR-BSI were obtained retrospectively before June 2006 and prospectively thereafter.

Because many gram-negative species are waterborne, we collaborated with a plastics engineer to investigate possible water-related mechanisms of catheter contamination. We observed that exposure of the catheter hub connection to water (eg, while showering) allows water to track along the threads of the connection (Figure 1*A*). If the catheter hub connection is opened while the threads are wet, water flows to the end of the catheter hub, allowing hydrophilic organisms to enter the catheter (Figure 1*B*).

Thus, in July 2007, 2 new preventive measures for reducing the risk of CR-BSI were implemented. First, a closed-hub system (BD Q-Syte Closed Luer Access; Becton Dickinson) with a unique split-septum device for penetration by a standard male luer was introduced. The split septum has a smooth surface that is simple to disinfect, and the large size and curved shape of the split septum provide convenient access and connection. A closed-hub system had not been used previously because of concerns of accidental disconnection with other systems that were tried briefly in 1998. Thus, before the introduction of the closed-hub system, patients directly connected the infusion tubing to the CVC. Second, we implemented a method to protect the connections to the catheter hub from exposure to tap water. This approach involved waterproofing the catheter connections during showering by means of a sealable plastic wrap (Glad Press’n Seal; Glad Products).

Assessment of CR-BSI Rates

We defined an occurrence of CR-BSI by a positive result of culture of a blood sample obtained from a peripheral vein and no apparent source of infection other than the catheter. Two positive culture results in the same patient occurring at least 21 days apart were considered to be 2 separate CR-BSI events. Rates of CR-BSI were calculated as the number of infections per 1,000 catheter-days (1 catheter-day corresponded to 1 day of IV prostanoid therapy). Rates of CR-BSI before and after preventive measures were introduced in July 2007 were compared. We also compared CR-BSI rates between patients who received epoprostenol and patients who received treprostinil. In addition, the causative bacterial species (ie, gram-negative or gram-positive pathogen) was documented for each CR-BSI event. Of note, CVC insertion site infections were not considered to be CR-BSIs.

Statistical Methods

Rates of CR-BSI were calculated on a monthly basis during the study. The cumulative CR-BSI rates (including all infections) and the rates of infection caused by gram-negative and gram-positive pathogens were modeled by generalized linear regression that used the negative binomial with a log link. The number of treatment-days was specified as an offset variable to normalize the fitted cell means to a per 1,000 treatment-day basis. Variables denoting type of therapy, whether a closed-hub system was used, and the interaction between therapy and the closed-hub system were included in the model as covariates. χ^2 tests based on contrasts of the estimated regression coefficients were used to test all comparisons of interest. All analyses were performed using PROC GEN-MOD in SAS software, version 9.2 (SAS Institute).

RESULTS

A total of 50 patients were treated with IV prostanoid therapy for 41,840 catheter-days (epoprostenol for 25,273 catheter-days and treprostinil for 16,567 catheter-days) from January 2003 through December 2008. Mean CVC (IV prostanoid) exposure was approximately 2.3 years per patient. During the entire study period, the mean rate of CR-BSI was 0.87 infections per 1,000 catheter-days, with a peak in CR-BSI rate observed in June 2006 (Figure 2). Statistical process control charts tracking CR-BSI rates during the month of June 2006 exceeded 3 standard deviations; there was concern that CR-BSI preventive techniques were inadequate or not adhered to by patients or that there was a new source of infection. However, with the exception of the outbreak in June 2006, there was no apparent shift or change in the incidence of CR-BSI after the introduction of treprostinil.

Incidence rates by type of organism and IV prostanoid and 95% CIs are summarized in Table 1. During the study period, rates of CR-BSI were significantly higher among patients treated with treprostinil than among patients treated with epoprostenol (1.38 infections per 1,000 catheter-days vs 0.51 infections per 1,000 catheter-days; $P < .01$). Although the incidence of infection caused by gram-positive pathogens was comparable between patients treated with treprostinil and patients treated with epoprostenol (0.49 infections per 1,000 catheter-days vs 0.43 infections per 1,000 catheter-days; $P = .81$), there was a significantly higher incidence of infection caused by gram-negative pathogens among patients treated with treprostinil (0.91 infections per 1,000 catheter-days vs 0.08 infections per 1,000 catheter-days; $P < .01$).

Documented causative bacterial pathogens are summarized in Table 2. Eight infections caused by gram-positive pathogens and 15 infections caused by gram-negative pathogens were associated with treprostinil, whereas 11 infections caused by gram-positive pathogens and 2 infections caused by gram-negative pathogens were associated with epoprostenol. The

majority (13 [68%]) of the 19 infections caused by gram-positive pathogens were attributed to *Staphylococcus* species. Causative gram-negative pathogens included *Stenotrophomonas* and *Klebsiella* species.

In July 2007, measures implemented to reduce the risk of CR-BSI included the introduction of a closed-hub system and the use of a sealable wrap to waterproof the infusion system connections during showering. The number of CR-BSIs before and after intervention is summarized in Figure 3. There were a total of 34 events before intervention and 2 CR-BSI events after intervention.

Overall, preventive measures reduced the rate of CR-BSI among patients treated with either prostanoid from 1.04 to 0.24 infections per 1,000 catheter-days (Table 1; $P = .02$). There was a significant reduction in the incidence of CR-BSI among patients treated with treprostinil after implementation of preventive measures (1.95 infections per 1,000 catheter-days before July 2007 vs 0.19 infections per 1,000 catheter-days after July 2007; $P < .01$). There was no significant reduction in the incidence of CR-BSI among patients treated with epoprostenol after the implementation of preventive measures (0.54 infections per 1,000 catheter-days before July 2007 vs 0.33 infections per 1,000 catheter-days after July 2007; $P = .61$). Since the introduction of measures to prevent contamination, there has been only 1 case of CR-BSI (caused by a gram-positive pathogen) in a patient receiving epoprostenol and only 1 case of CR-BSI (caused by a gram-negative pathogen) in a patient receiving treprostinil.

DISCUSSION

The occurrence of CR-BSI has important implications for patient morbidity and mortality as well as healthcare costs. Potentially severe systemic complications may increase mortality rates associated with CR-BSI; for example, sepsis is lethal in 20%–50% of severely affected patients, and sepsis is currently the tenth leading cause of death overall in the United States.[15] Bloodstream infections can also lead to costly hospitalizations. In this context, CR-BSIs are associated with healthcare costs approaching $60,000 per infection, resulting in an estimated cumulative cost of $300 million to more than $2 billion annually.[16] Therefore, reducing the risk of CR-BSI is an important goal of therapy for PAH.

In this observational study, implementing a closed-hub system and maintaining dry infusion line connections decreased the overall incidence of CR-BSI among pediatric patients with PAH treated with IV prostanoid therapy. Of note, the introduction of preventive measures significantly reduced the rate of CR-BSI among patients receiving treprostinil, including a reduction in the incidence of gram-negative infection, which appeared to be more common among treprostinil-treated patients. The reasons for the increased risk of CR-BSI caused by gram-negative pathogens with treprostinil, compared with epoprostenol, are unknown but have been suggested potentially to be related to differences in patient behavior or to differences in medication properties.[4] The terminal elimination half-life of treprostinil is much longer than that of epoprostenol (approximately 4 hours vs approximately 6 minutes).[17,18] Although unproven, patients who receive treprostinil may be more apt to disconnect the infusion line from their CVC because of the medication's longer half-life, which may increase the risk of catheter hub contamination during exposure to air or moisture.[4] The difference in the storage and preparation of the treprostinil and epoprostenol may potentially influence CR-BSI rates, because treprostinil is a multiuse vial and epoprostenol is a single-use vial. However, treprostinil vials contain 0.3% metacresol, and multiple vials and cassettes from treprostinil-treated patients with CR-BSI were negative for bacteria.

In addition, the pH of treprostinil is neutral (6.0–7.2),[17] and the treprostinil was reconstituted with sterile water for injection or 0.9% normal saline, whereas epoprostenol reconstituted with Flolan sterile diluent for injection has an alkaline pH (10.2–10.8).[18] The package insert for treprostinil was recently changed to allow its use with Flolan sterile diluent on the basis of a study showing that treprostinil (0.004 mg/mL) is stable for 52 hours in this diluent (pH, 10.5).[19] As part of the same study, antimicrobial tests showed log reductions of 4.20 and 4.53 in *Escherichia coli* and *Pseudomonas aeruginosa* populations, respectively. A previous study demonstrated little change in populations of the same bacteria in treprostinil with sterile saline diluent. Of interest, treprostinil with Flolan sterile diluent or normal saline are both bactericidal against *Staphylococcus aureus*.[19,20] The effect of increasing the pH of the treprostinil infusion on the incidence of CR-BSI will be tracked in the future.

The results of our study are consistent with a previous report by Akagi et al[11] in which protection of the catheter hub connection led to a significant reduction in the risk of CR-BSI. Use of a closed-hub system may minimize bacterial contamination by limiting exposure of the catheter connection to the environment.[11] Although the treprostinil group had a significant decrease in CR-BSI, the decrease noted in the epoprostenol group did not reach statistical significance. There was, however, a trend toward further improvement that may be clinically important. Before implementation of the closed-hub system, the higher pH of epoprostenol may have provided some antimicrobial protection, especially against gram-negative bacteria.

Different types of catheter hub systems are available. However, split-septum devices may be preferred over mechanical valve devices, but mechanical valve devices with a flat, smooth surface amenable to preaccess disinfection may be considered.[21] In another study by Rupp et al,[22] a transition from a split-septum device to a positive-pressure displacement valve led to an approximate 3-fold increase in the rate of BSI (approximately 4 infections per 1,000 CVC-days to approximately 12 infections per 1,000 CVC-days). After a transition back to the split-septum device, CR-BSI rates returned to normal levels. These data demonstrate the importance of selecting access devices that minimize exposure to potential contaminants and that can be adequately disinfected.

Our study suggests that, in addition to the implementation of a closed-hub system, the waterproofing of catheter hub connections during showering may be an effective preventive measure for managing the risk of CR-BSI among patients with PAH. The catheter hub is often the point of entry for pathogens that cause CR-BSI,[13,14] and hub connections may be exposed to hydrophilic gram-negative pathogens (eg, *Pseudomonas*, *Stenotrophomonas*, *Acinetobacter*, or *Serratia* species) during showering.[21] None of the currently available closed-hub systems provide a waterproof seal for the catheter hub threads. Further investigation into newer hubs that prevent water contamination is warranted. If a connection is exposed to water, patients should be counseled to not disconnect to change out their system until the threads are dry, because this appears to be the point at which contamination occurs. We found that protecting the catheter hub connection with a sealable wrap during showering effectively kept it dry, which may have contributed to the observed reduction in the incidence of CR-BSI.

Interpretation of this study is limited by several factors, including the observational study design. Increased education and surveillance with regard to catheter-related infection may have also influenced our results. Patient complacency with regard to aseptic technique must also be considered. Guidelines for the prevention of catheter-related infection[16,21] recommend proper hand hygiene (ie, washing hands with conventional antiseptic-containing soap and water or with waterless alcohol-based gels or foams) and the use of gloves when

manipulating the CVC. In addition, wiping the access port with 70% alcohol and accessing the port only with sterile devices may minimize contamination. These guidelines were again addressed with patients and caregivers. In addition, the number of catheter-days after implementation of the interventions was a relatively small proportion of the overall experience (approximately 20%). Nevertheless, there was a robust CVC duration overall, with a mean of more than 2 catheter-years per patient. Also, we did not measure patient compliance with respect to maintaining dry connections. Finally, only BSIs determined by the investigators to be attributed to the catheter were included, although these infections likely accounted for the majority of BSIs reported in the PAH population.

In summary, we report that the implementation of a closed-hub system and the waterproofing of catheter hub connections during showering reduced the rate of CR-BSI in our cohort of pediatric patients who were receiving IV prostanoid therapy, including a significant decrease in the rate of infections caused by gram-negative pathogens. Further investigation with regard to the use of the closed-hub system and to improvements in protecting the delivery system against contamination is warranted to establish best practices for managing the risk of CR-BSI among patients who require long-term indwelling CVCs. In addition, there is a need to track the impact of increasing the pH of treprostinil with Flolan sterile diluent on CR-BSI. Implementing current evidence-based recommendations for the prevention of CR-BSI[16,21] is encouraged for all PAH centers.

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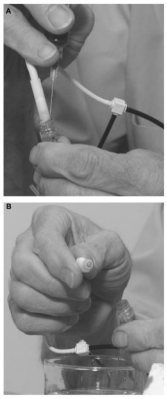

FIGURE 1.
Pathogen entry into the central venous line may occur at the catheter hub. *A*, The dye follows the thread track. *B*, Contamination with disconnection is evident.

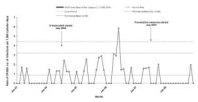

FIGURE 2.
Monthly rates of catheter-related bloodstream infection (CR-BSI) during intravenous (IV) prostanoid use throughout the study period (January 2003–December 2008). The mean CR-BSI rate was 0.77 infections per 1,000 catheter-days. NNIS, National Nosocomial Infections Surveillance; SD, standard deviation; TCH, The Children's Hospital; UCL, upper confidence limit.

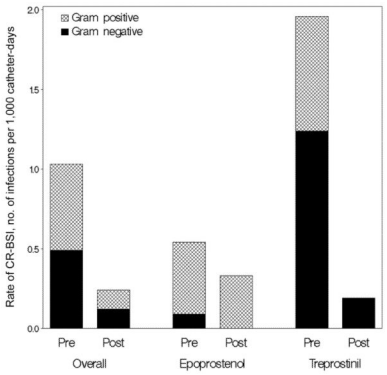

FIGURE 3.

Rates of catheter-related bloodstream infection (CR-BSI) overall and by prostanoid treatment (epoprostenol and treprostinil) before and after implementation of preventive measures (pre and post, respectively). Preventive measures markedly reduced the rate of CR-BSI attributed to gram-positive pathogens and to gram-negative pathogens in patients who received treprostinil, whereas in patients who received epoprostenol, data reflect a nonsignificant decrease.

TABLE 1

Rates of Catheter-Related Bloodstream Infection (CR-BSI) by Prostanoid Treatment

Treatment	No. of catheter-days	Rate of CR-BSI, no. of infections per 1,000 catheter-days			
		All	*P* for all CR-BSIs [a]	Caused by gram-positive pathogens	Caused by gram-negative pathogens
Overall	41,840	0.87 (0.60–1.24)		0.46 (0.28–0.74)	0.41 (0.24–0.70)
Total treprostinil	16,567	1.38 (0.89–2.13)	<.01	0.49 (0.23–1.03)	0.91 (0.55–1.50)
Total epoprostenol	25,273	0.51 (0.29–0.90)		0.43 (0.23–0.83)	0.08 (0.02–0.32)
Either prostanoid treatment					
Before preventive measures	33,532	1.04 (0.71–1.51)	.02	0.54 (0.33–0.90)	0.49 (0.28–0.88)
After preventive measures	8,308	0.24 (0.06–0.98)		0.12 (0.03–1.73)	0.12 (0.02–0.88)
Treprostinil					
Before preventive measures	11,286	1.95 (1.28–2.96)	<.01	0.72 (0.34–1.54)	1.24 (0.73–2.09)
After preventive measures	5,281	0.19 (0.03–1.34)		0	0.19 (0.03–1.34)
Epoprostenol					
Before preventive measures	22,246	0.54 (0.31–0.95)	.61	0.45 (0.23–0.88)	0.09 (0.02–0.36)
After preventive measures	3,027	0.33 (0.05–2.34)		0.33 (0.04–2.45)	0

NOTE. Data are mean value (95% confidence interval) unless otherwise indicated.

[a] *P* values apply to all CR-BSIs.

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TABLE 2

Pathogens Associated with Catheter-Related Bloodstream Infection (CR-BSI) Events during Intravenous Prostanoid Treatment

	No. of CR-BSI events, by treatment	
Pathogen	**Treprostinil**	**Epoprostenol**
Gram-positive species		
Staphylococcus aureus	3	7
Staphylococcus intermedius	0	1
Staphylococcus hominis	1	0
Staphylococcus epidermidis	1	0
Tsukamurella species	0	1
Corynebacterium jeikeium	1	2
Mycobacterium fortuitum	2	0
Total	8	11
Gram-negative species		
Acinetobacter lwoffi	0	1
Acinetobacter baumannii	0	1
Pseudomonas species	1	0
Stenotrophomonas species	4	0
Enterobacter species	2	0
Klebsiella species	4	0
Escherichia coli	2	0
Citrobacter freundii	2	0
Total	15	2