Special Section

Guidelines for the Prevention of Central Venous Catheter-Related Bloodstream Infections with Prostanoid Therapy for Pulmonary Arterial Hypertension

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The inception and completion of this document is the work of a collection of dedicated healthcare providers in the field of pulmonary hypertension medicine. It should be used as a guideline for best clinical practice. Every attempt was made to ensure the relevance and timeliness of the information included.

Intravenous prostanoids are the backbone of therapy for advanced pulmonary arterial hypertension (PAH) and have improved long-term outcome and quality of life.[1-4] Currently, two prostanoids are approved by the US Food and Drug administration for parenteral administration: epoprostenol (Flolan) and treprostinil (Remodulin).[5] Chronic intravenous therapy presents considerable challenges for patients and caregivers who must learn sterile preparation of the medication, operation of the pump, and care of the central venous catheter. Central line infections and bacteremia are well-documented risks of long-term intravenous therapy and may significantly contribute to morbidity and mortality.

The incidence of catheter-related bloodstream infection (CR-BSI) in 192 patients treated with epoprostenol at two pulmonary hypertension centers (335,285 medicine days) was 0.15 per 1000 medicine days, with *Staphylococcus aureus* and *Micrococcus* spp being the most common pathogens identified.[6] Recently, the Centers for Disease Control and Prevention investigated a possible increase in Gram-negative CR-BSI in patients treated with treprostinil. In a retrospective evaluation of seven centers with 51,183 intravenous prostanoid medicine days, the BSI incidence by pooled mean was higher for patients receiving treprostinil than for those receiving epoprostenol (1.11 vs 0.43). In addition, treprostinil patients had a higher incidence of Gram-negative bacteremia (0.73 vs 0.06).[7] Retrospective evaluation at two centers of 224 patients with 146,093 treatment days found the incidence of BSI for patients receiving epoprostenol and treprostinil was 0.55 cases per 1000 medicine days; Gram-negative pathogens were reported in 0.18 cases per 1000 medicine days. Patients treated with treprostinil had a higher incidence of BSI in comparison with epoprostenol (1.13 vs 0.42 per 1000 treatment days) and a higher incidence of CR-BSI due to Gram-negative pathogens (0.81 vs 0.04 BSI per 1000 treatment days).[8]

The mechanisms for the presumed increase in Gram-negative CR-BSIs in patients receiving intravenous prostacyclins are unknown. From the literature, it is clear that Gram-negative pathogens predominate in patients with malignancies or compromised mucosal barriers because of transmigration of gut bacteria.[9] In the case of pulmonary hypertension patients it is unclear if prostacyclin therapy affects mucosal integrity or if gut edema from right heart failure is contributing. These will be active areas of ongoing investigation. The catheter hub is known to be an important source of CR-BSI. It is also suggested that the infusion system connections may be exposed to hydrophilic Gram-negative pathogens such as *Pseudomonas, Stenotrophomonas, Acinetobacter* and *Serratia* during bathing or showering. A closed-hub system may decrease bacterial contamination of the hub;[10,11] however, the type of needleless catheter connector may also impact the incidence of CR-BSI.[12,13] It is important that treating physicians keep these potential mechanisms in mind when implementing and using these guidelines.

Italics indicate direct quotes from *Guidelines for the Prevention of Intravascular Catheter-Related Infections* developed by the Healthcare Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention (HICPAC/CDC).[14]

The HICPAC/CDC system for categorizing recommendations is as follows:

- Category 1A: Strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiologic studies
- Category 1B: Strongly recommended for implementation and supported by some experimental, clinical, or epidemiologic studies and a strong theoretical rationale
- Category 1C: Required by state or federal regulations, rules, or standards
- Category II: Suggested for implementation and supported by clinical or epidemiologic studies or a theoretical rationale
- Unresolved issue: Represents an unresolved issue for which evidence is insufficient or no consensus regarding efficacy exists

Editor's Note: The guidelines presented here will also be published in *Pulmonary Hypertension Reviews*, a companion journal to the *International Journal of Clinical Practice*.

1. General principles[14]

a. *Use a* cuffed and tunneled *central venous catheter (CVC) with the minimum number of ports or lumens essential for the management of the patient. Category 1B*
b. *No firm recommendation can be made for a preferred site of insertion to minimize infection risk for a tunneled CVC, although the subclavian position is associated with lower overall infection risks. Unresolved issue*
c. *Maintain sterile barrier precautions for insertion and aseptic technique for care of intravascular catheters. Category 1A*
d. *Do not submerge the catheter under water. Showering should be permitted if precautions can be taken to reduce the likelihood of introducing organisms into the catheter (eg, if the catheter and connecting device are protected with an impermeable cover during the shower). Category II*
e. *Swimming is not recommended. Category II*
f. Removal of catheter is recommended if CR-BSI is clearly documented. Do not use the "sterilize the line" approach. Category II
g. Clearance of bacteremia should be documented by repeat blood cultures a minimum of 4 days after institution of appropriate antibiotic therapy and by clinical defervescence prior to reinsertion of a new catheter. Category II
h. Duration of intravenous antibiotic therapy (IV ABX) is determined by removal of the catheter and dictated by:
    i. Type of organism
    ii. Presence or absence of valvular heart disease (tricuspid insufficiency in PH patients). Minimum of 14 days of IV ABX if present and 7 to 10 days if absent. Category IB
    iii. Suspicion of potential endocarditis. It is recommended that a low threshold for obtaining a transesophageal echocardiogram be used in the setting of *Staphylococcus* bacteremia-related CR-BSI. If clinical suspicion is high, a minimum of 6 weeks of IV ABX is required. Category IB

2. Hand hygiene[14]

a. *Observe proper hand-hygiene procedures by washing hands either with conventional antiseptic-containing soap and water or with waterless alcohol-based gels or foams. Observe hand hygiene before and after palpating catheter insertion sites, as well as before and after inserting, replacing, accessing, repairing, or dressing an intravascular catheter. Category 1A*
b. *Use of gloves does not obviate the need for hand hygiene. Category 1A*

3. Catheter hub[10,11,12,14,15]

a. A closed-hub system with a needleless intravascular device is recommended to decrease the number of times the central venous catheter is opened. Category II
b. A split septum needleless intravascular device may be preferred over the mechanical valve device. A mechanical valve device with a flat, smooth surface for preaccess disinfection may be considered. Category II
c. Change the hub device weekly in accordance with manufacturer's recommendations and after blood draws. Category II
d. *Minimize contamination risk by wiping access port with 70% alcohol and accessing the port only with sterile devices. Category 1B*
e. Clean threads of the CVC with alcohol wipe only when visibly soiled. Do not allow alcohol to enter the end of the catheter hub. Category II
f. Do not change the needleless intravascular device attached to the CVC if water is present in the connection. Category II

4. Catheter site care[14,16]

a. *Use either sterile gauze or sterile, transparent semipermeable dressing to cover the catheter site. Category IA*
b. *No recommendation can be made regarding the necessity for any dressing on well-healed exit sites of long-term cuffed and tunneled CVCs. Unresolved issue*
c. *Wear clean or sterile gloves when changing the dressing on intravascular catheters. Category 1C*
d. Use mask and sterile gloves when cleaning the catheter site. Category II
e. *Replace the catheter-site dressing when it becomes damp, loosened, or soiled, or when inspection of the site is necessary. Category 1A*
f. *Replace dressings on CVC sites every 2 days for gauze dressing and at least every 7 days for transparent dressings. Category 1B*
g. *Replace dressing used on new tunneled CVC sites no more than once per week, until insertion site has healed. Category 1B*
h. *If the patient is perspiring, or if the site is bleeding or oozing, a gauze dressing is preferable to a transparent, semipermeable dressing. Category II*
    i. Disinfect clean skin with an appropriate antiseptic before catheter insertion and during dressing changes. Although a 2% chlorhexidine-based preparation is preferred, tincture of iodine, an iodophor, or 70% alcohol can be used. Category 1A
j. *No recommendation can be made for the use of chlorhexidine in infants aged less than 2 months. Unresolved issue*
k. *Do not use topical antibiotic ointment or creams on insertion sites because of their potential to promote fungal infections and antimicrobial resistance. Category 1A*
l. *No recommendation can be made for the use of chlorhexidine sponge dressings to reduce the incidence of infection. Unresolved issue*

5. Prostanoid reconstitution: Category II[14,17-20]

a. Unopened vials may be stored at ambient room temperature according to the manufacturer's storage guidance. Do not use vials beyond expiration date on vial.
b. Access vials with a needle, bevel up at a 45-degree angle, or with a split septum vial adaptor for needless reconstitution

c. Opened vials
   i. Epoprostenol
      1. Single-dose vial only
      2. Reconstitute using appropriate manufacturer's sterile diluent
   ii. Treprostinil
      1. Multiuse vial stable up to 30 days after opening and initial vial insertion
      2. Reconstitute with 0.9% sodium chloride or Sterile Water for Injection
      3. Vial integrity is influenced by the number of vial punctures and appropriate puncture technique
         a. Needle access: use 20-gauge needle or smaller. Vial puncture should not exceed 30 times in 30 days.
         b. Needless access: single access with split septum vial adaptor
      4. It is preferred to store opened vials in a refrigerator
      5. Prefilled cassettes of normal saline are not recommended. If used, recommend storing in a refrigerator.

6. Prostanoid administration[14,17,19]

a. *Replace administration sets, including secondary sets and add-on sets, no more frequently than at 72-hour intervals, unless catheter-related infection is suspected. Category 1A*
b. *Do not use filters routinely for infection-control purposes. Category 1A*
c. Do not use catheter for administration of blood products or parenteral nutrition. Category II
d. Prostacyclins: Category II
   i. Epoprostenol
      1. May be administered up to 48 hours after reconstitution of the solution if kept cold (36-46°F or 2-8°C) for a total of 48 hours; 24 hours in refrigerator (available for emergency use); 24 hours on pump with ice packs
      2. Reconstituted epoprostenol is stable at room temperature of less than 77° F (25°C) for up to 8 hours.
   ii. Treprostinil:
      1. May be administered up to 48 hours after reconstitution at room temperature (less than 37°C)

7. Normal saline and heparin flush solutions: Category II[14]

a. Single-dose vials are preferred to multidose vials. Refrigerate multidose vials after they are opened. A split septum vial adaptor or needle access is recommended for multidose vials.
b. Prefilled syringes may be used only if "ready for sterile field"

8. Antibiotic lock solution[14]

Do not routinely use antibiotic lock solutions. Use prophylactic antibiotic lock solution only in special circumstances (eg, in treating a patient with a long-term cuffed or tunneled catheter or port who has a history of multiple CR-BSIs despite optimal maximal adherence to aseptic technique). Category II

9. Prophylactic antibiotics[14]

Do not administer intranasal or systemic antimicrobial prophylaxis routinely before insertion or during use of an intravascular catheter to prevent catheter colonization or BSI. Category 1A

10. Surveillance[14]

Conduct surveillance to determine CR-BSI rates, monitor trends in those rates, and assist in identifying lapses in infection control practices. Category 1A ■

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Disclosures

Ms. Doran is a consultant for Actelion, Gilead, and United Therapeutics. Dr Ivy is a consultant for Actelion, Pfizer, Gilead, and United Therapeutics. Dr Barst is a consultant for Actelion, Pfizer, Gilead, Lung Rx, Novartis, Eli Lilly, and MondoBiotech. Dr Hill receives research grants from Actelion, Encysive, EPIX, Gilead, Lung Rx, Pfizer, United Therapeutics, and Lilly/ICOS and is on the Medical Advisory Boards for all except EPIX and Lilly. Dr Murali receives research grants from Actelion, Pfizer, and United Therapeutics and is a consultant for Actelion, Gilead, and United Therapeutics. Dr Benza is a consultant for Actelion, Pfizer, Gilead, and United Therapeutics.

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przeszczepow pluc. System taki od jakiegos czasu funkcjonuje w Europie i niektore centra zajmujace sie przeszczepami moga poszczycic sie osiagnieciami w systemie ustalania priorytetow dla pacjentow oczekujacych na przeszczep.

W Polsce przeszczepy pluc wykonywane sa w tylko jednym osrodku i dopiero niedawno udalo sie stworzyc dobrze funkcjonujacy program, ktory jednak w chwili obecnej sluzy raczej pacjentom z choroba zwloknieniowa pluc a nie z nadcisnieniem plucnym. Poniewaz w Polsce, mozliwosc wykonania przeszczepow pluc u pacjentow z nadcisnieniem plucnym jest ograniczona, wspolpracujemy z prof. Walterem Klepetko i jego zespolem z Wiednia. Interesujace jest, ze poza plucami Polska posiada dobrze rozwiniety system przeszczepow innych narzadow takich jak serca, watroby, trzustki i dlatego jestesmy przekonani, ze w najblizszej przyszlosci pacjenci z zawansowanym nadcisnieniem plucnym beda mieli wieksza szanse na przeszczep.

Wybor optymalnej terapii dla pacjentow z zaawansowana choroba jest zawsze trudny. Jakkolwiek terapia prostacyklina powinna byc czescia procedury leczniczej dla pacjentow wysokiego ryzyka, to dostepnosc do tego typu leczenia w Europie nie ma jednolitego charakteru. W Polsce stosowanie parenteralnej prostacykliny ograniczone jest przez aspekty finansowe i jest oparte o podanie na indywidualizowane leczenie, kierowane do Narodowego Funduszu Zdrowia. Procedura uzyskiwania finansowania musi byc powtarzana co trzy miesiace. Jakkolwiek nie zmienia to podejscia, co do sposobu leczenia pacjentow to jest uciazliwe pod wzgledem logistycznym.

Jestem wdzieczny, za umozliwienie mi partycypowania w inauguracyjnej, dyskusji „Kacika Miedzynarodowego" i mam nadzieje, ze przyczyni sie to do zwiekszenia zainteresowania projektami miedzynarodowymi i wspolpraca w zakresie zaawansowanych badan naukowych, edukacji i zwiekszenia zainteresowania nadcisnieniem plucnym niezaleznie od istniejacych granic.

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Od redakcji: Oczywiste jest, ze istnieje potrzeba, aby spolecznosc miedzynarodowa miala swiadomosc istnienia PHA i Postepow w Nadcisnieniu Plucnym. Skoordynowany wysilek, zapoczatkowany przez Czlonka Zarzadu Dr Eli Gabbay, powinien w ciagu najblizszych miesiecy, przyniesc wzrost swiadomosci na temat nadcisnienia plucnego, PHA i wydawnictwa „Postepy w Nadcisnieniu Plucnym". W nastepnym numerze, polecamy miedzynarodowe spojrzenie na zagadnienie Chorob Tkanki Lacznej opatrzone komentarzem klinicznym. – RJO