Management of a Patient with Catheter-Related Bloodstream Infection

Charmaine E. Lok


Introduction
For most American Society of Nephrology (ASN) Kidney Week attendees, case-based clinical nephrology talks are one of the most exciting venues. The Nephrology Quiz and Questionnaire (NQQ) is the essence of clinical nephrology and represents what drew all of us into the field of nephrology. This year’s NQQ in surprisingly temperate Chicago, with full-house attendance, was no exception. The expert discussants prepared vignettes of puzzling cases, which illustrated some topical, challenging, or controversial aspect of the diagnosis or management of key clinical areas of nephrology. These eight interesting patients were presented and eloquently discussed by our four expert ASN faculty. Subsequently, each discussant prepared a manuscript summarizing his or her case discussions, which serves as the main text of this article (Mark A. Perazella and Michael Choi, co-moderators).

Patient
A 71-year-old woman who is diabetic has been on hemodialysis (HD) for 3 months via a right internal jugular tunneled cuffed catheter. She has been assessed by the surgeon and is booked to have left vascular access (arteriovenous fistula) surgery in the near future. She has residual renal function, with >200 ml/d urine output. Today, after the first 15 minutes of HD, she develops nausea and rigors and has a temperature of 38.5°C. Her BP drops from 145/75 to 105/62 mmHg, and her heart rate is 120 beats per minute (regular).

On examination, she is diaphoretic and pale. On cardiac auscultation, she has a normal S1/S2, with no murmurs or rubs. Auscultation of the chest is normal. Examination of her central venous catheter (CVC) exit site reveals erythema, tenderness, and a nonpurulent exudate. The abdomen is benign. There are no obvious noncatheter-related causes of infection.

Question 1
Which is the best course of action?

A. Obtain cultures at the exit site and start empirical oral antibiotics
B. Start intravenous antibiotics and remove the CVC at the bedside
C. Obtain cultures from the exit site, obtain blood culture from each lumen of the catheter (hubs), and start empirical intravenous antibiotics that consider local bacterial resistance patterns or antibiograms and cover the most common infecting gram-positive and -negative organisms found in the patient’s HD unit
D. Obtain cultures from the exit site, one from the catheter lumen (hub), and one from the bloodline and start empirical intravenous antibiotics that consider local bacterial resistance patterns or antibiograms and cover the most common infecting gram-positive and -negative organisms found in the patient’s HD unit
E. Start empirical antibiotics without cultures: the diaries unit and laboratory are geographically apart, and the delivery and process times are excessive

Of note, in all scenarios A–E, if the patient’s hemodynamics did not quickly improve, the patient would be presumed to be septic and transferred to a monitored acute care setting for further management.

Discussion of Question 1
The correct answer is D. Our patient has a catheter-related bloodstream infection (CRBSI). The signs and symptoms are indicative of hemodynamic instability associated with CRBSI and possibly sepsis and are not merely from a localized type of infection, such as an exit site or tunnel infection. Thus, only treating a local infection—a menos —merely obtaining cultures from the hub and exit site is inadequate to do so (choice C; see below). Thus, empirical treatment of the patient with systemic antibiotics and managing the catheter without a proper diagnosis or processes to do so are the wrong course of action; therefore, choices B and E are incorrect.

Indeed, we will return to question 1 after we first answer the very important question of how to make a diagnosis of CRBSI. Until recently, the diagnosis of CRBSI should have followed recommendations from the updated guidelines provided by the Infectious Disease Society of America (IDSA) in 2009 (1).

Question 2
Which IDSA statement on the diagnosis of CRBSIs is true?
A. For suspected CRBSI, paired blood samples drawn from the catheter and a peripheral vein should be cultured before initiation of antimicrobial therapy

B. If a blood sample for culture cannot be drawn from a peripheral vein, it is recommended that two blood samples should be obtained through different catheter lumens

C. A definitive diagnosis of CRBSI requires that the same organism grows from at least one percutaneous blood sample culture and the catheter tip

D. A definitive diagnosis of CRBSI requires that two blood samples for culture be obtained (one from a catheter hub and one from a peripheral vein) that meet CRBSI criteria for quantitative blood cultures or differential time to positivity

E. All of the above

Discussion of Question 2

The correct answer is E. Although all of the above correctly reflect IDSA statements, it is important to understand some of their important details, because they are relevant to their application in nephrology practice and our patients on dialysis. In particular, let us review criteria for quantitative blood cultures and differential time to positivity as follows. Quantitative blood cultures require that there be a threefold higher count of CFU per milliliter in the catheter hub culture compared with the peripheral venous blood culture. The differential time to positivity requires that the blood culture from the arterial or venous catheter hub turns positive at least 2 hours before the peripheral blood culture. Typically, signs and symptoms related to CRBSI do not occur on dialysis until after dialysis has been initiated, when the blood is circulating through the dialysis circuit. The perturbation of the organisms and release of endotoxins from the catheter biofilm occur with alterations in blood flow precipitated by the dialysis procedure, causing the patient’s signs and symptoms. Thus, blood circulating through an infected catheter during dialysis (typically at >300 ml/min in a well functioning HD catheter) before cultures are obtained may dilute the density of micro-organisms in the catheter, potentially rendering the quantitative blood cultures and differential time to positivity criterion invalid for the diagnosis of CRBSI in patients on HD. Thus, on review, choice D is not a good option. It must be remembered that HD catheters become part of a dynamic continuous closed circuit that both receives and delivers blood during HD. This is different from other types of catheters used for the unidirectional administration of agents, where the diagnosis of CRBSI using the quantitative blood culture and differential time to positivity criterion makes sense. Indeed, the data that form the basis of the IDSA 2009 update recommendations on quantitative cultures originate from temporary CVCs primarily used for unidirectional medication and fluid infusions in intensive care settings or are generalized from permanent CVCs used for chemotherapy, total parenteral nutrition, or other non-HD use not applicable to HD. Given the pathophysiology of CRBSI in patients on HD (2), the timing and onset of symptoms, and their relationship to the dialysis procedure, these criteria do not make sense for patients on HD.

If quantitative blood samples are not attainable, then the diagnosis can be made if the HD CVC tip grows the same micro-organism as that from the peripheral venous culture (requires catheter removal for diagnosis). This alternate diagnostic option is also impractical and further places patients at unnecessary risks associated with catheter intervention and may leave the patient without access for dialysis. Thus, choice C is not a good option. Sometimes, the clinician is inadvertently placed at a crossroads when opposing recommendations by different subspecialty groups are expected to be upheld. For example, the infectious disease specialty wants blood cultures from peripheral veins. However, nephrologists are keenly aware that, in patients on HD, peripheral venipuncture is often not possible, is impractical, or is purposefully avoided to preserve veins for future arteriovenous access creation. Thus, choice A is incorrect from a nephrology perspective.

In reality, most dialysis units diagnose CRBSI by attaining one or more sets of blood cultures from the HD circuit, concurrent with the exclusion of other infectious sources, without attempting venipunctures for peripheral blood culture (3). Given the above set of conundrums and discrepancies between ideal and real world practices in diagnosing CRBSI, Quittnat et al. (4) sought to evaluate and validate the IDSA recommendations in the real world of caring for patients on HD. Over an approximately 3-year period, all patients on HD in a large dialysis facility with suspected CRBSI (n=178) had four sets of blood cultures taken, one each from the following: the peripheral vein, arterial and venous catheter hubs, and peripheral dialysis circuit. Outcomes were adjudicated by an independent multidisciplinary HD infection control committee, which included an infectious disease practitioner, a nephrologist, a microbiologist, a vascular access coordinator, and a pharmacist. The key finding was that concurrent blood cultures from the HD circuit and the venous catheter hub outperformed all other combinations; they had a sensitivity of 93%, specificity of 97%, and accuracy of 95% (thus, choice B is incorrect). Of note, the IDSA guideline–recommended combination of peripheral vein and arterial hub blood cultures was the least sensitive, specific, and accurate. Thus, in question 1, choice C is incorrect, and answer D is correct. Lastly, the diagnostic criteria using measured differential time to positivity were met in less than one third of events. These findings are relevant to the care of our patients, because they permit us to avoid unnecessary peripheral vein punctures and use the dialysis circuit instead. It also highlights the importance of re-evaluating—with the need, sometimes, to challenge—established processes that are not fully suitable to nephrology practices, especially if they have been adopted by other specialties without the necessary supporting evidence that they are applicable to nephrology.

The patient is started empirically on vancomycin and a third generation cephalosporin. The next time that she comes to dialysis, her exit site and blood culture results reveal a staphylococcal source of infection. She continues to be febrile but is not hypotensive. Her catheter was removed, and a new one inserted at another site. A catheter exchange over a guidewire was not attempted given the suspicion of an exit site infection (redness, tenderness, and discharge).
The patient’s fever quickly resolves within the next 24 hours. She completes her course of intravenous antibiotics without symptoms or complications. After 2 weeks of discontinuing her antibiotics, she develops a low-grade fever and nausea, having a similar prodrome as her first episode of CRBSI.

**Question 3**
Which event is possible in this patient?

A. The patient has a new CRBSI with a different infecting organism
B. The patient is experiencing the same CRBSI with the same organism
C. She has a retained infected fibrin sheath that is perpetuating the original CRBSI
D. The patient has a new source of infection unrelated to her catheter
E. All of the above may be possible

**Discussion of Question 3**
The correct answer is E. Blood cultures and sensitivities must be taken before initiating antibiotics to properly identify the organism, treat the infection with the correct antibiotics, and avoid antibiotic resistance. Because all of the above choices may be possible, a very careful and detailed history and a physical examination are necessary to rule in or out a new source of infection (because choices A and B may be correct). It can be very challenging in our patients on dialysis, with issues to consider that may be unique to patients on HD. For example, if the previously infected catheter was removed without removal of the fibrin sheath (if present), such an infected fibrin sheath could be a source of continual infection (5) (choice C may be correct). The effective management of such a fibrin sheath, if present, is unclear in terms of management of CRBSI and needs to be studied to provide guidance.

However, there is guidance provided by the Centers for Disease Control and Prevention on the evaluation and reporting of non-CRBSIs (which would be a new source of infection in this patient; choice D may be correct) (6). The Centers for Disease Control and Prevention uses a practical approach to reporting new dialysis events, using the initiation of intravenous antibiotics as a marker of infectious dialysis events. There must be 21 or more days from the end of one intravenous antimicrobial course to the beginning of a second intravenous antimicrobial start for two starts to be reported as separate dialysis events, even if different antimicrobials are used (7).

After a thorough history and physical examination, the patient is now found to have an infected foot ulcer that is causing a secondary bloodstream infection. It is appropriately treated. However, she is frightened of having another CRBSI infection and asks you what you will do to help her prevent future episodes of CRBSI. She notes that your facility has a CRBSI rate of 2.7/1000 catheter-d.

**Question 4**
Which prophylactic option is appropriate for this patient?

A. Prophylaxis at the exit site with a polyantibiotic ointment to be applied at dressing changes
B. Interdialytic CVC locking with a thrombolytic agent—recombinant tissue plasminogen activator (r-TPA)—once per week until her fistula is created and usable
C. Interdialytic CVC locking with gentamicin-heparin after each dialysis indefinitely
D. Use a shower technique for catheter infection prophylaxis
E. Options A and B

**Discussion of Question 4**
The correct answer is E. Because CRBSI is associated with significant morbidity and mortality, proper prophylaxis against CRBSI is critical. To effectively implement a prophylactic strategy, two important points should be considered: (1) the baseline CRBSI rate in your facility (it should be used as a benchmark to determine if your prophylactic strategy is effective) and (2) to target your prophylactic strategy on the basis of the pathophysiology of CRBSI.

In this case, the facility has a CRBSI rate of 2.7/1000 catheter-d. The literature has reported a range of 0.9–5.5/1000 catheter-d (3). Our patient is in a facility that has a “good” rate (Table 1) (8) that can improve.

To start, it will be a given that general universal precautions are in place and that health care providers and patients are aware of best practices for HD catheter care, including excellent hand hygiene. As part of general hygiene, whether a patient can shower with a catheter after the exit site is healed without increased risk of CRBSI is still unclear. A recent pilot randomized, controlled trial showed no difference in CRBSI rates and feasibility in conducting a larger definitive trial to answer this question (9). Until then, choice D is incorrect, and showering should be discouraged if the exit site is not completely healed. The potential increased risk will be apparent and in accordance to the pathophysiology of CRBSI as follows.

The basic pathophysiology of CRBSI includes two main routes for organism entry into the bloodstream: an extraluminal route and an intraluminal route (2). The extraluminal route involves organisms entering via the external catheter surface at the time of catheter insertion or thereafter before complete exit site healing and endothelialization of the subcutaneous tunnel. Organisms migrate to the catheter tip, where hematogenous spread occurs. The

| Table 1. Catheter-related bloodstream infection rates and facility performance |
|---|---|
| Rate, per 1000 catheter-d | Performance |
| ≤1.0 | Excellent |
| 1–2.0 | Very good |
| 2.1–3.0 | Good |
| 3.1–5.0 | Fair |
| 5.1–7.0 | Poor |
| >7.0 | Really bad |

Modified from reference 8, with permission.
intraluminal route involves direct transfer of organisms to the catheter interior when it is accessed for any reason (e.g., connecting/disconnecting lines from dialysis). Irrespective of route, organisms come from a variety of sources: typically from the patient’s own skin flora or health care providers’ contact (e.g., directly from their [gloved] hands). Although extraluminal organism entry tends to predominate early on after catheter insertion, the risk of intraluminal organism entry persists as long as the patient uses the catheter. The common final pathway is the development of the biofilm, which houses and propagates organism growth and eventual spread (2). Thus, strategies to prevent CRBSI target the extraluminal route by creating barriers to organism entry and disinfecting at the exit site, whereas those targeting the intraluminal route aim to sterilize the lumen or disrupt the catheter biofilm after organisms have entered.

Choice A targets the extraluminal route of organism entry. Several meta-analyses have consistently found topical antibiotics to be effective in reducing CRBSI. For example, James et al. (10) found that topical antibiotics lowered the CRBSI rate (rate ratio, 0.22; 95% confidence interval [95% CI], 0.12 to 0.40), the exit site infection rate (rate ratio, 0.17; 95% CI, 0.08 to 0.38), the requirement for catheter removal, and hospitalization for infection. The application of antimicrobial ointment is advocated by several subspecialty societies, including the Centers for Disease Control and Prevention, the IDSA, the Society of Critical Care Medicine, and several nephrology societies (e.g., Canadian, European, and others). Over a decade ago, there were earlier concerns of emergence of mupirocin resistance (11), but none have not been reported due to its use at the HD catheter exit site for CRBSI prophylaxis. The use of povidone-iodine antiseptic ointment or bacitracin/gramicidin/polymyxin B ointment (Polysporin Triple) at the exit site after catheter insertion and at the end of each HD session or with dressing changes is recommended. In the United States, the triple antibiotic ointment equivalent of bacitracin/gramicidin/polymyxin B substitutes gramicidin with neomycin. Long-term follow-up of the polyantibiotic ointment at the exit site for CRBSI prophylaxis has shown consistent efficacy without antibiotic resistance, fungal infections, or adverse interaction with catheters used (12).

To target the intraluminal route of organism entry and CRBSI, intradialytic catheter lock solutions comprising various combinations of antibiotics and anticoagulants have been evaluated for CRBSI prophylaxis. A recent network meta-analysis showed significant reductions in CRBSI with catheter locking with gentamicin plus citrate (odds ratio, 0.07; 95% CI, 0.00 to 0.48) and gentamicin plus heparin (odds ratio, 0.04; 95% CI, 0.00 to 0.23) compared with heparin alone (13). The included studies were relatively short; thus, the emergence of gentamicin resistance remains a concern. This concern is highlighted by Landry et al., who reported a large reduction in CRBSIs (from 17.0 reduced to 0.83 per 1000 catheter-d) in >1400 patients with a prophylactic gentamicin/heparin lock (14). However, long-term follow-up over 4 years found that using gentamicin lock led to the development of serious gentamicin-resistant organisms and adverse outcomes. Prophylactic gentamicin lock for CRBSI was subsequently discontinued. It is this concern for the emergence of resistant organisms that underlies the lack of a recommendation for the routine use of any prophylactic antibiotic lock from the Centers for Disease Control and Prevention and other organizations. Thus, choice C is incorrect.

Choice B is correct. Given the pathophysiology of CRBSI, the presence of fibrin sheath and intraluminal thrombus may act as a nidus for intraluminal-sourced CRBSI. Would reducing the thrombus reduce CRBSI? A multicenter, randomized, placebo, controlled trial, PREvention of Catheter Lumen Occlusion with r-TPA versus heparin (the PreCLOT Study) evaluated the effect of once weekly intradialytic locking with r-tPA (1 mg per lumen) versus heparin on HD catheter malfunction and CRBSI (15). Once weekly intradialytic locking with r-tPA was associated with less catheter malfunction and lower CRBSI rates (0.4/1000 versus 1.37/1000 patient-d in the heparin lock group). However, the main barrier to CRBSI prophylaxis with once weekly r-tPA locking is its potentially high financial cost. However, after an economic evaluation of r-tPA use by the PreCLOT Study protocol, it was concluded that, assuming continual effectiveness of the prophylactic strategy, the overall costs of the strategies were similar. Cost-savings from a lower risk of hospitalization for CRBSI partially offset the increased cost of r-tPA. This strategy may be more cost effective in HD facilities where the CRBSI rate is high (16). Importantly, the most cost effective and best method of CRBSI prophylaxis is to avoid HD catheter use as much as possible.

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Disclosures
None.

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