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Lalathaksha Kumbar and Jerry Yee

Infection-related causes are second only to cardiovascular events for mortality among end-stage renal disease patients. This review will provide an overview of hemodialysis catheter-, graft-, and fistula-related infections with emphasis on diagnosis and management in specific settings. Use of catheters at the initiation of dialysis has remained unchanged at 80%. Of all access-related bloodstream infections (BSIs), 70% occur in patients with catheters. The risk factors for BSIs in tunneled, cuffed catheters include the duration of the catheter, past catheter-related bacteremia, left-sided internal jugular vein catheters, hypoalbuminemia, and immunosuppression. Surprisingly, human immunodeficiency virus infection has not been associated with a higher risk of catheter-related bacteremia. Catheter-related bloodstream infection is a clinical definition that requires specific laboratory testing to identify the catheter as the source of the BSI. A central line–associated bloodstream infection is a primary BSI in a patient who had a catheter within the 48-h period before the development of the BSI with no other identifiable source. Guidewire exchange of catheter is a viable alternative in select patients to aid in preserving venous access sites. Catheter lock therapy can decrease infectious complications and mortality. Arteriovenous graft infections are prevalent with significant morbidity. Studies evaluating the impact of stent use in infection risks of the arteriovenous graft are sorely needed.

Key Words: Arteriovenous graft, Infection, CRBSI (catheter-related bloodstream infection), Tunneled catheter, Hemodialysis

An estimated 30 million people in the United States have chronic kidney disease (CKD) with nearly 500,000 undergoing maintenance hemodialysis (HD).[1] The cost to care for patients with end-stage renal disease (ESRD) was approximately $34 billion in 2015[1] and every day in the hospital is expected to raise patient care expense by 0.8%.[2] Risk of hospitalization in patients with CKD is almost triple that of the patient without CKD (614 vs 227 hospitalizations/1000 at-risk patient-years).[1] On average, an ESRD patient is admitted to the hospital about twice a year and has an extremely high 30-day readmission rate of 34.6%. Cardiovascular events and infection continue to be the leading causes of hospitalization, although marked improvements have been noted in the rates of hospitalization. Vascular access infection accounts for nearly 28% of all infections affecting ESRD hospitalizations. The annual all-cause mortality rate for patients with ESRD on HD is 170 deaths per 1000 at-risk patient-years. Infection-related causes are second only to cardiovascular events as a cause for mortality among ESRD patients when withdrawal from dialysis is excluded.[3]

It is imperative to identify and mitigate infection risk in ESRD patients on HD. Among the various HD access routes, tunneled, cuffed catheters (TCCs) have the highest risk of infection compared with arteriovenous fistulae (AVFs). Arteriovenous grafts (AVGs) assume an intermediate position in this unfortunate hierarchy of infection.[4] Patients with TCCs had a 53% increased risk of all-cause mortality, 2- and 3-fold higher risk for fatal and nonfatal infections, respectively, and a 68% higher risk for hospitalization than patients with AVFs.[5] Patients using AVGs had a 38% risk for fatal infections and 16% additional risk of mortality compared with those with AVFs. The severe consequences of different HD access-related infections warrant ongoing and comprehensive knowledge of this field. This review will discuss multiple HD access-related infections, diagnosis, and management along with an emphasis on specific settings.

TUNNELED DIALYSIS CATHETER

Nearly 80% of patients starting HD use TCC as their first vascular access.[1] Catheter usage rate has remained unchanged for many years. The association of TCC use and bloodstream infections (BSIs) has been known for over 20 years.[6] The catheter-related BSI (CRBSI) rate is a reportable parameter for surveillance and also a benchmark and performance indicator for both hospitals and dialysis units.[7] The Centers for Disease Control and Prevention suggest vascular access-related infection rates in dialysis units to be reported as the number of events per 100/patient-months on dialysis.[8] In 2014, the National Healthcare Safety Network reported 29,516 BSIs from 6005 HD centers.[9] Nearly 75% of these infections were related to vascular access, and 70% of all access-related BSIs (ARBSIs) were in patients with a TCC. Overall, pooled mean BSI and ARBSI rates per 100 central venous catheter patient-months were 2.16 and 1.83, respectively. Hospitalizations occurred for 25.1% of vascular access infections and 10.8% of local access site infections with death occurring in 1352 (0.8%) of all dialysis events. Two percent of BSIs and 1.6% of ARBSIs resulted in fatalities. The problem of infection associated with TCC is indisputable. The risk factors for BSI in TCC include the duration of the catheter,[10] past catheter-related bacteremia,[11] left-sided internal jugular vein catheters,[12] hypoalbuminemia, and immunosuppression. Surprisingly, the human immunodeficiency virus infection has not been

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associated with a higher risk of catheter-related bacteremia.[13]

MICROBIOLOGY OF ACCESS-RELATED INFECTION

The recent National Healthcare Safety Network report on ARBSI associated with in-center HD highlights the continued dominance of *Staphylococcus aureus* (*S. aureus*), followed by *Staphylococcus epidermidis* and other coagulase-negative staphylococci, together accounting for nearly 56% with another 12% being gram-negative organisms. Among the *S. aureus* group, 40% were methicillin resistant,[9] although the rate of invasive methicillin-resistant *S. aureus* (MRSA) infections in patients on dialysis is declining.[14] *S. aureus* is known to cause high morbidity, mortality, and hospitalization along with secondary metastatic infections such as endocarditis, osteomyelitis, septic arthritis, epidural abscess, and cross-infection of implantable cardiac devices and other intravascular devices. Dialysis units are a perfect setting for cross-contamination and acquisition of multidrug-resistant (MDR) organisms. In a prospective cohort study of an outpatient HD unit, serial surveillance cultures for MDR gram-negative bacteria, vancomycin-resistant enterococci, and MRSA in patients undergoing chronic HD, nearly 28% were colonized with one or more MDR organisms.[15] Specimens were collected from rectum, nares, and skin (a 5 × 5-cm area in the jugulodigastric and inguinal regions). Risk factors for colonization included residence in a long-term facility or recent antibiotic use, both of which are common in patients undergoing HD. By four months into the study, 40% of patients had acquired at least one MDR organism, suggesting a real problem of cross-contamination. In a prospective cohort study from Taiwan, MRSA carriers had nearly three times higher risk of all-cause mortality, five times higher risk of infection-related mortality, and almost three times higher risk of recurrence than MRSA noncarriers.[16] MDR carrier states are not benign. Preventive measures aimed at cross-contamination and colonization must be an integral part of infection control in dialysis units.

CLINICAL SUMMARY

- More than two-thirds of access-related bloodstream infections are due to catheter infections.
- Management of catheter-related bloodstream infections should be based on available access sites, patient status, and virulence of the organism.
- Infection of abandoned arteriovenous grafts should be included during the evaluation of sepsis in patients on hemodialysis.
- When feasible, the complete removal of an arteriovenous graft is preferred.

PATHOGENESIS

The cuff in a TCC impedes direct migration of organisms, mitigating the most likely cause of infection with nontunneled dialysis catheter. Direct contamination of the catheter or hub, hematogenous seeding, or contaminated infusates are other possible routes of infection. Factors affecting the pathogenesis of CRBSI include, but are not limited to, the catheter material and fibrin sheath around the catheter[17] and intrinsic virulence factors of the organism, including the extracellular polymeric substance produced by the adherent organisms.[18] Biofilm formation heightens the pathogenicity of various microorganisms by allowing them to resist host defense mechanisms or by increasing antimicrobial resistance agents. Catheters can cause mural thrombus in the vein; a characteristic noted to predispose to catheter colonization and infection.[19] This association has led to an emphasis on preventing catheter-related thrombus as an additional mechanism for reducing CRBSI.

DIAGNOSIS OF CATHETER-RELATED INFECTION

The determination of infection in patients with TCC for dialysis is debatable. Exit-site infection and tunnel infections are relatively easy to diagnose (Fig 1). Intravascular catheter-related infections are frequently described by two terms, i.e., CRBSI and central line–associated BSI (CLABSI).[20] Although different, these terms are often used interchangeably. CRBSI is a clinical definition used to diagnose and treat patients and requires specific laboratory testing to identify the catheter as the source of the BSI. A CLABSI is a primary BSI in a patient with a catheter inserted within 48 hours before developing the BSI and no other identifiable source of infection. CLABSI is used for surveillance purposes. BSIs are often secondary to other sources not easily recognized, leading to overestimation of the actual incidence of CRBSI. In their 2009 guidelines, the Infectious Diseases Society of America (IDSA) advocated the definition of CRBSI as "bacteremia or fungemia in a patient who has an intravascular device and >1 positive blood culture result obtained from the peripheral vein; clinical manifestations of infection (e.g., fever, chills, and/or hypotension); and no other apparent source for BSI (with the exception of the catheter).[21] One of the following should be present: a positive result of semiquantitative (115 culture forming units (cfu) per catheter segment) or quantitative (1102 cfu per catheter segment) catheter culture, whereby the same organism (species) is isolated from a catheter segment and a peripheral blood culture; simultaneous quantitative cultures of blood with a ratio of 13:1 cfu/mL of blood (catheter vs peripheral blood); differential time to positivity (growth in a culture of blood obtained through a catheter hub is detected by an automated blood culture system at least 2 hours earlier than a culture of simultaneously drawn peripheral blood of equal volume)." These recommendations are based on data from nontunneled catheters used in intensive care setting mainly for medication and fluid administration or from long-term catheters used for chemotherapy, total parenteral nutrition, and/or other non-HD uses. This definition and workup are not suitable for patients receiving outpatient HD. Two significant parameters used in the definition of CRBSI, quantitative blood cultures and time to differential positivity, are

Figure 1. Infection of exit site and tunnel.

difficult to use in outpatient dialysis centers. Positive quantitative blood cultures need a 3-fold higher count of cfu per milliliter in the catheter hub culture than the peripheral venous blood culture. The differential time to positivity needs blood culture from the catheter hub to turn positive at least 2 hours before the peripheral blood culture.[22] In a well-functioning HD catheter, blood flow might dilute the density of microorganisms in the catheter, rendering advantages of quantitative blood cultures muted. A closed circuit-like HD tubing is not similar to unidirectional catheters used in intensive care units in which the criteria of quantitative and differential time to positivity were based on the IDSA guidelines. Obtaining a second peripheral venous sample for culture is against the principle of vein preservation for future access needs in patients on HD. Overall, the 2009 IDSA guidelines do not address the needs for diagnosis of CRBSI in the HD population.

Lok[23] reported on the optimal methodology for diagnosis of CRBSI in patients receiving HD using a TCC. The effort was to validate the 2009 IDSA recommendations on the determination of CRBSI in HD patients using a TCC, especially the use of differential time to positive culture. In a prospective study of patients receiving HD with a TCC in Canada, there were 178 suspected CRBSI events in 87 patients, out of which 100 events had blood cultures drawn when there were symptoms and signs of infection, suggesting a CRBSI. The source of blood samples was from the blood circuit, catheter hub, or peripheral veins. Of these 100 events occurring in 62 patients, 55% had no bacterial growth on blood culture. Patients had been onantibiotics before drawing blood cultures in five events. Twenty-seven events had growth of the same microorganism in all the blood cultures drawn from different sites. The average time from HD initiation to obtaining the culture was 2 hours 18 minutes. The average transit time of culture bottles to the microbiology laboratory and start of cultivation was 5 hours 54 minutes. This transit time might be much longer in the real-world scenario with many dialysis units often located in far-flung areas with scheduled blood sample pickups during the day. The sensitivity and specificity of different sites of cultures were very high with no significant difference. Cultures from the HD circuit had the highest sensitivity, specificity, and accuracy (93.5%, 100%, and 95%, respectively). Criteria of time to positivity confirming CRBSI as per IDSA 2009 guidelines were met in less than one-third of the events (33% arterial hub and 29% venous hub). Obtaining blood cultures within the first 30 minutes of the dialysis session did not improve the likelihood of positive differential time to positivity. Only 56% of the events had blood cultures obtained from a peripheral vein, highlighting the problem of peripheral venous access in patients with ESRD. Although the study validated the current practice of diagnosis of CRBSI in the majority of outpatient HD patients, the findings were unable to support the IDSA 2009 guideline recommendations, especially in the context of the need for peripheral vein sample and differential time to positivity. The current definition of CRBSI is pragmatically unsuitable for the chronic HD population and is overdue for an update. Management strategies that advocate catheter removals as first-line management can thus promote accelerated venous access site exhaustion. Future CRBSI definitions should incorporate objective diagnostic parameters to mitigate accelerated venous access site losses in the HD population.

MANAGEMENT OF CATHETERS IN CRBSI

The least contentious step in catheter-related infection is the administration of antibiotics. Once a diagnosis of CRBSI is confirmed and causative organism identified, the institution of appropriate antibiotics is recommended along with an evaluation for metastatic infectious foci such as endocarditis and osteomyelitis. Management of the culprit catheter is debatable. IDSA guidelines recommend catheter removal as part of the management, especially when associated with metastatic infections, severe sepsis, or specific virulent organisms such as *S. aureus*, *Pseudomonas*, fungi, and mycobacteria or less virulent but hard to eradicate organisms. In ESRD patients with catheters and uncomplicated CRBSI not due to the organisms mentioned previously, the IDSA guidelines provide an option of not removing the catheter. Strict adherence to the IDSA guidelines can lead to accelerated loss of venous access sites for catheter insertion, potentially expediting the progression toward terminal access scenarios culminating in high mortality. Several nonrandomized studies evaluating catheter exchange vs removal and delayed insertion have been reported.[24] Most of the studies were retrospective, small, with heterogeneous outcome measures, and not an accurate comparison of catheter exchange vs catheter removal and reinsertion. Catheter salvage without guidewire has been reported with some benefits. The

need to preserve venous access has been the primary driver for considering alternatives. Frequently, catheter salvage is equated to access site salvage. A recent meta-analysis reviewed all studies evaluating various catheter management strategies in the treatment of catheter-related bacteremia.[25] Studies included stable CRBSI with three possible approaches, including antibiotic alone, antibiotic locks, and guidewire exchanges with the hypothesis of equal cure rates with any of these options. The studies were predominantly observational with some chart reviews unifying CRBSI definition and various treatment cure definitions. Statistically significant heterogeneity of the cure proportions within each treatment group was noted. Cure rates were not different, and follow-up time did not affect the cure rate. Longer follow-up time did not display larger cure proportions. After accounting for the type of treatment, differences in cure proportions were noted, with the highest cure for coagulase-negative staphylococci, followed by gram-negative rod bacteremia and *S. aureus*. Among *S. aureus* infections, guidewire exchange achieved significantly higher cure proportion than both systemic antibiotics and antibiotic lock solution (odds ratio, 3.33 [95% confidence interval (CI), 1.17 to 9.46; $P = 0.02$] and odds ratio, 4.72 [95% CI, 1.79 to 12.46; $P = 0.002$], respectively), but it was not compared with catheter removal and delayed insertion. Information on delayed metastatic infections from recurrent *S. aureus* infection associated with guidewire exchange is sorely needed.

A common fear in using guidewire exchange in infections with organisms such as *S. aureus* is that the catheter goes over a part of the wire that would not have been cleaned. Some of the currently available dialysis catheters have an inner stylet that extends beyond the tip of the catheter and isolates the inner lumen of the catheter from the guidewire, eliminating any contact with the new catheter while preserving the access site. Another criticism of guidewire exchange has been the contact of the catheter with the tunnel, but there are techniques to create a new tunnel and exit site while preserving the venous entry site. The primary intention of adapting guidewire exchange is to safeguard the venous access site. A randomized controlled interventional trial comparing the effect of guidewire exchange with catheter removal and delayed insertion in patients with highly virulent organisms on treatment cure rate and delayed complications is needed. Such a study will be hard to conduct in the western hemisphere, whereas researchers from Egypt are reporting the results of a similar study, which is likely the only randomized controlled trial in the recent era addressing this issue.[26] Each arm had 339 patients who were matched for demographics and organism type. No statistically significant differences were found in the catheter infection-free survival time, recurrent CRBSI, or mortality, but as anticipated, catheter removal with delayed insertion had more extended hospitalizations. Information regarding organism identification and metastatic infection was, however, lacking. Although small in number, six patients in the catheter removal group had access site exhaustion leading to the use of transhepatic, translumbar, and peritoneal dialysis. This subgroup is probably highly prevalent in clinical practice. Robust data on the incidence of exhausted access sites of catheter removal and delayed insertion are needed. Catheter management in CRBSI thus remains a significant unmet need of a patient on HD.

ANTIBIOTIC LOCKS AND CONNECTOR DEVICES IN CRBSI PROPHYLAXIS

Antimicrobial lock (AML) therapy involves instillation of a concoction of an antibiotic and an anticoagulant into the intraluminal portion of a dialysis catheter between treatments to sterilize the interior of the catheter from the biofilm. Antibiotic locks are used as part of the treatment of CRBSI and, more controversially, as prophylaxis to prevent a CRBSI episode. Although prophylactic use of gentamicin with heparin AML is known to reduce CRBSI by >95%, the emergence of resistant organisms has been the primary driver for lack of consensus on its use.[27] A prospective observational trial using a lower concentration of gentamicin with citrate as anticoagulant reported a decrease in mortality after AML (adjusted hazard ratio, 0.32; 95% CI, 0.14–0.75) with a 73% reduction in CRBSIs in association with a decline in gentamicin resistance, which highlights the ongoing controversy in this field.[28] Although the debate on antibiotic resistance continues, alternative agents such as Taurolidine, ethanol, and combination concoctions including 7% sodium citrate, 0.05% methylene blue, and 0.165% parabens, are being studied for prophylactic use with promising results.[29,30]

Catheter hub colonization can be a potential source of infection. Closed connector systems (Tego®) are Food and Drug Administration–approved connector devices for use in HD catheters.[31] This device creates a mechanically and microbiologically closed system when attached to the hub of a catheter, eliminating open catheter hubs and lowering the chance of contamination and infection. CUROS®, a 70% isopropyl alcohol–impregnated port protector, has shown significant improvement in CLABSI rate among oncologic patients with catheters.[32] CUROS® is also used in combination with Tego® among patients with HD catheters. Clearguard® is a cap that features a rod extending into the HD catheter hub. The rod and cap threads are dry-coated with chlorhexidine. Once applied like a standard catheter hub cap, chlorohexidine mixes with catheter lock solution proximal to the clamp to kill >99.99% of common pathogenic organisms. In an open-labeled, cluster randomized trial, Clearguard® showed a significant improvement in CRBSI in comparison with a combination of Tego® and CUROS® among patients with HD catheters.[33] Another novel antimicrobial device containing chlorhexidine digluconate infused into the catheter lumen during locking has shown promising results against *S. aureus* in animal studies.[34] These devices and emerging advances in drug delivery along with multidrug nonantibiotic catheter lock solutions offer a ray of hope to prevent the development of CRBSIs.

Advances in catheter-coating technology provide another option in CRBSI prophylaxis. Nanosilver deposition over polyurethane dialysis catheters has been reported to impede adhesion of *S. aureus* on the surface of

the catheters.[35] The development of *S. aureus* biofilms has been prevented for upto 3 days using an organoselenium compound in HD catheters in an in vivo study.[36] Bismuth coating is reported to reduce bacterial colonization of temporary nontunneled HD catheters.[37] Adoption of novel coating technology in the long-term tunneled dialysis catheter is slow and infrequent likely due to economic and market constraints. Large comparative clinical trials with infectious complications as an endpoint are sorely needed.

Infectious Complications of Arteriovenous Grafts

AVGs are second after TCCs regarding infection risk. Unlike TCCs that can be removed with a simple procedure, AVGs, once implanted, require additional surgery, which is generally more extensive. Frequently, a segment of AVG adjoining the arterial anastomosis and venous anastomosis might be retained to avoid more extensive vascular dissection and reconstruction. During a patient's dialysis lifetime, many AVGs are abandoned and retained. Infections in AVG can present as clinically apparent signs such as cellulitis, edema around the graft, erythema, tenderness, pus, and frequently thrombosis[38] (Fig 2). Routes of infection could be direct inoculation, hematogenous spread, and/or colonization. Abandoned AVGs can lead to significant infectious complications, and a high degree of suspicion is warranted. Also, evidence shows that abandoned, retained AVGs may contribute to the inflammatory state in association with erythropoietin resistance in dialysis patients.[39,40] In an observational report of cultures from clots extracted during thrombectomy procedures, significant bacterial growth was revealed without clinical bacteremia.[39] Diagnosis of a clinically symptomatic AVG infection is challenging. Indium uptake scan[41] and fluorodeoxyglucose positron emission tomography/computed tomography[42] have been reported to identify infection in clinically asymptomatic and abandoned AVGs and further correlated with positive microbiological growth. Gram-positive organisms, especially *S. aureus*, are the predominant cause of infections in AVGs.[43] Over the last decade, the use of endovascular stents in the management of AVG dysfunction has increased. Covered stents used to treat an intragraft pseudoaneurysm were associated with subsequent graft infection compared with bare or covered stents deployed within the graft for other reasons: 42.1% vs 18.2% ($P = .011$).[44] The site of stent deployment is also important with intragraft location associated with a higher incidence of graft infection than those deployed at the venous anastomosis or outflow vein: 26.9% vs 6.9% ($P < .001$). Management of infected graft material varies based on clinical presentation. Total graft excision, including anastomosis and likely arterial repair, is indicated in patients with severe sepsis or when the entire graft is bathed in pus. Subtotal graft excision involves leaving a remnant of the oversewn small cuff of prosthetic material on an underlying patent artery. Partial graft excision is when only a limited portion of the infected graft is removed and a new graft is rerouted through an adjacent sterile tissue to maintain patency of the original graft.[45] The difficulty in total resections could be complicated by increasing the use of endovascular stents at the vein graft anastomosis. Remnants of the graft material could lead to reinfection rate as high as 15% while avoiding extensive vascular reconstruction.[46] Newer graft materials have lower infection risks, although the site of graft placement may also affect the risk of infection.[47,48] Drug-eluting AVGs are very promising. Heparin-coated AVG is the only drug-coated AVG that is commercially available currently. Animal studies using triple antimicrobial coated AVGs have reported a significant reduction of infection. Although in a nascent stage, electrospun nanofiber technology for drug delivery offers novel therapeutic options.[49] A study in rabbits using a vancomycin-eluting AVG has demonstrated sustained delivery of vancomycin to the surrounding tissues.[50] Future adaption of this novel technology with a bioengineered AVG could herald a new era of vascular access choices.

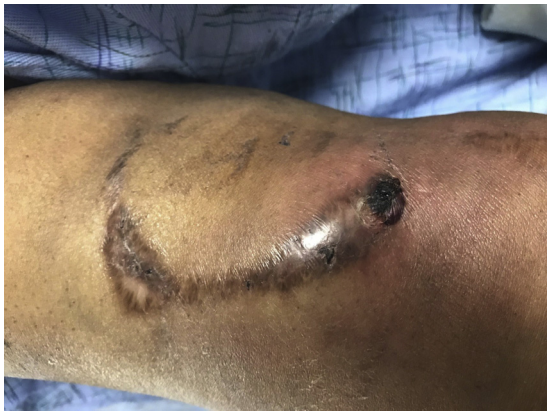

Figure 2. Infected arteriovenous graft with erythema over the cannulation area.

Infectious Complications of Arteriovenous Fistulas

Conventionally, AVF is considered to have a low infectious risk with two recent meta-analyses reporting a rate of 2-4%[4,51] and a rate of 0.018/100 access days.[51] Infections associated with AVF are generally perivascular cellulitis with classic signs of localized erythema, swelling, and tenderness. It is not uncommon to observe infection-associated abnormalities such as an aneurysm with an overlying ulcerated skin or abscess from an infected needle puncture site. Infected ulcers overlying AVF are prone to life-threatening hemorrhage and demands emergent surgical intervention. Needle puncture site infection has been a major concern in buttonhole cannulations. Bacterial colonization of the buttonhole cannulation tract may lack classic clinical signs.[52] In addition, colonization of buttonholes with *S. aureus* significantly increases the likelihood of a clinical access-related infection (4.97 event rates of access-related infection/1000 access days). Nearly 30% of patients with colonization also have asymptomatic bacteremia, raising the risk of endocarditis. Widespread use of buttonhole cannulation techniques in dialysis units could lead to *S. aureus* infection rates similar to TCC access.[53] The problem is compounded in nocturnal home HD

patients who use buttonhole cannulation with nearly 3 times higher access-related infection than conventional in-center HD.[54] Infectious complications along with difficult to achieve AVF maturations warrant a serious review of AVF as being the most preferred HD access.

CONCLUSION

Infectious complications of dialysis access carry significant risk of morbidity and mortality. Arteriovenous fistula continues to be the access with the least risk of infection. Catheters have the highest risk of infection with continued controversy on the optimal management of the catheter during a CRBSI episode. An individualized approach to catheter management in CRBSI with careful access site availability, to avoid exhaustion of access sites, is warranted. AVG can provide an alternative low-infection risk access compared with TCC, but significant infection-related morbidity still exists.

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