

## Central Venous Dialysis Catheters: Catheter-Associated Infection

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### ABSTRACT

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Tunneled dialysis catheters (TDC) are extensively used for long-term venous hemodialysis access and their use is frequently associated with infectious complications. Catheter-related bacteremia (CRB) is the most common and important infection associated with TDC use and may be caused by a wide variety of Gram-positive or Gram-negative organisms. Prevention of CRB can be difficult despite use of rigorous infection-control techniques for catheter insertion and access. A number of antibacterial catheter-packing

solutions hold promise for reduction of CRB. Treatment of CRB with antibiotics alone yields poor results and may increase the risk for other infectious complications, especially endocarditis. In selected cases where initial infection control can be achieved with antibiotics, guidewire exchange of the TDC results in cure rates equivalent to those of TDC removal and subsequent replacement. Dialysis programs should monitor TDC infections with attention to incidence, bacteriology, and outcomes.

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### Clinical Spectrum

Tunneled dialysis catheters (TDC) are commonly used for permanent or long-term temporary venous hemodialysis access. Despite increasing awareness of the superiority of autologous arteriovenous (AV) fistulae and the need for early referral for access creation, patients frequently present for dialysis without a useable AV access. Others require TDC in the setting of failed AV access, peritoneal dialysis, or renal transplant.

In 1999 the total number of hemodialysis patients in the United States exceeded 211,000 (1). Although the precise number of these patients dialyzing with a TDC is unknown, in 1996 the prevalence of TDC use in the first 60 days after initiation of hemodialysis was 18.9%, and after 60 days, 12.9% (2). The 1999 U.S. Renal Data System (USRDS) survey showed that catheters were used in 30% of incident hemodialysis patients and 23% of all hemodialysis patients (3). Catheters were used for longer than 90 days in 14% of all hemodialysis patients. Therefore between 30,000 and 50,000 U.S. hemodialysis patients are now dialyzing with a TDC. If these patients experience bacteremia at recently reported rates of 2.0 (4) to 5.5 (5) episodes per 1000 catheter-days, then there are 22,000–100,000 cases of catheter-related bacteremia (CRB) annually in the United States. A significant number of these result in hospitalization and require

additional surgical procedures, including catheter removal or replacement. Many patients suffer direct or indirect complications of sepsis. The morbidity and cost of CRB must therefore be astronomical. CRB is arguably the most common and important complication associated with the use of TDC (6).

### Types of TDC-Associated Infections

Exit site infection (ESI) is defined as localized infection of the skin and soft tissue around the exit site. Erythema, purulent drainage, and local tenderness are typically present. Usually the subcutaneous cuff is not involved, although in some cases it may be affected. Fever and other signs of systemic infection are absent. With TDC, bacteremia has not been shown to be clearly associated with ESI, although one study of noncuffed, temporary dialysis catheters reported a strong relationship between ESI and CRB (7). It is plausible that the presence of infection in close proximity to the catheter tract and ports might increase the risk for bacteremia, with or without a subcutaneous cuff and tunnel.

Not all erythema or drainage from an exit site represents ESI, and there is a degree of subjectivity in the clinical diagnosis of ESI. Furthermore, culture of the exit site is not diagnostic of ESI and can only be interpreted in the context of the clinical findings, since the exit site is not sterile. Recent reports of ESI incidence range from 1.2 (5) to 2.2 (8) per 1000 catheter-days. ESI may result from inadequate skin disinfection at the time of TDC placement, incorrect suture material or technique, improper exit site care by dialysis clinic staff, or poor patient hygiene. The site should be cleaned with

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disinfecting agents appropriate for the catheter material and a sterile dressing applied at each dialysis session until the site is fully healed, clean, and dry (usually 2–3 weeks).

At least one study has demonstrated a higher incidence of infection at the insertion site of nontunneled venous catheters using transparent occlusive dressings versus dry gauze (9), although this has not been studied for TDC. Based on this observation and Disease Outcomes Quality Initiative (DOQI) guidelines (10), many clinics have adopted the use of dry gauze dressings. One consideration in favor of an occlusive dressing is its ability to secure the catheter to the chest wall and reduce traction on the exit site, cuff, and anchoring sutures, especially in patients with poor tissue integrity and delayed healing. We have seen several catheters dressed with dry gauze become inadvertently dislodged in the first few weeks after insertion, so we prefer transparent dressing for its added mechanical benefit until the cuff is fully anchored.

Once the ESI is well healed and the cuff firmly anchored in the subcutaneous tunnel, the role for regular exit site care and dressing is less clear. Regular washing with soap and water, with the site left open to air, may be appropriate for some patients, similar to the care of a mature peritoneal dialysis catheter exit site. The presence of suture material at or near the exit site may trap debris, prevent drainage, and limit proper cleaning of the site, contributing to the risk for infection. Silk suture material will cause tissue inflammation and trap bacteria in its filaments and should never be used at a TDC exit site. Nylon or other nonabsorbable monofilament suture is preferred and should be secured in such a way that it does not lie directly against the exit site.

Most ESI are caused by Gram-positive organisms including *Staphylococcus aureus* and *S. epidermidis*, although a wide variety of bacteria can be involved. ESI can usually be treated effectively with oral or intravenous antibiotics. In more severe cases or those that fail to respond to antibiotics, revision of the catheter with creation of a new exit site remote from the infected area may resolve the ESI, although this strategy has not been rigorously studied. If these measures fail, the TDC may ultimately need to be removed.

Tunnel infections are invasive soft tissue infections that extend along the subcutaneous tunnel toward the vein. These typically involve the cuff and exit site, although in some cases they may appear only in the tunnel proximal to the cuff, with no drainage or communication to the exit site. Tenderness, swelling, and erythema along the catheter tract are typical, with purulent drainage from the exit site that may be more copious than that seen with simple ESI. Fever and other signs of systemic infection are often present, and bacteremia may occur. In most series, tunnel infection is relatively uncommon; a recent report showed an incidence of 0.12 per 1000 catheter-days (5).

Tunnel infection requires immediate catheter removal and cannot be managed with any catheter-sparing procedure. In rare cases of tunnel infection where there are few venous access alternatives and thus a compelling reason to attempt preservation of the venous access site, one can exchange the TDC with extensive revision of the

tunnel to a clean site remote from the clinically infected area. However, this must be considered a relatively high-risk, low-yield strategy.

## Catheter-Related Bacteremia

Ultimately, ESI and tunnel infections are not the most important infectious complications of TDC. ESI is fairly common but should be largely preventable with proper insertion technique and subsequent catheter care. It is associated with low morbidity and can usually be treated effectively. Tunnel infection is a disaster, but it is rare and can probably be prevented by the same measures used for ES care. CRB remains the major drawback of TDC use. CRB is common and is associated with high cost and morbidity. It may be caused by suboptimal insertion technique or catheter care, but it appears to occur at high frequency in the best hands, suggesting that there are factors that remain out of our control.

## Epidemiology and Microbiology

Patients with CRB may present with signs and symptoms of systemic infection ranging in severity from minimal to life-threatening. Fever and shaking chills are typical. Nausea, vomiting, back pain, headache, myalgia, arthralgia, and changes in mental status can also occur. Patients may develop hypotension, which can be absolute or relative. Some patients present to dialysis with little or no evidence of infection and then develop septic symptoms shortly after initiation of hemodialysis via the TDC, suggesting a release of bacteria or endotoxin from a sequestered source.

Early reports of TDC used for short-term venous access suggested that CRB was uncommon, with infection rates from 0.15 to 0.21 per 1000 catheter-days (11, 12). Other reports of longer-term TDC use reported CRB rates from 0.5 to 0.7 per 1000 catheter-days (13, 14), suggesting higher incidence with increased duration of catheter use. Others have reported no infections whatsoever from TDC (15). Most of these reports were small series that lacked descriptions of precise catheter-access techniques, rigorous methodology for diagnosis of CRB, or method of determining catheter-days at risk for calculation of infection rates. Therefore, it is difficult to interpret, compare, or critique these studies.

Dryden et al. (14) reported very low rates of CRB, 0.5 per 1000 catheter-days, and attributed this in part to excellent nursing access protocol, including use of sterile gloves. Curiously, these authors also reported a relatively high rate of catheter wound infections, 4.5 per 1000 catheter-days. Marr et al. (16) published a large prospective study of CRB using a well-defined system for measuring catheter-days and a very stringent definition of CRB based on positive peripheral blood cultures. This group reported 3.9 episodes per 1000 catheter-days, considerably higher than most previous reports. In this study, risk factors for CRB included prior episode of CRB and “immunocompromised status,” including HIV, cancer, or chronic corticosteroid use. Age and diabetes mellitus were not associated with higher risk.

Subsequent papers by Beathard (17) and Saad (5) reported similar CRB rates, 3.4 and 5.5 episodes per 1000 catheter-days, respectively. Mokrzycki et al. reported no higher incidence of CRB in HIV-positive patients at 2.2 per 1000 catheter-days versus 2.5 in HIV-negative control patients (8).

It should be noted that these studies came from large, well-established programs that would be expected to offer high-quality dialysis and nursing care. In this context, such relatively high rates of CRB are alarming. It is likely that some programs and facilities experience even higher rates of CRB but that these are not reported in the literature. The reasons for this apparent change and widespread variation in the incidence of CRB are not at all clear. Our program saw a marked decrease in CRB infection rates from 5.5 to 3.8 per 1000 catheter-days, with no objective change in catheter placement technique or access protocol. These differences in the rates of CRB between or within programs may be related to nursing technique, but the specific differences in the catheter access procedures often are elusive.

Most early reports of CRB showed a predominance of Gram-positive organisms, chiefly *Staphylococcus* species (18–20). Similar findings were reported recently by Rocklin et al. with 82% Gram-positive and only 7% Gram-negative (21). In contrast, the studies by Marr (16), Beathard (17), and Saad (5) reported a wide variety of Gram-negative organisms isolated from 32% to 45% of CRB episodes. *Enterococcus* species were reported in 8–20% of isolates. The results of these three studies are summarized in Table 1. The reasons for this apparent shift in microbiology over time and differences between programs are unknown, but there are obvious important implications for treatment.

When bacteremia occurs in a patient with a TDC, a distinct source of infection is not usually apparent. It is often assumed that the primary route of entry is via the catheter ports, with organisms that might be expected to colonize the skin or hardware. Enteric Gram-negative organisms and *enterococcus* might obtain access to the bloodstream in the same way. There is no evidence that TDC are susceptible to infection from “normal” transient bacteremia related to tooth brushing or bowel movement, but this possibility exists. The chance of bacteria tracking up the catheter tunnel into the vein is minimized by the presence of a subcutaneous cuff on most TDC, but noncuffed catheters do not appear to have any higher incidence of infection (22). Other infectious sources may include urine, dialysis graft, cutaneous ulcer, and gingival disease. Clearly, there must be a careful search for alternative sources in all patients with a TCD who present with bacteremia, and when found, these sources need to be addressed as indicated.

In most cases of suspected CRB, cultures are drawn from the dialysis lines while the patient is receiving dialysis. Cultures may also be drawn directly from the catheter ports. Although this will increase the chance for false-positive cultures, specificity for true infection will be high if the clinical suspicion for sepsis is high. Blood cultures drawn directly from a peripheral vein are the “gold standard” for diagnosis of sepsis, although when the patient is receiving hemodialysis, the extracorporeal circuit is a direct extension of the systemic circulation and it is not clear that there is any difference. Peripheral venipuncture may be difficult or impractical in busy outpatient dialysis patients, limiting the use of peripheral cultures for diagnosis of sepsis.

A method for establishing a catheter as the source of infection using differential quantitative cultures from the catheter and peripheral blood has been proposed (23), but this has not been studied for TDC and is not routinely available in clinical microbiology laboratories. Perhaps the most practical compromise is to draw two sets of cultures, one directly from the catheter or dialysis blood tubing, and the other drawn peripherally. In the absence of a proven source, it is probable that any bacteremia associated with a TDC has critical implications for that catheter since it must be considered primarily or secondarily infected, possibly making identification of the original source moot.

### Treatment of CRB

Treatment considerations for CRB include stabilization of acutely septic patients, choice and duration of antibiotic therapy, and management of the catheter itself. Severely ill patients with hemodynamic or respiratory instability require hospitalization, and immediate catheter removal is usually recommended in these cases. In these patients, hemodialysis should not be initiated or continued via the TDC unless absolutely necessary for treatment of pulmonary edema or hyperkalemia, because this will likely increase the severity and duration of bacteremia. The decision to remove a TDC for suspected CRB must often be made clinically prior to blood culture results and individualized based on the severity of sepsis, comorbid illnesses, status of permanent arteriovenous access, and alternatives for venous access.

Once CRB is suspected and blood cultures are drawn, antibiotics should be administered in all cases. If the suspicion for CRB is high enough to warrant a blood culture, then it is mandatory that it be treated immediately pending the result of cultures. The choice of initial antibiotics must be guided by a number of factors, including severity of clinical sepsis, patient comorbidities,

TABLE 1. Studies of CRB incidence and bacteriology

	Incidence CRB per 1000 Days	Gram-positive organisms (%)	Enterococcus species (%)	Gram-negative organisms (%)	Polymicrobial (%)
Marr (16)	3.9	67	8	32	11
Beathard (17)	3.4	81	17	28	16
Saad (5)	5.5	67	20	45	21

known previous infections in that patient, and the spectrum of infections in the dialysis unit. Lower-risk patients may be safely managed with relatively narrow initial antibiotics such as cefazolin (24). In higher-risk patients with severe clinical sepsis, initial coverage must consider methicillin resistant *Staphylococcus aureus* (MRSA), *enterococcus*, and *pseudomonas*. This may require vancomycin and an antipseudomonal cephalosporin (e.g., ceftazadime or cefepime) or aminoglycoside. In these situations, it is potentially dangerous to rely entirely on the aminoglycoside for Gram-negative coverage, given unpredictable peak levels (compounded by a tendency to underdose dialysis patients) and variable residual renal function potentially leading to subtherapeutic levels during the first 24–48 hours of treatment. The risks of encouraging vancomycin-resistant *enterococci* (VRE) with overuse of vancomycin are well known (25), and for this reason, one must be hesitant to use this drug as “routine” initial treatment for CRB. Nevertheless, this drug remains an essential alternative for many patients, either as initial empiric therapy or as treatment for a specific susceptible organism (26).

When vancomycin is used, it is essential to dose effectively. The common practice of giving 1 g weekly is insufficient in most dialysis patients, especially those dialyzing with high-flux membranes or those with significant residual renal function. Higher-dose vancomycin, 25 mg/kg, has been shown to achieve acceptable trough levels at 1 week in anuric hemodialysis patients using high-flux dialyzers (27). Alternatively, 20 mg/kg vancomycin supplemented with an additional 500 mg after each dialysis session achieves therapeutic levels (28) and may be better suited for patients with significant residual renal function. This issue is especially important for freestanding clinics where vancomycin levels cannot be obtained immediately and level-based dosing is likely to result in therapeutic gaps that may contribute to treatment failure and possible emergence of vancomycin resistance.

As soon as culture results are available, antibiotic coverage must be tailored to the specific organisms. In most cases one can select effective agents that can be dosed at dialysis only, obviating the need for another intravenous access, prolonged hospitalization, or home antibiotics. If cultures are negative, the decision to treat will depend largely on the initial clinical suspicion for infection. Prolonged treatment of at least 3 weeks with intravenous antibiotics is generally recommended. These considerations for antibiotic therapy apply regardless of how the TDC is managed, although in cases where the TDC is removed, shorter courses or oral antibiotics may be effective.

The major management dilemma is whether to attempt salvage of the TDC if the catheter does not require immediate removal for control of sepsis. Typically over the first 24–48 hours of antibiotic treatment there should be resolution of fever and other clinical signs of sepsis. If significant symptoms persist beyond 48 hours despite effective antibiotics, then salvage is not an option and the TDC should be removed. If the patient has responded well to initial antibiotic therapy, it is often tempting to simply continue treatment with antibiotics

and leave the catheter alone. However, this approach has proved ineffective, with recent reports showing only 32% (16) to 37% (5) success. At least part of the reason for this very poor response may be the presence of biofilm on the catheter surface that affords protection from antibiotics (17). Inadequate antibiotic levels within the catheter lumen may also be a factor.

Guidewire exchange to salvage infected TDC has been reported in small series to be effective in >80% of uncomplicated CRB (19, 29). Beathard compared outcomes of attempted TDC salvage in 114 cases using three methods (17). In patients with a clean exit site, simple guidewire exchange via the exit site resulted in 88% cure. Patients with possible exit site infection had guidewire exchange via a new tunnel and exit site with 75% cure. Patients with more severe infection had catheter removal and then replacement after defervescence, resulting in 87% cure. Robinson et al. reported a series of 23 patients using guidewire exchange for CRB with a similar success rate in of 82% (30).

I reported an 81% cure rate in 43 cases treated with guidewire exchange (5). In this study, outcome was not associated with organism type, although subanalysis was limited by small numbers. Nevertheless, there was no evidence that Gram-negative infection, *pseudomonas*, or *S. aureus* responded worse to guidewire exchange than the group as a whole.

Tanriover et al. reported outcomes of CRB treated with guidewire exchange versus TDC removal and replacement 3–10 days later (31). Although there was a high rate of infection in replacement catheters (46%), infection-free survival of the replacement catheter was no different in the two groups, suggesting that guidewire exchange was equivalent to removal and delayed replacement. There was a striking increase in risk for reinfection in patients with albumin <3.5 g/dl, but no effect of age, gender, diabetes status, or organism type. Based on these consistent data, it is clear that antibiotics alone are not suitable for treatment of CRB and that guidewire catheter exchange is as effective as catheter removal and delayed replacement in selected patients.

Another consideration when treating CRB is the delivery of sufficient antibiotic to the infected surface of the catheter. Intravenous antibiotics that achieve sufficient blood levels may result in effective doses to the extra-luminal surface, depending on the effects of the biofilm or fibrin sheath. However, the internal lumen of the catheter, when packed with heparin, will not be exposed to effective antibiotic levels by the intravenous route. An antibiotic-lock technique may improve results in treatment of nondialysis venous catheters (32). The role for antibiotic packing of infected TDC is not clear, but failure to deliver antibiotics to the internal lumen of the catheter may contribute to the very poor reported responses to antibiotics without device removal or exchange. One recent report of bacteremia in patients with the Dialock subcutaneously implanted hemodialysis access (Biolink Corp., Middleboro, MA), describes successful treatment of CRB using systemic antibiotics combined with a variety of antibiotic-heparin-locking solutions (33). In this application, where catheter

exchange is considerably more involved than a TDC, antibiotic locks may have a critical role.

### Prevention

Prevention of CRB must start with proper nursing access procedure. No pharmacologic maneuver will ever compensate for sloppy catheter-access technique or patient self-care. The method for accessing a TDC is fairly well established. The ports should be thoroughly soaked with a povidone-iodine solution for at least 5 min and allowed to dry. These important details may be easily overlooked in well-intentioned but misguided efforts to avoid soiling patients' clothing and quickly initiate treatment. The nurse or technician and the patient should be masked, and the operator should wear clean, nonsterile gloves. Some programs use sterile gloves for this procedure (14), but this has not been shown to be beneficial and makes little intuitive sense since there are clearly nonsterile aspects to the procedure. It is essential that the catheter port be opened only briefly and then connected directly to the dialysis tubing.

Importantly, once dialysis has begun every subsequent catheter access or de-access should be performed in the same way. This may be neglected when changing lines due to poor flow, system clotting, or interruption of the procedure in response to patient need. The role for prophylactic antibiotic administration prior to invasive procedures has not been studied, but it is likely that the catheter is at risk for infection from transient bacteremia. Therefore, following published guidelines for bacterial endocarditis prophylaxis is recommended for patients with TDC (34).

A number of catheter-packing protocols have been proposed for preventing CRB. A mixture of concentrated gentamicin and sodium citrate virtually eliminated CRB in a preliminary uncontrolled study (35). The ability to prevent Gram-positive infections was attributed to the very high concentration of gentamicin. Heparin was not used in conjunction with gentamicin due to concerns about precipitation, although subsequent studies have shown that, in a lower concentration, gentamicin (5 gm/ml) is stable with 5000  $\mu$ /ml heparin in vitro (36) and this combination may warrant additional study. Preliminary data also show improvement in the rate of CRB with the use of concentrated gentamicin alone (with no anticoagulant) versus heparin alone for packing TDC (37). While anticoagulant-free packing might be expected to result in a higher incidence of catheter malfunction or thrombosis, this was not observed.

Concentrated sodium citrate (with or without gentamicin) has been shown in one study to be an effective anticoagulant for packing TDC, which also reduced the rate of CRB when compared with heparin packing (38). The incidence of CRB using heparin packing was approximately 4.2 episodes per patient-month, 2.7% using 10% citrate with gentamicin, 1.7% with 20% citrate with gentamicin, 1.8% using 23% citrate alone, and 0% using 47% citrate alone. This article proposes that the effectiveness of concentrated citrate as an

antibacterial agent might be related to both its hypertonicity and a lower tendency to form biofilm on the catheter surface. A recent report of an adverse patient outcome following inadvertent systemic administration of 47% citrate (39) has limited the application of this protocol pending further clinical study. Using the antimicrobial agent tauridine combined with citric acid and sodium citrate as a packing solution has been reported to reduce the rate of CRB to 0.3 per 1000 catheter-days (40).

It appears clear that one of several alternative regimens for packing TCD may result in significantly lower rates of CRB when combined with excellent catheter access technique. All these methods have merit but will require further study to demonstrate long-term efficacy and safety.

### Complications of CRB

Considering the high incidence of CRB and the multiple severe comorbidities frequently seen in dialysis patients, one would expect a large number of complications from CRB. Somewhat surprisingly, the incidence of most severe complications appears to be relatively low. Most studies to date have shown a very low rate of mortality directly attributed to CRB (5, 17), although Marr reported deaths in 2 of 41 episodes (16). One paper reported a high incidence of epidural abscess complicating CRB (41). These findings have not been reported by others and may have resulted from prolonged bacteremia associated with attempts to treat CRB without catheter removal or exchange. Marr also reported a very high incidence of infectious complications from CRB (9 out of 41 episodes, 22%) with 6 patients developing osteomyelitis, four bacterial endocarditis (BE), and one septic arthritis. In contrast, other studies have reported few infectious complications, with BE occurring in 1.6% to 3.5% of cases (5, 17). It is important to consider BE in all cases of CRB, especially those that involve *S. aureus* and prolonged or recurrent bacteremia and fever. Echocardiography is typically used as an adjunct to the clinical diagnosis of BE, and because of its enhanced sensitivity, transesophageal echocardiography (TEE) is frequently performed (42). BE may be overdiagnosed if every valvular irregularity is interpreted as an active vegetation. Strict criteria should be used for the diagnosis of BE, and in the absence of a standard for diagnosis of BE in the dialysis population with CRB, one must be very careful when interpreting TEE.

### Recommended Clinical Approach to CRB

Every dialysis program should include careful attention to the problem of TDC infections starting with timely creation of arteriovenous access and continuing with efforts to maintain this as a functional access, thereby minimizing the frequency and duration of use of TDC. Infection rates and bacteriology should be continuously monitored. High rates of infection or unusual

bacteriology should trigger immediate review of catheter placement and access procedures. Dialysis nurses and technicians should be made aware of the importance of infection associated with TDC and provided with regular training to ensure optimal practice. The patient, dialysis staff, and physician must be vigilant for signs of potential infection, and when CRB is suspected, blood cultures must be performed and antibiotics initiated without delay. Each unit should develop an empiric antibiotic regimen of choice based on its known spectrum of organisms; in most cases this should include an agent effective against Gram-negative as well as Gram-positive organisms. Alternatives include cefazolin, vancomycin, and aminoglycoside or antipseudomonal cephalosporins such as ceftazidime.

Severe or complicated infections should be managed with immediate catheter removal. CRB should not be treated with antibiotics alone because this approach is not often successful and may increase complications. In most cases where the infection can be initially controlled using antibiotics, the catheter should be exchanged over a guidewire, resulting in a much improved cure rate compared with that of antibiotic treatment alone. Although no catheter-packing solution has been thoroughly investigated and shown to be both safe and effective, there exist a number of promising methods for reducing CRB. Each unit should evaluate which, if any, of these methods is currently suitable.

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