Strategies to Prevent Infections in Dialysis Patients

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Summary

Infections are the second leading cause of death among patients with end-stage kidney disease, behind only cardiovascular disease. In addition, patients on chronic dialysis are at a higher risk for acquiring infection caused by multidrug-resistant organisms and for death resulting from infection owing to their likelihood of requiring treatment that involves invasive devices, their frequent exposure to antibiotics, and their impaired immunity. Vascular access is a major risk factor for bacteremia, hospitalization, and mortality among hemodialysis (HD) patients. Catheter-related bacteremia is the most severe central venous catheter (CVC)-related infection and increases linearly with the duration of catheter use. Given the high prevalence of CVC use and its direct association with catheter-related bacteremia, which adversely impacts morbidity and mortality rates among HD patients, several prevention measures aimed at reducing the rates of CVC-related infection have been proposed and implemented. As a result, a large number of clinical trials, systematic reviews, and meta-analyses have been conducted to assess the effectiveness, clinical applicability, and long-term adverse effects of such measures.

Peritoneal dialysis chronic treatment without the occurence of peritonitis is rare. Although most cases of peritonitis can be treated adequately with antibiotics, some cases are complicated by hospitalization or a temporary or permanent need to abstain from using the peritoneal dialysis catheter. Severe and long-lasting peritonitis can lead to peritoneal membrane failure, requiring the treatment method to be switched to HD. Some measures as patients training, early diagnosis, and choice of antibiotics can contribute to the successful treatment of peritonitis. Finally, medical directors are key leaders in infection prevention and are an important resource to implement programs to monitor and improve infection prevention practices at all levels within the dialysis clinic.

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Data from the US Renal Data System indicate that infections are the second leading cause of death among patients with end-stage kidney disease,[1] accounting for approximately 10% to 13% of all deaths in 2020,[2,3] behind only cardiovascular disease.

In patients on peritoneal dialysis (PD) in 2020, infections caused nearly 17% of fatalities[4,5] and were the leading cause of hospitalizations among patients undergoing PD and have been the second leading cause, behind cardiovascular disease, of hospitalizations among patients treated with hemodialysis (HD). However, in 2020, driven by coronavirus disease-2019, hospitalizations for infectious causes surpassed those for cardiac causes in the hemodialysis population.[6,7]

Patients with chronic kidney disease and end-stage kidney disease are at higher risk of contracting bacterial infections, particularly urinary tract infections, pneumonia, and sepsis, when compared with the population with normal kidney function.[8-10]

They are also more likely to have an infection at the time of hospitalization.[11] Because of their propensity for causing sepsis, infections related to dialysis access devices are potentially catastrophic.[11,12] The annual mortality rate secondary to sepsis is 100- to 300-fold higher in patients on dialysis.[12]

In addition, patients on dialysis are at a higher risk for acquiring infection caused by multidrug-resistant organisms and for death resulting from infection owing to their likelihood of requiring treatment that involves invasive devices, their frequent exposure to antibiotics, and their impaired immunity.[13,14] As reported by the US Renal Data System, death resulting from infection in patients older than age 65 years is approximately twice that of younger patients.[3]

This article reviews prophylactic and treatment measures against access-related infections in patients on chronic dialysis, identifying their potential advantages and limitations.

ACCESS-RELATED INFECTIONS IN PATIENTS ON CHRONIC HD

HD is the most widely used dialysis modality worldwide and requires vascular access. Access options include an arteriovenous fistula (AVF), arteriovenous grafts, and a central venous catheter (CVC), which either can be tunneled or not tunneled.[15,16]

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Infection is still the main cause of morbidity and mortality in patients treated with HD, despite advances in preventive care and antimicrobial therapy. Among patients with chronic kidney disease undergoing dialysis in the United States, the total death rate is 176 per 1,000 patient-years and septicemia accounts for approximately 26 per 1,000 patient-years.[17-20]

Vascular access is a major risk factor for bacteremia, hospitalization, and mortality among HD patients. The type of vascular access most associated with bloodstream infection (BSI) is CVC (48%-73%), which also increases morbidity and mortality rates, as well as HD costs.[18-21]

Others infections related to catheter use are exit site infections (ESIs) and tunnel infections. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines discourage the use of catheters as vascular access for HD and recommend that less than 10% of patients should be using them for access.[21-23] However, the use of catheters for permanent HD access and, consequently, the number of prevalent HD patients dialyzing through a CVC has increased progressively.

According to the National Kidney Foundation, the number of prevalent patients dialyzing through a catheter increased from 19% in 1998 to 27% in 2002.[21] Today, more than 80% of incident HD patients and 18% of prevalent patients use a CVC in the United States, a reduction from 27% to 18% in prevalent patients.[21-25] Data from the Dialysis Outcomes and Practice Patterns Study showed that 18% and 34% of prevalent patients use CVC in Europe and Canada, respectively.[21-26]

Catheter-related bacteremia (CRB) is the most severe CVC-related infection. CRB is defined by the Centers for Disease Control and Prevention (CDC) as bacteremia in a patient with an intravascular catheter, with at least one positive blood culture obtained from a peripheral vein, clinical manifestations of infection (ie, fever, chills, and/or hypotension), and no other apparent source for the infection.

This can be determined through either positive semiquantitative (>15 colony-forming units/catheter segment) or quantitative (>103 colony-forming units/catheter segment) culture, whereby the same organism is isolated from the catheter segment and a peripheral blood sample; simultaneous quantitative cultures of blood samples with a ratio of ≥5:1 (CVC versus peripheral) and a differential period of CVC culture versus peripheral blood culture positivity of more than 2 hours.[24]

However, in recent review articles, the standards requiring peripheral blood cultures have been questioned regarding the difficulties in performing venipuncture from HD patients, the fragility of vessels, peripheral vascular disease, and the priority of preserving veins for fistula creation. Thus, simpler requirements, especially for epidemiological surveillance purposes, have been proposed to define CRB as positive blood cultures obtained from the catheter and blood line connected to the CVC, determining differential time to positivity.[25-27]

There are scarce data on epidemiology of ESI related to tunneled CVC, and most studies have focused only on CRB.[17] ESI in the tunneled CVC ranged from 0.35 to 8.30 episodes per 1,000 catheter days.[28-31]

Goulart et al[28] evaluated 385 patients undergoing HD who required insertion of tunneled and cuffed CVCs at the University Brazilian Hospital between March 1, 2010, and March 1, 2015. One hundred ninety patients (50.6%) had an ESI and 87 patients (22.6%) had an ESI and BSI caused by the same agent. According to Goulart et al,[28] the overall incidence of ESI was 3.50 per 1,000 catheter days. Risk factors for ESI were the presence of diabetes and tunneled CVCs implanted in the femoral site (relative risk [RR], 1.56; 95% confidence interval [CI], 1.35-1.89, and RR, 1.62; 95% CI, 1.22-1.94, respectively; both $P < .05$). The most frequent agents of ESI were gram-negative (69%), mainly *Serratia marcescens, Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* extended-spectrum β-lactamase–producing. Across the time period, there was a change in etiologic agents; *Pseudomonas* and extended-spectrum β-lactamase agents became more frequent, whereas *Proteus* and *E coli* became less frequent ($P < .05$). Among gram-positive agents, 59% were resistant to methicillin. On the other hand, gram-negative bacilli often were not multidrug-resistant. The catheter was removed in 17% of patients and the main reasons for catheter removal were unsuccessful treatment of ESI, *Pseudomonas* as the etiologic agent ($P = .04$), and BSI caused by the same agent that caused an ESI ($P = .03$). Catheter survival was shorter in the ESI group (log rank, 2.92; $P < .001$).[31]

The CRB rate was highest in HD patients using a CVC and increased linearly with the duration of catheter use. The incidence of CRB ranged between 0.5 and 6.1 episodes per 1,000 catheter days.[24,32] Several multicenter randomized studies have shown that the rate of catheter-related CRB is much higher than that of AVF-related BSI. CRB can lead to bacterial endocarditis, epidural abscess, septic arthritis, and septic embolism.

CVC entails a risk of developing sepsis two- to five-fold higher than AVF, and therefore is associated with a 25% increase in cost.[10] CVC use is associated with an independent increase in mortality rate.[26]

Rates of mortality from infection within the first year of HD are currently 2.4 times greater than in 1981, a fact widely attributed to the use of CVC. In addition to the potential complications inherent to infectious processes, the rate of adverse cardiovascular events increased (up to two-fold) after an episode of sepsis. As a result, morbidity, hospitalization rates, and treatment costs increased, whereas survival rates decreased.[19,24]

Within 24 hours after insertion, microorganisms often form a biofilm in 100% of the catheters.[27] Many

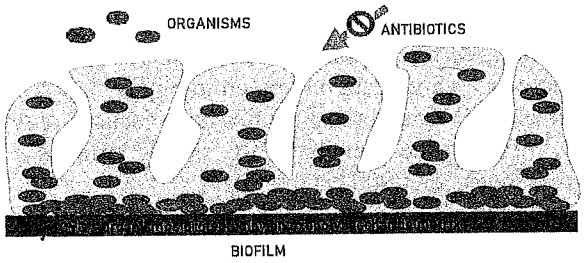

Figure 1. Biofilm pathogenesis. CVC, central venous catheter.

microorganisms may adhere to the CVC surface or become incorporated within a fibrin sheath that envelops the CVC. The adherence of organisms to the catheter surface initiates biofilm production. Biofilm is a community of organisms protected by an exopolysaccharide matrix that is stimulated and secreted by the organisms. Mature biofilms develop high resistance to systemic antibiotics, requiring high concentrations for bacteria elimination.[24,27,33-35] Figure 1 shows the biofilm pathogenesis.

There are two main routes by which organisms enter the bloodstream to cause CRB: an extraluminal pathway and an intraluminal pathway. The extraluminal pathway involves initial contact between skin surface organisms and the external surface of the catheter at the time of CVC insertion, or before complete exit site healing and subcutaneous tunnel endothelialization. The intraluminal pathway involves transfer of organisms by contact from the hands or skin accessing CVC tips.[23,25,33]

Given the high prevalence of CVC use and its direct association with CRB, which adversely impacts morbidity and mortality rates among HD patients, several prevention measures aimed at reducing the rates of CVC-related infection have been proposed and implemented.[33]

As a result, a large number of clinical trials, systematic reviews, and meta-analyses have been conducted to assess the effectiveness, clinical applicability, and long-term adverse effects of such measures.

Prophylactic Nonantimicrobial Measures Against Central Venous Catheter–Related Infections in Hemodialysis

The training and education of health care personnel in manipulating catheters regarding universal hygiene precautions has been noted as the key step toward infection prevention.[28]

The introduction of a catheter care protocol, which followed the guidelines published in 2002 from the CDC, resulted in a decrease in CRB incidence from 6.7 to 1.6 episodes per 1,000 catheter days.[30] Top general precautions include washing hands with conventional soap and water or with alcohol-based hand rubs before and after palpating catheter insertion sites, and before dressing a CVC.[33,35]

The use of a sterile gown, sterile gloves, and sterile full-body drape during CVC insertion is defined as a maximum sterile barrier. In a randomized controlled trial, maximal sterile barrier precautions were compared with sterile gloves and a small drape during the placement of a CVC. The maximum sterile barrier group had fewer episodes of both catheter colonization and BSIs (RR, 0.32; 95% CI, 0.10-0.96; P = .04 and RR, 0.16; 95% CI, 0.02-1.30; P = .06, respectively).[33]

Other measures include selection of the solutions used for exit site cleaning, dressing material, catheter antimicrobial impregnation, catheter material, topical ointments, and intraluminal compounds known as lock therapy.[28,30]

Superior skin and exit site cleaning have been shown using chlorhexidine >0.5%. However, 70% alcohol or 10% povidone–iodine remain effective alternatives if chlorhexidine cannot be used.[24,33]

A meta-analysis of 4,143 catheters (1,493 CVCs, 53 of which were used for HD), suggested that chlorhexidine gluconate reduced the risk for CRB by 49% (95% CI, 0.28-0.88) when compared with povidone–iodine. The absolute risk reduction was 7.1% for colonization and 1.1% for BSI. The test for heterogeneity of treatment effect was significant for catheter colonization (P < .001), but not for CRB (P = .200).[17] Available evidence has indicated that the use of chlorhexidine would result in a 1.60% decrease in the incidence of CRB, a 0.23% decrease in the incidence of death, and a savings of $113 per catheter.[14] Recent data indicated no significant difference between transparent semipermeable dressings, and standard gauze dressings regarding CVC-related infections in HD patients. The CDC recommends the use of a chlorhexidine-impregnated sponge dressing for temporary, short-term catheters in patients older than 2 months of age, if the CRB rate is not decreasing despite proper personnel education and training.[33]

Specific recommendations regarding the use of tunneled catheters and the infection preventive measures that should be taken during their use remain unavailable and surrounded by controversy.[30]

The material the catheter is made from influences microbial adherence and the ability to form a biofilm. Polytetrafluoroethylene or polyurethane catheters have been associated with fewer infectious complications.[33]

Most dialysis catheters are made of silicone or polyurethane. However, whether these materials differ in their susceptibility to biofilm formation after catheter placement has not been investigated.[35]

The use of catheters coated with antimicrobial agents in intensive care units is associated with reduced catheter colonization and decreased catheter-related BSI incidence, and therefore would be a useful option for HD in patients at high risk for CRB.[35-38] However, the few studies addressing the impregnation of tunneled

catheters for HD as a prophylactic measure against infections have shown conflicting results.[35]

Topical Antibiotics

The application of topical antibiotic ointments at the CVC exit site has been shown to be associated with a 75% to 93% reduction in the risk of CRB. However, some agents are incompatible with some catheters, making it necessary to check manufacturers' recommendations before applying any agents on catheters.[39]

Mupirocin, povidone–iodine, triple antibiotic ointment (gramicidin + bacitracin + polymyxin B), and medical honey have been the most commonly studied substances.[14] In 2002, Johnson et al[39] conducted a randomized trial comparing the effect of exit site application of mupirocin versus no ointment in 50 HD patients with tunneled catheters. Mupirocin reduced the incidence of exit site infection (6.6 episodes per 1,000 catheters days versus 0 in the mupirocin group; $P < .050$) and CRB (35% versus 7% in the mupirocin group; $P < .010$), and also increased median bacteremia-free survival from 55 to 108 days (log-rank score, 7.0; $P < .010$). This improved infection-free survival was explained by a reduction in *Staphylococcal* infection (log-rank, 10.7; $P = .001$).[25]

James et al,[40] in a meta-analysis involving 15 studies with HD patients, evaluated the efficacy of topical antibiotic use or lock therapy compared with nonuse of antibiotics for a reduction of CRB and ESI related to the catheter. Both prophylactic antibiotic therapies reduced BSI rates and catheter withdrawal compared with nonuse of prophylactic antibiotics. The antibiotic at the exit site also reduced ESI rates (0.06 versus 0.41 infections per 100 catheter days), and this reduction was not observed in studies containing lock therapy. However, in the studies analyzed, several types of antibiotics and other associated interventions were used, making it difficult to analyze the individual impact of the topical antibiotic, in addition to a short follow-up period.

In 2010, Cochrane published a review on interventions to prevent CRB in HD patients. The analysis included 10 studies, totaling 786 patients; the studies evaluated interventions with topical use of mupirocin, triple Polysporin, povidone–iodine, or medicinal honey, versus placebo, another antiseptic, or no topical antibiotic. They found that the use of ointment with mupirocin reduced the risk of ESI caused by *Staphylococcus aureus* (RR, 0.18; 95% CI, 0.06-0.60; $P < .05$) and CRB (RR, 0.17; 95% CI, 0.07-0.43; $P < .05$), and triple Polysporin ointment reduced the risk of CRB (RR, 0.4; 95% CI, 0.19-0.86; $P < .05$) and all-cause mortality (RR, 0.22; 95% CI, 0.07-0.74; $P < .05$), but with no effect on mortality related to infection. Povidone–iodine ointment reduced the risk of CRB (RR, 0.10; 95% CI, 0.01-0.72; $P < .05$), but the use of topical honey did not significantly reduce either the risk of ESI or the risk of bacteremia associated with a catheter when compared with mupirocin or povidone–iodine ointment.[41]

Since 2011, the CDC has recommended the use of ointment in the exit site of the catheter after insertion and in each HD session. The use of povidone–iodine ointment or the ointment containing bacitracin, gramicidin, or polymyxin B is recommended, but the latter is no longer available in the United States and has never been available in Brazil. The use of ointment containing bacitracin, neomycin, or polymyxin B is cited as an option, but there is a lack of studies showing efficacy in the prevention of ESI and CRB. Other options would be mupirocin or for the dressing to be impregnated with chlorhexidine. However, the CDC emphasizes the risk of developing bacterial resistance, the possibility of the ointment being ineffective against the pathogens responsible for the infections, and the possible chemical interaction between the ointment ingredients and the catheter material.[42,43] However, despite mentioning the use of antibiotics and the use of medicinal honey in the exit site as a preventative measure of CRB associated with the catheter, because there are no studies that evaluate the development of bacterial resistance in the long term, the KDOQI guideline does not include this practice in its recommendations.[21]

Thus, routine use of topical antibiotics in the exit site of CVC is not widely used and should be based on the rates of local infections and the practice of each center.[44]

Antimicrobial Lock Solutions

Although some studies between 2006 and 2010 assessed the efficacy of antimicrobial lock solutions (ALS) in preventing BSI, most of them had significant limitations: these included the use of a small number of patients; many studies being retrospective, while others, despite being prospective, had short follow-up periods; some studies included patients with short-term and long-term catheters; and some studies used several solutions concomitantly, with or without antibiotics.[45-47]

Labriola et al[48] published a meta-analysis in 2007 that included eight randomized studies (829 patients, 882 catheters, and 90,191 catheter days) comparing ALS with a standard heparin lock in CRB prevention. Although four of the studies included tunneled catheters, only one included exclusively nontunneled catheters, and three studies included both tunneled and nontunneled catheters. ALS significantly reduced the risk of CRB (risk ratio, 0.32; 95% CI, 0.10-0.42; $P < .05$). The authors concluded that the significant reduction in the incidence of CRB achieved in the ALS groups was similar to published reports from units with low bacteremia incidence and, presumably, stricter hygienic measures.

Furthermore, the limited follow-up evaluation of the studies included in this meta-analysis did not allow for

the assessment of the onset of adverse events or bacterial resistance with longer use of lock therapy.

In 2008, Jaffer et al[49] performed a meta-analysis of seven studies including a total of 624 patients and 819 catheters (448 tunneled, 371 nontunneled) to determine the efficacy of ALS in reducing CRB in HD patients. Catheter-related infection was 7.72-fold less likely when using antibiotic lock solutions times (95% CI, 5.11-10.33; $P < .05$). The absence of mechanical complications, such as catheter occlusion, was another positive effect observed in the patients receiving ALS. The studies included in this meta-analysis used different concentrations of different substances, including gentamicin, minocycline, citrate, taurolidine, cefotaxime, and cefazolin. The major limitation of this review was the relatively short duration of follow-up evaluation of the included studies, which did not allow for the opportunity to assess long-term adverse events, such as development of antibiotic resistance and systemic toxicity.

Yahav et al[50] conducted a systematic review of 16 randomized controlled trials that compared single or combination antimicrobial catheter lock solutions with heparin or another antimicrobial for the prevention of infections in HD patients. The rates of CRB were significantly lower with antibiotic catheter lock solutions compared with heparin lock alone, both per patient (RR, 0.44; 95% CI, 0.38-0.50; $P < .05$) and per catheter day (RR, 0.37; 95% CI, 0.30-0.47; $P < .05$). Catheter removal rates were significantly lower in the intervention group per patient (RR, 0.35; 95% CI, 0.23-0.55; $P < .05$; 5 trials; 552 patients) and per catheter day (RR, 0.34; 95% CI, 0.21-0.55; $P < .05$; 135,769 catheter days). The emergence of clinically significant resistant strains was reported in five trials, including 316 patients receiving intervention and 211 control patients. Only one case of gentamicin-resistant *S aureus* was reported in a patient receiving gentamicin and citrate during 16 months of follow-up evaluation. ESIs were reduced in the intervention group, but without statistical significance. In studies of nonantibiotic antimicrobial catheter lock solutions, CRB rates were significantly lower with ALS than with heparin alone per patient (RR, 0.46; 95% CI, 0.29-0.71; $P < .05$; four trials; 642 patients) and per catheter day (RR, 0.48; 95% CI, 0.30-0.76; $P < .05$; 60,149 catheter days).

In 2011, a meta-analysis of nine trials showed a significant benefit in favor of the antibiotic-based solutions in HD patients with tunneled catheters. CRB baseline risk was three per 1,000 catheter days, corresponding with the number needed to treat of three patients to prevent one CRB. Snaterse et al[51] concluded that to determine the efficacy of the routine use of antibiotic lock solutions in HD patients, other factors should be considered, such as the side effects of antibiotics, including the induction of microbial antibiotic resistance and cost effectiveness.

In 2014, Zhao et al[52] published a meta-analysis that included 13 randomized studies with 1,770 patients and 221,064 catheter days followed up for 5 years, comparing 4% sodium citrate versus heparin (1,000 U/mL) locks. The rate of CRB was significantly lower in the citrate group (hazard ratio, 0.39; 95% CI, 0.27-0.56; $P < .001$) when it was associated with other substances, such as gentamicin ($P < .001$) or taurolidine ($P = .003$). Taurolidine is a taurine derivative that binds to the wall of bacteria and fungi, promoting the death of these agents. This acts as a disinfectant without inducing bacterial resistance induction.

Previous studies have shown that taurolidine has been able to reduce CVC biofilm in vitro and in vivo.[53-57] In relation to locking prophylactic therapy with taurolidine, two meta-analyses were published between 2013 and 2014. The first included six randomized controlled trials (431 patients, 86,078 day catheters), the use of taurolidine solutions in antibiotic lock of CVC (HD, parenteral nutrition, and pediatric oncology patients) was associated significantly with a reduction in the incidence of CRB compared with heparin (RR, 0.34; 95% CI, 0.21-0.55; $P < .0001$).[56] However, only the reduction in the number of CRB by gram-negative bacteria was statistically significant with the use of the taurolidine lock (RR, 0.27; 95% CI, 0.11-0.65; $P < .05$). There were no differences between groups (taurolidine versus heparin) in relation to catheter occlusion owing to thrombosis, with no bacterial resistance to taurolidine in the studies evaluated. However, the authors concluded that the results should be analyzed with caution because of the small sample size of the studies and the lack of methodologic rigor.

In 2014, Liu et al[56] also published a meta-analysis and systematic review comparing locking with taurolidine versus heparin in patients on CVC and risk of infection, with an overall reduction in the incidence of CRB (RR, 0.47; 95% CI, 0.25-0.89; $P < .05$), but with no effect on infections caused by gram-positive bacteria. The incidence of thrombosis differed between the groups, with the highest percentage of events in the taurolidine group (RR, 2.11; 95% CI, 1.16-2.09; $P < .05$).

Few studies have found the impact of prophylactic lock therapy on CVC in the prevention of catheter ESI. In 2014, a meta-analysis was published of 23 randomized studies, 16 of which included patients with HD, with a 69% reduction in central-line blood stream infections, defined as the presence of laboratory-confirmed CRB in any patient with CVC at the time or within 48 hours before infection, using antimicrobial lock solutions compared with heparin (RR, 0.31; 95% CI, 0.24-0.40; $P < .05$), and with a 32% reduction in ESI (RR, 0.68; 95% CI, 0.49-0.95; $P < .05$).[50] A possible justification for this effect would be the extravasation that occurs in the CVC, depending on the density of the solution used, type and site of the catheter and position of the body, doses of antimicrobials close to the minimum inhibitory concentration for

some pathogens, and consequent systemic maintenance of the subcutaneous tissue near the catheter orifice, reducing ESI rates. There were no differences in all-cause mortality among 13 studies that analyzed this outcome (RR, 0.84; 95% CI, 0.64-1.12; $P < .05$). Sensitivity analysis also was performed to assess the effect of lock therapy on centers with low BSI rates, including studies with fewer than 1.15 events per 1,000 catheters-day (six trials) and found that the relative rate of BSI reduction remained significant in the subanalysis (RR, 0.32; 95% CI, 0.17-0.60; $P < .05$).

Finally, two other meta-analyses were published with different approaches, which also observed the superiority of the substances in lock in relation to rates of catheter-related CRB. In 2016, Wang et al[58] published a Cochrane review of 27 randomized studies with a mean follow-up period of 6 months, comparing lock therapy with alternative anticoagulant solutions. The primary end point was evaluation of catheter dysfunction, with no statistical difference in the three groups studied. In the individual agent analysis, recombinant tissue plasminogen activator was the only lock solution that showed a reduction in catheter malfunction (RR, 0.58; 95% CI, 0.37-0.91; $P < .05$).

Regarding the secondary end points, there was a significant reduction in CRB rates only in the group with a lock of alternative anticoagulant solutions (HR, 0.46; 95% CI, 0.36-0.66; $P < .05$), but it was not possible to evaluate CRB in the group with a low dose or no dose of heparin. In the individual analysis of alternative solutions, except ethanol, all other lock therapies reduced the incidence of CRB (citrate, antibiotics, and recombinant tissue plasminogen activator).

However, the interpretation of the evidence from the study is limited by the variations in the interventions tested and the results reported, and randomized trials of high methodologic quality are required. The second study, published in 2017 by Zhang et al,[59] was a meta-analysis that, unlike the others cited, compared the effectiveness of antimicrobial solutions in locking each other in the prophylaxis of catheter-related infections in HD. This Bayesian network meta-analysis included 18 studies with 2,395 patients and analyzed 10 lock therapy strategies (including the control group). Gentamicin + citrate (overall response, 0.07; 95% CI, 0.00-0.48; $P < .05$) and gentamicin + heparin (overall response, 0.04; 95% CI, 0.00-0.23; $P < .05$) were significantly more effective in reducing rates of catheter-related CRB when compared with the use of heparin only locks. Regarding the incidence of ESI and all-cause mortality, no significant difference in the intervention effect was detected for all lock solutions when compared with heparin. All solutions were similar for catheter-related CRB, ESI, and all-cause mortality, when compared.

Table 1 summarizes the major characteristics of the meta-analysis studies from the past 15 years on prophylactic antibiotic topical and lock therapy for HD-tunneled catheters.

Although recent meta-analyses have shown favorable results related to the use of antimicrobial lock therapy in reducing the rates of catheter-related infection, the latest update to the KDOQI guidelines recommends the use of lock therapy only in scenarios in which the benefits outweigh the potential risks of selecting for antibiotic-resistant infections, which includes patients at high risk of BSI or dialysis centers where BSI rates are greater than 3.5 events/1,000 catheter-days.[21]

ACCESS-RELATED INFECTIONS IN PATIENTS ON CHRONIC PD

Chronic treatment with PD without the occurrence of peritonitis is rare. Although most cases of peritonitis can be treated adequately with antibiotics, some cases are complicated by hospitalization or a temporary or permanent need to abstain from using the PD catheter. Severe and long-lasting peritonitis can lead to peritoneal membrane failure, requiring the treatment method to be switched to hemodialysis.[61,62]

Peritonitis is suspected when the patient presents turbid peritoneal effluent. This is confirmed by an effluent cell count characterized by a white blood cell count greater than 100/μL, with at least 50% polymorphonuclear cells. Peritonitis should be considered in the differential diagnosis of all patients with abdominal pain, even if the peritoneal effluent is clear. For patients on automated PD with a short dwell time, a lower effluent cell count containing predominantly polymorphonuclear cells can be compatible with peritonitis. Other signs or symptoms of peritoneal inflammation may be present, such as Blumberg's sign, nausea, vomiting, or fever. A differential diagnosis of cloudy effluent may include chemical peritonitis, eosinophilia, hemoperitoneum, malignancy, chylous effluent, and specimen taken from the "dry" abdomen.[62]

Peritonitis has been the focus of several studies performed by our research group,[63–72] including discussion of the risk factors, etiologies, microbial susceptibility, and therapeutic protocols. We have a cumulative experience of 27 years, and although an overall reduction in peritonitis incidence has been observed during this period, this reduction occurred predominantly during the first 17 years despite several recent technological advances.

In the long series reported by van Esch et al,[62] improvement in the rate of peritonitis coincided with an advancement in technologies, particularly disconnection systems. van Esch et al[62] also noted that measures to prevent against infection, including the application of antibiotics at the exit site of the catheter and replacement of the dialysis solution with a biocompatible fluid, have little impact on the incidence of peritonitis.

Table 1. Summary of the Meta-Analyses Using Prophylactic Antimicrobial Therapy in Hemodialysis Central

Study	Year	Studies, N; Patients, N	Groups	Results	Adverse Events	Strengths and Limitations
James et al[40]	2008	15 randomized trials; 2,395 patients	CG: heparin; TG: topical and LS ATBs	LS and topical decreased BSI rates Only topical ATBs reduced ESI rates 0.06 versus 0.41 ESIs per 100 catheter days	NR	LS and topical decreased BSI rates Topical ATBs reduced ESI rates
McCann et al[41]	2010	10 randomized trials; 786 patients	CG: placebo; TG: topical mupirocin, triple Polysporin, iodine–povidone, honey	Topical drugs versus placebo mupirocin, triple Polysporin and iodine–povidone, decreased risk for BSIs Only triple Polysporin reduced risk for death Honey did not reduce risk for ESIs or BSIs	NR	Mupirocin; triple Polysporin and iodine–povidone, decreased risk for BSIs
Labriola et al[48]	2008	09 randomized trials; 829 patients 501 TCCs 381 NTCCs	CG: heparin; TG: three trials ATB + heparin Two trials: citrate One trial: ATB + EDTA	LS versus heparin RR, 0.32; 95% CI, 0.10-0.42	Dizziness Paresthesia Metallic taste >Bleeding in heparin group	LS decreased BSI rates Adverse events
Jaffer et al[49]	2008	07 randomized trials; 624 patients 448 TCCs	CG: heparin; TG: three trials ATB + heparin Two trials: citrate + ATB	LS versus heparin 7.72 lower risk 95% CI, 5.10-10.30	Dizziness > bleeding in heparin group	LS decreased BSI rates Adverse events
Yahav et al[50]	2008	16 randomized trials; 924 patients 371 NTCCs	CG: heparin; TG: six trials ATB + heparin One trial: ATB Four trials: citrate One trial: citrate + ATB One trial: citrate + EDTA	LS versus heparin RR, 0.44; 95% CI, 0.38-0.50	ATB group emergency resistant strains <Thrombosis in TG >Bleeding in CG Dizziness and rash	LS decreased BSI rates Adverse events
Snaterse et al[51]	2011	16 randomized trials	CG: heparin; TG: five trials ATB + heparin One trial: ATB + EDTA Three trials: citrate + ATB one study in NTCC One study in both Six studies in oncology One study in neonates	LS versus heparin Three patients treated for prevention of one BSI episode	NR	LS decreased BSI rates
Zhao et al[52]	2014	13 randomized trials; 1,770 patients	CG: heparin; TG: 4% sodium citrate	Citrate versus heparin HR, 0.39; 95% CI, 0.27-0.56	Dizziness only when associated with gentamicin or taurolidine	Citrate is better than heparin in the prevention of BSI
Liu et al[55]	2014	03 randomized trials	CG: heparin; TG: taurolidine	Taurolidine versus heparin HR, 0.47; 95% CI, 0.25-0.89	>Thrombosis in TG No effect in G+ bacteria	Taurolidine decreased BSI rates Adverse events

(*continued on next page*)

Table 1 (*Continued*)

Study	Year	Studies, N; Patients, N	Groups	Results	Adverse Events	Strengths and Limitations
Zcharioudakis[57]	2014	23 randomized trials	CG: heparin; TG: 4% sodium citrate	Heparin versus ATB ATB reduced the risk for BSI in 69% and for ESI in 32% HR, 0.31; 95% CI, 0.24-0.40; and HR, 0.68; 95% CI, 0.49-0.95	NR	Citrate is better than heparin in the prevention of BSI
Wang et al[58]	2016	27 randomized trials	CG: heparin; TG: ATB	ATB versus heparin Heparin reduced risk for BSI HR, 0.45; 95% CI, 0.36-0.66	>Thrombosis in TG No effect in G+ bacteria NR	Heparin decreased BSI rates
Zang et al[59]	2016	18 randomized trials; 2,395 patients	CG: heparin; TG: ATB or citrate	ATB or citrate versus heparin Citrate + gentamicin reduced risk for BSI HR, 0.07; 95% CI, 0.01-0.48	NR	Citrate + gentamicin decreased BSI rates

Abbreviations: ATB, antibiotic; BSI, bloodstream infection; CG, control group; EDTA, ethylenediaminetetraacetic acid; ESI, exit site infection; HR, hazard ratio; LS, lock solution therapy; NR, not reported; NTCC, nontunneled central venous catheter; RR, relative risk; TCC, tunneled central venous catheter; TG, treatment group.
Reprinted with permission from Kapoian et al.[60]

Several reports have suggested that the PD modality is not associated with a higher likelihood of developing peritonitis. Analysis of the nationwide prospective Brazilian PD study cohort, in which groups were balanced for several covariates using propensity score matching, showed that the PD modality was not associated with any differences in time until first peritonitis or with technique failure.[63]

Lan et al[69] showed that automated PD was associated with a borderline reduction in the likelihood of a first episode of gram-positive peritonitis compared with continuous ambulatory peritoneal dialysis, and with lower rates of culture-negative peritonitis and higher rates of gram-negative peritonitis. The peritonitis outcomes were comparable between modalities.

A study including 1,321 incident PD patients showed that peritonitis was associated independently with a higher risk of all-cause mortality, infection-related mortality, and cardiovascular mortality. Further analysis showed that the impact of peritonitis on mortality was more significant in patients who had undergone PD for longer than 2 years. Given the poor outcome of peritonitis in these long-term PD patients, reducing the incidence rate of peritonitis remains the most important challenge in the management of this population of patients.[69]

In the final section of the PD infection guidelines published by the International Society for Peritoneal Dialysis (ISPD),[67] relevant problems related to peritonitis were identified as future research targets. Some of these will be the focus of this article.

Impact of Patient Training

One problem to be addressed is in relation to PD training strategies. One of the key recommendations of the ISPD guidelines for patient training is to apply andragogy (adult learning), which requires the ability to plan training as well as prior knowledge of the learner, who, in this case, is the patient or caregiver. Thus, to implement this strategy, dialysis nurses must have some knowledge of adult learning. There is little information about the influence of the experience of the PD nurse on peritonitis incidence, and the current evidence is conflicting. The most important factor related to patient training to reduce the risk of peritonitis is considered the ability of the nurse trainer. The services should include educational programs, interactive training, and the application of educational materials that cover prevention, hygiene, care of the exit wound, the various sources of contamination, and early identification of infection.

Figueiredo et al[71] suggested that a minimum of 15 hours of initial training should be given to all PD patients, determined from assessing the impact of training characteristics on the rate of peritonitis in a large Brazilian cohort (Brazilian PD study). In their study, Figueiredo et al[61] showed an association between training

patterns and peritonitis incidence in which the total number of training hours, regardless of the number of hours per day, was associated with worse rates of peritonitis, in addition to a smaller center size and the training time related to catheter implantation.

Improving Diagnosis

Recognizing and incorporating techniques that can shorten the time required to identify the pathogen species is critical, and also can assist in the identification of rare or unknown pathogens. The application of matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry has been compared with conventional methods in regard to the time required for pathogen identification and the impact on clinical outcomes in patients with PD-related peritonitis (Table 2). The MALDI-TOF mass spectrometry method was found to identify the causative microorganism more quickly, and patients also had a shorter hospital stay.[70]

Our center reported results from a historical series of peritonitis patients found to be infected with coagulase-negative *Staphylococcus*, identified based on the characteristics of the bacterial cells, which were seeded onto blood agar. The isolates were submitted to catalase and coagulase tests, allowing their identification. After identification and susceptibility testing, strains were frozen and stored at 280°C in trypticase soy broth with 15% glycerol. Phenotypic identification was confirmed by polymerase chain reaction of internal transcribed spacer regions after the extraction of whole bacterial nucleic acids. MALDI-TOF Biotyper (Bruker Daltonik) and/or partial sequencing of *rpoB*, followed by Basic Local Alignment Search Tool analysis, was performed. *Staphylococcus epidermidis* was found to be the most frequent cause of peritonitis (62.6%), followed by *Staphylococcus haemolyticus* (11.3%), *Staphylococcus warneri* (7%), *Staphylococcus cohnii* (5.2%), and *Staphylococcus hominis* (4.3%). Seven other species were identified, accounting for 9.6% of cases. Therefore, our study presented novel information on peritonitis caused by coagulase-negative *Staphylococcus*. Information on this topic still is limited despite the recommendations in the ISPD guidelines, which emphasize the importance of differentiating between *Staphylococcus* species that cause peritonitis.[64,65]

Another study from our center evaluated a series of fungi isolated from peritonitis patients (n = 23). *Candida parapsilosis* was the main species (9 of 23), followed by *Candida albicans* (5 of 23), *Candida orthopsilosis, Candida tropicalis, Candida guilliermondii*, and *Kodamaea ohmeri*. All isolates were susceptible to amphotericin B, voriconazole, and caspofungin, whereas *C albicans* isolates were susceptible to all antifungal agents tested. Resistance to fluconazole was observed in three *C orthopsilosis* isolates, and dose-dependent susceptibility to this antifungal was observed in *C parapsilosis* and *K ohmeri*. Estimates of biofilm production were high or moderate for most isolates, especially *C albicans* and *C parapsilosis*, with marked variation among isolates. This study, performed in a group of Brazilian patients, reinforced that fungal peritonitis is caused mainly by *C parapsilosis*, a prevalent group of yeasts. In addition, they present significant variation in susceptibility to antifungals and biofilm production, thus contributing to the complexity and severity of clinical features.[66]

Antibiotic Resistance Is an Increasing Problem

Our group has noted a higher requirement for antibiotic replacement in recent years, with increased resistance of

Table 2. Time to Pathogen Identification in Peritoneal Dialysis–Related Peritonitis Using the Conventional Standard Method and MALDI-TOF MS

Pathogen	Pathogens Identified, n; Time to Pathogen Identification, Hours, Means ± SD		*P* value (difference in hours)
	Conventional standard method	MALDI-TOF MS method	
All pathogens	98; 135 ± 55	57; 71 ± 37	<.001 (64)
Gram positive*	60; 129 ± 26	32; 77 ± 47	<.001 (52)
Gram negative†	35; 130 ± 32	24; 65 ± 17	<.001 (65)
Staphylococcus species	33; 127 ± 27	14; 90 ± 67	<.001 (37)
Streptococcus species	23; 132 ± 24	17; 64 ± 18	<.001 (68)
Escherichia coli and *Klebsiella* species	19; 130 ± 25	15; 63 ± 15	<.001 (67)
Gram-negative pathogens other than *E coli* and *Klebsiella* species	16; 131 ± 39	9; 69 ± 21	<.001 (64)

Abbreviation: MALDI-TOF MS, matrix-assisted laser desorption ionization time-of-flight mass spectrometry.

*Includes *Streptococcus* species (viridans streptococci, *S pneumoniae*, and other *Streptococcus* species) and *Staphylococcus* species (*S aureus* and coagulase-negative staphylococci).

†*Escherichia coli, Klebsiella* species, *Proteus* species, *Pseudomonas* species, *Acinetobacter baumannii, Citrobacter koseri, Enterobacter* species, *Serratia marcescens, Haemophilus influenzae, Burkholderia* species, *Pasteurella multocida*, and *Fusobacterium* species.Adapted with permission from Lin et al.[72]

coagulase-negative staphylococci to cephalothin. The oxacillin resistance rate has been reported to be 69.6%, which likely explains the number of cases being treated with vancomycin.[64]

Vancomycin has been the antibiotic of choice for the treatment of methicillin-resistant *S aureus* infections for decades. Relatively recently, however, vancomycin-intermediate-susceptible *S aureus* has been reported. The most important risk factor for decreased vancomycin susceptibility is in vivo selection pressure. To prevent the development of vancomycin-intermediate-susceptible *S aureus*, prolonged or inappropriate use of vancomycin and suboptimal vancomycin levels should be avoided. In relation to PD, intermittent antibiotic administration regimens have been administered owing to convenience and a lower risk of accidental contamination of the system. However, the risk of local subtherapeutic levels is high. Thus, De Vriese and Vandecasteele[73] suggested reversion to continuous therapy because of the combined advantage of a high local concentration and low systemic exposure. Furthermore, this practice favors reduced susceptibility to vancomycin and preserves residual renal function.

A report from India by Prasad et al[74] found that 15.6% of *E coli* isolates were resistant to amikacin and 37.5% were resistant to gentamycin. Resistance to aminoglycosides was high in nonfermenters (47% in *Acinetobacter* species and 34.6% in *P aeruginosa*). Vancomycin-resistant enterococci accounted for 15.4%, and 28.6% were methicillin-resistant staphylococci.

Newer Antibiotics for the Treatment of Peritonitis

The choice of antimicrobials for the initial treatment of PD-related peritonitis is crucial for a favorable outcome. There is no consensus regarding the best therapy because few prospective controlled studies have been published, and the published systematic reviews have not reported the superiority of any class of antimicrobials. In a proportional meta-analysis, Barretti et al[75] reported that glycopeptide plus ceftazidime appears to be superior to other regimens for the initial treatment of PD peritonitis. This result should be considered carefully because it does not exclude the necessity of monitoring the local microbiologic profile in each dialysis center when choosing an initial therapeutic protocol.

Table 3. Use of Newer Antibiotics in the Treatment of Drug-Resistant Gram-Positive Bacterial Peritonitis

Antibiotic	Organisms	Route	Dose	Adverse Effects	Remarks
Linezolid	MRSE, MRSA, VISA, VRSA, VRE	PO/IV	600 mg twice daily	Myelosuppression, neuropathy (optic and peripheral)	Consider therapeutic drug monitoring in elderly patients and/or prolonged therapy required (>2 weeks) Closely monitor hematologic parameters and reduce to 300 mg twice daily if myelosuppression IP dosage unknown
Daptomycin	MRSE, MRSA, VRE, VISA, VRSA	IV	4-6 mg/kg Q48h	Myopathy, rhabdomyolysis, eosinophilic pneumonia, peripheral neuropathy	Monitor CPK levels and follow muscle pain or weakness Consider systemic steroid if eosinophilic pneumonia
		IP	100 mg/L loading, then 20 mg/L maintenance		Limit the dwell time to 6 hours and do not mix with icodextrin
Tigecycline	MRSE, MRSA, VRE	IV	100 mg loading, then 50 mg Q12h	Liver dysfunction, pancreatitis	IP dosage unknown
Moxifloxacin	MRSE, MRSA	PO/IV	400 mg Q24h	Prolonged QT interval, CNS side effects including seizure, peripheral neuropathy, spontaneous tendon rupture	Little antipseudomonal activity IP dosage unknown
Quinupristin/ dalfopristin	MRSE, MRSA, VRSA, VRE (*Enterococcus faecium* only)	IV + IP	IP 25 mg/L in alternate exchange given in conjunction with IV 500 mg Q12h	Infusion site pain, edema, inflammation, thrombophlebitis	Ineffective against *E faecalis*

Abbreviations: CNS, central nervous system; CPK, creatine phosphokinase; IP, intraperitoneal; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; PO, per oral (orally); Q12h, every 12 hours; Q24h, every 24 hours; Q48h, every 48 hours; VISA, vancomycin-intermediate *Staphylococcus aureus*; VRE, vancomycin-resistant enterococcus; VRSA, vancomycin-resistant *Staphylococcus aureus*.
Adapted with permission from Szeto.[76]

Table 4. Infection Control Issues in Conditions for Coverage

Isolation of hepatitis B–positive patients
Contact precautions for skin wounds and fecal incontinence
Strict hand hygiene
Environmental cleaning and disinfection of dialysis stations
One-way flow of supplies and medications
Routine serologic testing of hepatitis B and C
Immunization for hepatitis B, influenza, and pneumococcus
Infection control training of staff and patients
Infection surveillance (eg, catheter-related bacteremias)

Adapted with permission from Kapoian et al.[60]

The treatment of drug-resistant bacterial peritonitis is challenging. Newer antibiotics with activities against drug-resistant, gram-positive bacteria have been developed. In most circumstances, methicillin-resistant staphylococci peritonitis responds to vancomycin. If vancomycin cannot be used because of an allergy and/or nonsusceptibility, linezolid and daptomycin are the drugs of choice. Daptomycin, in particular, has excellent antibiofilm activity. Other options include teicoplanin and tigecycline. The recommended dose, route of administration, major side effects, and precautions when using these antibiotics are summarized in Table 3.

However, many of these have not been tested formally in PD patients. Future studies are required to obtain pharmacokinetic data and evaluate the efficacy and safety of these newer antibiotics in PD patients. Effective treatment options for multidrug-resistant, gram-negative bacteria are limited. Polymyxins can be considered, but evidence on dosage adjustment in PD patients is lacking.[76]

In conclusion, peritonitis remains a major concern for many patients and doctors, and may influence the selection of this type of renal replacement. Peritonitis has a substantial impact on the success of the technique, the outcome, and cost. Therefore, prevention and accurate diagnosis are critical. Empiric treatment should be rapid, highly effective, and with rare side effects. The current guidelines of the ISPD are of great value; however, they should not be interpreted as dogmas. Optimization for specific local conditions should be encouraged.

ROLE OF THE MEDICAL DIRECTOR IN INFECTION CONTROL IN DIALYSIS UNITS

Health care–associated infections are a common yet preventable cause of dialysis morbidity and mortality. Medical directors are key leaders in infection prevention and are an important resource to implement programs to monitor and improve infection prevention practices at all levels within the dialysis clinic.

Medical directors should help develop and review protocols guiding practice for tasks such as minimizing

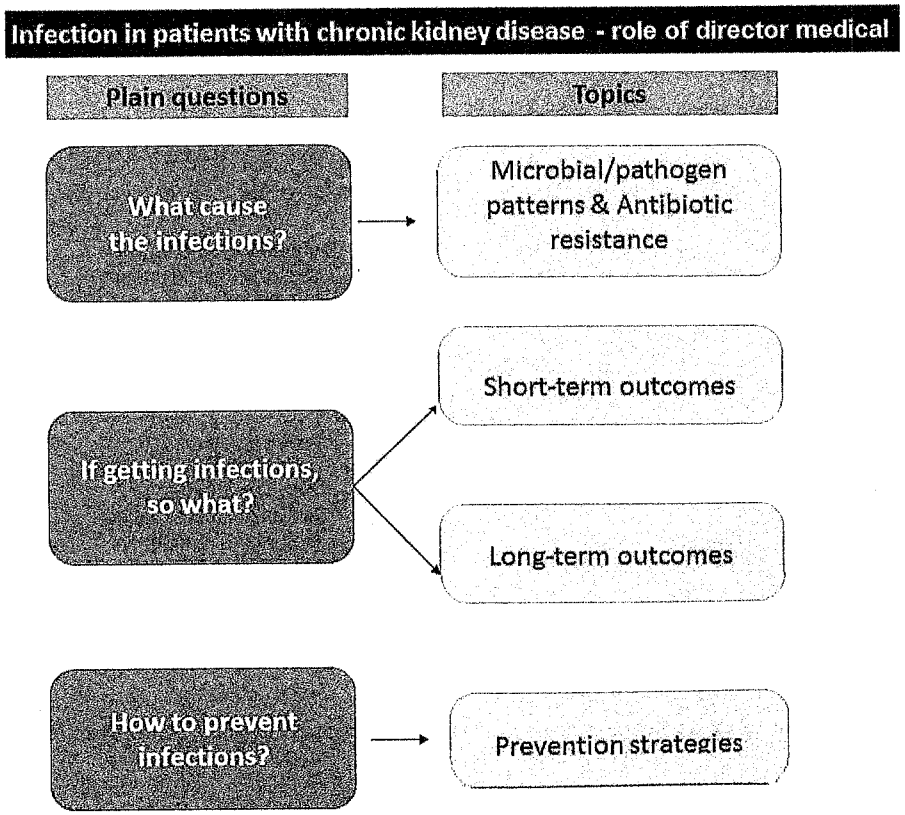

Figure 2. Infections in patients with chronic kidney disease. Role of the medical director.

use of dialysis catheters, implementing the CDC protocol, taking care of patients with multidrug-resistant organism infections, and performing universal vaccination to help avoid preventable health care–associated infections.

The CDC "scrub the hub" protocol involves using one of several acceptable antiseptics, including .0.5% chlorhexidine gluconate with alcohol, 70% alcohol, or 10% povidone–iodine. After application, the solution should be allowed to dry completely to impart maximal effect. The effect might be enhanced if an antiseptic pad is used rather than a swab or other delivery system because a pad can conform to the surface irregularities of the catheter. Particular attention should be paid to the catheter hub and its connecting limb, both of which are scrubbed starting at the catheter hub (with caps removed), and ensuring that the threads are cleaned of any residual debris or blood. The scrubbing action then continues to move along the catheter limb in a direction toward the patient and away from the open threaded end of the hub. If vascular access–related infection or the blood stream infection rates are unacceptably high, medical directors should review clinic policies and practice and recommend changes as indicated.[77]

Medical directors also should institute policies regarding hand hygiene, environmental and dialysis equipment disinfection, and other processes of care that will allow the clinic to optimize care for their dialysis patients. Some of the infection control issues for which the medical director has ultimate leadership responsibility are summarized in Table 4 and Figure 2.

More importantly, medical directors serve as role models both to clinic staff and to other health care practitioners. Medical directors must set the policy standards and lead by example. They are under the scrutiny of patients, colleagues, and dialysis staff who see whether they wash their hands, wear gloves, and disinfect their stethoscopes between patients.

Medical directors should send a consistent message to the entire dialysis community, including other practitioners, that these elements are not trivial. When other nephrologists or health care practitioners do not follow policies, it is the medical director who must let them know, firmly but respectfully, that this behavior will not be tolerated in the dialysis clinic. Medical directors are entrusted with the lives of all the patients who receive dialysis in their clinics and must protect all of them at all times.

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