

DIALYSIS CATHETER INFECTION

Lucas do Nascimento Freire

Resident Doctor in Internal Medicine at
Hospital Universitário de Vassouras
Vassouras, Rio de Janeiro, Brazil
<http://lattes.cnpq.br/3870344853129443>

Aline Campos dos Santos Silva

Resident Doctor in Internal Medicine at
Hospital Universitário de Vassouras
<http://lattes.cnpq.br/8372426156642893>

Caroline Azevedo Brim

Resident Doctor in Internal Medicine at
Hospital Universitário de Vassouras
Vassouras, Rio de Janeiro, Brazil
<http://lattes.cnpq.br/5399578360753073>

Natshara Carolina Rodrigues Ferreira

Doctor and Specialist in Internal Medicine at
the
Vassouras, Rio de Janeiro, Brazil
<http://lattes.cnpq.br/0221258430586521>

Francielly Hungria de Paula Alves Fontoura

Resident Doctor in General Surgery at the
Hospital Universitário de Vassouras (HUV)
Vassouras, Rio de Janeiro, Brazil
<http://lattes.cnpq.br/7744278693175534>

Leticia do Nascimento Freire

Medical Student at the Universidade de
Vassouras and Nurse at the Universidade de
Vassouras
Vassouras, Rio de Janeiro, Brazil
<https://lattes.cnpq.br/1980098234467328>

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Patrick de Abreu Cunha Lopes

Student of the Medicine course at the Universidade de Vassouras and Scientific Initiation Student at PIBIC at the Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ).
Rio de Janeiro, Brazil
<http://lattes.cnpq.br/9719714143799267>

Fernanda da Costa Barros Teixeira Carvalhedo

Doctor, Specialist in Family and Community Medicine and Specialist in Internal Medicine at the Hospital Universitário de Vassouras. Professor and Master's student at the Universidade de Vassouras. Postgraduate student in Palliative Care at PUC Minas. Vassouras, Rio de Janeiro, Brazil
<http://lattes.cnpq.br/2473578040190006>

Abstract: Annually, the number of patients on hemodialysis in Brazil and in the world grows, mainly with the increasing number of cases of Arterial Hypertension, Diabetes and Obesity, resulting from the demographic transition. Avoiding the catheter is the obvious best strategy to reduce episodes of bloodstream infection. Interventions such as early referral of patients to nephrologists, multidisciplinary teams, and vascular access coordinators who provide patient education; implantation of arteriovenous grafts for early cannulation for hemodialysis; and urgent-onset peritoneal dialysis have been shown to be effective in decreasing catheter use. New interventions for prophylaxis of catheter-associated bloodstream infection include the following: (1) clear chlorhexidine-impregnated exit site dressing; (2) a chlorhexidine coated stem hub device; and (3) an antimicrobial, preferably antibiotic-free, lock. There may be an important and underused role for *S. aureus* nasal decolonization protocols with mupirocin for hemodialysis patients. A combination of these interventions may be ideal. Finally, identifying barriers to safe practices in the hemodialysis setting, using human factors systems engineering, will undoubtedly prove invaluable in reducing infections in the future.
Keywords: Hemodialysis, Dialysis Catheter, Microbiological Profile, Infection

INTRODUCTION

Among the modalities of Renal Replacement Therapy (RRT), Hemodialysis (HD) is one of the main forms. It is widely used in both chronic kidney disease (CKD) and Acute Kidney Injury (AKI) settings. To make this feasible, it is necessary to ensure a large-caliber vascular access route, the main ones being the Double Lumen, Triple Lumen Catheter (which can be temporary or long-term) or through arteriovenous grafts (VAS) and arteriovenous fistulas (AVF), the latter

being the most indicated in chronic renal patients¹.

Patients on hemodialysis in a central venous catheter with vascular access are at risk of infections. Catheter-related bloodstream infection is one of the most serious catheter complications in hemodialysis patients. Its clinical and microbiological diagnosis is challenging. The implementation of empirical antibiotic therapy is based on old recommendations that propose the combination of a molecule targeted at methicillin-resistant *Staphylococcus aureus* and an active beta-lactamine in *P. aeruginosa*, and also adapting this probabilistic treatment by performing a microbiological record at a local scale, which rarely it is made.

According to the 2019 Brazilian Census of Nephrology, there are 139,691 patients on hemodialysis in Brazil, and it is estimated that the number of patients will continue to increase in the coming years, given the increase in cases of diabetes, obesity and arterial hypertension in recent years, resulting from the phenomenon of demographic transition. Such diseases are the main causes of chronic kidney disease in the world.²

Due to the presence of continuous vascular access, patients undergoing hemodialysis, especially those using a venous catheter as a route, are more susceptible to infectious complications, especially from microorganisms originating from the skin. In rarer cases, the infection may also be related to the use of equipment and solutions. In a study carried out in the United States, carried out with 500 patients on hemodialysis using the venous catheter as a route, the cumulative risk of developing such a complication reached 50% in 6 months.³

Hemodialysis catheter-related bloodstream infection presents an important risk factor related to morbidity and mortality in these patients. Studies show that sepsis is the

second leading cause of death in patients with end-stage renal disease, the main one being cardiovascular diseases. Patients on hemodialysis also have a risk of hospitalization twice as high as patients who do not undergo HD, and it is estimated that about 20% of such hospitalizations are related to vascular access complications.^{2,3}

Arteriovenous fistula is less related to complications and is indicated in all patients on chronic hemodialysis. The awareness of the use of AVF as the preferred access route came mainly with the launch of the Fistula First Breakthrough Initiative (FFBI), by the National Kidney Foundation, in 2003, demonstrating the lowest rate of complications and mortality in these patients. In 2006, the FFBI was already present in the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, but several questions were raised due to the AVF's lifespan, the difficulty of maintaining access, the chance of early loss and other factors. In 2019, the KDOQI suggested starting, together with the admission of the patient who went on hemodialysis, a "Life Plan for CKD", carrying out an individualized planning, updated annually and documented in the medical record from the first access to the planning of next routes if the route primary device fails or needs replacement.⁴

However, in the Brazilian reality, there is difficulty in making fistulas. According to the 2019 Brazilian Census of Nephrology, there is increasing use of long-term catheter and arteriovenous prostheses instead of making fistulas. There is no data in the Census on the percentage of fistula creation, but they deduce that there has not been an evident growth, based on the stability of the proportion of patients with the use of temporary catheter.²

Such patients usually present symptoms related mainly to the presence of bacteremia, the main ones being fever, chills, tachycardia. On physical examination, there may be

hyperemia or hardening <2cm of the catheter exit hole, which may be associated with the aforementioned symptoms of bacteremia. In some cases, the evolution to a septic condition and even septic shock and death.^{4,5}

Among the main germs involved, *S. aureus* and *S. epidermidis* stand out, responsible for about 70% to 90% of catheter infections. The accesses in the upper extremities (Jugular or Subclavian Vein) are more related to the incidence of Gram-positive germs, while those in the lower extremities (Femoral Vein) are more related to Gram-Negatives.⁵

Current guidelines recommend early initiation of antibiotic therapy after collection of blood cultures (2 sets – 01 peripheral and 01 from the catheter if possible), and it is essential to collect this test before starting antibiotics. Most antibiotics, in the scenario of patients with CKD, can be administered after the dialysis session, and may not generate the need for hospitalization of these patients. ^{4,6}

Antibiotic therapy must be broad-spectrum, covering gram-positives and negatives, such as Vancomycin and Piperacillin + Tazobactam, and subsequently adjusted according to the sensitivity profile of the microorganism isolated in the culture. At the Hospital Universitário de Vassouras, the patient who develops such a complication usually undergoes the initial antibiotic therapy regimen with Vancomycin + Gentamicin, in regimens 48 hours after the hemodialysis sessions, providing greater dosage comfort and can be performed outside the hospitalization regime.^{4,5}

Considering the high prevalence of this complication in hemodialysis patients and the risk of progression to severity, the present study will aim to propose an initial empirical antibiotic therapy regimen.

Dialysis catheter-related bloodstream infection is a highly prevalent problem in patients on hemodialysis who use a catheter

as a route. Due to the high rate of evolution to mortality, early antibiotic therapy that provides coverage for the main related germs becomes essential.

MATERIAL AND METHODS

A review of the current literature was carried out. The following databases were consulted: MEDLINE (PubMed); base; Web of Science, Google Scholar. Conference abstracts/articles have been deleted from Embase. No other limits have been applied. All retrieved records were organized using the Endnote citation management software version 20. For the removal of duplicates, a review software and literature review citation screening software were used.

The search strategy was designed to capture articles on dialysis catheter infection. The searches were complemented by manual searching and retrieval of any additional articles that met the eligibility criteria that were cited in our reference lists.

RESULTS

INTERVENTIONS FOR CATHETER REDUCTION

There are several interventions that can decrease the incidence and prevalence of catheters in hemodialysis patients. There is evidence that early referral of patients to nephrologists, multidisciplinary teams and vascular access coordinators who guide patients; implantation of early grafts; and urgent-onset peritoneal dialysis may play a role in decreasing catheter use.

The early referral of patients with CKD to the nephrologist results in discussions about choosing the dialysis modality and, from there, leads to timely referral for placement of permanent vascular access, to a transplant center for enlistment or planning for peritoneal catheter insertion. In a small study of 135 patients, early referral (>4 months before dialysis initiation) to a nephrologist was associated with an increased likelihood of starting hemodialysis using a permanent

vascular access (48% early referral versus 4% late referral) 7. Similarly, in a large cohort study of 2398 incident hemodialysis patients, late referral to a nephrologist (<90 days from hemodialysis initiation) was associated with a 42% higher risk of initiating hemodialysis with a catheter in compared to those seen by a nephrologist earlier in the course of his kidney disease 8.

There is modest evidence that when multidisciplinary teams (made up of doctors, nurses, social workers and nutritionists) provide education to patients, whether in pre-hemodialysis or at the beginning of hemodialysis, the prevalence of catheters decreases 9,10. In the Treatment Options Program, implemented by a large dialysis organization, patients were instructed on the choice of modality and pre-hemodialysis vascular access. Hemodialysis patients enrolled in this program (n=2800) were less likely to initiate hemodialysis with a catheter compared with matched control patients (n=2800) (63.2% versus 75.8%; $P < 0.001$) 9. Similar findings were reported in the Treatment-Centered Patient Incident Management Actions program, also implemented by a large dialysis organization. When patients received education at the start of hemodialysis using a multidisciplinary team, the proportion of patients with arteriovenous fistula or graft versus catheter was significantly higher for patients in the intervention group at 6 months 10. Contrary to the positive results of these studies, a quality improvement initiative using a multidisciplinary vascular access team to educate patients starting hemodialysis in Canadian units did not show a decrease in catheter-free arteriovenous fistula use at 1 year 11.

The use of a vascular access coordinator can significantly shorten the initiation of hemodialysis with a catheter. A quality improvement project in Australia reported

that pre-hemodialysis patient education and coordination by a vascular access coordinator resulted in a significant decrease in catheter-initiated hemodialysis (from 39% to 25%) ($P = 0.007$) and a reduction in the total number of catheter days (2833 versus 4685 days) 12. Similar findings were reported in a program in the United States, where implementation of a comprehensive access program led by a vascular access coordinator resulted in a significant reduction in prevalent catheter use >90 days after hemodialysis initiation (from 11% to 6%; $P < 0.001$) 12. The use of a vascular access coordinator in the hemodialysis unit can also improve outcomes after an episode of catheter-associated bloodstream infection. A quality improvement project in the Bronx and Connecticut (n = 223 episodes of catheter-associated bacteremia) reported a significant reduction in recurrent bacteremia at 3 months (from 18% to 6%; $P < 0.02$) and death from sepsis (6% versus 0%; $P = 0.05$) in hemodialysis units with a vascular access coordinator 13.

In patients in need of urgent-onset dialysis, creation of an early-cannulation arteriovenous graft and placement of a peritoneal dialysis catheter for immediate use are additional options available to reduce catheters. In a randomized controlled trial, patients in need of urgent vascular access for hemodialysis were randomized to receive an early cannulated arteriovenous graft (n = 60) or a tunneled catheter (n = 61) 14. At 6-month follow-up, infections blood flow developed more frequently in the catheter group (16.4%) compared to the arteriovenous graft group (3.3%; $P = 0.02$). In a retrospective study from China, 96 patients who started dialysis with a peritoneal dialysis catheter were compared with 82 patients who started with a hemodialysis catheter 15. A significantly higher incidence of bloodstream infection occurred in the hemodialysis catheter group

at 30 days (catheter 11% hemodialysis versus 0 peritoneal catheter; $P = 0.003$). Although both studies were single-center studies with a small number of patients, they suggest that avoiding catheters may reduce bloodstream infections in patients with ESRD on dialysis.

CHALLENGES FOR ADHERENCE TO THE MAIN INTERVENTIONS

The rate of catheter use is high among new hemodialysis initiations. Newly started patients are typically placed on late dialysis shifts available at the three medical centers where the authors work. To the extent that this is true across the United States, the result would be a disproportionately high number of catheter-dependent patients on late shifts. Furthermore, in about half of the states, only nurses, but not patient care technicians, are allowed to connect and disconnect catheter patients 26. The high burden of catheter-dependent patients on these late shifts is compounded by the restriction of catheter care. The catheter to nurses and represents a huge burden for the nursing team. It is not uncommon for a nurse to be responsible for five or more catheter-dependent patients. A high patient-nurse ratio on dialysis has been associated with more frequent access infections 27.

A recent observational study reported the counterintuitive finding that the frequency of catheter-associated bloodstream infection in a given hemodialysis unit was inversely related to the proportion of patients who used a catheter in that unit 28. In other words, the higher the proportion of catheter-dependent patients, the lower the frequency of catheter-associated bloodstream infection. A possible explanation for this surprising finding may be that in hemodialysis units where a higher proportion (>20%) of patients use a catheter, there may be a higher percentage of healthier patients, therefore less prone to infections.

It can be speculated that these healthier patients may be suitable for an arteriovenous fistula or graft, and may not have a catheter if they were on dialysis in units with lower catheter percentages (<10%). Catheter-dependent patients in facilities with lower catheter percentages (<10%) may have more comorbidities and be unsuitable for other forms of vascular access and therefore be at higher risk of infection 29,30. An alternative explanation is that, in units with a high percentage of catheters, experienced staff, who frequently perform catheter care, may better adhere to key infection prevention techniques. Furthermore, in an effort to reduce catheter-associated bloodstream infection, new interventions have been developed to reduce bacterial colonization at the catheter exit site and lumen. These measures are described in the following sections.

INTERVENTIONS DIRECTED AT THE CATHETER EXIT SITE: OINTMENTS

Topical antimicrobial ointments that are applied to the catheter exit site are recommended at the time of catheter insertion and at each hemodialysis session 31,32. The Centers for Disease Control and Prevention recommends the use of triple polysporine antibiotic ointment (bacitracin/gramicidin/polymyxin B) or povidone-iodine ointment, which has been shown to be associated with a 75% to 93% reduction in bloodstream infection associated with catheter 33,34,35. Polysporine ointment was also associated with a significant reduction in mortality, and long-term follow-up for 6 years was not associated with a change in microbiological isolates over time 36,37. Unfortunately, gramicidin is not available in the United States, although polysporin ointments containing bacitracin/zinc/polymyxin B are in clinical use but have not been rigorously studied for catheter-

associated bloodstream infection prophylaxis. Mupirocin was also associated with an 85% reduction in the rate of bloodstream infection; however, there are reports of the development of resistant microbes with the routine long-term use of mupirocin 38, 39 . Medicinal honey was shown to be similar in efficacy to mupirocin in a small study 40. The advantage of medicinal honey is that it has a low probability of selection for resistant strains and is effective against antibiotic-resistant microorganisms. Well-designed and adequately powered studies are needed before medicinal honey can be recommended for prophylaxis of catheter-associated bloodstream infection. When using any ointment, verification of catheter compatibility is mandatory, and a chart is available on the Centers for Disease Control and Prevention website.

ANTIMICROBIAL DRESSINGS

In the updated 2017 guidelines from the Centers for Disease Control and Prevention, chlorhexidine-impregnated sponge dressings are recognized as an alternative to ointments for prophylactic use in short-term non-tunneled catheters 41. These recommendations were based on studies performed in hospitalized patients, who are not on hemodialysis. Chlorhexidine is a non-antibiotic antimicrobial agent; therefore, the risk of selecting resistant organisms is minimal. Chlorhexidine-impregnated dressings were associated with a 70% reduction in bloodstream infection rates 42,43. Data from studies performed on catheters used for hemodialysis are conflicting 34,35. A study comparing a chlorhexidine-impregnated sponge dressing with a transparent dressing at the catheter exit site found no difference in bloodstream infection 46. In contrast, a recent quality improvement project reported a 50% reduction in bloodstream infection using clear chlorhexidine-impregnated dressings

(changed weekly) compared to the control group using dry gauze dressings with antibiotic ointment applied to the site. catheter exit (changed three times weekly) 37. The weekly cost per patient of the chlorhexidine dressing regimen was double that of the standard dressing, which may be offset by the overall cost savings of a reduction in bloodstream infections. Unfortunately, while a reduction in bloodstream infection saves on overall health care costs, the savings are not realized by the dialysis provider.

ANTIMICROBIAL BLOCKING SOLUTIONS

Antimicrobial blocking solutions are highly concentrated antiseptic agents that are instilled into the catheter when the catheter is not in use, thus targeting the intraluminal entry route 38,39. An antiseptic agent is required to prevent colonization and biofilm formation, thereby reducing catheter-associated bloodstream infections. Antiseptic catheter lock agents can consist of an antibiotic or non-antibiotic solution, and both types of catheter locks have been shown to effectively reduce the incidence of catheter-associated bloodstream infections in clinical trials. Routine use of an antibiotic-containing catheter lock to prevent bloodstream infections in hemodialysis may result in the emergence of resistant organisms and has led to the development of safer non-antibiotic locks. The second component added to most antimicrobial locks is an anticoagulant, used to prevent catheter dysfunction. Heparin promotes biofilm formation, while citrate at concentrations $\geq 0.2\%$ prevents biofilm formation, making citrate advantageous 40.

ANTIBIOTIC BLOCKADES

A variety of antibiotic-containing blocking agents have been studied for the prevention of catheter-associated bloodstream infection

in the hemodialysis setting 41,42. Current recommendations from the Centers for Disease Control and Prevention are for limited use of prophylactic antimicrobial block solutions in catheter-dependent hemodialysis patients who have a history of multiple bloodstream infections. Prophylactic use of combined antibiotic-anticoagulant catheter lock solutions is associated with a significant reduction in bloodstream infections (50% to 100% reduction range). The antibiotics used as catheter lock solution in these trials were gentamicin, tobramycin, minocycline, cefotaxime, vancomycin, cefazolin and trimethoprim, with gentamicin being the most studied. Early trials, which used a relatively high dose of gentamicin (4-27 mg/ml), reported that gentamicin alone was as effective as other antibiotic combinations and had a broad spectrum of activity against Gram-positives (including *Staphylococcus aureus*). and Gram-negative bacteria at drug levels achieved in the catheter lumen. The emergence of gentamicin-resistant strains of *Enterococcus* and *Staphylococcus* have been associated with severe episodes of bloodstream infection, and one death has been reported using a gentamicin blockade (4 mg/ml) 43. In more recent studies, using a lower concentration of gentamicin blockade (range 0.32-1.7 mg/ml), no resistance to gentamicin was observed during long follow-up periods, and in one study the rate of resistance decreased, although an explanation for this finding is unclear. . In one study, a low dose of gentamicin (0.32 mg/ml)-citrate (4%) was associated with a significant reduction in bloodstream infections, infection-related hospitalizations, and patient mortality 56. If a block is used of gentamicin, a low-dose formulation (0.32 mg/ml) is recommended. In a recent retrospective cost-effectiveness analysis from New Zealand, routine use of a gentamicin-

containing catheter block was associated with significantly lower rates of catheter-associated bloodstream infection, which translated into significant cost savings 57 Inpatient costs associated with treating catheter-associated bloodstream infection were NZ\$27,792 per 1,000 catheter-days (heparin-only blockade) versus NZ\$10,608 (gentamicin-heparin) and NZ\$1,898 (gentamicin-citrate). Concerns about antibiotic resistance associated with the prophylactic use of antibiotic catheter-blocking solutions have precluded their adoption by consensus guidelines.

INTERVENTIONS USING DECOLONIZATION PROTOCOLS S. AUREUS: INTRANASAL MUPIROCI OINTMENT

Nasal transport of *S. aureus* is associated with an increased risk of hemodialysis catheter-associated bloodstream infections. Decolonization protocols performed in the hemodialysis environment are described in Table 4(96-100). _ Intranasal mupirocin prophylaxis was associated with 94%–100% efficacy for nasal decolonization and a significant reduction in the incidence of *S. aureus* catheter-associated bloodstream infections. *S. aureus* decolonization protocols are effective and cost-effective (101). Bloom et al. (101) performed a decision analysis evaluating the clinical outcomes and cost-effectiveness of three possible management strategies in hemodialysis patients (1): screening for nasal carriers of *S. aureus* every 3 months and treating those with a positive test result. test with mupirocin; (2) treat all patients weekly with mupirocin; or (3) no prevention strategy, just treating the infection. Elimination of nasal transport of *S. aureus* with mupirocin markedly reduced the number of infections (approximately 50% reduction) and reduced healthcare costs related to treating infections when

they occur. The potential annual savings for Medicare (in 1996 US dollars) are projected to be \$784,000 to \$1,117,000 per 1,000 hemodialysis patients, depending on which prevention protocol was used. Mupirocin has not been widely adopted in the hemodialysis setting due to emerging resistance concerns, although reports of mupirocin resistance have been widely reported in hospitalized patients and long-term mupirocin use. The use of *S. aureus* decolonization protocols in catheter-dependent hemodialysis patients must be reviewed.

DISCUSSION

The population of patients treated by catheter hemodialysis is fragile, with a high risk of infection. Hemodialysis catheter-related bacteremia is one of the most serious complications, the incidence of which is increasing every year, in connection with the increased use of catheters as vascular access. However, clinical and microbiological diagnosis remains difficult. The implementation of probabilistic antibiotic therapy is based on old recommendations that recommend combining a molecule targeted to methicillin-resistant *Staphylococcus aureus*, as well as a beta-lactam active in *P. aeruginosa*, but also adapting this probabilistic treatment by performing a microbiological collection at the local level, the that is rarely done. In our hemodialysis center at the University Hospital of Bordeaux, an analysis of the bacteriological distribution of bacteremia associated with the hemodialysis catheter in the period 2018-2020 allowed us to propose, in agreement with infectious disease specialists, an appropriate probabilistic antibiotic therapy protocol. This approach allowed us to observe a low incidence of methicillin-resistant staphylococci, a zero incidence of staphylococci after a delay in catheter placement of more than 6 months, no multi-resistant *Pseudomonas*, and a very

low percentage of cephalosporin-resistant enterobacteriaceae. Regular updating of the microbiological epidemiology of bacteremia linked to hemodialysis catheters, associated with a partnership with the infectious disease team in its hemodialysis center, allowing adaptation of probabilistic antibiotic therapy, seems to have good feasibility and, in the long term, to favor the preservation of the microbial ecology on an individual and collective scale for the population of patients treated by hemodialysis.

Patients on hemodialysis in a central venous catheter with vascular access are at risk of infections. Catheter-related bloodstream infection is one of the most serious catheter complications in hemodialysis patients. Its clinical and microbiological diagnosis is challenging. The implementation of empirical antibiotic therapy is based on old recommendations that propose the combination of a molecule targeted to methicillin-resistant *Staphylococcus aureus* and an active beta-lactamine in *P. aeruginosa*, and also adapting this probabilistic treatment by performing a microbiological record on a local scale, which is rarely done. In another study at the hemodialysis center at the University Hospital of Bordeaux, an analysis of the microorganisms causing all catheter-related bloodstream infections during the period 2018-2020 allowed us to propose, in agreement with infectious disease specialists, a protocol for adapted probabilistic antibiotic therapy. This approach allowed us to observe a low incidence of methicillin resistance of *Staphylococcus*. For catheters inserted more than 6 months ago, we did not observe multidrug-resistant *Staphylococcus* or *Pseudomonas* and only 2% of cephalosporin-resistant Enterobacteriaceae. Frequent updating of the microbiological epidemiology of catheter-related bloodstream infection, in partnership with the infectology team of

each hemodialysis center, allowing for an adaptation of probabilistic antibiotic therapy, seems to have good feasibility. This strategy may favor the preservation of microbial ecology on an individual and collective scale in patients on maintenance hemodialysis.

approval of the device by regulatory agencies. Finally, identifying barriers to safe practices in the hemodialysis setting, using human factors systems engineering, will undoubtedly prove invaluable in reducing infections in the future.

FINAL CONSIDERATIONS

To avoid the catheter is the obvious best strategy to reduce episodes of bloodstream infection. Interventions such as early referral of patients to nephrologists, multidisciplinary teams, and vascular access coordinators who provide patient education; implantation of arteriovenous grafts for early cannulation for hemodialysis; and urgent-onset peritoneal dialysis have been shown to be effective in decreasing catheter use. However, in those patients where the use of a catheter is unavoidable, implementing a multi-directed approach to preventing infections is imperative. Active patient involvement and staff education on proper catheter care and better adherence to core interventions recommended by the Centers for Disease Control and Prevention is essential. The development of electronic checklists/audit tools for catheter care can also improve staff antiseptic technique and patient education in the hemodialysis unit. New interventions for prophylaxis of catheter-associated bloodstream infection include the following: (1) clear chlorhexidine-impregnated exit site dressing; (2) a chlorhexidine coated stem hub device; and (3) an antimicrobial, preferably antibiotic-free, lock. There may be an important and underused role for *S. aureus* nasal decolonization protocols with mupirocin for hemodialysis patients. A combination of these interventions may be ideal. Additional factors to consider when selecting a prophylactic strategy include effectiveness, cost, potential for adverse effects such as catheter dysfunction, and local availability/

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