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Haemodialysis catheter-related bloodstream infections: current treatment options and strategies for prevention

Anil K. Saxena, Bodh R. Panhotra

Division of Nephrology, King Faizal University, King Fahad Hospital, Hofuf, Al-Hasa, Saudi Arabia

Summary

Regardless of the repeated reservations raised by countless researchers with reference to the use of catheters as vascular access for haemodialysis (HD), central venous catheters (CVCs) remain irreplaceable tools of the modern dialysis delivery system as a reliable option for the clinical situations requiring instant access to circulation, for various reasons. Patients on long-term haemodialysis are therefore at a significantly high risk for catheter-related bloodstream infections (CRBSI) and ensuing serious complications. Although early systemic antibiotic treatment should include the coverage for *Staphylococcus aureus*, the pathogen with most devastating consequences including bacterial endocarditis; optimal treatment of CRBSI while preserving the catheter site, remains contentious. Nonetheless, catheter exchange over a guide wire and antimicrobial-anticoagulant "locks" have shown promising results as novel access salvage techniques. Despite the fact that a number of novel potentially useful strategies for the prevention of CRBSI are in the pipeline; equally essential however, remains the role of rigorous implementation of standard infection control measures for hygiene and aseptic handling of CVCs in long-term HD patients.

The policy of increasing the AVF (arteriovenous fistula) prevalence beyond 50% while minimising the use of CVCs, dependent largely upon the timely referrals and prudently implemented pre-ESRD program – ought to have a positive impact on long-term HD outcomes.

Key words: haemodialysis; CRBSI; epidemiology; treatment options; preventive strategies

Introduction

Optimal survival and the quality of life of patients with end stage renal disease (ESRD) on long-term haemodialysis (HD) is largely dependent upon the adequacy of dialysis through an appropriately placed and properly functioning permanent vascular access with minimal mechanical complications and infection rates. Vascular access-related blood-stream infections (VRBSI) and related complications requiring hospitalisation, account for nearly one third of the cost of ESRD management with reported mortality rates of 12–25.9% [1–4].

The majority of vascular access-related infections are catheter-related, suggestive of our continued dependence on central venous catheters (CVCs) to commence and carry out HD in routine and emergency situations. There are several reasons for this including the changing demographic profile of ESRD with more elderly and diabetic patients with poor vasculature being accepted onto HD-programs, medical emergencies arising as a result of variable course of chronic renal disease, and "late referrals".

Incidence and cost of treatment of catheter-related blood-stream infections (CRBSI)

Sizeable surveillance data suggest that the use of CVCs is associated with much higher blood stream infections (BSI) rates and average cost of BSI-related hospitalisation compared to arteriovenous grafts (AVG) and arteriovenous fistula (AVF) [2, 3].

The mean incidence of CRBSI for "temporary"-untunnelled catheters (UTCs) have been reported to be – 5.0 episodes/1000 catheter-days (range, 3.8–6.5/1000 catheter-days) and 3.5/1000 catheter-days (range, 1.6–5.5/1000 catheter-days) for "permanent"-tunnelled cuffed catheters (TCCs)

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Table 1

Type of vascular access and infection rates [5–8].

Vascular access type	infection rate
[A] Untunnelled central venous catheters	5.0 episodes /1000 catheter-days (range 3.8–6.5 episodes/1000 catheter-days)
Femoral	7.6 episodes/ 1000 catheter-days (>10% after one week)
Internal jugular	5.6 episodes/ 1000 catheter-days (>10% after 2–3 weeks)
Subclavian	2.7 episodes/1000 catheter-days (>10% after 4 weeks)
[B] Tunnelled cuffed central venous catheters	3.5 episodes/1000 catheter-days (range 1.6–5.5 episodes/1000 catheter-days)
[C] polytetrafluoroethylene arteriovenous graft	0.2 episodes/patient-year
[D] Primary arteriovenous fistula	0.05 episodes/patient-year

[5–8]. Among UTCs, femoral catheters (FC) have the highest infection rates (7.6 episodes/1000 catheter-days), compared with internal jugular (IJC, 5.6 episodes/1000 catheter-days) and subclavian catheters (SC, 2.7 episodes/1000 catheter-days) [5–8] (table 1).

The average cost of standard treatment of an episode of BSI has been reported to be in the range of US $ 3,700 to US $ 29,000 per survivor besides the cost of an additional mean hospital stay of 6.5 days [2, 3] Although the reported risk of BSI is higher for UTCs compared with TCCs, the management cost of TCC-related BSI is significantly higher than that of UTCs since the removal of TCC demands surgical skills (table 2).

Table 2

Type of vascular access and BSI-related cost of hospitalisation/admission [2, 3]. Cost per admission, in US $).

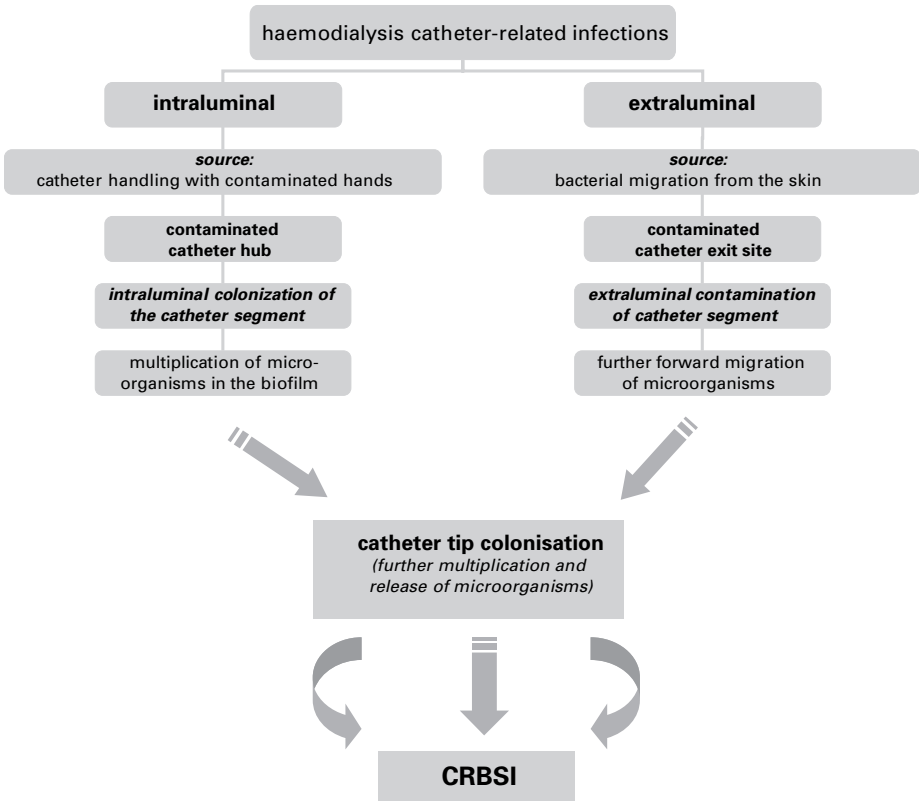
Untunnelled central venous catheters – UTC	16,896
Tunnelled Cuffed central venous catheters –TCC	25,683
Polytetrafluoroethylene arteriovenous graft	9,016
Primary arteriovenous fistula	5,650

Pathogenesis

CVCs get colonised either through extraluminal (skin-related) or intraluminal (hub or perfusate related) routes [9, 10]. In the first case, organisms migrate from the skin insertion site along the catheter up to the catheter tip, finally reaching the blood stream. In the second case the catheter hubs are contaminated during catheter manipulation by dialysis personnel. The colonised bacteria then spread through the lumen of the catheter. For long-term catheters particularly those that are cuffed and/or surgically planted, the hub is a major source of colonisation of catheters [11] (figure 1).

Figure 1

Pathogenesis of haemodialysis catheter-related bloodstream infections.
CDC definitions of catheter-related infections [11]:
Catheter exit-site infection: a positive (semi-) quantitative culture of the drainage material in the presence of redness, crusting and exudates at the catheter-exit site.
Catheter colonisation:
<10 CFUs (colony forming units) on quantitative cultures (vortex method),
<100 CFUs on quantitative cultures (Brun-Buisson method) or
<15 CFUs on semi-quantitative cultures (roll-plate technique) in the absence of clinical signs of infection at the catheter exit site.
Catheter-related bloodstream infection (CRBSI): the isolation of same organism (ie, identical species, antibiogram) from a quantitative culture of the distal segment of catheter and from the blood of a patient with clinical symptoms of sepsis and no other apparent source of infection.



Intravascular catheters become rapidly coated with some serum constituents such as fibrinogen, fibronectin and laminins that facilitate the attachment of Staphylococci to foreign material through microbial surface components recognising adhesive matrix molecules (MSCRAMM) mediated mechanisms [12, 13]. Additionally, *S. aureus* elaborates glycocalices which promote the bacterial colonisation and spread of infection even further [14].

ESRD patients are known to suffer from impaired immune defence mechanisms, attributable to the larger proportions of elderly polymorbid patients with conditions such as diabetes mellitus and malignancies in addition to malnutrition particularly related to uraemia and HD treatment [15–18]. Uraemia and inflammation induced by HD filters can cause oxidative stress and activation, apoptosis and reduced numbers of T-lymphocytes leading to defects in cell-mediated immunity [16–19]. In addition, MHC class II analogue protein (Map) expressed by *S. aureus* also attenuates host's cell-mediated immunity by reducing T-cell proliferative response to gram positive bacterial infections [19, 20].

Predisposing factors

The elderly, females, blacks, diabetics and obese patients with ESRD are less likely to have safe vascular access – native AVF – since o nly 23% of HD patients in the United States were dialysed through AVF in 1997 [21–23]. Elderly patients, 46% of whom at the beginning of HD have at least two comorbid conditions correlated with poor vasculature and/or limited life expectancy – are often considered unsuitable for PTFE graft/native AVF placement [23]. They are most likely to be left with CVCs as a sole option for survival on HD placing them at an added risk of development of CRBSI and ensuing serious complications [23] (table 3).

Table 3

Predisposing factors for HD catheter-related blood stream infections [3, 5, 15–19, 21–25, 29, 31, 46, 72].

Elderly
Female gender
Obesity
Blacks
Diabetes mellitus
Nasal carriage of *S. aureus*
Dialysis through CVCs
Past history of BSI
Hypoalbuminaemia (malnutrition)
Immunocompromised host
Oxidative stress (CVCs, PTFE, dialyser membrane/ filters)
Haemodialysis nurse-understaffing
"Late" referrals

Patients on long-term HD particularly the elderly and diabetics are at increased risk of *S. aureus* nasal carriage; the literature reports up to 60% carriage rate in these patients [24–29]. Since *S. aureus* disseminates from the nasal reservoir to hands and skin infecting vascular access sites – these nasal carriers are at a higher risk of developing vascular access-related infections [27–29]. Von Eiff et al. reported that *S. aureus* blood isolates from HD patients with BSI were clonally identical to those obtained from their nasal specimens, in 82.2% of cases, suggesting that the organisms in the blood stream originated from the patient's own nasal flora [27].

Moreover, in those patients who in the course of their progressive renal failure, are referred "late" to the nephrologists – the use of CVCs with their inherent infective complications becomes inevitable [30]. The high risk HD environment for transmission of nosocomial infections presents a pressing demand for extra skilful nursing care besides upholding sound levels of hygiene and cleanliness. Understaffing plays a key role in the development of CRBSI; the risk of infection has been reported to rise significantly, with nursing staff reduction below a critical level [31].

Major complications

Metastatic complications occur in a large proportion of patients with CRBSI; these include endocarditis, osteomyelitis, septic arthritis, septic pulmonary emboli, and spinal epidural abscesses [32, 33] (table 4).

S. aureus has a unique predilection to cause fatal infections among those who have intravascular prosthetic devices such as CVCs [12]. The tip of the indwelling catheter is positioned in the atrium, close to the cardiac valves. Therefore, these access systems carry a special risk of infective endocarditis (IE) [34]. In Marr's original description, 22% (9/41) of patients developed complications such as osteomyelitis, septic arthritis, IE and death [35]. In another description by Marr et al. 65 episodes of *S. aureus* bacteraemia (1.2 episodes/ 100 patient-months) were identified among HD patients, 44% of the patients developed complications including IE among 12% of cases. Sixty seven percent of the patients in this study group were dialysed via CVCs indicating that catheters were the greatest risk factor for the development of infective endocarditis in this cohort [36].

In a recent retrospective cohort study from

Table 4

Incidence of complications of HD catheter-related blood stream infections [1, 4–8, 10, 15, 22, 28, 30, 32–39, 41, 71, 72].

Sepsis syndrome	6.9–12%
Endocarditis	5.8–9.8%
Osteomyelitis	2.3%
Septic arthritis	2.3%
Septic pulmonary emboli	not available
Spinal epidural abscesses	1.2%
Death	12–25.9%

Taiwan [37], undertaken to determine IE and the mortality risk factors among HD patients (n = 288), the prevalence of IE of 6.9%, (20/288) was reported. The most common pathogen was *S. aureus* (12/20, 60.0%). The overall mortality in HD patients with IE was 60.0%, while in patients with MRSA associated endocarditis, it was 100%.

Early reports suggesting that infective endocarditis was not so frequent – may have been underreporting the incidence since transthoracic echo (TTE) is relatively less sensitive compared with transoesophageal echocardiography (TEE). The evidence of infective endocarditis was detected using TEE in 19% of patients with negative TTE and 21% in patients with indeterminate TTE findings [38]. Unexplained infectious problems in patients with these access systems should always prompt a careful search for access infection and endocarditis [37].

Spectrum of CRBSI-associated bacterial flora

The rate of complications with Gram positive bacteraemia is nearly twofold compared with those with Gram negative bacteraemia; *S. aureus* had been associated with most devastating metastatic complications among HD patients owing to its predilection to adhere to heart valves and bone [36]. Specific microbial components adhesins mediate adherence of the organism to the host tissues by participating in remarkably sophisticated interactions with host molecules [12]. A class of cell surface adhesins – MSCRAMMs specifically interacts with extracellular matrix components and plays an important role in host tissue colonisation, invasion, and as a key factor for *S. aureus* virulence [13].

Data from Duke's medical centre, USA showed that over 60% of vascular access-related infections were Gram positive cocci yet Gram negative bacilli made up significant proportion (24%), as well [36]. In another study 52% of vascular access-related infections were caused by Gram positive cocci, 26.7% by Gram negative bacilli while approximately 20% were polymicrobial [8] (table 5). However, HD cohort at our centre revealed relative predominance of Gram negative bacilli (54.0%) as a group, over *S. aureus* (30.4%) among patients with VRBSI [39] (figure 2).

Table 5

Bacterial flora frequently associated with HD catheter-related blood stream infections* [5, 7, 8, 15, 28, 34–36, 39].

Gram positive cocci	52–70%
S. aureus	21.9–60%
S. epidermidis	8.8–12.6%
MRSA**	6.0–8.0%
Enterococcus faecalis	2.4–8.0%
Gram negative bacilli	24–26.7%
Pseudomonas aeruginosa	2.3–15.2%
Escherichia coli	10.4%
Acenetobacter spp.	12.8%
Serratia marcesens	1.2–2.3 %
Klebsiella pneumoniae	6.4%
Enterobacter cloacae	8.8%
Polymicrobial	16.2–20%

* As data are obtained from different studies with multivariate analysis for each of these factors; the sum of percentages would not add up to 100%.

** MRSA: Methicillin-resistant *Staphylococcus aureus*

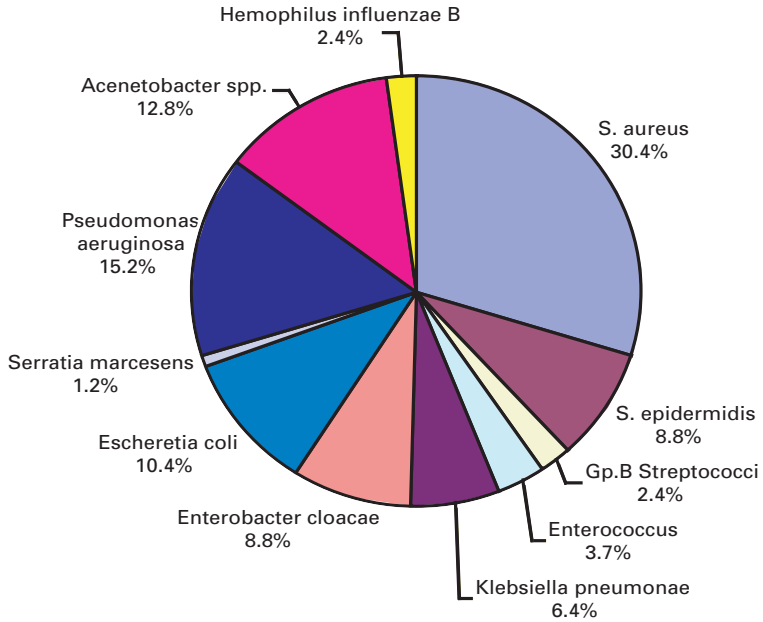


Figure 2
Prevalent bacterial flora associated with vascular access-related bloodstream infections in a large haemodialysis centre of Eastern Province of Saudi Arabia.

Treatment options

The optimal management of infected HD catheters continues to be controversial. The reluctance shown by the nephrologists and vascular surgeons in removal of the infected catheters is basically for the reason that the majority of patients with tunnelled catheter have already exhausted other options for dialysis-access.

Removal of central venous catheters

However, based on National Kidney Foundation – Dialysis Outcomes Quality Initiative (NKF-DOQI) Clinical Practice Guidelines for vascular access – update, (2000) – removal of infected HD catheters is strongly recommended under clinical situations listed in table 6 [40].

Antibiotic access salvage and duration of antibiotic therapy

Marr et al. (1997) proposed antibiotic salvage of vascular catheters as an alternative to CVC removal in a preliminary trial. In their series of 38 patients in whom bacteraemia was medically treated while the catheter remained in place; approximately 32% of the catheters were successfully salvaged by using this approach [35]. In another series of 85 patients, vascular access salvage carried out at our tertiary care centre, empirical amikacin-vancomycin therapy was successful in 56.4% patients having VRBSI [39]. Systemic antibiotics therapy was continued post-HD for five successive dialysis sessions in patients with temporary vascular accesses (UTCs) and for 7–10 consecutive dialysis sessions in patients with permanent vascular accesses (TCCs, PTFE grafts and AVFs). A cure was defined as a 45 days symptom free interval after antibiotic therapy [41]. The higher success rate compared to that of Marr's et al. could be due to inclusion of AVF and PTFE grafts in our study; the success of the antibiotic therapy alone has been reported to be a much higher for AVFs and PTFE grafts, whereas the yield is rather low in case of infected CVCs [42, 43]. However, another group from the same institution reported a clustering of epidural abscesses that occurred in patients undergoing HD during the study period, suggesting that antibiotic treatment alone may not be effective in eradicating the infection and entirely risk free; generally, it cannot be considered as an alternative to catheter removal [33].

Thus, systemic antibiotics despite achieving adequate plasma therapeutic levels have low access salvage rates since antibiotics fail to diffuse in sufficient concentration inside the catheter lumen where the actual bacterial seeding occurs among bacteraemic patients [44].

Catheter exchange over guide wire

Exchange of the catheter over guide wire, during or after parenteral broad spectrum antibiotic treatment (which hopefully sterilises the access site), was thought to be a logical extension of antibiotic access salvage technique. Shaffer et al. [45] observed encouraging preliminary results with this approach in 10 patients; three patients needed a second exchange to eliminate the infection. Robinson et al. [32] reported similar findings from a series of 23 patients with bacteraemia which was treated with catheter exchange and three weeks of treatment with antibiotics. Catheter sites with tunnel infections were excluded. This procedure yielded eradication of the infection in 82% of access sites at 90-day follow-up.

Beathard [46] in his prospective observational study of two years demonstrated equal outcomes with guidewire exchange compared with delayed catheter placement. The author categorised HD patients (n = 114) with infected catheters into three groups-first, those with bacteraemia and minimal symptoms, second, those with tunnel or exit-site involvement and bacteraemia and, third, those with severe clinical symptoms. In the first group (n = 49), the catheters were exchanged over a wire, and antibiotic therapy was instituted for 3 weeks; the success rate was 88% at 45 days. The second group (n = 28), patients with tunnel or exit site involvement, was treated with catheter exchange, creation of a new tunnel, and antibiotics, with a 75% success rate. In the third group (n = 37), in whom the catheter was removed, antibiotic therapy was instituted awaiting clearance of bacteraemia, and then a new catheter was placed. The success rate was 86.5% at 45 days. Authors concluded that guidewire exchange of catheter had the advantage of removing the infected catheter and the adherent biofilm while preserving the vascular access sites. CRBSI was handled either by guidewire exchange with creation of new tunnel or catheter removal and delayed replacement.

Table 6

Suggested indications for HD catheter removal* [40].

Persistence of fever and positive blood cultures while being on appropriate antibiotics for 36–48 hours.
Recurrence of fever and bacteraemia despite adequate dosage and duration of systemic antibiotic administration.
Exit site infections extending to catheter tunnel with severe sepsis.
CRBSI associated with hypotension or signs of cerebral hypoperfusion.
Septic thrombosis of great veins as determined by a Doppler flow study.
Infective endocarditis and systemic septic embolisation.

* Based upon NKF-DOQI Clinical Practice Guidelines for vascular access-update, 2000, National Kidney Foundation, New York.

Tanriover et al. [47] in a more recent study, compared the two strategies (catheter removal with delayed replacement and catheter exchange over a guide wire with creation of new tunnel) in a total of 69 catheters and followed the infection-free survival of new catheter; patients in both the groups received three weeks of intravenous antibiotics. Although infection-free survival of new catheters was comparable, serious complications occurred in 19% of patients that included sepsis syndrome, endocarditis, septic arthritis, and septic emboli – in both the groups. Thus, despite promising results, the procedure remains controversial [48].

Severe catheter sepsis with systemic septic complications remains an indication for immediate catheter removal, whereas mildly symptomatic bacteraemia may be treated with catheter exchange and systemic antibiotics. Moreover, bacteraemia with tunnel tract involvement should also prompt catheter removal as it is less likely to respond to antibiotic therapy due to insufficient penetration of systemic antibiotics to the tunnel-site [40]. The NKF-DOQI Working Group, cautions that 3 weeks of systemic antibiotic therapy is needed to treat CRBSI and that a new permanent access should not be placed until cultures have been negative for at least 48 hours after cessation of antibiotic therapy [49].

Antimicrobial-anticoagulants lock technique

The antibiotic lock technique permits the *in situ* treatment of colonised CVCs by intraluminal sterilisation through instillation of antibiotic solution with twin aims of improving the rates of catheter salvage and reducing the risks of antibiotic side effects. This technique in combination with concurrent administration of systemic antibiotics brought about the eradication of CRBSI in up to 90% of patients receiving home parenteral nutrition without catheter removal [50]. In American Society of Nephrology (ASN) meeting (1997), based on their findings of a 4 year trial and relationship between infection and thromboses, Sodermann et al. [51], reported that, a gentamicin and Tricitrasol (trisodium citrate) mixture 'locked' into the HD catheter weekly was a superior approach to catheter salvage and virtually reduce the incidence of CRBSI to zero compared with the routine locking of heparin alone in the CVCs after each HD session. In a small observational trial, continuous antibiotic infusion followed by antibiotic-heparin lock using vancomycin or ciprofloxacin successfully eradicated BSI in 100% of the HD patients (n =13) within 48 hours without any complications exclusive of CVC removal [52].

In several recent studies [53, 54], an antibiotic-heparin/citrate lock has been reported to be associated with reduced risk of bacterial colonisation of CVCs and consequent decrease in septicaemic episodes. A number of third generation cephalosporins, ciprofloxacin, vancomycin and gentamicin have been found to be appropriate for the antibiotic-heparin lock. A fairly lower dose of antibiotics (10 mg/ml for cephazolin, ceftazidime and vancomycin, each and 5 mg/ml for gentamicin) as compared to their systemic dosage – is required to fill the lumina of CVCs to sterilise and prevent further bacterial colonisation during interdialysis period (48 to 72 hours) [55]. The theoretical advantages of this technique over systemic antibiotic administration are that relatively higher concentrations are delivered directly to the site of infection enhancing the likelihood of sterilising the catheter's luminal surfaces, lower incidence of antibiotic toxicity, less risk of promoting drug resistance (as there is no spill out of drug into the circulation) and greater practicality in out-patients setting. However, regardless of the reasonably lower regional doses of antibiotics in the catheter "lock" solutions, aminoglycoside-associated ototoxicity has recently been reported [56, 57]. Yet, antibiotic locks appear to be a plausible and attractive option to conventional modes of treatment of colonised CVCs [58–61]. Large multicentre controlled trials are indeed necessary to provide the substantial evidence for the efficacy of antibiotic lock technique in the management of CRBSI.

Strategies for prevention of CRBSI

Back to basic principles, practices, policies and programs

Maximal sterile barrier precautions, asepsis and catheter dressing

Full barrier precautions during the vascular access placement (sterile gloves, long-sleeved sterile gowns, mask, cap and large sterile sheet drape) reduce the incidence of VRBSI compared with standard (sterile gloves and small drape) precautions [62]. Hence, comprehensive strictly enforced hygienic safety measures as a part of standard CVCs care are essential while placement and handling of HD catheters-in order to prevent intraluminal colonisation.

Povidone-iodine and alcohol are the most widely used antiseptic for cleansing catheter insertion sites; studies failed to show any statistically significant difference in the incidence of CRBSI when chlorhexidine was used as a cleansing agent [62–64]. In patients with an allergy to povidone-iodine, alternative agents such as triple antibiotic ointment (polymyxin, bacitracin and neomycin) were used as a substitute. However, prophylactic efficacy of polyantimicrobial gel remains to be es-

tablished; due to increased catheter colonisation with *Candida* species following use of triple antibiotic ointment its application is currently not recommended [65].

Dry gauze dressings rather than transparent film dressings are recommended because transparent film dressings pose a greater threat of exit site colonisation [66]. The use of dry gauze dressing and povidone iodine and mupirocin ointment at the catheter exit site can reduce the incidence of exit site infections, especially in patients who have nasal carriage *S. aureus* (relative risk, RR, 0.1, 95% CI, 0.0–0.7) [67, 68]. In a randomised controlled trial, Australian investigators found that the thrice-weekly application of 2% mupirocin ointment to cuffed haemodialysis exit sites markedly reduced sepsis episodes and prolonged catheter survival. No adverse effects were noted, and antimicrobial resistance was not induced [67]. Mupirocin ointment may however adversely affect the integrity of polyurethane catheters [69, 70].

Proper selection of site for catheter placement

Several prospective, observational studies using multivariate analysis found that the risk of infection was significantly increased with insertion into internal jugular vein compared with insertion into subclavian vein [71–73]. Therefore; catheter placement into the subclavian vein is preferable to reduce the risk of infection. However, the risk must always be weighed against non-infectious complications (pneumothorax and bleeding, in the short-term and subclavian stenosis in the long-term) associated with subclavian vein insertion. The risk of bacterial colonisation (Hazard ratio, 4.2, 95% CI, 2.0–8.8) and deep vein thrombosis is much higher with insertion of catheter into femoral vein than with subclavian or internal jugular vein insertion [72–74]. For this reason, femoral venous catheterisation should be limited to circumstances that prevent the use of alternative access sites.

Nasal decolonisation of bacterial flora

A number of studies have shown that nasal decolonisation of *S. aureus* by means of nasal applications effectively reduces the incidence of VRBSI among dialysis patients [75, 76]. Nonetheless, the efforts to realise long-term elimination of *S. aureus* from the anterior nares through decolonising agents such as oral rifampicin and mupirocin nasal applications had been associated with the development of side effects, emergence of resistance and recolonisation of *S. aureus*, once the drug was discontinued [77, 78]. Additionally, these decolonising agents lack standardised schedules for application and their optimal duration of use is also not known.

However, decolonisation realised prior to placement of permanent vascular accesses (AVF/ PTFE graft/ TCC) through short-term use of decolonising agents may have potential to reduce the dialysis access infections perhaps without side effects and emergence of resistance.

NKF-DOQI recommended policy of AV Fistula optimisation; limiting the use of CVCs

Timely placement of a reliable permanent vascular access is crucial for the quality HD care. The NKF-DOQI guidelines emphasise native AVF as the access of choice for incident patients. However, recent data from the Dialysis Outcome and Practice Patterns Study (DOPPS) revealed that just 24% of patients in US used AVF for HD; prevalence of AVF was significantly associated with younger age, male gender, lower body mass index, non-diabetic status, lack of peripheral vascular disease, and no angina pectoris.

Several studies have shown that that exceeding the NKF-DOQI goal of more than 50% fistula placement is achievable in the USA and elsewhere [79, 80]. Optimised AVF placement has been reported to be associated with improved patient outcomes in terms of reduction in the incidence of VRBSI and the costs of ESRD even among high-risk groups, such as-diabetics, elderly and those with nasal carriage of *S. aureus* [81, 82]. Strategies to increase AV fistula formation require early referral to nephrologists and early placement of AVF through a carefully established and prudently planned pre-dialysis program.

Novel strategies in evolution

Use of antiseptic / antimicrobial coated or impregnated catheters

The strategy of coating catheters with antimicrobial/antiseptic agents to prevent CRBSI finds its basis in the fact that catheter surface represents the real battlefield between microorganisms and the body defence mechanisms. Various antiseptic/antimicrobials have been used to coat the surfaces of catheters to prevent bacterial colonisation, including chlorhexidine, silver sulphadiazine, minocycline, rifampicin and, vancomycin.

Maki et al. [83], incorporated chlorhexidine gluconate and silver sulphadiazine (CH/SS) to the external surface of antiseptic catheters and compared their efficacy with uncoated catheters. Antiseptic catheters were less likely to be colonised at removal than were control catheters ($P = <0.005$) and were nearly 5 times less likely to produce BSI ($P = 0.03$). The result of this study could not be confirmed through further prospective randomised studies [84, 85]. Heard et al. [85], found no significant difference between the rates of CRBSI in the catheters coated with CH/SS and those uncoated.

Raad et al. found the synergistic combination of minocycline and rifampicin (M/R) to be efficacious in preventing bacterial colonisation of slime-producing strains of *S. epidermidis* and *S. aureus* on the catheter surfaces [86, 87]. This group also found that the catheters coated with M/R had significantly better in vitro inhibitory activity against *S. epidermidis*, *S. aureus* and *Enterococcus faecalis* strains than did catheters coated with vancomycin ($P <0.05$).

Darouiche et al. [88], found that catheters im-

pregnated with M/R were three times less likely to be colonised than were the those impregnated with CH/SS (7.9% vs. 22.8%, *P* <0.001). Catheters coated with M/R were also 12 fold less likely to be associated with CRBSI than were the catheters coated with CH/SS (0.3% vs. 3.4%, *P* <0.001). These catheters had more durable antimicrobial activity of 4 weeks compared to less than 3 weeks for CH/SS catheters [89].

In general, antimicrobial coated catheters have a shorter antimicrobial durability and higher cost. They are, however, important novel additions to the group of CRBSI preventive strategies. Their use for vascular access awaits further study because only limited data to support their efficacy among long-term HD patients are available at present [90, 91].

Antibiotic-heparin/citrate locks

Recently antibiotic-heparin/citrate locks, investigated for the prevention of gram-positive CVC-related bacteraemia among neutropenic cancer patients, have shown encouraging results; none of the 60 patients receiving vancomycin-heparin lock developed CRBSI over an average of ten days of observation period [92].

Dogra et al. [93], conducted a double-blind randomised study of 112 TCCs in 83 patients to compare heparin (5000 U/ml) with catheter-restricted filling of gentamicin/citrate (40 mg/ml and 3.13% citrate; ratio 2:1) as catheter-lock solutions. The primary end point was CRBSI. Significantly lower incidence of CRBSI (0.03 vs. 0.42 per 100 catheter-days, P = 0.003) and considerably higher mean infection-free catheter survival (282 days vs. 181 days, P = 0.002) were observed in the gentamicin group compared to that of heparin group. However, predialysis gentamicin levels were found to be significantly higher in patients randomised to gentamicin group (2.8 mg/L vs. (<0.2 mg/L, P = 0.008) compared to those of heparin). Authors cautioned to establish the safety of "locked" dose of gentamicin for ototoxicity before the technique was adopted.

In a prospective randomised controlled study [94], carried out at Louisiana State University Health Services Center in Shreveport, USA, patients (n = 14) with TCC locked with a gentamicin (40 mg/ml) plus trisodium citrate (final concentration –4.6%) were evaluated for the CRBSI, thrombosis episodes and catheter-survival rates against those locked with heparin, alone (n = 19). Group with gentamicin-citrate lock had reasonably lower incidence of CRBSI (0.62 vs. 2.11/1000 patient-days, OR 2.947, 95% CI, 1.365–6.520), catheter thrombosis episodes (2.5 vs. 3.2/1000 patient-days, OR 1.412, 95% CI, 0.729–2.740) and significantly longer mean catheter-survival percentage at 60 days following placement (74.0 ± 12 vs. 59.0 ± 11, OR 1.978, 95% CI 1.043–3.761, *P*- 0.0) than the control group. However, the study was prematurely terminated following FDA's ban on the use of Tricitrasol (46.7%) as catheter lock despite the fact that a much lower concentration of trisodium citrate (4.6%) was being used in this study and weekly predialysis gentamicin levels were measured to assess systemic toxicity [95].

McIntyre et al. [61], in a recent randomised controlled study (n = 50) compared gentamicin and heparin (5 mg/mL) locked tunnelled CVC group with that of catheter-restricted filling of standard heparin (5000 IU/mL) alone, regarding the number of BSI episodes, haemoglobin levels and Epoetin requirement. The gentamicin-locked group recorded just one BSI episode (0.3/1000 catheter days) compared to 10 episodes in six patients in the heparin alone group (4/1000 catheter days, P = 0.02). Use of antibiotic locking was also associated with significantly higher mean haemoglobin levels (P = 0.003) and a lower mean Epoetin requirement (P = 0.04).

In view of the recently reported aminoglycoside "lock" ototoxicity [55, 56], cefotaxime (10 mg/ml) in combination with heparin (5000 U/ml) for catheter-restricted filling of CVCs (n = 67) was used in a prospective observational study carried out at this centre to examine the lock's efficacy in the prevention of CRBSI [96]. A significant reduction in the incidence of CRBSI was observed compared with that of historical controls (0.55 vs. 1.19 episodes/1000 catheter-days, 95% CI, 1.03–7.61, p <0.001) [83]. Cefotaxime was chosen on account of its broad spectrum and reported high clinical and microbiological safety profile [97].

Although antibiotic-heparin locks are not in routine use in patients undergoing HD, yet; it appears that "locks" have enough potentials to effectively prevent the episodes of CRBSI among HD patients. There remains however, a theoretical risk of development of antibiotic resistance under long-term antibiotic locks application.

Nonantibiotic locks

Based on the fact that hypertonic saline has been safely used to treat a variety of medical conditions including dialysis-induced hypotension and the bactericidal properties of concentrated saline are enhanced by acidification, Moore et al. [98], developed a novel nonantibiotic locking method that retained undiluted anticoagulant (heparin, 5000 U/mL) at the catheter tip and undiluted bactericidal solution (acidified concentrated saline – ACS solution) at the catheter hub using a very small air bubble (0.1 mL) in between to prevent the mixing of the two solutions through diffusion. In an in-vitro study Twardowski et al. [99] demonstrated significantly superior bactericidal properties of ACS solution (0.9 mL of 27% saline solution with a pH of 2.0), compared with other nonantibiotic antibacterial agents – povidone iodine, sodium hypochlorite, and chlorhexidine which destroyed the bacteria immediately (0 hr) in 89% Vs 70, 66, and 59% of the samples, respectively. At 6 hr, 100% of the samples from the ACS, povidone iodine and chlorhexidine demonstrated zero bacterial growth. The ability to kill the most

of the common organisms responsible for access infections could make ACS a potentially attractive option to reduce incidence of CRBSI in HD patients.

Promising prospective strategies

Owing to our expanding knowledge in the field of molecular pathogenesis of vascular catheter infections including the understanding of the mechanisms of bacterial adherence to the catheter surface, biofilm formation and maturation; future prospects for the development of "dream catheter" with "bioactive" surface conferring thromboresistant and infection-resistant properties are not very far off. Ample progress made during the last decade that was directed to intercept these mechanisms undoubtedly would enable us to prevent microbial colonisation of "future" catheters.

Covalently linked heparin on the surface of CVCs

This strategy is attractive since it does not incorporate antimicrobial agents. A study of covalently linked heparin on the surface of CVCs to reduce the risk for CRBSI was indeterminate (OR, 0.0, 95% CI, 0.0–1.5) [100]; nonetheless, additional clinical trials are needed.

Electrically charged ionic silver catheters

Electrically charged catheters prevent colonisation by various microbes, but there are no published clinical trials of these catheters [101]. A study of externally coated catheter with silver was inconclusive as well (RR-0.5, 95% CI, 0.2–1.0) [102]; again further clinical trials are warranted.

S. aureus adhesins-blocking antibodies

Alternatively, greater understanding of the mechanism of *S. aureus* binding to the catheter surface *in vivo* that involves fibronectin-specific adhesins will help to prevent CRBSI [103]. Identification of epitopes in the *S. aureus* fibronectin-binding protein for the generation of adhesins-blocking antibodies to coat future catheters with similar antiadhesin molecules may help in preventing *S. aureus* infections [104]. Antibodies that block the fibronectin-binding protein adhesin of *S. aureus* have been developed [105].

Inhibitors of S. aureus acyl homoserine lactone-based chemical messengers that control bacterial gene expression

Quorum (a form of microbial communication) sensing among microbes is obligatory for the maturation of biofilm [106]. The development of bacterial biofilms on the surface of foreign bodies involves cell-to-cell signaling by acyl homoserine lactone-based chemical messengers that control bacterial gene expression [107]. Prevention of microbial growth on the surface of future intravascular catheters may be mediated by inhibitors of these chemical messengers [108].

Likewise, gene products of an identified operon mediate the *S. epidermidis* autoregulation and biofilm formation so commonly encountered on the surface of colonised CVCs [109]. Blocking the expression of this operon may prevent adherence of *S. epidermidis* to catheter surface.

Conclusions

HD patients are at considerably high risk for CRBSI and ensuing serious complications as CVCs remain the only reliable option to gain instant dialysis-access for the patients requiring HD during emergency situations. *S. aureus* is the principal pathogen implicated in most of the episodes of CRBSI. Treatment of CRBSI remains controversial even with the relatively novel technique of delayed replacement of CVC with creation of a new tunnel even with encouraging results. Antimicrobial-anticoagulant "locks" have also shown promising results in several recent randomised controlled trials in the treatment and prevention of CRBSI. However, clinical situations such as severe catheter sepsis with systemic septic complications and bacteraemia with tunnel tract involvement, should prompt immediate catheter removal. The effective implementation of standard infection control measures for handling of CVCs remains indispensable as a valuable approach for the prevention of CRBSI in the vulnerable group of HD patients.

The NKF-DOQI recommended policy of optimisation of AVF prevalence to at least 50% while limiting the use of CVCs with timely referrals and the effective implementation of a carefully planned pre-ESRD policy, should improve the long-term HD outcomes further.

Correspondence:
Dr. Anil K. Saxena, MD; FRCP
Consultant Nephrology & Deputy Chief
Division of nephrology
Postgraduate Department of Medicine
King Fahad Hospital & Tertiary care Centre
King Faisal University
Hofuf, Al-Hasa-31982
Saudi Arabia
E-Mail: dranil_31982@yahoo.com

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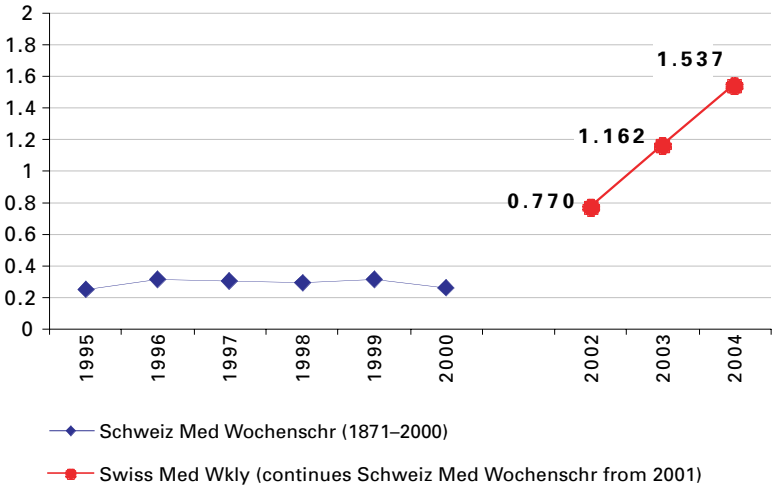

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