Vascular Access Infections: Epidemiology, Diagnosis, and Management

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Abstract Infection is the most challenging and lifethreatening complication of vascular access and causes significant morbidity, loss of access, and mortality. The aims of this review are to determine the magnitude of the infection problem, identify possible factors, and provide an update on the management of vascular access infections. Infections account for approximately 15% to 36% of all deaths in dialysis patients (the second leading cause after cardiovascular events) and for about 20% of admissions. Several studies demonstrate a hierarchy of infection risk from temporary catheter, tunnelled cuffed catheter, arteriovenous grafts, to arteriovenous fistula in decreasing order. Suspicion of infection must be followed by appropriate blood cultures, including possible simultaneous sampling from a peripheral vein and the access. The best way to treat vascular access infection is prevention, bearing in mind the idea "fistula first" and "lines last", with the appropriate use of arteriovenous grafts and newer devices sandwiched in between.

Keywords Arteriovenous (AV) fistula · AV grafts · Bacteraemia · Catheter related infection · Central venous catheter · Graft infection · Haemodialysis · Morbidity · Prophylactic antibiotics · Vascular access infection

Introduction

Repeated access to the circulation is required in the following situations: patients on maintenance hemodialysis

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Gastroenterology, Surgery & Renal Services Directorate, Plymouth Hospitals NHS Trust, Derriford Hospital, Plymouth PL6 8DH, UK e-mail: Jacob.akoh@phnt.swest.nhs.uk (HD), patients with a long-term need for blood sampling or intravenous treatments, and patients with long-term intravenous (total parenteral) nutrition. For such patients, achieving a durable and reliable vascular access is the most important determinant of successful therapy whether in the initial phase of surgical treatment, chemotherapy, or in the chronic phase of management of advanced cancer and longterm HD. The commonly used types of vascular access include native or autogenous arteriovenous (AV) fistula; prosthetic AV grafts; central venous catheters (CVC), both temporary and cuffed tunnelled; and implanted vascular access devices (VAD).

The majority of patients needing chronic vascular access need it for HD, and it is perhaps not surprising that most of the literature concentrates on vascular access for this purpose. In spite of the "fistula first initiative" [1], recruitment of elderly patients on to dialysis, prevalence of diabetes mellitus, and increasing proportion of long-term dialysis patients have led to an increase in the proportion of patients requiring more complex vascular access modalities for long-term HD. Despite notable developments in vascular access technology, access-related morbidity remains the major concern for patients requiring long-term therapy. Vascular access infection can result from contamination during the insertion/construction of the access, from the repeated use of the access, or intervention to prolong the use of access.

Infection constitutes the most challenging and lifethreatening complication of vascular access and causes significant morbidity, loss of access, and mortality [2, 3, 4-7]. Admission to hospital due to infection in HD patients is associated with an increased risk of myocardial infarction, congestive cardiac failure, peripheral vascular disease, and stroke [8]. Bacteraemia may be a potentially preventable cardiovascular risk factor in dialysis patients. Sepsisrelated death is 100 times greater in dialysis patients than in the general population, with infection-related death and allcause mortality being highest in those with CVC [1]. Vascular access infections result in excess health care costs in HD patients and other relevant patient populations. Moreover, repeated use of antibiotics to treat infections has been associated with the emergence of multi-resistant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci [9].

Improved diagnostic methods for vascular access– associated infection have the potential of facilitating prompt implementation of targeted treatment and reducing loss of access [10•]. The aims of this review are to determine the magnitude of the infection problem, identify the possible factors, highlight new ways of making effective diagnosis, and to provide an update on the management of vascular access infections.

Epidemiology

Vascular access is a recognized risk factor for infection in HD patients. Published results of infection rates are generally higher than the agreed target levels of 1% for AV fistula, 10% for AV grafts, and 50% for tunnelled CVC at 1 year [11]. Infections account for approximately 15% to 36% of all deaths in the dialysis population (the second leading cause after cardiovascular events) and for about 20% of admissions. Bloodstream and non-bloodstream infections in HD-dependent patients with fistula or graft access incur high costs and long inpatient stays [12].

Responsible Organisms

Staphylococcus species are the leading cause of infection in patients with established renal failure (ERF) [13, 14]. *S. aureus* CVC infection is significantly associated with the development of infectious complications (osteomyelitis, infective endocarditis) and also is an independent risk factor for recurrence of infection [15]. Li et al. [3•] examined the clinical and economic outcomes associated with *S. aureus* bacteremia and other *S. aureus* infections in 3359 HD patients using AV fistula or grafts. Of these, 279 (8.3%) developed infection, with 12-week mortality rates for bloodstream and non-bloodstream infections of 20.2% and 15.7%, respectively.

The pattern of microbes responsible for infection varies depending on the type of access. Pooled data show that *Staphylococcus epidermidis* is responsible for most CVC infections whereas *S. aureus* is more common with AVF and AV grafts [14, 16, 17•]. Alexandraki et al. [18] reviewed the microbiological patterns of bacteremic HD patients with tunnelled CVC and reported 203 organisms

were isolated from 153 positive blood cultures over a 5-year period. Gram-positive, Gram-negative, and fungal species represented 55.7%, 43.3%, and 1% of isolates, respectively. Candidemia accounts for approximately 1% to 2% of all cases of catheter-related bloodstream infections [18, 19], although the rate could be higher depending on the presence of such risk factors as recent surgery, cortico-steroids, antibiotic therapy, low albumin level, malignancy, or organ transplantation.

Risk Factors for Vascular Access Infection

The risk of vascular access infection depends on the interaction between access and patient characteristics, intervention by patient or health workers, and the center where the patient is managed.

Type of Access

The type of vascular access is a well-recognized risk factor for bacteremia [12, 14, 20]. Several multicenter studies demonstrate a hierarchy of infection risk associated with vascular access type (Table 1) [13, 14, 20–23].

CVC: Despite recent initiatives promoting the AV fistula as the initial, primary, and sole vascular access to be used by HD patients with a recommended decrease in prevalence of tunnelled cuffed CVC to less than 10%, the prevalence of tunnelled cuffed catheters for HD access has increased [1]. Eighty-two percent of patients started dialysis with a CVC in the United States in 2006 [24]. This excessive use of CVC may be due to poor planning for dialysis initiation and is associated with a high hospitalization rate due to infection. Compared with dialysis using AV fistulas, longterm dialysis with tunnelled cuffed catheters is associated with two- to threefold increased risk of death, a five- to 10fold increased risk of serious infection, increased hospitalization, a decreased likelihood of adequate dialysis, and an increased number of vascular access procedures [25]. Among 1,919 isolates in 1,747 positive blood cultures in patients with access-related bacteremia, 1,244 (66%) were in patients with CVC [16]. CVC are associated with the highest risk of infection-related and all-cause mortality compared with the autogenous AV fistula and synthetic AV grafts [22]. In a study involving 2,230 permanent silicone CVC implanted in 1,749 patients, Lemaire et al. [2] found an overall incidence of bacteremia of 0.51 per 1,000 catheter-days, identifying a previous history of a bacteremia, diabetes mellitus, duration of catheter use>90 days, and hypertension as significant risk factors. Bacteremia is more likely in patients with S. aureus nasal carriage, older catheters, and catheter exit site infections.

VAD: Totally implanted VAD are frequently used in children who have long-term requirements for access to the

Table 1 Infection rates according to vascular access	type
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Author	Study type	Infection rate per 1,000 patient-days				Comment
		Temporary CVC	Tunnelled CVC	AV Graft	AV Fistula	
Taylor et al. [20] ^a (2002)	Prospective	22.5	15.5	2.5	1	11 centers
Tokars et al. [16] (2002)	Surveillance	3.99	2.81	0.45	0.19	109 centers
Saeed Abdulrahman et al. [14] ^b (2002)	Prospective	12.1	4.33	1.84	1.84	Graft and fistula combined
Stevenson et al. $[21]^a$ (2002)	Prospective	32.6	13.6	2.2	1	6 centers
Colville and Lee [23] 2006	Retrospective	20.2	4.02	2.86	0.4	
Ponce et al. [13] (2007)	Prospective	6.33	3.33	1.33	0.73	5 centers

^aRisk of vascular access infection relative to arteriovenous fistula

^b Rates recalculated

AV arteriovenous, CVC central venous catheter

circulation. Infection risk of VAD is similar to that of AV fistula. A retrospective analysis of 225 VADs implanted in 217 patients (chemotherapy in 66.2% of patients, drug-infusion treatment in 31.6% of patients, and total parenteral nutrition in 2.2% of patients) reported infection in five patients (2.2%) [26]. VAD-related infection accounts for 50% of *S. aureus* bacteremia per 1,000 hospital discharges per month [27].

AV grafts: A large prospective cohort study involving one third of the Canadian HD population found a 19.7% probability of polytetrafluoroethylene (PTFE) graft infection compared with 4.5% for autogenous AV fistula [28]. More recent reports show wide variation in the incidence of AV graft infections, ranging from 3.5% to 17.3% [7, 29, 30]. AV graft infections are more likely in patients with diabetes mellitus, insertion in the thigh, history of multiple infections, surgical revisions, immunocompromised state, hypoalbuminemia, obesity, and thrombosed abandoned AV grafts [7, 29].

Access in Lower Limb

Although insertion sites in the upper limb are preferred for AV grafts because of the lower risk of associated sepsis, when exhausted the thigh is the next favored site [31]. Englesbe et al. [6] reported that 27% of the femoral AV grafts were lost to sepsis, whereas other reports [30, 31] indicated no associated increased morbidity or risk of graft loss. Antoniou et al. [32] performed a systematic review to clarify conflicting results regarding the feasibility of lower limb AV grafts and found access loss due to infection was more common in upper and mid-thigh grafts than femoral vein transposition (18.40%, 18.33% vs 1.61%). Inserting a thigh AV graft to the common femoral vessels in close proximity to the groin requires dissection through dense lymphatic tissues, which is believed to result in a higher risk of infection and complications. Despite an increased

risk of infection and limb ischemia [33], thigh AV grafts should be preferred to CVC, as the rate of infection and mortality remains lower with higher blood flows and dialysis adequacy [34].

Center Effect

There is conflicting evidence for a center effect on the incidence of vascular access infections. In a multicenter study involving 796 patients in seven US centers, Tokars et al. [35] identified the specific dialysis unit as independent risk factors for vascular access infection (relative hazard varying from 1.0 to 4.1 among the centers). Another study involving 76 US centers showed that infection rates were similar among 51 centers but different in 25 others [16]. However, a similar but retrospective cohort study of 621 patients initiating hemodialysis in seven Canadian dialysis centers showed that the risk of access-related infection was not center dependent [36-].

Viral Infection and Vascular Access

Due to the diminished immune status, the use of a vascular access other than an AV fistula may favor increased rates of infection among HIV-infected and hepatitis C virus (HCV)-infected individuals. Following preliminary work that suggested an association between HCV infection and bacteremia in dialysis patients with CVC, Reddy et al. [37•] conducted a two-phase clinical study to define the association between HCV infection and bacteremia in HD patients with catheters. They showed that HCV-positive patients had a significantly greater prevalence of bacteremia than HCV-negative patients (61% vs 7.7%). Furthermore, the presence of detectable virus was associated with an increase in the incidence of bacteremia (40% vs 0% for patients with and without detectable virus, respectively). It is thought that HCV

infection may lead to an immunocompromised state through chronic liver disease, direct effects on humoral immune responses, or inhibition of phagocytosis.

Percutaneous Interventions

The infection risk of percutaneous dialysis access procedure is low, and routine administration of antibiotic prophylaxis may not be warranted. Salman and Asif [38] reported a large series of percutaneous interventions including percutaneous balloon angioplasty (1,310 AV fistulae, 768 AV grafts), 26 endovascular stent insertions, thrombectomy (106 AV fistula, 110 AV grafts), and 283 tunnelled CVC insertion/exchange. In their series, only one patient (0.04%) post-angioplasty and one patient (0.3%) after tunnelled catheter placement developed clinical infection.

The technique of cannulation of AV grafts or AV fistula is also thought to influence infection rates. The rope-ladder puncture technique, with cannulation along the whole length of the vessel trajectory, was traditionally common in HD patients with autogenous AV fistula. However, the increasingly complex HD population has necessitated an alternative needling possibility, known as the buttonhole technique, which inserts needles at exactly the same location during every dialysis session. In a study to investigate the effect of both cannulation techniques on the incidence of vascular access, van Loon et al. [39] demonstrated that the buttonhole technique was associated with a higher incidence of access infections compared to the rope-ladder method.

Metastatic and Rare Infection Complications

Metastatic infectious complications include endocarditis [6], discitis [7], myocardial abscess, arthritis [40], and endophthalmitis secondary to infection of AV fistula cannulation site abscess [41]. Twenty-two percent of HD patients with CVC who developed *S. aureus* bacteremia subsequently developed osteomyelitis, septic arthritis, and endocarditis and progressed to death, regardless of whether the CVC was removed or exchanged [40].

Infective endocarditis is more frequent in patients on maintenance HD than in the general population, and vascular access is the more frequently identified port of infection. The vascular access may interfere with the treatment of infective endocarditis by acting as a persistent nidus of infection or in the case of CVC, a new substitute catheter may act to maintain the infection. In one study, upon diagnosis of infective endocarditis, 12 patients were temporarily switched to peritoneal dialysis with a hospital mortality of 8.3% in contrast to 55.5% mortality in nine patients who remained on HD [42].

Diagnosis

Patients requiring long-term vascular access, whether for HD, cancer treatment, or nutrition, generally have impaired immune responses, are severely or chronically ill, and may undergo repeated intervention of such accesses. Consequently, they are at high risk for infections. The same factors stated above may mask early features of infection, making it difficult to determine whether infection is due to the vascular access or other causes.

Vascular access infection is defined as local signs (pus, redness, or swelling) at the vascular access site or a positive blood culture with no known source other than the vascular access, and hospitalization or receipt of an intravenous antimicrobial [35]. The source of a positive blood culture is designated as the vascular access if there are local signs in addition to access drainage, pain, an open area, or positive culture from the access showing the same organism found in blood [16]. The term secondary bacteraemia is used to describe a positive blood culture with a source different from the vascular access. A tunnel infection refers to inflammation in the tissue overlying the CVC and extending>2 cm from the exit site or beyond the cuff, if present [36•]. Exit site infection refers to inflammation (erythema, tenderness, induration, or purulence) limited to the area surrounding the exit site. CVC-related bacteremia is defined as isolation of the same organism (identical biotype and susceptibility pattern) from both the cuffed CVC and peripheral blood culture, provided the time to positivity from the CVC sample was>120 min [17•]. Metastatic infections are mainly diagnosed on the basis of a positive blood culture in addition to evidence of vascular access infection and specific features due to infection of the particular site or organ.

Whenever there is a strong suspicion of a vascular access infection, it is important to draw blood for culture. The type of isolated organism may indicate the source of infection. Simultaneous sampling from a peripheral vein and the access (eg, CVC) is important for diagnosis [43••]. This may be difficult to achieve in some HD patients with exhausted access sites. In such cases, two or more samples should be drawn through different lumens [43••]. However, the insensitive or nonspecific nature of clinical diagnostic criteria for CVC-related infection makes over-diagnosis likely, resulting in unnecessary removal of the CVC. Catheter-sparing diagnostic methods, such as differential quantitative blood cultures and differential time to positivity, have emerged as reliable diagnostic techniques [44].

A novel technique for diagnosing vascular access infection was described by Millar et al. [10•]. When phenotypic characterization of bacteria fails, 16S-rDNA– based identification offers a useful alternative, as it provides unambiguous data for even rare isolates. Blood samples were collected for quantitative 16S-rDNA analysis from VAD in 260 of 301 patients presenting with fever at participating centers of the UK Children's Cancer and Leukaemia Group. The positive predictive value (for probable or possible infection) was 88% (95% CI, 70%–98%) with 0.25 pg/µL of bacterial DNA, and 100% (95% CI, 83%–100%) with>0.5 pg/µL. Identifications derived from the DNA sequence were consistent with the blood culture identification for 15 of the 17 episodes with a DNA sequence identification [10•]. A bacterial DNA concentration>0.5 pg/µL in blood drawn from a CVC at a time of fever presentation positively correlated with VAD-associated infection and predicted an increased risk of VAD removal.

For predicting CVC-related bacteremia, endoluminal cultures with a time to positivity of ≤ 14 h had sensitivity and specificity of 52.1% and 97.7%, respectively, suggesting that endoluminal cultures may predict the risk of developing CVC-related bacteremia. Surveillance cultures from either the arterial or venous lumen could, therefore, be used to triage individual HD patients who might benefit from specific intervention measures [17•]. This method is readily available at no risk to the patient.

Management

Prevention

Infection control requires a co-ordinated approach involving the multidisciplinary team, the affected patient (hygiene is a critical factor), the patient's relatives, and visitors. A confidential questionnaire survey of 190 gualified nurses in nine HD units in the Republic of Ireland revealed knowledge and adherence to best practice in infection control was less than satisfactory [45]. A change initiative involving adoption of appropriate cannulae and administration sets to minimize infection risk reduced the incidence of MRSA and health care-acquired infection cases resulting from peripheral venous cannulation [46]. Training and support to encourage the adoption of best practice, in conjunction with regular follow-up audits, can lead to a reduction in infection rates and general improvements in the quality of access care. Dendle et al. [27] demonstrated the potential for huge cost savings by introducing a structured program to investigate all health care-associated S. aureus bacteremias, rather than only infections with MRSA, revealing a large under-recognized burden of potentially preventable infections. Ongoing quality assurance, risk management measures should be made to monitor the incidence of infection and to evaluate the response to patient and staff education.

Avoidance of CVC

Avoiding the use of CVC or even minimizing their use would significantly reduce the overall burden of vascular access-related infections. Continuous quality improvement schemes adopted by multidisciplinary teams are effective in increasing the proportion of established dialysis patients using autogenous fistulae. Determined efforts to insert autogenous access and only using prosthetic access as a last resort have kept the prevalence of AV grafts at a relatively low level in some centers [30], but it has also increased the need for preoperative diagnostic and therapeutic procedures, a high number of primary AV fistula failures, and paradoxically, an increased use of CVC with its attendant consequences [1].

When CVC are used, adherence to evidence-based catheter insertion and maintenance practices can positively influence bacteremia rates. Effective prevention strategies, including cutaneous antisepsis, maximum sterile barrier, antimicrobial catheters, and antimicrobial catheter lock solution [44], have been used but avoidance of CVC use is the best way to decrease the incidence of these devastating infections [47]. Rabindranath et al. [48•] reviewed 29 trials with 2,886 patients and 3,005 catheters and showed that use of antimicrobial catheter locks significantly reduced the rates of CVC-related bacteremias and exit site infections. Exit site antimicrobial application also significantly reduced infection rates. However, antimicrobial coating of HD catheters and the use of perioperative antimicrobials did not result in significant reduction in rates of bacteremia and exit site infections. There is evidence that meticulous attention to detail and observation of strict aseptic protocols are effective in preventing CVC-related infection. VAD insertion in a pediatric series according to standardized protocol, dressing, post-operative care, and monitoring by dedicated nurses was associated with no infection at 1 month post-surgery [49].

The effects of a new long-term subcutaneous vascular access device were studied in access-challenged patients who were poor candidates for fistulas or grafts due to venous outflow obstruction. The Hemodialysis Reliable Outflow (HeRO) device consists of a 6-mm expanded polytetrafluoroethylene graft attached to a 5-mm nitinolreinforced silicone outflow component designed to bypass venous stenoses and enter the internal jugular vein directly, providing continuous arterial blood flow into the right atrium. The HeRO device was studied in a multicenter clinical trial to test the hypothesis that access-challenged patients would experience a statistically significant reduction in bacteremia rates compared with a CVC literature control of 2.3/1,000 days. The HeRO device was implanted in 36 access-challenged patients who were followed for a mean of 8.6 months (9,931 patient-days). The HeRO-

related bacteremia rate was 0.70/1,000 patient-days (all occurring during the bridging period when a CVC was still implanted), a statistically significant reduction in HeRO-related bacteremia compared with CVC literature [50•].

Prophylactic Antibiotics

When inserting AV grafts, prophylactic antibiotics are recommended to reduce the risk of infection due to intraoperative contamination. Eradication of nasal carriage should result in a lower incidence of graft infection. Most National Health Service hospitals in the United Kingdom now screen patients for MRSA prior to admission to hospital. Perhaps long-term dialysis patients should also undergo screening periodically, as is practiced to good effect in the author's center. Three monthly screenings and pre-emptive eradication therapy has produced excellent results.

Though a single intravenous dose of 750 mg of vancomycin administered 6 to 12 h prior to vascular access placement may be beneficial, the time course and bacteriology of most prosthetic AV graft infections suggest

inoculation of skin flora due to poor needling techniques or seeding from distant sites such as intravenous catheters [30]. Whether to administer vancomycin regularly to patients on chronic HD or to rely only on a careful aseptic technique when needling AV graft as a way of preventing infection is not fully resolved.

Removal of Infected Access

CVC

Management decisions regarding catheter-related bloodstream infection include catheter removal or exchange, use of antimicrobial catheter lock solution, and the type and duration of systemic antimicrobial therapy. Such decisions depend on the identity of the causative organism, the clinical and radiographic manifestations suggesting a complicated course, the underlying condition of the host, and the availability of other vascular access sites [44].

There is continuing disagreement concerning the removal of potentially infected tunnelled dialysis catheter. CVC salvage is associated with a high treatment failure rate

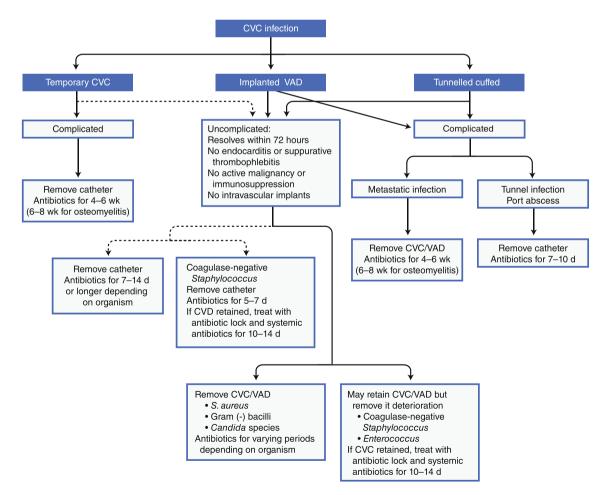


Fig. 1 Algorithm for management of central venous catheter (CVC) and implanted vascular access device (VAD) infections

probably due to the presence of biofilm. Bacterial incorporation into this matrix of polysaccharide and protein shields it from systemic antibiotics. Infection persists until the intra- and extraluminal biofilm is removed [15]. A dialysis catheter should be removed when an infection involves a temporary hemodialysis catheter, sepsis, a tunnel tract infection, or evidence of a metastatic infectious complication. In catheter-related candidemia, catheter exchange over a guide wire in conjunction with antifungal therapy for 2 weeks is considered to be effective and safe, with the same rate of recurrence of candidemia (15%) within 3 months as compared with prompt catheter removal with delayed replacement [19]. The management of infected CVC/VAD is summarized in Fig. 1 (based on the 2009 update guidelines for intravascular catheter-related infections [43••]).

AV Graft

The critical issues in the management of AV graft infection are the need to remove the infection and to provide/ maintain HD access with reduced morbidity. Treatment involves intravenous antibiotics (to cover both grampositive and gram-negative organisms) and graft excision (total, in septic patients or when graft bathed in pus; subtotal, when all of the graft is removed except an oversewn small cuff of prosthetic material on an underlying patent vessel; and partial, when a limited portion of AV graft is removed and a new jump graft inserted through adjacent sterile tissue [7]). A localized abscess around the graft may be amenable to limited excision and bypass of the infected segment, but if infection occurs before the graft is embedded into tissue, the whole graft should be excised. Total or subtotal graft excision had a successful outcome in all cases, whereas partial graft excision was accompanied by graft patency and wound healing in only 74% [7]. The need to completely excise an infected AV graft is sometimes counterbalanced by the compelling need to provide vascular access for dialysis in a patient with limited access options [5]. Prolonged antibiotic therapy for up to 4 weeks in selected patients has been practiced by some.

Conclusions

Vascular access infection is responsible for much morbidity and mortality in patients dependent on their use. AV fistula continues to prove to be the near ideal vascular access for most patients, but not all can have this access modality. AV grafts are associated with higher levels of complications and require more interventions than autogenous AV fistula. CVC-associated infection accounts for 66% of vascular access infections and CVC avoidance must remain a cardinal principle of vascular access provision. The increased use of catheters with associated increases in patient morbidity and mortality must be rapidly addressed to decrease the unacceptably high rates of catheter-related infection. This review supports the need for a comprehensive vascular access management strategy, including existing clinical practice guidelines concerning the prevention, diagnosis, and treatment of bacterial infections in patients requiring long-term vascular access. The best way to treat vascular access infection is prevention, bearing in mind "fistula first" and "lines last", with the appropriate use of AV grafts and newer devices sandwiched in between.

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Disclaimers None

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