Current Management of Vascular Access

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Optimizing vascular access outcomes remains an ongoing challenge for clinical nephrologists. All other things being equal, fistulas are preferred over grafts, and grafts are preferred over catheters. Mature fistulas have better longevity and require fewer interventions, as compared with mature grafts. The major hurdle to increasing fistula use is the high rate of failure to mature of newly created fistulas. There is a desperate need for enhanced understanding of the mechanisms of failure to mature and the optimal type and timing of interventions to promote maturity. Grafts are prone to frequent stenosis and thrombosis. Surveillance for graft stenosis with preemptive angioplasty may reduce graft thrombosis, but recent randomized clinical trials have questioned the efficacy of this approach. Graft stenosis results from aggressive neointimal hyperplasia, and pharmacologic approaches to slowing this process are being investigated in clinical trials. Catheters are prone to frequent thrombosis and infection. The optimal management of catheter-related bacteremia is a subject of ongoing debate. Prophylaxis of catheter-related bacteremia continues to generate important clinical research. Close collaboration among nephrologists, surgeons, radiologists, and the dialysis staff is required to optimize vascular access outcomes and can be expedited by having a dedicated access coordinator to streamline the process. The goal of this review is to provide an update on the current status of vascular access management.

Arteriovenous Fistulas

Why Should We Increase Fistula Use?

A mature access is one that can be cannulated reproducibly with two needles and deliver a high enough dialysis blood flow (approximately 300 ml/min) to deliver an adequate dialysis dose. Failure to mature is the major obstacle to increasing fistula use in the US dialysis population. Cumulative access patency (from creation to permanent failure) is superior for fistulas than grafts, if one excludes fistulas that fail to mature (1). However, fistulas fail to mature at a higher rate than do grafts (2–5). Therefore, when one includes failures to mature in calculating vascular access outcomes, the cumulative survival of fistulas and grafts is similar (Figure 1A) (2–10). However, once they are successfully used for dialysis, grafts require far more interventions than do fistulas to maintain long-term patency for dialysis. On the average, the annual frequency of intervention (elective angioplasty, thrombectomy, or surgical revision) in mature accesses is approximately four-fold higher for grafts than for fistulas (Figure 1B) (2–5,7–9,11). Thus, long-term patency for dialysis can be maintained in fistulas with far fewer interventions than with grafts (Table 1).

Fistula use is much higher among hemodialysis patients in Europe and Japan, as compared with those in the United States (12,13). Similarly, there are marked differences in fistula prevalence among different dialysis networks within the United States, with the highest frequencies observed in the Northeast and the lowest in the Southeast (14). Finally, even within a single metropolitan area, there are marked variations in fistula prevalence among individual dialysis units (15). Importantly, the international, regional, and local differences in fistula prevalence persist even after adjustment for multiple demographic and clinical factors. These analyses highlight the importance of practice patterns in affecting fistula use and contributed to the 2001 Kidney Disease Outcomes Quality Initiative (K/DOQI) Vascular Access guidelines (16), followed by the "Fistula First" national initiative (17). The goal was to increase fistula use in the United States by promoting a major shift in practice patterns. Specifically, nephrologists and surgeons are provided with educational tools to increase fistula placement, as well as concrete feedback about how one's local dialysis unit's performance compares with others.

Measures to Increase Fistula Prevalence

Ideally, every patient would initiate dialysis with a mature fistula suitable for cannulation. Striving for this goal requires a number of intermediate steps, including pre-ESRD care by a nephrologist, pre-ESRD access surgery, adequate fistula maturation, and successful fistula cannulation by the dialysis staff. This sequence is akin to running a hurdle race (Figure 2), in that all steps have to be performed in sequential order, and failure of any step results in a patient who initiates dialysis with a catheter. Approximately one third of US patients lack nephrology follow-up before initiation of dialysis (13). Among those with pre-ESRD nephrology follow-up, one third do not have access surgery before starting dialysis (18). Finally, approximately one third (20 to 50%) of new fistulas fail to mature (1). The cumulative effect of not overcoming these successive hurdles is that 60 to 65% of patients in the United States initiate
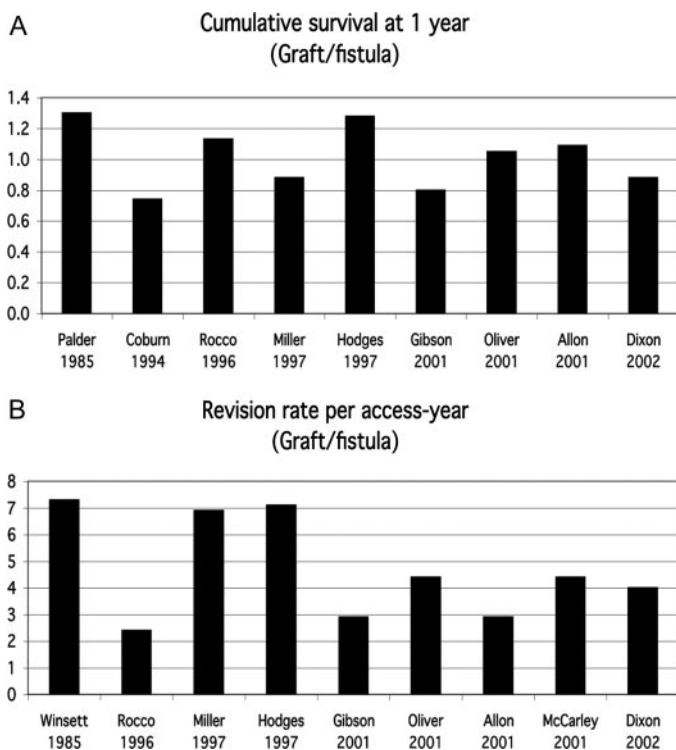
Figure 1. Comparison of graft and fistula outcomes in dialysis patients. (A) Cumulative access survival at 1 yr (from access creation to permanent failure, regardless of number of interventions required to maintain access patency). Bars represent ratio of cumulative survival in grafts *versus* fistulas reported in different large series. Note that the ratio is approximately 1.0, indicating comparable cumulative survival of grafts and fistulas. (B) Revision rate per access-year for fistulas and grafts. Revisions include elective angioplasty, thrombectomy, and surgical revision. Bars represent ratio of revision rate in grafts *versus* fistulas reported in different large series. Note that all of the ratios are >1, with a median ratio of 3 to 4:1, indicating a much higher revision rate in grafts than in fistulas.

hemodialysis with a catheter (12,19). Even 60 d after initiation of dialysis, 46% of patients are catheter dependent (19).

Specific measures may increase the proportion of patients who have chronic kidney disease (CKD) and clear each fistula hurdle (Table 2). Enhancing pre-ESRD nephrology follow-up requires raising the awareness by primary care physicians of how to diagnose CKD and when to refer patients to a nephrologist (12,20,21). Similarly, increasing the frequency of predialysis access placement entails educating nephrologists and patients with CKD about the optimal timing of access placement and providing surgeons with accurate vascular mapping and awareness of the types of fistulas. Improving fistula maturation requires a better understanding of why some fistulas fail to mature, diagnostic tools to identify immature fistulas and the specific reasons for their immaturity, and implementing surgical or radiologic interventions to convert immature fistulas to ones that are suitable for dialysis. Finally, concerted efforts are needed to enhance the proficiency of dialysis staff in the clinical assessment of new fistulas and proper cannulation techniques

Table 1. Unanswered questions about access management

Fistulas
- What are the reasons for failure to mature?
- Can we predict which patients are at high risk for failure to mature?
- What is the optimal test and timing to assess immature fistulas?
- Which immature fistulas can be salvaged by specific interventions, and what is the nature and optimal timing of these interventions?
- Can pharmacologic interventions improve fistula maturation?

Grafts
- Does graft monitoring/surveillance with preemptive angioplasty improve graft outcomes?
- Is any method of monitoring/surveillance superior for detecting stenosis?
- What are the cellular mechanisms that lead to neointimal hyperplasia?
- Can pharmacotherapy prevent graft stenosis/thrombosis?

Catheters
- What is the preferred treatment of catheter thrombosis?
- Which catheters with low dialysis blood flows require thrombolytic therapy?
- What is the optimal therapy of clotted catheters?
- What is the optimal clinical management of catheter-related bacteremia?
- How can catheter-related bacteremia be prevented?

to avoid infiltration (22). Close collaboration among nephrologists, surgeons, radiologists, and the dialysis staff is required to optimize these efforts and can be expedited by having a dedicated access coordinator to streamline the process (23).

Preoperative vascular mapping provides the surgeon with precise information about the diameter of the artery and vein and the presence of vein stenosis or thrombosis and frequently leads to a change in the intended access (24). In selected patients, additional imaging is indicated to exclude the presence of central vein stenosis or thrombosis. A dramatic increase in fistula placement was observed by several centers after implementation of routine preoperative vascular mapping (2,7,9,25–28). Among patients who are referred for their initial vascular access surgery, placement of a forearm fistula is feasible in only 40 to 50% (2,3,7,9). However, placement of an upper arm fistula (brachiocephalic or transposed brachiobasilic) is possible in an additional 25 to 35% of patients. Thus, some type of fistula can be placed in at least 75% of patients, with the remainder requiring creation of a graft (2,3,7,9).

Primary fistula failure, as a result of early thrombosis or failure to mature, is a major hurdle to increasing fistula prevalence (1). It is more common in women (29,30), nonwhite patients, older patients, and those with vascular disease (31).
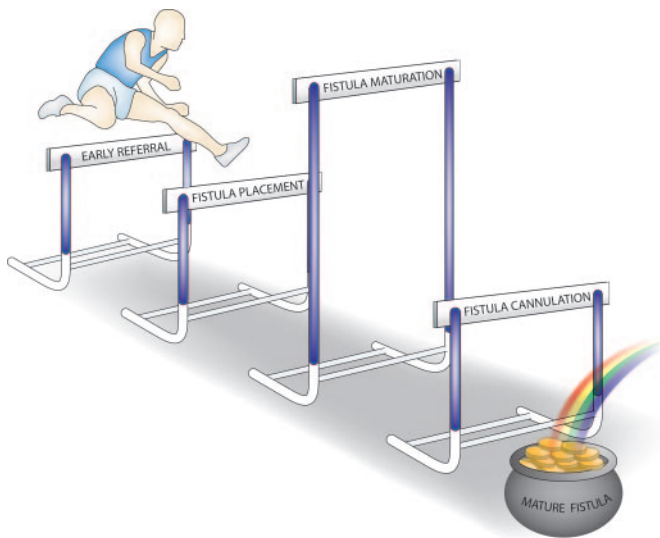
Figure 2. The "fistula hurdle." Several hurdles must be overcome successfully to ensure that a patient initiates dialysis with a mature fistula. These include early referral of patients with chronic kidney disease to a nephrologist, fistula placement well before reaching ESRD, adequate fistula maturation, and successful cannulation of the fistula by the dialysis staff. Failure to achieve any step results in a patient who initiates dialysis with a catheter.

Table 2. Measures to increase fistula prevalence[a]

Pre-ESRD nephrology care (12,20,21)
Preoperative vascular mapping (2,7,9,25–28)
arterial diameter ≥2.0 mm
venous diameter ≥2.5 mm
patent venous drainage system (no stenosis or thrombosis)
absence of central vein stenosis or thrombosis (venogram or MRV in selected patients)
Postoperative sonographic assessment of fistulas (34)
early (4 to 6 wk) postoperative imaging in clinically immature fistulas
criteria for mature fistulas
fistula diameter ≥4 mm
access flow ≥500 ml/min
distance from skin ≤5 mm
assess for remediable anatomic lesions
stenosis
accessory veins
excessively deep fistula
Salvage procedures for immature fistulas (30,36–42)
angioplasty or surgical revision for stenosis
ligation of accessory veins
superficialization of deep fistulas
Improve proficiency of dialysis staff in cannulation of new fistulas (13,22)
Surveillance for stenosis (46)
Thrombectomy of clotted fistulas (47–51)

[a]MRV, magnetic resonance venography.

Relatively little has been published on the natural history of new fistulas, the specific reasons for their failure to mature, the best test to use and time to assess their likelihood of success, and the optimal interventions to promote their maturation (32). The maximal increase in fistula diameter and blood flow occurs within the first few weeks of their placement (33–35). A postoperative ultrasound may help in assessing fistula maturation. In one study, fistulas with a diameter ≥4 mm and blood flow ≥500 ml/min had a 95% likelihood of successful use for dialysis, whereas those that fell below both thresholds had only a 33% chance of success (34).

Clinical evaluation or postoperative imaging of immature fistulas frequently reveals one or more anatomic lesions that possibly contribute to their immaturity. The three most common abnormalities observed are focal stenosis near the anastomosis or in the draining vein, presence of large accessory veins, and excessively deep fistulas (1). Radiologic or surgical interventions to correct the underlying lesion have been reported to convert an immature fistula to one that is usable for dialysis in 44 to 97% of cases (30,36–42). Specifically, stenosis can be treated by angioplasty or surgical revision, accessory veins can be ligated surgically, and excessively deep fistulas can be superficialized. Radiologic salvage procedures can be performed safely in patients with stage 4 CKD with a low (<10 ml) dosage of radiocontrast, without precipitating the need for acute dialysis (43). There is a dearth of prospective studies evaluating the frequency of different anatomic lesions in immature fistulas, the success rate of specific interventions in promoting maturity, and the optimal timing of such interventions.

Early thrombosis (within 6 wk of creation) occurs in approx-imately 25% of fistulas and may be related to a hypercoagulable state resulting from surgery, as well as local vascular injury. A meta-analysis of several small, randomized clinical trials using a short perioperative course of antiplatelet agents suggested that they may reduce the risk for early fistula thrombosis (44). An ongoing multicenter, double-blind, randomized clinical trial sponsored by the National Institutes of Health is evaluating the efficacy and safety of clopidogrel in prevention of early fistula thrombosis (45).

The challenges in maintaining long-term fistula patency continue after maturity has been achieved. Needle infiltration of new fistulas is a relatively frequent complication, which occurs most commonly in older patients. A single major infiltration prolongs catheter dependence by a median of 3 mo (22). Although fistulas require far fewer interventions than do grafts, they still develop stenosis and thrombosis. A randomized study found that flow monitoring for stenosis, in conjunction with preemptive angioplasty or surgical revision, improved fistula survival (46). Thrombectomy of clotted fistulas requires more time and expertise than thrombectomy of grafts, entailing a significant learning curve. A number of centers with an aggressive and timely approach to clotted fistulas have reported a 28 to 74% 6-mo primary patency after thrombectomy (47–51).

Arteriovenous Grafts

Outcomes of Clotted Grafts

Thrombosis accounts for approximately 80% of graft failures (52,53). Thrombosed grafts usually have an underlying stenosis, most commonly at the venous anastomosis or in the draining vein (54–56). Salvage of clotted grafts requires thrombectomy, as well as angioplasty or surgical revision of the underlying stenosis. However, the primary patency (intervention-free survival) is considerably worse after treatment of clotted grafts, as compared with elective angioplasty of patent grafts with stenosis. After elective angioplasty, the primary graft patency is 70 to 85% at 3 mo and 47 to 63% at 6 mo (51,54–58). In contrast, after thrombectomy and angioplasty of clotted grafts, the primary patency is only 33 to 63% at 3 mo and 11 to 39% at 6 mo (51,55,59–66). Comparison of outcomes of 656 radiologic graft interventions performed at a single dialysis center found a 3-mo primary patency of 71% after elective angioplasty, as compared with 30% after treatment of clotted grafts (55).

Given the dismal outcomes of clotted grafts, it would be desirable to identify prospectively grafts that are at risk for thrombosis and intervene prophylactically to prevent the graft from clotting. Because graft thrombosis is usually superimposed on hemodynamically significant stenosis, it is a plausible hypothesis that timely detection and correction of the stenosis will prevent graft thrombosis. Achieving this goal requires having a simple, cheap, reproducible, and sensitive method to monitor for graft stenosis.

Mechanical Interventions to Reduce Graft Thrombosis

There are four major approaches for detection of graft stenosis. Clinical monitoring consists of physical examination (absent thrill, abnormal bruit, or distal edema), abnormalities identified during dialysis sessions (prolonged bleeding from needle sites or difficulty in cannulation), or an unexplained decrease in Kt/V on a constant dialysis prescription (56). Graft surveillance relies on documentation of increased intra-access pressure or decreased access flow arising from significant stenosis. The three major surveillance methods require using specialized equipment and trained staff (67–70). The positive predictive value of various monitoring tests for >50% graft stenosis has been determined by obtaining fistulograms in patients with abnormal monitoring parameters. A positive predictive value ranging from 70 to 100% has been documented for clinical monitoring (56,58,70–72), static venous pressure (67), flow monitoring (69,73), and Duplex ultrasound (72).

Not all grafts with stenosis are at risk for thrombosis (74,75). In two observational studies, patients with a high likelihood of graft stenosis by abnormal surveillance criteria had a relatively low (approximately 40%) likelihood of clotting during the ensuing 3 mo, in the absence of any intervention (74,75). Given that only approximately 50% of grafts with significant stenosis are at risk for thrombosis, implementation of a program for stenosis surveillance, with aggressive referral for preemptive angioplasty, necessarily results in many superfluous interventions. Nevertheless, it may be an acceptable tradeoff to do some superfluous angioplasties in exchange for reducing the frequency of graft thrombosis.

Several observational studies have evaluated the impact of introducing a graft monitoring program in a dialysis center on the frequency of graft thrombosis. Each reported a substantial decrease (by 41 to 77%) in the rate of graft thrombosis during the monitoring/surveillance period, as compared with the historical control period. This reduction in graft thrombosis was observed for clinical monitoring (23,58,71), dialysis venous pressure measurements (67,76), and flow monitoring (11).

Six randomized studies, using a variety of graft surveillance methods, evaluated the impact of stenosis surveillance with preemptive angioplasty on graft outcomes (72,73,77–80) (Table 3). The frequency of angioplasty was always higher in the surveillance groups, documenting that surveillance increases the detection of stenotic lesions. Unfortunately, five of the six studies were negative, showing no difference in thrombosis-free survival or cumulative graft survival between the surveillance group and the control subjects. Only one study observed a superior graft survival in patients who underwent stenosis surveillance (79). Given the relatively low enrollment in these

Table 3. Randomized clinical trials on graft surveillance[a]

Reference	Surveillance Method	No. of Patients		PTA/yr		Improved Outcomes with Surveillance?	
		Control	Surveillance	Control	Surveillance	Decreased Thrombosis?	Increased Cumulative Survival?
Lumsden *et al.*, 1997 (78)	Doppler ultrasound	32	32	0	1.5	No	N/A
Ram *et al.*, 2003 (80)	Access flow	34	32	0.22	0.34	No	No
	Doppler ultrasound		35		0.65	No	No
Moist *et al.*, 2003 (73)	Access flow	53	59	0.61	0.93	No	No
Dember *et al.*, 2004 (77)	Static DVP	32	32	0.04	2.1	No	No
Malik *et al.*, 2005 (79)	Doppler ultrasound	92	97	N/A	N/A	N/A	Yes
Robbin *et al.*, 2006 (72)	Doppler ultrasound	61	65	0.64	1.06	No	No

[a]DVP, dialysis venous pressure; N/A, not available; PTA, percutaneous transluminal angioplasty.

studies, they may have been underpowered to detect a relatively modest beneficial effect of access surveillance, but they seem to exclude a more substantial benefit. An ongoing randomized study is evaluating whether the use of a portable ultrasound device decreases graft failure. This study, with a planned enrollment of 220 patients, should be completed in mid-2008 (ClinicalTrials.gov identifier NCT00309348). In view of the preponderance of negative randomized studies, it is disappointing that the 2006 KDOQI vascular access guidelines continue to promote uncritically surveillance for graft stenosis and preemptive angioplasty as a method to reduce graft thrombosis (81).

Why does graft surveillance with preemptive angioplasty not decrease graft thrombosis? The benefit of angioplasty is short-lived. Two studies using access flows as a surrogate measure of graft stenosis documented a return of access flows to preangioplasty levels in 20% of patients within 1 wk and in 40% within 1 mo (69,73). Stenosis after angioplasty develops faster than does *de novo* access stenosis, suggesting that the vascular injury that is produced by angioplasty accelerates the underlying process (82). How can the benefit of angioplasty be enhanced? A pilot study suggested that vascular brachytherapy increases the primary patency of grafts after angioplasty (83). Two retrospective studies suggested that stents, by creating a rigid scaffold for the vessel, prolong graft patency after thrombectomy and angioplasty (84,85). However, randomized studies to address this issue are sorely lacking.

Pharmacologic Interventions to Reduce Graft Thrombosis
A series of elegant pathologic and immunochemical studies have elucidated the cellular mechanisms that culminate in graft stenosis (86,87). Access failure results from aggressive vascular neointimal hyperplasia, characterized by proliferation of vascular smooth muscle cells and accumulation of matrix, that progressively occludes the vascular lumen (87). A number of vasoactive substances that modulate vasoconstriction, inflammation, and thrombosis may affect the severity of neointimal hyperplasia. Thus, the variability in vascular access outcomes among patients is likely related to the integrity of the endothelium, as well as individual variations in the expression of these vasoactive substances. Given the disappointing results of mechanical approaches (preemptive angioplasty) in preventing graft failure, a pharmacologic approach to prevent neointimal hyperplasia may be more productive.

A number of completed or ongoing clinical trials have addressed this important clinical question (Table 4). Dipyridamole inhibits vascular smooth cell proliferation *in vitro* (88), and a small, single-center, double-blind, randomized clinical trial demonstrated a 50% reduction in graft thrombosis in patients who received dipyridamole, as compared with the placebo control subjects (89). An ongoing large, multicenter, randomized clinical trial sponsored by the National Institutes of Health is evaluating the efficacy of Aggrenox (long-acting dipyridamole and low-dosage aspirin) in preventing graft failure (90). Similarly, a very small, single-center, double-blind, randomized clinical trial reported that fish oil reduces graft thrombosis (91), and a large, ongoing, randomized, multicenter study is evaluating this agent (92). Another randomized clinical trial found that low-intensity anticoagulation with warfarin did not reduce graft thrombosis but was associated with an excess of life-threatening hemorrhagic events (93). Similarly, the combi-

Table 4. Pharmacologic prophylaxis of graft stenosis/thrombosis (randomized studies)

Reference	Drug	Status of Study	No. of Patients	Results
Sreedhara *et al.*, 1994 (89)	Dipyridamole, aspirin, or dipyridamole + aspirin	Completed	84	Decreased graft thrombosis with dipyridamole (with or without aspirin); aspirin alone tended to increase thrombosis
Dixon *et al.*, 2005 (90)	Aggrenox (long-acting dipyridamole + low-dosage aspirin)	Ongoing (to end in January 2008)	1056 (target)	Pending
Schmitz *et al.*, 2002 (91)	Fish oil	Completed	24	Decreased graft thrombosis with fish oil
Lok, 2006 (92)	Fish oil	Ongoing (to end in June 2009)	232 (target)	Pending
Crowther *et al.*, 2002 (93)	Warfarin	Completed	107	No decrease in graft thrombosis, but increased major bleeds with warfarin
Kaufman *et al.*, 2003 (94)	Clopidogrel + aspirin	Completed	200	No decrease in graft thrombosis, but increased major bleeds with clopidogrel + aspirin

nation of clopidogrel and aspirin was no better than placebo in preventing graft thrombosis but doubled the risk for bleeding complications (94). Perivascular delivery of antiproliferative drugs permits achieving high local drug levels while avoiding systemic toxicity. Two studies using a porcine arteriovenous graft model demonstrated reduction of neointimal hyperplasia and graft stenosis by perivascular delivery of paclitaxel (95,96). No human studies have been reported to date using local drug delivery systems to prevent graft failure.

Dialysis Catheters

Treatment of Catheter Thrombosis or Malfunction

When catheter dysfunction occurs immediately after insertion, placement is likely to be the problem. However, if a catheter that has previously functioned well begins to develop flow problems, an intraluminal or extraluminal thrombus is likely. Catheter thrombosis is recognized in extreme cases by the inability to aspirate blood from the dialysis port. In less extreme cases, it manifests as suboptimal dialysis blood flow with high negative arterial pressures, resulting in recurrent dialysis machine alarms.

Low catheter blood flows may be corrected by forceful aspiration and flushing with a small syringe, changing the patient's position, or switching the arterial and venous lines. When these measures are unsuccessful, malfunctioning catheters can be treated empirically by instillation of a thrombolytic agent (urokinase, 5000 units/ml, or tissue plasminogen activator, 2 mg per port) into the catheter lumen for 30 to 60 min. If the first thrombolytic instillation is unsuccessful in resolving the flow problem, then a second instillation can be tried. Urokinase was withdrawn from the US market because of a viral contamination but is available in Europe. The published trials have varied in their definition of catheter adequacy after treatment with a thrombolytic agent (minimal acceptable blood flow and duration of benefit) but reported success in 60 and 95% of catheters (97–102). The benefit is often short-lived, with a median time of 4 wk before requiring another thrombolytic instillation (97,103).

If catheter malfunction persists despite repeated thrombolytic instillations and the flow is insufficient to provide an adequate dialysis dose, then the catheter should be exchanged over a guidewire. The catheter should be imaged to evaluate for the presence of a fibrin sheath, which may need to be disrupted in selected cases. A randomized study found that fibrin sheath stripping was comparable to urokinase infusion for management of malfunctioning dialysis catheters in terms of primary patency (104). A second randomized study observed superior primary patency after catheter exchange, as compared with fibrin sheath stripping (105). Dysfunction is more common in femoral catheters than in internal jugular vein catheters (106). The reason is not entirely clear but may be due in part to a kinking of femoral catheters when the patient is sitting (hip flexion).

Catheter-dependent patients are at risk for receiving inadequate dialysis. In one study, the proportion of dialysis patients with a Kt/V <1.2 was 25.2% in those using catheters, as compared with 9.7% of those with a permanent access (107). The 2006 KDOQI guidelines recommend instillation of a thrombolytic agent into all catheters with a persistently low dialysis blood flow rate (<300 ml/min) (81). This recommendation has been challenged recently (108). In a large prospective study, a low urea reduction ratio was documented in only 22% of patients with consistently low dialysis blood flows. The authors recommended that treatment with thrombolytic agents be reserved for the subset of patients who are unable to achieve their target Kt/V with the existing catheter flow rate (most commonly, large men).

Prophylaxis of Catheter Thrombosis

To prevent catheter thrombosis, dialysis nurses routinely instill an anticoagulant solution into both catheter ports at the end of each dialysis session. Heparin is the primary choice in the United States, whereas citrate is used commonly in Europe. There is no consensus about the optimal concentration of heparin, with concentrations ranging from 1000 to 5000 U/ml used at different dialysis centers. Even when the volume of lock solution is meticulously matched to that of the lumen, an aliquot always leaks systemically (109). In one prospective study, instillation of a heparin lock (5000 U/ml) into the catheter lumens after dialysis prolonged the partial thromboplastin time for 3 to 4 h (110). This may increase the risk for serious bleeding complications in susceptible patients.

Few studies have compared the efficacy and safety of heparin and citrate locks (Table 5). In a small prospective study, one catheter lumen was instilled with 30% citrate and the other with

Table 5. Anticoagulant lock solutions for prophylaxis against catheter thrombosis[a]

Reference	Study Design	Thrombolytic Instillations per 1000 Catheter-Days			Catheter Exchanges Caused by Malfunction per 1000 Catheter-Days		
		Citrate	Heparin	P	Citrate	Heparin	P
Dogra *et al.*, 2002 (114)	RCT	N/A	N/A	0.82	N/A	N/A	
Grudzinski *et al.*, 2006 (112)	Retro	3.2	4.1	0.07	1.9	1.8	0.89
Lok *et al.*, 2006 (113)	P-NR	3.3	5.5	0.002	1.6	3.0	0.01
Weijmer *et al.*, 2005 (115)[b]	RCT	40% of catheters	46% of catheters	0.56	0.8	0.7	0.64

[a]P-NR, prospective, nonrandomized; RCT, randomized clinical trial; Retro, retrospective.
[b]Major bleeds occurred in 0.6 of citrate group *versus* 2.0 per 1000 catheter-days of heparin group (*P* = 0.01).

heparin (5000 U/ml). There was no difference in the frequency of thrombosis between the two lumens (111). A large retrospective study found no difference between heparin and citrate locks in terms of the frequency of thrombolytic instillation or catheter exchange as a result of malfunction (112). A prospective study evaluated catheter thrombosis in two consecutive time periods, one in which heparin was used and the second in which citrate was used. The frequencies of tissue plasminogen activator instillation and catheter exchange as a result of malfunction both were lower with the citrate lock, as compared with the heparin lock (113). In a randomized comparison of 4% citrate and heparin (5000 U/ml), the frequency of urokinase instillation was similar (114). Finally, a randomized study comparing 30% citrate with heparin (5000 U/ml) observed similar frequencies of urokinase instillation and catheter exchange as a result of malfunction but a three-fold higher risk for major bleeding complications in the heparin group (115). In summary, citrate locks are at least as effective as heparin in preventing catheter thrombosis but less likely to induce systemic bleeding. Finally, heparin-induced thrombocytopenia affects 1 to 4% of hemodialysis patients and precludes further use of heparin (116,117).

A randomized study compared fixed low-dosage warfarin (1 mg/d) with placebo for prophylaxis against catheter-related thrombosis (118). There was no difference in the risk for thrombosis among the two treatment groups. A recent randomized trial observed a dramatic reduction of catheter thrombosis in patients who were treated with therapeutic warfarin (target international normalized ratio 1.8 to 2.5), in conjunction with ticlopidine. Remarkably, none of the patients in this study experienced a bleeding complication (119).

Catheter-Related Vascular Stenosis and Thrombosis

Catheters can produce stenosis or thrombosis of the central vein in which they are inserted (120). This complication is more common with subclavian catheters than with internal jugular catheters (121) but can also occur with internal jugular veins after prolonged use. Routine ultrasounds that were obtained in 143 asymptomatic patients with a history of tunneled dialysis catheters documented partial or complete internal jugular vein thrombosis in 26% (122). The risk for pulmonary embolism with catheter-related central vein thrombosis is unknown. A minority of patients with central vein stenosis present with diffuse ipsilateral upper extremity edema, which can be treated with angioplasty, but the clinical benefit is short-lived because of rapid recurrence of the stenosis (123). Refractory central vein stenosis can be treated with stent deployment, but the outcomes are disappointing, with a 1-yr primary patency of only 14 to 25% (123–126). Many patients require repeated angioplasty of central vein stenosis because of recurrent upper extremity edema. A previously unrecognized central vein stenosis may become clinically evident after creation of an ipsilateral vascular access. If the stenosis cannot be resolved, then ligation of the vascular access may be required to alleviate the edema.

Symptomatic lower extremity deep vein thrombosis has been reported in 26% of patients with tunneled femoral catheters (106). None had symptomatic pulmonary emboli. Because the femoral catheter represented their last possible access, they received anticoagulation without removal of the catheter. Fortunately, it was possible to resolve the thrombosis while salvaging the catheter, so dialysis delivery was not jeopardized. In the rare patient in whom bilateral femoral catheters have failed, a transhepatic or translumbar tunneled catheter may be placed as a last-ditch option (127,128).

Diagnosis and Treatment of Catheter-Related Bacteremia

Bacteremia frequently complicates catheter use in hemodialysis patients (129). It occurs less commonly with tunneled than nontunneled dialysis catheters (130,131). In a prospective follow-up of 108 patients with tunneled dialysis catheters, the first episode of catheter-related bacteremia developed in 35% within 3 mo and in 48% after 6 mo (107). The frequency of catheter-related bacteremia has ranged from 2.0 to 5.5 episodes per 1000 catheter-days at several dialysis centers (114,130,132–139). A serious complication (endocarditis, osteomyelitis, septic arthritis, epidural abscess, or death) occurs in 5 to 10% of patients with catheter-related bacteremia (129) and is 3.5-fold more likely when the infection is due to *Staphylococcus aureus* (140).

By the most rigid criteria, diagnosis of catheter-related bacteremia requires positive blood cultures obtained from the catheter and from a peripheral vein, with the quantitative colony count being at least four-fold higher in the catheter sample (141). This level of proof may be difficult to achieve in dialysis patients because most US dialysis units are freestanding, peripheral veins are often unavailable, blood cultures are shipped to remote laboratories, and handling of culture bottles is not standardized (129). Moreover, there may be no difference in the colony counts between the catheter and the peripheral vein if the blood cultures are drawn while the patient is undergoing dialysis. A more practical definition is the presence of positive blood cultures in a febrile catheter-dependent patient, in the absence of alternative sources of infection upon clinical evaluation (129).

The initial choice of antibiotics in patients with catheter-related bacteremia is empiric and requires knowledge of the typical organisms that are grown at that dialysis center and their pattern of antibiotic sensitivities. In some European and Asian dialysis units, catheter-related bacteremia is almost exclusively due to *S. epidermidis*, and anti-staphylococcal antibiotics are sufficient in those units. In contrast, several US centers have observed a substantial proportion (20 to 40%) of infections with a Gram-negative rod (132–135,137,138,142). This pattern of organisms mandates empiric therapy including an antibiotic with broad-spectrum coverage against a variety of Gram-negative organisms, such as an aminoglycoside or a third-generation cephalosporin. The latter agent may be preferred because of the high (approximately 33%) risk for aminoglycoside ototoxicity in dialysis patients (143). In centers with frequent methicillin-resistance *Staphylococcus* infections, vancomycin should be included in the initial choice of antibiotics. Serum antibiotic levels are not readily available at most freestanding dialysis units. However, vancomycin at 20 mg/kg for the loading dose and 500 mg after subsequent dialysis sessions results in therapeutic vancomycin levels (144). Similarly, cefazolin 1 g

after each dialysis session produces therapeutic drug levels (145).

Once the organism and its sensitivities are available, it is important to switch to the most narrow-spectrum antibiotic that is feasible, so as to limit the emergence of highly resistant infections. The optimal duration of antibiotic therapy for uncomplicated catheter-related bacteremia is uncertain. The Infectious Diseases Society of America recommends a 2-wk course (141), whereas KDOQI recommends at least 3 wk (81). Bacteremia that is complicated by metastatic infection requires a 6-wk course (141).

If a patient's fever persists 2 to 3 d after initiation of systemic antibiotics (next dialysis session), then the catheter must be removed. However, there is an ongoing controversy about the optimal management of the dialysis catheter in the remaining patients (those without persistent fever) (129). One option is to continue systemic antibiotics alone, in an attempt to salvage the infected catheter. This approach should be discouraged, because bacteremia recurs in approximately 75% of patients once the course of antibiotics has been completed (98,135,138,146,147). In a recent prospective study, the risk for treatment failure was five-fold higher in patients with attempted catheter salvage, as compared with patients in whom the infected catheter was removed (140). A second option is to remove the catheter promptly once bacteremia has been confirmed. The patient then undergoes dialysis with a temporary catheter, and a new tunneled catheter is inserted once the bacteremia has resolved. Although this approach removes the source of infection, it subjects the patient to multiple access procedures and disrupts the outpatient dialysis schedule. A third approach is to replace the infected catheter for a new one over a guidewire. This option limits each patient with catheter-related bacteremia to one access procedure and minimizes the impact on outpatient dialysis. A number of uncontrolled studies have documented high cure rates with catheter-related bacteremia after catheter exchange over a guidewire (132,138,148,149). Moreover, a nonrandomized, controlled study observed similar infection-free catheter survival among patients with catheter exchange over a guidewire and those who were treated with catheter removal and delayed placement of a new catheter (142). The efficacy of guidewire exchange in resolving catheter-related bacteremia may have been overestimated in these studies, given that approximately 20% of patients required immediate catheter removal and were excluded from the analysis of outcomes.

Antibiotic Locks for Treatment of Catheter-Related Bacteremia

There has been a growing appreciation of the importance of biofilm in the pathogenesis of catheter-related bacteremia (150–153). Biofilm forms on the inner lumen of central vein catheters within 24 h of their insertion. Bacteria in biofilm are resistant to the antimicrobial action of antibiotics at standard therapeutic plasma concentrations but are frequently susceptible to higher concentrations. An "antibiotic lock" is a concentrated antibiotic solution that is instilled into the lumen of the dialysis catheter,

in conjunction with an anticoagulant (Figure 3). The goal of an antibiotic lock is to sterilize the catheter biofilm while salvaging the catheter. A number of studies that were performed in tunneled dialysis catheters (133,137,154–156), as well as those used for chemotherapy or total parenteral nutrition (155,157–160), have documented an approximately 70% clinical cure rate in patients who were treated with systemic antibiotics in conjunction with an antibiotic lock. No randomized studies have compared the antibiotic lock approach with routine catheter replacement in patients with dialysis catheter-related bacteremia. However, in nonrandomized, controlled studies infection-free catheter survival was similar with both treatment strategies (133,137).

The success rate of an antibiotic lock in curing catheter-related bacteremia is highly dependent on the organism (137,155,156). The cure rate was 87 to 100% for Gram-negative infections, 75 to 84% for *S. epidermidis* infections, but only 40 to 55% for *S. aureus* infections. Thus, the overall success of an antibiotic lock in curing an unselected group of catheter-dependent dialysis patients may vary substantially depending on the distribution of infecting organisms. Of interest, treatment failure with *S. aureus* bacteremia is four times more common even in treatment regimens that do not involve an antibiotic lock (140).

Regardless of one's preferred strategy for managing catheter-related bacteremia, it is imperative to have a designated individual track the results of the blood cultures and ensure that the
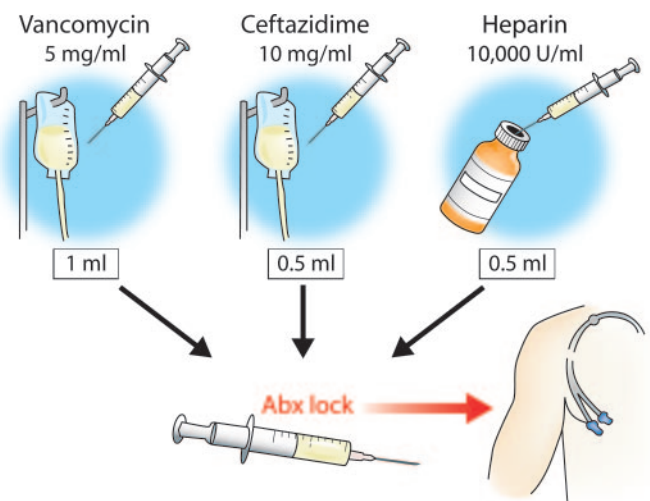

Figure 3. How to administer an antibiotic lock in patients with catheter-related bacteremia. The dialysis nurse prepares the antibiotic lock by mixing an aliquot of antibiotic from the solution used for systemic administration with an aliquot of heparin into a single syringe. Note that the final antibiotic concentration in the lock is approximately 100-fold higher than therapeutic plasma antibiotic concentrations. The antibiotic-heparin lock solution is instilled into each catheter port at the end of the dialysis session and aspirated immediately before initiation of the next dialysis session. If the systemic antibiotic regimen is changed, then the antibiotic lock components are changed accordingly. Once the course of systemic antibiotics is completed, standard heparin locks are resumed.

appropriate type and dosage of antibiotics is used. A collaborative team approach decreases recurrent bacteremia and death from sepsis, as compared with the usual physician-managed care (161).

Prophylaxis of Catheter-Related Bacteremia
Minimizing catheter-related bacteremia requires the dialysis staff to follow aseptic technique, including washing hands, wearing clean gloves, and minimizing the duration of air exposure of the catheter lumens. The catheter hubs should be soaked with 2% chlorhexidine or povidone-iodine before connection and disconnection of the catheter from the dialysis tubing. Both the dialysis staff and the patient should wear masks when the catheter lumen is exposed. There does not seem to be a difference between application of gauze and transparent dressing to the exit site between dialysis sessions. Conscientious adherence with this protocol can substantially reduce—but not eliminate—the frequency of catheter-related bacteremia (162).

Given that biofilm is the major source of catheter-related bacteremia, an antimicrobial catheter lock solution may reduce catheter-related bacteremia (129). Potential lock solutions include standard antibiotics (129) or antimicrobial agents, such as taurolidine and 30% citrate (163–165). Five randomized clinical trials documented substantial efficacy of antibiotic locks (gentamicin, minocycline, or cefotaxime) in prophylaxis against catheter-related bacteremia (114,166–169) (Table 6). An additional three studies documented marked reductions in the frequency of catheter-related bacteremia with the use of taurolidine or 30% citrate lock solutions (115,170,171).

An alternative approach to instilling antimicrobial lock solutions is to apply a topical antibiotic ointment at the exit site, in an attempt to sterilize the skin flora from which the biofilm derives infection. Two randomized studies, one using topical mupirocin and a second using Polysporin ointment, demonstrated marked reduction in the frequency of catheter-related bacteremia (134,172). Whether applied as a lock solution or as an ointment, there is a potential concern that long-term use of prophylactic antibiotics may produce highly resistant infec-

tions. An antibacterial honey (Medihoney) applied to the exit site has been shown to be equivalent to mupirocin ointment for prophylaxis of catheter-related bacteremia (173). Finally, a *S. aureus* vaccine provides partial protection against *S. aureus* bacteremia in hemodialysis patients with grafts and fistulas (174); it is unknown whether this approach would prevent catheter-related bacteremia.

Tradeoffs of Vascular Accesses
The Fistula First initiative has indeed been successful in increasing fistula placement in the United States. In the 5-yr period between 1998 and 2003, fistula prevalence increased from 26 to 35% (175). An unintended consequence of this initiative was a concurrent increase in catheter prevalence from 19 to 27%. Mortality is two- to three-fold higher in patients who initiate dialysis with a catheter, as compared with those who use a fistula (176,177). Moreover, mortality is reduced by approximately 50% in patients who switch from a catheter to a permanent access (fistula or graft), as compared with those who remain catheter dependent (178). Clearly, a dialysis patient with a working fistula is better off than one with a working graft. However, a patient with a working graft is better off than one with an immature fistula and prolonged catheter dependence with all its complications. A subset of patients are at high risk for primary fistula failure and may be predicted by simple clinical parameters (31).

The benefit of fistulas over grafts may have been overestimated in much of the literature, owing to the exclusion of fistulas that fail to mature from the overall analysis. The cost–benefit of the two types of access is less clear when intention-to-treat analysis is performed. In this regard, a recent observational study compared multiple outcomes in patients who received an upper arm fistula or graft after failure to mature of a forearm fistula (179). As compared with patients who received a secondary graft, those who received a fistula had a higher failure-to-mature rate, required more interventions to achieve maturation, had more prolonged catheter dependence, and experienced more episodes of catheter-related bacteremia.

Table 6. Catheter lock solutions for prophylaxis against CRB[a]

Reference	Type of Lock Solution	Rate of CRB (per 1000 catheter-days)	
		Control	Intervention
Dogra *et al.*, 2002 (114)	Gentamicin	4.2	0.3
McIntyre *et al.*, 2004 (167)	Gentamicin	4.0	0.3
Kim *et al.*, 2006 (166)	Gentamicin/cefazolin	3.1	0.4
Nori *et al.*, 2006 (168)	Gentamicin	3.1	0
	Minocycline		0.4
Saxena *et al.*, 2006 (169)	Cefotaxime	3.6	1.7
Allon, 2003 (170)	Taurolidine	5.6	0.6
Betjes and van Agteren, 2004 (171)	Taurolidine	2.1	0
Weijmer *et al.*, 2005 (115)	30% citrate	4.1	1.1

[a]CRB, catheter-related bacteremia.

However, once access maturation was accomplished, fistulas required far fewer interventions than did grafts to maintain long-term patency for dialysis.

The tradeoffs between fistulas and grafts in a given patient depend on the likelihood of fistula maturation, the frequency of catheter-related bacteremia, and the patient's life expectancy. For example, in a patient who is at high risk for an immature fistula and has a relatively limited life expectancy (<2 yr), placement of a graft may be more cost-effective. A carefully conducted randomized clinical trial is sorely needed to quantify the tradeoffs of fistulas *versus* grafts with respect to patient morbidity, mortality, quality of life, and economic costs.

Disclosures

None.

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