Hemodialysis Tunneled Catheter Noninfectious Complications

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Abstract

Noninfectious hemodialysis catheter complications include catheter dysfunction, catheter-related thrombus, and central vein stenosis. The definitions, causes, and treatment strategies for catheter dysfunction are reviewed below. Catheter-related thrombus is a less common but serious complication of catheters, requiring catheter removal and systemic anticoagulation. In addition, the risk factors, clinical manifestation, and treatment options for central vein stenosis are outlined.

Abrégé

La défaillance du cathéter, la formation d'un thrombus en raison de la présence du cathéter et la sténose des veines centrales constituent les principales complications non infectieuses associées à l'utilisation d'un cathéter pour la dialyse. Les définitions de la défaillance du cathéter, ses causes ainsi que les stratégies de traitement préconisées sont discutées dans le présent chapitre. La formation d'un thrombus due à la présence du cathéter est plus rare. Elle représente néanmoins une complication sérieuse qui requiert le retrait du cathéter et l'administration d'un anticoagulant systémique. Enfin, ce chapitre expose les facteurs de risque, les manifestations cliniques ainsi que les options de traitement associés à la sténose des veines centrales.

Keywords

catheter dysfunction, catheter-related thrombus, central vein stenosis

Introduction

Although considered second and third options to arteriovenous (AV) access, hemodialysis central venous catheters are still frequently used in both incident and prevalent hemodialysis patients. These catheters are associated with both infectious and noninfectious complications, leading to increased morbidity and mortality in this population.[1] These complications can occur at the time of catheter insertion (eg, bleeding, pneumothorax) or may develop at any time over the duration of catheter use. Infectious complications are discussed elsewhere (see Miller et al[2]). Below we review noninfectious complications including common problems such as catheter thrombosis and dysfunction, and central vein stenosis.

Catheter Dysfunction

There are a variety of definitions for catheter dysfunction in the literature (Table 1). The National Kidney Foundation Dialysis Outcome and Quality Initiative defines catheter dysfunction as failure to attain and maintain an extracorporeal blood flow, Qb, of 300 mL/min or greater at a prepump arterial pressure more negative than −250 mm Hg.[3] Approximately one-third of tunneled catheter removals are attributed to inadequate blood flow for dialysis.[3] However, with newer large bore catheter designs that can deliver higher Qb (>400 mL/min), it is possible catheter dysfunction may be present even before the Qb goes down to less than 300 mL/min.[4] Conversely, some patients will have Qb consistently below 300 mL/min, yet achieving all other targets implying adequate dialysis. Therefore, Qb alone may not be adequate for the detection of catheter dysfunction.

An analysis of data from DaVita dialysis facilities and the US Renal Data System of hemodialysis patients receiving treatment exclusively through a catheter showed that catheter dysfunction, as defined by blood flow rate less than 300 mL/min, occurred in almost two-thirds of patients during at least 1 treatment and 30% had 1 or more catheter dysfunction

Table 1. Proposed Definitions for Catheter Dysfunction.[3,5,8]

High arterial pressures (<−250 mm Hg)
High venous pressures (>250 mm Hg)
High pressure alarms
Decreased blood flow rates
Inability to withdraw and/or flush catheter lumens
Need to reverse lines
Reduced urea clearance (Kt/V < 1.2, or urea reduction
  ratio < 65%)

sessions per month.[6] This may lead to interventions, such as instillation of thrombolytic agents and/or catheter exchange after failure of conservative measures and medical management to attain adequate blood flow. Consequences include disruption in the delivery of dialysis care and increase in health resource utilization.[7]

Etiology of Catheter Dysfunction

Early catheter dysfunction. Early catheter dysfunction, which is most likely to occur within the first week of insertion, generally occurs as a result of mechanical issues, including patient malpositioning, mechanical kinking of the catheter (Figure 1), and incorrect catheter tip location.[8,9] To reduce the risk of dysfunction, the catheter tip should be positioned at the junction of the superior vena cava and right atrium,[10-12] and this position should be confirmed with fluoroscopy. This may be more important for placement of left-side catheters compared with the right. In a retrospective review of 532 tunneled internal jugular vein catheter insertions in 409 patients, catheters terminating in the superior vena cava or pericavoatrial junction had more episodes of catheter dysfunction or infection than catheters terminating in the mid- to deep right atrium (0.84 vs 0.35; *P* = .006).[13] This difference was not observed for right internal jugular catheters based on
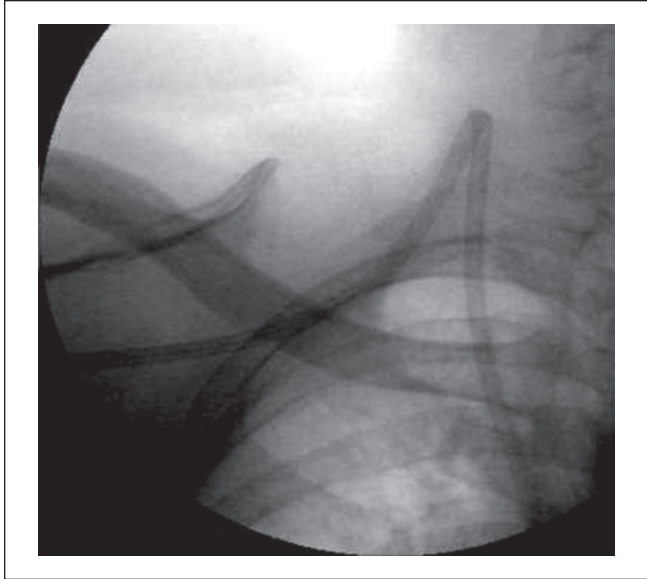

Figure 1. Radiograph of kinked catheter that can cause mechanical obstruction to blood flow.
Source. Courtesy of The Atlas of Dialysis Vascular Access by Dr. Vacchharajani, esrdncc.org/wp-content/uploads/2015/12/Access-Atlas.pdf.

tip position. Thus, early dysfunction should prompt consideration of catheter position, especially if the tip of the catheter is not positioned deep enough, or is touching the vessel wall. The problem can sometimes be resolved simply by repositioning the patient or adjusting the patient's neck position, which may fix a kink or move the catheter tip away from a vessel wall.

Late (delayed) catheter dysfunction. Late or delayed dysfunction refers to any catheter that previously functioned well but then later becomes dysfunctional, and therefore can occur weeks, months, or even years after its insertion. Injury to the

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Figure 2. A fibrin sheath extending from the cuff to the tip of the catheter.
Source. Courtesy of *The Atlas of Dialysis Vascular Access* by Dr. Vacchharajani, esrdncc.org/wp-content/uploads/2015/12/Access-Atlas.pdf.

vascular wall occurs at the time of catheter insertion, and any manipulation or repositioning of the catheter can lead to further injury. This results in both turbulent blood flow around the catheter and stimulation of the coagulation and inflammatory cascades.[9] A fibrin sheath (Figure 2), a combination of fibrinogen, lipoproteins, albumin, and coagulation factors, begins to form within 24 hours of catheter insertion.[14] Leukocytes adhere to the catheter surface, microorganisms get embedded, and over the next few weeks collagen is deposited as venous wall smooth muscle cells migrate toward the catheter tip. The sheath may partially or completely encase the catheter, extending beyond the catheter tip, leading to the disturbance of catheter blood flow. It is also associated with the development of thrombosis and infections.

Thrombosis. Thrombus-related catheter occlusion may occur in both early and late catheter dysfunction, although more commonly associated with late dysfunction. Intimal vessel injury, turbulent blood flow, and activation of coagulation cascades, with fibrin sheath formation, are major contributors to thrombus formation. Thrombus can occur intraluminally causing direct obstruction to blood flow, or extraluminally. Extraluminal thrombus such as right atrial or mural thrombus may cause extrinsic compression of the catheter, resulting in poor blood flow and inadequate dialysis.

Prevention of Catheter Dysfunction

Catheter instillation solutions

- Anticoagulant solutions

Locking solutions are instilled into catheters between hemodialysis treatments to maintain catheter patency, while at the same time have minimal risk of systemic anticoagulation. Sodium citrate (4%) or concentrated heparin solutions (1000 units/mL) are the current standard recommended locking solutions.[15] A meta-analysis of 13 randomized trials comparing heparin- and citrate-based locking solutions did not show any difference in thrombolytic use or catheter removal for poor flow.[16] There may be a benefit with the use of citrate in terms of reduced bleeding events; however, only 2 of 13 studies included in the meta-analysis reported bleeding episodes as an outcome.[17,18] Considerations such as infection prevention and local practice patterns, in addition to the above data, should be taken into account for the choice of locking solution in clinical practice.

- Recombinant tissue plasminogen activator

The Prevention of Catheter Lumen Occlusion with Recombinant tissue plasminogen activator vs heparin, pre-CLOT trial was a multicenter randomized controlled trial, which compared heparin (5000 U/mL) locking solution 3 times weekly with a regimen where tissue plasminogen activator (tPA; 1 mg in each lumen) was substituted for heparin at the midweek session (with heparin used in the other 2 sessions).[19] Overall catheter malfunction was lower in the tPA group, occurring in 22 of 110 patients (20%) compared with 40 of 115 patients (34.8%) in the heparin arm, an almost 2-fold higher risk of catheter malfunction in the heparin arm (hazard ratio, 1.91; 95% confidence interval [CI], 1.13-3.22; $P = .02$). Catheter-related and all-cause bacteremia rates were also lower in the tPA group compared with the heparin group. However, the study ended early due to difficult recruitment and had high discontinuation rates, precluding some subgroup analyses. Furthermore, the cost of managing patients with tPA was higher than managing those with heparin. Notably, a later economic evaluation of the pre-CLOT data showed that the higher cost of tPA compared with heparin was partially offset by cost savings from lower risk of hospitalization for catheter-related bacteremia in the tPA group, and increased use of rescue tPA for catheter malfunction in the heparin group.[20] Further study is warranted to determine if the routine use of tPA is superior to heparin- or citrate-based instillation protocols.

Systemic pharmacologic therapy

- Antiplatelet agents

These medications reduce platelet aggregation and inhibit thrombus formation, and are used for both primary and secondary prevention of thrombotic events. Commonly prescribed antiplatelet agents are aspirin and clopidogrel, whereas ticlopidine and sulfinpyrazone are less frequently used. Two systematic reviews examining the role of antiplatelet agents in maintaining hemodialysis vascular access have not provided any clear direction regarding their use for the prevention of catheter thrombosis.[21,22] In the most recent systematic review, only 1 small trial of 38 catheter patients was included in the analysis and did not show any significant difference in thrombosis between the use of aspirin versus warfarin.[21] The review by Hiremath et al examining bleeding risk in end-stage renal disease patients prescribed antiplatelet agents, with the secondary outcome

Table 2. Thrombolytic Regimens.

Type	Dose	Time	Delivery
Nonfunctioning catheter (Qb < 150/200 mL/min or inability to withdraw) (short or long dwell)	Typical dose: 2 mg tPA instillation (1 mg in each lumen) Alternative dose: 2 mg tPA per lumen	30 min after instillation (short dwell) Alternative: wait additional 2 h (long dwell) if 30 min fails[28]	tPA instilled as dwell for 30-60 min Alternatives: push one-third of dose every 10 min; advance the initial pushed tPA at 10- to 15-min intervals with 0.3 mL saline, or deliver via infusion pump over 30 min
Poor functioning catheter with dialysis stopped	2-4 mg tPA	As above	As above
Poor functioning catheter with dialysis ongoing (eg, Qb > 200 mL/min) but frequent alarms (intradialytic infusion)	2-4 mg tPA	Over 1 h	Via infusion pump—delivered in the dialysis circuit with catheter lumens reversed for 30 min, then with normal positions for next 30 min
Poor functioning catheter post dialysis (lock, post hemodialysis dwell, overnight dwell)	1-2 mg tPA per lumen	Until next dialysis	tPA instilled as push; allowed to dwell in catheter lumen for 48-72 h, until the next hemodialysis session

Note. tPA = tissue plasminogen activator.

of access thrombosis, included 3 studies of hemodialysis patients with catheters. Catheter patency improved with antiplatelet agents; however, weaknesses in the study design and methodology precluded any definitive conclusions.[22] In addition, the potentially higher risk of bleeding should be considered if one wants to use an antiplatelet agent for this indication.[22,23]

- Oral anticoagulants

Warfarin has also been studied for the prevention of catheter malfunction but failed to show a significant benefit in a systematic review of randomized controlled trials comparing anticoagulant interventions with conventional care for the prevention of catheter malfunction in hemodialysis patients.[24] In addition, warfarin is associated with a significantly higher risk of bleeding in dialysis patients; therefore, risks and benefits should be carefully weighed before using anticoagulation for this indication.[25,26]

Treatment of Catheter Dysfunction

Thrombolytic agents and protocols. Before using a thrombolytic agent, conservative measures such as flushing the catheters with saline, checking for kinks, and patient repositioning should be performed. Other considerations include reconstitution and stability of tPA. Several studies have examined the use of tPA protocols in the treatment of catheter dysfunction and/or occlusion. Some suggested methods of use are provided in Table 2. A prospective nonrandomized study of 172 catheters comparing alteplase use at the clinical discretion of the dialysis team versus a protocolized approach with specific defined criteria for use did not show any differences in alteplase use or catheter exchange rates between the 2 groups.[27] Another prospective, randomized, multicenter study

compared an alteplase push protocol with a dwell protocol in 82 patients in an intention to treat analysis. No statistical difference was observed between the 2 groups in the primary outcome of achieving a post-thrombolytic blood flow greater than or equal to 300 mL/min; however, the study did not reach the sample size of 180 patients to detect 20% difference between the groups, at 80% statistical power.[28] The comparison of alteplase tissue plasminogen activator high-dose vs low-dose in restoring hemodialysis catheter function, ALTE-DOSE study was a retrospective, single-center study comparing the efficacy of 1.0 mg/lumen with 2.0 mg/lumen tPA to each lumen of the catheter and allowed to dwell for 30 minutes on the restoration of function in thrombotic dysfunctional catheters.[8] In this study, catheter loss was significantly higher in those who received 1 mg/lumen compared with those receiving 2 mg tPA (HR, 2.75; 95% CI, 1.25-6.04).

Interventional therapies

Angioplasty (fibrin sheath plasty). When catheters are changed for malfunction, the presence of fibrin sheath has been reported to be as high as 70%. One trial reported that performing an angioplasty to disrupt the fibrin sheath at the time of catheter exchange resulted in longer catheter patency, as well as modest gains in blood flow and clearance.[29] Observational studies show rates of subsequent infection or catheter dysfunction post catheter exchange in patients who had undergone fibrin sheath disruption are similar to those who had catheter exchange without angioplasty because a fibrin sheath was not present.[30,31]

Fibrin sheath stripping. Fibrin sheath stripping can be done using a snare or an intravascular brush.[32,33] The literature is primarily in the form of uncontrolled case reports and case series, and does report good short-term safety and success rates; however, long-term data on efficacy are lacking.[34]

Central Vein Stenosis

Overview and Pathophysiology

Central vein stenosis remains one of the most common vascular access–related complications, with an occurrence rate of up to 40% in prevalent hemodialysis patients despite implemented measures to reduce risk factors associated with stenosis.[35,36] Central vein stenosis is primarily caused by prior or current use of central venous devices such as hemodialysis catheters,[35,37-40] peripherally inserted central venous catheters (PICCs),[41,42] and cardiac implantable electronic devices (CIEDs).[37,43-48] Common sites where stenosis occurs include the subclavian vein, innominate vein (brachiocephalic vein), cephalic arch (subclavian-cephalic junction), and superior vena cava.

The initial injury occurs as a direct vascular injury at the time of catheter insertion, which is then perpetuated by the presence of an indwelling foreign body causing turbulent blood flow and mechanical irritation. Subsequent to vessel wall trauma, there is increased inflammation, activation of leukocytes, and release of myeloperoxidase, resulting in the activation of the coagulation cascade. These changes lead to smooth muscle cell proliferation and vein wall thickening.[9,37,49,50] Stenosis of central veins may interfere with the creation and development of an AV access. Furthermore, symptoms of central vein stenosis may not manifest until creation of an AV access in the ipsilateral extremity; thus, the true incidence and prevalence of stenosis is unknown because rates reported in the literature are limited to symptomatic patients.[37]

Risk Factors for Central Vein Stenosis

Increased risk for the development of central vein stenosis is associated with the location of a central venous device. Subclavian vein catheters have the highest risk of stenosis, occurring in approximately 30% to 50% of patients.[35,51-55] However, despite generally recognized as lower risk than subclavian vein catheterization, internal jugular catheters are frequently associated with stenosis, with incidence as high as 25% to 40% in some studies.[56-59] In one study of 143 patients with a right internal jugular catheter, venous occlusion was detected by ultrasound in 62%.[58] The left internal jugular vein carries even higher risk of central vein stenosis than the right internal jugular, likely due to its complex anatomical pathway and multiple angulations.[37,60] Increased number of catheter placements[52,53] and longer duration of catheter placement[35,52] are also associated with higher incidence of stenosis.

Any central vein device predisposes one to the risk of central vein stenosis. Indwelling CIEDs causing central vein stenosis have been reported in 22% to 64% nonhemodialysis patients, although many were incidentally detected radiographically without symptoms of venous hypertension.[45-47] However, several studies of hemodialysis patients demonstrate symptomatic stenosis in hemodialysis patients, especially those with ipsilateral AV access creation.[43,44,48] Central vein stenosis is estimated to occur in about 10% of all patients with a PICC. A retrospective study of 119 nondialysis patients with PICC placement showed venous thrombosis rates of 23% overall, with the lowest rate of 10% in the brachial vein but 57% in the cephalic vein.[41,42] Subcutaneous ports for chemotherapy are also associated with increased risk for stenosis.[61]

Clinical Manifestations of Central Vein Stenosis

The symptoms of central vein stenosis occur as a result of venous hypertension behind the obstruction. However, this may often go undetected unless there is an ipsilateral functioning AV access. Detection may also occur incidentally during the evaluation of a dysfunctional AV access.

Symptomatic[37-40] features of central vein stenosis vary, depending on the site of obstruction. Arm edema, pain, and erythema from venous engorgement are common, sometimes even leading to skin breakdown. Other findings included ipsilateral breast swelling and dilated collateral veins on the upper chest, shoulder, and upper arm (*Atlas of Dialysis Vascular Access*; esrdncc.org/wp-content/uploads/2015/12/Access-Atlas.pdf). Patients may develop superior vena cava syndrome and rarely pleural effusions. Several AV access findings may occur when a patient develops central vein stenosis, including engorged, pulsatile AV fistula, positive arm elevation test, increased difficulty in needling the access, increased bleeding time after removal of needles due to elevated venous pressure, and poor dialysis adequacy.

Diagnosis of Central Vein Stenosis

Central venous stenosis may be suspected in any patient with a previous history of central venous access. A higher index of suspicion should occur in anyone with a history of multiple catheters, especially if any physical examination features of central vein stenosis (see above) are present. Several diagnostic imaging modalities may be used to confirm the diagnosis.

- Duplex ultrasonography

Ultrasound is suboptimal for the evaluation of central veins due to interference by the bony thorax and overlapping soft tissue. However, ultrasound avoids the use of radiocontrast and could be considered in those in whom contrast should be avoided (eg, contrast allergy).

- Angiography

Angiography is the preferred tool to demonstrate significant stenosis (>50%), but it is often difficult to determine clinically significant stenosis on angiography alone. The presence

of dilated collateral veins centrally usually support that stenosis is clinically significant.

- Magnetic resonance angiography

It is recommended that this imaging modality be avoided in stage 4 to 5 chronic kidney disease and dialysis patients, due to the possibility of nephrogenic systemic fibrosis with gadolinium use in this patient population.

Management of Central Vein Stenosis

Conservative management. No intervention is required in asymptomatic patients whose access flows and function are not compromised. These patients require close observation for new development of symptoms, when intervention may then be required. Patients with chronic central vein stenosis who demonstrate compensation with development of collateral veins can also be managed conservatively without interventions.

Percutaneous transluminal angioplasty. Angioplasty is the treatment of choice for managing symptomatic central vein stenosis.[62] It can be performed alone or with stenting, but reported patency rates are highly variable between studies, attributable to numerous factors including criteria for intervention, and differences in techniques. Initial success with angioplasty without stenting ranges between 70% and 90% in most studies.[63-65] Primary unassisted patency rates varies from 23% to 63% at 6 months, decreasing to 12% to 50% at 12 months.[63-68] Most patients require repeated angioplasties because lesions often recur. For resistant lesions or rapidly recurring lesions that recur within 6 weeks to 3 months, balloon angioplasty using a cutting balloon may have better results or may require angioplasty plus stenting.[69,70] However, angioplasty with stenting has only shown marginal improvement in patency rates compared with angioplasty alone.[37,71] It is difficult to compare results of different studies because sites of lesion, technique, and type of stent (eg, bare metal vs covered stent) all affect the outcomes. Recommendations are to consider stenting lesions with elastic recoil of the vein leading to residual stenosis or lesions that recur rapidly (within 3 months) after angioplasty.[62,72] However, some experts may advocate exploring other sites for new access in these situations.

Surgery. Surgery should be considered when repeated angioplasty with or without stenting is not successful.[66,73,74] Surgery may be difficult, often associated with significant morbidity and therefore should be considered a last resort when angioplasty with or without stenting has failed. Surgical options depend on area of central stenosis and approaches include the following:

- Bypass graft from axillary vein to jugular vein
- Bypass graft from subclavian vein to internal or external jugular vein
- Internal jugular vein to axillary vein transposition
- Bypass graft from axillary vein to ipsilateral femoral vein
- Bypass graft to the atrium
- Jugular vein turndown procedures.

Other Complications

Catheter-Associated Thrombus

Thrombi can form on catheters, leading to serious complications including pulmonary embolism, septic emboli, long-term central venous stenosis, and cardiac arrhythmias.[75] The optimal management of catheter thrombus remains controversial, due to lack of data. When catheter-related thrombus is detected, patients are usually treated with anticoagulation, using the same International Normalized Ratio, INR target as for patients with deep venous thrombosis, but often for only 3 months. Usually the catheter is not removed (unless no longer needed). The duration of anticoagulation could vary depending on the extent of thrombosis, risk of bleeding, and the ongoing need for continued use of a catheter. However, no randomized trial has been conducted specifically in the dialysis population.

Catheter-related right atrial thrombus is a potentially serious complication of hemodialysis catheters, associated with an overall mortality rate of 18%.[76] In a systematic review of 71 reported cases of catheter-related right atrial thrombus in dialysis patients, the authors recommended removal of the dialysis catheter and anticoagulation if the thrombus was less than 6 cm. In those patients with contraindications to anticoagulation, thrombus greater than 6 cm, or cardiac abnormalities surgical thrombectomy should be considered.[77] Other considerations include catheter exchange over guidewire with tip in superior vena cava rather than right atrium or thrombolysis. If anticoagulation is initiated, it is not clear how long it should be continued, given the propensity of major hemorrhage in dialysis patients.[25]

Difficult-to-Remove Embedded Catheter

Many case reports and case series describe tunneled catheters that cannot be removed despite dissection of the cuff. These catheters are embedded or tethered inside the central vein system. Various approaches have been described, including open surgery, cutting and burying, and endoluminal dilatation (Figure 3). Burying the catheter could potentially lead to infection[77]; a single-center experience of endoluminal dilatation suggests this approach may result in uncomplicated removal of such catheters.[78]

Last Option Access

In patients who have stenosed and/or occluded central veins, it is sometimes difficult to obtain access to the internal
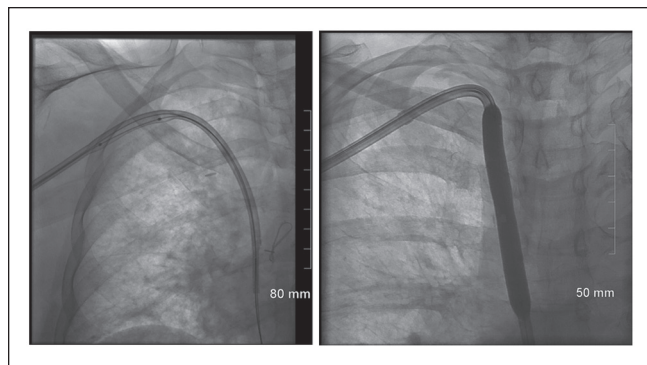
Figure 3. Balloon-assisted endoluminal dilatation for the removal of embedded catheters.
Source. Photo courtesy of Dr Adnan Hadziomerovic, Department of Medical Imaging, The Ottawa Hospital and University of Ottawa.

jugular or subclavian veins. The options for these patients are often limited and require skilled interventionalists; hence, optimal approaches will be dictated by local experience and expertise. The most commonly used last access options include transfemoral and translumbar catheters, and the Hemodialysis Reliable Outflow (HeRO) vascular access device. These are discussed in detail in "Last Access Options" section in MacRae et al.[79]

Summary

- Catheter dysfunction is a frequent and common cause of catheter loss. It may occur early, most often the result of mechanical issues or late, most often due to thrombotic occlusion or fibrin sheath.
- Sodium citrate (4%) or concentrated heparin solutions (1000 units/mL) are the current standard recommended anticoagulant locking solutions infused into the catheter lumens to maintain catheter patency between hemodialysis treatments.
- Antiplatelet agent and systemic oral anticoagulation have not proven beneficial in improving catheter patency and may increase risk of bleeding.
- Thrombolytic agents can be used to successfully restore patency in thrombotic/occluded catheters. If unsuccessful, catheter exchange with fibrin sheath plasty is recommended.
- Central vein stenosis is a common vascular access complication, occurring in up to 40% of hemodialysis patients with a catheter.
- Central vein stenosis is often asymptomatic until creation of an ipsilateral AV access.
- Reduce risk factors for central vein stenosis: minimize number and exposure time to central venous catheters, CIEDs, PICCs. Attempt creation of AV access on the opposite side of any central venous access device.
- Symptomatic CVS should be treated with percutaneous transluminal angioplasty. Stenting is generally not recommended except for recoil elastic lesions and

recurrence within 3 months of angioplasty. Surgery should be considered a last resort.
- Right atrial thrombus is a less common but serious complication of catheters, requiring systemic anticoagulation and possibly catheter removal.
- In the event of poor AV access and/or loss of upper extremity central veins, alternative access options include transfemoral catheters, translumbar catheters, and the HeRO device. These options require skilled interventionalists, and optimal approaches are dictated by local experience and expertise.
- Balloon-assisted endoluminal dilatation can be used for removal of embedded catheters.

Ethics Approval and Consent to Participate

Ethics approval and consent to participate was not required for this trial.

Consent for Publication Availability

Consent for publication was obtained from all authors.

Availability of Data and Materials

There is no data to share.

Author Contributions

L.M.M. designed, coordinated, and drafted the review and provided critical review of the manuscript at all stages. J.M.M. conceived, designed, and coordinated the review, and critically revised the manuscript. M.K. helped draft the manuscript and provided critical review. E.C., C.L., L.M.M., J.K. helped draft the manuscript and provided critical review. C.D., P.P., M.O., and R.L. provided critical review. S.H. helped design and drafted a significant portion of the manuscript and provided critical review. All authors read and approved the final manuscript.

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