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Acute and Chronic Catheter in Hemodialysis

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1. Introduction

Reliable and sustained access to the circulation is mandatory for the provision of long-term hemodialysis which is critical to the survival of patients with end-stage renal disease (ESRD). An ideal vascular access provides adequate blood flow to meet the hemodialysis prescription, with minimal complications due to infection or thrombosis. The natural arteriovenous fistula (AVFs) comes closest to meeting these criteria while arteriovenous grafts (AVGs) and central venous catheters (CVCs) present other vascular access options. In the United States, promoting a major shift in using fistula as first-choice vascular access has been strongly recommended by the 2001 Kidney Disease Outcome Quality Initiative (K/DOQI) vascular access guideline (NKF-DOQI 2001) and the "Fistula First" national initiative (Tonnessen et al 2005). Ideally, every patient would initiate dialysis with a mature fistula suitable for cannulation. In real clinical setting, this is not true due to combination of the following factors including (i) lacking nephrology follow-up at the time of ESRD, (ii) late nephrology referral, (iii) poor or no planning of fistula placement, (iv) inadequate fistula maturation and (v) poor vascular preparation due to prior venous cannulation.

In current practice, 20-50% of attempted AVFs fail to mature adequately. Despite a recent increase in the number of prevalent patients dialyzing with an AVF (47%) in the US following the fistula-first initiative, 28% of prevalent patients remain dependent on an AVG and 25% on a CVC. In Canada, recent data demonstrate that 50% of patients use an AVF, while 39% and 11% depends on a CVC or AVG, respectively (James et al 2009).

Sadly, hemodialysis CVCs are increasingly being introduced in patients requiring emergency or chronic renal replacement therapy. Table 1 outlines the advantages and disadvantages of CVCs. The percentages of patients undergoing dialysis with vascular catheters are increasing in Europe, ranging from 15% (Germany) to 50% (United Kingdom) of all hemodialysis patients. In the United States, up to 60% of patients start hemodialysis with CVCs (Pisoni et al 2002). Over the last decade, the number of patients using CVCs for hemodialysis doubled (Rayner et al 2004). According to the Dialysis Outcomes and Practice Patterns Study, 18% of patients with end-stage renal failure in the United States and 24% of those in Great Britain have been dialysed with such catheters (Quarello et al 2006). Table 2 summarizes the indication for using CVCs. Recent studies indicate that CVCs are used in 20-25% of incident (<6 months) chronic kidney disease (CKD) stage 5 patients and still used in 10-20% of prevalent hemodialysis patients (> 6 months) (Rayner et al 2004a, Moist et al 2007). The use of CVCs has been complicated by higher rates of thrombosis, dysfunction,

and infection compared with AVFs. As a result of this, maintaining CVCs is associated with high costs (Lacson et al 2007). The increased use of CVCs requires a maximal precaution in its management and a stringent practice to reduce its risk and complications.

Advantages	Disadvantages
High success rate	High morbidity caused by thrombosis and infection
Insertion into multiple sites	Risks of permanent central venous stenosis or occlusion
Maturation time not required	Lower blood flow rates requiring a longer dialysis time
No venepuncture	
No hemodynamic consequences	
Easy replacement	
Functional for months (chronic tunneled CVC)	
Ease of correcting thrombotic complications	

Table 1. Advantages and disadvantages of central venous catheters for hemodialysis

<ul style="list-style-type: none"> • Pending maturation of arteriovenous fistula • Providing temporary dialysis treatment for patients undergoing maintenance peritoneal dialysis but complicated by peritonitis such that the infection can be controlled and the peritoneum be rested • Awaiting for living-related donor transplantation • "Bridging dialysis" followed failed previous vascular or peritoneal access allowing planning of long-term access • Permanent vascular access when other sites for arteriovenous fistula or grafts are exhausted
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Table 2. Indications for central venous hemodialysis catheters

2. Types of central venous catheters

There are two main categories of hemodialysis catheters: (i) non-tunneled, uncuffed, designed for short-term venous access of up to three weeks and (ii) tunneled, cuffed catheters for longer use. An ideal CVC is biologically neutral and does not induce venous or catheter lumen thrombosis; its surface is coated with an agent, which prevents migration and multiplication of bacteria. It should enable continuous dialysis with the blood flow through the catheter > 350-400 ml/min. Moreover, it ought to be non-traumatic, soft, easy to insert, mechanically durable, bending-resistant, comfortable for the patient and inexpensive. A comparison of acute and chronic central venous catheters is shown in Table 3.

i. Temporary acute catheters

Acute untunneled CVCs are used in emergency situations (dialysis, plasma exchange, hemofiltration or hemoperfusion) or as a short-term bridging access (ideally < 7 days). The advantages of these catheters are their ease of insertion (even by the bedside), the ability to insert them in multiple sites in almost any patient and the lack of hemodynamic compromise associated with their use. Internal jugular vein is the preferred site as

anatomically this provides the most direct route to the superior vena cava and right atrium. The vein should be localized by ultrasound (+/- Doppler). Insertion into the left internal jugular vein is associated with a higher incidence of central stenosis and poorer patency. For selected cases requiring short-term dialysis, the femoral vein can also be used. Subclavian vein should be discouraged as it may jeopardize the long-term arteriovenous access options with complication of subclavian stenosis. The catheters are usually inserted using the Seldinger technique. The catheter can be used immediately after confirming correct placement with fluoroscopy.

Acute	Chronic
For use of < 7 days	For use of > 3 weeks
Most are not tunneled and without a retention cuff - conical tip for easy insertion	Most are tunneled with a retention cuff - soft tip
Most are dual lumen with venous port 2-3 cm distal of arterial port	Thermoplastic polyurethane - larger internal diameter, biocompatible, nonthrombogenic
Polyurethane - stiff and withstanding high pressure	Carbothane - copolymer with strength for longevity and softness for flexibility
Silicone - larger lumen but needs a peel-away sheath	Silicone - larger lumen but needs a peel-away sheath, biocompatible, less thrombogenic

Table 3. Comparison between acute and chronic central venous catheters

To ensure continuous, independent blood flow, catheters are double-lumen. The distal part has two separate openings; one collecting the patient's blood - "arterial", located 2-3 cm from the catheter end and the second one pumping the blood to the patient - "venous", placed at its end. Temporary catheters are usually made of stiff materials: polyurethane or polyvinyl, and thus are easier to introduce along the guidewire and a hemostasis valve is not needed. The sharp distal tip facilitates the insertion through the subcutaneous tissues. Compared to soft catheters, they are more resistant to bending in the vessel. At body temperature, after contact with the bloodstream, they become plastic, which reduces the risk of vessel damage. Temporary CVCs have no cuffs but are quipped with dacron muffs. The insertion does not require "tunnelization", thus fast access to the circulatory system can be provided. They vary in length, therefore the proper choice is easier depending the puncture site and availability of a central vessel. They may be used for several days or up to three weeks. Their main advantage is easy insertion into the vessel using the Seldinger technique with easy replacement not requiring expensive accessory devices, (which may not be always available) such as fluoroscopy or ultrasound. Generally, the blood flow through temporary CVCs is limited to 200-250 ml/min.

The newer catheters are made of silicone with bigger internal diameter which ensures the blood flow of 400 ml/min. Some of them are tunneled. Silicone is thermoset and thus the catheter is soft. Hence it has to be inserted using a dilator and peel-away sheath. Other materials include polyurethane which is thermoplastic and softens at body temperature. This reduces endothelial damage and thrombogenicity (Leblanc et al 1997). The tunneled catheters can be introduced either antegrade (skin to insertion site) or retrograde (insertion site to skin). The position of soft CVCs should be confirmed by fluoroscopy.

ii. Long-term tunneled catheters

Tunneled CVCs with cuffs are made of silicone, silastic or carbothane elastomer, polyurethane co-polymer and polycarbonate – these materials are softer and more plastic than those used in temporary catheters. Therefore, they are usually inserted using the Seldinger technique via peel-away sheath. Subcutaneous tunnelization and a cuff are to stabilize the catheter and prevent the spread of infections. The soft silastic elastomer enables the placement of the distal catheter tip in the right atrium, which should be confirmed by fluoroscopy. Bigger internal diameters (thicker catheters) provide better blood flows and a wider dilator or sequential dilator is frequently used.

The first model of a tunneled catheter was PermCath, an oval catheter with two circular canals. Subsequent models (e.g. Vas Cath) were designed with an internal septum dividing the internal lumen into two parts. The oval transverse section of the catheter facilitated its insertion through the peel-away sheath. The third popular option was the introduction of two catheters with a single lumen – Tesio or its modification. One collected the blood through the opening in the superior vena cava and the other one supplied blood through the opening in the right atrium. Other than the catheter body and lumen, the design of the shape of catheter tips is also emphasized for better blood flow, improved reliability and minimizing recirculation (Ash 2008).

The newest catheters implanted surgically are equipped with a subcutaneous port (Morgan 2001, Ross 2001), which reduces percutaneous device-related complications. In most cases, the port consists of a chamber made of a titanium, ceramics or other neutral plastic materials with silicone membrane and an attachable catheter. The silicone membrane enables repeated penetrations (about 1000-2000), depending on the product and size of the puncture needle. The entire system is placed under the skin, which prevents infections or accidental opening. There are different configurations of the catheter and port chamber from using two single catheters each attached to a single chamber port to a double-lumen catheter connected to a two-chamber port. The vascular port implantation is based on the same principles as those for central venous access except the ports are placed in a subcutaneous pocket. The port can be punctured with normal hemodialysis needles or needles with special make that does not cut an opening in the membrane. The main reason of low popularity of hemodialysis ports is their relatively high cost.

3. Percutaneous insertion of central venous catheter

As mentioned, the right internal jugular vein is the preferred site as the curve of the catheter is straight thus achieving the best result. If the left internal jugular vein is used, negotiation of the curve at the venous entry to the superior vena cava may require experience and care. Moreover, one must choose a longer catheter as compared with right jugular vein puncture. The length of catheter introduced from neck or thoracic access should enable its distal end to reach the right atrium when a soft catheter is used or be placed in the superior or inferior vena cava when the catheter is stiff. It is recommended to place hemodialysis CVCs under fluoroscopic screening to avoid trauma with the guidewire in the inferior vena cava during insertion and the distal part of catheter in the upper right atrium upon completion of placement (Lin et al 1998, Keenan 2002).

The first choice for catheterization is the right internal jugular vein, followed by the right external jugular vein, left internal jugular vein, left external jugular vein, and finally femoral

veins or external iliac veins (Maya et al 2005). The vein should be localized by ultrasound and can be differentiated from the artery by Doppler. The probe should first be placed on the head of the sternomastoid muscle and then moves down towards the clavicle. The puncture site should be as low as possible but above the clavicle whereas the exit of the subcutaneous tunnel should preferably be below the clavicle.

Femoral and external iliac veins may be used for CVC insertion in bed-ridden patients or in the intensive care setting, particularly in patients requiring artificial lung ventilation, after head and neck trauma with numerous catheters and drains of the neck and thorax as well as those with tracheostomy (Zaleski et al 1999, Mathur et al 1993). Patients with kidney transplant potential should avoid femoral vein catheterization. With catheter insertion in the groin, meticulous hygiene of the puncture site is required. The patency period from the insertion to removal is markedly shorter in femoral vein access compared to catheters inserted through the internal jugular vein.

4. Catheterization-related complications

Irrespective of the type (non-tunneled or tunneled) or design (straight or with formed shape), their use is likely to be associated with complications (Table 4) (Morgan 2001, Ross 2001).

Early	Late
Inadvertent arterial puncture and central vessel perforation	Infection
Hemothorax	Central vein thrombosis
Pneumothorax	Catheter thrombosis formation
Pericardial tamponade	Central vein stenosis
Atrial perforation	Catheter dysfunction (can be early due to kinking)
Dissection/occlusion of carotid artery	Permanent vascular ingrowth
Arrhythmias	
Air embolism	
Retroperitoneal hemorrhage (for femoral vein insertion)	
Primary failure - technical error	

Table 4. Complications of central venous catheters insertion

The incidence of complications reaches 5.9% with catheter insertion based only on topographic anatomy even with experienced clinicians (McDowell et al 1993). In contrast, the incidence of procedure-related complications in central venous catheterization under ultrasound guidance is only 0.8% (Trerotola et al 1997). Ultrasound-guided catheterization also limits the incidence of failures related to catheter insertion and reduces complications and necessity of multiple punctures of a vessel (Randolph et al 1996). Early complications which are mainly "surgical" include pneumothorax, pleural or mediastinal hemotoma, air embolism, thoracic tract injury, damage to nervous structures within the neck and thoracic region, puncture of the cardiac cavities, or cardiac arrest (Feldman et al 1996) (Figure 1). Non-surgical complications include cardiac arrhythmia and insertion site infection.



Fig. 1. Plain Chest Xray showing a CVC placed in the left internal jugular vein protruding out of the vessel wall (arrow)

Long-term complications are equally important. The common ones are thrombotic complications, vascular stenosis and catheter-related bacteremia (CRB). To reduce their complications, the internal surface of catheters is often coated with heparin. Coating or impregnation of catheters with silver salts and antibiotics reduces the colonization of bacteria.

4.1 Catheter dysfunction

The 2006 National Kidney Foundation K/DOQI guidelines defines access dysfunction as the inability to achieve blood flow (Q_b) ≥ 300 ml/min during the first 60 minutes of hemodialysis despite at least one attempt to improve flow (National Kidney Foundation 2006). Since then, larger bore catheter design allows much higher Q_b (> 400 ml/min) to be achieved at the same prepump pressure. Hence, waiting until Q_b declines to 300 ml/min in these catheters may be inappropriate, missing the opportunity to detect catheter dysfunction earlier.

Early identification of catheter dysfunction enables prompt intervention and salvage. Catheter occlusion can be caused by kinking or malposition and these may be detected during the first hemodialysis session. Other causes of catheter dysfunction include leakage, drug precipitation, thrombus formation and growth of a fibrin sheath. Thrombus-related occlusion typically occurs late either with or without a fibrin sheath. The clinical features of different thrombotic occlusive complications are summarized in Table 5. Catheter

dysfunction is frequently associated with recirculation that exerts a deleterious effect on dialysis efficiency and patient outcome (Leblanc et al 1997).

Complications	Features	Symptoms
Mural thrombus	Fibrin from vessel wall injury connected to fibrin-coated catheter leading to increased risk of venous thrombosis	Leakage of infusate from the insertion site, swelling, pain, tenderness, engorged vein
Intraluminal thrombus	Fibrin forms inside the catheter lumen causing partial or completion occlusion	Unable to infuse and/or withdraw blood
Fibrin sheath	Fibrin adheres to the external surface encasing the catheter and frequently extending the length of the catheter; thrombi trapped between sheath and catheter tip	Unable to infuse and/or withdraw blood
Fibrin tail or flap	Fibrin extends from the end of the catheter causing partial occlusion (fibrin tail acts as an one-way valve)	Able to infuse but not withdraw blood

Table 5. Different thrombotic occlusive complications related to central venous catheter for dialysis

Before the tunneled CVC thrombosis occurs, prophylactic inhibition of coagulation cascade should be considered. The earlier results of various antiplatelet agents and anticoagulation were not encouraging. Better patency has been maintained with catheter locking solutions between dialysis sessions. The standard protocol has been heparin instillation (1000 to 10000 units/ml) into the lumens in a volume sufficient to fill to the lumen tip (the lock). The heparin concentration is reduced because catheter lumens have increased in volume so as to reduce the possibility of unintentional systemic anticoagulation. Trisodium citrate with its antithrombotic and potentially antibacterial properties has also been tested as a locking solution. The American Society of Diagnostic and Interventional Nephrology Clinical Practice Committee recommends using a locking solution of 1000 units/ml heparin or 4% trisodium citrate to maintain CVC patency (Fuchs et al 1999).

Most recently, a Canadian multicenter study showed the once weekly use of recombinant plasminogen activator (1 mg in each lumen), as compared with heparin (5000 units/ml) thrice weekly, as a locking solution for CVC significantly reduced the incidence of catheter dysfunction and bacteremia (Hemmelgarn et al 2011).

4.2 Central thrombosis formation

Mural thrombosis in the superior vena cava and the right atrial wall associated with CVC placement is detected in one-third of patients but often remains asymptomatic [26]. Treatment by infusion of a fibrinolytic agent produces good results but angioplasty and stenting may be required for organized thrombosis.

4.3 Central vein stenosis

The incidence of central vein stenosis is considerable. As with fibrin sheath, central vein stenosis should be identified with a superior vena cavogram performed by removing the old

catheter over the working guidewire followed by a pigtail catheter insertion (Figure 2). The management of central stenosis is evolving. Whenever found, endovascular balloon angioplasty should be attempted to a minimum of the contiguous uninvolved vein (Quinn et al 1995). Unfortunately, central vein stenosis tends to recur (Quinn et al 1995, Kovalik et al 1994). The use of flexible stents has gained popularity recently despite the long term outcome is not well defined.



Fig. 2. Patient with a non-functioning left internal jugular vein hemodialysis catheter. Left subclavian venogram showed stenosis at proximal superior vena cava (arrow) with multiple collaterals in the neck (arrowheads).

4.4 Fibrin sheath

Fibrin sheaths account for 13-57% of catheter dysfunction (Suhocki et al 1996). The formation begins 24 hours after placement and it develops into a full-length sleeve after 5-7 days (Faintuch et al 2008). The sheath first occurs when fibrin adheres to the external surface before encasing the catheter and frequently extending the length of the catheter. The sheath seems to originate from the insertion site or the cuff and tends to migrate down the length of the catheter causing occlusion. Thrombi may also be trapped between sheath and catheter tip. A permcathogram done by injecting contrast through the catheter ports under fluoroscopic screening may show a persisting filling defect at the catheter tip or reflux of the contrast along the sheath in a retrograde direction (Figure 3). Fibrin sheaths may be treated by prolonged infusion of fibrinolytic agents (urokinase 30000 units/hour via each port x 4 hours or recombinant tissue plasminogen activator of 2.5 mg diluted in 50 ml normal saline

at a rate of 17 ml/hour through each port x 3 hours), mechanical stripping using a snare inserted via the femoral vein by exchange of catheter over a guidewire (Suhocki et al 1996, Faintuch et al 2008, Goldberg et al 1985). Diverse degree of success in fibrin sheath stripping is reported from different centers.

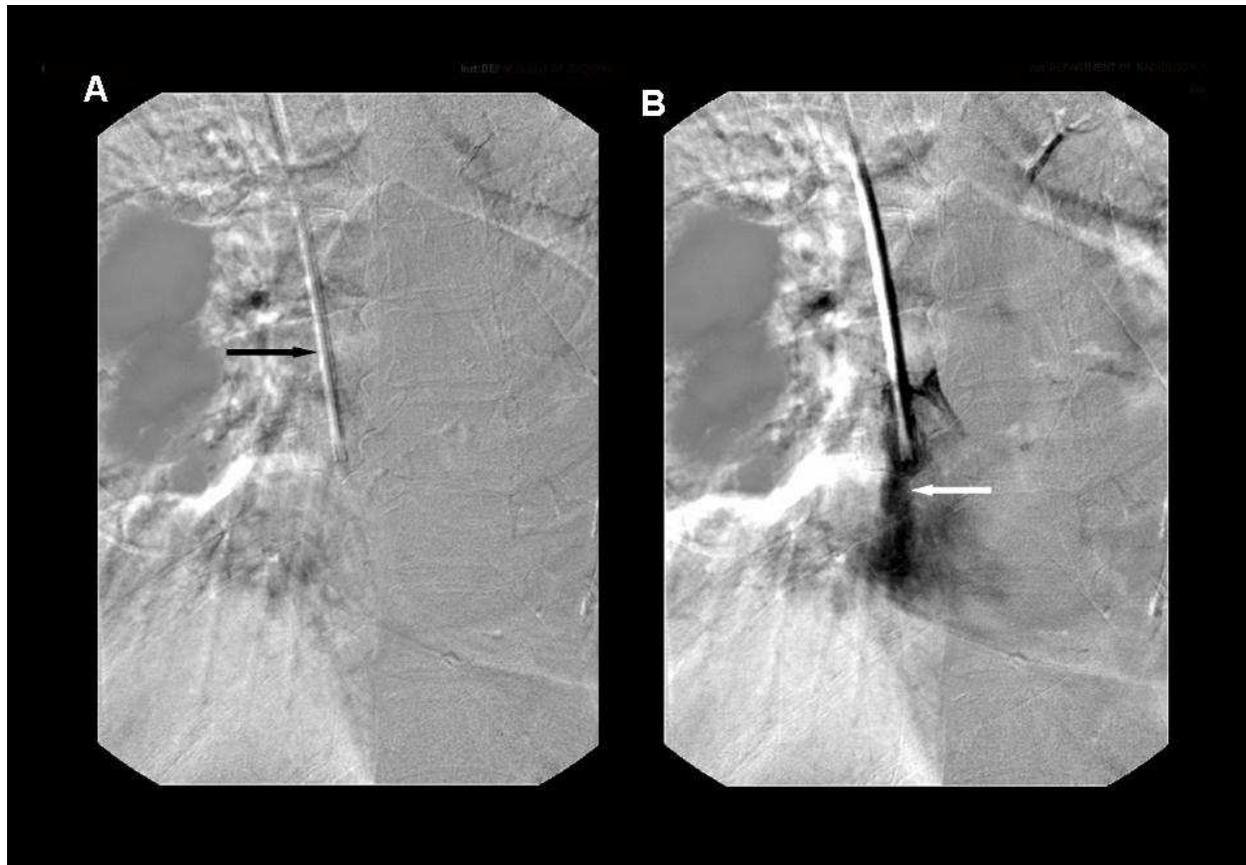


Fig. 3. (A) A fibrin sheath (arrow) formed inside the lumen of the CVC. (B) A permcathogram done showing a persisting filling defect (arrow) in the catheter lumen and reflux of the contrast at the catheter tip.

4.5 Catheter-related bacteremia

Catheter infection is a major cause of morbidity and mortality responsible for 6-28% of catheter failures (Bagui et al 2007). Diagnosis of catheter-related bacteremia (CRB) requires at least one of the following criteria: (a) clinical exit site infection with evidence of inflammation within 2 cm of sites; (b) definite organism grew from blood culture and catheter with no other apparent source of infection; (c) probable blood stream infection with defervescence after catheter removal when both blood and catheter tip infection is not confirmed in a symptomatic patients with no apparent source of infection; (d) possible blood stream infection in a symptomatic patients with defervescence after catheter removal, but remains culture negative.

The causative organisms are predominantly gram positive (~50%), gram negative bacilli (~25%) or polymicrobial (~20%). The most common occurrence is through the migration of skin organisms along the external surface of the catheter from the exit site wound or via the catheter lumen due to breakdown of aseptic technique. The organism can be embedded in a biofilm layer that confers protection from antibiotic therapy (Passerini et al 1992). Infection

occurs when the organisms on the catheter exceed a certain quantitative threshold. Ninety percent of exit site infections respond to oral antibiotics without the necessity of catheter removal. Oral antibiotics can be used for minor infection but intravenous antibiotics should be administered if there is a discharge from the tunnel /exit site. If the infection fails to resolve with these measures, the catheter should be removed and replaced through a different track. Systemic sepsis or bacteremia carries a higher morbidity. K/DOQI guidelines recommend rapid removal of catheters in unstable patients with bacteremia or in stable patients if remain symptomatic 36 hours after achieving serum concentration of bactericidal antibiotics. In these cases, antibiotics should be administered for 14-21 days.

Reference	Type of locking solution	Intervention	Control
Dogra <i>et al.</i> 2002	Gentamicin	0.3	4.2
McIntyre <i>et al.</i> 2004	Gentamicin	0.3	4.0
Bleyer <i>et al.</i> 2005	Minocycline	0	0.472
Kim <i>et al.</i> 2006	Gentamicin/Cefazolin	0.4	3.1
Saxena <i>et al.</i> 2006	Cefotaxime	1.7	3.6
Nori <i>et al.</i> 2006	Gentamicin	0	4.0
	Minocycline	0.4	4.0
Filiopoulos <i>et al.</i> 2011	Gentamycin	2.7	9.9
	Taurolidine/Citrate	3.7	9.9
Allon 2003	Taurolidine	0.6	5.6
Betjes and van Agteren 2004	Taurolidine	0	2.1
Weijmer <i>et al.</i> 2005	Citrate (30%)	1.1	4.1

Rate of CRB (per 1000 catheter-days)

Table 6. Catheter locking solutions for prophylaxis against catheter-related bacteremia (CRB)

Prophylaxis of catheter-related bacteremia has been studied with standard antibiotics or antimicrobial agents such as taurolidine and 30% citrate as catheter locking solution. Seven randomized clinical trials documented substantial efficacy of antibiotic locks (gentamicin, minocycline or cefotaxime) in prophylaxis against catheter-related bacteremia (Dogra *et al.* 2002, McIntyre *et al.* 2004, Bleyer *et al.* 2005, Kim *et al.* 2006, Saxena *et al.* 2006, Nori *et al.* 2006, Filiopoulos *et al.* 2011). An additional four studies documented reduction in frequency of catheter-related bacteremia using taurolidine or citrate as locking solution (Filiopoulos *et al.* 2011, Allon 2003, Betjes *et al.* 2004, Weijmer *et al.* 2005). These studies are summarized in Table 6.

4.6 Permanent vascular ingrowth

Tissue ingrowth into the catheter lumen occurs when the tissue entraps the catheter onto the endothelial surface of the vessel. There is no standard management for this problem. Surgical approach of a thoracotomy is required as cut down on to the internal jugular vein for catheter is not usually possible.

5. Other accesses for insertion of central venous catheter

If the jugular veins are not accessible for long-term placement, the subclavian vein opposite the dominating side can be used. The nephrologist must realize the risk of subclavian stenosis (Feldman et al 1996, Can 2008). The subclavian vein should never be catheterized on the side of the unhealed arteriovenous fistula.

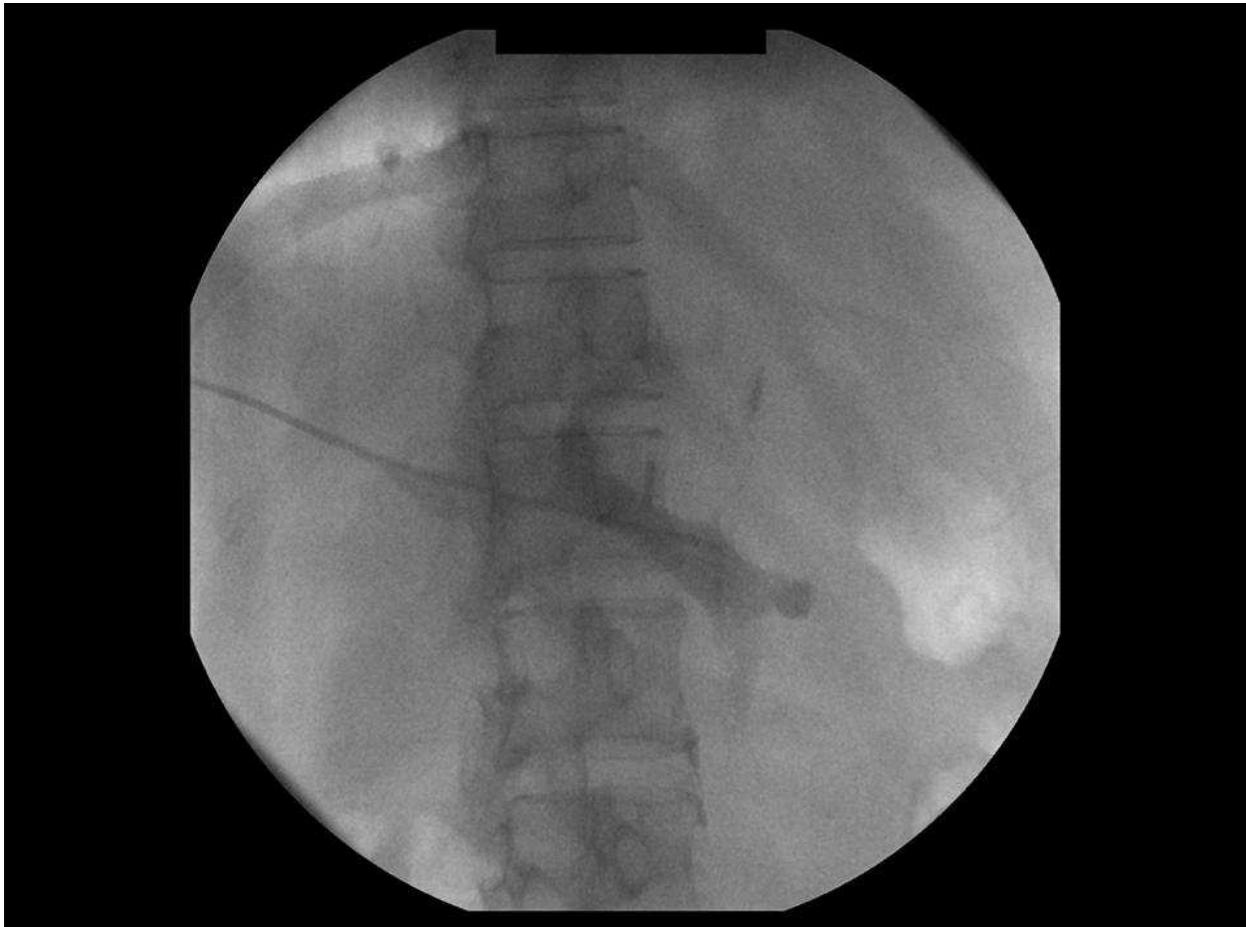


Fig. 4. Transhepatic placement of a Retrocath (45 cm long, 16Fr) into the portal vein. Contrast was injected to confirm the successful cannulation of the portal venous system.

Other alternative sites have been used for CVC placement when none of the typical central accesses is available. Such procedures must be conducted by an experienced interventional radiologist in a fully equipped facility. Alternative methods may be used: catheterization of the inferior vena cava, or hepatic, translumbar, renal, intercostal and mediastinal veins.

The translumbar approach to cannulation of the inferior vena cava, first described in 1971, has gained renewed attention as an alternative method for CVC access. High adequacy dialysis with low rates of catheter-related infection has recently reported from a single center study (Power et al 2009). The catheter care protocols, a policy of clinically appropriate catheter salvage with empirical broad-spectrum antibiotics and prior experience with translumbar catheter may also have influenced the outcome.

Transhepatic placement of hemodialysis catheter first described in 1994 can be associated with infrequent complications such as line sepsis, catheter migration, thrombosis and bleeding (Smith et al 2004). These complications can be minimized when the procedure is performed by an interventional radiologist who is familiar with portal venogram (Figure 4)

(Yap et al 2010). In exceptional lack of options, transrenal access into the renal vein with consequent insertion of a tunneled catheter has been attempted (Murthy et al 2002).

6. Conclusion

Hemodialysis central venous catheters CVCs are commonly used in patients with renal failure requiring dialysis once other vascular options have been exhausted. Long-term catheters should be inserted using the Seldinger technique with a dilator and hemostasis valve under ultrasound guidance and fluoroscopic screening. Tunneled catheters with cuffs may be used both temporarily and permanently. The subcutaneous tunnel and cuff ensure stabilization of their position and limiting the migration of microorganisms on its external surface hence reducing the risk of infections. Finally, it must be emphasized that a well-functioning arteriovenous fistula is the best vascular access inducing the lowest number of complications.

7. Acknowledgement

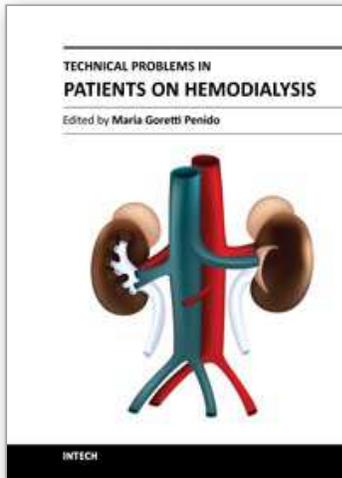
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This book provides an overview of technical aspects in treatment of hemodialysis patients. Authors have contributed their most interesting findings in dealing with hemodialysis from the aspect of the tools and techniques used. Each chapter has been thoroughly revised and updated so the readers are acquainted with the latest data and observations in the area, where several aspects are to be considered. The book is comprehensive and not limited to a partial discussion of hemodialysis. To accomplish this we are pleased to have been able to summarize state of the art knowledge in each chapter of the book.

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