


# Practical Aspects of Nontunneled and Tunneled Hemodialysis Catheters

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## Abstract

Nontunneled hemodialysis catheters (NTHCs) are typically used when vascular access is required for urgent renal replacement therapy. The preferred site for NTHC insertion in acute kidney injury is the right internal jugular vein followed by the femoral vein. When aided by real-time ultrasound, mechanical complications related to NTHC insertion are significantly reduced. The preferred site for tunneled hemodialysis catheters placement is the right internal jugular vein followed by the left internal jugular vein. Ideally, the catheter should be inserted on the opposite side of a maturing or planned fistula/graft. Several dual-lumen, large-diameter catheters are available with multiple catheter tip designs, but no one catheter has shown significant superior performance.

## Abrégé

En situation d'insuffisance rénale aigüe, les cathéters de dialyse non tunnelisés sont utilisés lorsqu'un accès vasculaire est requis de façon urgente pour entreprendre un traitement de suppléance de la fonction rénale. L'implantation de ce type de cathéter se fera préférentiellement dans la veine jugulaire interne droite sinon dans la veine fémorale. Il est possible de réduire de façon significative les complications mécaniques liées à son insertion en suivant la procédure par échographie. La veine jugulaire interne droite constitue également le site privilégié pour l'insertion d'un cathéter de dialyse tunnelisé. Toutefois, dans ce cas, le deuxième choix se portera sur la veine jugulaire interne gauche plutôt que sur la veine fémorale. Dans tous les cas, l'insertion du cathéter devra se faire du côté opposé à une fistule en cours de maturation, ou d'une fistule ou d'une greffe anticipée. De nombreux modèles de cathéters de grand diamètre, à double lumière et à pointes variées sont disponibles, mais aucun d'eux n'a démontré de performance supérieure à l'usage.

## Keywords

nontunneled hemodialysis catheters, tunneled hemodialysis catheter, site selection, catheter insertion, catheter removal, exit-site care

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## Nontunneled (Temporary) Hemodialysis Catheters

Nontunneled hemodialysis catheters (NTHCs) are typically used when vascular access is required for urgent renal replacement therapy (RRT). Because of the important role NTHCs play in enabling timely RRT, proficiency in NTHC insertion is a requirement of nephrology training in Canada.<sup>1</sup> In the setting of acute kidney injury (AKI), when the duration of RRT is difficult to predict, NTHCs are the recommended initial vascular access.<sup>2</sup> However, due to an increased risk of complications, NTHCs are the least preferred access for chronic hemodialysis patients.<sup>3–5</sup>

## Mechanical Complications of NTHCs

*Acute mechanical complications of NTHCs.* Mechanical complications related to NTHC insertion are common with vascular injury or hematoma occurring in up to 5% of insertions.<sup>5</sup> Other mechanical complications such as pneumothorax, pneumopericardium, and air and guidewire embolism occur less often but can be fatal.<sup>5</sup> Although the life-threatening complications of NTHC insertion are typically related to insertions at the internal jugular site, fatal complications related to femoral NTHC insertion have been reported. Severe bleeding, typically retroperitoneal, occurs in approximately 0.5% of femoral insertions.<sup>6</sup> Given that



NTHCs are most frequently used in critically ill patients, the consequences of catheter-related complications may be more likely to be attributed to concurrent illness, resulting in underreporting.

Cardiac arrhythmias are a potentially serious complication of all central venous catheter insertions that typically relate to overinsertion of the wire used to insert the catheter using the Seldinger technique.<sup>7</sup> Notably, overinsertion of the wire (defined as being more than 20 cm) was a frequent error made by Canadian nephrology trainees and medical residents undergoing testing of their NTHC insertion skills using a realistic patient simulator.<sup>8</sup> Patients with AKI are at increased risk of serious ventricular arrhythmias during catheter insertion relative to patients with end-stage renal disease or normal kidney function.<sup>7</sup>

**Long-term mechanical complications of NTHCs.** Given an increased risk of central venous stenosis, NTHC insertion into subclavian veins should be avoided whenever possible.<sup>2</sup> Stenosis may also occur following catheter insertion at other sites but is thought to occur less frequently.<sup>2</sup> The risk of stenosis may be related to the extent of direct contact between the catheter side wall and the vascular endothelium. Increased venous curvature is likely to result in increased contact between the catheter side wall and the vein wall: Therefore, catheters in left-sided subclavian and internal jugular veins may carry greater risk of stenosis compared with right-sided ones<sup>2</sup> (see “Central Vein Stenosis” section in Miller et al<sup>9</sup>).

**Use of ultrasound to reduce mechanical complications.** The use of real-time ultrasound guidance when inserting catheters has been shown to dramatically reduce the risk of mechanical complications (Table 1). The evidence for the use of ultrasound is detailed according to insertion site.<sup>10,11</sup>

- Internal jugular vein

A 2011 systematic review by Rabindranath et al<sup>11</sup> included 7 randomized controlled trials of hemodialysis patients

(n = 767 with 830 internal jugular catheter insertions) requiring catheter insertion. Studies of patients with both tunneled catheters and NTHCs were included in the analysis. They concluded that real-time ultrasound significantly reduced arterial punctures (Relative risk, RR, 0.22; 95% confidence interval [CI], 0.06-0.81) and hematomas (RR, 0.27; 95% CI, 0.08-0.88). In addition, catheter insertions using ultrasound were significantly faster and more likely to be associated with successful insertion on the first attempt (RR, 0.40; 95% CI, 0.29-0.56).<sup>11</sup> The use of real-time ultrasound for internal jugular NTHC insertions is now widely considered to be the standard of care.<sup>11-13</sup>

- Femoral vein

Due to relatively lower risk of life-threatening complications (eg, pneumothorax), ultrasound is less commonly used with femoral NTHC insertion, compared with internal jugular insertion.<sup>14</sup> However, there is evidence that ultrasound reduces complications to femoral site insertion too.<sup>14</sup> Prabhu et al<sup>15</sup> randomized 110 critically ill patients who required femoral NTHC insertion for urgent RRT into real-time ultrasound-guided insertion versus insertion using anatomic landmarks alone. The use of ultrasound was associated with a significant reduction in complications as well as significantly better first-attempt and overall insertion success. Notably, operator experience with femoral NTHC insertion did not correlate with the likelihood of complications. Given that ultrasound is widely available for internal jugular NTHC insertions and is benign, some authors have advocated that the use of real-time ultrasound should become the standard of care for femoral NTHC insertions.<sup>3</sup>

- Subclavian vein

Subclavian sites should be avoided whenever possible because of increased risk of central venous stenosis.<sup>2</sup> When necessary, subclavian vein catheter insertions should be performed by operators experienced with this approach.

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**Table 1.** Advantages of Ultrasound Use for NTHC Insertion.

NTHC site	Advantages of ultrasound use
Internal jugular	<p>Reduced arterial punctures, hematomas</p> <p>Faster catheter insertions</p> <p>Catheter insertions more likely to be successful on the first attempt</p> <p>Use is widely considered to be the standard of care</p>
Femoral vein	<p>Significant reduction in complications</p> <p>Increased first-attempt successful catheter insertion and overall insertion success</p> <p>Some authors advocate real-time ultrasound should be the standard of care for femoral NTHC insertions</p>
Subclavian vein	<p>Avoid whenever possible due to increased risk of central venous stenosis</p> <p>Should be performed by operators experienced with this approach</p>

Note. NTHC = nontunneled hemodialysis catheter.

### Infectious Complications of NTHCs

NTHCs are associated with higher risk of infection compared with both tunneled hemodialysis catheters and nontunneled central venous catheters.<sup>16,17</sup> One systematic review reported a catheter-related bloodstream infection (CRBSI) rate of 4.8 per 1000 catheter days with NTHCs, compared with 2.8 per 1000 catheter days with other types of central venous catheters.<sup>16</sup> Given their ease of removal, the potentially serious sequelae of CRBSIs, and the importance of source control, NTHCs should be removed immediately if there is an exit-site infection or CRBSI.<sup>18</sup>

### Optimal Site Selection for NTHC Insertion

The 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines for AKI provided an ungraded recommendation regarding site selection for NTHC insertion in the context of AKI<sup>2</sup>:

- First choice: right internal jugular vein
- Second choice: femoral vein
- Third choice: left internal jugular vein
- Last choice: subclavian vein with preference for the dominant side.

With respect to critically ill, bedbound patients, the Cathedia study randomized 750 patients to either femoral or internal jugular NTHC insertion for acute RRT.<sup>19</sup> Using catheter bacterial colonization at the time of catheter removal as a proxy for infectious complications, there were no differences in infection between those with femoral versus internal jugular NTHCs. There was also no significant difference in the rate of CRBSI between the 2 groups. However, in a prespecified subgroup analysis according to body mass index (BMI),

those in the highest BMI tertile (>28.4) had a significantly increased risk of catheter colonization with femoral versus internal jugular NTHCs, whereas patients in the lowest BMI tertile (<24.2) had a significantly reduced risk of catheter colonization with femoral versus internal jugular NTHCs, suggesting that femoral NTHCs may even be preferable in this limited subset of patients requiring RRT for AKI.

### Factors That Influence Site Selection: Internal Jugular Versus Femoral Vein

- Internal jugular
  - Ambulatory patients and those for whom lower extremity mobility is required for rehab
  - Immediate postoperative major abdominal surgery (eg, abdominal aortic aneurysm repair)
  - Active infections affecting groin area, such as acute diarrheal illness or fungal infections
  - Morbid obesity with pannus
  - Prior vascular surgeries (eg, bypass) affecting the groin or lower leg
  - Local expertise and an ultrasound available
- Femoral
  - Chronic dialysis patients in whom a functional fistula, graft, or peritoneal dialysis catheter is present or possible in the near future
  - Patients requiring emergency hemodialysis when the operator is inexperienced or does not have access to ultrasound
  - Severe coagulopathy

### Accidental Removal of NTHC

Temporary NTHCs are occasionally, unintentionally dislodged by patients or staff in the inpatient setting: A study of patients with nontunneled catheters (but not necessarily hemodialysis, HD catheters) in intensive care unit showed that the rate of accidental removal of internal jugular catheters and femoral catheters was 0.26 and 0.16 per 100 catheter days, respectively.<sup>20</sup> Death from exsanguination has been reported following accidental temporary HD catheter removal in the inpatient setting.<sup>21</sup> This highlights the importance of ensuring that temporary HD catheters remain adequately secured using sutures or an adhesive device specifically intended for that purpose, for the entire duration that they remain in place.

### Timing of Switching From an NTHC to Tunneled Central Venous Catheter Following AKI

Contrary to studies that previously suggested the risk of CRBSIs with NTHCs increases exponentially over time,<sup>18</sup> the Cathedia study demonstrated that catheter colonization occurs in a linear fashion over time.<sup>19</sup> This supports the idea that NTHCs should not be routinely replaced, and conflicts

with the National Kidney Foundation Kidney Disease Outcomes Quality Initiative, KDOQI recommendation that NTHCs should be used for less than 1 week.<sup>22</sup> The KDOQI recommendation may be appropriate for chronic hemodialysis patients in whom NTHC use should always be minimized in favor of more permanent access. It is less applicable to patients with AKI in whom the duration for which RRT will be required is unclear. For example, in the large randomized controlled trials (RCTs), RENAL<sup>23</sup> and ATN,<sup>24</sup> which examined dosing of RRT for, the mean duration for which RRT was implemented was 12 to 13 days. The related question of when to switch from an NTHC to a tunneled catheter in patients who do not recover from AKI has not been addressed by prospective studies. The consensus KDIGO recommendation is that, in the context of AKI, NTHCs should be converted to tunneled catheters as soon as it becomes clear that renal recovery is unlikely in the near term.<sup>2</sup>

## Summary

- NTHCs are typically used for vascular access for urgent hemodialysis.
- In general, the preferred site for NTHC insertion in AKI is the right internal jugular vein followed by the femoral vein; however, additional factors should be taken into account to ensure optimal site selection.
- When aided by real-time ultrasound, mechanical complications related to NTHC insertion are significantly reduced.
- NTHCs should be removed immediately if there is evidence of an exit-site infection or a CRBSI related to the NTHC.
- For chronic hemodialysis patients, permanent access is recommended over NTHC.
- Replacement of NTHC is recommended as soon as it becomes clear that renal recovery is unlikely in the near term.

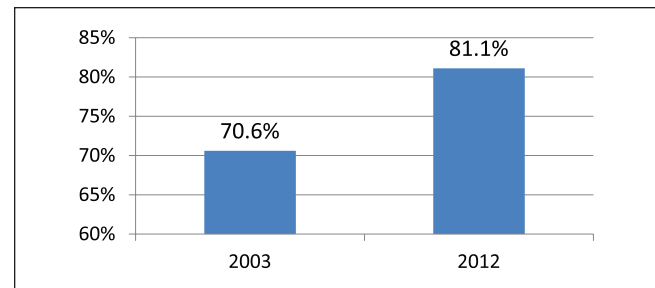
## Tunneled Hemodialysis Catheters

Canadian Society of Nephrology, CSN guidelines published in 2006 and augmented by a report from the CSN Vascular Access Working Group in 2012 recommended that the preferred access for hemodialysis is the radiocephalic native vessel arteriovenous fistula (AVF).<sup>25,26</sup> Despite this recommendation, the use of tunneled central venous catheters continues to increase in most Canadian hemodialysis units (Figure 1).<sup>27</sup>

CSN guidelines 2006 are found here: [https://www.csnsn.ca/images/Docs\\_Misc/Clinical\\_Practices\\_Guidelines\\_dox/CSN\\_Guidelines\\_2006.pdf](https://www.csnsn.ca/images/Docs_Misc/Clinical_Practices_Guidelines_dox/CSN_Guidelines_2006.pdf).

## Indications for Tunneled Catheter Use

Catheters are an important option for vascular access. They can be used immediately after insertion, can be used for



**Figure 1.** Prevalence of central venous catheters among incident hemodialysis patients in Canada.

long periods of time (assuming no complications), and provide painless hemodialysis access. There are multiple reasons for the high prevalence of catheter use including the following:

- Increasing age of patients initiating hemodialysis
- Increasing number of comorbid conditions including significant vascular disease
- Inadequate preparation prior to the need to initiate hemodialysis
- Inability of patient/family to make a modality choice in a timely manner
- Scheduled living donor transplant
- Patient choice
- Fear of needles
- Late referral.

However, there are many disadvantages of catheter use. Immediate complications that may occur include bleeding, catheter malposition, pneumothorax, air embolism, and vascular injury.<sup>5</sup> Long-term complications include catheter thrombosis, central vein stenosis, fibrin sheath formation, and catheter-related infections with their sequelae.<sup>28</sup> Therefore, clinical scenarios where tunneled cuffed hemodialysis catheter use may be appropriately considered include the following:

- Access of choice for temporary hemodialysis for longer than 2 to 3 weeks
- Permanent hemodialysis access when no other access (including peritoneal dialysis) is possible
- When a fistula or graft is maturing or healing
- When a peritoneal dialysis catheter is planned or healing
- When a live donor transplant is scheduled

Contraindications to tunneled catheter insertion include coagulation problems International normalized ratio, (INR, >1.5 or platelet count, <50 × 10<sup>9</sup>/L) and active septicemia.<sup>29,30</sup> In these situations, temporary, noncuffed, nontunneled hemodialysis catheters should be used.<sup>31</sup>

## Tunneled Cuffed Catheter Insertion

### Choice of Catheter

Several dual-lumen, large-diameter catheters are available.<sup>12,31-35</sup> Catheter materials include silastic elastomers of polyurethane or silicone.<sup>5,31,32,34</sup> There are multiple different catheter tip designs, but no one design has shown significant superior performance in blood flows, recirculation, or decreased catheter thrombosis or fibrin sheath formation.<sup>34</sup> A recent randomized trial of catheters with symmetrical tip cut and laser-cut side slots reported lower requirement for thrombolysis but no difference in primary patency or infection rates.<sup>36</sup> Antimicrobial or heparin-impregnated catheters have been reported to decrease incidence of catheter-related infections in the short term.<sup>37,38</sup> The efficacy of the coating, however, in the long term has not been demonstrated. Therefore, routine use of antimicrobial or heparin-impregnated catheters is not recommended.<sup>33,39</sup>

### Catheter Site Selection

The preferred site for catheter placement is the right internal jugular vein followed by the left internal jugular vein. Ideally, the catheter should be inserted on the opposite side of a maturing or planned arteriovenous access.<sup>12,28,32,33,39</sup>

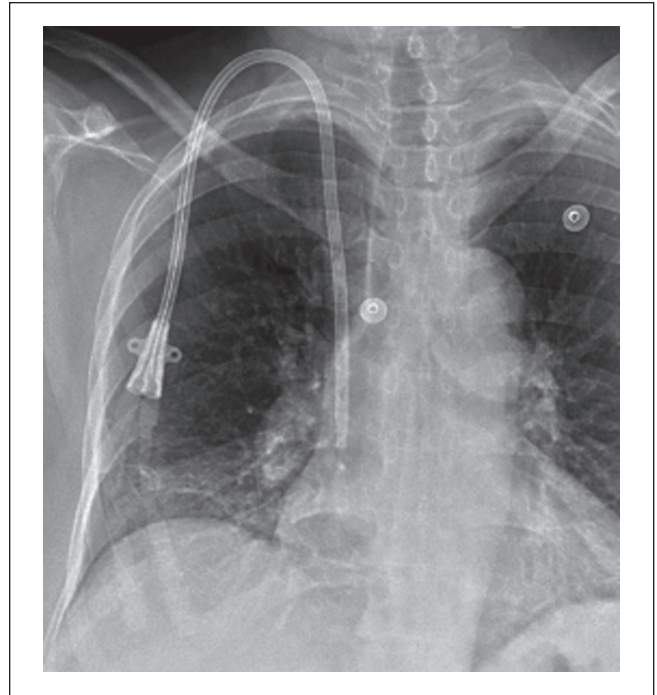
- Common femoral veins can be used when the central veins are occluded. The catheter must be greater than 20 cm in length to minimize recirculation, but catheters longer than 35 cm should be avoided, as flow rate decreases with increasing catheter length.
- Subclavian veins should be avoided whenever possible because of the increased incidence of venous stenosis which may compromise future arteriovenous access options.<sup>12,32,33,39</sup>
- If all of the above venous sites are not an option, percutaneous translumbar insertion into the inferior vena cava, transhepatic, or external jugular catheters can be considered (see “Atypical Tunneled Catheter Placement” section in MacRae et al<sup>40</sup>).

### Catheter Placement Technique

YouTube video link for catheter insertion: <http://www.youtube.com/watch?v=HE5QhsPRaPU>

Informed consent is required before any catheter insertion. Sterile technique should be followed in the interventional radiology suite, operating room, and any procedure room. Preprocedure sedation with fentanyl and/or midazolam should be considered for patient comfort.

The catheter is inserted percutaneously using a modified Seldinger guidewire technique using either fluoroscopy or ultrasound. Ultrasound-guided puncture of all venous sites is mandatory.<sup>5,12,29,33,35,39,41</sup> If available, fluoroscopy should be used to position the tip of the catheter in the mid-right atrium



**Figure 2.** Radiograph of a right internal jugular tunneled central venous catheter with catheter tip placed in right atrium. Source. Atlas of Dialysis Vascular Access. [esrdncc.org/wp-content/uploads/2015/12/Access-Atlas.pdf](http://esrdncc.org/wp-content/uploads/2015/12/Access-Atlas.pdf).

when the patient is supine (see Figure 2) and at the junction of the superior vena cava and right atrium when the patient is sitting.<sup>12,33,35</sup> If fluoroscopy is not used during insertion, a chest x-ray is recommended post procedure to ensure proper position and avoid complications.

There should be an anchor suture at the exit site and a closure suture at the puncture site. The puncture-site sutures can generally be removed in 10 to 14 days; however, practice is variable and, in some centers, dissolvable sutures are used in this location. The exit-site (anchor) suture can often be removed after 3 weeks for most catheters (refer to specific catheter monograph), but again practice between centers may vary. Prophylactic antibiotics are not recommended at the time of catheter insertion as there is no evidence to show that it prevents catheter colonization or bloodstream infections. Furthermore, routine use of prophylactic antibiotics may increase the risk of antibiotic-resistant organisms.<sup>29,35</sup>

### Prolonged Exit-Site Bleeding Following Tunneled Catheter Insertion

Minor, self-limited oozing at the exit site following insertion of a tunneled catheter is a frequent occurrence; however, less than 0.1% of patients experience prolonged oozing or overt bleeding that requires a transfusion or other intervention.<sup>42</sup>

When prolonged oozing or bleeding occurs in the absence of hypotension or other contraindications, the patient should be maintained in an upright position so as to reduce central venous pressure. While coagulopathy should be corrected, this is rarely an issue as tunneled catheters are typically not inserted without first having checked that the platelet count and INR are acceptable. If uremic bleeding is suspected, administration of desmopressin (DDAVP) or other agents may be considered.<sup>43</sup>

If application of pressure dressings and/or local pressure remains ineffective at stemming oozing or bleeding, placement of a purse-string suture at the tunnel exit site can often facilitate hemostasis.<sup>44</sup> This should be performed using aseptic technique, taking special care to avoid nicking the catheter.<sup>45</sup>

## Tunneled Cuffed Catheter Care

### Locking Solutions

Sodium citrate (4%) or concentrated heparin solutions (1000 units/mL) are standard locking solutions, whereas higher concentration heparin (5000-10 000 units/mL) is reserved for patients who develop catheter thrombosis with heparin 1000 units/mL.<sup>46</sup> There have not been any differences demonstrated between these 2 solutions in terms of the outcomes thrombolytic use or catheter removal for poor flow.<sup>47</sup> However, bleeding rates may be lower with citrate use, compared with heparin.<sup>47,48</sup> In addition, certain biofilm characteristics have been associated more frequently with heparin than with citrate use.<sup>49</sup> At higher concentrations of citrate, there is a risk of hypocalcemia and cardiac arrhythmias.<sup>50</sup>

Antibiotic locks have been associated with fewer catheter-related infections, but reported studies have small sample size and short periods of follow-up, and therefore, use should be dictated by local infection rates<sup>51,52</sup> (see “Antimicrobial Locks” and “Definitive Management” sections in Miller et al<sup>53</sup>).

### Exit-Site Care

Exit-site care is extremely important in maintaining a healthy access and minimizing infection. Masks or face shields for both the patient and the health care provider should be worn at the time of dressing change to the exit site and when accessing the catheter. Staff accessing the catheter should practice proper hand hygiene and wear clean gloves.<sup>54,55</sup> Other measures at the time of exit-site dressing change include the following:

- Use either a sterile gauze or transparent semipermeable dressings to cover the catheter exit site. The frequency of exit-site dressing changes is controversial. CSN guidelines (2006) recommend dressing changes at every hemodialysis treatment.<sup>25</sup>

- Application of povidone-iodine or polysporin ointment to the exit site is used in some centers.<sup>35,54,56,57</sup> Local infection rates should be considered when making decisions about the use of these ointments.
- Mupirocin ointment has been shown to reduce exit-site infections and catheter-related bacteremia<sup>58</sup>; however, it is not widely adopted due to risk of developing antimicrobial resistance and fungal infection.<sup>56,57</sup>
- Some ointments may not be compatible with certain hemodialysis catheters. It is therefore necessary to review manufacturer’s recommendations before applying any ointments to the catheter site.<sup>55</sup>

## Tunneled Cuffed Catheter Removal

### Planned Catheter Removal

Videos of cuffed catheter removal can be found at [https://www.youtube.com/watch?v=0IfjE0G9C\\_M](https://www.youtube.com/watch?v=0IfjE0G9C_M) or [https://www.youtube.com/watch?v=DGya15H\\_Jfw](https://www.youtube.com/watch?v=DGya15H_Jfw)

Local anesthetic, sterile technique, and minor surgical cutdown can be used to free the cuff if the catheter has been in place for greater than 3 weeks. Simple traction can be used to remove catheters that have been in place for less than 3 weeks. In case of sepsis, the catheter tip should be sent for culture. In some cases, catheter removal may be difficult as the catheter may be tethered or embedded, at which time assistance from interventional radiology or surgery should be considered (see “Difficult-to-Remove Embedded Catheter” section in Miller et al<sup>9</sup>).

### Accidental Tunneled Catheter Removal

Accidental removal of a tunneled catheter through the exit site is an infrequent occurrence; however, “some patients do arrive in a dialysis unit holding the catheter in their hands.”<sup>59</sup> The frequency with which this occurs has not been described for a large cohort of hemodialysis outpatients. There is likely an increased risk of unintentional dislodgement of catheters in the acute period following catheter insertion. This relates to the line being held less securely in place within the subcutaneous tissues prior to the occurrence of cuff fibrosis. The fibrous cuff is usually incorporated into the subcutaneous tissue after 3 weeks following insertion but can take up to 8 weeks in patients receiving corticosteroids.<sup>60</sup> After fibrotic tissue has become integrated into the catheter cuff, the tunneled catheter is more secure; however, accidental removal is still possible. Even following cuff fibrosis, tunnel infections can disrupt the cuff’s attachment to subcutaneous tissue and facilitate catheter removal whether intentional or unintentional. Although a new site for catheter insertion is mandatory if there is any suggestion of underlying infection, a small case-series study reported successful replacement of accidentally dislodged via the old exit site using fluoroscopic guidance.<sup>59</sup>

## Summary

- Tunneled central venous catheters are commonly used for hemodialysis access, with incident use in Canadian facilities approximately 80%.
- While arteriovenous access is recommended, clinical situations where catheters may be considered include temporary hemodialysis greater than 2 to 3 weeks, while an arteriovenous access is maturing, while a peritoneal dialysis catheter is planned or healing, when a live donor transplant is scheduled, and when no other access (including peritoneal dialysis) is possible.
- Several dual-lumen, large-diameter catheters are available and may be derived from silastic elastomers of polyurethane or silicone. Multiple catheter tip designs exist, but no one design has shown significant superior performance.
- Sterile technique during catheter insertion and removal is mandatory.
- Catheters are inserted percutaneously using a modified Seldinger guidewire technique using either fluoroscopy or ultrasound.
- The preferred site for catheter placement is the right internal jugular vein followed by the left internal jugular vein. Ideally, the catheter should be inserted on the opposite side of a maturing or planned arteriovenous access.
- Subclavian veins should be avoided whenever possible due to the increased incidence of venous stenosis.
- Exit-site care is extremely important in reducing the risk of catheter-related infections.

## 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.

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## Author Contributions

E.C. and J.K. are co-first authors who drafted and critically revised the manuscript. J.M. conceived, designed, and coordinated the review, and critically revised the manuscript. S.H., C.L., and L.M. helped design and draft the manuscript and provided critical review. C.D. and M.K. provided critical review. M.O. helped draft the manuscript and provided critical review. L.M.M. designed and

coordinated the review, and drafted and provided critical review of the manuscript at all stages. All authors read and approved the final manuscript.

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