

Management of occlusion and thrombosis associated with long-term indwelling central venous catheters

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Long-term central venous catheters (CVCs) are important instruments in the care of patients with chronic illnesses, but catheter occlusions and catheter-related thromboses are common complications that can result from their use. In this Review, we summarise management of these complications. Mechanical CVC occlusions need cause-specific treatment, whereas thrombotic occlusions usually resolve with thrombolytic treatment, such as alteplase. Prophylaxis with thrombolytic flushes might prevent CVC infections and catheter-related thromboses, but confirmatory studies and cost-effectiveness analysis of this approach are needed. Risk factors for catheter-related thromboses include previous catheter infections, malposition of the catheter tip, and prothrombotic states. Catheter-related thromboses can lead to catheter infection, pulmonary embolism, and post-thrombotic syndrome. Catheter-related thromboses are usually diagnosed by Doppler ultrasonography or venography and treated with anticoagulation therapy for 6 weeks to a year, dependent on the extent of the thrombus, response to initial therapy, and whether thrombophilic factors persist. Prevention of catheter-related thromboses includes proper positioning of the CVC and prevention of infections; anticoagulation prophylaxis is not currently recommended.

Introduction

For patients with chronic illnesses, long-term central venous catheters (CVCs) provide easy venous access for laboratory tests, drug delivery, and parenteral nutrition. However, several complications that result from the use of CVCs, including sepsis, extravasation of infusions, and venous thrombosis, can increase associated morbidity and mortality. These complications can also interrupt and delay treatment for the underlying disease and thereby affect outcome. In this Review, we discuss the diagnosis, management, and prevention of catheter occlusions and catheter-related thromboses, the most common complications of CVCs. Since the incidence, risk factors, and management of occlusion and catheter-related thromboses differ between long-term and short-term CVCs, we focus on long-term catheters only. For the purposes of this Review, long-term CVCs include subcutaneously tunnelled catheters or implanted ports, but do not include those placed in the intensive care or perioperative setting, haemodialysis catheters, and catheters intended for short-term use. The Kids with Catheter-Associated Thrombosis (KIDCAT) study recently investigated thrombosis of short-term CVCs.¹

CVC occlusion occurs in 14–36% of patients within 1–2 years of catheter placement.^{2–8} A CVC occlusion can be partial, in that blood cannot be aspirated but infusion through the catheter is possible, or complete, with neither aspiration nor infusion possible. A CVC occlusion can arise from mechanical obstruction, precipitation of drugs or parenteral nutrition preparations, or from thrombotic obstruction. Catheter-related thrombosis occurs in up to 50% of children and 66% of adults with a long-term CVC, and can cause long-term vascular complications.^{9–21} In a survey of health-care workers from Children's Cancer Study Group centres in the UK, CVC occlusion and catheter-related thrombosis were judged clinically important by 80% and 70% of the respondents,

respectively. However, the investigators reported substantial variation in the diagnosis, management, and prevention of CVC occlusions and associated thrombotic complications.²²

Central venous catheter occlusion

Causes of central venous catheter occlusion

Accurate diagnosis of the cause of catheter occlusion is essential to effectively treat the problem. Table 1 lists causes and recommendations for management of catheter occlusions. An obstruction can occur secondary to various mechanical problems, including an uncommon, but potentially life-threatening, pinch-off syndrome (figure 1, table 1).^{26–28} Drugs or parenteral nutrition preparations can also obstruct flow through the catheter; obstruction can be acute or gradual. Inappropriate concentrations or incompatible mixtures can cause drugs to precipitate within the catheter lumen (eg, precipitation of calcium phosphate crystals after co-delivery of inappropriate concentrations of calcium and phosphorus), which can result in catheter occlusion. Precipitation can also occur if the pH of an infusion is too alkaline or acidic. Parenteral nutrition preparations can leave a lipid residue that can obstruct a CVC.^{23,24,29}

Catheters can also become occluded secondary to a thrombotic process, such as a fibrin sheath around the

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Search strategy and selection criteria

We searched Medline and PubMed for articles published in the English language from 1965 to January, 2009, with the keywords "central venous catheter", "central venous access device", and "central venous line" associated with "occlusion", "obstruction", and "catheter-related thrombosis". We only included articles that assessed long-term CVCs. In some instances, review articles were selected over original articles because of space constraints.

	Diagnosis	Treatment	Level of evidence*
Mechanical obstruction			
Kink in catheter or tubing, tight suture, or clamp closed on external catheter ²³⁻²⁵	Inspect catheter	Correct mechanical dysfunction	5
Port access needle dislodged or occluded in port ²⁶⁻²⁸	Assess port access needle placement	Replace needle if necessary	5
Catheter tip blocked by vessel wall ²³⁻²⁵	Reposition patient	Reposition patient	5
Pinch-off syndrome ²⁶⁻²⁸	Fluoroscopy	Remove catheter if at risk for fracture	3b
Obstruction related to drug or parenteral nutrition			
Low pH (acidic) ^{23,24,29,30}	Review drug	Hydrochloric acid 0.1 mol/L†	4
High pH (basic) ^{23,24,29,31}	Review drug	Sodium hydroxide 0.1 mol/L or sodium bicarbonate 1.0 mol/L	4
Calcium phosphate precipitate ^{24,25,29,30,32}	Review drug	Hydrochloric acid 0.1 mol/L†	4
Lipid emulsion ^{24,25,29,33}	Review parenteral nutrition preparations	Ethanol 70%	4
Thrombotic obstruction			
Fibrin sheath or intraluminal clot ^{34,35}	Radiography after instillation of contrast into the catheter (linogram)	Intraluminal thrombolytic drugs	1b
Mural thrombus or venous thrombosis ^{34,35}	Ultrasound or venography	Anticoagulant treatment (rarely resolves with intraluminal thrombolytic drugs)	2c

*Levels of evidence as defined in Oxford Centre for Evidence Based Medicine.³⁶ †No longer used in some institutions because of concern about damage to the catheter wall.

Table 1: Causes of central venous catheter occlusions⁵ and recommendations for treatment

catheter tip, an intraluminal blood clot, or a venous thrombosis, which can occur separately or in combination (figure 2). A fibrin sheath is one of the most common causes of thrombotic obstruction. It can occur within 24 h after CVC placement and usually develops within 2 weeks.^{9,13,37} One autopsy study of patients with a long-term CVC showed that a fibrin sheath encased the catheter tip in every case.³⁷ The fibrin sheath does not usually affect catheter function, but might cause a partial obstruction by creating a one-way valve over the catheter tip. The negative pressure created when attempting to aspirate blood creates suction, which pulls the fibrin sheath over the CVC tip and prevents withdrawal of blood. The obstruction resolves when the negative pressure is relieved (eg, during infusion or flushing the catheter), which allows easy flow of fluids into the CVC.³⁸ Although a fibrin sheath does not usually cause any clinical manifestations, there is a small risk of embolisation of the fibrin material.¹⁸

Intraluminal clots account for 5–25% of all catheter occlusions and can cause complete catheter obstruction. Catheter-related venous thrombosis refers to a thrombus that develops near to a CVC. A mural thrombus is a blood clot that adheres to the vessel wall and can occlude the tip of the catheter, but does not completely occlude the vein in which the catheter is positioned (figure 2). A

deep vein thrombosis refers to a catheter-related thrombosis that occludes the vein.¹⁸

Management

Mechanical obstruction of catheter

A standard procedure should be followed to diagnose and manage CVC obstruction (figure 3). First, any obvious mechanical obstruction (eg, a kink in the catheter tubing, a suture that is too tight, a clamp inadvertently left closed, a catheter tip blocked by the blood vessel wall, or a malpositioned subcutaneous port access needle [also known as a Huber needle]) should be ruled out by carefully inspecting the CVC. The patient should be repositioned—for example, by raising the ipsilateral arm, having the patient sit or stand, or rolling the patient onto one side. A dye study can also be used to diagnose an internal kink in the catheter.

Catheter obstruction related to drug or parenteral nutrition preparation

If a mechanical obstruction is not found, obstruction by drug or parenteral nutrition preparation should be investigated (figure 3). Appropriate treatment depends on the suspected cause of the occlusion. Obstructions thought to be caused by precipitation of drugs with low pH or calcium phosphate crystals that become insoluble in basic solutions can be treated with hydrochloric acid (0.1 mol/L).^{23,24,29,30,32} Although our centre still uses this method, the practice has been discontinued in some institutions because of concern about damage to the wall of the catheter. Obstructions caused by drugs with high pH that precipitate in an acidic environment (eg, phenytoin) are treated with sodium bicarbonate (1.0 mol/L) or sodium hydroxide (0.1 mol/L).^{23-25,29,31} A lipid residue from parenteral nutrition can be successfully cleared with a 70% ethanol solution; however, no large studies of this approach have been done and side-effects include dizziness, fatigue, and light-headedness.^{23-25,29,33}

Thrombotic catheter obstruction

After ruling out mechanical dysfunction and drug-related or parenteral nutrition-related causes, the next step is to look for thrombotic obstruction (table 1). A contrast study of the catheter (sometimes called a linogram) can be used to detect an intraluminal clot or fibrin sheath. However, a common practice is to treat suspected thrombotic occlusions empirically with thrombolytic drugs. A treatment frequently used in the USA for CVC occlusions is alteplase (2 mg per 2 mL).^{34,39-44} A dose of 2 mL, or 110% of the volume of the catheter lumen if less than 2 mL (maximum dose 2 mg), is placed in the catheter lumen. Alteplase catalyses the conversion of clot-bound plasminogen to plasmin and initiates fibrinolysis (figure 4). Haire and colleagues⁴³ showed that a 2 mg dose of alteplase was more effective than urokinase (5000 IU) for the treatment of

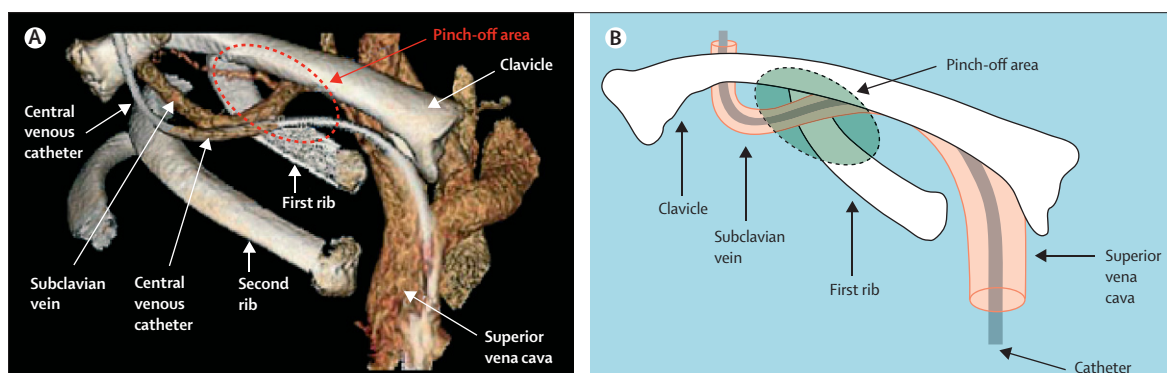


Figure 1: The pinch-off syndrome

The catheter passes through the narrow angle between the first rib and the lateral portion of the clavicle (the pinch-off area), placing it at risk for compression or transection. In panel A (a three-dimensional CT image), the catheter passes through the pinch-off area parallel to the subclavian vein then inserts into the superior vena cava. In panel B, the catheter inserts into the subclavian vein and is intravenous when it passes through the pinch-off area. Catheters that are external to the subclavian vein when they pass through the pinch-off area, as in panel A, have a greater risk of pinch-off syndrome and fracture.¹

radiographically proven thrombotic occlusion of a CVC (assessed by both catheter function and clot resolution via radiological assessment) after a dwell time of 120 min.

In the COOL trial (Cardiovascular Thrombolytic used to Open Occluded Lines), catheter occlusion was cleared after 120 min in 74% of 69 patients who were given one 2 mg dose of alteplase compared with only 17% of 70 patients given placebo. The proportion of patients with catheter clearance after up to two doses of alteplase was 90% (62 of 69 patients); there were no reports of major haemorrhage.³⁹ Larger studies subsequently confirmed the safety and efficacy of alteplase given at various time intervals in different long-term catheters, including peripherally inserted central catheters,^{40,44} with one study reporting major haemorrhage in three (0.3%) of 997 patients.⁴⁰

After alteplase was shown to be successful for the treatment of CVC occlusion in adults, it was proven safe and effective in children, with catheter clearance rates of 85–95% and no reports of major haemorrhage.^{45–48} A subsequent subset analysis of paediatric patients in the COOL trial⁴¹ and an open-label, single-arm, multicentre trial⁴² with the same dosing regimen and dwell times as those used in the COOL trial supported the finding that alteplase was as effective in children as in adults, with catheter clearance rates of 83–87% and no evidence of major haemorrhage.^{41,42}

Current recommendations include delivery of a thrombolytic agent into the catheter lumen with a dwell time of at least 30 min and a repeated dose if needed.³⁴ If catheter patency is not restored, a low dose of alteplase can be infused over 6–8 h. Ultrasonography, venography, or other diagnostic study is warranted if venous thrombosis is suspected (table 1, figure 3).

If treatment with a thrombolytic agent does not clear the catheter, a guide wire can be inserted through the catheter lumen to dislodge a thrombus at the tip of the CVC. Fibrin sheath stripping has also been used for CVC

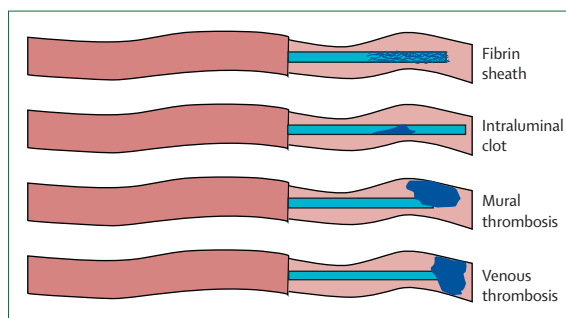


Figure 2: Types of thrombotic occlusion

occlusion that is resistant to drug management. The procedure uses femoral venous access to pass a vascular snare device to dislodge and remove the fibrin sheath.⁴⁹ Although effective, these procedures are more invasive and are only used when necessary.

New thrombolytic agents

New thrombolytic drugs with potentially higher efficacy and shorter dwell times than alteplase are being investigated; however, the trials published so far have been non-randomised and undertaken in small patient cohorts (table 2). One promising new thrombolytic drug is reteplase, a variant of alteplase; reteplase's structural differences increase its half-life and thrombus penetration. In adults, reteplase effectively restored patency to occluded CVCs, with catheter clearance seen in 67–74% of treated patients after a dwell time of 30–40 min, compared with 52% of patients given alteplase with a dwell time of 30 min (table 2; figure 5).^{40–42,44,51,52} Reteplase was also effective after longer dwell times, with overall catheter clearance rates near 96% and no reports of major haemorrhage (table 2; figure 5).^{51–53} Although reteplase seems to be more effective in a shorter dwell time than alteplase, prospective randomised trials with larger numbers of patients are needed to show superior efficacy and adequate safety of this drug.

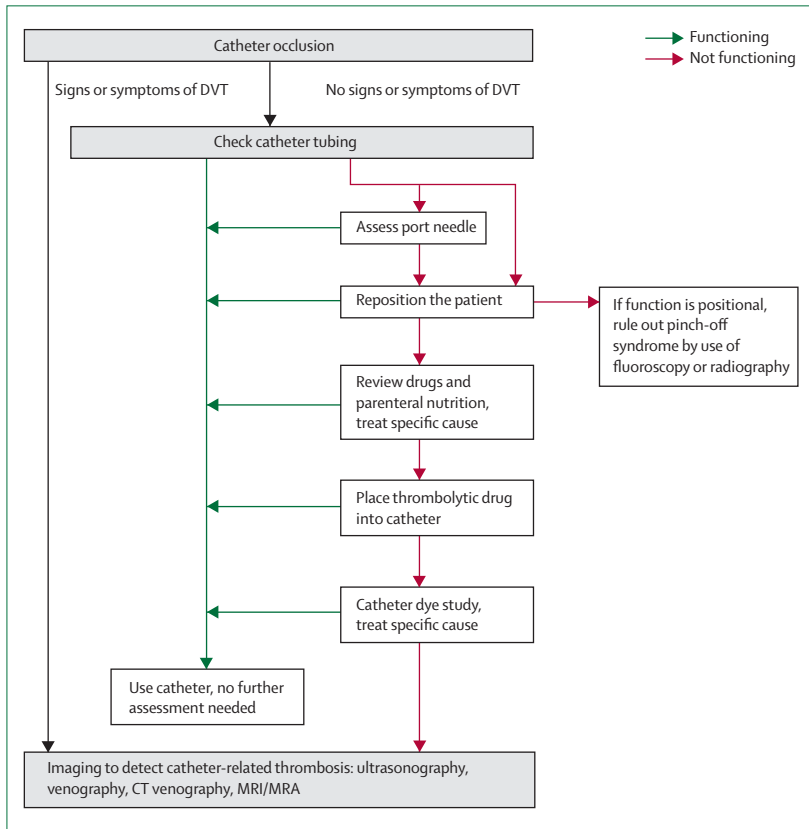


Figure 3: Algorithm for management of a central venous catheter obstruction
 DVT=deep-vein thrombosis. MRI=magnetic resonance imaging. MRA=magnetic resonance angiography.

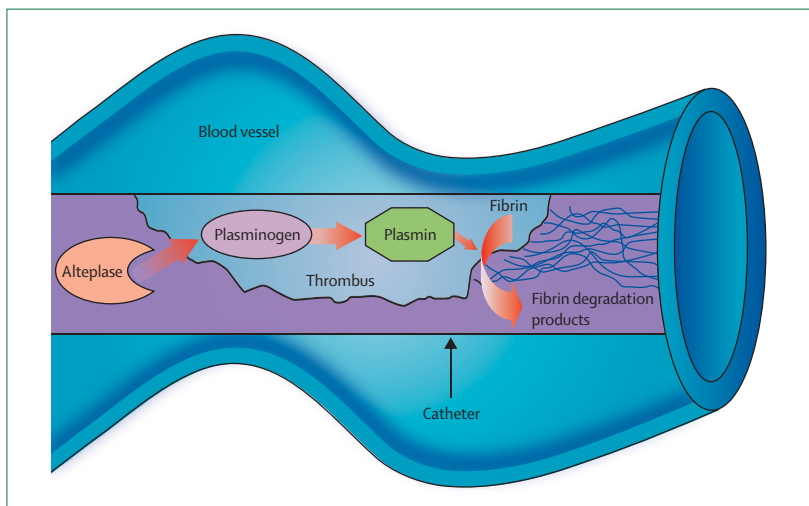


Figure 4: Mechanism of action of tissue plasminogen activator
 Tissue plasminogen activator catalyses the conversion of plasminogen to plasmin, which then cleaves fibrin into fibrin degradation products to dissolve the thrombus.

Recombinant urokinase has been studied as a potential candidate for the management of CVC occlusions in adults. Recombinant urokinase seems to have greater efficacy than alteplase within the first 30 min, with a mean of 60% of patients with catheter clearance (table 2; figure 5).^{40-42,44,54-56} Whether recombinant urokinase is

more effective than alteplase at timepoints beyond 30 min remains to be studied. Recombinant urokinase is less effective than reteplase at all timepoints (figure 5),⁵¹⁻⁵⁶ and the frequency of major haemorrhage was 0.6% within 72 h and 1.8% within 30 days of treatment.⁵⁶ In one study in cancer patients, a higher dose of recombinant urokinase increased the risk of bleeding but did not improve catheter clearance rates.⁵⁴ Although only a trial that directly compares the three drugs can unequivocally establish the most effective and safe treatment, existing data suggest that recombinant urokinase is more effective than alteplase at early timepoints but less so after two doses, and is less effective than reteplase at all timepoints for treatment of occluded catheters.

Alfimeprase (ARCA Biopharma, Colorado, USA) is a new thrombolytic agent under investigation for its ability to clear catheter occlusions. Its site of action is different from that of other thrombolytic drugs and independent of the plasminogen activation system. Alfimeprase is a recombinant form of the metalloproteinase fibrolase that binds to the A α chain of fibrin to directly degrade the thrombus (table 2).^{50,57} These characteristics are probably the cause of the rapid onset of drug action; rapid inactivation of alfimeprase by plasma α 2 macroglobulin might account for the lack of systemic side-effects associated with the drug.

A phase II randomised, double-blind, multicentre, dose-ranging trial compared the safety and efficacy of three doses of alfimeprase (0.3 mg, 1.0 mg, and 3.0 mg) with that of the standard 2 mg dose of alteplase in 55 adult patients.⁵⁰ A 3 mg dose of alfimeprase was more effective than alteplase within the first 30 min and cleared 40% of catheters in 5 min and 60% at 30 min; alteplase cleared 0% and 23%, respectively. However, after the initial dose of alfimeprase, no additional catheters were cleared after 30 min until a second dose was given (table 2, figure 5).^{40-42,44,50} This finding suggests that despite its rapid onset of action, a second dose of alfimeprase might be needed if patency is not restored shortly after administration of the initial dose. There were no episodes of major haemorrhage in the 55 patients, but a larger study is needed to further document the frequency of serious side-effects.

Prophylaxis

To prevent thrombotic CVC occlusions, most institutions that use long-term CVCs have standard protocols for the method and frequency of flushing the catheter. However, there is insufficient evidence on which to base universal guidelines for these practices, specifically with regard to the type of solution used (10 U/mL heparin vs 100 U/mL heparin vs normal saline) and frequency of flushing the catheter. For peripheral intravenous catheters, studies in adults have shown no difference in efficacy between a saline or heparin lock, although these results have not been corroborated

	Definition	Mechanism of action	Maximum dwell time (per dose)	Weighted mean proportion of catheter clearance at 30 min with first dose (% [SE])	Overall weighted mean catheter clearance with two doses (% [SE])
Alteplase ^{39-42,44-48,50}	Tissue plasminogen activator made via recombinant DNA technology from vascular endothelial cells	Converts clot-bound plasminogen to plasmin	30–120 min	52.1% (2.6)	86.1% (1.7)
Reteplase ⁵¹⁻⁵³	A variant of tissue plasminogen activator that lacks several structural domains. It does contain the kringle-2 and protease structures	Converts clot-bound plasminogen to plasmin	30–60 min	69.8% (5.8)	95.2% (2.8)
Recombinant urokinase ⁵⁴⁻⁵⁶	The DNA recombinant form of urokinase, a physiological thrombolytic agent from renal parenchymal cells	Converts clot-bound plasminogen to plasmin	15–30 min	59.7% (3.2)	72.5% (2.7)
Alfimeprase ^{50,57}	A truncated form of the metalloproteinase fibrolase. It is made via recombinant DNA technology	Binds A α chain of fibrin to directly degrade thrombus	15–120 min	60% (30.0)	80% (24.8)

Table 2: Thrombolytic treatment

uniformly in children.⁵⁸⁻⁶⁰ For CVCs, some studies have suggested that there is no difference between a saline and heparin lock.⁶¹⁻⁶³ One study in children showed no difference in catheter occlusion or clot formation when flushing the external catheter twice a day with a heparin solution (10 U/mL) versus once a week with a saline solution.⁶² There is general consensus that subcutaneous ports should be flushed once a month; however, one retrospective study in adults showed that ports flushed less frequently were not associated with an increased occurrence of catheter complications.⁶⁴ Although the literature suggests that the current practice of frequent heparin locks for CVCs might not be necessary, randomised studies are needed to identify the ideal flush solution, its concentration, and delivery schedule for each type of long-term CVC.

Investigators have also studied methods such as anticoagulation prophylaxis to prevent thrombotic catheter occlusions.^{2,65} Two recent studies including one large, prospective, randomised phase III multicentre trial, showed a substantially lower occurrence of catheter occlusions in children who received urokinase prophylaxis (19–23%) than in controls (31–68%).^{2,65} However, to achieve this modest decrease in the frequency of CVC occlusion, treatment with urokinase every 1–2 weeks in all patients for several months was needed. Urokinase is expensive and has potential side-effects; treatment with many doses for the sole purpose of reducing catheter occlusions might not be justified, since catheter clearance rates are 80–90% with one to two doses of thrombolytic treatment.

Prevention of CVC occlusion might not be the only benefit of thrombolytic prophylaxis. Results from both urokinase studies^{2,65} showed that prophylaxis decreased the frequency of catheter-related infections, which accords with the conclusions of a meta-analysis that assessed routine urokinase use in patients with a CVC.⁶⁶ Studies also suggest that urokinase prophylaxis might lower the rate of catheter-related thrombosis.^{2,65} In several small studies, treatment with alteplase once a month decreased the number of infections associated with long-term CVCs in patients with haemophilia,

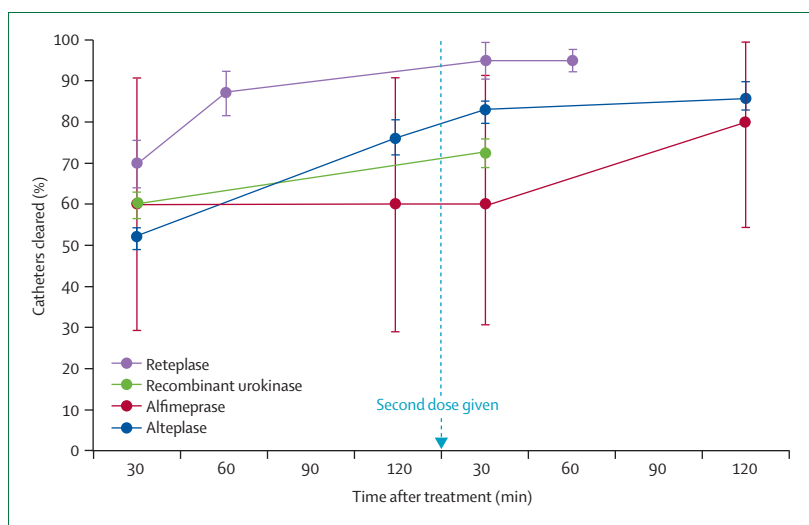


Figure 5: Cumulative mean rate of catheter clearance after treatment with a thrombolytic agent
In the 16 studies represented in this figure, if the catheter did not clear within 120 min, a second dose of the agent was given.^{39-42,44-48,50-57} Error bars show SEs.

lending support to the concept that clot lysis might reduce the frequency of catheter-related infections.⁶⁷ However, whether monthly alteplase decreases thrombosis is not known. All potential risks and benefits of prophylaxis, including effect on complications associated with catheter occlusions (catheter infections, catheter-related thromboses, and the need for catheter removal), costs, and side-effects must be considered to define the optimum strategy.

Prevention of catheter-related thromboses has also been addressed. Results from early studies suggested that the frequency of asymptomatic catheter-related thrombosis was substantially lower in adult patients given prophylactic low doses of warfarin than in patients given no warfarin;^{68,69} one study reported development of catheter-related thrombosis in 37.5% of 40 controls compared with only 9.5% of 42 treated patients.⁶⁸ However, subsequent trials showed no benefit of low-dose warfarin prophylaxis.^{70,71} Similar studies were done to assess the effect of low-molecular-weight heparin prophylaxis. Although an early study in adults

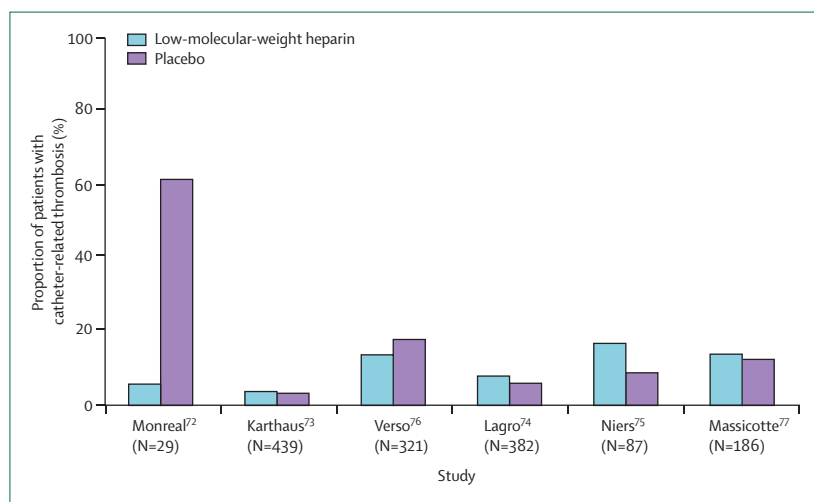


Figure 6: Proportion of patients with catheter-related thrombosis after prophylaxis with low-molecular-weight heparin or placebo in six randomised trials⁷²⁻⁷⁷
Only the study by Lagro et al⁷⁴ included solely symptomatic patients.

showed lower rates of asymptomatic catheter-related thrombosis in the active treatment group than in controls,⁷² these results were not repeated in subsequent randomised, placebo-controlled trials that investigated symptomatic and asymptomatic catheter-related thrombosis in adults⁷³⁻⁷⁶ and children⁷⁷ (figure 6). The study in children had to be stopped early because of slow patient accrual; however, at the time of termination there was no difference in the rate of asymptomatic catheter-related thrombosis between those who had received low-molecular-weight heparin prophylaxis and controls.⁷⁷

Potential side-effects of heparin treatment must be taken into account when considering thromboprophylaxis for patients. Heparin-induced thrombocytopenia is one such complication; however, it occurs less frequently with low-molecular-weight heparins. Osteoporosis and osteopenia have been reported after long-term heparin treatment, and patients on low-molecular-weight heparin with renal dysfunction are at increased risk for bleeding.⁷⁸

A meta-analysis showed that although there was no harm, there was also no additional benefit of thromboprophylaxis, substantiating the current recommendation by the American College of Chest Physicians that patients with a long-term CVC should not receive anticoagulation prophylaxis.^{34,35,79} One of the limitations of the meta-analysis was the heterogeneity of the definition and the method of diagnosis for catheter-related thrombosis. Larger studies with more homogeneous patient cohorts and similar outcomes are needed to definitely prove whether or not there is a benefit to antithrombotic prophylaxis. Most importantly, such studies must be done in patients at very high risk of CVC occlusion and catheter-related thrombosis, since the potential benefits could outweigh risks and costs in this group.

Catheter-related thromboses

Patients with long-term CVCs are prone to catheter-related thrombosis because of the direct effects of the catheter on adjacent veins and blood flow, the underlying disease and its treatment, the nature of substances being infused, and the location and time of placement of the catheter.⁸⁰ Catheter-related thromboses most often occur in the upper extremity where most long-term catheters are located.⁸¹ Symptoms include pain, tenderness to palpation, swelling, oedema, warmth, erythema, and development of collateral vessels in the surrounding area.³⁸ Symptomatic catheter-related thrombosis occurs in up to 28% of adults and 12% of children with a CVC; however, most catheter-related thromboses are asymptomatic, occurring in up to 66% of adults and 50% of children with a CVC.^{9-11,15-20} Reported proportions vary considerably depending on criteria for studying patients and imaging used for diagnosis.

Some studies have shown that the risk of catheter-related thrombosis might be related to the position of the catheter; increased risk is associated with catheters located in the left subclavian vein or with malposition of the catheter.^{9,18,34,82-84} Previous catheter infections are also a risk factor for the development of catheter-related thrombosis.^{10,17,80,85} Some bacteria, especially those that cause most catheter infections, are highly thrombogenic and create a favourable environment for the development of a thrombus. Indirect comparisons have suggested that upper-extremity deep-vein thromboses occur less frequently with subcutaneous ports than with external catheters; however, this finding has not been confirmed. Studies have shown that increases in lumen size and lumen number heighten the risk of catheter-related thrombosis, probably because of increased disruption of the vascular endothelium.^{20,84,86}

Complications

Catheter-related thromboses can lead to further complications such as increased risk of subsequent catheter infections, pulmonary embolism, post-thrombotic syndrome, and persistent vascular compromise.^{10,18,21,38,80} Microbiological studies have shown that proteins within a clot, such as fibrinogen and fibronectin, attract staphylococcal species and enhance their adherence to the catheter surface, thereby increasing the risk of catheter infection.^{86,87} A study of 38 Hickman catheters in children reported that 18% of 28 patients who developed a clot also had a catheter-related bloodstream infection, whereas no infections were reported in ten patients without clots.⁸⁸

Pulmonary embolism occurs symptomatically in 5-14% of adult patients with an upper-extremity deep-vein thrombosis and asymptotically in 15-36%.^{17,89-91} According to a Canadian registry, pulmonary embolism developed in 16% of 244 children with a catheter-related thrombosis (13% non-fatal and 3% fatal).^{92,93}

Post-thrombotic syndrome is a long-term complication of deep-vein thromboses that presents with oedema, skin hyperpigmentation, and pain, with more severe cases associated with skin ulceration.⁸ Post-thrombotic syndrome occurs in 27–88% of all deep-vein thrombosis cases; there is, however, a higher percentage of occurrence in patients with lower-extremity deep-vein thrombosis, and a 7–46% occurrence in patients with upper-extremity deep-vein thrombosis with a weighted mean of 15%.^{14,94,95} This trend might explain the low frequency of post-thrombotic syndrome in patients with catheter-related thrombosis, since most CVCs are located in the upper extremities, whereas deep-vein thromboses that are not associated with a CVC occur more frequently in the lower extremities. Factors that increase the risk for post-thrombotic syndrome include raised factor VIII and D-dimer concentrations at the time of thrombosis and persistent high concentrations thereafter, absence of clot resolution, many vessels affected by the original deep-vein thrombosis, delay in initiating deep-vein thrombosis treatment, recurrence of the deep-vein thrombosis, and long duration of follow-up.^{8,12,14,16,94,95} Post-thrombotic syndrome can be difficult to treat and might not develop until many years after the original venous insult; thus, long-term follow-up after diagnosis and treatment of deep-vein thrombosis is needed.

Patients with catheter-related thrombosis can also have persistent vascular occlusion for years after the catheter has been removed, which increases their risk for post-thrombotic syndrome and recurrent thrombosis.²¹ Hence, catheter-related thrombosis is a serious complication that can have important consequences if it is not diagnosed and treated appropriately.

Diagnosis

If a catheter-related thrombosis is suspected, venography or Doppler ultrasonography can help to assess the venous system. Although venography is the current gold standard for diagnosis, it is often not undertaken because it is invasive and requires exposure to intravenous contrast and radiation. Ultrasonography is a suitable alternative that is non-invasive, readily available, and accurate.⁹⁶ In adults, ultrasonography has a sensitivity of 78–100% and a specificity of 86–100% for diagnosis of symptomatic upper-extremity deep-vein thrombosis.^{97–99} However, these results have not been replicated in children. One study in children that compared the two methods showed that ultrasonography had a sensitivity of only 37% for diagnosis of an asymptomatic upper-extremity deep-vein thrombosis, whereas venography had 79% sensitivity.¹⁰⁰ The investigators reported that ultrasonography was reliable for the detection of deep-vein thrombosis in the jugular veins, but not in vessels within the thorax, such as the subclavian veins.¹⁰⁰ These limitations are thought to be a result of the shadows on the ultrasound image caused

by the clavicle, sternum, and lungs surrounding the central vessels and the inability to compress areas of the subclavian veins secondary to the overlying clavicles (compressibility is used to assess for presence of a thrombus during ultrasonography).¹⁰¹ We now need to establish the sensitivity and specificity of ultrasonography for the diagnosis of symptomatic upper-extremity deep-vein thrombosis in children.

Other methods, such as CT venography and magnetic resonance imaging and angiography, are also being investigated for use in the diagnosis of upper-extremity deep-vein thrombosis. CT venography exposes the patient to radiation, but the addition of three-dimensional reconstruction might aid in diagnosis. Magnetic resonance imaging and angiography do not require contrast or exposure to radiation, but the presence of motion artifact makes accurate diagnosis of an intrathoracic deep-vein thrombosis difficult.⁹⁹ Further studies need to assess the optimum diagnostic approach and the role of each radiographic method. However, we recommend that when a catheter-related thrombosis is suspected in any patient, an ultrasound is undertaken in the first instance. If the ultrasound result is negative and an upper-extremity deep-vein thrombosis is suspected on the basis of convincing clinical evidence, venography should be done for a complete assessment.^{97–99} Additional studies on the use of these techniques for the detection of upper-extremity deep-vein thromboses in children are warranted.

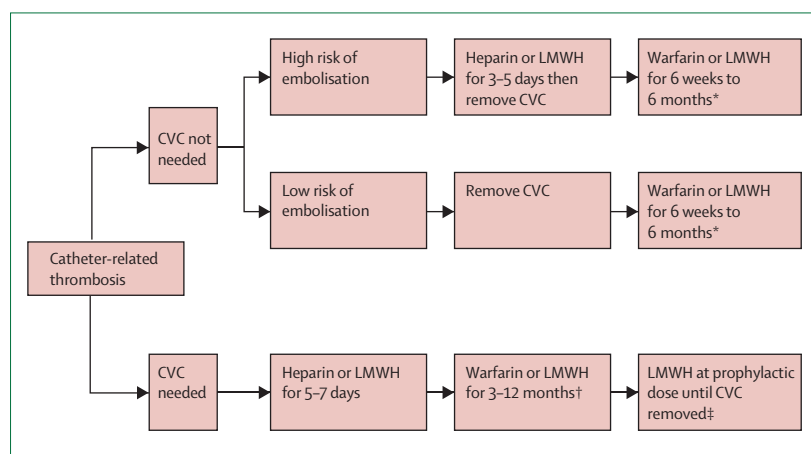


Figure 7: Recommended algorithm for the management of catheter-related thrombosis

CVC=central venous catheter. LMWH=low-molecular-weight heparin. The duration of anticoagulation treatment needed is dependent on a range of clinical factors.^{34,35} *If the CVC is removed after development of catheter-related thrombosis, no prothrombotic risk factors remain, and the clot is small and does not completely obstruct the vein, 6 weeks of anticoagulation might be adequate. A longer duration of anticoagulation is recommended for large, obstructing clots and when prothrombotic risk factors are present after CVC removal. †In patients with no prothrombotic risk factors whose CVC has been removed, most physicians consider 3 months of anticoagulation to be adequate. In patients with cancer, LMWH is preferred over warfarin because the rate of recurrent thrombosis is twice as high with warfarin, and the duration of anticoagulant therapy should be at least 6 months, and possibly 1 year or longer. ‡In a patient with catheter-related thrombosis whose CVC is left in place after 3–12 months of anticoagulation treatment, prophylactic doses of anticoagulant treatment are recommended, especially if other prothrombotic risk factors are present, as is the case for most patients with cancer.

Management

Because there are few prospective studies of treatment of catheter-related thrombosis, optimum management continues to be controversial. Recent guidelines suggest that patients with catheter-related thromboses should be divided into two categories on the basis of whether or not they continue to need central venous access (figure 7).³⁴ For patients who have developed a catheter-related thrombosis but no longer need a CVC or in whom the CVC is no longer functioning, guidelines from the American College of Chest Physicians (ACCP) recommend removal of the catheter after 3–5 days of anticoagulation treatment. However, some clinicians think that the CVC can be removed once a patient has been appropriately anticoagulated, as defined by an appropriate partial thromboplastin time if unfractionated heparin is used (1.5–2.5 times the normal range, which should be based on the normal values determined by each individual laboratory, measured about 4 h after any change has been made to the infusion) or an appropriate anti-Xa concentration if low-molecular-weight heparin is used (between 0.6 U/mL and 1.0 U/mL, measured 4 h after the medication is given).¹⁰² It should be noted that in adults, an adequate anti-Xa concentration has not been associated with improved clinical outcomes with low-molecular-weight heparin, and that some clinicians do not advocate routine monitoring of anti-Xa in uncomplicated patients. In paediatric patients, the response to low-molecular-weight heparin is less predictable and most clinicians advocate measurement of anti-Xa concentration until it is within a therapeutic range (0.6–1.0 U/mL) and then periodic measurement to ensure that the concentration remains within that range. The length of time a patient should be anticoagulated after removal of the CVC is controversial. Although some physicians advocate anticoagulation for 3 months after removal, others might shorten the course depending on the patient and the severity of the clot.^{34,35}

For most patients who continue to need central venous access, the catheter can be left in place and anticoagulation treatment started. However, for some patients who develop a thrombosis that is life-threatening or permanent and in patients for whom anticoagulation is contraindicated, the CVC would probably need removal irrespective of the patient's need for central venous access. Current recommendations for patients who retain their catheter are initial anticoagulation for several days with unfractionated heparin or low-molecular-weight heparin, followed by at least 3 months of anticoagulation with a vitamin-K antagonist (eg, warfarin) or low-molecular-weight heparin.^{17,34,35} Low-molecular-weight heparin is the preferred option for cancer patients since it prevents recurrent thrombosis more effectively than warfarin.¹⁰³ Additionally, warfarin interferes with some chemotherapy regimens and is more difficult to adjust when thrombocytopenia

occurs.¹⁰³ Thrombolytic treatment for an upper-extremity deep-vein thrombosis is not recommended for initial therapy of a catheter-related thrombosis.^{34,35} Additionally, if the catheter remains in place once the course of full-dose anticoagulation is complete, the American College of Chest Physicians recommends continued anticoagulation treatment at a prophylactic dose until the catheter is removed.^{34,35} However, some paediatric patients need an indwelling catheter for a long period secondary to their treatment regimens and long-term anticoagulation prophylaxis might be difficult to continue. Therefore, clinicians sometimes individualise the duration of anticoagulation for catheter-related thrombosis on the basis of the size and location of the clot, perceived length of time the patient has had the thrombosis, persistence of risk factors such as continued use of thrombophilic drugs (eg, glucocorticoids and L-asparaginase), and the length of time for which the catheter is needed. Clinicians who treat adults should refer to the recently updated American College of Chest Physicians guidelines.³⁵

Conclusion

The underlying cause of a catheter occlusion determines its appropriate treatment, but most occlusions are thrombotic and should be treated with thrombolytic agents. Alteplase is widely used in North America but new agents have shown promising improvements in efficacy and onset of action. Further studies are needed to compare new thrombolytic agents with those currently available.

Thrombotic CVC occlusions can cause catheter-related thromboses, which can lead to post-thrombotic syndrome, pulmonary embolism, and an increased risk of catheter infections. Although prevention of catheter-related thromboses is key to reducing the number of subsequent complications, effective prophylactic measures have not been established. Despite the consensus that catheter-related thromboses mandate immediate anticoagulation treatment, there is substantial variation in the treatment of patients who need central venous access for long durations. Future research should focus on optimum strategies for prevention, diagnosis, and treatment of CVC occlusions and catheter-related thrombosis, and the role of new thrombolytic agents in clinical practice.

Contributors

All authors participated in the design, writing, and review of the manuscript. All authors saw and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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