Approach to thrombotic occlusion related to long-term catheters of hemodialysis patients: a narrative review

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Abstract

Currently, permanent catheters (pCVC) are becoming an alternative vascular access for long-stay patients in whom arteriovenous access cannot be made. Occlusion is a commun mechanical complication related to pCVC, leading to inadequate dialysis dose and frequent changes of local catheter location, which can cause exclusion of vascular sites. The aim of this study was to perform a narrative review of treatment of pCVC thrombotic occlusion in HD patients. The treatment of CVCP thrombosis typically consists on the saline infusion or administration of thrombolytics such as tissue plasminogen activated, reteplase and urokinase. There are few studies on the use of alteplase in pCVC clogged in oncology area and in dialysis population, and they all report success with the use of thrombolytic therapy ranging from 80-95% of cases, using 1mg/ml. Due to the high cost of alteplase, studies have suggested that cryopreservation and fractionated alteplase dose have made its use financially viable.

Keywords: catheter obstruction; central venous catheters; hemodialysis units, hospital; kidney failure, chronic.

An overview of chronic kidney disease

Chronic kidney disease (CKD) is a frequent condition characterized by progressive irreversible loss of renal function.[1,2] CKD is a serious global public health issue. The disease is expected to cause significant increases in the number of kidney transplants and patients on dialysis. According to Lugon *et al.*,[3] the world is facing an epidemic of CKD, with patient numbers growing at a faster pace in developing nations.

The number of individuals with CKD in the United States has been estimated to grow from 470,000 in 2004 to over 2.2 million in 2030.[4] In Brazil, the 2004 Census of the Brazilian Society of Nephrology revealed that 59,153 individuals were on dialysis; in 2012, the number grew to 97,586, or 475 patients per million population.[5]

Hypertension and *diabetes mellitus* are the most important factors associated with progression of CKD.[1,6]

The Kidney Disease Outcomes Quality Initiative (KQOQI) Clinical Practice Guidelines published by the National Kidney Foundation categorizes CKD patients into five functional stages based on their glomerular filtration rates (GFR), as shown in Table 1.[1,7]

Hemodialysis is the most widely used mode of therapy for patients with stage-5 CKD. The 2012 Census of the Brazilian Society of Nephrology reported that 97,586 patients were on dialysis in Brazil; 89.4% were treated with HD, 5.3% with continuous ambulatory peritoneal dialysis (CAPD), 4.9% with automated peritoneal dialysis (APD), and 0.4% with intermittent peritoneal dialysis (IPD).[8]

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Table 1 Chronic kidney disease staging proposed by the KDOQI and updated by the National Collaborating Centre For Chronic Conditions 2013

CKD Stage	Glomerular filtration rate*	Proteinuria
1	≥ 90	Yes
2	60-89	Yes
3 A	45-59	Yes/No
3 B	30-44	
4	15-29	Yes/No
5	< 15	Yes/No

* mL/min/1,73 m^2.

Central venous catheters used as HD access devices

The KDOQI[9,10] defines optimal HD access as the one that offers adequate blood flow for the prescribed dialysis regimen, a long life, and low rates of mechanical and infectious complications. Autogenous arteriovenous fistulae (AVF) are the option that more closely meets the criteria above, as they provide the best five-year patency rates, lower rates of mechanical and infectious complications, and require fewer interventions than other HD access devices.

Arteriovenous (AV) grafts - a flexible curved or straight plastic tube indirectly connecting an artery and a vein in one of the patient's limbs - may also be used. However, an AV graft is approximately four times more expensive than an AVF, offers a shorter life than an AVF, and presents increased risk of infection, thrombosis, and stenosis.[11]

A double lumen catheter may be inserted into a central vein and used as a hemodialysis access device. When used for more than three weeks, non-tunneled, non-cuffed catheters, also known as short-term catheters, may yield high rates of infection. These catheters are best used in emergency dialysis patients or while the vascular access matures.[12] Catheters equipped with felt or Dacron cuffs reduce the incidence of infectious and mechanical complications and should be used whenever patients require long-term catheters.[11]

Long-term tunneled catheters allow for increased blood flow and provide for better dialysis dosage management. Once they are made of silicone or Carbothane, these catheters produce less bacterial adherence, lower rates of infection and central vessel stenosis when compared to short-term catheters.[12,13]

Although AV fistulae are clear favorites for patients on HD, AV grafts are disproportionately used in the United States and, in global terms, central venous catheters (CVC) are excessively relied on.[12] The KDOQI discourages the use of CVC in HD patients, suggesting that only 10% of the cases require this mode of access.[5] However, in the 1980s central venous catheters began to be used as permanent venous access devices for patients on HD. Consequently, the number of prevalent patients on HD equipped with CVC increased. In the United States, initiatives to reduce the use of AV grafts resulted in increased use of CVC. Today, more than 80% of incident patients on dialysis use CVC. According to the National Kidney Foundation, the share of prevalent patients on dialysis implanted with catheters grew from 19% to 27%.[5]

In Brazil, 9.4% of the patients on HD in 2007 used CVC for access devices *versus* 11.4% in 2008.[8] The 2011 Census of the Brazilian Society of Nephrology reported a prevalence of 14.2% in the use of CVC.[5] Rates of CVC use in Brazil are low and close to the levels recommended by the KDOQI. Nevertheless, a relatively small number of RRT centers (55% of 13 centers) responded the Census survey, and these rates may have been underestimated.[5] Additionally, non-tunneled catheters are predominantly used in Brazil for their lower cost and ease of insertion by a nephrologist. According to the KDOQI, short-term non-tunneled catheters should be used for no longer than seven days and reserved for emergency situations, hospitalized patients, and individuals with acute kidney injury. In chronic cases, these devices must be changed for long-term tunneled catheters, because even though they have higher rates of infection and dysfunction than native fistulae, these rates are still lower when compared to the rates associated with the use of temporary CVC.[13,14]

Complications related to central venous catheters used as HD access devices

Permanent venous catheters (PVCs) are being developed as an alternative to long-term vascular

access devices for patients in whom an arteriovenous access can not be made, such as obese individuals, children, and patients with multiple prior vascular access devices without a viable site for the implantation of a new device.[9,15,16]

However, mechanical and infectious complications have been reported in individuals offered permanent venous catheters, with significant impact on patient morbidity and mortality and sizable increases in the expenses incurred in the treatment of these complications, including hospitalization, medication - namely thrombolytic agents and antibiotics - and the implantation of additional catheters.[17]

According to the United States Renal Data System (USRD), infection is second only to cardiovascular disease in the list of leading causes of death of patients on dialysis, despite the progress seen in preventive care and the development of novel antimicrobial drugs. The reported death rate of patients with stage-5 CKD in the United States is 176/1000 patient-years, with bloodstream infections accounting for close to 26/1000 patient-years.[18-20] Seventy-five percent of the infection-related deaths are caused by sepsis.[19] The incidence of catheter-related bacteremia ranges from 4.1 cases per 1,000 patient-days to as many as 19.8 cases per 1000 patient-days.[21] A trial carried out in two centers recently published by our group showed that the prevalence of bloodstream infections (BI) in patients managed with prophylactic antibiotic lock therapy (ALT) was statistically lower than the prevalence observed in patients given heparin to seal the PVC (0.57 x 1.74 events per 1000 catheter-days, p = 0.005); the individuals given prophylactic ALT had longer BI-free survival (log-rank = 17.62, p < 0.0001) and had the catheter implanted for more days (171 days (79-256) *vs.* 203 days (111.5 to 326), p = 0.015).[22]

The most common mechanical complications related to permanent venous catheters are occlusions and blood flow reductions, which may negatively impact the dosing of dialysis and lead to frequent catheter changes, thus exhausting possible sites for catheterization.[16]

The KDOQI defines access dysfunction as the inability to achieve blood flow rates (Qb) of 300 ml/min or less within the first 60 minutes of HD.[13]

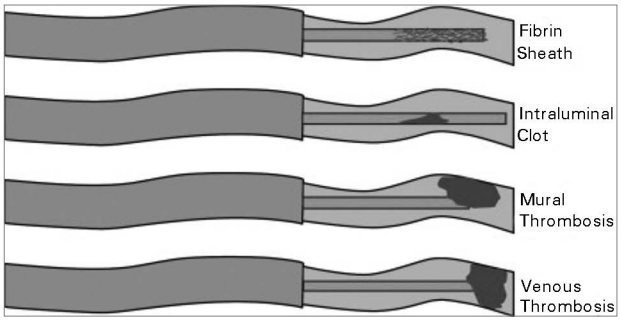
Occlusion may be partial or complete, and has been defined as the difficulty infusing fluids into or removing fluids from the catheter. Occlusion may occur as a consequence of a number of factors, such as obstruction secondary to the formation of a fibrin sheath or thrombi, mechanical occlusion due to poorly positioned or twisted catheters, and occlusion by drugs.[16]

Thrombosis is the most frequent cause of occlusion in HD patients. Deitcher *et al.*[22] estimated that thrombosis accounts for 25% of the cases of CVC occlusion and recommended the use of anteroposterior chest X-ray images to eliminate occurrences of CVC poor positioning.[23]

Fibrin adhesion compromises the long-term patency of catheters. The sheath, initially composed of fibrinogen, albumin, lipoprotein, and coagulation factors, begins to form 24 hours after the implantation of the CVC.[24] The fibrin sheath attracts platelets and coagulation factors and promotes the adhesion of white blood cells.[25] Figure 1 illustrates the thrombotic occlusion formation process. Over the course of weeks and months, collagen adheres to the smooth muscle cells of the venous wall and migrates toward the tip of the catheter. The rate of occurrence of these processes varies among patients, depending on their inherited and acquired traits. When coagulation overwhelms the endogenous fibrinolytic system, thrombi may accumulate in the catheter. Catheter-associated thrombosis may be categorized as extrinsic, when the thrombi are located externally to the catheter, or intrinsic, when the thrombi are in the lumen of the catheter or along its surface.[22,26]

Few studies have described the risk factors associated with thrombotic occlusion of the catheter, and none have looked into this issue in populations on dialysis. Volume depletion, hypotension, hypercoagulability, vascular wall trauma, poor catheter tip positioning, drug infusion, and parenteral nutrition rank among risk factors.[25] Possible consequences of thrombotic occlusion are CVC-related infection, pulmonary embolism, and post-thrombotic syndrome.[27]

Figure 1. Thrombotic occlusion types - Lancet, 2009.



Treating thrombotic occlusions of long-term catheters used in hemodialysis patients

The treatment of CVC thrombosis usually involves the infusion of 0.9% sodium chloride or thrombolytic agents such as tissue plasminogen activator, reteplase or urokinase.[16]

Infusion of saline solution may be the most cost-effective treatment for CVC obstruction, but it is not a safe option for the patient, as thrombi may become loose with manipulation of the occluded CVC. According to the KDOQI, urokinase is the drug of choice for the treatment of malfunctioning CVC, as it resolves 70-90% of the cases of obstruction.[13] If a first infusion fails to remove the obstruction, patients should be further studied with the aid of X-ray imaging.

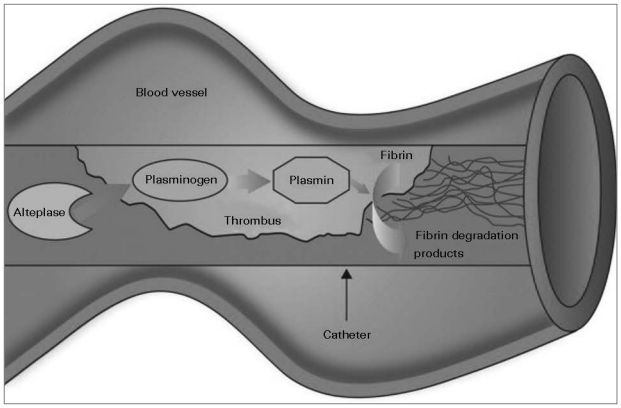
Timoney *et al.*[16] described alteplase, a recombinant protein with a low incidence of allergic reactions (0.02%), as a safe alternative to urokinase. The authors showed that vials with 50 mg of alteplase may be aseptically reconstituted into 50 ml of sterile water and then divided into portions of 2.5 ml and stored in labeled vials at -20 °C for up to 30 days. Administration is safe, with no reported cases of bacterial or fungal vial contamination after the storage period. This may be a safe, effective, and cost-effective alternative to urokinase for patients with occluded central venous lines.

Alteplase, reteplase, and urokinase catalyze the conversion of the plasminogen bound to the clot into plasmin, thus initiating fibrinolysis,[27-29] as shown in the diagram below (Figure 2).

Clinical trials and systematic reviews on the treatment of thrombotic occlusions

The few studies carried out on the use of alteplase to treat obstructed long-term catheters in cancer

Figure 2. The mechanism of action of the tissue plasminogen activator. The tissue plasminogen activator converts plasminogen into plasmin, which then cleaves fibrin into fibrin degradation products to dissolve the thrombus. Adapted from Baskin *et al.*, Lancet, 2009.[29]



and dialysis populations have reported success rates ranging between 80% and 95%, as shown in Table 2.

Timoney *et al.*[16] reported a success rate of 81% when alteplase at 1 mg/ml was infused for 45 minutes in the lumen of 168 catheters of patients on chemotherapy. No adverse events were described.

In another study, Deitcher *et al.*[22] reported success rates ranging from 52% to 78% when 2 mg of alteplase were infused for 30 to 120 minutes in the lumen of nonfunctioning permanent venous catheters of patients on chemotherapy. The catheters still obstructed were infused a second time with 2 mg of alteplase for 30 to 120 minutes, and success rates increased to 83% to 87%. Thus, the procedure using up to two infusions of 2 mg of alteplase is safe and effective to restore flow in obstructed PVCs.[23]

Haire *et al.*[30] showed that 2 mg of alteplase cleared thrombotic occlusions more effectively (74%) than 5000 IU of urokinase (17%) infused for 120 minutes in the catheters of chemotherapy patients ($p = 0.03$). Ninety percent of the catheters requiring a second infusion of alteplase were successfully unclogged. The safety and efficacy of alteplase were also shown in pediatric patients on chemotherapy, with a reported success rate of 85% and no cases of bleeding.[29] Multicenter trial COOL found that alteplase was as effective in children or adults, with 83% to 87% of the occlusions resolved.[28]

Mark *et al.*[31] included 570 permanent venous catheters in a prospective study with patients on HD and analyzed the use of alteplase in reestablishing

Table 2 Main characteristics of recent studies on the treatment of thrombotic occlusion

Study	Year	Patients	Thrombolytic agent	Outcomes	Adverse events
Timoney *et al.*	2002	Patients on chemotherapy, 168 CVCs	Alteplase for 45 min	Success rate of 81%	None
Deitcher *et al.*	2002	Patients on chemotherapy, 995 patients	Alteplase for 30 to 120 min Second infusion 2 mg of alteplase for 30 to 120 min	Success rates of 52% to 78% Success rates of 83% to 87%	None
Haire *et al.*	1994	Patients on chemotherapy, 50 CVCs	Alteplase for 120 min was more effective than 5000 IU of urokinase	Success rate of 85%	None
Ponec *et al.*	2001	Patients with CVCs fewer on HD. 149 patients	Group 1: alteplase, alteplase, and placebo Group 2: placebo, alteplase, and alteplase	Success rates of 74% in the alteplase groups and 17% in the placebo group. After one or two infusions, function was restored in 90% of the patients	None
Shen *et al.*	2003	Pediatric and adult patients on HD with CVCs. 122 patients	Alteplase (2 mg/ml) infused in the lumen of dysfunctional catheters and assessed after 30 and 120 min	Success rate of 87% after up to two infusions of alteplase. Flow was restored in 30 min in 70 patients (57%) after one infusion with alteplase.	None
Zacharias *et al.*	2003	Patients on HD. 30 patients	Alteplase/Urokinase	Alteplase (87,8%) *et al.* urokinase (75%)	None
Mark *et al.*	2002	Patients on HD. 570 CVCs	Alteplase	Alteplase was used in 2.77% of the dialysis sessions with a mean time between interventions of 27 days	None
Vercaigne *et al.*	2012	Patients on HD. 82 CVCs	Alteplase/alteplase followed by saline solution	Success rates of 65% and 82%	None
Hilleman *et al.*	2011	Patients on HD 210 CVCs	Reteplase/alteplase/ tenecteplase	Reteplase success rate of 88% Alteplase success rate of 81% Tenecteplase success rate of 41%	None
Mendes *et al.*	2013	Patients on HD. 152 CVCs	Alteplase	Success rate of 98%	None

blood flow rates from poor (< 200 ml/min) to adequate levels over a period of two and a half years. The authors described a mean PVC survival of 10.2 months and found that thrombosis was the most common cause for catheter removal (36.3%). Alteplase was used in 2.77% of the dialysis sessions with a mean time between interventions of 27 days.

Vercaigne *et al.*[32] looked into 82 occluded PVCs of HD patients treated with alteplase (group 1) or alteplase followed by saline solution (group 2), and reported success rates of 65% and 82%, respectively. The authors did not find statistically significant differences between the groups (p = 0.84) and considered the alteplase infusion protocol followed by saline solution to be effective, safe, and convenient.

In a systematic review, Hilleman *et al.*[33] analyzed the literature on the efficacy, safety, and cost-effectiveness of thrombolytic therapy for dysfunctional HD permanent venous catheters. In

the 18 studies meeting the inclusion criteria, higher success rates were found for reteplase (88%), followed by alteplase (81%), and tenecteplase (41%). The authors concluded that reteplase should be the thrombolytic agent of choice in the treatment of occluded CVC in centers with large numbers of patients on HD. However, this drug is not available in Brazil.

Another study[34] recently published by our group analyzed 152 PVCs implanted in 102 patients on HD and found that 147 of 179 episodes of obstruction (82.8%) were successfully resolved with a single infusion of alteplase (1 mg/ml), 27 (15.1%) after a second infusion, and five (2.8%) remained occluded. The residence time of the thrombolytic agent in the catheter was 40 minutes. In this study, 98% of the PVCs were successfully unclogged. There was a downward trend in the efficiency of alteplase removing occlusions of PVCs in the subclavian *versus* the jugular vein. Cryopreservation of alteplase also proved safe and effective.

Shen *et al.*[35] enrolled 995 pediatric and adult patients with implanted PVCs in a multicenter trial and reported a success rate of 87% in the removal of occlusions. The catheters were infused with the thrombolytic agent for 30 to 120 minutes. In 70 patients (57%), blood flow was reestablished with a single 30-minute infusion of alteplase. Success was not correlated with patient age, gender, body weight, type of CVC, or time with the catheter. There were no deaths or severe adverse events such as bleeding or embolism attributable to the treatment.

In addition to occlusion removal, another important factor to be considered is the restoration of blood flow with the use of a thrombolytic agent. Adequate blood flow rates are extremely important for patients on dialysis, so that the target Kt/V and prescribed fluid removal levels are attained. In the literature, occlusion removal is considered successful when blood flow rates are restored to levels greater than 250 ml/min. In a small randomized trial, Zacharias *et al.*[36] compared the efficacy of alteplase *versus* urokinase in reestablishing proper blood flow rates (> 200 ml/min) in partially and totally occluded venous catheters implanted in 30 patients on HD. The success rates observed in partially occluded PVCs were similar for both groups (87.8% *vs.* 75%, p = 0.205). However, the success rate in clearing totally occluded catheters was significantly higher when alteplase was used (88.2% *vs.* 42.8%, p = 0.018).

The few studies in which alteplase was used to remove CVC occlusions reported positive results and described extended life for the catheters implanted in patients on hemodialysis and chemotherapy. Alteplase can also be cryopreserved and fractioned, making it a more cost-effective thrombolytic agent. However, more and larger studies are needed to compare the efficacy, safety, and cost-effectiveness of different thrombolytic agents in the management of hemodialysis CVC mechanical dysfunctions and identify the factors associated with thrombotic occlusion.

References

1. Romão Jr JE. A Doença Renal Crônica: do Diagnóstico ao Tratamento. Prat Hosp 2007;52:183-7.
2. Romão Jr JE. Doença renal crônica: definição, epidemiologia e classificação. J Bras Nefrol 2004;26:1-3.
3. Lugon JR. Doença renal crônica no Brasil: um problema de saúde público. J Bras Nefrol 2009;31:2-5.
4. Stevens LA, Stoycheff N, Levey AS. Staging and management of chronic kidney disease. In: Greenberg A, ed. Primer on Kidney Diseases (5th ed). Philadelphia: Saunders Elsevier; 2009. p.436-45.
5. Sesso RCC, Lopes AA, Thomé FS, Lugon JR, Watanabe Y, Santos DR. Diálise crônica no Brasil - Relatório do Censo Brasileiro de Diálise, 2011. J Bras Nefrol 2012;34:272-7. DOI:http://dx.doi.org/10.5935/0101-2800.20120009
6. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39:S1-266.
7. Bastos MG, Kirsztajn GM. Chronic kidney disease: importance of early diagnosis, immediate referral and structured interdisciplinary approach to improve outcomes in patients not yet on dialysis. J Bras Nefrol 2011;33:93-108. PMID: 21541469
8. Censo Brasileiro de diálise 2012 [Acesso 3 Nov 2013]. Disponível em: http://www.sbn.org/pdf/socios2012.pdf
9. Besarab A, Raja RM. Acesso vascular para hemodiálise. In: Daugirdas JT, Ing TS. Manual de diálise. 3a ed. Rio de Janeiro: Medsi; 2003. p.68-102.
10. National Kidney Foudation. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for 2006 Updates: Hemodialysis Adeuqacy, Peritoneal Dialysis Adequacy, Vascular Access. Am J. Kidney Dis. 2006;48:S1-S322.
11. Lugon JR, Strogoff JP, Warrak MEA. Hemodiálise. In: Riella MC. Princípios de nefrologia e distúrbios hidroeletrolíticos. 4a ed. Rio de Janeiro: Guanabara Koogan; 2003.
12. Kim SH, Song KI, Chang JW, Kim SB, Sung SA, Jo SK, et al. Prevention of uncuffed hemodialysis catheter-related bacteremia using an antibiotic lock technique: a prospective, randomized clinical trial. Kidney Int 2006;69:161-4. PMID: 16374438 DOI:http://dx.doi.org/10.1038/sj.ki.5000012
13. III. NKF-K/DOQI Clinical Practice Guidelines for Vascular Access: update 2000. Am J Kidney Dis 2001;37:S137-81.

14. O'Grady NP, Alexander M, Dellinger EP, Gerberding JL, Heard SO, Maki DG, et al. Guidelines for the prevention of intravascular catheter-related infections. Centers for Disease Control and Prevention. MMWR Recomm Rep 2002;51:1-29.
15. Lok CE, Mokrzycki MH. Prevention and management of catheter-related infection in hemodialysis patients. Kidney Int 2011;79:587-98. PMID: 21178979 DOI:http://dx.doi.org/10.1038/ki.2010.471
16. Timoney JP, Malkin MG, Leone DM, Groeger JS, Heaney ML, Keefe DL, et al. Safe and cost effective use of alteplase for the clearance of occluded central venous access devices. J Clin Oncol 2002;20:1918-22. DOI: http://dx.doi.org/10.1200/JCO.2002.07.131
17. Chan MR, Yevzlin AS. Tunneled dialysis catheters: recent trends and future directions. Adv Chronic Kidney Dis 2009;16:386-95. DOI: http://dx.doi.org/10.1053/j.ackd.2009.06.006
18. Cheung AK, Sarnak MJ, Yan G, Berkoben M, Heyka R, Kaufman A, et al. Cardiac diseases in maintenance hemodialysis patients: results of the HEMO Study. Kidney Int 2004;65:2380-9. DOI:http://dx.doi.org/10.1111/j.1523-1755.2004.00657.x
19. Katneni R, Hedayati SS. Central venous catheter-related bacteremia in chronic hemodialysis patients: epidemiology and evidence-based management. Nat Clin Pract Nephrol 2007;3:256-66. DOI: http://dx.doi.org/10.1038/ncpneph0447
20. Jaber BL. Bacterial infections in hemodialysis patients: pathogenesis and prevention. Kidney Int 2005;67:2508-19. PMID: 15882306 DOI: http://dx.doi.org/10.1111/j.1523-1755.2005.00364.x
21. Biernat JC, dos Santos F, dos Santos AMG, Raubach AA, Souza M, Demin MSS, et al. Contaminação de Lúmen de Cateter de Hemodiálise: prevenção e tratamento com M-EDTA. J Bras Nefrol 2008;30:105-12.
22. Silva TN, de Marchi D, Mendes ML, Barretti P, Ponce D. Approach to prophylactic measures for central venous catheter--related infections in hemodialysis: a critical review. Hemodial Int 2014;18:15-23. DOI: http://dx.doi.org/10.1111/hdi.12071
23. Schon D, Whittman D. Managing the complications of long--term tunneled dialysis catheters. Semin Dial 2003;16:314-22. DOI: http://dx.doi.org/10.1046/j.1525-139X.2003.16060.x
24. Beathard GA. Catheter thrombosis. Semin Dial 2001;14:441-5. DOI:http://dx.doi.org/10.1046/j.1525-139x.2001.00109.x
25. Deitcher SR, Fesen MR, Kiproff PM, Hill PA, Li X, McCluskey ER.; Cardiovascular Thrombolytic to Open Occluded Lines-2 Investigators. Safety and efficacy of alteplase for restoring function in occluded central venous catheters: results of the cardiovascular thrombolytic to open occluded lines trial. J Clin Oncol 2002;20:317-24. DOI: http://dx.doi.org/10.1200/JCO.20.1.317
26. Liangos O, Gul A, Madias NE, Jaber BL. Long-term management of the tunneled venous catheter. Semin Dial 2006;19:158-64. DOI: http://dx.doi.org/10.1111/j.1525-139X.2006.00143.x
27. Besarab A, Pandey R. Catheter management in hemodialysis patients: delivering adequate flow. Clin J Am Soc Nephrol 2011;6:227-34. DOI: http://dx.doi.org/10.2215/CJN.04840610
28. Ponec D, Irwin D, Haire WD, Hill PA, Li X, McCluskey ER; COOL Investigators. Recombinant tissue plasminogen activator (alteplase) for restoration of flow in occluded central venous access devices: a double-blind placebo-controlled trial--the Cardiovascular Thrombolytic to Open Occluded Lines (COOL) efficacy trial. J Vasc Interv Radiol 2001;12:951-5. DOI:http://dx.doi.org/10.1016/S1051-0443(07)61575-9
29. Baskin JL, Pui CH, Reiss U, Wilimas JA, Metzger ML, Ribeiro RC, et al. Management of occlusion and thrombosis associated with long--term indwelling central venous catheters. Lancet 2009;374:159-69. DOI: http://dx.doi.org/10.1016/S0140-6736(09)60220-8
30. Haire WD, Atkinson JB, Stephens LC, Kotulak GD. Urokinase versus recombinant tissue plasminogen activator in thrombosed central venous catheters: a double-blinded, randomized trial. Thromb Haemost 1994;72:543-7. PMID: 7878629
31. Little MA, Walshe JJ. A longitudinal study of the repeated use of alteplase as therapy for tunneled hemodialysis catheter dysfunction. Am J Kidney Dis 2002;39:86-91. DOI:http://dx.doi.org/10.1053/ajkd.2002.29885
32. Vercaigne LM, Zacharias J, Bernstein KN. Alteplase for blood flow restoration in hemodialysis catheters: a multicenter, randomized, prospective study comparing "dwell" versus "push" administration. Clin Nephrol 2012;78:287-96. PMID: 22541682 DOI:http://dx.doi.org/10.5414/CN107351
33. Hilleman D, Campbell J. Efficacy, safety, and cost of thrombolytic agents for the management of dysfunctional hemodialysis catheters: a systematic review. Pharmacotherapy 2011;31:1031-40. DOI: http://dx.doi.org/10.1592/phco.31.10.1031
34. Mendes ML, Castro JH, Silva TN, Barretti P, Ponce D. Effective use of alteplase for occluded tunneled venous catheter in hemodialysis patients. Artif Organs 2014;38:399-403. DOI:http://dx.doi.org/10.1111/aor.12186
35. Shen V, Li X, Murdock M, Resnansky L, McCluskey ER, Semba CP; COOL Investigators. Recombinant tissue plasminogen activator (alteplase) for restoration of function to occluded central venous catheters in pediatric patients. J Pediatr Hematol Oncol 2003;25:38-45. PMID:12544772 DOI: http://dx.doi.org/10.1097/00043426-200301000-00009
36. Zacharias JM, Weatherston CP, Spewak CR, Vercaigne LM. Alteplase versus urokinase for occluded hemodialysis catheters. Ann Pharmacother 2003;37:27-33. DOI:http://dx.doi.org/10.1345/aph.1C105