ANNEXES TO CHAPTER 6

Clinical Question XXVIII. What is the best treatment for the persistent dysfunction of the tunnelled central venous catheter (stripping, fibrin sheath angioplasty, fibrinolytics or catheter replacement)?

A major cause of permanent dysfunction of the catheter is thrombosis, either intraluminal or due to the formation of a fibrin sheath.

Extrinsic thrombi are the result of formation of a mural thrombus, which may be located in the superior vena cava or right atrium, and can be serious and require systemic anticoagulation and removal of the catheter.

Intrinsic thrombi tend to lead to deficient flow through the catheter, and can be intraluminal, located on the catheter tip, or cause the formation of a peri-catheter fibrin sheath, with this being the most common form of thrombosis in tunnelled catheters.

A fibrin sheath is suspected clinically when saline can be infused but blood cannot be easily aspirated (valve mechanism) (Faintuch 2008).

We found several systematic or narrative reviews (Besarab 2011; Hilleman 2011; Kamper 2010; Faintuch 2008; Clase 2001) and were able to locate the corresponding RCT. The results of these RCT are summarised below.

Percutaneous fibrin sheath *stripping* versus urokinase infusion

The RCT by Gray (2000) compared 28 patients treated with percutaneous *stripping* with 29 treated with urokinase infusion (30,000 U/h, for a total of 250,000 U), for tunnelled catheters with flow rates less than 250 ml/min and established baseline flow rates ≥300 ml/min, or flow rates 50 ml/min less than higher established baseline flows. The results were as follows: - initial clinical success: 89% (25 of 28) for percutaneous stripping and 97% (28 of 29) for urokinase. - primary patency rates at 15, 30 and 45 days: 75% (n=20), 52% (n=13) and 35% (n=8), for percutaneous stripping and 86% (n=21), 63% (n=13) and 48% (n=9) for urokinase. - the median additional duration of catheter function was 32 days (95% CI: 18-48 days) for percutaneous stripping and 42 days (95% CI: 22-153 days) for urokinase. No statistically significant differences were found in the *catheter survival* curves (p=0.236).	**Moderate quality**

Percutaneous fibrin sheath *stripping* versus catheter exchange

RCT by Merport (2000) compared the efficacy of two treatments for tunnelled haemodialysis catheter malfunction: 15 percutaneous fibrin sheath stripping interventions versus 22 over-the-wire catheter exchange, in 30 adult patients with poorly functioning haemodialysis catheters (flow rates <200 ml/min). Overall technical success rate was 97%.	**Moderate quality**

Exchanged catheters were significantly more likely to provide *adequate patency for dialysis for as long as four months* (23% versus 0%; p=0.05), the primary outcome measure in that study. The *mean duration of catheter patency* was 52 days for catheter exchange vs 25 days for stripping (p<0.001). The *mean catheter patency* was 52.2 ± 43 days for the over-the-wire catheter exchange group and 24.5 ± 29.3 days for the group treated with percutaneous *stripping* (p<0.0001). After the catheter exchange, the *patency rates* at one, two, three and four months were 71%, 33%, 27% and 27%, compared to 31%, 16%, 7% and 0% after stripping (p=0.04). Costs were higher for stripping ($3,022 vs $2,586; p<0.01). It was concluded that *stripping* should not be considered as routine therapy for catheter malfunction.	
Balloon angioplasty disruption of the sheath versus non-intervention	
The RCT by Oliver (2007) was a pilot study which analysed the effectiveness of sheath angioplasty on the patency and function of the catheter in 18 patients randomised to balloon angioplasty versus 12 patients randomised to no treatment. The results were as follows: - the median time to repeat catheter exchange was 411 and 198 days respectively (p=0.17). - the median time to repeat intervention was 373 days and 97.5 days respectively (p=0.22). - blood flow was 340 vs 329 ml/min; p<0.001, difference statistically significant but clinically small (11 ml/min).	**Moderate quality**
Fibrinolytics	
No RCT have been found directly comparing different thrombolytics with each other.	
High-dose urokinase (100,000 IU) versus lower dose (25,000 IU) for catheter thrombosis The RCT by Donati (2012) compared two initial doses of urokinase for treatment of catheter thrombosis. Both groups were receiving prophylaxis with warfarin. The results were as follows: <u>Dose 25,000 IU</u> (29 cases) - adequate flow (≥250 ml/min) in four cases (13.7%), and the remaining 25 (86.3%) required subsequent addition of 50,000 IU, and then other 75,000 IU at the following haemodialysis session. <u>Dose 100,000 IU</u> (36 cases) - adequate flow (≥250 ml/min) in 36 cases (100%), and 12 events (33.3%) had to be treated with 100,000 IU at the following haemodialysis session.	**Moderate quality**
Tenecteplase versus placebo The RCT by Tumlin (2010) included 149 patients, 74 treated with tenecteplase for 1 hour, and 75 with placebo. The results were as follows: - catheters patent after the one-hour dwell: 22% of patients in the tenecteplase group compared to 5% of the placebo group (p=0.004).	**Moderate quality**

- change in blood flow: increase of 47 ml/min in the tenecteplase group versus 12 ml/min in the placebo group (p=0.008). Four catheter-related bloodstream infections were observed (one with tenecteplase, three on placebo) and one thrombosis (with tenecteplase).	
Short versus long alteplase dwell in catheter An RCT (McRae 2005) with 60 patients assessed the optimal dwell time of alteplase in the catheter, comparing one hour (26 patients) with more than 48 hours before the next haemodialysis session *[(1- or >48-h (to subsequent HD run)]*, 34 subjects. No statistically significant differences were found in any of the following outcome measures: - catheter patency rate: at the following haemodialysis session - 76.9% vs 79.4; after 2 weeks- 42.3% vs 52.9%. - survival of the catheter: median of 14 days for the short-dwell option and 18 for the long dwell (p=0.621). They consider that alteplase is a short-term option that allows a two-week window during which more definitive therapies should be instituted. Another RCT (Vercaigne 2012), with 82 patients, compared two alteplase delivery options, *push versus dwell (30 minutes vs 2 hours*). No statistically significant differences were found in any of the following outcome measures: - catheter patency rate: 82% (32/39) in the push protocol versus 65% (28/43) in the dwell protocol; p=0.08. - survival of the catheter until future need for catheter intervention: mean 65.5 vs 59.3 days; p=0.76. - post-thrombolysis blood flow: difference of means -16.26 ml/min (95% CI: -44.68 to 14.16; p=0.29). - litres processed per hour at the following haemodialysis session: difference of means 0.026 (95% CI: -1.302 to 1.353; p=0.969). They considered that the push protocol is effective and safe and more practical than the 2-hour dwell protocol.	**Moderate quality** **Moderate quality**
Summary of evidence	
Percutaneous fibrin sheath *stripping* versus urokinase infusion RCT with 57 patients found no statistically significant differences in catheter survival curves.	**Moderate quality**
Percutaneous fibrin sheath *stripping* versus catheter exchange RCT with 30 patients found that catheter exchange was significantly better than stripping for achieving adequate patency for dialysis for four months and that they obtained more days of mean catheter patency.	**Moderate quality**
Balloon angioplasty disruption of the sheath versus non-intervention RCT with 30 patients found no statistically significant differences between the two options in relation to the median time to repeat catheter exchange and the median time to repeat intervention, but the difference in the increase in blood flow (340 vs 329 ml/min) was statistically significant.	**Moderate quality**

High-dose urokinase (100,000 IU) versus lower dose (25,000 IU) for catheter thrombosis RCT with 65 patients found that the higher initial dose achieved better results in relation to achieving an adequate flow for haemodialysis and a lower final consumption of urokinase. Both groups were receiving prophylaxis with warfarin.	**Moderate quality**
Tenecteplase versus placebo RCT with 149 patients found differences in favour of tenecteplase in results for the *short term* in relation to the percentage of catheters patent at the end of a one-hour dwell and the increased blood flow rate.	**Moderate quality**
Short versus long alteplase dwell in catheter RCT with 60 patients found no statistically significant differences in relation to the catheter patency rate (at the following haemodialysis session and at 2 weeks) or survival of the catheter, and considered alteplase to be a short-term option that allows a two-week window during which more definitive therapies should be instituted. Another RCT, with 82 patients, compared two delivery options for alteplase, *push versus dwell*, and found no statistically significant differences in catheter patency rates or survival of the catheter until future need for catheter intervention, or in the post-thrombolysis blood flow or the litres processed per hour at the following haemodialysis session. They considered that the push protocol was effective and safe and more practical than the longer dwell protocol.	**Moderate quality**
Patients' values and preferences *No relevant studies related to this aspect have been identified.*	
Use of resources and costs *No relevant studies related to this aspect have been identified.*	
Recommendations	
Weak	We recommend using urokinase or catheter exchange for the treatment of fibrin sheath and not percutaneous stripping as routine intervention.
Weak	For catheter thrombosis, if it is to be treated with urokinase, we recommend using a high initial dose (100,000 IU) rather than a low dose (25,000 IU).
Weak	For treatment of catheter thrombosis, if it is to be treated with alteplase, we recommend using short-dwell protocols.

References

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Donati G, Coli L, Cianciolo G et al. Thrombosis of tunneled-cuffed hemodialysis catheters: treatment with high-dose urokinase lock therapy. Artif Organs 2012; 36(1):21-8.

Gray RJ, Levitin A, Buck D, Brown LC, Sparling YH, Jablonski KA, Fessahaye A, Gupta AK. Percutaneous fibrin sheath stripping versus transcatheter urokinase infusion for malfunctioning well-positioned tunneled central venous dialysis catheters: a prospective, randomized trial. J Vasc Interv Radiol 2000; 11: 1121-9.

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Hemmelgarn BR, Moist LM, Lok CE et al. Prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator. N Engl J Med 2011; 364(4):303-12.

Hilleman D, Campbell J. Efficacy, safety, and cost of thrombolytic agents for the management of dysfunctional hemodialysis catheters: a systematic review. Pharmacotherapy 2011; 31(10):1031-40.

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Merport M, Murphy TP, Egglin TK, Dubel GJ. Fibrin sheath stripping versus catheter exchange for the treatment of failed tunneled hemodialysis catheters: randomized clinical trial. J Vasc Interv Radiol 2000; 11: 1115-20.

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Tumlin J, Goldman J, Spiegel DM et al. A phase III, randomized, double-blind, placebo-controlled study of tenecteplase for improvement of hemodialysis catheter function: TROPICS 3. Clin J Am Soc Nephrol 2010; 5(4):631-6.

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 Oct;78(4):287-96.

Table 1. STUDIES EXCLUDED

Study	Cause for exclusion
Hemmelgarn 2011	RCT on prevention not on treatment.
Guttmann 2011	Population not representative as they are not on haemodialysis

GRADE TABLES

Date: 2013-12-12
Question: Should Percutaneous fibrin sheath stripping or urokinase infusion be used for the treatment of the persistent disruption of the tunnelled catheter?
Bibliography: Gray RJ, Levitin A, Buck D, Brown LC, Sparling YH, Jablonski KA, Fessahaye A, Gupta AK. Percutaneous fibrin sheath stripping versus transcatheter urokinase infusion for malfunctioning well-positioned tunneled central venous dialysis catheters: a prospective, randomized trial. J Vasc Interv Radiol 2000; 11: 1121-9

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Percutaneous fibrin sheath stripping**	**Urokinase infusion**	**Relative (95% CI)**	**Absolute**		
Median duration of the additional function of the catheter (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	28	29	-	0 higher (0 to 0 higher)	MODERATE	CRITICAL
Primary patency at 45 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	8/28 (28.6%)	9/29 (31%)	-	310 fewer per 1000 (from 310 more to 310 more)	MODERATE	CRITICAL
								0%		-		

Initial clinical success												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	25/28 (89.3%)	28/29 (96.6%)	RR 0.92 (0.8 to 1.07)	310 fewer per 1000 (from 310 more to 310 more)	MODERATE	CRITICAL
								0%		-		

[1] Wide confidence interval.

Date: 2013-12-12
Question: Should percutaneous fibrin sheath stripping or catheter exchange be used for the treatment of the persistent disruption of the tunnelled catheter?
Bibliography: Merport M, Murphy TP, Egglin TK, Dubel GJ. Fibrin sheath stripping versus catheter exchange for the treatment of failed tunneled hemodialysis catheters: randomized clinical trial. J Vasc Interv Radiol 2000; 11: 1115-20.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Percutaneous fibrin sheath stripping	Catheter exchange	Relative (95% CI)	Absolute		
Patency suitable for dialysis for four months												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	15	22	-	-	MODERATE	CRITICAL
								0%		-		
Mean patency (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	15	22	-	mean 0 higher (0 to 0 higher)	MODERATE	CRITICAL

[1] Confidence interval not available. Small sample.

Date: 2013-12-14
Question: Should balloon angioplasty of the sheath or no intervention be used for the treatment of the persistent disruption of the tunnelled catheter?
Bibliography: Oliver MJ, Mendelssohn DC, Quinn RR, Richardson EP, Rajan DK, Pugash RA, Hiller JA, Kiss AJ, Lok CE. Catheter patency and function after catheter sheath disruption: A pilot study. Clin J Am Soc Nephrol 2007, 2: 1201–1206.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Balloon angioplasty of the sheath**	**No intervention**	**Relative (95% CI)**	**Absolute**		
Mean time to repeat the catheter exchange (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	18	12	-	median 0 higher (0 to 0 higher)	MODERATE	CRITICAL
Median time to repeat the intervention (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	18	12	-	median 0 higher (0 to 0 higher)	MODERATE	CRITICAL
Blood flow (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	18	12	-	mean 0 higher (0 to 0 higher)	MODERATE	CRITICAL

[1] Wide interval.

Date: 2013-12-14
Question: Should low-dose (25,000 IU) or high-dose (100,000 IU) urokinase be used to treat catheter thrombosis?
Bibliography: Donati G, Coli L, Cianciolo G et al. Thrombosis of tunneled-cuffed hemodialysis catheters: treatment with high-dose urokinase lock therapy. Artif Organs 2012; 36(1):21-8.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Low-dose urokinase (25,000 IU)**	**High-dose (100,000 IU)**	**Relative (95% CI)**	**Absolute**		
Adequate flow (≥250 ml/min)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/29 (13.8%)	36/36 (100%)	RR 0.15 (0.06 to 0.36)	850 fewer per 1000 (from 640 fewer to 940 fewer)	MODERATE	CRITICAL
								0%		-		

[1] Allocation concealment not declared.

Date: 2013-12-14
Question: Should tenecteplase or placebo be used to treat catheter thrombosis?
Bibliography: Tumlin J, Goldman J, Spiegel DM et al. A phase III, randomized, double-blind, placebo-controlled study of tenecteplase for improvement of hemodialysis catheter function: TROPICS 3. Clin J Am Soc Nephrol 2010; 5(4):631-6.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Tenecteplase**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Catheters patent one hour after the infusion												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/74 (21.6%)	4/75 (5.3%)	RR 4.05 (1.42 to 11.56)	163 more per 1000 (from 22 more to 563 more)	HIGH	CRITICAL
								0%		-		
Change in blood flow (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	74	75	-	mean 4.05 higher (1.42 to 11.56 higher)	HIGH	CRITICAL

Date: 2013-12-14
Question: Should short or long alteplase dwells in catheter be used for the treatment of the persistent disruption of the tunnelled catheter?
Bibliography: MacRae JMLG, Djurdjev O, Shalansky S, Werb R, Levin A, Kiaii M. Short and long alteplase dwells in dysfunctional hemodialysis catheters. Hemodial Int 2005;9:189–95.

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 Oct;78(4):287-96. doi: 10.5414/CN107351.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short alteplase dwell	Long dwell in catheter	Relative (95% CI)	Absolute		
Catheter patency rate												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	65	77	not pooled	not pooled	MODERATE	CRITICAL
Catheter survival (Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	65	77	-	not pooled	MODERATE	CRITICAL

[1] One of the non-blind studies and without allocation concealment.