

ANNEXES TO CHAPTER 6

**Clinical Question XXX. Is the use of antibiotic prophylaxis justified to lock a tunnelled central venous catheter for haemodialysis?**

Several systematic reviews have been found that analyse this issue (Snaterse 2010; Rabindranath 2009; Jaffer 2008; James 2008; Yahav 2008; Labriola 2008). The reviews only analyse the risk of bacteraemia. They do not include information about other possible outcomes of interest, such as mortality, catheter survival rates, or episodes of hospitalisation.

The following sections are based on the Snaterse review (2010), as it is the most recent search, includes separate information for tunnelled catheters and provides a risk-of-bias assessment on the available evidence. The systematic review by Snaterse (2010) located eight RCT, covering a total of 123,300 catheter-days, which analysed the use of solutions with antibiotics against solutions with heparin as lock solutions for *tunnelled cuffed catheters*.

The authors of the review indicate that there is a risk of publication bias, because the funnel plot shows under-representation of studies with no effect or negative effect. They also point out that none of these studies were double-blind, raising the risk of performance bias by healthcare professionals, and that the treatment blinding was only adequate in four of the eight studies and that only one of them carried out an intent-to-treat analysis. They consider that the quality of evidence is low to moderate.

**Low quality**

They found the underlying risk of catheter-related bacteraemia to be similar across studies, with a mean baseline risk of 3.0 bacteraemia events per 1,000 catheter-days. The insertion time of the catheter varied from 37 to 365 days, with a mean of 146 days.

With regard to the risk of bacteraemia, when compared to use of a heparin-only lock solution, statistically significant differences were found in favour of the antibiotic prophylaxis, both combined with heparin and combined with citrate, but not for antibiotic plus ethylenediaminetetraacetic acid (EDTA).

Difference in risk of bacteraemia per 1,000 catheter-days:

- antibiotics + heparin versus heparin: -2.08 (95% CI: -2.64 to -1.53) (five studies with 108,313 catheter-days; I<sup>2</sup>: 0%. Note: one of the studies was on 4503 catheter-days with non-tunnelled catheters).
- antibiotics + citrate versus heparin: -2.88 (95% CI: -4.34 to -1.41) (three studies with 15,036 catheter-days; I<sup>2</sup>: 0%).
- antibiotics + ethylenediaminetetraacetic acid (EDTA) versus heparin: -0.47 (95% CI: -1.40 to 0.45; 1.53; one study with 4454 catheter-days).

In relation to what may be the best antibiotic regimen, they report that there were only two studies, with very few patients, with no statistically significant differences being found between different solutions that included antibiotics (citrate/gentamicin, minocycline/EDTA, vancomycin/heparin, vancomycin/ciprofloxacin/heparin).

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<p>Furthermore, they report that the potential benefits in relation to the prevention of bacteraemia must be weighed against the possible negative effects, such as the development of resistant bacteria, side effects for patients, or the cost-effectiveness of such interventions.</p> <p>They comment that in 2000, the American FDA prohibited the use of citrate in catheter-locking solutions due to an incident with one patient treated with citrate at high concentrations.</p> <p>However, the authors of the review state that RCT should be conducted to compare citrate solutions with antibiotic-based solutions, as citrate is an antibacterial product that does not develop bacterial resistance and can be cheaper than antibiotics.</p> <p>They also confirm that their review supports the stance of the Centers for Disease Control and Prevention (CDC) in not recommending the routine use of antibiotic-based catheter lock solutions.</p>	
<b>Summary of evidence</b>	
<p>Evidence comes from RCT with low quality and risk of bias, added to which is a potential publication bias, which find that solutions with antibiotics + heparin or antibiotics + citrate are more effective than heparin alone in preventing catheter-related bacteraemia.</p>	<b>Low quality</b>
<p><b>Patients' values and preferences</b>  <i>No relevant studies related to this aspect have been identified.</i></p>	
<p><b>Use of resources and costs</b>  An observational study conducted in Spain (López 2007) reported that after introducing locking with 5% sodium heparin and antibiotics, they observed a clear increase in poorly functioning catheters, which had to be unblocked with urokinase, leading to increased cost and the risk of side effects of the anticoagulation.</p>	
<b>Recommendations [Proposal]</b>	
<b>Weak</b>	<p>We do not recommend routine use of antibiotic lock solutions as prophylaxis for tunnelled catheters for haemodialysis.</p>
<b>References</b>	
<p>Hockenhull JC, Dwan K, Boland A, Smith G, Bagust A, Dünder Y, Gamble C, McLeod C, Walley T, Dickson R. The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation. <i>Health Technol Assess.</i> 2008 Apr; 12(12): iii-iv, xi-xii, 1-154.</p> <p>Jaffer Y, Selby NM, Taal MW, Fluck RJ, McIntyre CW. A meta-analysis of hemodialysis catheter locking solutions in the prevention of catheter-related infection. <i>Am J Kidney Dis.</i> 2008 Feb; 51(2):233-41.</p> <p>James MT, Conley J, Tonelli M, Manns BJ, MacRae J, Hemmelgarn BR; Alberta Kidney Disease Network. Meta-analysis: antibiotics for prophylaxis against hemodialysis catheter-related infections. <i>Ann Intern Med.</i> 2008 Apr</p>	

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Labriola L, Crott R, Jadoul M. Preventing haemodialysis catheter-related bacteraemia with an antimicrobial lock solution: a meta-analysis of prospective randomized trials. *Nephrol Dial Transplant*. 2008 May; 23(5):1666-72.

López MA, López N, Franch MA, Bauzá MJ. Cebado profiláctico de catéteres permanentes: ¿causa de obstrucción? *Revista Seden* 2007, 10, 4. Acceso el 4/12/2013 in: [www.revistaseden.org/imprimir.asp?idArticulo=1823](http://www.revistaseden.org/imprimir.asp?idArticulo=1823).

McCann M, Moore ZEH. Interventions for preventing infectious complications in haemodialysis patients with central venous catheters. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No.: CD006894.

Rabindranath KS, Bansal T, Adams J, Das R, Shail R, MacLeod AM, Moore C, Besarab A. Systematic review of antimicrobials for the prevention of haemodialysis catheter-related infections. *Nephrol Dial Transplant*. 2009 Dec; 24(12):3763-74.

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*. 2013 Aug 14.

Snaterse M, Rüger W, Scholte Op Reimer WJ, Lucas C. Antibiotic-based catheter lock solutions for prevention of catheter-related bloodstream infection: a systematic review of randomised controlled trials. *J Hosp Infect* 2010 May; 75(1):1-11.

Yahav D, Rozen-Zvi B, Gafer-Gvili A, Leibovici L, Gafer U, Paul M. Antimicrobial lock solutions for the prevention of infections associated with intravascular catheters in patients undergoing hemodialysis: systematic review and meta-analysis of randomized, controlled trials. *Clin Infect Dis*. 2008 Jul 1; 47(1):83-93.

**Table 1. STUDIES EXCLUDED**

Study	Cause for exclusion
McCann 2010	Cochrane Review which does not include antibiotic prophylaxis. Quote: "This review did not examine interventions relating to CVC locking solutions as they are the focus of the following Cochrane review ' <i>Antibiotic lock therapy for preventing dialysis catheter-related infections in haemodialysis patients</i> '."
Silva 2013	Narrative review

GRADE TABLES

Date: 2013-12-05

Question: Should antibiotics + heparin vs heparin be used in the priming of the tunnelled catheter for haemodialysis?

Bibliography: Snaterse M, R ger W, Scholte Op Reimer WJ, Lucas C. Antibiotic-based catheter lock solutions for prevention of catheter-related bloodstream infection: a systematic review of randomised controlled trials. J Hosp Infect 2010 May; 75(1):1-11.

Quality assessment							No of catheter-days		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics + heparin	Heparin	Relative (95% CI)	Absolute		
<b>Difference of bacteraemia risk per every 1,000 catheter days: (Better indicated by lower values)</b>												
5	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias <sup>1</sup>	52875	55438	-	risk difference 2.08 lower (2.64 to 1.53 lower)	���� LOW	CRITICAL

<sup>1</sup> The authors of the revision stress that there is risk of publication bias, because the funnel graph shows an under-representation of studies with no effect or negative effect . They also note that none of those studies were double-blind, which introduces a performance bias by the professionals, and that the concealment of the treatment was appropriate only in four of the eight studies and that one of them performed an intention-to-treat analysis . They believe that the quality of the evidence is low to moderate.

Date: 2013-12-05

Question: Should antibiotics+ citrate vs heparin be used in the priming of the tunnelled catheter for haemodialysis?

Bibliography: Snaterse M, Rüger W, Scholte Op Reimer WJ, Lucas C. Antibiotic-based catheter lock solutions for prevention of catheter-related bloodstream infection: a systematic review of randomised controlled trials. J Hosp Infect 2010 May; 75(1):1-11.

Quality assessment							No of catheter-days		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics+ citrate	Heparin	Relative (95% CI)	Absolute		
<b>Difference of bacteraemia risk per every 1,000 catheter days: (Copy) (Better indicated by lower values)</b>												
3	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias <sup>1</sup>	9348	5688	-	Risk difference 2.88 lower (4.34 to 1.41 lower)	LOW	CRITICAL

<sup>1</sup> The authors of the revision stress that there is risk of publication bias, because the funnel graph shows an under-representation of studies with no effect or negative effect . They also note that none of those studies were double-blind, which introduces a performance bias by the professionals, and that the concealment of the treatment was appropriate only in four of the eight studies and that one of them performed an intention-to-treat analysis . They believe that the quality of the evidence is low to moderate.

Date: 2013-12-05

Question: Should antibiotics + EDTA vs heparin be used in the priming of the tunnelled catheter for haemodialysis?

Bibliography: Snaterse M, R ger W, Scholte Op Reimer WJ, Lucas C. Antibiotic-based catheter lock solutions for prevention of catheter-related bloodstream infection: a systematic review of randomised controlled trials. J Hosp Infect 2010 May; 75(1):1-11.

Quality assessment							No of catheter-days		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics + EDTA	Heparin	Relative (95% CI)	Absolute		
<b>Difference of bacteraemia risk per every 1,000 catheter days: (Copy) (Copy) (Better indicated by lower values)</b>												
1	randomised trials	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias <sup>1</sup>	2336	2118	-	Risk difference 0.47 lower (1.40 lower to 0.45 higher)	���� LOW	CRITICAL

<sup>1</sup> The authors of the revision stress that there is risk of publication bias, because the funnel graph shows an under-representation of studies with no effect or negative effect . They also note that none of those studies were double-blind, which introduces a performance bias by the professionals, and that the concealment of the treatment was appropriate only in four of the eight studies and that one of them performed an intention-to-treat analysis . They believe that the quality of the evidence is low to moderate.