Should *non-tunnelled* central venous catheters be covered by chlorhexidine dressings?

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Until now, chlorhexidine is the only antimicrobial agent used in catheter dressings. According to our knowledge there are two types of chlorhexidine dressings, i.e. Biopatch^{R} and Tegaderm^{TM}. All trials included in this review investigated Biopatch^{R}. No trials were found comparing Biopatch^{R} with Tegaderm^{TM}.
The systematic review on the effect of chlorhexidine dressings consists of two parts which are published separately on the website of the WIP.
Part I: Should non-tunnelled CVCs be covered by chlorhexidine dressings?
Part II: Should tunnelled CVCs be covered by antimicrobial dressings?

The following question was answered by a systematic review of the literature:
Should non-tunnelled central venous catheters (CVCs) be covered by chlorhexidine dressings versus standard dressings to reduce the occurrence of catheter-related bloodstream infection (CRBSI)?

Study population: patients with non-tunnelled CVCs
Comparison: chlorhexidine dressing versus standard dressing
Outcome: CRBSI

Methods

Data sources
Publications were retrieved by a search of Medline and the Cochrane Library up to 31 March 2010. The search strategy in Cochrane was: (central venous catheter* OR tunnelled intravascular catheter* OR catheter-related) AND (antimicrobial OR antiseptic* OR chlorhexidine* OR Biopatch OR disinfectant*) AND (dressing* OR sponge OR Biopatch). To identify randomised controlled trials in Medline the following search strategy was used: ((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR "clinical trial" [tw] OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND

(mask* [tw] OR blind* [tw])) OR "latin square" [tw] OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT human [mh])) AND (central venous catheter* OR tunnelled intravascular catheter* OR catheter-related) AND (antimicrobial OR antiseptic* OR chlorhexidine* OR Biopatch OR disinfectant*) AND (dressing* OR sponge OR Biopatch). In addition, the lists of references of all identified trials were checked for more trials.

Selection criteria

All randomised and quasi-randomised trials comparing antimicrobial dressings versus standard dressings for non-tunnelled central venous catheters and catheter-related bloodstream infection as the outcome measure were included. Studies in neonates were excluded.

Assessment of trial quality

Three reviewers assessed trial quality independently by evaluating each study to determine concealment of treatment allocation, double blinding, completeness of follow-up, use of intention-to-treat analysis, selective reporting of events and premature discontinuation of the trial due to benefit. Central randomization, sealed envelopes or a similar method was assumed to yield adequate randomization. The description of dropouts was considered adequate if the number of patients lost and reasons why patients were lost were reported according to allocation to treatment. Disagreements were resolved by consensus.

Review methods

Data were extracted by three reviewers independently and compared. Disagreements were resolved by consensus. Data from the original publications were used to calculate the relative risk (RR) with a 95% confidence interval (CI). Data were combined in the analysis where appropriate, using a random-effects model. The quality of evidence for CRBSI was assessed by using the Grade approach[1].

Results

Seventy six potentially relevant studies were initially identified by our search. By judgment of titles and abstracts, ten studies appeared to fulfil the selection criteria. Out of the ten studies, six papers were excluded after reading the whole article. The

reasons for exclusion are listed in Table 1. Four parallel-group randomised controlled trials were included in the review[2-5].

Excluded studies

See Table 1

Assessment of trial quality

See Table 2

Study population, interventions and outcome definitions

See Table 3

Summary estimates of associations between treatment and control group

See Figure 1

Summary of Findings table (GRADE)

See table 4

Table 1 Excluded studies

	Reasons for exclusions
Crawford[6]	NOT RCT
Garland[7]	Neonates
Hanazaki[8]	Another question was answered
Ho[9]	Systematic review: included neonatology; included an article which was not published; pooled too heterogeneous data;
Chambers[10]	Another question was answered
Roush[11]	Not primary study

Table 2 Assessment of trial quality

	Concealment of allocation	**Placebo-controlled**	**Description of dropouts (%)**	**Analysis by intention-to-treat**	**Stopping trial early to benefit**	**Selective reporting of events**
Levy 2005	Unclear	No*	Inadquate NR%	Unclear	No	No
Roberts 1998	Unclear	No	Inadequate 18%	No	No	No
Ruschulte 2009	Inadequate#	No*	Adequate 0%	Yes	Yes; planned sample size, interim analysis and stopping rules were reported correctly	No
Timsit 2009	Adequate#	No^	Adequate 7.7%	No	No	No

Information requested from the original authors by mail

* Microbiology laboratory personnel were blinded

^ Microbiology laboratory personnel and outcome assessors were blinded; not blinded for investigators and ICU staff

Table 3 Study populations, interventions and outcome definitions

	Setting	**Treatment (T) and control group (C)**	**Duration of catheterisation**	**End of study protocol**	**Definition of catheter-related bloodstream infection; n / N**	**Baseline risk in control group**
Levy 2005	Pediatric cardiac intensive care patients who required a CVC (internal	T: Biopatch™ covered by a transparent polyurethane insertion site dressing C: transparent polyurethane insertion site dressing	Mean days (SD) T: 4.67 (1.91) days	CVC no longer required; mechanical or infectious	Bacteremia with isolation of the same organism from the tip of the CVC and blood (unclear whether blood was drawn by the CVC or by	4%

	jugular vein; non-tunneled) for > 48 hours	Note: Biopatch™ not changed routinely	C: 4.35 (2.2) days	complications of CVC;	peripheral puncture) T: 4 / 74; C: 3 / 71 Local redness (adverse events) T: 4 / 74 C: 1/ 71	
Roberts 1998	ICU patients (40 CVCs in 32 patients) Note: catheters were randomised; patients could be multiple enrolled	T: Biopatch™ covered by an Opsite IV 3000™ occlusive dressing C: Opsite IV 3000™ occlusive dressing Note: Biopatch™ routinely changed every 5 days and as necessary	Mean days (range) T: 7 (4 – 12) C: 6 (2 – 14)	Not reported	CRBSI defined as any infection in which the organism isolated from the CVC tip and / or exit site was the same as that isolated from a clinical isolate associated with raised temperature and white cell count. T: 1 / 17; C: 0 / 16	O%
Ruschulte 2009	In-patients with CVCs for cancer chemotherapy; CVCs were expected to remain in place for at least 5 days Note: anti-infective-treated CVCs were used	T: Biopatch™ covered with a transparent polyurethane dressing C: standard transparent polyurethane dressing Note: Biopatch™ were changed weekly and as necessary	Mean T: 16.6 days C: 15.8 days	Catheters no longer needed or CVC-related infection	CVC-related bloodstream infection: Defined as positive catheter blood cultures and positive peripheral blood cultures according to the time-to-positivity method; and clinical symptoms T: 19 / 4986 catheter days C: 34 / 4795 catheter days Or T: 19 / 300 catheters C: 34 / 301 catheters	

					Adverse events: No adverse events due to chlorhexidine were observed.	
Timsit 2009	1636 adult ICU patients (3778 catheters) from 3 university and 2 general hospitals, who required an arterial catheter, a CVC, or both for 48 hours or longer	T1: Biopatch™ covered by a semipermeable transparent dressing; 3 days-change C1: standard dressing; 3 days change T2: : Biopatch™ covered by a semipermeable transparent dressing; 7 days-change C2: standard dressing; 7 days change Note: 1) The dressing was changed 24 hours after catheter insertion and as necessary; 2) The Biopatch™ was applied to the entire skin surface at and around the insertion site;	Median days (interquartile range) T1/2: 6 (4-10) C1/2: 6 (4-10) Mean days in 3-days group T1: 7 days C2: 7.2 days	Follow-up until 48 hours after ICU discharge Catheters removed if no longer needed (usually before ICU discharge), or CRI suspected;	Major CRI Defined as clinical sepsis with or without bloodstream infection a) 3-days change group T1: 2 / 952 catheters; C1: 10 / 863 catheters T1: 2 / 6664 catheter days C1: 10 / 6214 catheter days [ln IDR -1.6794; SE (ln IDR) = 0.7746] b) 7-days change group T2: 8 / 1001 catheters C2: 9 / 962 catheters T2: 8 / ?? catheter days C2: 9 / ?? catheter days ??: data not given by author Catheter-related bloodstream infection Defined as bacteremia with	Major CRI a) 3-days 1.2% b) 7-days 0.9% Catheter-related bloodstream infection

					isolation of the same organism from the tip of the CVC and blood a) 3-days change group T1: 1 / 952 catheters C1: 10 / 863 catheters T1: 1 / 6664 catheters C1: 8 / 6214 catheters [ln IDR -2.1494; SE (ln IDR) = 1.0601] b) 7-days change group T2: 5 / 1001 catheters C2: 9 / 962 catheters T2: 5 / ?? catheter days C2: 9 / ?? catheter days ??: data not given by author Severe CHGIS-associated contact dermatitis leading to permanent removal of the CHX dressing In 8 patients (10 catheters)	a) 3-days 1,2% b) 7-days 0.9%

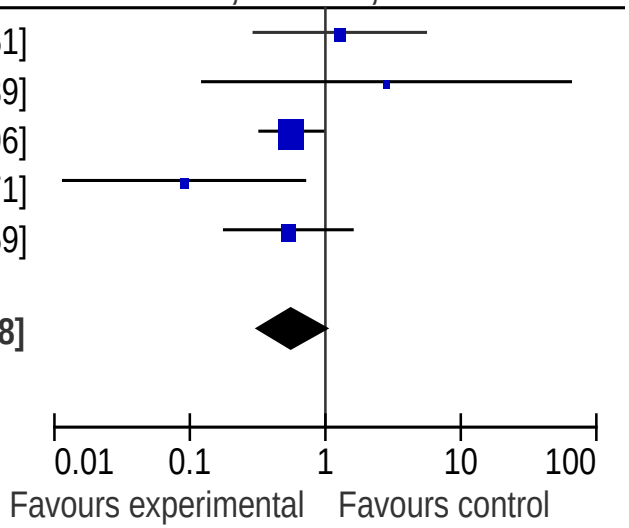
Figure 1 and 2 Summary estimates of association between antimicrobial and standard dressings for central venous catheters expressed as relative risk (RR) and 95% confidence interval (CI)

Figure 1 Outcome: catheter-related bloodstream infection

	Experimental		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Levy 2005	4	74	3	71	15.2%	1.28 [0.30, 5.51]	
Roberts 1998	1	17	0	16	3.9%	2.83 [0.12, 64.89]	
Ruschulte 2009	19	300	34	301	48.9%	0.56 [0.33, 0.96]	
Timsit 3-day 2009	1	952	10	863	8.5%	0.09 [0.01, 0.71]	
Timsit 7-day 2009	5	1001	9	962	23.5%	0.53 [0.18, 1.59]	
Total (95% CI)		**2344**		**2213**	**100.0%**	**0.57 [0.30, 1.08]**	
Total events	30		56				

Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 5.39$, df = 4 (P = 0.25); $I^2 = 26\%$

Test for overall effect: Z = 1.71 (P = 0.09)

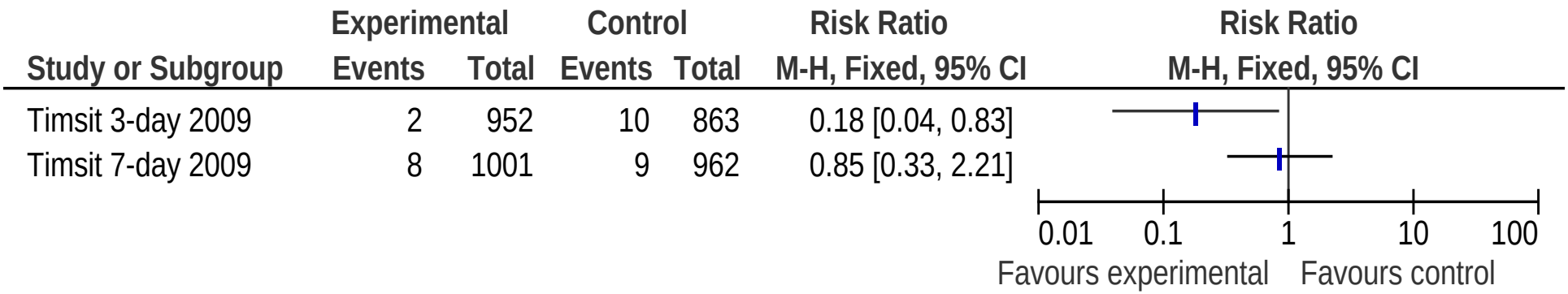


Comment ad Figure 1 and 3:

Timsit / CRBSI 3-days change group: the RR and the IDR agreed.

Timsit / CRBSI 7-days change group: we were unable to calculate the incidence density ratio in the 7-days change group, because the authors did not supply the number of catheter days despite several requests.

Figure 2 Outcome: major CRI



Comment ad Figure 2 and 4:

Timsit / major CRI 3-days change group: the RR and the IDR agreed.

Timsit / major CRI 7-days change group: we were unable to calculate the incidence density ratio in the 7-days change group, because the authors did not supply the number of catheter days despite several requests.

Figure 3 and 4 Summary estimates of association between antimicrobial and standard dressings for central venous catheters expressed as incidence density ratio (IDR) and 95% confidence interval (CI)

Figure 3 Outcome: catheter-related bloodstream infection

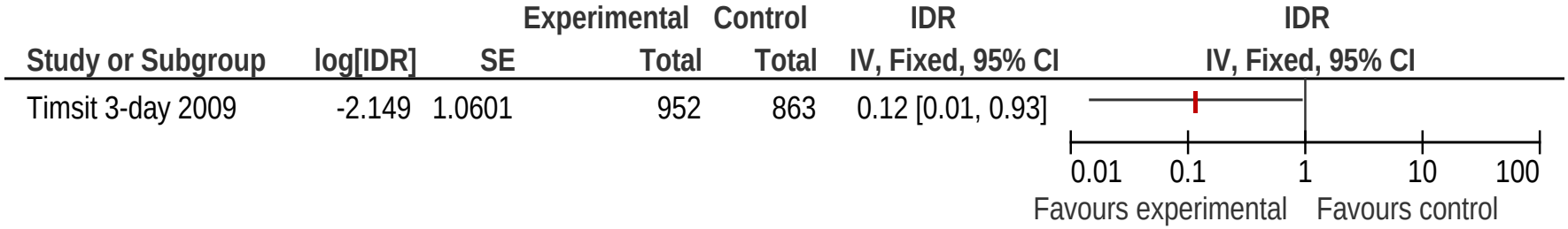


Figure 4 Outcome: major CRI

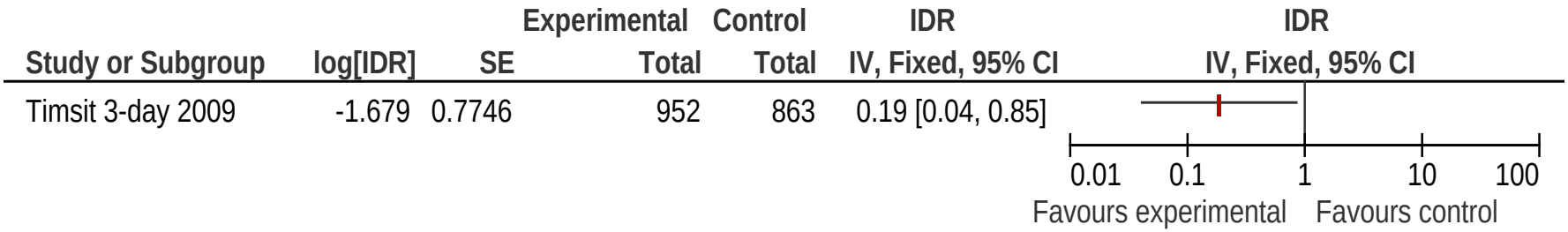


Table 4 Summary of Findings table (GRADE)

chlorhexidine dressing compared to standard dressing for patients with non-tunnelled CVCs

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk **standard dressing**	Corresponding risk **chlorhexidine dressing**				
Catheter-related bloodstram infection / RR Follow-up: 4-7 days	**25 per 1000**	**14 per 1000** (8 to 27)	**RR 0.57** (0.3 to 1.08)	4557 (4 studies)	**very low**[1,2,3]	
Major CRI / RR Follow-up: median 6 days	See comment	See comment	See comment	3778 (1 study)	**very low**[3,4,5]	See footnote[5]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

Very low quality: We are very uncertain about the estimate.

[1] None of the trials were placebo-controlled; one trial had inadequate allocation concealment; two trials had unclear allocation concealment
[2] We did not downgrade the quality of evidence although two trials did not define catheter-related bacteraemia according to CDC criteria.
[3] The 95% CI includes negligible effect, benefit and harm; low number of events;
[4] Not placebo-controlled
[5] Unexplained marked statistical heterogeneity; differences in duration of catheterization between the 3-day change group and the 7-day change group might have been an important source of the statistical heterogeneity. we were not able to check this hypothesis, because the authors did not supply the number of catheter days in the treatment and control group of the 7-day change group.

Conclusion

The evidence of the benefit of antimicrobial dressings in patients with non-tunnelled CVCs for a mean duration of catheterisation of 4 to 7 days is very uncertain. Four trials compared Biopatch^{TM} covered by standard catheter site dressings to standard catheter site dressings and found that Biopatch^{TM} were of benefit regarding catheter-related bloodstream infection (CRBSI) (RR 0.57; 95% CI 0.30 to 1.08). The quality of the available evidence is very low because of serious limitations in study quality and very serious imprecision.

One trial found that Biopatch^{TM} were of benefit regarding CRBSI and major catheter-related infections (CRI) when dressings were changed routinely every 3 days (RR); the same trial found that it was uncertain whether Biopatch^{TM} were of benefit or harm with regard to CRBSI and major CRI when the dressings were changed every 7 days. It was not possible to adjust for possible differences in catheterization time within the 7-days change group (by calculating the incidence density ratio), because the authors did not supply the number of catheter days despite several requests.

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