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Preventing haemodialysis catheter-related bacteraemia with an antimicrobial lock solution: a meta-analysis of prospective randomized trials

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Abstract

Background. Catheter-related bacteraemia (CRB) is a major cause of morbidity and mortality in haemodialysis patients. Interdialytic locking of catheters with antimicrobial agents has recently been investigated for the prevention of CRB. We performed a meta-analysis of randomized controlled trials (RCT) to determine the efficacy of antimicrobial lock solutions (ALS) in the prevention of CRB in haemodialysis patients.

Methods. We collected from Medline, Web of Science, the Cochrane Library and major nephrology journals, all relevant references (January 1990–March 2007). We selected RCT comparing an ALS to a standard heparin lock in CRB prevention. We extracted data concerning study quality, patient characteristics and CRB incidence. The relative risk (RR) of CRB was calculated as Ln (CRB incidence control/CRB incidence experimental) using both a fixed- and a random-effects model.

Results. Eight studies were included, involving 829 patients, 882 catheters and 90 191 catheter-days. The use of an ALS significantly decreased the risk of CRB (RR 0.32; 95% CI 0.10–0.42). Borderline heterogeneity was observed in the fixed-effects model ($Q = 14.42$; $P = 0.071$). Despite the under-representation of small negative studies, the high number of additional trials necessary to reverse the final effect strengthens the confidence in the overall results. Subgroup analyses stratified by the presence of diabetes, duration of follow-up, biochemical markers, proportion of tunnelled cuffed catheters, intranasal mupirocin use and citrate use in the ALS did not show significant differences, except a higher efficacy of gentamicin-containing lock solutions ($P = 0.003$).

Conclusions. The use of ALS reduces by about a factor 3 the risk of CRB in haemodialysis patients. The achieved absolute incidence is similar to the best-published figures (presumably related to stricter hygienic measures). The limited follow-up of the studies does not exclude the onset of adverse events or bacterial resistance with longer use of ALS.

Keywords: bacteraemia; catheter; haemodialysis; lock solution

Introduction

Since their introduction 20 years ago, the use of tunnelled cuffed haemodialysis catheters (TCC) has increased in parallel with the age and comorbidity of haemodialysis patients. The main factors limiting the long-term use of haemodialysis catheters are poor flow and catheter-related infections, especially catheter-related bacteraemia (CRB). The prevention of CRB remains a significant challenge because of the associated high morbidity and mortality [1]. An incidence of two to three CRB episodes per 1000 catheter-days is considered relatively low [2–5], with most studies reporting four to six episodes per 1000 catheter-days [6–11]. A number of strategies have been tried to reduce the incidence of CRB; they include the use of strict hygienic measures, antibiotic-impregnated catheters, eradication of *Staphylococcus aureus* nasal carriage and prophylactic antibiotic ointment on the exit site [11]. A recent promising approach has been used to instillate an antimicrobial solution into the lumen(s) of the catheter (lock solution) at the end of each haemodialysis session in order to prevent intraluminal colonization and the development of a biofilm. The rationale for the use of an antimicrobial lock solution (ALS) is the high intraluminal concentration achieved, with subsequent elimination of the internal biofilm. The biofilm constitutes a permanent source of bacteraemia, as well as a key factor favouring bacterial resistance [12]. Several, but not all, studies including TCC and/or not tunnelled haemodialysis catheters (NTC) have shown a reduction in CRB incidence by using ALS as compared with heparin alone [10,13–23].

We report a meta-analysis of prospective, randomized controlled trials of the efficacy of an ALS compared with

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a standard heparin lock solution, in the prevention of CRB in haemodialysis patients with TCC or NTC.

Methods

The QUORUM (quality of reporting of meta-analysis) checklist [24] was followed for the selection of studies, data abstraction and synthesis and reporting of the results.

- *Search criteria:* Pubmed, Medline, Web of Science, the Cochrane Library databases and major nephrology journals were searched for publications from 1990 until March 2007. No language restriction was applied. The following keywords were used alone or in combination: dialysis, catheter lock, bacteraemia, sepsis, septicaemia, infection and prophylaxis. Only published, randomized, controlled studies performed in humans were included. Studies in abstract form of scientific conferences were not included.
- *Inclusion criteria:* To be included in the meta-analysis, a study had to meet the following criteria: to be a randomized trial comparing an ALS (with or without antibiotics) with a standard heparin lock solution (5000 U/ml); to report the incidence of CRB as principal outcome with sufficient information to allow the calculation of a relative risk; to use a clear definition of CRB and to detail the procedure followed in case CRB was suspected. Studies that focused on lock solutions for other haemodialysis vascular accesses than TCC or NTC, dealt with the treatment of CRB rather than with prophylaxis, did not use CRB incidence as outcome measure or were not published in peer-reviewed journals were excluded.
- *Outcome measures:* The primary end point was CRB, defined as bacteraemia without other obvious sources than the haemodialysis catheter, with signs consistent with systemic infection [2]. Other end points like exit-site infection, catheter colonization or catheter malfunction were not considered.
- *Data extraction:* Using an Excel data form, we extracted data concerning size of the study sample, characteristics of patient population, type of lock solution, type of catheters (TCC/NTC), catheter vintage (new/prevalent catheters), catheter site (jugular/subclavian/femoral), concomitant use of nasal mupirocin, type of CRB pathogen (Gram positive/Gram negative), duration of the follow-up and biochemical markers (haemoglobin, serum ferritin and albumin). Randomization and blinding procedures were also evaluated.
- *Statistical analysis:* The incidence of CRB was compared between the two arms (i.e. effect size of control versus experimental) and expressed as the natural logarithm of the ratio of the incidence of CRB per 1000 catheter-days or Ln (CRB rate control group per 1000 catheter-days/CRB rate experimental group per 1000 catheter-days). The variance of the incidence rate ratio was calculated using the simplified formula of Hasselblad and McCrory [25], with confidence intervals calculated by bootstrap ($n = 1000$). The results were then retransformed to obtain a relative risk (RR) estimate [26]. All analyses were performed with Metawin 2.1 release 4.8 (Sinauer Associates, Sunderland, MA, USA). Predefined subgroup analyses were performed. We also reported in this case the between-studies (QB) and total-variance (QT). In order to make possible the calculation of the Ln (CRB control/CRB experimental), the 0 incidence reported in four studies was arbitrarily transformed to 0.5.

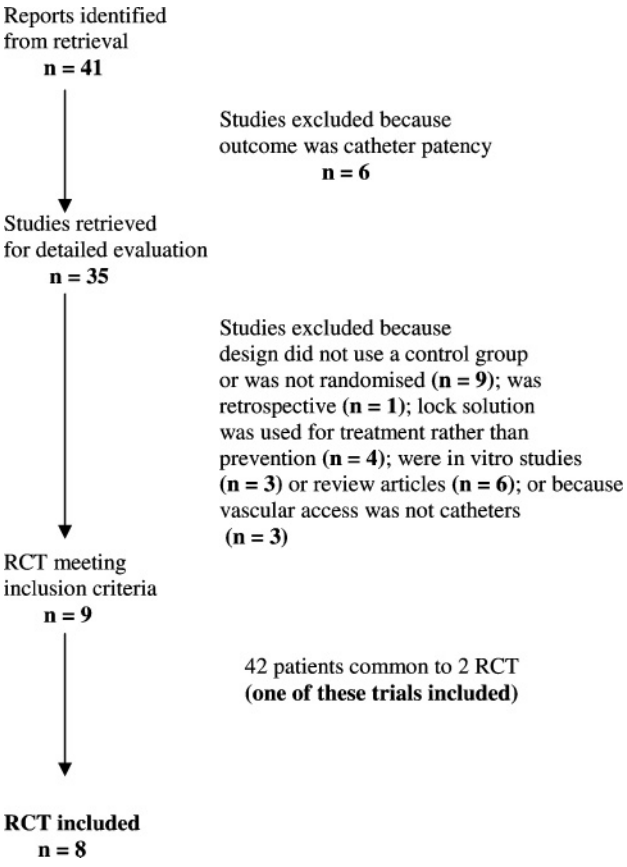

Fig. 1. Flow diagram followed for the selection process of studies included in the meta-analysis.

Results

Search results

Our search yielded 41 published reports (Figure 1); 32 were excluded because they only evaluated catheter patency ($n = 6$), were retrospective ($n = 1$), did not have a randomized, controlled study design ($n = 9$), were review articles ($n = 6$), were concerned with treatment rather than prevention of CRB ($n = 4$) and were *in vitro* studies ($n = 3$), or because the studied type of vascular access was a subcutaneous device rather than catheters ($n = 3$). Nine randomized, controlled trials fulfilled inclusion criteria [2,14–21]. The characteristics of these included trials are shown in Table 1. Five were double-blind [14,16–18,21] and the other four were open-label [2,15,19,20]. Because two studies had the same first author and inclusion period [18,21], we considered the possibility that some patients had been included in both studies. This was confirmed by their first author (Saxena, personal communication); 42 patients were common to both trials [18,21]. In the absence

Table 1. Characteristics of studies and patients fulfilling inclusion criteria in the meta-analysis

Reference	Number of centres	Tested lock solution	Maximal follow-up days	Number of patients	Diabetes (%)	Number of catheters	Catheter days	TCC (%)
Dogra *et al.* [14]	2	Gentamicin–citrate (40 mg/ml) (3.13%)	288	79	38	108	5 923	100
McIntyre *et al.* [15]	1	Gentamicin–heparin (5 mg/ml)	365	50	13	50	5 722	100
Betjes *et al.* [2]	1	Taurolidine–citrate (1, 35%) (4%)	90	58	32	76	3 404	23
Bleyer *et al.* [16]	1	Minocycline–EDTA (3 mg/ml) (30 mg/dl)	360	57	22	57	4 454	17.5
Weijmer *et al.* [17]	10	Citrate (30%)	400	291	58	291	16 547	33.7
Saxena *et al.* [18]	1	Cefotaxime–heparin (10 mg/ml)	365	113	42	119	43 435	100
Nori *et al.* [19]	3	Gentamicin–citrate (4 mg/ml) (3,13%)	160	40	22	40	3 736	100
		Minocycline-EDTA (3 mg/ml) (30 mg/dl)	160	41	20	41	4 187	100
Kim *et al.* [20]	1	Cefazolin-gentamicin-heparin (10 mg/ml) (5 mg/ml)	60	120	63	120	4 517	0
Saxena *et al.* [21]*	1	Cefotaxime-heparin (10 mg/ml)	547	96	96	110	39 785	100

The concentration of the various components of lock solutions is mentioned in brackets.
[a]Study excluded because 42 patients are common with reference 18.

of a prompt availability of patient-level data for both trials, we only included the trial with the highest number of catheter-days and patients [18] and thus excluded the other [21]. Thus, a total of 829 patients, 882 catheters and 90 191 catheter-days were available for analysis. The type(s) of ALS used in the experimental arm(s) of the eight studies are detailed in Table 1.

All eight studies reported some information about randomization procedures, but in some cases it was not completely detailed. According to the CONSORT statement for quality of reporting of randomized trials [27], only five studies provided sufficient information about the method used to generate the random allocation sequence [2,14,17,18,20] and only two of them reported on the method to implement the random sequence [14,18]. Only one of these used an optimal decentralized or 'third-party' method to conceal the sequence until interventions were assigned [14], as recommended by the CONSORT statement. Only two of four double-blind studies gave detailed description of the blinding procedure [16,17].

Five studies described exit-site care procedures [2,14,17,18,20]. Preparation and instillation of the lock solution were detailed in only three trials [14,18,19]. In three studies, an additional technique of the prevention of CRB (intranasal mupirocin) was used [2,14,17] whereas in one study, this procedure was not used [15], and in the last four, no information was given [16,18–20]. In all trials but one, catheters were included from the date of their insertion; only Nori *et al.* included both new and prevalent catheters [19]. One study included exclusively NTC [20], while three studies [2,16,17] included both TCC and NTC and the other four, TCC only. Overall, 501 TCC and 381 NTC were included. Maximum follow-up ranged from 60 to 400 (median 288) days. Six trials evaluated the incidence of exit-site infection and two assessed the incidence of colonization [2,16]. All but one study [19] reported on the micro-organisms responsible for CRB.

The criteria used for CRB diagnosis in each study were as follows: a positive bacterial blood culture drawn from the catheter with no other apparent source of infection in a symptomatic patient [2]; at least one positive blood culture either from the catheter or from a peripheral vein in a symptomatic patient without other obvious cause of infection [17]; isolation of the same organism from a semiquantitative culture of the catheter tip (>15 colony-forming units), a peripheral blood sample and a catheter blood sample [16,20] and criteria of definite or probable bloodstream infection according to the Centers for Disease Control (CDC, Atlanta, GA, USA) [28] in four studies [14,15,18,19]. These CDC definitions are as follows: (i) definite bloodstream infection: isolation of the same organism from a semiquantitative culture of the catheter tip (>15 colony-forming units per catheter segment) and from a peripheral or catheter blood sample in a symptomatic patient with no other apparent source of infection; (ii) probable bloodstream infection: defervescence after antibiotic therapy with or without removal of the catheter in the setting where blood cultures confirm infection but the catheter tip does not, or the catheter tip confirms infection but blood cultures do not in a symptomatic patient with no other apparent source of infection. Cases meeting the CDC definition of possible bloodstream infection (defervescence after removal of the catheter in the absence of laboratory confirmation of a bloodstream infection in a symptomatic patient with no other apparent source of infection) were not considered as CRB in these four trials. CRB was treated with an empirical regimen including vancomycin and an aminoglycoside in two studies [15,18], while in the other six no information was given. Catheters were removed/changed if signs of sepsis persisted 48 h after initiation of antibiotic therapy [15,17,18]. In two of these studies, a new CRB was recorded if it occurred ≥2 weeks after the cessation of initially successful antibiotic therapy for the first CRB episode [15,18]. Another trial defined CRB relapse (leading to catheter removal) as CRB

Table 2. Incidence of CRB in included trials

Reference	CRB incidence (episodes per 1000 catheter-days)		
	ALS	Control	RR (95% CI)
Dogra *et al.* [14]	0 (0.5)	2.65	0.058 (0.01–0.46)
McIntyre *et al.* [15]	0.308	4.049	0.076 (0.01–0.42)
Betjes *et al.* [2]	0 (0.5)	2.122	0.155 (0.02–1.35)
Bleyer *et al.* [16]	0 (0.5)	0.472	0.453 (0.04–5.69)
Weijmer *et al.* [17]	1.067	4.066	0.263 (0.13–0.54)
Saxena *et al.* [18]	1.672	3.607	0.463 (0.31–0.69)
Nori *et al.* [19]	0 (0.5) (a)	4.037	0.062 (0.01–0.5)
	0.408 (b)	4.037	0.101 (0.02–0.58)
Kim *et al.* [20]	0.44	3.119	0.141 (0.02–0.81)

ALS: antimicrobial lock solution; CRB: catheter-related bacteraemia; RR: relative risk. The study of Nori *et al*. [19] included two experimental groups: gentamicin–citrate (a) and minocycline–EDTA (b). In order to make possible the calculation of the Ln (CRB control/CRB experimental), the 0 incidence reported in four studies was arbitrarily transformed to 0.5.

recurring within 3 weeks after stopping antibiotic treatment [17]. The other trials did not define CRB relapse.

Overall effect

The incidence of CRB in all arms of each trial is listed in Table 2. The overall summary risk ratio using the fixed effects model was 0.32 (95% CI 0.10–0.42), indicating a significantly reduced risk of CRB in patients randomized to receive an ALS (Figure 2). There is some hint to the existence of borderline heterogeneity between studies as shown by the *Q*-test in the fixed-effects model. This is confirmed by the difference between the results of fixed- and random-effects models (Table 3). Therefore, subgroup analyses were performed with a random-effects model as well. Including in the meta-analysis trial [21] instead of [18] did not modify the overall effect (data not shown).

After excluding one study that did not provide enough information to determine the incidence of CRB relapses [18], the overall summary risk ratio still pointed to a strong protective impact of ALS (data not shown).

Subgroup analyses

Subgroup analyses stratified by the presence of diabetes, duration of follow-up, albumin serum level, ferritin serum level, proportion of TCC, use of intranasal mupirocin and use of citrate or gentamicin in the lock solution were performed. The type of experimental ALS did influence the overall efficacy; it was better when it included gentamicin (Table 4A). The between-studies variance was high compared to the overall variance (62%). Excluding the study of Weijmer [17] that used citrate alone did not change the results. Given the small number of studies in each subgroup, a chance finding can, however, not be excluded. The use of citrate alone (one study) or in combination with an antibiotic (three studies) was not significantly better than the other ALS, given the wide overlapping confidence intervals, although it appeared to explain 20.2% of the overall variance ($P = 0.134$). There was no significant effect of the maximum follow-up time, proportion of diabetic patients, proportion of TCC, mean albumin and ferritin serum levels and use of intranasal mupirocin on the overall RR between control and experimental patients (data not shown).

Publication bias

From the visual inspection of the Funnel plot one may observe an under-representation of small studies with a low or no effect (Figure 3). The fail-safe numbers using Rosenthal's and Orwin's methods (with a minimal standardized effect size of 0.2) are respectively 254 and 42 for the fixed-effects model and 143 and 57 for the random-effects model. Using as a rule of thumb the critical number of studies $(5n + 10) = 55$ as suggested by Rosenthal [29], one may, nevertheless, be confident in the overall results.

Adverse events

No serious adverse event related to the ALS was reported in any of the nine included trials. The most common adverse events were dizziness, paresthesias and metallic taste [14,17]. Weijmer *et al.* observed a significantly greater incidence of major bleeding episodes with heparin than with citrate 30% [17]. In a study using citrate (3.13%) and gentamicin (40 mg/ml) [14], the median pre-dialysis plasma level of gentamicin was 2.8 mg/l. With a lower gentamicin dosage (5 mg/ml) Mc Intyre *et al.* measured pre-dialysis gentamicin plasma levels <0.2 mg/l [15]. The other two studies using gentamicin (5 and 4 mg/ml respectively) [19,20] did not report gentamicin plasma levels. No study reported CRB due to bacteria resistant to the antibiotic included in the lock solution.

Discussion

Given that CRB is associated with a high morbidity, mortality and cost in haemodialysis patients, the use of ALS may offer a promising way to prevent this complication. This meta-analysis shows that the use of an ALS decreases the risk of CRB by approximately a factor 3. Although the under-representation of small studies with a non-significant or negative effect suggests an overestimation of the effect of ALS, the high number of additional trials necessary to reverse the final effect strengthens the confidence in the overall results.

The overall RR is mainly driven by the two largest studies [17,18]. Not surprisingly, small trials tended to show a better effect than the largest ones. The exceptions are the small-sized studies of Bleyer *et al.* [16] and Betjes *et al.* [2], which showed a non-significant result (see Figure 2). In the latter, however, CRB-free survival was better in the ALS than in the control group ($P = 0.047$). In the absence of information on CRB-free survival in some other trials, we used as end point of this meta-analysis the incidence of CRB, thus potentially underestimating the actual impact of the ALS in that trial [2]. The borderline heterogeneity in the fixed-model effects can be explained by the choice of gentamicin for the lock solution. We could not study the impact of low versus high concentrations of citrate

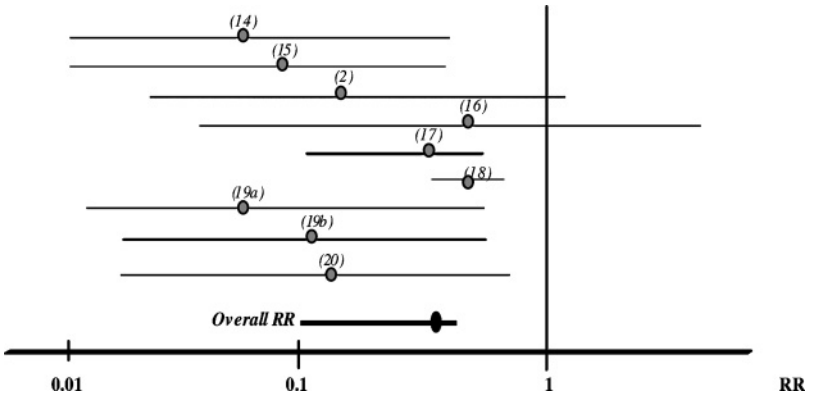

Fig. 2. Forest plot: fixed effects. The relative risk of CRB in the eight studies included in our meta-analysis. The bold line represents the overall relative risk. The summary risk ratio is 0.32 (95% CI 0.10–0.42), indicating a significant protective effect of an antimicrobial lock solution in the prevention of CRB.

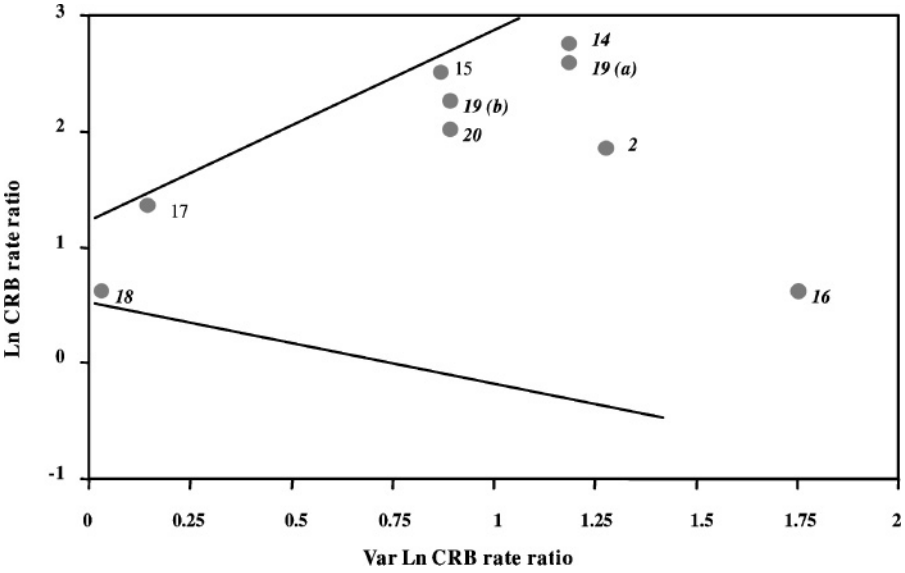

Fig. 3. Funnel plot. The Funnel plot shows the under-representation of small studies with a low or no effect.

Table 3. Overall effects of antimicrobial lock solutions for the prevention of CRB in haemodialysis patients

	Effect size (95% CI)	Relative risk (95% CI)	*Q*-test
Fixed effects	1.14 (0.88–2.31)	0.32 (0.10–0.42)	14.42 ($P = 0.071$)
Random effects	1.62 (1.14–2.35)	0.20 (0.09–0.32)	6.16 ($P = 0.629$)

Table 4. Effect of a lock solution containing gentamicin versus other lock solutions (random-effects model)

	Number of studies	Effect size (95% CI)	RR (95% CI)	QB	QT
Gentamicin	4[a]	2.50 (2.12–2.82)	0.08 (0.06–0.12)	8.99 ($P = 0.003$)	14.42 ($P = 0.071$)
Other lock	5[a]	0.97 (0.79–1.97)	0.38 (0.14–0.45)		

RR: relative risk; QB: variance between studies; QT: overall variance.
[a]Including one experimental arm of the study of Nori *et al.* [19].

because three studies used low (3.13 to 4%) concentrations [2,14,19], whereas only one study used citrate 30% [17]. Weijmer *et al.* reported a trend towards a greater reduction of CRB incidence for TCC than for NTC [17]. Our analysis did not detect a difference between TCC and NTC, possibly because of the under-representation of NTC.

Overall, the use of ALS can be considered as a good technique for the prevention of CRB. Nevertheless, it should be pointed out that the studies of Betjes *et al.* and Bleyer *et al.* [2,16], with a marginal or non-significant effect, both reported a low CRB incidence in the control group (2.1 and 0.4 episodes per 1000 catheter-days, respectively). Thus, whether ALS would have a similar preventive impact in units with a low baseline incidence of CRB (and presumably stricter hygienic measures) remains to be demonstrated. Interestingly, a recent randomized controlled trial with a baseline incidence of 0.6 CRB episodes per 1000 catheter-days did not demonstrate a significant prevention with citrate 46.7% ($P = 0.88$) [22]. This study was not (yet) published, and therefore not included in our meta-analysis. Similarly, a retrospective study of the incidence of CRB before versus after switching from heparin to citrate 4% did not show any reduction of CRB (0.77 versus 0.94 CRB episodes per 1000 catheter-days, respectively; $P = 0.36$) [23]. In most of the trials included in this meta-analysis, the absolute incidence of CRB with an ALS is similar to the rates reported in observational studies [3,4,30,31]. On the other hand, some trials showed a dramatic reduction of CRB after reinforcing the basic hygienic precautions in the care of catheters [32,33]. Therefore, one must be cautious when formulating recommendations on the basis of the overall results of our meta-analysis. As suggested by Bleyer in a recent narrative review [34], the first logical step of a preventative strategy is to intensify the education of all dialysis unit staff members on adequate catheter care. The use of additional prevention methods like ALS could be reserved to patients at high risk of infection (such as diabetics, carriers of femoral catheters or individuals with a history of recurrent CRB) or subjects in whom a CRB would lead to dramatic consequences (such as patients with artificial heart valves, pacemakers, vascular grafts, . . .).

It is obvious that ALS must have anticoagulant properties to maintain good catheter function. Most of the trials having studied catheter patency did not observe a difference in ALS compared to heparin, with the exception of one trial [18] that showed a lower rate of catheter thrombosis (13.7 versus 36.2%; $P < 0.001$) and better thrombosis-free TCC survival ($P = 0.023$). However, we did not include in the meta-analysis data concerning the effect of ALS on catheter patency because of the lack of detailed information in most of the trials.

With the exception of the detectable gentamicin plasma levels measured by Dogra *et al.* when using a high concentration of gentamicin in the ALS [14], no potentially serious adverse event related to ALS was reported in the included studies. It is of interest that Weijmer *et al.* observed significantly fewer bleeding episodes with citrate 30% than with heparin ($P = 0.01$) [17]. Overall, the average follow-up limited to about 1 year, however, does not exclude the onset of serious adverse events or bacterial resistance with more prolonged use of ALS. Although subgroup analyses showed a better effect of lock solutions containing gentamicin, prolonged use of gentamicin locks raises obvious concerns of potential toxicity and growing bacterial resistance. Admittedly, there was no clinical evidence of ototoxicity but formal audiology testing was not performed in the studies using gentamicin. Such concerns are probably minimal with citrate and taurolidine, as a result of their different mechanism of action.

One might make the objection that the difference between definitions of CRB could have influenced the overall risk. Four definitions of CRB were used in the included trials, more [14–16,18–20] or less [2,17] restrictive. Given that only two studies (a small one [2] and a large one [17]) used the less restrictive definition, the difference between the size of the two cohorts (more versus less restrictive) precluded a meaningful subgroup analysis. Nevertheless, although the only study without a significant effect used a restrictive definition of CRB [16], most of the trials with a positive significant effect also used a restrictive definition. In addition, a more or less restrictive end point could modify the absolute risk, but should not change the RR. Thus, a marked bias in the overall results appears unlikely.

On the other hand, we were concerned by the fact that the risk reduction could have been overestimated as a result of the recording of CRB relapses (potentially more frequent in the control group) as new CRB episodes. In one of the two largest studies, there was no information about the number of infected patients [18]. In the remaining trials, the number of CRB episodes and infected patients coincided, except in one [15] in which the second CRB episode observed in four patients was due to a micro-organism different from that causing the first CRB, thus excluding a relapse. After exclusion from the meta-analysis of the study [18] without information on the number of patients with CRB, the overall risk ratio still showed a strong protective effect of ALS, again supporting the overall results of this meta-analysis.

Conclusion

Catheter interdialytic locking with an ALS reduces the incidence of CRB by about a factor 3. However, the achieved incidence of CRB in the ALS groups is similar to published reports from units with low CRB incidence (and presumably stricter hygienic measures). The limited follow-up of studies included in this meta-analysis does not exclude the onset of adverse events or bacterial resistance with longer use of ALS.

Conflict of interest statement. None declared.

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