

Meta-analysis: Antibiotics for Prophylaxis against Hemodialysis Catheter–Related Infections

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Background: Catheter-related infections cause morbidity and mortality in patients undergoing hemodialysis.

Purpose: To examine whether topical or intraluminal antibiotics reduce catheter-related bloodstream infection compared with no antibiotic therapy in adults undergoing hemodialysis.

Data Sources: Electronic databases, trial registries, bibliographies, and conference proceedings up to October 2007, with no language restrictions.

Study Selection: Two reviewers independently selected randomized, controlled trials using topical or intraluminal antibiotics for prophylaxis of infection in adults with catheters who are undergoing hemodialysis.

Data Extraction: Two independent reviewers assessed studies for inclusion, quality, and extracted data.

Data Synthesis: Fixed-effects models were used to estimate pooled rate ratios for outcomes. Topical antibiotics reduced the rate of bacteremia (rate ratio, 0.22 [95% CI, 0.12 to 0.40]; 0.10 vs. 0.45

case of bacteremia per 100 catheter-days), exit-site infection (rate ratio, 0.17 [CI, 0.08 to 0.38]; 0.06 vs. 0.41 case of infection per 100 catheter-days), need for catheter removal, and hospitalization for infection. Intraluminal antibiotics reduced the rate of bacteremia (rate ratio, 0.32 [CI, 0.22 to 0.47]; 0.12 vs. 0.32 case of bacteremia per 100 catheter-days) and need for catheter removal. Intraluminal antibiotics did not significantly reduce the rate of exit-site infection, and no hospitalization data were available for these agents.

Limitations: The evidence base included only 16 trials, and most had less than 6 months of follow-up. Only one third of studies were blinded. Publication bias was evident.

Conclusion: Both topical and intraluminal antibiotics reduced the rate of bacteremia as well as the need for catheter removal secondary to complications. Whether these strategies will lead to antimicrobial resistance and loss of efficacy over longer periods remains unclear.

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Although arteriovenous fistulas are the preferred vascular access for patients receiving long-term hemodialysis, central venous catheters remain a common form of access for many patients (1, 2). In North America, catheters are currently used in as many as 60% to 70% of incident and 30% to 40% of prevalent patients undergoing hemodialysis (1, 3). Catheter use is associated with increased patient morbidity and mortality, including a 10- to 20-fold greater risk for bacteremia than with fistulas (2). The resulting 0.16 to 0.66 catheter-related bloodstream infection that occurs for every 100 catheter-days may partly explain the 2- to 3-fold increased risk for death associated with catheter use among patients undergoing hemodialysis (2, 4, 5).

Techniques to reduce catheter-related infection risk include strict adherence to sterile technique and use of chlorhexidine or povidone–iodine cleaning solutions with catheter care (2, 6, 7). Recent strategies to further reduce catheter-related infection rates include use of antibiotic

ointments applied around the catheter exit site and antibiotics locked in the intraluminal portion of the catheter between dialysis sessions. However, many studies of these strategies are limited by small sample sizes and short follow-up, and some are published only in abstract form. In addition, because these interventions are not without risk or cost, the role of antibiotic prophylaxis for catheter-related infection remains unclear (8). To help clarify the role of these strategies, we reviewed randomized, controlled trials (RCTs) that assessed the efficacy of topical and intraluminal antibiotics for primary prophylaxis against catheter-related bloodstream infection in adult hemodialysis patients.

METHODS

Data Sources and Searches

Two reviewers searched MEDLINE (1966 through October 2007), EMBASE (1980 through October 2007), and Cochrane Central Register of Controlled Trials (1996 through October 2007) according to a standardized protocol by using the OVID search engine. We developed the following 3 comprehensive search themes by using text word and database-specific thesaurus terms: catheter-related bloodstream infection (searching for *catheter-related bloodstream infection*, *bacteremia*, or *septicemia*), dialysis (searching for *renal dialysis*), and *catheter* (searching for *indwelling catheter*, *catheterization*, *central venous catheter*, or *hemodialysis catheter*). We combined these themes by using

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the Boolean “and” operator. We used a filter described by Egger and colleagues (9) to limit our search to RCTs. We supplemented citations identified from electronic databases by reviewing the reference lists of all identified research and review articles, reviewing abstracts of the American Society of Nephrology Annual Meeting from 1999 to 2006, and searching clinical trial registries (www.clinicaltrials.gov, www.isrctn.org, www.vacsp.gov, and www.controlled-trials.com/mrct).

Study Selection

The 2 reviewers independently evaluated articles for eligibility in a 2-stage procedure. In the first stage, all identified abstracts were reviewed. In the second stage, we performed a full-text review of articles that met the inclusion criteria and articles for which there was uncertainty as to eligibility. Articles selected by either reviewer were reviewed by both reviewers in the second stage and evaluated for inclusion and exclusion criteria. Inclusion criteria were study design (RCT), study population (adults receiving long-term hemodialysis using a central venous catheter), intervention (use of an antibiotic applied topically to the catheter exit site or instilled intraluminally into the catheter), comparison (with another or no antimicrobial agent), and outcome

Context

Catheter-related infections are a major cause of illness among hemodialysis patients.

Contribution

This systematic review found 16 randomized trials that evaluated antibiotic prophylaxis for adults receiving long-term hemodialysis with a central venous catheter. The trials assessed the potential benefits of applying antibiotics topically to the catheter exit site or instilling them intraluminally into the catheter. Compared with no antibiotic therapy, prophylaxis with either topical or intraluminal antibiotics reduced bloodstream infections and the need for catheter removals.

Caution

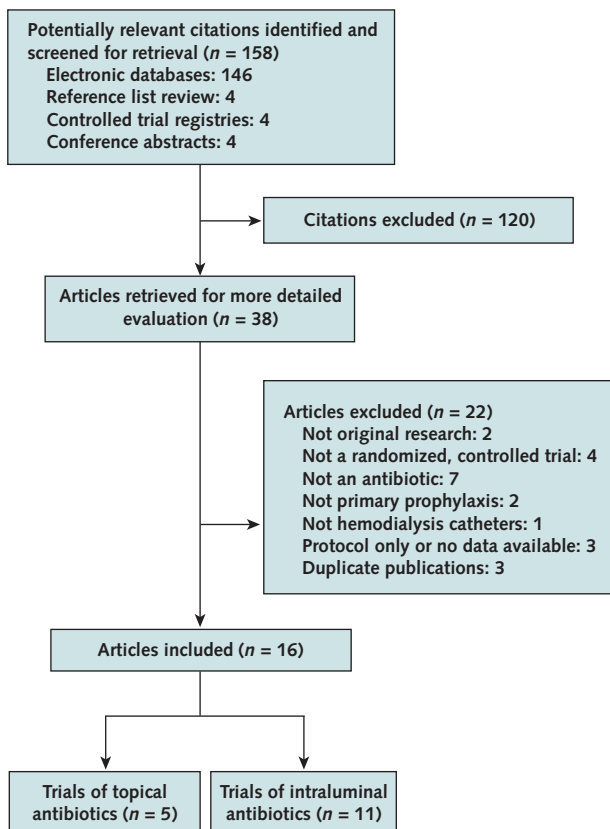
Most trials were short in duration and were not blinded.

Implication

Topical or intraluminal antibiotic prophylaxis may reduce catheter-related bloodstream infections in hemodialysis patients.

—The Editors

Figure 1. Study flow diagram.



(catheter-related bloodstream infection rate or secondary outcomes of interest). Both published and unpublished studies were eligible for inclusion regardless of language. We excluded studies in children and studies in which an antibiotic was used for treating an established line infection or for prophylaxis after a previous catheter-related bloodstream infection.

Data Extraction and Quality Assessment

We performed data extraction and reporting according to the recommendations of the QUORUM (Quality of Reporting of Meta-analyses) statement (10). Both reviewers independently extracted data from all primary studies that fulfilled the inclusion criteria; disagreement was resolved by consensus. The primary outcome was rate of catheter-related bloodstream infection by any organism, commonly defined as a positive blood culture in a febrile, catheter-dependent patient in the absence of alternative sources of infection on clinical evaluation. The secondary outcomes were rates of *Staphylococcus aureus*, catheter-related bloodstream infection, catheter exit-site infection, catheter removal secondary to complications, hospitalization for infection, death, adverse events, or isolation of antimicrobial-resistant organisms. The 2 reviewers independently scored the methodological quality of the studies, including the Jadad score (11). Allocation concealment was considered adequate if the study used an off-site or independent source to assign treatment or used opaque, sealed envelopes for assignment. We contacted authors of stud-

Table 1. Description of Included Trials*

Study, Year (Reference)	Country	Patients, n	Mean Follow-up, d	Hemodialysis Catheter Type; Location; Participants with Prevalent Catheters	Co-intervention
Topical antibiotic trials					
Sesso et al., 1998 (16)	Brazil	136	34	Nontunneled; 29% IJ, 71% SC; 0%	Aseptic technique
Krishna et al., 2001 (17)	India	174	24	Temporary; IJ, Fem; NR	Povidone-iodine
Johnson et al., 2002 (18)	Australia	50	40	Tunneled; 100% IJ; 0%	Aseptic technique; povidone-iodine, 10%
Lok et al., 2003 (20)	Canada	169	143	Tunneled; 100% IJ; 67%	Aseptic technique; chlorhexidine, 0.5%
Johnson et al., 2005 (19)	Australia	101	95‡	Tunneled; 100% IJ; 0%	Aseptic technique; povidone-iodine, 10%
Intraluminal antibiotic trials					
Cooper and Saad, 1999 (21)	United States	36	86	Tunneled; NR; 100%	NR
Pervez et al., 2002 (22)	United States	36	87	Tunneled; 100% IJ; 0%	Aseptic technique; povidone-iodine, 10%; sterile plastic bag over catheter hub
Dogra et al., 2002 (23)	Australia	83	75	Tunneled; 91% IJ, 9% SC; 0%	Aseptic technique; nasal mupirocin, chlorhexidine or iodine
McIntyre et al., 2004 (24)	United Kingdom	50	114	Tunneled; IJ, SC; 0%	NR
Betjes and van Agteren, 2004 (25)	Netherlands	58	59	24% tunneled, 76% nontunneled; 82% IJ or SC, 18% Fem; 0%	Aseptic technique; nasal mupirocin, chlorhexidine or iodine
Bleyer et al., 2005 (26)	United States	60	78	86% tunneled, 14% nontunneled; NR; 0%	NR
Zhang et al., 2006 (27)	China	101	92	Tunneled; NR; NR	NR
Nori et al., 2006 (28)	United States	62	101	Tunneled; 100% IJ; 100%	NR
Kim et al., 2006 (29)	Korea	120	38	Temporary; 100% IJ; 93%	National Kidney Foundation infection prophylaxis guidelines
Saxena et al., 2006 (15)	Saudi Arabia	96	414	Tunneled; 74% IJ, 26% SC; 0%	NR
Al-Hwiesh and Abdul-Rahman, 2007 (30)	Saudi Arabia	63	236	Tunneled; 89% IJ, 11% Fem; 0%	Aseptic technique; iodine solution

* Fem = femoral vein; IJ = internal jugular vein; NR = not reported; SC = subclavian vein.

† All trials administered the prophylactic antibiotic at the end of each dialysis session, except for the study by Lok et al. (20), in which polysporin was applied after each dialysis session for 2 weeks and then once per week thereafter.

‡ Median.

§ Medihoney Pty, Brisbane, Australia.

|| Nori et al. (28) compared 3 groups: a gentamicin and citrate lock group (n = 20), a minocycline and EDTA lock group (n = 21), and a heparin-only control group (n = 20).

ies published only in abstract form to obtain additional study information and confirm final results.

Statistical Analysis

We summarized outcomes from trials by using rate ratios (number of events per 100 catheter-days in the prophylaxis group vs. the control group) to best account for studies with more than 1 infection per patient, as well as the varying follow-ups between groups. For studies in which 1 group contained no events, we approximated rate ratios by adding 0.05 to each group of the trial (9). Because of the differences in antimicrobial application site, we analyzed results for topical and intraluminal antibiotic agents separately. We further stratified studies by individual antibiotic in secondary

analyses. We used fixed-effects models created by using the inverse variance method to produce pooled rate ratios with 95% CIs for study outcomes in the primary analysis (9). We performed sensitivity analyses by using risk ratios (number of events per patient in the prophylaxis group vs. the control group) as the measure of effect, counting the first infectious event per patient, in fixed-effects models of Mantel and Haenszel (9). Similarly, we analyzed mortality outcomes by using risk ratios. We evaluated the presence of heterogeneity across trials by using the *I*² statistic, which quantifies the percentage of variability that can be attributed to between-study differences (12). Because we found no significant heterogeneity, we did not perform random-effects anal-

Table 1—Continued

Antimicrobial and Anticoagulant Used		Mean Age, y	Diabetes Mellitus, %	Outcomes Reported
Control Group	Intervention Group†			
Povidone-iodine, 10%; heparin, 1000 U/mL	Mupirocin ointment, 2%; heparin, 1000 U/mL	47	18	Bacteremia, <i>Staphylococcus aureus</i> bacteremia, exit-site infection, catheter removal, hospitalization for infection, adverse events
None, NR	Mupirocin ointment, 2%; NR	NR	NR	<i>S. aureus</i> bacteremia
None; heparin, 1000 U/mL	Mupirocin ointment, 2%; heparin, 1000 U/mL	55	40	Bacteremia, <i>S. aureus</i> bacteremia, exit-site infection, catheter removal, adverse events, antimicrobial resistance
Placebo ointment; heparin, 10 000 U/mL	Polysporin triple-antibiotic ointment; heparin, 10 000 U/mL	66	62	Bacteremia, <i>S. aureus</i> bacteremia, exit-site infection, catheter removal, hospitalization for infection, mortality
Mupirocin ointment, 2%; heparin, 1000 U/mL	Medihoney§; heparin, 1000 U/mL	58	35	Bacteremia, <i>S. aureus</i> bacteremia, exit-site infection, adverse events, antimicrobial resistance
None; heparin, 5000 U/lumen	Gentamicin, 40 mg/mL; none	NR	NR	Bacteremia
None; heparin, 1000 U/mL	Gentamicin, 20 mg/mL; citrate, 4.67%	50	42	Bacteremia, catheter removal, adverse events
None; heparin, 5000 U/mL	Gentamicin, 27 mg/mL; citrate, 1%	57	48	Bacteremia, <i>S. aureus</i> bacteremia, exit-site infection, adverse events, mortality
None; heparin, 5000 U/mL	Gentamicin, 5 mg/mL; heparin, 5000 U/mL	61	26	Bacteremia, <i>S. aureus</i> bacteremia, exit-site infection, catheter removal, adverse events
None; heparin, 5000 U/mL	Taurolidine, 1.35%; citrate, 4%	54	27	Bacteremia, <i>S. aureus</i> bacteremia, exit-site infection, catheter removal, adverse events
None; heparin	Minocycline, 3 mg/mL; EDTA, 30 mg/mL	54	39	Bacteremia, catheter removal
None; heparin, 45 mg/mL	Gentamicin, 4 mg/mL; heparin, 45 mg/mL	NR	NR	Bacteremia, adverse events
None; heparin, 5000 U/mL	Gentamicin, 4 mg/mL; citrate, 3.13% or minocycline, 3 mg/mL; EDTA, 30 mg/mL	58	56	Bacteremia, mortality
None; heparin, 1000 U/mL	Cefazolin, 10 mg/mL, and gentamicin, 5 mg/mL; heparin, 1000 U/mL	55	53	Bacteremia, <i>S. aureus</i> bacteremia, adverse events
None; heparin, 5000 U/mL	Cefotaxime, 10 mg/mL; heparin, 5000 U/mL	59	100	Bacteremia, <i>S. aureus</i> bacteremia, exit-site infection, catheter removal, adverse events, antimicrobial resistance, mortality
None; heparin, 5000 U/mL	Vancomycin, 25 mg/mL, and gentamicin, 40 mg/mL; heparin, 5000 U/mL	47	21	Bacteremia, exit-site infection

yses. We also tested for publication bias by using funnel plots, the Begg test for asymmetry, and an Egger test for trials of intraluminal antibiotics (9). We did not test for publication bias for trials of topical antimicrobial agents because of the small number of these studies. All statistical analyses were performed by using Stata, version 9.2 (Stata, College Station, Texas).

RESULTS

Identification of Studies

Figure 1 summarizes the progress through the stages of the systematic review. Of 158 unique citations, we excluded 120 on initial screening, leaving 38 articles for full-text review. We identified duplicate publications (13) of 3 studies; 2 were full reports of RCTs previously published as abstracts, whereas 1 (14) overlapped with a separately published study (15). Of the 16 articles that met inclusion criteria for the systematic review, 13 were published in peer-reviewed journals and 3 were published in abstract form only. Both reviewers agreed on the studies selected for meta-analysis and their validity assessments.

Study Characteristics

Table 1 shows the details of the trials that met our inclusion criteria. A total of 1395 participants were included from 16 trials. We identified 5 trials of topical antibiotics comprising 630 patients who were followed for a total of 45 929 catheter-days (16–20). Three trials (16–18), comprising 360 participants, compared mupirocin ointment with no antibiotic prophylaxis, whereas 1 trial (20) compared polysporin triple-antibiotic ointment with no prophylaxis. One trial (19) compared mupirocin ointment with Medihoney (Medihoney Pty, Brisbane, Australia), an irradiated antibacterial honey. This was the only study in which both study groups included an antimicrobial agent, and we could therefore not include it in the meta-analysis comparing antibiotic prophylaxis with no prophylaxis. We identified 11 trials that compared intraluminal antibiotics with a strategy consisting of no antibiotic prophylaxis, comprising 765 patients followed for a total of 100 167 catheter-days (15, 21–30). The interventions consisted of gentamicin in 6 trials (21–24, 27, 28) comprising 347 participants, minocycline in 2 trials

Table 2. Quality Assessment of Included Trials*

Study, Year (Reference)	Allocation Concealment	Randomized	Blinding	Intention to Treat	Loss to Follow-Up Described	Loss to Follow-Up, %	Source of Funding	Jadad Score
Sesso et al., 1998 (16)	Yes	Yes	No	Yes	Yes	0	Public	3
Krishna et al., 2001 (17)	Unclear	Yes	NR	Unclear	No	NR	NR	1
Johnson et al., 2002 (18)	Yes	Yes	No	Yes	Yes	0	NR	3
Lok et al., 2003 (20)	Yes	Yes	Patients, clinicians, microbiologists, pharmacists, data managers	Yes	Yes	0	Public	5
Johnson et al., 2005 (19)	Yes	Yes	No	Yes	Yes	0	NR	3
Cooper and Saad, 1999 (21)	Unclear	Yes	NR	Unclear	No	NR	NR	1
Pervez et al., 2002 (22)	Unclear	Yes	No	Unclear	No	NR	Private	2
Dogra et al., 2002 (23)	Unclear	Yes	Investigators, patients, renal and microbiology staff	Yes	Yes	0	NR	5
McIntyre et al., 2004 (24)	Yes	Yes	No	Yes	No	NR	NR	2
Betjes and van Agteren, 2004 (25)	Unclear	Yes	No	Unclear	No	NR	NR	2
Bleyer et al., 2005 (26)	Unclear	Yes	All except pharmacists	Unclear	No	NR	NR	4
Zhang et al., 2006 (27)	Unclear	Yes	NR	Unclear	No	NR	NR	1
Nori et al., 2006 (28)	Unclear	Yes	No	No	Yes	0	NR	3
Kim et al., 2006 (29)	Unclear	Yes	Patients, hemodialysis nurses	Yes	No	NR	NR	4
Saxena et al., 2006 (15)	Yes	Yes	Investigators, microbiologists, hemodialysis staff	No	Yes	2	NR	5
Al-Hwiesh and Abdul-Rahman, 2007 (30)	Unclear	Yes	No	Unclear	No	NR	NR	1

* NR = not reported.

(25, 26, 28) comprising 102 participants, taurolidine in 1 trial (25), cefazolin and gentamicin in 1 trial (29), cefotaxime in 1 trial (15), and vancomycin and gentamicin in 1 trial (30). Nori and colleagues (28) used 2 active comparator groups in their study in addition to the control group.

The sample size of the included trials ranged from 36 to 174 participants. The mean age of participants was 55 years, 58% were men, and the prevalence of diabetes ranged from 18% to 100%. Most trials (11 of

16 trials) (15, 18–24, 27, 28, 30) studied tunneled catheters only; however, 5 trials (16, 17, 25, 26, 29) included nontunneled catheters. In 10 studies, patients were randomly assigned after insertion of a new catheter, whereas patients with prevalent catheters were selected in 4 studies (20, 21, 28, 29).

Validity Assessment

The quality of the trials varied (Table 2). Five trials were reported as blinded, although only 1 trial (20) re-

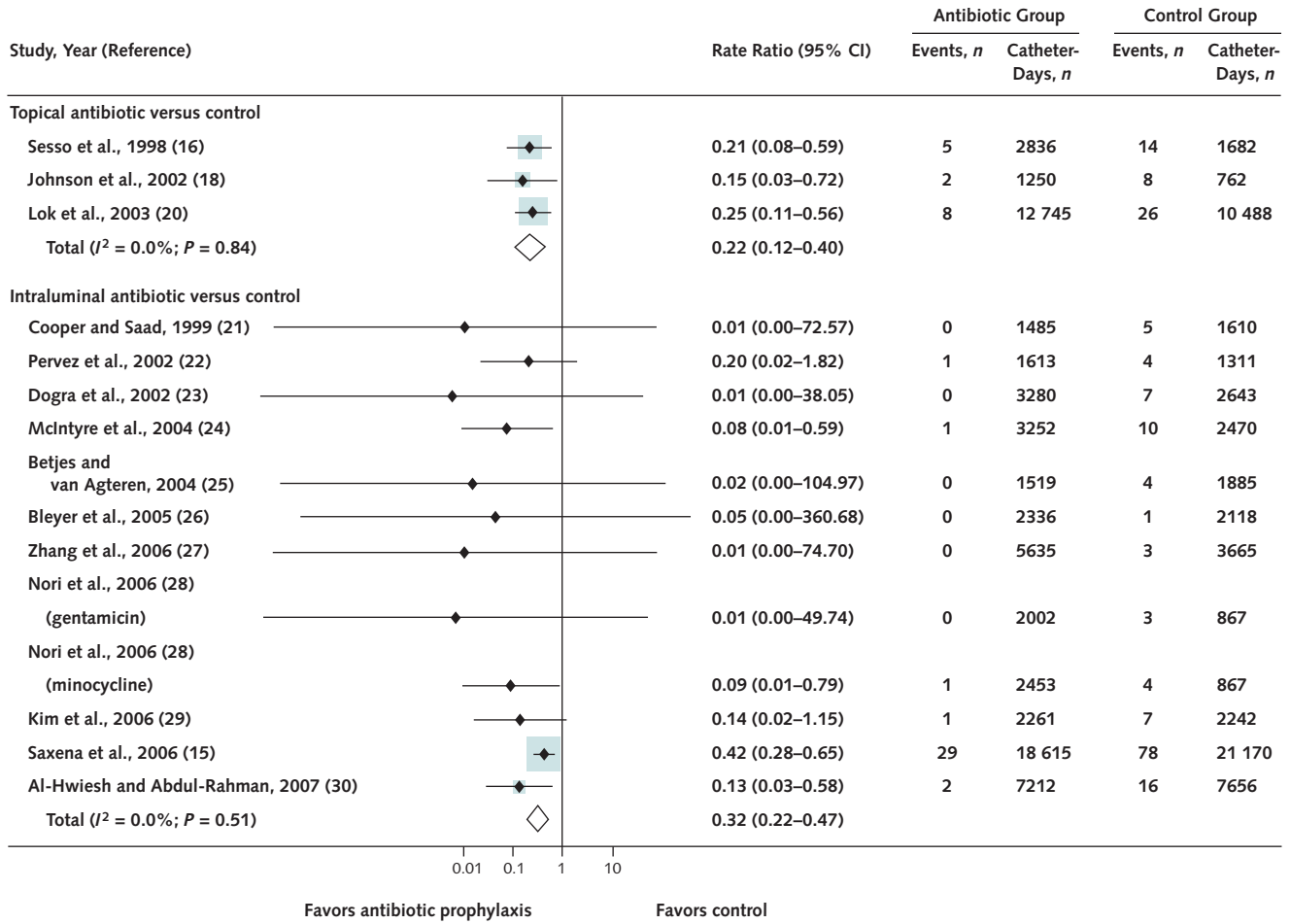
Table 3. Pooled Outcomes from Trials of Topical or Intraluminal Antibiotics versus No Antibiotics

Antibiotic	Catheter-Related Bloodstream Infection		<i>Staphylococcus aureus</i> Catheter-Related Bloodstream Infection		Exit-Site Infection	
	Trials, n	Rate Ratio (95% CI)	Trials, n	Rate Ratio (95% CI)	Trials, n	Rate Ratio (95% CI)
Topical antibiotics						
All topical agents	3	0.22 (0.12–0.40)	4	0.14 (0.06–0.30)	3	0.17 (0.08–0.38)
Mupirocin	2	0.19 (0.08–0.45)	–	–	–	–
Polysporin triple-antibiotic ointment	1	0.25 (0.12–0.56)	–	–	–	–
Intraluminal antibiotics						
All intraluminal agents	11†	0.32 (0.22–0.47)	5	0.62 (0.32–1.19)	4	0.82 (0.47–1.43)
Gentamicin	6	0.09 (0.02–0.38)	–	–	–	–
Taurolidine	1	0.02 (0.00–104.97)	–	–	–	–
Minocycline	2	0.09 (0.01–0.72)	–	–	–	–
Cefazolin–gentamicin	1	0.14 (0.02–1.15)	–	–	–	–
Cefotaxime	1	0.42 (0.28–0.65)	–	–	–	–
Vancomycin–gentamicin	1	0.13 (0.03–0.58)	–	–	–	–

* Refers to all-cause mortality for topical antibiotics and to mortality attributed to catheter-related bacteremia for intraluminal antibiotics.

† Total sums to >11 because a study separately compared 2 different antibiotics with controls.

Figure 2. Forest plot of studies comparing the effect of topical or intraluminal antibiotics versus no antibiotics on the rate of catheter-related bloodstream infection in hemodialysis patients.



Solid diamonds represent point estimates, lines represent 95% CIs, and shaded boxes represent the percentage of weight contributed by each study. Open diamonds represent pooled results and are centered on the pooled point estimate, with length representing the pooled 95% CI.

Table 3—Continued

Catheter Removal for Complication		Hospitalization for Infection		Mortality*	
Trials, n	Rate Ratio (95% CI)	Trials, n	Rate Ratio (95% CI)	Trials, n	Rate Ratio (95% CI)
3	0.36 (0.25–0.52)	2	0.24 (0.12–0.47)	1	0.22 (0.07–0.74)
–	–	–	–	–	–
–	–	–	–	–	–
5	0.37 (0.23–0.59)	0	–	3	0.55 (0.24–1.28)
–	–	–	–	–	–
–	–	–	–	–	–
–	–	–	–	–	–
–	–	–	–	–	–
–	–	–	–	–	–

ported using a placebo control. Six trials reported methods to ensure allocation concealment. Seven trials reported on losses to follow-up; 2% of participants or fewer were lost in all these studies. We identified no important baseline differences between treatment groups in the trials.

Topical Antibiotics

Table 3 summarizes pooled results for studies of topical antibiotics. Prophylaxis with topical agents significantly reduced the rate of catheter-related bloodstream infections (0.10 vs 0.45 case of bacteremia per 100 catheter-days; rate ratio 0.22 [95% CI, 0.12 to 0.40]; 3 trials, $I^2 = 0\%$) (Figure 2). When analyses were further stratified by topical agent (Table 3), reductions in bacteremia remained significant for both topical mupirocin and polysporin triple-antibiotic ointment. We found that topical agents decreased the rate of *S. aureus* bacteremia (0.08 vs. 0.58 case of bacteremia per 100 catheter-days; rate ratio, 0.14 [CI, 0.06 to 0.30]; 4 trials, $I^2 = 0\%$). We observed a reduction in the rate of exit-site infection (0.06 vs. 0.41 infection per 100 catheter-days; rate ratio, 0.17 [CI, 0.08 to 0.38]; 3 trials, $I^2 = 0\%$). In addition, we found that use of topical agents reduced the rate of catheter removal due to complications on the basis of 3 trials (Figure 3) and the rate of hospitalization for infection on the basis of 2 trials. The trial by Lok and colleagues (20) was the only trial to report on mortality, which was significantly lower for patients receiving polysporin triple-antibiotic ointment than for those who received placebo. In the only trial with an active

comparator group, no difference was found in bacteremia rates between those who received topical mupirocin ointment and those who received topical antibacterial honey (19).

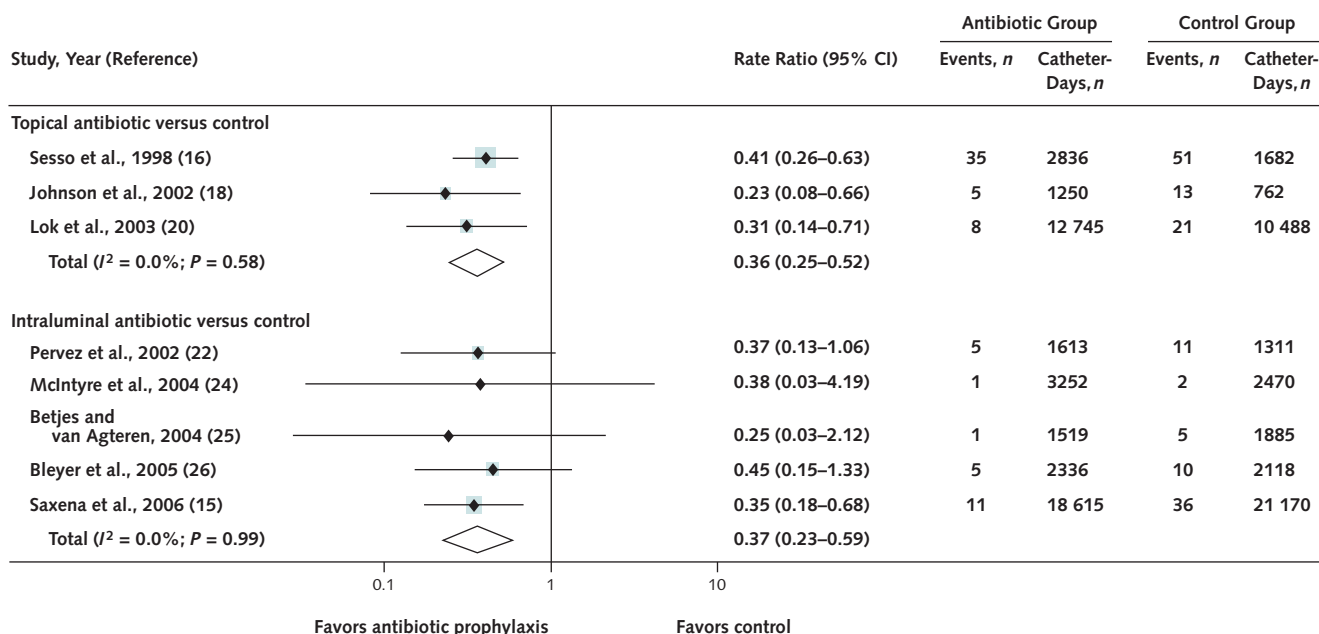
Intraluminal Antibiotics

Table 3 summarizes pooled results for studies of intraluminal antibiotics. Prophylaxis with intraluminal agents significantly reduced the rate of catheter-related bloodstream infection (0.12 vs. 0.32 case of bacteremia per 100 catheter-days; rate ratio, 0.32 [CI, 0.22 to 0.47]; 11 trials, $I^2 = 0\%$) (Figure 2). When further stratified by antibiotic type (Table 3), the reductions in bacteremia rates remained significant for locks containing gentamicin, minocycline, cefotaxime, and vancomycin and gentamicin but not for those containing taurolidine or cefazolin and gentamicin. We found no significant reduction in the rate of *S. aureus* bacteremia or that of exit-site infection. On the basis of 5 trials, intraluminal antibiotics reduced the rate of catheter removal due to complication by 63% (Figure 3). The results from 3 trials (14, 23, 28) indicate a non-statistically significant trend toward fewer deaths attributed to catheter-related infection for patients who received intraluminal antibiotics compared with control patients.

Adverse Events and Antimicrobial Resistance

Adverse event reporting was limited in most trials. Ototoxic symptoms were reported in 4 of 42 patients receiving a high concentration of intraluminal gentamicin in

Figure 3. Forest plot of studies comparing the effect of topical or intraluminal antibiotics versus no antibiotics on the rate of catheter removal due to complication in hemodialysis patients.



Solid diamonds represent point estimates, lines represent 95% CIs, and shaded boxes represent the percentage of weight contributed by each study. Open diamonds represent pooled results and are centered on the pooled point estimate, with length representing the pooled 95% CI.

1 trial (23); however, no adverse events were reported in 7 other studies of intraluminal antibiotics (15, 21, 22, 24, 25, 27, 29), including 5 gentamicin trials. No adverse reaction was reported for topical antibiotics. No mupirocin- or cefotaxime-resistant strains were isolated among the 3 trials that reported monitoring for drug-resistant bacterial isolates (15, 18, 19).

Sensitivity Analysis

In analyses that used risk ratios for first bloodstream infection per patient, we again observed significant reductions in the risk for bacteremia with topical antibiotics (risk ratio, 0.29 [CI, 0.17 to 0.49]) and with intraluminal antibiotics (risk ratio, 0.20 [CI, 0.13 to 0.30]), suggesting that the results of the primary analysis were not dependent on repeated infections in the same patients over time. To explore the influence of the heavily weighted trial by Saxena and colleagues (15) on reducing the magnitude of the treatment effects, we performed analyses that excluded this trial. In the absence of this study, we observed a greater reduction in the relative rate of catheter-related bloodstream infection with intraluminal antibiotic prophylaxis (rate ratio, 0.11 [CI, 0.05 to 0.25]). Similarly to the primary analysis, we observed no statistically significant reductions in the rates of catheter-related bloodstream infection with *S. aureus* (rate ratio, 0.30 [CI, 0.06 to 1.45]) or exit-site infection (rate ratio, 0.63 [CI, 0.31 to 1.27]) with intraluminal antibiotics.

Publication Bias

We found evidence of publication bias among studies of intraluminal agents by using Egger ($P = 0.001$) and Begg ($P = 0.085$) tests. Analysis of the funnel plot suggested an absence of publication of small studies that showed lesser benefits for intraluminal antibiotics than seen in the identified trials.

DISCUSSION

In this meta-analysis of 15 studies comprising 1294 patients undergoing hemodialysis, both topical and intraluminal antibiotic prophylaxis reduced the rate of catheter-related bloodstream infection compared with no prophylaxis. Topical antibiotic prophylaxis also reduced the rate of exit-site infection, although we did not observe this benefit for pooled studies of intraluminal antibiotics. Our analysis also revealed that use of topical or intraluminal agents reduced the rate of catheter removal due to complication. Rates of hospitalization for infection were reduced with topical antibiotic prophylaxis; however, no studies of intraluminal antibiotics reported this outcome.

These findings provide evidence for the short-term efficacy of antibiotic prophylaxis. Assuming 95 000 episodes of catheter-related bacteremia annually in the U.S. population undergoing hemodialysis (1, 2), even 50% uptake of topical antibiotic use in prevalent hemodialysis patients might prevent as many as 37 000 episodes of bloodstream

infection per year. This effect is noteworthy because catheter-related bloodstream infection is associated with high rates of hospitalization (31), treatment-related costs (32), and significant morbidity and mortality and in many cases requires the removal of the catheter (31). With admission costs associated with catheter-related infections in the U.S. population undergoing hemodialysis estimated to average \$23 451 per hospitalization (33), such a reduction would be expected to translate into substantial cost savings.

The clinical benefit of antibiotic prophylaxis is further supported by our finding that both topical and intraluminal antibiotics reduce the need for catheter removal due to complication, which may help preserve critical vascular access sites. Finally, results from 1 study suggest that prophylaxis against catheter-related infection with topical polysporin may reduce all-cause mortality, although this must be interpreted with caution because this result was limited to a secondary outcome and was not observed in other studies. Further research is needed to prove reductions in all-cause mortality with these strategies.

Despite the accumulation of RCTs supporting the efficacy of antibiotic prophylaxis for catheter-related bloodstream infections, the implementation of these agents in clinical practice has been limited. One reason is the potential for development of antimicrobial resistance and speculation that this may lead to the emergence of drug-resistant bacterial isolates and loss of efficacy over time (8, 34). Mupirocin resistance has been reported in other settings (35–37), and although isolation of antibiotic-resistant isolates was not observed in the RCTs that included monitoring for drug-resistant organisms, longer durations of exposure may be needed for resistance to evolve (15, 34). The potential for development of antibiotic resistance with long-term use warrants further study, and hemodialysis centers that use antibiotic prophylaxis should implement surveillance programs and report the emergence of drug-resistant isolates to clarify this concern.

Although recent guidelines published by the Canadian Society of Nephrology (7) have recommended the use of a topical antibiotic for prophylaxis, the 2006 update to the vascular access guidelines of the National Kidney Foundation Dialysis Outcomes Quality Initiative refrained from making such a recommendation (2). Given the high risk for bloodstream infections and poor clinical outcomes, we feel the demonstrated efficacy of topical agents supports their use. Because preventing bacteremia is a worthwhile objective in its own right, clinicians may consider using intraluminal antibiotics to reduce rates of catheter-related bloodstream infection; however, they should recognize that this is not yet proven to result in reduced hospitalization or improved patient survival.

Our study has limitations that stem from the designs of the individual trials as well as the methods of meta-analysis itself. First, several trials lacked adequate allocation concealment and blinding, which may leave them vulnerable to bias and overestimation of the beneficial effects of

antibiotic prophylaxis. However, the studies that contributed the most weight to this meta-analysis were also the most methodologically stringent, and given the homogeneity of results across studies, it is unlikely that smaller, poorer-quality trials significantly biased the pooled estimates. Second, several types of antimicrobial agents were used in individual trials, and although significant reductions in rates of catheter-related bloodstream infections were observed for many of these individual agents, we do not know which is the most effective of these agents for prophylaxis against bacteremia. In addition, no trial addressed the effect of combining topical with intraluminal antibiotics, although the effectiveness of each strategy on its own would suggest that combination therapy is not warranted. Third, many trials did not report important resource and clinical outcomes, such as hospitalization or death, although bacteremia and catheter removal due to complications are important and clinically relevant outcomes. Finally, most studies were of short duration and modest size, and generalizability is therefore limited.

All meta-analyses are inherently vulnerable to publication bias. We attempted to minimize this bias by searching sources of both published and unpublished material; however, we did detect evidence of publication bias among studies of intraluminal antibiotics. Although the smaller studies in this meta-analysis may bias estimates in favor of antibiotics, it is reassuring that the greatest weight in this analysis came from studies with the most conservative estimates, and we observed no significant heterogeneity between trials. Furthermore, given the strength of the observed effects, these results are unlikely to represent a type I error.

In summary, our meta-analysis indicates that antibiotics applied topically or intraluminally to catheters prevent catheter-related bloodstream infections and promote catheter survival, thus supporting their short-term use in adults with catheters who are undergoing hemodialysis. Further research in this area should focus on important clinical end points, including death; explore long-term efficacy; and resolve concerns about the development of antibiotic resistance.

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