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Mupirocin for preventing exit-site infection and peritonitis in patients undergoing peritoneal dialysis

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Abstract

Objectives. Recently, there have been increasing concerns about the emergence of mupirocin resistance and increased infections due to lowered inhibition of *Staphylococcus aureus*. We conducted this systemic analysis to find out whether the application of mupirocin was effective for the prevention of exit-site infection (ESI) and peritonitis in patients undergoing peritoneal dialysis (PD).

Methods. Recruited studies met the following criteria: they were randomized controlled trials or historical cohort studies; subjects consisted of adults (age, $\geq$ 18 years) undergoing PD; mupirocin treatment was administered to the therapy group and placebo or no treatment was administered to the control group. The primary extracted data were the difference in the episodes of ESI and peritonitis *S. aureus* or other organisms among treatment and control groups.

Results. Fourteen studies described in 13 articles and a total of 1233 patients versus 1217 controls were included in the analysis. Of the 13 articles, 6 were newly published articles that had not been analysed previously and 3 were randomized controlled trials. The application of mupirocin decreased the risk by 72% [95% confidence interval (CI): 0.60–0.81] in ESI and by 70% (95% CI 0.52–0.81) in peritonitis due to *S. aureus* among all patients undergoing PD. Treatment of mupirocin reduced the risks of ESI and peritonitis due to all organisms by 57% (95% CI: 0.46–0.66) and 41% (95% CI: 0.24–0.54), respectively. Based on the six newly published articles, the reduced risk rate for mupirocin therapy was found to be 80% (95% CI: 0.39–0.93, $P = 0.004$) in ESI and 91% (95% CI: 0.72–0.97, $P < 0.0001$) in peritonitis due to *S. aureus*; 70% (95% CI: 0.47–0.82, $P < 0.0001$) in ESI and 42% (95% CI: 0.25–0.55, $P < 0.0001$) in peritonitis due to all organisms among mupirocin-treated and -untreated subjects. Based on the three randomized controlled trials, ESI and peritonitis due to *S. aureus* were found to be reduced by 73% (95% CI: 0.63–0.80, $P < 0.0001$) and 40% (95% CI: 0.17–0.56, $P = 0.002$), respectively. Interestingly, although mupirocin treatment can reduce the risk rate of ESI by 46% (95% CI: 0.35–0.55, $P < 0.00001$), it cannot decrease the risk rate of peritonitis due to all organisms ($P = 0.56$).

Conclusions. Mupirocin prophylaxis was effective on preventing ESI and peritonitis due to *S. aureus* and other organisms in PD patients.

Keywords: exit-site infection; mupirocin; peritoneal dialysis; peritonitis

Introduction

Peritonitis remains the most serious complication of peritoneal dialysis (PD). Gram-positive organisms such as *Staphylococcus* are among the common causes of peritonitis in PD patients. Exit-site infection (ESI) was mostly caused by *Staphylococcus aureus*. ESI was also considered as severe infection and independently predisposed the patients to peritonitis, and was estimated to occur at a rate of 0.11 events per patient-year [1–3]. Prevention of peritonitis and ESI was essential for successful long-term PD.

Mupirocin was most commonly used as a prophylaxis agent. It was a topical antibiotic with excellent activity against gram-positive organisms, but had little or no effect on *Pseudomonas* or other gram-negative bacteria. In a retrospective, historical cohort study, the routine application of mupirocin to the exit site with each dressing change was found to decrease the rate of ESI by one-third [4]. The routine application of an antibacterial cream or ointment to the catheter exit site was a strategy that had been studied to reduce the rate of peritonitis and was recommended by the International Society for Peritoneal Dialysis (ISPD) [5].

S. aureus has been historically the predominant gram-positive bacteria in ESI. Recently, however, trends have shown a shift in the distribution of causative organisms from gram-positive to gram-negative infection [6,7]. Infections with fungi, mycobacterium and other organisms have also been reported [8]. However, mupirocin did not afford protection against gram-negative or fungal infections. Increasing concerns about bacterial resistance, particularly in *S. aureus,* have been widely reported with the use of mupirocin ointment [9,10]. There were also concerns about

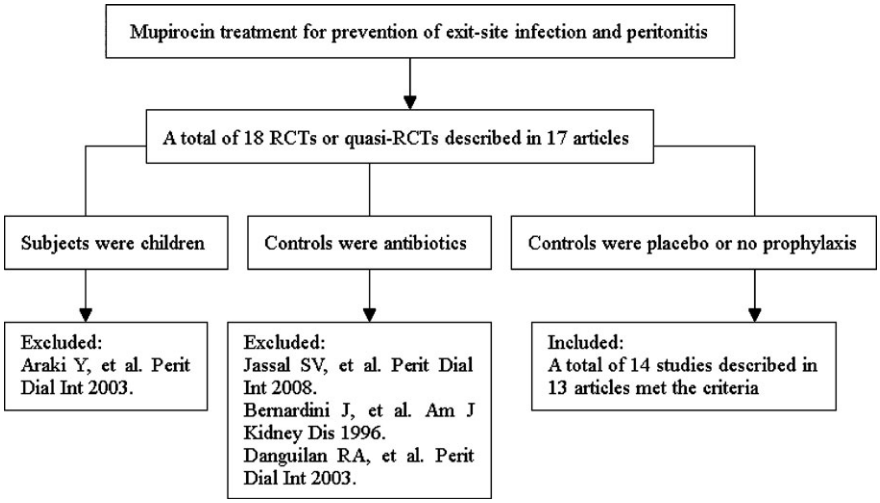

Fig. 1. Flow diagram for inclusion and exclusion of studies.

the emergence of mupirocin resistance among *S. aureus* isolates [11].

Several studies evaluated the efficacy of intranasal or cutaneous mupirocin application among the dialysis population [12,13]. Both of the studies demonstrated a risk reduction in the rate of *S. aureus* infection among mupirocin-treated patients, although the magnitude of effect varies considerably among different studies. Some of the studies involving mupirocin treatment dated back to the 1990s when ESI and peritonitis rates were much higher than those observed more recently. Thus, the applicability of these studies to contemporary practice was questionable.

To evaluate the benefits and harms of mupirocin treatment in PD patients, we conducted this systemic analysis to find out whether the application of mupirocin was effective on prevention of ESI and peritonitis in PD patients.

Methods

Searching strategy

Published human studies involving mupirocin for prevention of ESI and peritonitis in patients undergoing PD were identified through computerized literature searching using MEDLINE, EMBASE, Cochrane Database, Science Citation Index and the listed references of retrieved articles. Index search terms included the medical subject heading terms 'peritoneal dialysis', 'continuous ambulatory peritoneal dialysis', 'continuous cyclic peritoneal dialysis', 'mupirocin', '*S. aureus*', 'peritonitis' and 'exit-site infection'. The search was restricted to English-language trials published up to March 2009.

Inclusion and exclusion criteria

The following criteria were used in selecting studies for inclusion: (1) the research population consisted of adults (age $\geq$ 18 years) undergoing PD; (2) the study was a randomized controlled trial (RCT) or a cohort study; (3) mupirocin treatment was administered to the therapy group, and placebo or no therapy was administered to the control group; and (4) the primary outcome was a difference in the rate of *S. aureus* infection (ESI or peritonitis) among mupirocin-treated and -untreated patients undergoing PD. Studies comparing the efficacy of mupirocin with that of other antibiotics were excluded. Reviews, editorials, abstracts only and case reports were also excluded.

Data extraction

Extraction of data was performed by two investigators (Gaosi XU and Weiping TU) independently. Each investigator was blinded to another one's data extraction. Data from each trial were extracted using standard data extraction forms, verified for consistency and accuracy and entered into a computerized database. Extracted information including year of publication, study design, number of patients enrolled, patient characteristics (age, sex and percentage of nasal carriers of *S. aureus*), intervention (dosage, dosage form, frequency, duration, and site of application of mupirocin), duration of follow-up. When more than one publication of the same trial existed, only the publication with the most complete data was included. Further information obtained from authors was requested by written or electronic correspondence and included in this analysis. The quality of the RCTs was determined using Jadad's quality assessment score [14]. Discrepancies in data extraction were discussed, and resolution required consent from these two investigators.

Statistical analysis

Data from individual trials were analysed using the risk ratio (RR) measurement and its 95% confidence intervals (CI). Heterogeneity of treatment effects between studies was formally tested using the Q (heterogeneity χ^2) and I^2 statistics. When P-value for homogeneity was <0.05, a random effect model using the DerSimonian-Laird method was selected. In contrast, the fixed effect model was used.

For each outcome, publication bias was assessed by the funnel plot. Begg's test for the testing of publication bias was also performed by the STATA statistical software version 8.1 (Stata Corporation, College Station, TX, USA). A P-value of <0.05 was considered statistically significant. All statistical analyses were performed using the RevMan statistical software version 4.2 (Cochrane Library, UK) for the meta-analysis.

Results

Study inclusion

A total of 18 RCTs or cohort studies described in 17 articles met the inclusion criteria. One study was subsequently excluded for children subjects. Other three articles were excluded for the use of antibiotics in the control groups (Figure 1). Thus, a total of 14 studies described in 13 articles with 1233 patients versus 1217 controls were included in the analysis.

Table 1. Characteristics of studies comparing mupirocin prophylaxis with no prophylaxis in peritoneal dialysis populations

Reference	Year	Study design	Mupirocin administration	No. of subjects in the mupirocin group	No. of subjects in the control group	Episodes of ESI				Episodes of peritonitis			
						Study group		Control group		Study group		Control group	
						A	B	A	B	A	B	A	B
[15]	2007	Historical cohort	Nasal ointment	49	49	21	–	35	–	0	2	1	1
[16]	2005	Historical cohort	Cream	40	40	2	4	6	10	0	12	7	21
[17]	2004	Historical cohort	Cream	86	113	2	6	16	33	0	22	8	24
[18]	2003	Historical cohort	Cream	18	18	0	2	9	8	0	9	5	16
[19]	2003	RCTs	Nasal ointment	73	81	0	4	11	2	1	5	11	2
[20]	2000	Historical cohort	Cream	58	42	1	4	6	10	0	8	4	11
[21]	2000	Historical cohort	Cream	143	148	3	13	10	26	4	32	10	47
[22]	2000	Historical cohort	Nasal ointment	129	63	5	17	8	4	1	7	5	11
[23]	1999	Historical cohort	Nasal ointment	24	24	2	6	11	7	1	–	5	–
[24]	1999	RCTs	Nasal ointment	134	133	24	33	85	21	29	7	45	2
[4]	1998	Historical cohort	Cream	181	181	3	4	21	6	11	77	35	124
[4]	1998	Historical cohort	Cream	70	118	4	2	17	14	4	34	20	60
[25]	1996	RCTs	Nasal ointment	134	133	14	19	44	10	18	59	24	40
[26]	1993	Historical cohort	Nasal ointment	94	74	2	6	14	5	2	–	18	–

ESI: exit-site infection; RCTs: randomized controlled trials; A: no. of infection episodes caused by *S. aureus*; B: no. of infection episodes caused by other factors including other Gram-positive, Gram-negative, mixed infection, no growth and missing.

Study characteristics

The descriptive summary results for each study are reported in Table 1. Of the 14 studies [4,15–26], 3 were RCTs [19,24,25] in which prospective controls were used. All RCTs were of medium-high methodologic quality, according to Jadad's quality score [14]. The remaining 11 studies were nonrandomized historical cohort studies. Four studies [23–26] restricted the enrollment of patients with *S. aureus* nasal colonization; the remaining 10 trials included all patients, regardless of *S. aureus* colonization status. The site, frequency and duration of mupirocin treatment differed among all the studies.

Mupirocin treatment in preventing of exit-site infection

By using the random effects model and the fixed effects model, the summary RR values of mupirocin versus placebo or no prophylaxis for *S. aureus* and other organism infection among all PD patients were analysed. The application of mupirocin decreased the risk by 72% (95% CI: 0.60–0.81) in ESI due to *S. aureus* among all patients undergoing PD ($P < 0.0001$, Figure 2). Treatment of mupirocin reduced the risks of ESI due to all organisms by 57% (95% CI: 0.46–0.66, $P < 0.0001$, Figure 3). Based on the six newly published articles, the reduced risk rate for mupirocin treatment was found to be 80% (95% CI: 0.39–0.93, $P = 0.004$) in ESI due to *S. aureus* and 70% (95% CI: 0.47–0.82, $P < 0.0001$) in ESI due to all organisms among mupirocin-treated and -untreated subjects. Based on the three randomized controlled trials, ESIs due to *S. aureus* were found to be reduced by 73% (95% CI: 0.63–0.80, $P < 0.0001$). In addition, mupirocin treatment can reduce the risk rate of ESI by 46% (95% CI: 0.35–0.55, $P < 0.00001$) among all organisms infection.

Mupirocin treatment in preventing of peritonitis

Among patients undergoing PD, mupirocin therapy significantly reduced the rate of *S. aureus* infections risk by 70% (95% CI: 0.52–0.81) in peritonitis ($P < 0.00001$, Figure 4). The application of mupirocin reduced the risks of peritonitis due to all organisms by 41% (95% CI: 0.24–0.54, $P < 0.0001$, Figure 5). Based on the six newly published articles, the reduced risk rate for mupirocin treatment was found to be 91% (95% CI: 0.72–0.97, $P < 0.0001$) in peritonitis due to *S. aureus* and 42% (95% CI: 0.25–0.55, $P < 0.0001$) in peritonitis due to all organisms among mupirocin-treated and -untreated subjects. Based on the three randomized controlled trials, peritonitis due to *S. aureus* was found to be reduced by 40% (95% CI: 0.17–0.56, $P = 0.002$). Interestingly, mupirocin treatment cannot decrease the risk rate of peritonitis due to all organisms ($P = 0.56$).

Publication bias

The funnel plot of studies included in this meta-analysis did not disclose any publication bias. We conducted Begg's tests to evaluate the publication bias by STATA software and revealed no significant heterogeneity in the studies of meta-analysis.

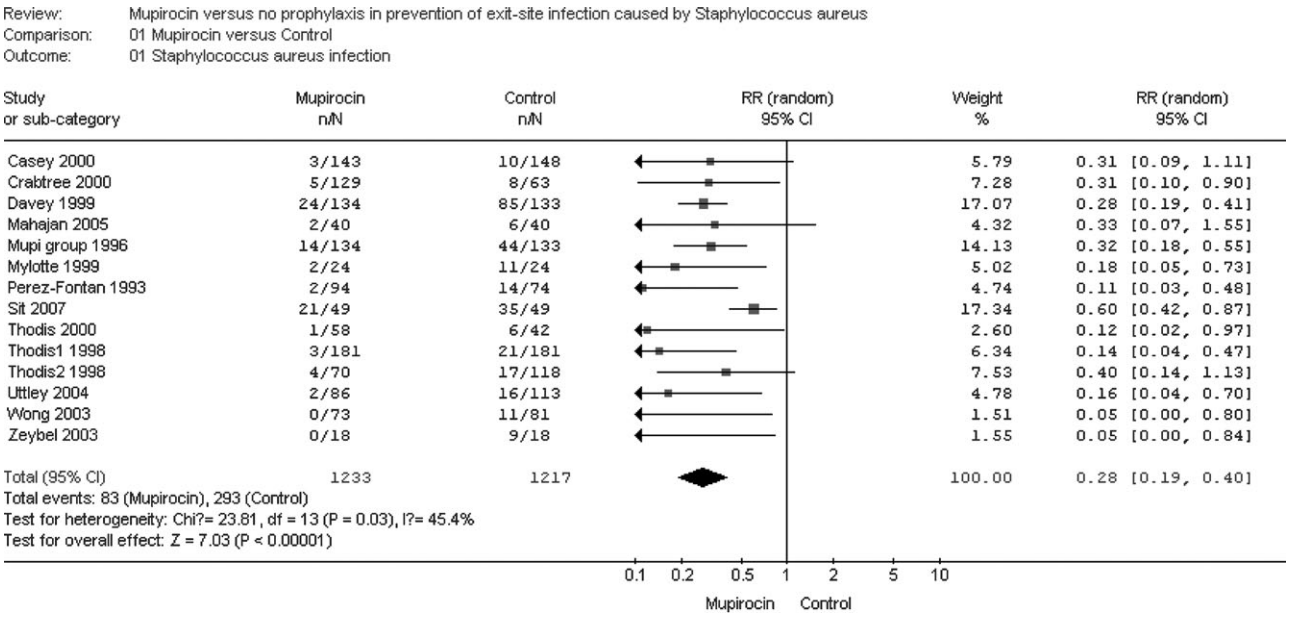

Fig. 2. Mupirocin versus no prophylaxis in prevention of ESI due to *S. aureus*.

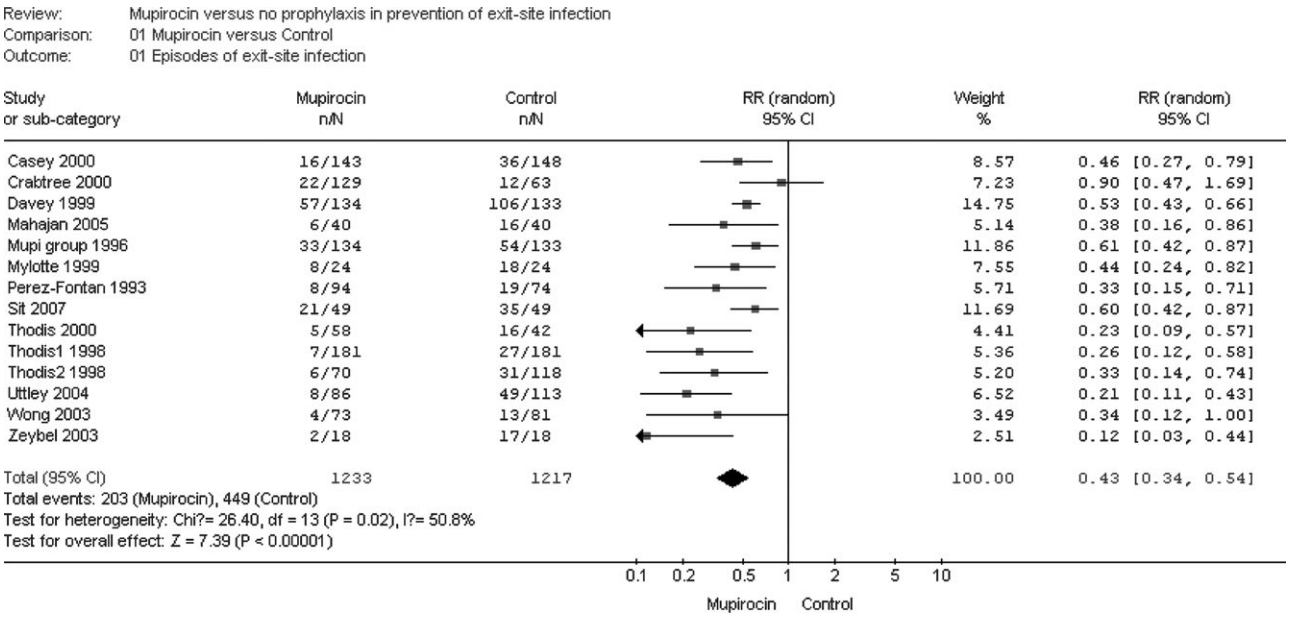

Fig. 3. Mupirocin versus no prophylaxis in prevention of ESI.

Discussion

Mupirocin was first used in 1980 and has been applied extensively to prevent *S. aureus* infections in patients undergoing PD. The International Society for Peritoneal Dialysis (ISPD) guidelines currently recommended exit-site mupirocin application for all PD patients at an increased risk of *S. aureus* infections, including *S. aureus* carriers and immunocompromised patients. A major problem that may appear during the long-term mupirocin application is the development of antibiotic resistance [27]. Annigeri *et al*. reported that mupirocin-resistant *S. aureus* was determined to be 3% of the total study population and 15% of the total *S. aureus* isolates [9]. In a 625-bed teaching hospital, a marked increase in the point prevalence of methicillin-resistant *S. aureus* (MRSA) infection among inpatients led to widespread mupirocin administration to all patients in 1992 [11]. This intervention led to a rapid increase in mupirocin resistance, from 2.7% of MRSA isolates in 1990 to 65% in 1993. Concern about the emergence of mupirocin resistance may be the main factor that limits its use [9,28].

Trials that address the efficacy of mupirocin for prevention of *S. aureus* ESI or peritonitis have conflicting conclusions [22,26]. Discordant results among published studies

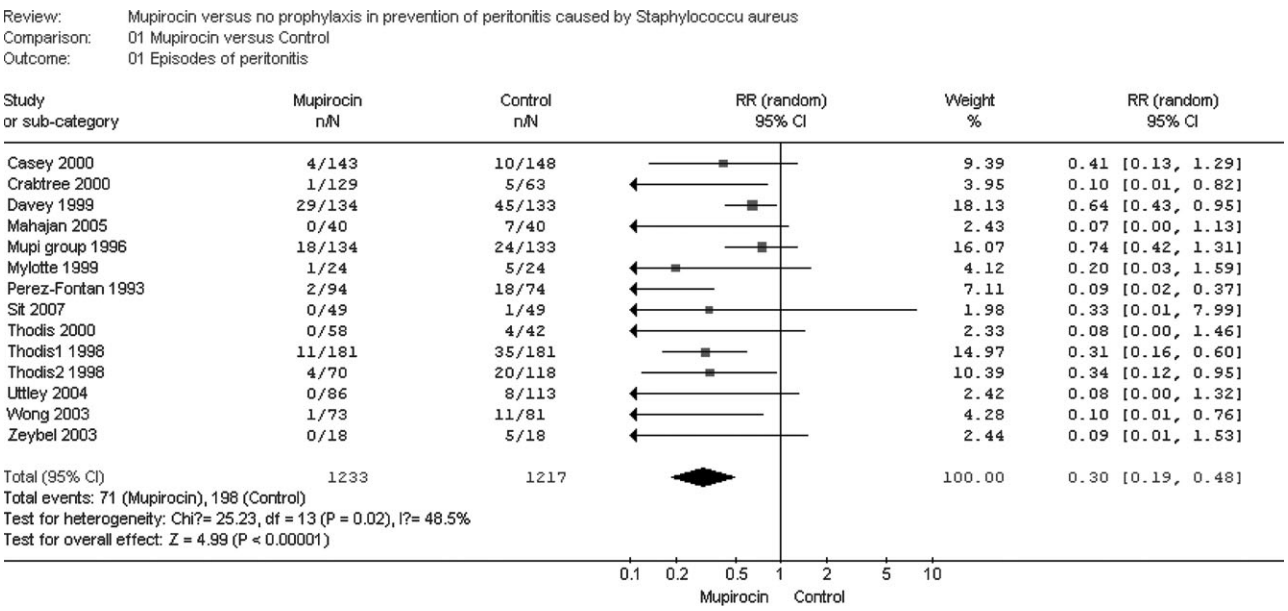

Fig. 4. Mupirocin versus no prophylaxis in prevention of peritonitis due to *S. aureus*.

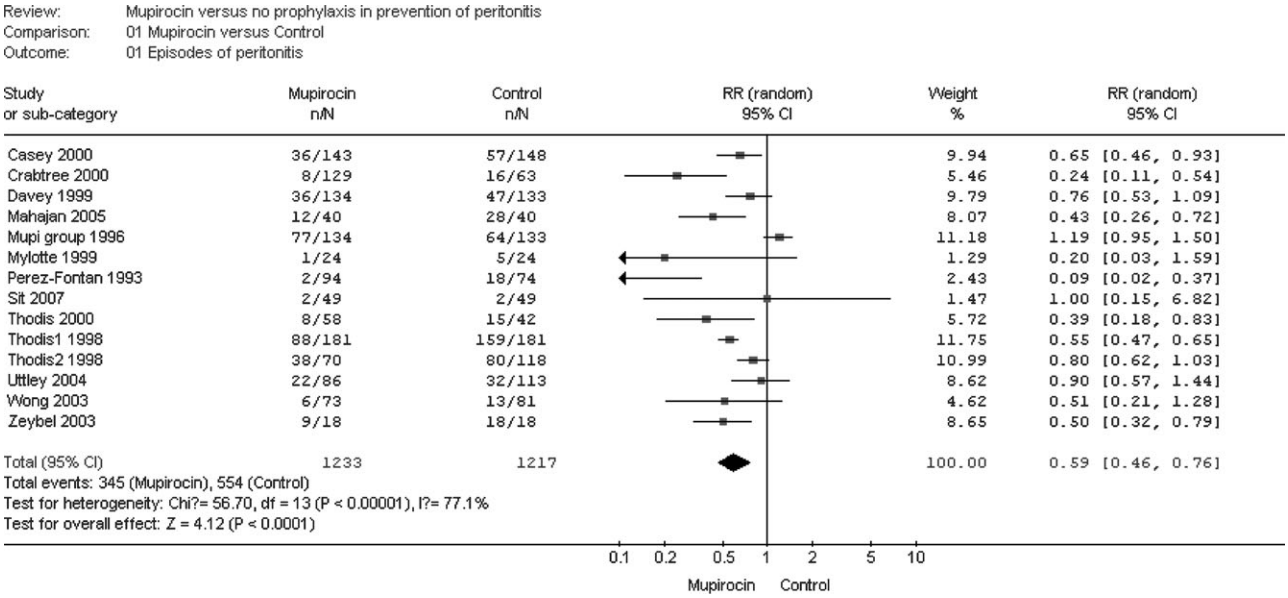

Fig. 5. Mupirocin versus no prophylaxis in prevention of peritonitis.

and varying estimates of the risk reduction may be due to difference in the study design and patient population, including type of dialysis modality, mupirocin regimen or type and definition of infections. This systematic review of the literature quantified the benefit of topical mupirocin therapy in preventing *S. aureus* infections among patients undergoing PD. Overall, mupirocin therapy significantly reduced the risk rates of developing ESI and peritonitis among all PD patients, based on either the total of 14 fully published studies or the 6 newly published articles. Interestingly, based on the three RCTs, mupirocin treatment cannot decrease the risk rate of peritonitis due to all organisms ($P = 0.56$). This discrepancy may be explained by population limitations in the existed randomized controlled trials. Future longitudinal studies are needed to define the decrease in the episodes of *S. aureus* infection and the emergence of mupirocin resistance.

Although mupirocin treatment cannot play a role in *Pseudomonas*, gram-negative bacteria or fungal infections, it was effective in reducing the infection rates due to all organisms in both the total of 14 fully published studies and the 6 newly published articles (Figures 2–5). Compared with previously published meta-analysis [12,13], the reduced infection rates were higher in the six newly published articles (80% in the rate due to *S. aureus*; 70% in the rate due to all organisms, respectively). This discrepancy was not clear and could be explained by the differences in study designs and population limitations between these systemic reviews.

Finally, there are several limitations to this meta-analysis. First, because of an insufficient number of randomized controlled trials, other study designs (i.e. historical cohort study) were included in this analysis. Secondly, trials that did not show that mupirocin prophylaxis had a benefit in decreasing the number of ESI and peritonitis may not have been published, thereby biasing the results towards a beneficial effect of mupirocin prophylaxis. Nevertheless, the optimal strategy for using this topical antimicrobial and minimizing the emergence of resistance was still unclear.

Conflict of interest statement. None declared.

(See related article by B. Piraino. Mupirocin for preventing exit-site infection and peritonitis in patients undergoing peritoneal dialysis. Was it effective? *Nephrol Dial Transplant* 2010; 25: 349–352.)

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