

Antibiotics to Prevent Infection of Simple Wounds: A Meta-Analysis of Randomized Studies

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A meta-analysis was conducted to determine whether prophylactic systemic antibiotics prevent infection in patients with nonbite wounds that are managed in the emergency department (ED). A literature search was performed to identify published, randomized trials of prophylactic antibiotics for nonbite wounds. Blinded review of trial methods was used to select trials that randomly assigned patients to antibiotic or control groups and analyzed results by intention to treat. Of 9 randomized trials, 7 (with 1,734 study subjects) were accepted for analysis. The odds ratio for infection in treated patients compared with controls was used as the measure of effect, and a summary odds ratio was calculated. Patients treated with antibiotics had a slightly greater incidence of infection compared with untreated controls: odds ratio 1.16 (95% confidence interval [CI] 0.77 to 1.78). Even among patients treated with a penicillinase-resistant antibiotic (5 trials with 1,204 patients), there was no benefit from treatment; odds ratio 1.00 (95% CI 0.59 to 1.71). In conclusion, there is no evidence in published trials that prophylactic antibiotics offer protection against infection of nonbite wounds in patients treated in EDs. (Am J Emerg Med 1995;13:396-400. Copyright © 1995 by W.B. Saunders Company)

Simple nonbite wounds are commonly managed in emergency departments (EDs). Several authors¹⁻⁴ recommend against the routine use of prophylactic systemic antibiotics to prevent infection in these wounds. Some authors suggest the use of antibiotics for wounds that are at high risk for infection.^{2,3,5,6}

One argument against the use of prophylactic antibiotics for simple wounds is that they are ineffective. Another argument is that infections in these wounds are so rare that even if antibiotics are effective, the potential benefits do not outweigh the associated costs and risks.

All published trials of prophylactic antibiotics for simple wounds have concluded that there was no statistically significant benefit from treatment.⁷⁻¹⁵ But the size of individual trials may have limited their power to find a true difference between treatment and control groups. Meta-analysis can be helpful in this situation by summarizing results across studies to provide a quantitative summary estimate of the effect of antibiotic prophylaxis. This report applies meta-analysis

to controlled trials that were designed to test the hypothesis that prophylactic systemic antibiotics prevent infection in patients who are treated in EDs for simple nonbite wounds.

METHODS

Medical literature was searched to find published randomized trials of prophylactic systemic antibiotics for nonbite wounds managed in EDs. A computer MEDLINE search used the terms "wound infection" and "antibiotics" and covered the period 1966 through December 1993. The search was not limited to articles in English. The bibliographies of clinical trials and reviews were examined to find further trials. A study was selected for possible inclusion in the meta-analysis if the authors stated that they had randomly assigned patients with uninfected wounds to an antibiotic treatment group or a control group and then followed patients for the occurrence of infection. The methods of each selected trial were abstracted so they could be reviewed by one of the authors without knowledge of the antibiotic used, the location of the study, or the study results. Studies were included in the meta-analysis if the results were analyzed by treatment assigned, thereby preserving the randomized design.

For each trial a 2 × 2 table was created to summarize the number of patients reported as infected or not infected in each treatment arm. Three studies had three treatment arms, which were two systemic antibiotic regimens and one control group.^{10,12,14} The antibiotic groups were combined for the main analysis. One study had a third treatment group which underwent wound irrigation with an antibiotic; this arm of the study was excluded from analysis.⁸

The measure of effect we used was the odds ratio: the odds of infection among those given antibiotics divided by the odds of infection among the controls. Infections were rare enough that the odds ratio approximates the relative risk. A test for heterogeneity was conducted to test the hypothesis that the true odds ratio was the same across all studies. The summary odds ratio for all studies was calculated using the Mantel-Haenszel method,¹⁶ and 95% confidence intervals (CIs) for odds ratios were calculated using an exact method.¹⁷ We also explored the possibility that a substantially different summary effect might be seen in certain subgroups of study results.

RESULTS

The literature search identified 9 studies⁷⁻¹⁵ that randomly assigned patients with nonbite wounds to systemic antibiotic therapy or a control group. All the patients were treated in EDs, although one study¹⁰ included a small number of patients who had wound repair in an operating room.

The blinded reviewer concluded that 2 of the trials^{9,13} failed to preserve the randomized design, and these were excluded from the meta-analysis. One of the excluded studies⁹ randomized 1,133 patients but reported results for only 20.3% of the total: 67 patients on antibiotics and 204 controls. The other excluded study¹³ analyzed the results by

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TABLE 1. Randomized Studies Included in Meta-Analysis of Antibiotics for Prophylaxis of Infection in Simple Lacerations

Trial (year)	Antibiotic	Inclusion	Exclusions
Beesley et al (1975) ⁷	Flucloxacillin plus ampicillin	Hand wounds only	Age ≤5 years Tendon, bone, or joint involvement "Obviously contaminated"
Day (1975) ⁸	Triplopen*	Sutured wounds only	Wound ≥4 hours old Contaminated, deep, or contused wounds No tetanus booster within 5 years Allergy to antibiotics On antibiotics
Roberts and Teddy (1977) ^{10†}	Triplopen* or flucloxacillin	Sutured hand wounds only	Nerve or tendon involved Fracture requiring fixation Allergy to penicillin Wound not suitable for primary closure Patient lived outside local area
Hutton et al (1978) ¹¹	Triplopen*	Sutured hand wounds only	Wound not suitable for primary closure Allergy to penicillin On antibiotic Antibiotic in last 2 weeks No history of any tetanus immunization Admitted patients Wound >4 hours old
Worlock et al (1980) ¹²	Cephalexin‡	Hand wounds only	Established infection Allergy to cephalosporins Renal failure Age <13 years
Grossman et al (1981) ¹⁴	Oral cephalexin or cefazolin	Sutured hand wounds only	Wound to nerve or tendon Fracture Patient had diabetes Patient steroid-dependent Penicillin allergy
Thirlby et al (1983) ¹⁵	Cephalexin	Sutured wounds only	Bite wounds Wound >8 hours old Patient has diabetes or is on steroids or chemotherapy Allergy to cephalosporins Mouth wounds

* Triplopen (Glaxo; United Kingdom) is a mixture of sodium penicillin, procaine penicillin, and benethamine penicillin that is administered intramuscularly.

† This study included 23 patients who had wounds repaired in the operating room.

‡ There were two doses of cephalexin used, either 250 mg or 500 mg orally every 6 hours for 4 days. These were combined for the analysis.

assigning the patients in the antibiotic group who failed to take the medication to the control group; this resulted in 160 patients on treatment and 234 controls.

Of the 7 studies^{7,8,10-12,14,15} that were accepted for the main analysis (Table 1), 5 were performed in the United Kingdom^{7,8,10-12} and 2 in the United States.^{14,15} All the studies used either penicillins or cephalosporins, 5 studies^{7,10,12,14,15} used antibiotics that were resistant to penicillinase, and 4 studies^{8,10,11,14} used parenteral antibiotics. Of the 5 studies^{7,10,12,14,15} that used oral antibiotics, 2 assessed self-reported compliance with therapy.^{7,10} Although the studies had different inclusion and exclusion criteria, from a clinical point of view the criteria were fairly similar except that 5 studies^{7,10-12,14} were limited to hand wounds and 5 studies^{8,10,11,14,15} were limited to sutured wounds. Three studies used a double-blind design^{7,12,14} and 1 study⁸ stated that the physician who evaluated the wound for infection did not know the patient's treatment group. Five studies made a statement concerning criteria for judging wound infection.^{8,10,12,14,15}

The rates of follow-up were very similar, ranging from 89.7% to 94.7% (Table 2). Two studies^{8,15} simply presented the results as if all patients had received follow-up and we suspect that the number of patients actually entered into each trial arm was not reported. One of these studies⁸ reported equal numbers of patients in the treated and control

groups, suggesting that the randomized design was preserved. In the other trial,¹⁵ results were reported for 227 patients on treatment and 272 controls, a substantial imbalance that raises the possibility that randomization was not fully successful or that the authors departed from an intention-to-treat analysis.

The cumulative incidence of infection among the controls ranged from 1.1% to 12.0% with a mean of 6.0% (95% CI 4.5% to 8.0%) across all studies. Patients on antibiotics had a greater cumulative incidence of infection compared with controls in 6 studies (Table 3).^{7,8,11,12,14,15} Patients treated with antibiotics had a slightly greater incidence of infection compared to controls: odds ratio = 1.16 (95% CI 0.77 to

TABLE 2. Further Details of Randomized Studies Included in Meta-Analysis of Antibiotics for Prophylaxis of Infection in Simple Lacerations

Trial	Blinded	Number of Patients Entered	Number With Reported Results (%)
Beesley et al ⁷	Double	145	130 (89.7%)
Day ⁸	Single	?	112 (?)
Roberts and Teddy ¹⁰	No	338	305 (90.2)
Hutton et al ¹¹	No	301	285 (94.7)
Worlock et al ¹²	Double	118	105 (90.0)
Grossman et al ¹⁴	Double	280	265 (94.6)
Thirlby et al ¹⁵	No	?	499 (?)

TABLE 3. Results of Randomized Studies of Antibiotics for Nonbite Wounds

Trial	Antibiotic		Controls		Odds Ratio*	95% CI
	Total	Infected (%)	Total	Infected (%)		
Beesley et al ⁷	64	1 (1.6)	66	1 (1.5)	1.03	0.01 to 82.22
Day ⁸	56	12 (21.4)	56	4 (7.1)	3.55	0.97 to 16.00
Roberts et al ¹⁰	205†	18 (8.8)	100	12 (12.0)	0.71	0.31 to 1.68
Hutton et al ¹¹	142	10 (7.0)	143	9 (6.3)	1.13	0.40 to 3.25
Worlock et al ¹²	71‡	5 (7.0)	34	2 (5.9)	1.21	0.19 to 13.36
Grossman et al ¹⁴	174§	2 (1.1)	91	1 (1.1)	1.05	0.05 to 62.42
Thirlby et al ¹⁵	227	16 (7.0)	272	17 (6.3)	1.14	0.52 to 2.46
SUMMARY	939		762		1.16	0.77 to 1.78

* The odds ratio approximates the relative risk of infection among patients administered antibiotics compared with controls.

† 100 patients received Triplopen and 105 received flucloxacillin.

‡ 36 patients received cephalexin 250 mg 4 times a day for 5 days and 35 patients received 500 mg 4 times a day for 5 days.

§ 96 patients were given oral cephalexin and 78 were given intramuscular cefazolin. This study reported the number of patients assigned to treatment rather than the number evaluated in follow-up.

1.78) (Figure 1). The test for heterogeneity was not significant ($P = .5$).

We examined the possibility that a different summary of the evidence might suggest a different result (Table 4). First, studies limited to sutured wounds were considered to see if a beneficial effect of antibiotics might be found in this group.^{8,10,11,14,15} Second, studies limited to wounds of the hand were summarized.^{7,10-12,14} Third, studies that used a double-blind design were summarized^{7,12,14}; unblinded patients in the control group may be more likely than those on antibiotic to return for possible infection, and a physician's knowledge of treatment status might affect the diagnosis of infection. Fourth, we summarized results for oral antibiotics.^{7,10,12,14,15} Fifth, results were summarized for parenteral regimens.^{8,10,11,14} In some cases these summaries used part of the data from a study; in these instances, all the controls

for that study were included.^{10,14} Sixth, we summarized the results for studies that used penicillinase-resistant antibiotics, in case they had a more powerful effect.^{7,10,12,14,15} Seventh, 2 trials^{10,14} required the presence of pus to diagnose infection, and the number of wounds with pus could be extracted from 2 other studies^{8,12}; summary results using pus as the endpoint were calculated. Eighth, we excluded the study by Day⁸; this study showed a very high rate of infection in the patients on antibiotics and we wanted to test the impact of this single study on the summary results. In addition this study had an error in reporting the results; a figure and a table report 56 patients who received penicillin, whereas the text says 48 patients received that medication. Finally, we summarized results for all 7 studies^{7,8,10-12,14,15} plus the 2 studies^{9,13} that we had excluded, to test the effect of that exclusion. The summary odds ratios for infection in patients who received antibiotics compared with controls ranged from 0.91 to 1.41 in the various subgroups, suggesting that antibiotic therapy was not helpful in any subgroup (Table 4). Even the summary estimate that excluded the study by Day⁸ resulted in an odds ratio of 0.98 (95% CI 0.63 to 1.55), consistent with essentially no beneficial effect of antibiotics. Including the 2 studies^{9,13} that were omitted from the meta-analysis because of design flaws resulted in no change in the relative risk estimate: odds ratio 1.16 (95% CI 0.82 to 1.64).

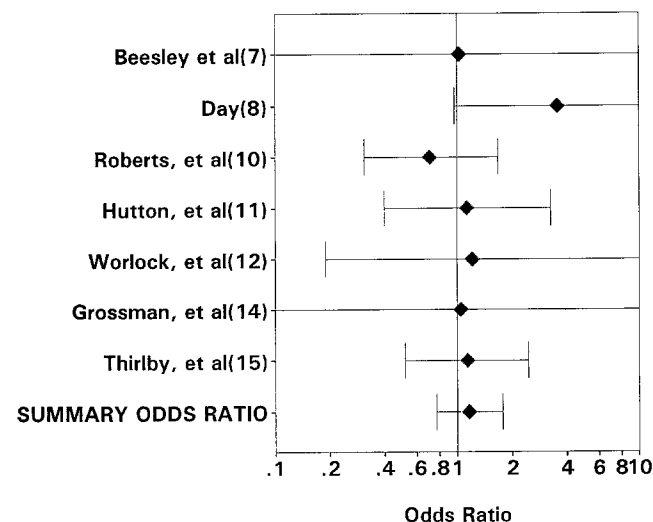


FIGURE 1. Odds ratio estimates and 95% CIs for individual studies and the summary odds ratio for all studies. The odds ratio closely approximates the relative risk of infection among patients administered antibiotics compared with controls. An odds ratio estimate less than 1.0 indicates that antibiotic treatment reduces the risk of infection, whereas an estimate greater than 1.0 favors the control group. The reference number is given for individual studies.

TABLE 4. Summary Odds Ratios for Subgroups of Studies

Subgroup	Odds Ratio*	95% CI
All 7 studies ^{7,8,10-12,14,15}	1.16	0.77 to 1.78
Sutured wounds ^{8,10,11,14,15}	1.41	0.84 to 2.38
Hand wounds ^{7,10-12,14}	0.91	0.51 to 1.62
Double-blind design ^{7,12,14}	1.13	0.29 to 5.31
Oral antibiotics ^{7,10,12,14,15}	0.97	0.56 to 1.66
Intramuscular antibiotics ^{8,10,11,14}	1.27	0.71 to 2.28
Penicillinase-resistant antibiotics ^{7,10,12,14,15}	1.00	0.59 to 1.71
Pus used as the endpoint ^{8,10,12,14}	0.94	0.47 to 1.97
All 7 studies ^{7,10-12,14,15} except Day ⁸	0.98	0.63 to 1.55
All 7 studies ^{7,8,10-12,14,15} plus the two excluded studies ^{9,13}	1.16	0.82 to 1.64

* The odds ratio approximates the relative risk of infection for patients on antibiotics compared with controls.

DISCUSSION

Seven published randomized clinical trials have tested the ability of antibiotics to prevent infection of simple nonbite wounds that are managed in EDs.^{7,8,10-12,14,15} The summary estimate of the relative risk for infection among patients given antibiotics compared with controls is 1.16 (95% CI 0.77 to 1.78).

A meta-analysis based on published studies can be influenced by publication bias, which occurs when studies with statistically significant results are preferentially published compared with studies that favor the null.¹⁸⁻²⁰ This bias is not likely to affect our analysis, however, because none of the trials reported a statistically significant treatment benefit. Selection bias can influence the results of a meta-analysis,²² but we selected studies using a blinded reviewer who did not know the results of the trials. In addition, a sensitivity analysis showed that inclusion of the rejected trials would not have changed the summary estimate of treatment effect. Data extraction is another potential source of bias,²¹ but the treatment groups and end points were clearly reported in nearly all the trials used for this analysis. One trial had an apparent error in its reporting of the results⁸ in that the text and table disagreed; we accepted the table as correct, but had we made the alternative choice, the apparent deleterious effect of antibiotics in this trial would have been even greater.

The summary estimate of treatment effect assumed that all the antibiotic regimens were equally effective. This assumption may not be true; some regimens may be effective while others are not. We summarized study results by the method of antibiotic administration (oral or intramuscular) and we separately summarized results for penicillinase-resistant antibiotics. None of these analyses showed a benefit of antibiotics.

The trials all used somewhat different entry criteria. But only 1 of the 7 trials showed a beneficial effect of treatment; this trial¹⁰ was limited to patients with sutured hand wounds. Two other trials limited to this group of patients reported better results among the controls.^{11,14}

Five of 7 trials stated their criteria for wound infection; 2 trials required the presence of pus,^{10,14} and 3 accepted pus or other signs of inflammation as evidence of infection.^{8,12,15} Two trials^{8,12} provided results in such a way that the number of wounds with frank pus could be extracted, and when these are combined with the trials that used pus as an end-point,^{10,14} the summary odds ratio (Table 4) was very similar to that of all the studies, suggesting that the definition of end point does not explain the apparent lack of efficacy of antibiotics.

One reason that antibiotics might have been ineffective in preventing infection is that patients did not take them. It seems doubtful that this could fully explain the lack of benefit that we found. First, the failure of some patients to take the medication could reduce the size of a beneficial treatment effect, but would not lead to a finding of no benefit at all. Second, we found no evidence of benefit even when antibiotics were administered intramuscularly.

Another reason that antibiotics might not be beneficial is that they were not given promptly enough. Some authors have argued that speed is important if antibiotics are to be

effective,^{1,2,22,23} and intravenous administration in the ED has been advocated.⁶ However, the apparent benefit of oral antibiotics in preventing infection in patients with bite wounds^{24,25} makes it appear that neither speed nor parenteral therapy are necessary for the success of prophylactic antibiotics in at least some wounds.

A limitation of our meta-analysis is our inability to examine certain subgroups of patients. Although some studies gave information on depth, type, or age of the wound,^{8,10,14,15} the results were not crosstabulated by treatment and outcome and therefore could not be extracted for analysis. Future clinical trials might examine the effect of antibiotics in specific groups of patients classified by wound type or age of wound. Presenting subgroup information crosstabulated by treatment group and outcome would facilitate new meta-analytic summaries.

CONCLUSION

We conclude that the existing evidence provides little justification for administration of antibiotics to prevent infection in patients with simple nonbite wounds. Antibiotics appear to have no beneficial effect in this setting. Whether antibiotics can prevent infection in a subgroup of nonbite wounds is not known. Similarly, it is not known if antibiotics can prevent infection in certain populations that have special risk factors for infection, eg, patients with diabetes. These would be suitable questions for future trials.

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