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Prophylactic Antibiotics in Chest Trauma: A Meta-analysis of High-quality Studies

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Abstract

Background: Use of antibiotics in patients with isolated chest trauma is controversial. Available studies offer contradictory results because of small sample sizes. However, information provided by recent randomized controlled trials (RCT) included in a systematic review and meta-analysis could help solve the controversy. We performed a systematic review using high-quality information related to the use of antibiotics in patients with a chest tube.

Methods: We developed a systematic review to evaluate the effectiveness of prophylactic antibiotics in chest-trauma patients. Studies included were class I RCT comparing prophylactic antibiotics versus placebo in patients with isolated chest trauma. Main outcomes were posttraumatic empyema and pneumonia.

Results: Five Class I studies were selected. There were statistically significant differences regarding the frequency of posttraumatic empyema (RR 0.19) and pneumonia (RR 0.44) in favor of the use of prophylactic antibiotics when compared with placebo.

Conclusions: The use of prophylactic antibiotics in patients with chest trauma decreases the incidence of posttraumatic empyema and pneumonia.

The administration of antibiotics to chest-trauma patients requiring closed thoracostomy continues to be controversial. The conclusion of the latest recommendations from the Eastern Association for the Surgery of Trauma (EAST)[1] is that the existing class I studies[2–5] do not provide sufficient evidence to support the decision of using prophylactic antibiotics in patients with chest trauma. However, an editorial by Wilson and Nichols[6] published in the same issue examined the weaknesses of that management guideline and emphasized the conclusions of two prior meta-analyses that favored the use of antibiotics as a means to prevent pneumonia and empyema.

This discussion led to the design of a multicenter trial in order to solve the matter. Maxwell *et al.*[7] reported their trial findings in October 2004. They were unable to demonstrate the usefulness of antibiotics in reducing the frequency of empyema. However, the authors point out to the small sample of subjects recruited, that turned out to be only 20% of the sample size estimated before the study, resulting in a weak conclusion due to the trial's lack of power. The purpose of this paper is to assess the effectiveness of prophylactic antibiotics in chest-trauma patients requiring a chest tube, including the most recent data from high-quality randomized controlled trials (RCT).

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MATERIALS AND METHODS

The study included a systematic review of the literature and a meta-analysis of the randomized class I clinical trials previously identified by Luchette *et al.*[1] plus the

Table 1.
Characteristics of randomized controlled trial (RCT) class I studies

Trial name	Year	Antibiotic type	Antibiotic group; n	Empyema in antibiotic group; n (%)	Pneumonia in antibiotic group; n (%)	Control group; n	Empyema i n control group; n (%)	Pneumonia in control group; n (%)
Grover	1977	Clindamycin	38	1 (2.6%)	4 (10.5%)	37	6 (16.2%)	13 (35.1%)
Stone	1981	Cefamandole	40	1 (2.5%)	0 (0%)	43	2 (4.7%)	5 (11.6%)
Cant	1993	Cefazolin	57	0 (0%)	7 (12.3%)	56	5 (8.9%)	19 (33.9%)
Nichols	1994	Cefonicid	63	0 (0%)	0 (0%)	56	3 (5.4%)	3 (5.4%)
Maxwell	2004	Cefazolin	153	2 (1.3%)	12 (7.8%)	71	4 (5.6%)	2 (2.8%)
Total			351	4 (1.1%)	23 (6.6%)	263	20 (7.6%)	42 (16.0%)

most recent results of the multicenter study by Maxwell *et al.*[7] The subjects were patients with penetrating or blunt trauma with no concomitant injuries, who required placement of a chest tube as part of their management. For inclusion, w e required that the trials should compare the use of antibiotics against the use of placebo and, whenever possible, the type of antibiotic used should provide adequate coverage for *Staphylococcus aureus*, the most frequently isolated microorganism in cases of posttraumatic empyema. The outcomes assessed included the frequency of empyema and pneumonia, bearing in mind that the best marker for antibiotic effectiveness is the frequency of empyema, not of pneumonia, due to the multiple factors influencing the latter.

A search in MEDLINE Pubmed was conducted using the terms ''trauma,'' ''chest,'' and ''antibiotic,'' with the aim of identifying other randomized clinical trials published after the paper by Luchette *et al.*[1] There was only one article (Maxwell *et al.*[7]) consistent with the class 1 characteristics according to the recommendations of the Agency for Health Care Policy and Research of the US Department of Health and Human Services. The data were extracted by one of the authors, and a statistical analysis was performed using Stata 6.0 software. Results for each outcome were measured using the risk ratio (RR) with a 95% confidence interval. The *Q* test was used for heterogeneity analysis, with $P < 0.05$ considered significant. The influence of heterogeneity was assessed using the I^2 test.[8] The Mantel–Haenszel fixed-effects model was used to measure overall effects on outcome. The heterogeneity of the results was explained qualitatively. Results are presented using forest plot graph.

A sensitivity analysis was performed excluding the Grover *et al.*[2] trial due to questions concerning microbiological coverage of the used antibiotic (clindamycin) compared with antibiotics used in other trials (cephalosporins). A subgroup analysis was also applied to the studies that assessed the use of the antibiotics for a 24-hour period (Cant *et al.*[4] and Maxwell *et al.*[7]) or during more than 24 hours (Stone *et al.*[3], Nichols *et al.*[5], Grover *et al.*[2] and Maxwell *et al.*[7]).

RESULTS

Besides the aforementioned trials by Grover *et al.*[2], Stone *et al.*[3], Cant *et al.*,[4] and Nichols *et al.*[5], the Maxwell *et al.*[7] study was included among those that fulfilled the methodological characteristics of a class 1 trial.[9] A total of 614 patients in 5 RCTs were reviewed: 351 in the group receiving antibiotics, and 263 in the placebo group. Characteristics of included studies are shown in Table 1.

The frequency of empyema was 1.1% in the antibiotic group versus 7.6% in the placebo group, and pneumonia rate was 6.6% in the antibiotic group versus 16% in the placebo group. As summary results from the meta-analysis, it was found that the use of prophylactic antibiotics had an RR of 0.19 (95% CI 0.07–0.5) for the development of empyema and 0.44 (95% CI 0.27–0.73) for the development of pneumonia. No statistical heterogeneity was identified ($P = 0.88$ for empyema and $P = 0.07$ for pneumonia) (Fig. 1A, B).

In the sensitivity analysis excluding Grover's study, there was no variation in final results related to empyema (RR 0.20, 95% CI 0.06–0.6). However, this analysis showed differences in pneumonia results (RR 0.50, 95% CI 0.28–0.9), where the heterogeneity test was statistically significant ($P = 0.046$, I2 = 62%) (Fig. 2A, B).

The subgroup analysis for empyema revealed an RR of 0.16 (95% CI 0.04–0.70) in the studies using antibiotics for more than 24 hours and an RR of 0.16 (95% CI 0.05–0.51) in those using antibiotics for more than 24 hours (Fig. 3A, B).

For pneumonia, subgroup analysis revealed a RR of 0.38 (95% CI 0.13–1.12) in the studies using antibiotics over 24 hours, and a RR of 0.36 (95% CI 0.15–0.87) in those using antibiotics for more than 24 hours (Fig. 4A, B).

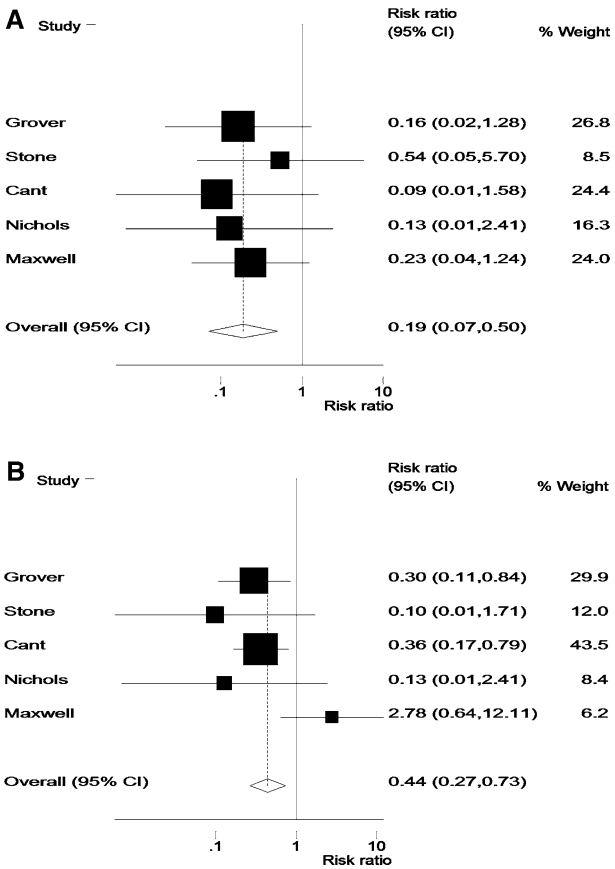

Figure 1. Forest plot for empyema (**A**) and pneumonia (**B**) in the global group of studies that used prophylactic antibiotics versus placebo. **A**. Forest plot for empyema. **B**. Forest plot for pneumonia.

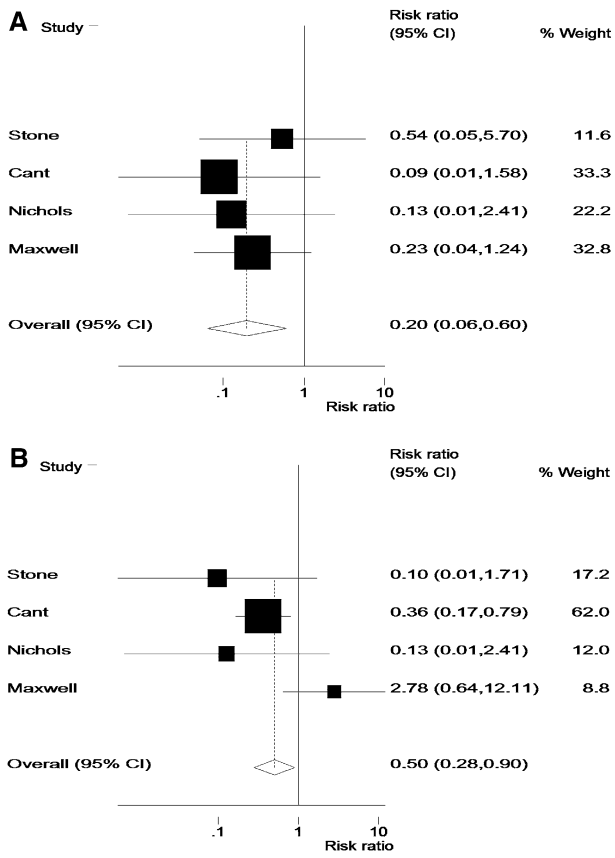

Figure 2. Forest plot for empyema (**A**) and pneumonia (**B**) excluding the study by Grover. **A**. Forest plot for empyema. **B**. Forest plot for pneumonia.

DISCUSSION

The use of prophylactic antibiotics in patients with chest trauma requiring a chest tube has been an ongoing debate among trauma surgeons. Two prior meta-analyses reported a protective effect against the development of posttraumatic empyema and pneumonia.[10,11] However, those studies were criticized because they included trials of poor methodological quality and clinical variations among patients.[1] The recommendations issued by EAST[1] following those meta-analyses stated that the high-quality class I trials did not offer sufficient evidence to support the use of prophylactic antibiotics in patients with chest trauma. However, this conclusion was based on single trials with not enough power to conclude that there was no difference between strategies, and a meta-analytical synthesis was not attempted. Nevertheless, a more recent clinical experiment that fulfills quality requirements contributed additional information. Specific methodological and clinical features suggested by EAST guarantee a better study design and conduction in comparison with older trials. A larger sample size compared with previous trials and a multicenter design that increase external validity help elucidate the issue. Although the study published recently by Maxwell *et al.*[7] did not include a sufficient number of subjects in order to settle the discussion, it did provide information that can be used in a meta-analysis. Meta-analysis can be used to combine data from RCTs that cannot answer a clinical question individually because of low power derived from a small sample size. The inclusion of new trials improves precision of effect measures such as RR or odds ratio (OR), helping to identify clinical differences that are not statistically significant in individual trials.

By itself, the Maxwell study did not show a statistically significant difference between the use of prophylactic antibiotics and the development of empyema and pneumonia because of the small sample size, which did not reach the number suggested by sample size calculation. Nevertheless, its data were included in this new meta-analysis, which shows a clear protective effect for posttraumatic empyema when antibiotics are used, lowering the frequency of empyema from 7.6% to 1.14% and the frequency of pneumonia from 16% to 7.6%.

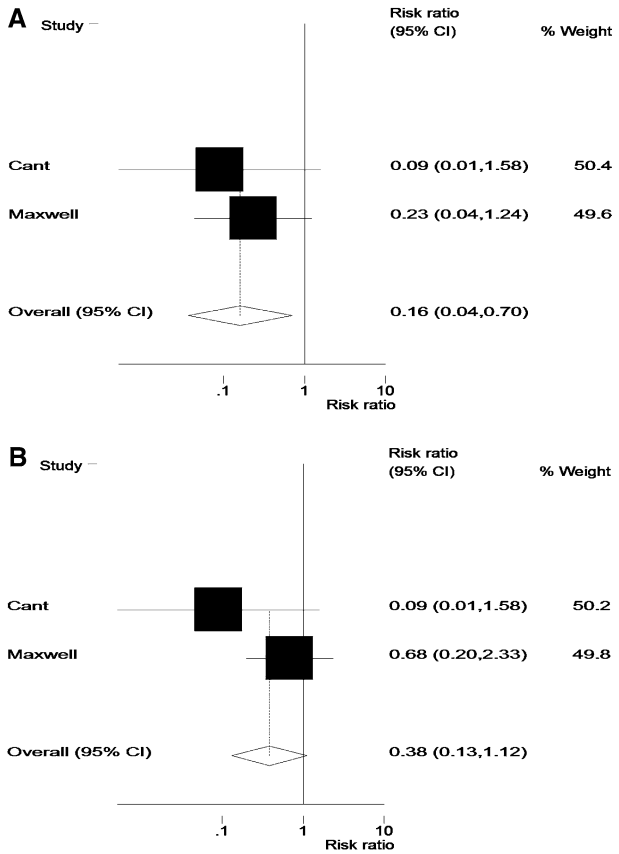

Figure 3. Forest plot for empyema (**A**) and pneumonia (**B**) in the subgroup of studies that used prophylactic antibiotics for 24 hours versus placebo. **A**. Forest plot for empyema. **B**. Forest plot for pneumonia.

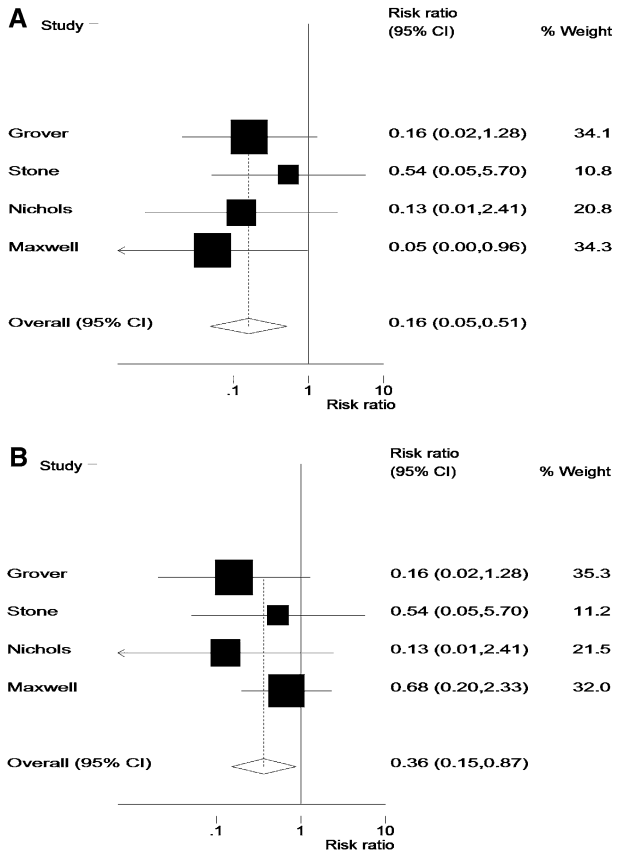

Figure 4. Forest plot for empyema (**A**) and pneumonia (**B**) in the subgroup of studies that used prophylactic antibiotics for more than 24 hours versus placebo. **A**. Forest plot for empyema. **B**. Forest plot for pneumonia.

Sensitivity analysis, a common tool used in meta-analyses and economic studies, offers the possibility of providing the consistency of overall conclusions, even when some variations related to methodological quality and clinical factors are made. In this meta-analysis, antibiotic coverage was a clinical factor that could influence results because one study used an antibiotic not included in the group of cephalosporins. Moreover, this study shows that after sensitivity analysis excluding an older trial that used a limited-spectrum antibody against *S. aureus*, conclusions regarding empyema remain the same. On the other hand, RR for pneumonia was protective, but results are not strong because of heterogeneity. Although there is no clear explanation, this is probably due to the higher frequency of pneumonia reported by Maxwell *et al.*[7] in the antibiotic group. This result does not contradict the protective findings for empyema. Moreover, the effect expected from the use of antibiotics is to prevent pleural infections. Pneumonia in these patients is multifactorial, and its late onset leads to suspicion of the effects of other variables, such as prolonged orotracheal intubation and admission to the intensive care unit. Based on given results, it is possible to recommend the use of a cephalosporin as a protective intervention against the development of empyema and pneumonia in patients with chest trauma requiring closed thoracostomy.

Regarding the duration of antibiotic use, the subgroup analysis showed that protection against empyema is similar whether they are used for 24 hours or for longer. These findings are consistent with recent recommendations on the use of antibiotics in trauma cases with adequate source control.[12] If results obtained with the use of antibiotics in other fields with greater contamination, such as abdominal trauma, are extrapolated.[13–16] there would be no reason to prolong the use of antibiotics for more than 24 hours. There is a tendency to think that the presence of a chest tube in the pleural space might favor the onset of empyema and that, consequently, antibiotics should be used over the entire thoracostomy period. However, some authors have determined that the most important factor for the development of empyema is incomplete drainage,[17,18] and in spite of using antibiotics, if the chest tube does not drain adequately, all other interventions are meaningless.

On the other hand, the evidence available from the subgroup analysis for the outcome of pneumonia suggests that the use of antibiotics should continue for more than 24 hours, at least during the time the chest tube is in place, as determined by trial protocols. As discussed previously, the purpose of providing prophylactic antibiotics is not to prevent pneumonia. Considering posttraumatic pneumonia is known to occur more frequently in patients sustaining blunt trauma and that lung contusion is a determinant risk fractor,[19,20] extending antibiotic therapy would only be advisable in these patients. However, there are no clinical studies supporting such an assertion. In order to design a study to solve this question, the number of patients required would be close to 2,500, which is quite improbable even under the best circumstances of participation and collaboration, as shown by the Maxwell study.

CONCLUSION

The use of prophylactic antibiotics is recommended in patients with isolated chest trauma requiring closed thoracostomy as a protective measure against the development of posttraumatic empyema and pneumonia.

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