Antibiotic prophylaxis for wound infections in total joint arthroplasty

A SYSTEMATIC REVIEW

We reviewed systematically the published evidence on the effectiveness of antibiotic prophylaxis for the reduction of wound infection in patients undergoing total hip and total knee replacement. Publications were identified using the Cochrane Library, MEDLINE, EMBASE and CINAHL databases. We also contacted authors to identify unpublished trials.

We included randomised controlled trials which compared any prophylaxis with none, the administration of systemic antibiotics with that of those in cement, cephalosporins with glycopeptides, cephalosporins with penicillin-derivatives, and second-generation with first-generation cephalosporins.

A total of 26 studies (11 343 participants) met the inclusion criteria. Methodological quality was variable. In a meta-analysis of seven studies (3065 participants) antibiotic prophylaxis reduced the absolute risk of wound infection by 8% and the relative risk by 81% compared with no prophylaxis (p < 0.00001). No other comparison showed a significant difference in clinical effect.

Antibiotic prophylaxis should be routine in joint replacement but the choice of agent should be made on the basis of cost and local availability.

Although total hip replacement (THR) and total knee replacement (TKR) are considered to be ‘clean’ operations, approximately 1% to 5% of wounds develop a superficial or deep infection. The prevalence of peri-prosthetic infection is 1.3% after primary THR, 3.2% after revision THR, 2% after primary TKR and 5.6% after revision TKR.

The most prevalent organisms in prosthetic-related infections are the Gram-positive bacteria, Staphylococcus aureus and Staphylococcus epidermidis. They are normally present as skin flora and can adhere to implants and multiply in polymers. Increasing infection secondary to methicillin-resistant strains of Staph. aureus and Staph. epidermidis has also emerged. The classes of antibiotic used in the treatment of wound infections include the β-lactams such as cephalosporins, penicillin and its derivatives, glycopeptides such as teicoplanin, and aminoglycosides such as gentamicin.

In this article, we bring a previous systematic review up to date by identifying and reviewing the evidence for the influence of antibiotic prophylaxis on the reduction of wound infections in patients undergoing total joint replacement.

Materials and Methods

The following electronic bibliographic databases were interrogated: the Cochrane Library, Issue 2, 2006; OVID MEDLINE, 1966 to July 2007; OVID EMBASE, 1980 to 2006 week 23; and the Cumulative Index to Nursing and Allied Health Literature (CINAHL), 1982 to July 2007. In order to prevent time-lag bias and to identify unpublished studies, a search for grey literature was undertaken using the Google Scholar engine and AMEDEO Medical literature guide. We screened the reference lists of included articles to identify any further studies and contacted primary authors thus identified by email for additional unpublished clinical trials.

All the titles and abstracts were examined to assess their relevance to the review. Only studies meeting the following eligibility criteria were included: 1) types of participant, patients undergoing a primary or revision THR or TKR, irrespective of the type of prosthesis; 2) types of antibiotic administered at any time pre-operatively, irrespective of dose and route of administration and including β-lactams, glycopeptides, aminoglycosides and any others; 3) outcome, wound infection being defined as visible purulent exudate at the surgical site.
The methodological quality of the included studies was independently assessed by one reviewer (BA) using the predefined criteria described by the Delphi list. The following parameters were assessed: 1) the method of randomisation, classified as adequate (computer-generated random-number tables or similar methods), inadequate (the use of alternate days, coin tossing or similar methods) or unclear (process not reported); 2) treatment allocation concealment, classified as adequate (centralised or pharmacy-controlled or similar methods), inadequate (use of open random-number lists, sealed envelopes or similar methods) or unclear (not reported); 3) blinding, classified as triple (patient, health-care-provider and outcome-assessor blinded), double (patient and health-care-provider blinded), single (patient blinded) or unclear (no description); 4) baseline comparability, classified as adequate (similar groups) inadequate (groups not similar characteristics) or not reported – baseline comparability was not assessed using a statistical test, but was determined by casually reviewing the studies; 5) description of eligibility criteria as defined (inclusion criteria specified), undefined (inclusion criteria not specified), or not reported; 6) sample size, classified as reported (sample-size calculation undertaken) or not reported; 7) intention-to-treat analysis, classified as adequate (analysis reported on all of the randomised joint arthroplasties), inadequate (analysis not reported on all the randomised joint arthroplasties) or unclear (no reporting on how the analysis was undertaken); and 8) exclusion, classified as reporting the number of cases excluded (joint replacements lost to follow-up, withdrawals) or unclear (no report of exclusions).

Clinical outcome data were abstracted. When papers distinguished between the number of joints and patients randomised, we used the number of joints as our unit of analysis. We analysed the results of wound infection in all randomised joints. When this was not possible because of poor reporting, we used an available case analysis. When reported, we recorded the number of exclusions from the study, either without a justification or as a result of one or more of the following protocol violations: missing data, lack of resources, patient-related causes or requirement of additional surgery. We considered death without wound infection to be a competing risk, not an exclusion.

Statistical analysis. When appropriate we undertook a meta-analysis. A random-effects Mantel-Haenszel model was used for dichotomous data and the relative risk and 95% confidence interval (CI) were calculated. Inconsistency between trial results was assessed using the $I^2$ statistic, which is the proportion of variation that is due to statistical heterogeneity rather than chance. The $I^2$ values of 25%, 50%, and 75% were interpreted as representing low, moderate and high heterogeneity. The level of significance was set at 95%.

Results

The searches identified 354 citations including 11 from hand-searching, of which 316 were rejected on the basis that the title and abstract were irrelevant. There were 38 full papers retrieved involving 32 studies. Seven citations relating to six individual studies were excluded after reading the full paper, either because they were dose-finding studies or because wound infection was not a reported outcome. The remaining 26 RCTs were included in the systematic review. A flow chart detailing the study selection was compliant with the Quality of Reporting of Meta-Analysis (QUOROM) statement (Fig. 1). The searches identified 354 citations including 11 from hand-searching, of which 316 were rejected on the basis that the title and abstract were irrelevant. There were 38 full papers retrieved involving 32 studies. Seven citations relating to six individual studies were excluded after reading the full paper, either because they were dose-finding studies or because wound infection was not a reported outcome. The remaining 26 RCTs were included in the systematic review. A flow chart detailing the study selection was compliant with the Quality of Reporting of Meta-Analysis (QUOROM) statement (Fig. 1). The searches identified 354 citations including 11 from hand-searching, of which 316 were rejected on the basis that the title and abstract were irrelevant. There were 38 full papers retrieved involving 32 studies. Seven citations relating to six individual studies were excluded after reading the full paper, either because they were dose-finding studies or because wound infection was not a reported outcome. The remaining 26 RCTs were included in the systematic review. A flow chart detailing the study selection was compliant with the Quality of Reporting of Meta-Analysis (QUOROM) statement (Fig. 1).
and TKR patients, and undefined replacements and one THR, TKR and other undefined replacements and one undefined total joint replacement and other surgery such as gynaecological and gastrointestinal operations. Some studies failed to specify whether the operations were primary or revision, the numbers of primary or revision procedures and which types of prosthesis were used.

The methodological quality of the studies was variable. The method of randomisation was adequate in five studies and unclear in the remaining 21. Allocation concealment was adequate in four studies and unclear in the remaining 22.

Blinding was well-described in one triple-blind study, two double-blind studies and one single-blind study. In five double-blind and five single-blind studies there was insufficient information as to who was blinded. A total of 12 did not describe blinding. Baseline characteristics were adequately reported and well-balanced in 17 studies, but unclear in nine.

Eligibility criteria were undefined in one study and unclear in another. Four presented an intention-to-treat analysis, eight did not but gave sufficient data to allow us to do so. Four studies presented only enough information to reconstruct an available case analysis, and in ten there was insufficient information to determine whether the analyses were by intention-to-treat.

In five, fewer than 5% of patients were excluded from the analysis, in eight, between 5% and 20%, in two, more than 20% and in 11, the number of exclusions was unclear.

Eight studies defined wound infection as superficial or deep and five considered only deep infections. Nine did not provide a definition of wound infection, although one of these distinguished wounds which contained purulent exudate.

Follow-up periods ranged from ten days to ten years, with most not specifying the minimum and maximum follow-up times (we report only the latter). The follow-up time was unclear in two studies.

A total of 14 studies reported the route of administration of antibiotics for all doses and six reported the route for the first, but not the subsequent doses. The remaining six studies did not report the route of administration for all doses. The recorded route of administration in most studies was intravenous and only five used antibiotic-impregnated cement. Antibiotics were either administered pre-operatively, at the induction of anaesthesia, up to 24 hours before surgery, just before incision, intra-operatively or post-operatively. In seven studies, one treatment arm received a single dose compared with multiple doses in the other treatment arm. The duration of antibiotics also varied from one to 14 days.

In a pooled analysis of seven studies (n = 3065) the administration of antibiotics reduced the relative risk (RR) of wound infection by 81% (RR 0.19; 95% CI 0.12 to 0.31; chi-squared test, p < 0.00001). Because such events are rare, this translates to an absolute risk reduction of 8%, meaning that one wound infection would be prevented for every 13 people treated compared with no administration of antibiotics (risk difference -0.08; 95% CI -0.03 to -0.12). There was no statistical heterogeneity (I² = 0%).

The pooled analysis of three studies (n = 2388) comparing the administration of systemic antibiotics with that of antibiotic-impregnated cement found no significant difference in clinical effect (RR 0.88; 95% CI 0.59 to 1.31; chi-squared test, p = 0.52). There was a low level of statistical heterogeneity (I² = 36.9%).

The pooled analysis of five studies (n = 2625) comparing the use of cephalosporins with that of teicoplanin found no significant difference in clinical effect (RR 1.22; 95% CI 0.64 to 2.34; chi-squared test, p = 0.54). There was no statistical heterogeneity (I² = 0%).

The pooled analysis of three studies (n = 2879) comparing the use of cephalosporins with that of penicillin-derivatives found no significant difference in clinical effect (RR 1.17; 95% CI 0.31 to 4.41; chi-squared test, p = 0.81). There was a small amount of statistical heterogeneity (I² = 7.4%).

In the pooled analysis of eight studies (n = 2527) the administration of antibiotics reduced the relative risk (RR) of wound infection by 81% (RR 0.19; 95% CI 0.12 to 0.31; chi-squared test, p < 0.00001). Because such events are rare, this translates to an absolute risk reduction of 8%, meaning that one wound infection would be prevented for every 13 people treated compared with no administration of antibiotics (risk difference -0.08; 95% CI -0.03 to -0.12). There was no statistical heterogeneity (I² = 0%).

Discussion

Antibiotic prophylaxis is effective in reducing wound infection in patients following total joint replacement. There was insufficient evidence to suggest that there was a significant difference in the efficacy of cephalosporins compared with that of teicoplanin or penicillin-derivatives, or that a particular generation of cephalosporins was more effective than another. There was no difference in clinical effect whether antibiotics were administered systemically or through impregnated cement.

Two comparisons showed low levels of inconsistency between the results of primary studies. When comparing the use of systemic antibiotics with antibiotic-impregnated cement, one study appeared to be an outlier, despite being of similar methodological quality and incorporating comparable populations, interventions and outcome measures. Statistical heterogeneity in the comparison of cephalosporins with penicillin-derivatives was probably due to chance in the study of Jones and Wojeski, in which a single event resulted in a disproportionately large clinical effect because of the small sample size. The larger trial of Pollard et al was the most influential in the meta-analysis and represented a more reasonable estimate of effect.
There are discrepancies between our findings and those of a previous systematic review.5 The latter included studies in all languages, whereas time and resource constraints meant that we could not. Therefore, relevant non-English-language papers published since 1998 were not identified in our review. However, when it has any effect, the exclusion of non-English-language papers from systematic reviews usually exaggerates the estimate of clinical effect, because non-significant results may be more likely to be published in non-English-language journals.5 We avoided repeating comparisons made in the original review which we considered to be clinically uninformative, for example, those between cephamandole or teicoplanin and any other antibiotic. There are discrepancies between the number of wound infections reported for a study in the original review and in our review. The reasons were twofold. First, in three studies,36,39,50 the original review did not use outcome data from the longest available follow-up. Secondly, our analysis was, as far as possible, based on all randomised joints, while the original was not. Failure to analyse all randomised joints introduced bias into statistical analyses and increased the likelihood of false-positive results.

The identification of optimal dosages and the duration of systemic therapy was beyond this review. The original review found that single-dose or short-term administration was as effective as long-term administration, but with lower overall costs and reduced risk of toxicity or bacterial resistance.6 Therefore, teicoplanin was administered as a single dose and cephalosporins in fewer doses and over a shorter period than penicillin derivatives.

We identified a paucity of RCTs in this important area of clinical research, which could be because the rates of wound infection after total joint replacement are low. The reported rates for wound infection, however, may have been underestimated because most trials in this review varied in their definition of wound infection and follow-up period. Nevertheless, the demand for total joint replacement will increase in the coming years, predominantly because of an ageing population and there is consequently a greater need for further RCTs. We recommend that future research should focus on improving the rigour of RCTs in accordance with the CONSORT Standards.53 We suggest that any RCT should consider carefully its measure of outcome and adoption of a common internationally accepted definition to allow comparisons between trials.

Our results add to the evidence base on the prevention of post-operative infection in total joint replacement.36,57 For every 13 patients treated, rather than untreated, one wound infection would be prevented. Since the effect of post-operative infection in such patients is serious they should be offered antibiotic prophylaxis.58 Since our results show that there is no evidence that any type of antibiotic prophylaxis has better results than any others, selection should be on the basis of cost and local availability.

**Supplementary Material**

A further opinion by Professor S. Hughes is available with the electronic version of this article. In addition, supplementary tables and figures showing details of the studies and meta-analysis are available on our website at www jbjs org uk

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

**References**