Therapeutic Antibiotics for Hand Injuries:

a systematic review and meta-analysis

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Abstract

Background

Simple hand trauma is very common, accounting for 1.8 million emergency department visits annually in the USA alone. Antibiotics are widely used as post-injury prophylaxis for these injuries, but their efficacy is unclear. This meta-analysis assessed the effect of antibiotic prophylaxis versus placebo or no treatment on wound infection rates in surgically managed hand injuries.

Methods

Embase, MEDLINE, PubMed, Cochrane Central, ClinicalTrials.gov and the WHO International Clinical Trials Portal were searched for published and unpublished studies in any language from inception to September 2015. The primary outcome was the effect of antibiotic prophylaxis on wound infection rates. Open fractures, crush injuries and bite wounds were excluded. Study quality was assessed using the Cochrane risk of bias tool. Data were pooled using random-effects meta-analysis, and Risk Ratios (RR) and 95% confidence intervals (95% CI) obtained.

Results

13 studies (2578 patients) were included, comprising 5 double blind randomized controlled trials, 5 prospective trials and 3 cohort studies. There was no significant difference in infection rate between the antibiotic and placebo/no antibiotic groups (RR 0.89 [95% CI 0.65, 1.23], p=0.49). Subgroup analysis of the five double blind randomized controlled trials (864 patients), again found no difference in infection rate (RR 0.66 [95% CI 0.36, 1.21], p=0.18).

Conclusion

There was moderate quality evidence that routine use of antibiotics does not reduce the infection rate in simple hand wounds.

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Registration

PROSPERO registration: CRD42014014412

Introduction

Antibiotic resistance is a global problem requiring re-evaluation of our practice of antibiotic use[1]. Judicious antibiotic stewardship requires clinicians to establish an evidence-based rationale for antibiotic use and conduct rigorous appraisal of current evidence, dissemination of research findings and cross-specialty dialogue[1,2]. Policymakers are increasingly concerned with the problem; in the English NHS, infection prevention and control procedures became a statutory obligation on healthcare providers in 2015[3]. It is therefore timely to reassess the evidence for antibiotic use in common clinical scenarios.

In the context of hand injuries, evidence supports the use of post-injury antibiotic prophylaxis[4] in open fractures, crush injuries and human bites[5-7] . Evidence on the use of antibiotic prophylaxis for other hand trauma is limited. These injuries comprise between 1·6% and 30% of all emergency attendances[8-10] and constitute the largest economic impact of all injury types[11]. Given the perceived cost to limb and livelihood of a severe hand infection, the lack of a standardized rationale encourages antibiotic use[12].

This study sought to establish an evidence-based rationale for the prophylactic use of antibiotics in the management of open hand trauma. It aimed to evaluate systematically the available evidence from comparative studies and draw reasoned conclusions in order to disseminate clear guidance on how to best manage these injuries.

Methods

Search strategy

A search was performed of Medline and Embase via OvidSP (all fields), PUBMED (title/abstract), The Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials (searched 3 September 2015). The trial registries ClinicalTrials.gov and the WHO International Clinical Trials Portal (http://apps.who.int/trialsearch/Default.aspx) were also searched, to identify unpublished trials (searched 3 September 2015). The search strategy in box 1 was developed to retrieve all studies and reviews of antibiotic use for hand injuries in humans. Searches were not limited by date, language or publication status. Search results were independently screened for relevance by two authors (GM and MG). Full-text articles were retrieved via the Bodleian Library (Oxford, UK) and British Library (London, UK). Disagreements on study eligibility were resolved by consensus, with reference to the senior author if required. Study selection is outlined in figure 1. The study protocol was prospectively registered with the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO/, Trial ID: CRD42014014412).

All studies comparing the rate of wound infection in patients given an antibiotic versus either placebo or no antibiotic in the context of surgical treatment for a simple hand wound were included. Both adult and paediatric studies were included. Interventional and observational studies were included. Studies of bite wounds, fractures, crush injuries, areas other than the hand, experimental models and those with no control group were excluded. Where there were two or more clinically homogenous studies, data were pooled in a meta-analysis. For studies included in the meta-analysis, the outcome measure was the post-operative infection rate. Existing reviews were screened to ensure all relevant primary studies were included.

Data collection and analysis

Studies were assessed for risk of bias using the Cochrane Collaboration's tool[13](figure 2). Two authors (GM and MG) independently extracted data on the number, age and allocation of trial participants, the nature of the injury sustained, the dose, timing and choice of antibiotic used, the comparator used, and the post-operative infection rate.

As infection is a dichotomous outcome, risk ratios (RRs) and 95% confidence intervals (CI) were calculated for each trial. Two authors (MG and GM) assessed the participants, interventions and outcomes for clinical heterogeneity. Statistical heterogeneity of the included trials was assessed both by the χ^2 test and the I^2 statistic. A χ^2 test with $p < 0.10$ or an $I^2 > 50\%$ were taken to represent significant statistical heterogeneity. Due to the variety of trial methodologies and antibiotic regimes used, trial data were pooled using the random-effect model. The pre-specified sensitivity analysis was conducted according to the risk of bias judgment for allocation concealment ('high' versus 'unclear' versus 'low'), and for fixed-effect versus random-effects models for data synthesis. A pre-specified subgroup analysis of only randomized double-blind controlled trials was performed. A funnel plot was performed to investigate reporting bias. Statistical analysis was performed using RevMan 5.3 (Nordic Cochrane Centre, Copenhagen, 2014).

Results

346 records were screened and 25 full-texts were assessed for eligibility. A total of 13 studies[14-26] involving 2578 patients met the inclusion criteria and were suitable for meta-analysis. Within these studies, a more homogenous group of five prospective randomized trials with lower risk of bias involving 864 patients were also subjected to a separate pre-specified meta-analysis.

Of the thirteen studies included, five were randomized double blind controlled trials, five were prospective trials and three were observational cohort studies. Among the randomized controlled trials, the risk of bias was low in two relatively recent trials, high in two trials and one older trial did not describe its study design in sufficient detail to assess some forms of bias. All five prospective trials were at high risk of bias in at least one area, mostly due to lack of blinding. The three cohort studies (two prospective, one retrospective) are at inherently greater risk of bias due to their observational design, but do not map well to the domains assessed by the Cochrane risk of bias tool. The results are summarized in figure 2. All 13 studies assessed the use of antibiotics following surgery for hand injuries, either as the whole study or as a separately tabulated sub-group. Five studies had three arms, comparing different antibiotic regimes to control. Six studies gave a cephalosporin, four penicillin (flucloxacillin or co-amoxiclav) and three included any antibiotic prescribed. The trials were statistically homogenous (χ^2 p=0.77, I^2=0%) but due to the heterogeneity of regimes a random-effect model was used.

As shown in figure 2, antibiotics had no significant effect on the infection rate compared to patients given placebo or no antibiotics (RR 0.89 [95% CI 0.65, 1.23], p=0.49). This absence of effect persisted throughout the pre-specified sensitivity analysis. Restricting the meta-analysis to the five randomized double blind controlled trials still showed no effect for antibiotics (RR 0.66 [95% CI 0.36, 1.21], p=0.18).

A funnel plot of the studies (fig 4) revealed no obvious publication bias, although the interpretation of this is subjective and must be guarded given the relatively small number of studies.

Discussion

The main finding of this systematic review and meta-analysis in 2578 patients with hand injuries is that the use of a prophylactic course of antibiotics does not significantly reduce the subsequent infection rate when compared with a placebo or no antibiotics. This persisted throughout the pre-specified sensitivity analysis, and also when restricting the analysis to only RCTs. The findings suggest no benefit in the use of antibiotics in hand injuries, but relate only to simple hand injuries and specifically exclude open hand fractures, crush injuries, bite wounds and grossly contaminated injuries. Assuming an infection rate of 5.6% (the mean of the included studies), power of 0.8, and α of 0.5 (2 tailed), then 1752 patients would be needed to show a 50% reduction in infection (effect size); fewer than the 2578 in this meta-analysis, but greater than the 864 in the RCT-only subgroup.

This study should be interpreted in the context of its limitations. Only five of the thirteen included trials were double-blind randomized controlled trials. Many of the trials were relatively small and did not meet current reporting standards, making an accurate risk of bias judgment impossible. This is further complicated by the limitations of the Cochrane tool when applied to non-randomized studies. Subgroup analyses were not feasible, but may have established whether antibiotics were of benefit in some potentially high risk cases, for example smokers and type 2 diabetics. Furthermore, it is unclear whether the lack of apparent effect could be accounted for by failure of the antibiotic prescribed to provide adequate microbiological cover for the organism(s) subsequently responsible for infection. Given the choice of antibiotics to cover *staphylococci spp.* and *streptococci spp.*, this is unlikely. Finally, there is potential for significant variability in the surgical management of hand wounds, with factors including choice of skin preparation,[27] the timing and extent of surgical debridement,[18] choice of dressing and follow-up care affecting infection rates.

Wound contamination is a subjective judgement, but most studies in this meta-analysis used a variant of the classification adopted by the US Centres for Disease Control[28]. This places simple trauma under ‘Class III / Contaminated’, defined as “Open, fresh, accidental wounds” (Fig 5a). Wounds with extensive devitalised tissue (eg crush injuries), established pre-operative infection or high-bioburden contamination (eg marine, sewage or agricultural contamination) would fall under ‘Class IV / Dirty’ (Fig 5b) and were excluded.

The findings of this meta-analysis differ from studies of peri-operative antibiotic prophylaxis in both elective surgery[29] and from our own guidelines for lower limb trauma[30]. This underlines the role of antibiotics as an adjunct to rather than a substitute for, meticulous surgical wound management. They also differ from the recent evidence-based guidelines for plastic surgery from the American Association of Plastic Surgeons[31], although this is likely due to the different populations analysed (class III simple hand lacerations vs any contaminated hand surgery).

These injuries are extremely common and the global impact significant. The most conservative estimate published found they accounted for 1.8 million emergency department visits in 2007 in the USA (1·6% of all ED visits)[10]; some UK series place this figure as high as 30% of all emergency department visits[8,9,32]. Prophylactic courses of antibiotics are commonly prescribed for these injuries but with little evidence to justify their use. Adopting an evidence-based protocol could prevent hundreds of thousands or perhaps millions of unnecessary antibiotic exposures, reducing adverse events and costs as well as exercising antibiotic stewardship. Moreover, when faced with no justifiable reason for prescribing antibiotic prophylaxis in most cases, the focus should shift to delivering timely definitive surgical intervention. Although a "tipping point" has yet to be defined, it is reasonable to assume that there exists a time beyond which the persistence of an untreated open hand wound makes subsequent infection more likely.

Despite its limitations, the evidence presented is strong enough to base clinical decisions on, although the need for at least one adequately-powered, well-designed, multicentre randomized controlled trial remains. This ought to establish how long definitive closure may be delayed before infection rate rises significantly in the absence of antibiotic prophylaxis. This will address the important concern among surgeons that delays in finding theatre time to deal with the large number of open hand injuries contributes to infection, driving the use of antibiotics in these cases. Subgroup analyses to establish whether smokers and those with type 2 diabetes mellitus would benefit from antibiotic prophylaxis would also be of interest.

The UK National Institute for Health and Care Excellence (NICE) published guidance on antibiotic stewardship in August 2015, recommending that "Commissioners [of healthcare services] should ensure that antimicrobial stewardship operates across all care settings"[33].

With a further report expected on antibiotic resistance in March 2016, it is likely that antibiotic prophylaxis will come under increased scrutiny. This meta-analysis of the use of antibiotic prophylaxis in open hand trauma has found that antibiotics did not significantly decrease infection rate. This finding may be used to form the basis of an antibiotic stewardship protocol, advising that, for simple open hand wounds, there is no basis to support the use of antibiotic prophylaxis.

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Declaration of interests

All authors have completed the ICMJE form for disclosure of potential conflicts of interest (available on request from the corresponding author) and declare that (1) no author received support from any company for the submitted work; (2) no author had a relationship with any companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) no author has any non-financial interests that may be relevant to the submitted work.

Details of authors' contributions

All authors designed the study, and contributed to the manuscript. GRFM and MDG conducted the literature review and performed the meta-analysis, with detailed advice on study conduct from IAK.

Registration

This study is registered with the PROSPERO international prospective register of systematic reviews, at http://www.crd.york.ac.uk/PROSPERO/

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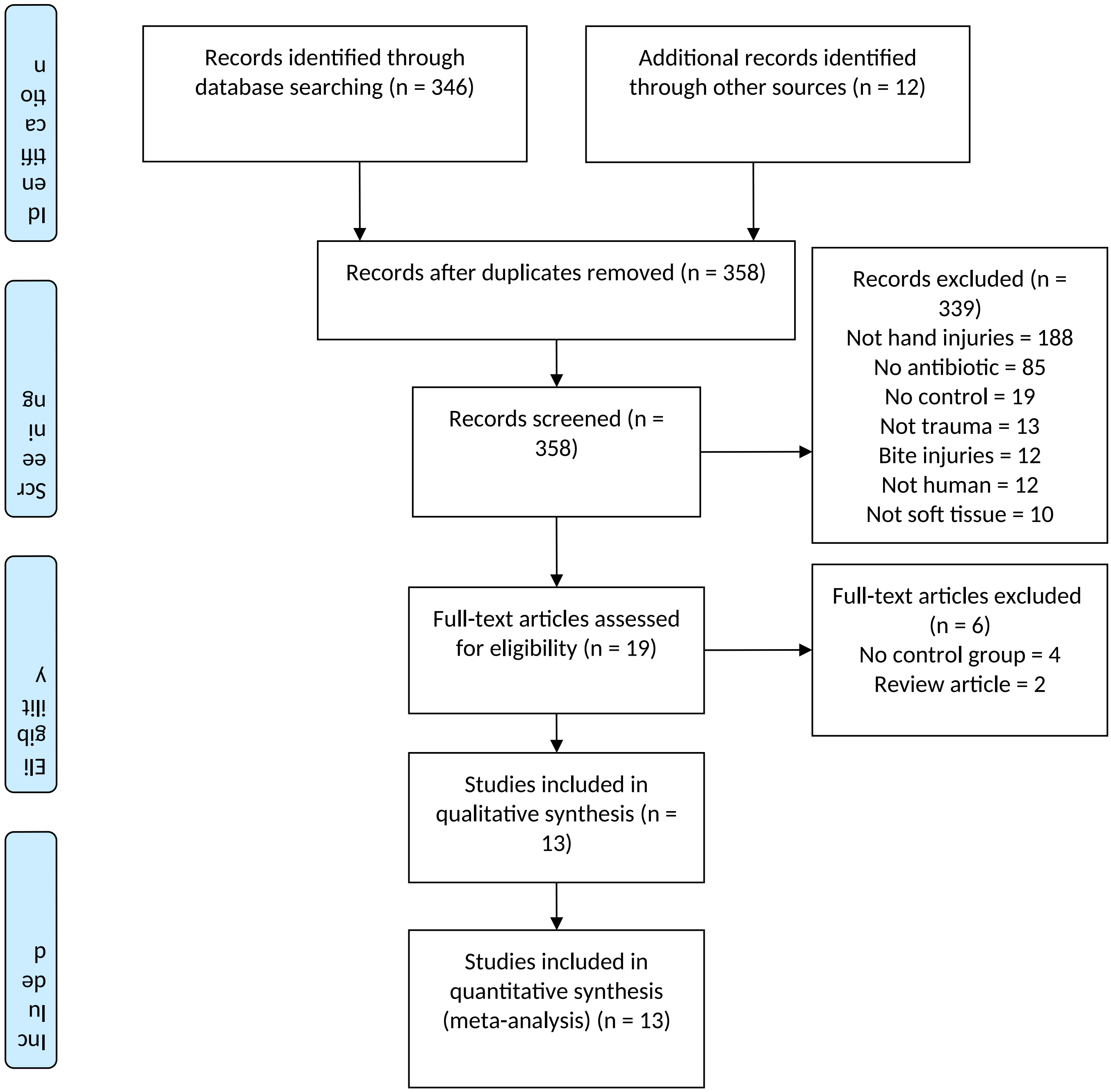

Figure 1 – PRISMA study flow diagram

Box 1 - Search terms
(((Injury[Title/Abstract] OR wound[Title/Abstract]) OR trauma[Title/Abstract]) OR laceration[Title/Abstract]) AND ((hand[Title/Abstract] OR finger[Title/Abstract]) OR digit[Title/Abstract]) AND ((antibiotic[Title/Abstract] OR antibacterial[Title/Abstract]) OR prophylaxis[Title/Abstract])