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[Intervention Review]

Chinese herbal medicines for treating skin and soft-tissue infections

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ABSTRACT

Background

Skin and soft-tissue infections (SSTIs) are common infections of the epidermis, dermis or subcutaneous tissue. SSTIs range in severity from minor, self-limiting, superficial infections to deep, aggressive, gangrenous, life-threatening infections. Some classifications divide SSTIs into 'complicated' and 'uncomplicated' infections based on clinical severity. Treatments of SSTIs involves antibiotic therapy, surgical debridement or drainage, and resuscitation if required. Sometimes these treatments are limited by high treatment costs, bacterial resistance to antibiotics and side effects, therefore, many people with SSTIs are turning to Chinese herbal medicines to treat this problem.

Chinese herbal medicines are natural substances that have been used for centuries in China where they are generally considered to be effective for SSTIs. Some Chinese herbal medicines have been shown to have antibacterial and anti-inflammatory properties, although a few herbal medicines have been reported to have side effects. Therefore there is a need to review the current clinical evidence systematically to inform current practice and guide future studies on Chinese herbal medicines for SSTIs.

Objectives

To evaluate the benefits and harms of Chinese herbal medicines for treating skin and soft-tissue infections (SSTIs).

Search methods

Searches were not restricted by date, language or publication status. In July 2014 we searched the following electronic databases: the Cochrane Wounds Group Specialised Register; the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*); Ovid MEDLINE; Ovid MEDLINE (In-Process & Other Non-Indexed Citations); Ovid EMBASE; Ovid AMED (Allied and Complementary Medicine); and EBSCO CINAHL.

Selection criteria

All randomised controlled trials (RCTs) in people with SSTIs that compared Chinese herbal medicines with another intervention or control.

Data collection and analysis

Two review authors screened the literature search results independently; there were no disagreements.

Main results

We identified no RCTs that met the inclusion criteria.

Authors' conclusions

There is currently no information available from RCTs to support or refute the use of Chinese herbal medicines in treating people with SSTIs.

PLAIN LANGUAGE SUMMARY

Should Chinese herbal medicines be used in patients with skin and soft-tissue infections?

What are skin and soft-tissue infections?
Skin and soft-tissue infections (SSTIs) are common infections of the skin or the tissue beneath the skin. They include impetigo, abscesses, cellulitis, erysipelas, necrotising (flesh-killing) skin infections, infections caused by animal or human bites or by animal contact, and infections after surgery.

Most SSTIs do not require treatment, but heal by themselves. Some SSTIs are more serious and can become life-threatening, and these need medical treatment.

What are Chinese herbal medicines?
Chinese herbal medicines are mostly extracts of plants, or parts of plants, that are used individually, or combined, as medicines. These traditional medicines have been used in China for centuries, and Chinese doctors currently prescribe them to treat SSTIs.

Why use Chinese herbal medicines for SSTIs?
In the Western world antibiotics are used to treat SSTIs, however antibiotics are expensive, can cause harms (side effects) as well as benefits, are not suitable for all people, and are becoming less effective as bacteria start to develop resistance to them. Alternative treatments need to be identified, and Chinese herbal medicines could provide that alternative.

The purpose of this review
The aim of this review was to see if medical research showed whether Chinese herbal medicines are an effective treatment for SSTIs. We wanted to compare the use of Chinese herbal medicines with other treatments, or a fake treatment (placebo), to see which produced a better outcome for patients in a particular type of medical study called a 'randomised controlled trial'.

Findings of this review
We could not find any randomised controlled trials that compared the use of Chinese herbal medicines for treating SSTIs with other treatments or a placebo. Therefore, we cannot support or refute the use of Chinese herbal medicines to treat SSTIs.

In future, we hope that randomised controlled trials will be conducted to evaluate the benefits and side effects of Chinese herbal medicines compared with current practice for the treatment of SSTIs. These trials would help people and doctors to decide on the best way to treatment SSTIs.

BACKGROUND

Skin and soft-tissue infections (SSTIs) are common infections of the epidermis, dermis or subcutaneous tissue (Stevens 2005). They include impetigo; abscesses, cellulitis and erysipelas; necrotising skin and soft-tissue infections; infections following animal and human bites; soft-tissue infections following animal contact; surgical site infections; infections in people whose immune systems are compromised, and iatrogenic infections caused by healthcare personnel or procedures.

SSTIs were described by Celsus in the first century as causing "calor, rubor, tumor and dolor" (heat, redness, swelling and pain) (Dryden 2010). These characteristics may be accompanied by signs and symptoms of systemic toxicity such as fever, malaise, nausea, hypothermia (low body temperature), tachycardia (heartbeat raised to more than 100 beats per minute), and hypotension (systolic blood pressure less than 90 mmHg, or 20 mmHg below baseline).

For most people these infections are treatable with antibiotics (Morris 2001), but longer-term problems, such as persistent swelling, recurrent episodes, bacterial resistance and side effects of the medication, can occur. Increasingly, people with SSTIs are turning to complementary and alternative medicine (CAM), including Chinese herbal medicines, in order to alleviate their symptoms and reduce the side effects of medications.

Description of the condition

SSTIs are common and range in severity from minor, self-limiting, superficial infections to life-threatening diseases, with or without open wounds or ulcers. There are many important underlying aetiologies (cause of disease), in particular diabetes. Classification of SSTIs can be based on clinical severity, clinical communicability, microbial cause, or anatomical site. Some classifications (such as that of the US Food and Drug Administration (FDA)) divide SSTIs into 'complicated' and 'uncomplicated' infections. Uncomplicated SSTIs are superficial infections amenable to treatment with antibiotics plus simple surgical incision where appropriate (e.g. simple abscesses, carbuncles, impetigo lesions, furuncles, cellulitis). Complicated SSTIs are infections involving the deeper tissues, such as subcutaneous tissue, fascia and skeletal muscle, or SSTIs in people with co-morbidities such as diabetes mellitus, HIV and other immunocompromising conditions (FDA 2013). Complicated SSTIs can be necrotising (causing cell death) or non-necrotising.

SSTIs are also divided into 'communicable (infectious)' and 'non-communicable' categories. Communicable SSTIs include infectious impetigo, anthrax, and bubonic plague (Stevens 2005), while non-communicable diseases include most of the soft-tissue infections (e.g. abscesses, cellulitis, erysipelas, necrotising fasciitis).

For some years the microbial causes of SSTIs have been recorded in the SENTRY Antimicrobial Surveillance Program database. This report presented data for a seven-year period (1998 to 2004) and ranked SSTIs according to the frequency of the pathogens involved, i.e. *Staphylococcus aureus* (42.8%), *Pseudomonas aeruginosa* (11.1%), *Escherichia coli* (9.0%), *Enterococcus* spp (species) (7.3%), *Klebsiella* spp (4.8%), *Enterobacter* spp (4.7%), β-haemolytic streptococci (4.3%), coagulase-negative staphylococci (4.0%), *Proteus mirabilis* (2.5%) and *Acinetobacter* spp (2.1%) (Fritsche 2007). However, this picture may change in the future with the rise in the number of community-acquired methicillin-resistant *S aureus* (MRSA)-related infections (Kluytmans-Vandenbergh 2006; Purcell 2005).

SSTIs involve skin infections, soft-tissue infections and trauma-related infections, so there are many differences in clinical manifestations and microbial causes. Although skin infections tend to be mild and superficial, necrotising skin and soft-tissue infections are often deep and devastating because they may involve the fascial or muscle compartments - or both - causing major destruction of tissue, which can lead to death (Stevens 2005). Trauma-related infections are at a higher risk of infection by specific pathogens such as *Aeromonas hydrophila*, Group A β-haemolytic *streptococcus*, and Clostridial spp (Behera 2011; Dryden 2010; Gold 1993;), due to exposure to water or contaminated objects. Such infections might seem innocuous at first, but can quickly become life-threatening; if physicians are aware of this risk, the likelihood of early recognition of these complications would increase (Nichols 2001).

SSTIs are frequently encountered in both community and hospital settings, but few data have been published about their incidence. According to the Centers for Disease Control and Prevention (CDC), 562,000 people were discharged with a hospital-acquired SSTIs, and SSTIs were the third most common cause of nosocomial (hospital-acquired) infections (Bounthavong 2010). A cohort study conducted in the USA from 1997 to 2002 indicated a higher incidence of SSTIs of 246 per 10,000 person-years (Ellis Simonsen 2006). In England alone, people admitted to hospital with a diagnosis of SSTI took up to 360,000 bed-days (UKDOH 2001). The morbidity and treatment costs associated with SSTIs are high, and treatment has become more complex due to the increasing prevalence of multiple-drug resistant pathogens. During the past decade the prevalence of antibiotic resistance among Gram-positive cocci (particularly *S aureus*) has increased sharply. A considerable variation in the MRSA rate has been noted between countries and continents. According to the SENTRY Antimicrobial Surveillance Program report, the highest MRSA rate was observed in North America (35.9%), compared with Latin America (29.4%), and Europe (22.8%). However, the MRSA rate varied considerably among European countries, ranging from 0.8% in Sweden, to 50% in Portugal (Fritsche 2007). Variability in MRSA rates was also apparent in Latin America, being 50% in Mexico, 38% in Chile, 29% in Brazil, 28% in Argentina, and 3% in Colombia and Venezuela combined (Moet 2007). Antibiotic resistance increases the length of stay in hospital, costs of treatment and mortality. A review of the epidemiology of severe *S aureus* infections in Europe reported that the overall seven-day case fatality rate was 19% (Lamagni 2008). A study from the USA reported that people with MRSA-infected surgical sites had a three-fold greater 90-day mortality rate, and a greater duration of hospitalisation after infection (a median of five additional days; P value < 0.001), than people infected by methicillin-sensitive *S aureus* (MSSA)(Engemann 2003). Median hospital charges were USD 92,363 for people with MRSA infections (Engemann 2003).

Description of the intervention

Uncomplicated and complicated SSTIs are treated differently and have different clinical outcomes. Uncomplicated SSTIs are usually treated with local care, with or without antibiotics, while the treatment of the most complicated SSTIs involves timely

surgical debridement or drainage, appropriate antibiotic therapy, and resuscitation, if required (Dryden 2010). Antibiotics are the conventional treatments for SSTIs, and may be discontinued once the infection is resolved or shows marked improvement in the clinical signs and symptoms of inflammation (Eron 2003). The most frequently used broad-spectrum antibiotics for treating SSTIs are β-lactams, glycopeptides, oxazolidinones (Fung 2003). However, there is variation in practice, and treatment options for SSTIs include many different oral and intravenous antibiotics. Infections are diagnosed and treated by general practitioners, emergency department doctors, dermatologists, paediatricians, surgeons and physicians from a variety of sub-specialties (BLS 2013; CREST 2005; Eron 2003; SFD 2001; Stevens 2005). Most cases of uncomplicated SSTI can be successfully treated with one to two weeks of therapy, while serious or complicated cases, such as necrotising fasciitis, may necessitate longer treatment (Eron 2003). Long-term use of antibiotics can lead to the development of bacterial resistance to the antibiotics (Austin 1999; Goossens 2005; Turnidge 2005), and to side effects (Kanwar 2007; Romano 2014). So sometimes conventional treatment of SSTIs is limited by bacterial resistance, side effects and high treatment costs.

Many people may not be good candidates for these established therapies because of their co-morbidities, advancing age or preference for treatment with Chinese herbal medicine. Chinese herbal medicines are natural substances that have been used to promote healing and alleviate pain in many countries, including China, Singapore, Thailand and Japan. In China, many people with SSTIs are increasingly turning to CAM, including Chinese herbal medicines. Chinese herbal medicines have been shown to have fewer adverse effects than antibiotics (Ernst 1995; Neil 1994; Westphal 1996), however, they are not totally without side effects, and there have been reports of them causing diarrhoea (Maechel 1992), sleep disturbance (Wilkie 1994), and nephropathy (kidney problems) (Lin 1994).

Chinese herbal medicines form the main part of traditional Chinese medicine (TCM), which have been used for centuries in China. Within the framework of TCM, Chinese herbal medicines include herbs and fungi, animal products, insect products, and minerals, often combined in a formula. An audit of 117 original research reports involving TCM or other natural products in the *Chinese Medical Journal* (2000 to 2009) found that there were different medicinal materials described in these reports: 74.4% were derived exclusively from plant material, 10.3% from animals, 3.4% from fungi, 1.7% from minerals and 10.3% were of mixed (plant/animal/fungal/mineral) composition (Collins 2011). Chinese herbal medicines are now included in the national essential drugs list of China. The Chinese State Food and Drug Administration enforces strict controls on the sale, inspection, and record keeping relating to Chinese herbal medicines (CPC 2010). Chinese herbal medicines are defined in this review as any medicine that has a plant-derived substance (products derived from raw or refined plants, or parts of plants e.g. leaves, buds, flowers, stems, roots or tubers), possibly in addition to ingredients from fungi (Poria cocos, polyporus), animals (e.g. prepared centipede or earthworm), minerals (e.g. borneol, raddle, gypsum fibrosum) etc.

TCM has unique theories regarding systems of diagnosis, aetiology and treatment. These theories are vital to its practice and include Yin-Yang, the five elements (fire, earth, metal, water and wood), Qi (vital energy) and blood, Zang-Fu (five viscera and six bowels), and channels and collaterals (meridian doctrine) (Cheng 2000; Liu C 1991). Chinese herbalists prescribe a mixture of herbs depending on the signs and symptoms the patient is experiencing and other disease information derived from four examinations. The four examinations include: observation; listening and smelling; inquiring; and feeling the pulse and palpation. Chinese herbalists analyse these to detect the cause and location of the disease and the relationship between pathogenic factors and vital energy; they then prescribe an appropriate mixture of herbs. Although based on well-established and long-standing recipes, Chinese proprietary medicines are usually formulated as tablets or capsules for convenience, commercial reasons or palatability. Usually there are four kinds of Chinese herbal medicines: single herbs, Chinese proprietary medicines, mixtures of different herbs, and integrative medicinal treatment, which is any one of the aforementioned three therapies plus Western pharmaceuticals (Liu J 2006; Vickers 1999).

Herbal medicines have been used for SSTIs, and aim to clear heat and eliminate toxins, improve circulation and dispel blood stasis. They can be used orally or topically, alone, or in combination with conventional Western medicine.

How the intervention might work

The combination and variety of medicinal herbs used for treating SSTIs depends upon the symptoms or causes of the infection. In China, Chinese herbs are generally considered to be effective and are commonly prescribed by physicians for patients with SSTIs. Some Chinese herbs are considered to have antibacterial and anti-inflammatory properties. In pharmacological experiments Radix scutellariae (the root of *Scutellaria baicalensis)* has been shown to have antiphlogistic (anti-inflammatory) properties (Huang 1990), *Coptis chinensis* has antibacterial activity against Gram-positive bacteria (Kim 2004), and *Sophora flavescens* has anti-inflammatory and antiproliferative activities (Zhou 2009). Although these properties have been observed, the mechanism by which these extracts work is unclear.

Why it is important to do this review

SSTIs cause a heavy public health and economic burden and many sufferers consult CAM practitioners for their symptoms. Alternative treatments need to be identified because of the high costs, bacterial resistance, and side effects associated with current established therapies, and the fact that they are not suitable treatments for many people: Chinese herbal medicines could offer such an alternative. In order to be recommended, however, there must be evidence of their efficacy and safety. Therefore, there is a need to review the current clinical evidence systematically in order to inform current practice and guide future studies on Chinese herbal medicines for SSTIs.

OBJECTIVES

To evaluate the benefits and harms of Chinese herbal medicines for healing skin and soft-tissue infections (SSTIs).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) that evaluate the effects of Chinese herbal medicines for treating skin and soft-tissue infections

(SSTIs). We excluded quasi-RCTs because of high risk of selection bias.

Types of participants

People of any age with an SSTI, irrespective of the diagnostic criteria used and underlying aetiologies (e.g. cellulitis, erysipelas, furuncles, simple abscesses, wound infections and deeper infections such as necrotising fasciitis, myositis and gas gangrene). We excluded trials in people with diabetic gangrene or surgical site infections.

Types of interventions

Chinese herbal medicines applied systemically or topically (or both), including herb extracts, single herbs, Chinese proprietary medicines or a combination of herbs prescribed by a Chinese practitioner (called 'individualised treatment'). We applied no limits on approval status, formulation or mode of administration for herbal medicines.

We planned to group the interventions as follows:

- single herb;
- Chinese proprietary herbal medicine (a fixed formulation of herbs produced by a pharmaceutical company, usually taken as pills, capsules or tablets);
- herbal mixture prescribed by herbalist (individualised treatment), usually tailored to an individual's pattern of symptoms.

We planned to exclude studies of integrative medicine, where Chinese herbal medicines were combined with Western medicine.

Comparison

Comparisons would have included placebo, standard care (including antibiotics), a non-medical treatment (for example, surgical procedure) or other interventions used with the intention of producing glycaemic control, promotion of healing or wound care. We planned to consider studies with co-interventions as long as there was no systematic difference in co-interventions between trial arms.

Types of outcome measures

We planned to consider all reported outcomes at all time points.

Primary outcomes

- Healing (defined as either the resolution of all clinical signs and symptoms of infection, as assessed by laboratory test or as defined by trialists) either as time to healing or proportion healed.

Secondary outcomes

- Adverse events.
- Duration of hospital stay.
- Duration of treatment.
- Costs.
- Mortality.

Search methods for identification of studies

Electronic searches

We searched the following databases:

- The Cochrane Wounds Group Specialised Register (searched 8 July 2014);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2014, Issue 6);
- Ovid MEDLINE (1946 to June Week 4 2014);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations 07 July, 2014);
- Ovid EMBASE (1974 to 07 July, 2014);
- Ovid AMED (Allied and Complementary Medicine) (1985 to June 2014);
- EBSCO CINAHL (1982 to 8 July 2014)

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) using the following search strategy:

#1 MeSH descriptor: [Herbal Medicine] explode all trees 53
#2 MeSH descriptor: [Plants, Medicinal] explode all trees 907
#3 MeSH descriptor: [Medicine, East Asian Traditional] explode all trees 890
#4 MeSH descriptor: [Drugs, Chinese Herbal] explode all trees 2594
#5 (chinese near/5 (herb* or medic* or drug*)):ti,ab,kw 6964
#6 (herb* near/5 (medic* or drug*)):ti,ab,kw 4188
#7 #1 or #2 or #3 or #4 or #5 or #6 8780
#8 MeSH descriptor: [Soft Tissue Infections] explode all trees 79
#9 MeSH descriptor: [Staphylococcal Skin Infections] explode all trees 164
#10 MeSH descriptor: [Cellulitis] explode all trees 116
#11 MeSH descriptor: [Erysipelas] explode all trees 18
#12 MeSH descriptor: [Furunculosis] explode all trees 9
#13 MeSH descriptor: [Abscess] explode all trees 481
#14 MeSH descriptor: [Surgical Wound Infection] explode all trees 2815
#15 MeSH descriptor: [Fasciitis, Necrotizing] explode all trees 3
#16 (soft next tissue next infection* or skin next infection*):ti,ab,kw 689
#17 (cellulitis or erysipelas or furuncul* or abscess* or absess* or "necrotizing fasciitis" or myositis or "gas gangrene"):ti,ab,kw 1917
#18 (surg* near/5 (wound* or incision* or site*)):ti,ab,kw 6636
#19 ((wound* or site* or incision*) near/5 infect*):ti,ab,kw 5688
#20 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 10878
#21 #7 and #20 53

The search strategies for Ovid MEDLINE, Ovid EMBASE, Ovid AMED and EBSCO CINAHL can be found in Appendix 1. We adapted the search strategies for Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL. We combined the Ovid MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (Lefebvre 2011). We combined the EMBASE search with the Ovid EMBASE filter developed by the UK Cochrane Centre (Lefebvre 2011). We combined the CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (SIGN 2011). There were no restrictions with respect to language, date of publication or study setting.

Searching other resources

We planned to scrutinise citations within all trials and review articles obtained to identify any additional trials.

Data collection and analysis

Selection of studies

Two review authors (YW, XC) independently scanned the title, abstract and keywords of every record retrieved to determine which studies required further assessment. We retrieved the full article when the information provided suggested the possibility that:

- the study compared Chinese herbal medicine with another intervention or control;
- the study had a prospective design.

If, from scanning the titles and abstracts, there was any doubt regarding these criteria, we retrieved the full article for clarification. Two review authors independently read the full paper to determine which studies met the inclusion criteria. The selection complied with Criteria for considering studies for this review (above), for Types of studies, Types of participants and Types of interventions. There were no disagreements between the authors regarding the inclusion or exclusion of studies. We planned to contact the authors of trials to provide missing data if necessary.

Data extraction and management

Independently, two review authors (YW, XC) planned to extract data concerning details of study population, intervention and outcomes using a standard data extraction form specifically adapted for this review. The data extraction form included the following items.

- General information: published/unpublished, title, authors, country of study, contact address, year of study, language of publication, year of publication, sponsor/funding organisation, setting.
- Methodological details: including criteria for 'Risk of bias' assessment (below).
- Intervention: descriptions of Chinese herbal medicines (dose, route, timing), descriptions of co-medication(s) (dose, route, timing).
- Participants: inclusion and exclusion criteria, total number in intervention and comparison groups, sex, age, baseline characteristics, withdrawals/losses to follow-up (with reasons), subgroups.
- Outcomes: proportion healed, eradication of defined infection, mortality related to SSTIs or treatment, adverse events, duration of treatment, duration of hospitalisation, costs and time to healing.

Assessment of risk of bias in included studies

Independently, two review authors (YW, XC) planned to assess each included study using the Cochrane Collaboration tool for assessing risk of bias (Higgins 2011a). This tool assesses six specific domains, namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues (e.g. if groups were similar at baseline for important prognostic indicators - area of redness and inflammation and generalised symptoms such as fever and malaise; and if co-interventions were avoided or similar between the treatment and control groups) (see Appendix 2 for details of the criteria on which we planned to base the judgement). We planned to assess blinding and completeness of outcome data for each outcome separately. We planned to complete a 'Risk of bias' table for each eligible study. We planned to discuss any disagreement amongst all review authors to achieve a consensus.

We planned to present an assessment of risk of bias using a 'Risk of bias' summary figure, which would present all of the judgements in a cross-tabulation of study by entry. This display of internal validity would have indicated the weight the reader might give the results of each study.

Measures of treatment effect

We planned to present dichotomous outcomes (e.g. proportion of infections healed, adverse events, mortality) as risk ratios (RR) with corresponding 95% confidence intervals (CI). We planned to present continuous data (e.g. duration of hospitalisation) as mean differences (MD) with corresponding 95% CI. We planned to consider time-to-event data (e.g. time to healing) if correctly analysed using survival methods that could account for censoring (i.e. just for the time that people were observed so it would have taken account of when they dropped out). It would have been inappropriate to report and analyse time to wound healing as if it were a continuous variable, unless everyone healed and there was no loss to follow-up.

Where included studies had more than two treatment arms, we planned to present the additional treatment arms in pair-wise comparisons. We planned to split the shared control group into two or more groups with smaller sample size, depending on the number of interventions studied (Higgins 2011b). For additional treatment arms that were not relevant, we did not plan to extract the data.

Unit of analysis issues

Cluster-RCTs (e.g. randomisation of clinics) that did not account for clustering during analysis would have had potential unit of analysis errors, resulting in artificially low P values and over-narrow confidence intervals. We planned to attempt to re-analyse studies with potential unit of analysis errors by calculating effective sample sizes where possible (Higgins 2011b). If a comparison had been re-analysed, we planned to quote the P value and annotate it with 're-analysed'. If this was not possible we planned to report only the point estimate (Donner 2001).

Dealing with missing data

If data had been missing from the trial reports, we had planned to contact the trial authors to request these values. If this had not been successful, we had planned to impute replacement values to compare data by meta-analysis. If this had been necessary, we had planned to perform sensitivity analyses to assess how sensitive the results were to reasonable changes in the assumptions that were made. Furthermore, we had planned to address the potential impact of missing data on the findings of the review in the Discussion (Higgins 2011b).

Data lose credibility if there is too great a degree of loss to follow-up (Xia 2010). We would have been forced to make a judgement about where this point lay for the trials likely to be included in this review. If more than 40% of data were unaccounted for by eight weeks (Xia

2010), we did not plan to extract the data in the trials concerned or use them within analyses.

Assessment of heterogeneity

We planned to assess population, methodology, intervention and outcome measures in each study for clinical heterogeneity to see if pooling of results was feasible. We planned to carry out assessment for heterogeneity using the Chi^2 test with significance being set at P value < 0.1. In addition we planned to use the I^2 statistic to estimate the total variation due to heterogeneity across studies (Higgins 2011b).

A number of options would have been available to us if we had identified heterogeneity amongst a group of trials. Firstly, we would have checked whether the data had been incorrectly extracted or entered into Review Manager (RevMan) 5.2 (RevMan 2012). Secondly, we would have conducted subgrouped analyses or meta-regression, to investigate whether heterogeneity was caused by severity of disease, patient characteristics or specific interventions. Thirdly, we would have conducted sensitivity analysis to assess the impact of outlying trials whose results conflicted with the rest of the trials. It would have been advisable to perform analyses both with, and without, outlying trials as part of the sensitivity analysis. The fourth option, in instances where there was no clinical or methodological heterogeneity and all studies had measured the same underlying effect, was the use of a fixed-effect statistical model. If there had been clinical or methodological heterogeneity, or both, and the studies had measured different underlying effects but were still sufficiently similar to make a pooled result useful, then we would have used a random-effects model and have investigated the heterogeneity using a priori sensitivity and subgroup analyses.

We planned to regard I^2 statistic values of less than 25% as representing low heterogeneity, in which case we planned to use a fixed-effect model for meta-analysis. We planned to consider values between 25% and 75% as representing moderate levels of heterogeneity, in which case we planned to use a random-effects model. If values of the I^2 statistic had been higher than 75%, indicating a high level of heterogeneity, or if most of the evidence had been non-blinded and subjective, we would not have undertaken meta-analysis, as it would not have been appropriate.

Assessment of reporting biases

Had enough trials been included in the review and been suitable for meta-analysis of a primary outcome (minimum 10 trials), we had planned to construct funnel plots. Funnel plots are figures where the trials' effects are plotted against sample size, and the final distribution of points is skewed and asymmetrical in the presence of publication bias and other biases. Funnel plot asymmetry, measured by regression analysis, would have predicted discordance of results when meta-analyses were compared with large single trials (Egger 1997).

Data synthesis

Independently, two review authors (YW, XC) planned to enter data into RevMan 5.2 using the duplicate data entry facility. We planned to summarize findings of individual studies in a narrative format. If there was sufficient homogeneity in populations, study design and outcome measures, we planned to pool results following assessment for statistical heterogeneity as described above.

Subgroup analysis and investigation of heterogeneity

We had planned to undertake a subgroup analysis if we had identified trials that were conducted in people with diabetes and in non-diabetic populations, in order to assess whether the treatment effect was modified by clinical and demographic variables.

Also, we had planned to repeat meta-analyses originally performed with a fixed-effect model using a random-effects model, and also meta-analyses originally performed with a random-effects model using a fixed-effect model, to establish the robustness of the results. If the conclusions had differed, we planned to explore reasons for this by looking at the study characteristics.

Sensitivity analysis

If a sufficient number of trials had been found, we planned to carry out sensitivity analysis to assess the robustness of the results as follows:

- exclusion of studies with inadequate or unclear (insufficient information to permit judgement) concealment of allocation;
- exclusion of studies in which outcome evaluation was not blinded or unclear (insufficient information to identify if outcome evaluation was blinded).

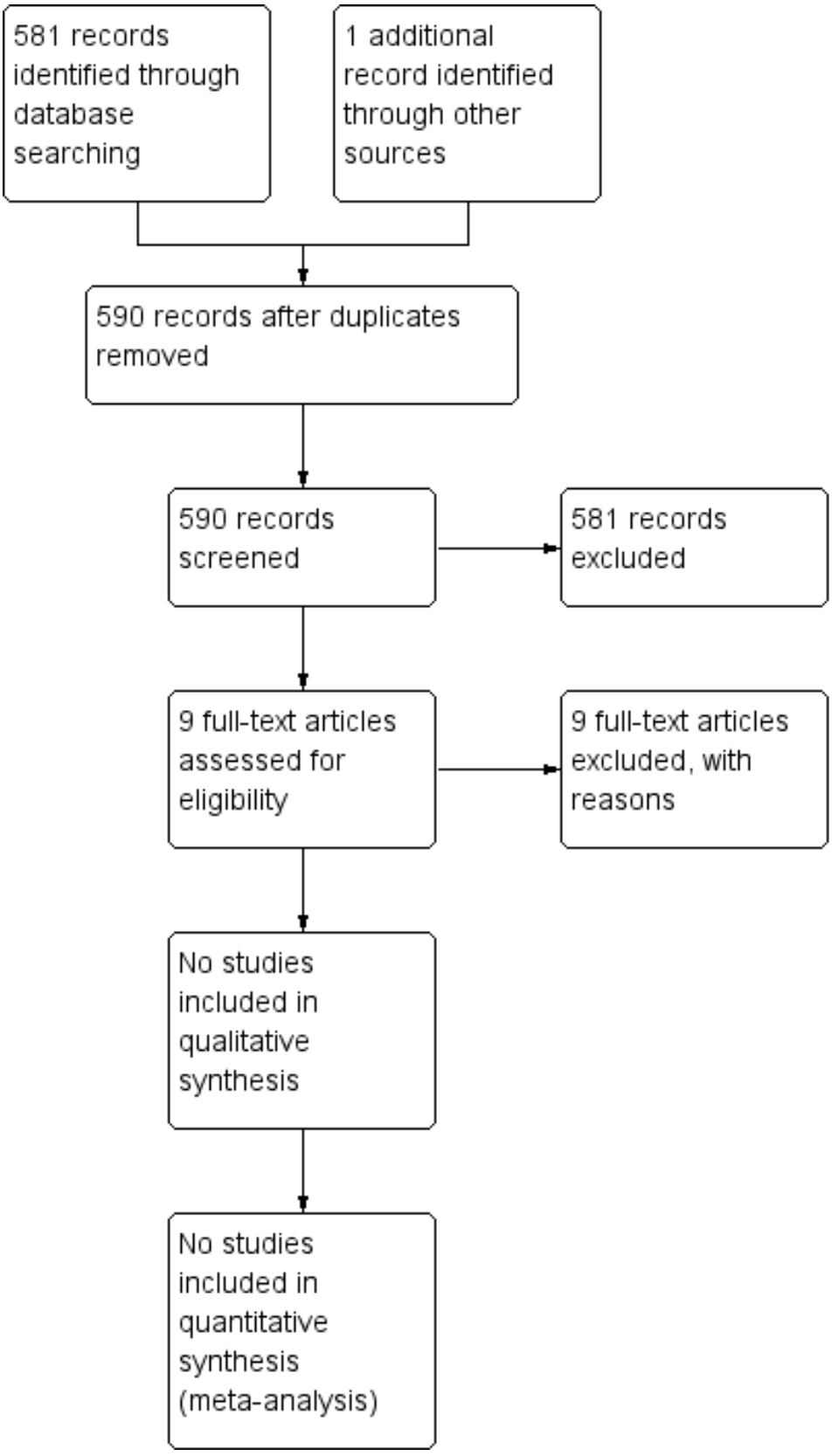
RESULTS

Description of studies

Results of the search

We screened 589 citations retrieved through searching electronic databases and one additional article through another sources; 581 citations were excluded after reading the titles and abstracts and applying our inclusion criteria. We retrieved full texts for nine articles that were excluded after further assessment. The study selection process is summarised in the PRISMA flow diagram (Liberati 2009). (Figure 1).

Figure 1. Study flow diagram.



Included studies

We identified no RCTs that fulfilled our inclusion criteria.

Excluded studies

Nine studies were excluded after assessment of the full text. Reasons for exclusion included:
• not a RCT (Ye 2011);
• not related to SSTIs: treated burns (Hirsch 2008; Panahi 2012), or measured wound healing (Leung 2012) or treated lower leg ulcer (Wei 2013) or measured incidence of infection (Zhang 2014);
• not related to Chinese herbal medicines: used traditional Chinese surgical treatment (Wang 2012), or iodophors (Gao 2007);
• not Chinese herbal medicines alone: combined acupuncture with Chinese herbal medicines (Chen 2007).

Risk of bias in included studies

No RCTs met the inclusion criteria for this review so we did not perform an assessment of risk of bias.

Effects of interventions

No RCTs met the inclusion criteria for this review so we could not establish the effects of Chinese herbal medicines on SSTIs.

DISCUSSION

Chinese herbal medicines have been used to treat skin and soft-tissue infections (SSTIs) for centuries in China (Wang 2008; Zhai 2002). In China, Chinese herbal medicines are generally considered to be effective and are commonly prescribed by physicians for patients with SSTIs (Cheng 2000; Zhai 2002). In addition some Chinese herbs have been shown to have antibacterial and anti-inflammatory properties (Chen 2013; Huang 1990; Kim 2004; Leach 2011; Liu 2007; Zhou 2009).

Clinical research on traditional Chinese medicines for SSTIs is mostly confined to case reports, controlled or uncontrolled observational studies, and non-randomised prospective studies. We could not identify any RCTs that fulfilled our inclusion criteria and therefore cannot draw any conclusions regarding the use of Chinese herbal medicines for treating SSTIs. A placebo-controlled, randomised, double-blind study is required to evaluate the effects and side effects of Chinese herbal medicines for healing SSTIs.

We recognise that there is no evidence on Chinese herbal medicines for SSTIs although these medicines are widely used in China for healing this type of infection. The absence of high quality evidence in this area sets a research agenda for the future.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence upon which to base the use of Chinese herbal medicines for treating skin and soft-tissue infections (SSTIs).

Implications for research

A placebo-controlled, randomised, double-blind study is required to evaluate the benefits and harms of Chinese herbal medicines for treating SSTIs. Feasibility and relevance to clinical practice might be improved if separate trials were conducted for different SSTIs (e.g. Chinese herbal medicines for treating erysipelas, Chinese herbal medicines for treating necrotising skin).

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Chen 2007	The intervention was not Chinese herbal medicines alone, but combined acupuncture with Chinese herbal medicines
Gao 2007	The intervention related to iodophors, not Chinese herbal medicines
Hirsch 2008	Trial investigated burns, not skin and soft-tissue infections
Leung 2012	Trial investigated wound healing, not skin and soft-tissue infections
Panahi 2012	Trial investigated burns, not skin and soft-tissue infections
Wang 2012	The intervention was traditional Chinese surgical treatment, not Chinese herbal medicines
Wei 2013	Not related to SSTIs, treated chronic lower leg ulcer
Ye 2011	This study was a non-randomised, non-blinded, self-controlled case study, not a randomised controlled trial
Zhang 2014	Not related to SSTIs, measured incidence of infection

APPENDICES

Appendix 1. Search Strategies

Ovid MEDLINE search strategy

1 exp Herbal Medicine/ (1397)
2 exp Plants, Medicinal/ (52023)
3 exp medicine, oriental traditional/ (14309)
4 exp Medicine, East Asian Traditional/ (14309)
5 exp Drugs, Chinese Herbal/ (28470)
6 (chinese adj5 (herb* or medic* or drug*)).tw. (21182)
7 (herb* adj5 (medic* or drug*)).tw. (12975)
8 or/1-7 (97642)
9 exp Soft Tissue Infections/ (2309)
10 exp Staphylococcal Skin Infections/ (4361)
11 exp Cellulitis/ (6533)
12 exp Erysipelas/ (1150)
13 exp Furunculosis/ (1302)
14 exp Abscess/ (48422)
15 exp Surgical Wound Infection/ (28418)

16 exp Fasciitis, Necrotizing/ (2093)
17 ((soft tissue or skin) adj5 infect*).tw. (15646)
18 (cellulitis or erysipelas or furuncul* or abscess* or absess* or necrotizing fasciitis or myositis or gas gangrene).tw. (69377)
19 (surg* adj5 (wound* or incision* or site*)).tw. (26529)
20 ((wound* or site* or incision*) adj5 infect*).tw. (39485)
21 or/9-20 (177506)
22 8 and 21 (298)
23 randomized controlled trial.pt. (377908)
24 controlled clinical trial.pt. (88775)
25 randomi?ed.ab. (330237)
26 placebo.ab. (147416)
27 clinical trials as topic.sh. (170927)
28 randomly.ab. (195454)
29 trial.ti. (119153)
30 or/23-29 (884650)
31 exp animals/ not humans.sh. (3964775)
32 30 not 31 (813398)
33 22 and 32 (29)

Ovid EMBASE search strategy

1 exp Drugs, Chinese Herbal/ (34656)
2 exp medicine, oriental traditional/ (2589)
3 exp Medicine, East Asian Traditional/ (2589)
4 exp Herbal Medicine/ (14910)
5 exp Plants, Medicinal/ (151132)
6 exp herbaceous agent/ (34656)
7 (chinese adj5 (herb* or medic* or drug*)).tw. (40035)
8 (herb* adj5 (medic* or drug*)).tw. (22247)
9 or/1-8 (210703)
10 exp soft tissue infection/ (7198)
11 exp staphylococcal skin infection/ (2892)
12 exp CELLULITIS/ (13420)
13 exp ERYSIPELAS/ (2455)
14 exp FURUNCULOSIS/ (1775)
15 exp ABSCESS/ (76847)
16 exp surgical infection/ (25719)
17 exp necrotizing fasciitis/ (4240)
18 ((soft tissue or skin) adj5 infect*).tw. (22653)
19 (cellulitis or erysipelas or furuncul* or abscess* or absess* or necrotizing fasciitis or myositis or gas gangrene).tw. (90549)
20 (surg* adj5 (wound* or incision* or site*)).tw. (38123)
21 ((wound* or site* or incision*) adj5 infect*).tw. (53620)
22 or/10-21 (240906)
23 9 and 22 (1232)
24 Randomized controlled trials/ (54403)
25 Single-Blind Method/ (18485)
26 Double-Blind Method/ (116620)
27 Crossover Procedure/ (39449)
28 (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or assign$ or allocat$ or volunteer$).ti,ab. (1344131)
29 (doubl$ adj blind$).ti,ab. (147903)
30 (singl$ adj blind$).ti,ab. (14625)
31 or/24-30 (1412806)
32 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ (20415374)
33 human/ or human cell/ (14875614)
34 and/32-33 (14828935)
35 32 not 34 (5586439)
36 31 not 35 (1220256)
37 23 and 36 (96)

OVID AMED search strategy

1 exp Herbal drugs/ (7336)
2 exp Plants medicinal/ (18955)

3 exp traditional medicine chinese/ (5395)
4 exp Drugs, Chinese Herbal/ (1792)
5 (chinese adj5 (herb* or medic* or drug*)).tw. (6731)
6 (herb* adj5 (medic* or drug*)).tw. (8411)
7 or/1-5 (27198)
8 exp Abscess/ (44)
9 exp Postoperative complications/ (986)
10 ((soft tissue or skin) adj5 infect*).tw. (228)
11 (cellulitis or erysipelas or furuncul* or abscess* or absess* or necrotizing fasciitis or myositis or gas gangrene).tw. (249)
12 (surg* adj5 (wound* or incision* or site*)).tw. (257)
13 ((wound* or site* or incision*) adj5 infect*).tw. (340)
14 or/9-13 (1884)
15 7 and 14 (105)
16 exp Randomized controlled trials/ (1663)
17 exp Clinical trials/ (3376)
18 exp Random allocation/ (312)
19 exp Double blind method/ (510)
20 (clin$ adj25 trial$).ti,ab. (4699)
21 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (2243)
22 exp Placebos/ (548)
23 placebo$.ti,ab. (2527)
24 random$.ti,ab. (13816)
25 exp prospective studies/ (737)
26 or/16-25 (18839)
27 15 and 26 (5)

EBSCO CINAHL search strategy

S32 S19 and S31
S31 S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30
S30 MH "Quantitative Studies"
S29 TI placebo* or AB placebo*
S28 MH "Placebos"
S27 TI random* allocat* or AB random* allocat*
S26 MH "Random Assignment"
S25 TI randomi?ed control* trial* or AB randomi?ed control* trial*
S24 AB (singl* or doubl* or trebl* or tripl*) and AB (blind* or mask*)
S23 TI (singl* or doubl* or trebl* or tripl*) and TI (blind* or mask*)
S22 TI clinic* N1 trial* or AB clinic* N1 trial*
S21 PT Clinical trial
S20 MH "Clinical Trials+"
S19 S11 and S18
S18 S12 or S13 or S14 or S15 or S16 or S17
S17 TI (herb* N5 medic* or herb* N5 drug*) or AB (herb* N5 medic* or herb* N5 drug*)
S16 TI (chinese N5 herb* or chinese N5 medic* or chinese N5 drug*) or AB (chinese N5 herb* or chinese N5 medic* or chinese N5 drug*)
S15 (MH "Medicine, Chinese Traditional+") or (MH "Medicine, Oriental Traditional+")
S14 (MH "Drugs, Chinese Herbal")
S13 (MH "Plants, Medicinal+")
S12 (MH "Medicine, Herbal+")
S11 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10
S10 TI (wound* N5 infection* or site* N5 infection* or incision* N5 infection*) or AB (wound* N5 infection* or site* N5 infection* or incision* N5 infection*)
S9 TI (surg* N5 wound* or surg* N5 incision* or surg* N5 site*) or AB (surg* N5 wound* or surg* N5 incision* or surg* N5 site*)
S8 cellulitis or erysipelas or furuncul* or abscess* or absess* or necrotizing fasciitis
S7 TI (soft tissue infection* or skin infection*) or AB (soft tissue infection* or skin infection*)
S6 (MH "Fasciitis, Necrotizing")
S5 (MH "Wound Infection+")
S4 (MH "Abscess+")
S3 (MH "Furunculosis")
S2 (MH "Cellulitis")
S1 (MH "Soft Tissue Infections")

Appendix 2. 'Risk of bias' criteria

1. Was the allocation sequence randomly generated?

Low risk of bias

The investigators describe a random component in the sequence generation process such as: referring to a random number table; using a computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots.

2. Was the treatment allocation adequately concealed?

Low risk of bias

Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomisation); sequentially-numbered drug containers of identical appearance; sequentially-numbered, opaque, sealed envelopes.

High risk of bias

Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially-numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

Unclear

Insufficient information to permit judgement of low or high risk of bias. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement, for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially-numbered, opaque and sealed.

3. Blinding - was knowledge of the allocated interventions adequately prevented during the study?

Low risk of bias

Any one of the following.

- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
- Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others was unlikely to introduce bias.

High risk of bias

Any one of the following.

- No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding.
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, and the non-blinding of others was likely to introduce bias.

Unclear

Either of the following.

- Insufficient information provided to permit a judgement of low or high risk of bias.
- The study did not address this outcome.

4. Were incomplete outcome data adequately addressed?

Low risk of bias

Any one of the following.

- No missing outcome data.
- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate.

- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes was not enough to have a clinically relevant impact on observed effect size.
- Missing data have been imputed using appropriate methods.

High risk of bias

Any one of the following.

- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size.
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
- Potentially inappropriate application of simple imputation.

Unclear

Either of the following.

- Insufficient reporting of attrition/exclusions to permit a judgement of low or high risk of bias (e.g. number randomised not stated, no reasons for missing data provided).
- The study did not address this outcome.

5. Are reports of the study free of suggestion of selective outcome reporting?

Low risk of bias

Either of the following.

- The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

High risk of bias

Any one of the following.

- Not all of the study's pre-specified primary outcomes have been reported.
- One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified.
- One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect).
- One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis.
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear

Insufficient information provided to permit a judgement of low or high risk of bias. It is likely that the majority of studies will fall into this category.

6. Other sources of potential bias

Low risk of bias

The study appears to be free of other sources of bias.

High risk of bias

There is at least one important risk of bias. For example, the study had extreme baseline imbalance.

Unclear

There may be a risk of bias, but there is either:

- insufficient information to assess whether an important risk of bias exists; or
- insufficient rationale or evidence that an identified problem will introduce bias.

CONTRIBUTIONS OF AUTHORS

Wang YF: conceived the review question, collected the referenced studies, analysed studies for inclusion, developed the review and co-ordinated the review development. Completed the first draft of the review and edited subsequent drafts. Made an intellectual contribution to the review, approved the final version of the review prior to submission.
Wang YJ: developed the review and performed part of writing or editing of the review. Made an intellectual contribution to the review and advised on part of the review.
Cui XJ: collected the referenced studies, analysed studies for inclusion, performed part of writing or editing of the review. Made an intellectual contribution to the review and advised on part of the review.
Que HF: developed the review and performed part of writing or editing of the review. Made an intellectual contribution to the review, advised on part of the review and is guarantor of the work.

Contributions of editorial base

Nicky Cullum: Approved the protocol and edited the review and approved the review prior to submission.
Sally Bell-Syer: co-ordinated the editorial process. Advised on methodology, interpretation and content. Edited the review.
Ruth Foxlee: designed the search strategy.
Amanda Briant: ran the searches for the review.

DECLARATIONS OF INTEREST

Wang YF: none known
Que HF: none known
Wang YJ: none known
Cui XJ: none known

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