# Antiseptics for burns (Protocol)

**Norman G, Dumville JC, Mohapatra DP, Hassan IA, Edwards J, Christie J**


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[Intervention Protocol]

# Antiseptics for burns

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## ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects and safety of antiseptics for the treatment of burns in any care setting.

## BACKGROUND

### Description of the condition

A burn has been defined as an injury to the skin or other organic tissue caused by thermal trauma (Hendon 2002). Burns are caused by heat (including contact with flames, high temperature solids (contact burns) and liquids (scalds)), chemicals, electricity, friction or abrasion, and radiation (including sunburn and radioactivity); respiratory damage, as a consequence of smoke inhalation, is also considered a type of burn (Hendon 2002).

### Incidence and impact

Burn injuries are a considerable source of morbidity and mortality (Mock 2008). As outlined by the World Health Organization, the burden of injury falls predominantly on people living in low- and middle-income countries; over 95% of the 300,000 annual deaths from fires occur in these countries (Mock 2008). Total burn mortality is inversely correlated with both national income and income inequality (Peck 2013). The much greater number of injuries resulting in disability and disfigurement are also disproportionately concentrated in low- and middle- income countries (Mock 2008). Fire-related burns have been estimated to account for 10 million lost disability-adjusted life years (DALYs) every year (Peden 2002), a figure which does not include the social and personal impact of non-disabling disfigurement.

Additional mortality and morbidity are caused by other types of burns including scalding, and electrical and chemical burns (American Burn Association 2013). Globally, children and young people, and women are disproportionately affected by burn injuries, while the types and causes of injury in children differ somewhat from those seen in adults (Peck 2012).

Although, both incidence of burns and associated morbidity and mortality are much lower in high-income countries, they are nevertheless significant. Annually in the United Kingdom (UK) around 250,000 people suffer a burn; 175,000 attend a hospital emer-

gency department with a burn and, of these, approximately 13,000 are admitted to hospital and 300 die (National Burn Care Review 2001). In the United States (US) the figures for those receiving medical treatment were 450,000 with 40,000 hospitalisations and 3,400 deaths (American Burn Association 2013). These data indicated that, in contrast to the global pattern, a majority of patients were male (69%), and while children aged under five years accounted for 20% of all cases, 12% were people aged 60 years or older (American Burn Association 2013).

### Burn severity and extent

The severity of burns is categorised by the depth of the tissues affected; in the case of burns to the skin, this is the layers of cells in the skin (Demling 2005). Epidermal burns (sometimes known as first degree burns) are confined to the epidermis (outer surface of the skin), are not usually significant injuries, and heal rapidly and spontaneously. Partial thickness burns (sometimes known as second degree burns) involve varying amounts of the dermis (skin) and may become deeper and heal with varying amounts of scarring, which will be determined partly by the depth of the burn. Partial thickness burns are divided into superficial and deep partial thickness wounds: superficial partial thickness burns extend into the papillary or superficial upper layer of the dermis, whilst deep partial thickness burns extend downward into the reticular (lower) layer of the dermis. Full thickness burns (sometimes known as third degree burns) extend through all the layers of the skin, while full thickness burns (sometimes called fourth degree burns) extend beneath the skin layers, into underlying structures (fat, muscle, bone) (Demling 2005; European Practice Guidelines 2002).

The age of patients affects their prognosis, with infants and older people having poorer outcomes (DeSanti 2005; Alp 2012). The area of a burn will also be key to the time taken to heal, and also to the risk of infection (Alp 2012). Burn size is determined by the percentage of the total body surface area that is burned; estimating this can be difficult, particularly in children; the most accurate method uses the Lund and Browder chart (Hettiaratchy 2004).

The depth of burn and its location may be predictors of psychological, social, and physical functioning following treatment (Baker 1996). Most extensive burns are a mixture of different depths, and burn depth can change and increase in the acute phase after the initial injury; the extent to which this occurs will depend on the effectiveness of the initial treatment (resuscitation) (Hettiaratchy 2004).

### Burn wound infection

Infections are a potentially serious complication in people with burns. US data indicated that over a 10 year period more than 19,000 complications in patients with burns were reported. While 31% of these were recorded as pulmonary complications, 17% were wound infections, or cellulitis, or both, and 15% were recorded as septicaemia (a serious life-threatening illness caused by bacteria in the bloodstream) or other infectious complications (Latenser 2007). We were unable to locate other large-scale international data for infection-related complication rates.

Up to 75% of all burn deaths following initial resuscitation are a consequence of infection rather than more proximal causes such as osmotic shock and hypovolaemia (types of changes in the concentration of fluids in the body) (Bang 2002; Fitzwater 2003). Although this figure includes other types of hospital/healthcare-acquired infections such as pneumonia, a substantial proportion follow an infection (Alp 2012) which would meet accepted criteria for infections of burn wounds (Peck 1998). Burn wound infections also contribute to morbidity, lengthening recovery times, and increasing the extent of scarring (Church 2006; Oncul 2009), as well as the pain experienced by patients (Tengvall 2006).

All open wounds offer an ideal environment for microbial colonisation. Most wounds will contain some micro-organisms but this will not necessarily lead to adverse events (AWMA 2011). Recently the view has developed that it is infection with sufficient and/or specific types of pathogenic micro-organisms, and possibly resulting biofilms (Percival 2004; Wolcott 2008) that may lead to negative outcomes and, potentially, delayed healing (Bowler 2003; Davies 2007; Madsen 1996; Trengove 1996). (Biofilms are formed by bacteria which grow on a surface to form a film of cells. Growing in this way can make them more resistant to bacteriocidal agents.) Previously it was thought that the critical factor was a threshold concentration of microbes (bioburden) (Robson 1968). However, the impact of microbial colonisation on wound healing is not independent of the host response. The ability of the host to provide adequate immune response is likely to be as critical, if not more so, in determining whether a wound heals, as the specifics of the flora in the wound.

Patients with burns have a particular vulnerability to infection, as a result of the loss of the physical barrier to infection, and the reduction in immunity mediated by the lost cells (Ninnemann 1982; Winkelstein 1984). Infections commonly occur in the acute period following the burn (Church 2006).

The spectrum of infective agents that can be present in the burn wounds varies. Nowadays, Gram-positive bacteria such as *Staphylococcus aureus (S. aureus)*, and Gram-negative bacteria such as *Pseudomona aeruginosa* (*P. aeruginosa)* are the predominant pathogens (Wibbenmeyer 2006), although other micro-organisms such as fungi, yeasts, and viruses can also be present (Church 2006; Polavarapu 2008). Multidrug-resistant micro-organisms, such as methicillin-resistant *S. aureus* (MRSA), are frequently and increasingly identified in burns (Church 2006; DeSanti 2005; Keen 2010).

## Description of the intervention

**Standard care**

The care for burn wounds is determined in part by their severity (depth), area, and location (National Network for Burn Care 2012). For significant injuries involving the lower layers of skin, standard care may involve a range of dressings, or skin substitutes, or both, (Wasiak 2013) and more complex interventions such as hyperbaric oxygen therapy and negative pressure wound therapy (Dumville 2012; Villanueva 2004). The nature and extent of the burn wound, together with the type and amount of colonising micro-organisms can also influence the risk of invasive infection (Bang 2002; Fitzwater 2003).

**Antiseptics**

Antiseptics are topical antimicrobial agents which are thought to prevent the growth of pathogenic micro-organisms without damaging living tissue (Macpherson 2004). Applications broadly fall into two categories: lotions used for wound irrigation, or cleaning, or both, with a brief contact time (unless used as a pack/soak), and products which are in prolonged contact with the wound such as creams, ointments, and impregnated dressings (BNF 2014).

Agents used primarily for wound irrigation/cleaning are commonly based on povidone-iodine, chlorhexidine and peroxide agents. Less commonly used are traditional agents such as gentian violet and hypochlorites. Longer contact creams and ointments include fusidic acid, mupirocin, neomycin sulphate and iodine (often as cadexomer iodine). Silver-based products such as silver sulfadiazine and silver-impregnated dressings are increasingly used, as are honey-based products.

The British National Formulary (BNF) categorises antimicrobial dressings under honey-based, iodine-based, silver-based, and other, which includes dressings impregnated with agents such as chlorhexidine or peroxides (BNF 2014). The choice of dressing for a burn wound is based on a number of factors including the need to accommodate movement, the minimisation of adherence to the wound surface, the prevention of infection, the ability to absorb wound fluid and maintain humidity, and the active promotion of healing (Wasiak 2013).

Antibiotics are substances that destroy or inhibit the growth of bacteria (Macpherson 2004) (normally by inhibiting deoxyribonucleic acid (DNA), protein synthesis or by disrupting the bacterial cell wall). Routine prophylaxis against infection with systemic antibiotics is not currently recommended. While it may reduce burn wound infections, or colonisation, or both, it does not decrease mortality, and may in fact increase the risk of selecting resistant micro-organisms such as MRSA (Avni 2010; Barajas-Nava 2013).

In contrast, antiseptics (the focus of this review) can be bacteriocidal (in that they kill micro-organisms) or they can work by slowing the growth of organisms (bacteriostatic) (Macpherson 2004), but they usually work without damaging living tissue. Antiseptics can reduce the presence of other micro-organisms such as viruses and fungi, as well as bacteria, and often work by damaging the surface of microbes (Macpherson 2004). According to the BNF (BNF 2014) antiseptics are used to reduce the presence of micro-organisms on living tissue.

### How the intervention might work

This review considers the use of antiseptics for both clinically infected and non-infected wounds. The rationale for treating clinically infected wounds with antiseptic agents is to kill or slow the growth of the pathogenic micro-organisms, thus preventing an infection from worsening and spreading (Kingsley 2004). In the case of burns, the prevention of infections, and systemic infections in particular, is especially important, as patients can have lowered immunity as a consequence of their injury (Church 2006). Improved healing may also result, although evidence on the association between wound healing and infection is limited (Jull 2013; O'Meara 2001; Storm-Versloot 2010).

There is a widely held view that wounds which do not have clear signs of clinical infection, but which have characteristics such as retarded healing, may also benefit from a reduction in bacterial load (bioburden). Again, evidence for this is limited (AWMA 2011; Howell-Jones 2005).

### Why it is important to do this review

Burn wounds are a source of substantial morbidity and mortality; much of this results from the original wound becoming infected (Latenser 2007). While infections pose real risks to burns patients, the problem of antibiotic and multi-drug resistance in bacteria continues to grow (Church 2006; DeSanti 2005; Keen 2010); alternatives to routine use of antibiotics for the minimisation of infection can be a key element of care.

There is a current published Cochrane review of antibiotics for the prevention (prophylaxis) of burn wound infection (Barajas-Nava 2013), while a second Cochrane review of antibiotics for the treatment of infected burn wounds is now underway (Lu 2015). This review of antiseptics complements these reviews and will complete the assessment of evidence for agents with antimicrobial properties in the care of all burn wounds, whether infected or not. There will be some overlap between this review and other Cochrane and non-Cochrane reviews of dressings for partial thickness burns (Wasiak 2013), and of individual agents with antiseptic properties for all types of wounds (Aziz 2012; Jull 2013; Storm-Versloot 2010). However, this review will provide a single synthesis of the randomised evidence relating to all antiseptics for any type of burn wound.

## OBJECTIVES

To assess the effects and safety of antiseptics for the treatment of burns in any care setting.

## METHODS

## Criteria for considering studies for this review

### Types of studies

We will include published and unpublished randomised controlled trials (RCTs), including cluster-RCTs, irrespective of language of report. We will only include crossover trials if they report outcome data at the end of the first treatment period, prior to crossover. We will exclude quasi-randomised studies.

### Types of participants

We will include studies enrolling participants of any age with burn wounds. We will include burns of any type, severity, extent or current infection status, managed in any care setting. We will accept authors' definitions of the category of burn represented in included trials. We will include trials of participants with burns, alongside people with other types of wounds where the participants with burns constitute at least 75% of the trial population.

### Types of interventions

The interventions of interest are topical antiseptic agents. We will include any RCT in which the use of a specific topical antiseptic is the only systematic difference between treatment groups. Control regimens may include placebo, an alternative antiseptic, another therapy such as antibiotics or isolation of the patient, standard care or no treatment. We will include studies which evaluate intervention schedules, including other therapies, provided that these treatments were delivered in a standardised way across the trial arms. We will exclude trials in which the presence or absence of a specific antiseptic was not the only systematic difference. We will also exclude evaluations of antiseptics used to prepare for the surgical treatment of burns (i.e. where antisepsis is part of the perioperative procedure).

We anticipate that likely comparisons will include use of different antiseptic agents, in particular, the use of different types of dressings impregnated with antiseptic agents; comparisons of impregnated dressings or other antiseptic preparations with standard care; and comparison of antiseptics with topical or systemic antibiotics. We anticipate that other elements of standard care may be co interventions in all trial arms.

### Types of outcome measures

#### Primary outcomes

The primary effectiveness outcome for this review is wound healing. Trialists use a range of different methods of measuring and reporting this outcome. We will consider that RCTs which report one or more of the following provide the most relevant and rigorous measures of wound healing:

- Time-to-complete wound healing (correctly analysed using survival, time-to-event approaches). Ideally the outcome will be adjusted for appropriate covariates e.g. baseline wound area/degree/duration.
- Proportion of wounds completely healed during follow-up (frequency of complete healing).

We will use and report the study authors' definitions of complete wound healing. We will report outcome measures at the latest time point available (assumed to be length of follow-up if not specified) and the time point specified in the methods as being of primary interest (if this is different from latest time point available).

Where both the outcomes above are reported, we will present all data in a summary outcome table for reference, but will focus on reporting time-to-healing. When time is analysed as a continuous measure, but it is not clear whether all wounds healed, or when change, or rate of change in wound size is reported without adjustment for baseline size, we will document the use of the outcome in the study, but we will not extract, summarise or use the data in any meta-analysis.

The primary safety outcome for the review is change in wound infection status (as defined by the study authors). In the case of wounds which are considered to be clinically infected at baseline, we will assess resolution of infections. In the case of wounds which are not considered to be clinically infected at baseline, we will assess the incidence of new infections. We will also assess the incidence of septicaemia, where data permit. We will not extract data on microbiological assays not clearly linked to a diagnosis of infection.

#### Secondary outcomes

We will include the following secondary outcomes.

- Adverse events.
  - Where reported, we will extract data on all serious adverse events and all non-serious adverse events. We will not report individual types of adverse events other than pain (see below) or infection (see Primary outcomes).
- Health-related quality of life.
  - We will include quality of life where it is reported, using a validated scale such as the SF-36 or EQ-5D, or a validated disease-specific questionnaire. Ideally, reported data will be adjusted for the baseline score.
- Pain (including pain at dressing change).
  - We will include pain only where mean scores with a standard deviation are reported using a scale validated for the assessment of pain levels, such as a visual analogue scale (VAS).
- Resource use (when presented as a mean with standard deviation).
  - We will include measures of resource use such as number of dressing changes, number of nurse visits, length of hospital stay, and need for other interventions.
- Costs associated with resource use (including estimates of cost-effectiveness).

- Mortality (overall and infection-related).

## Search methods for identification of studies

### Electronic searches

We will search the following electronic databases to identify relevant RCTs.

- The Cochrane Wounds Group Specialised Register
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, latest issue)
- Ovid MEDLINE (1946 to date)
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations)
- Ovid EMBASE (1974 to date)
- EBSCO Cumalative Index to Nursing and Allied Health Literature (CINAHL) (1982 to date)

We will use the following provisional search strategy in CENTRAL.
#1MeSH descriptor: [Anti-Infective Agents] explode all trees
#2MeSH descriptor: [Penicillins] explode all trees
#3MeSH descriptor: [Cephalosporins] explode all trees
#4MeSH descriptor: [Aminoglycosides] explode all trees
#5MeSH descriptor: [Quinolones] explode all trees
#6MeSH descriptor: [Clindamycin] explode all trees
#7MeSH descriptor: [Metronidazole] explode all trees
#8MeSH descriptor: [Trimethoprim] explode all trees
#9MeSH descriptor: [Mupirocin] explode all trees
#10MeSH descriptor: [Neomycin] explode all trees
#11MeSH descriptor: [Fusidic Acid] explode all trees
#12MeSH descriptor: [Framycetin] explode all trees
#13MeSH descriptor: [Polymyxins] explode all trees
#14MeSH descriptor: [Chlortetracycline] explode all trees
#15(antibiotic* or antimicrobial* or antibacterial* or penicillin* or cephalosporin* or aminoglycoside* or quinolone* or clindamycin or metronidazole or trimethoprim or mupirocin or "pseudomonic acid" or neomycin or "fusidic acid" or framycetin or polymyxin* or chlortetracycline):ti,ab,kw
#16MeSH descriptor: [Antisepsis] explode all trees
#17antiseptic*:ti,ab,kw
#18MeSH descriptor: [Soaps] explode all trees
#19MeSH descriptor: [Iodophors] explode all trees
#20MeSH descriptor: [Chlorhexidine] explode all trees
#21MeSH descriptor: [Alcohols] explode all trees
#22MeSH descriptor: [Hydrogen Peroxide] explode all trees
#23MeSH descriptor: [Benzoyl Peroxide] explode all trees
#24MeSH descriptor: [Gentian Violet] explode all trees
#25MeSH descriptor: [Hypochlorous Acid] explode all trees
#26MeSH descriptor: [Hexachlorophene] explode all trees
#27MeSH descriptor: [Potassium Permanganate] explode all trees
#28MeSH descriptor: [Silver] explode all trees
#29MeSH descriptor: [Silver Sulfadiazine] explode all trees
#30MeSH descriptor: [Honey] explode all trees
#31("soap" or "soaps" or iodophor* or povidone or iodine or chlorhexidine or betadine or "alcohol" or disinfectant* or "hydrogen peroxide" or "benzoyl peroxide" or "gentian violet" or hypochlorit* or eusol or dakin* or hexachlorophene or benzalkonium or "potassium permanganate" or "silver sulfadiazine" or "silver sulphadiazine" or honey*):ti,ab,kw
#32 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 90292
#33 MeSH descriptor: [Burns] explode all trees
#34 ("burn" or "burns" or "burned" or scald*):ti,ab,kw
#35 ("thermal" near injur*):ti,ab,kw
#36 #33 or #34 or #35
#37 #32 and #36 in Trials
We will combine the Ovid MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2011). We will combine the EMBASE search with the Ovid EMBASE filter developed by the UK Cochrane Centre (Lefebvre 2011). We will combine the CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN 2011). There will be no restrictions with respect to language, date of publication or study setting. We will also search the following clinical trials registries.

- ClinicalTrials.gov (http://www.clinicaltrials.gov/).
- WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/Default.aspx).
- EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/).

### Searching other resources

We will try to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials, as well as relevant systematic reviews, meta-analyses and health technology assessment reports.

## Data collection and analysis

### Selection of studies

Two review authors will independently assess the titles and abstracts of the citations retrieved by the searches for relevance. After this initial assessment, we will obtain full text copies of all studies considered to be potentially relevant. Two review authors will independently check the full papers for eligibility; disagreements will be resolved by discussion and, where required, the input of

a third review author. We will obtain translation support, where necessary, for non-English language reports. Where the eligibility of a study is unclear, we will attempt to contact study authors. We will record all reasons for exclusion of studies for which we had obtained full copies. We will complete a PRISMA flowchart to summarise this process (Liberati 2009).

Where studies have been reported in multiple publications/reports, we will obtain all publications. Whilst we will include each study only once in the review, we will extract data from all reports to ensure all available relevant data are obtained.

### Data extraction and management

We will extract and summarise details of the eligible studies. Where possible we will extract data by treatment group for the prespecified interventions and outcomes in this review. Data will be extracted independently by two review authors; discrepancies will be resolved through discussion or by consultation with a third reviewer. Where data are missing from reports, we will attempt to contact the study authors and request this information.

Where a study with more than two intervention arms is included, only data from intervention and control groups that meet the eligibility criteria will be extracted. Where the reported baseline data relate to all patients rather than to those in relevant treatment arms, we will extract the data for the whole trial and note this. We will collect outcome data for relevant time points as described in the Types of outcome measures.

Where possible, we will extract the following data:

- bibliographic data, including date of completion/ publication;
- country of origin;
- unit of randomisation (participant/wound);
- unit of analysis;
- trial design e.g. parallel; cluster;
- care setting;
- number of participants randomised to each trial arm and number included in final analysis;
- eligibility criteria and key baseline participant data including cause, depth, extent (area/proportion of total body surface area) and location of burns; ages of patients, and whether they have a diagnosis of infection at baseline;
- details of treatment regimen received by each group;
- duration of treatment;
- details of any co interventions;
- primary and secondary outcome(s) (with definitions and, where applicable, time-points);
- outcome data for primary and secondary outcomes (by group);
- duration of follow-up;
- number of withdrawals (by group) and number of withdrawals (by group) due to adverse events;
- publication status of study;
- source of funding for trial.

### Assessment of risk of bias in included studies

Two review authors will independently assess included studies using the Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011a). This tool addresses six specific domains: sequence generation, allocation concealment, blinding, incomplete data, selective outcome reporting and other issues. In this review we will record issues with unit of analysis, for example where a cluster trial has been undertaken but analysed at the individual level in the study report.

We will assess blinding of outcome assessment and completeness of outcome data for each of the review outcomes separately. We will present our assessment of risk of bias using two 'Risk of bias' summary figures; one is a summary of bias for each item across all studies, and a second shows a cross-tabulation of each trial by all of the risk of bias items.

We will summarise a study's risk of selection bias, detection bias, attrition bias, reporting bias and other bias. In many of the comparisons included in this review, we anticipate that blinding of participants and personnel may not be possible. For this reason the assessment of the risk of detection bias will focus on whether blinded outcome assessment was reported (because wound healing can be a subjective outcome, it can be at high risk of measurement bias when outcome assessment is not blinded). For trials using cluster randomisation, we will also consider risk of bias for recruitment bias, baseline imbalance, loss of clusters, incorrect analysis and comparability with individually-randomised trials (Higgins 2011b) (Appendix 2).

### Measures of treatment effect

We will report time-to-event data (e.g. time-to-complete wound healing) as hazard ratios (HRs) when possible, in accordance with the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). If studies reporting time-to-event data (e.g. time-to-healing) do not report a HR, then, when feasible, we plan to estimate this using other reported outcomes, such as numbers of events, through the application of available statistical methods (Parmar 1998; Tierney 2007). For dichotomous outcomes, we will calculate the risk ratio (RR) with 95% confidence intervals (CIs). For continuous outcome data, we will use the mean difference (MD) with 95% CIs for trials that use the same assessment scale. When trials use different assessment scales, we will use the standardised mean difference (SMD) with 95% CIs.

### Unit of analysis issues

Where studies have been randomised at the participant level and outcomes measured at the wound level, for example for wound healing, we will treat the participant as the unit of analysis when

the number of wounds assessed appears to be equal to the number of participants (e.g. one wound per person).

A possible unit of analysis issue that may occur is that randomisation has been carried at the participant level with the allocated treatment used on multiple wounds per participant (or perhaps only on some participants), but data are presented and analysed per wound (clustered data).

In cases where included studies contain some or all clustered data, we plan to report this, noting whether data had been (incorrectly) treated as independent. We will record this as part of the 'Risk of bias' assessment. We do not plan to undertake further calculations to adjust for clustering as part of this review.

### Dealing with missing data

It is common to have data missing from trial reports. Excluding participants from the analysis post randomisation, or ignoring participants who are lost to follow-up compromises the randomisation and potentially introduces bias into the trial. If it is thought that study authors might be able to provide some missing data, we will contact them; however, it is likely that data will often be missing because of loss to follow-up. In individual studies, when data on the proportion of burns healed are presented, we plan to assume that randomly assigned participants not included in an analysis had an unhealed wound at the end of the follow-up period (i.e. they will be considered in the denominator but not in the numerator). When a trial does not specify participant group numbers before dropout, we will present only complete case data. For time-to-healing analysis using survival analysis methods, dropouts should be accounted for as censored data. Hence all participants will be contributing to the analysis. We acknowledge that such analysis assumes that dropouts are missing at random and there is no pattern of missingness. We will present data for area change of burn and for all secondary outcomes as a complete case analysis.

For continuous variables e.g. length of hospital stay and for all secondary outcomes, we will present available data from the study reports/study authors and we do not plan to impute missing data. Where measures of variance are missing, we will calculate these, wherever possible (Higgins 2011a). If calculation is not possible, we will contact the study authors. Where these measures of variation remain unavailable and we cannot calculate them, we will exclude the study from any relevant meta-analyses that we conduct.

### Assessment of heterogeneity

Assessment of heterogeneity can be a complex, multi-faceted process. Firstly, we will consider clinical and methodological heterogeneity: that is the degree to which the included studies vary in terms of participants, interventions, outcomes, and characteristics such as length of follow-up. We will supplement this assessment of clinical and methodological heterogeneity by information regarding statistical heterogeneity - assessed using the Chi² test (we will consider a significance level of $P < 0.10$ to indicate statistically significant heterogeneity) in conjunction with the $I^2$ measure (Higgins 2003). $I^2$ examines the percentage of total variation across RCTs that is due to heterogeneity rather than chance (Higgins 2003). Very broadly, we will consider that $I^2$ values of 25%, or less, may mean a low level of heterogeneity (Higgins 2003), and values of 75% or more, indicate very high heterogeneity (Deeks 2011). Where there is evidence of high heterogeneity, we will attempt to explore this further (see Data synthesis).

### Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. Publication bias is one of a number of possible causes of 'small study effects', that is, a tendency for estimates of the intervention effect to be more beneficial in smaller RCTs. Funnel plots allow a visual assessment of whether small study effects may be present in a meta-analysis. A funnel plot is a simple scatter plot of the intervention effect estimates from individual RCTs against some measure of each trial's size or precision (Sterne 2011). Funnel plots are only informative when there are a substantial number of studies included in an analysis; we plan to present funnel plots for meta-analyses which include at least 10 RCTs using Review Manager 5.3 (RevMan 2014).

### Data synthesis

We will combine details of included studies in narrative review according to the comparison between intervention and comparator, the population and the time point of the outcome measurement. We will consider clinical and methodological heterogeneity and undertake pooling when studies appear appropriately similar in terms of burn type and severity, intervention type and antibacterial agent, duration of treatment and outcome assessment.

In terms of a meta-analytical approach, in the presence of clinical heterogeneity (review author judgement), or evidence of statistical heterogeneity, or both, we will use a random-effects model. We will only use a fixed-effect approach when clinical heterogeneity is thought to be minimal and statistical heterogeneity is estimated as non-statistically significant for the Chi-$^2$ value and 0% for the $I^2$ assessment (Kontopantelis 2013). We will adopt this approach as it is recognised that statistical assessments can miss potentially important between-study heterogeneity in small samples, hence the preference for the more conservative random-effects model (Kontopantelis 2012). Where clinical heterogeneity is thought to be acceptable, or of interest, we may meta-analyse even when statistical heterogeneity is high, but we will attempt to interpret the causes behind this heterogeneity and will consider using meta-regression for that purpose, if possible (Thompson 1999; Thompson 2002).

We will present data using forest plots, where possible. For dichotomous outcomes we will present the summary estimate as a

RR with 95% CIs. Where continuous outcomes are measured in the same way across studies, we plan to present a pooled MD with 95% CIs; we plan to pool SMD estimates where studies measure the same outcome using different methods. For time-to-event data, we plan to plot (and, if appropriate, pool) estimates of HRs and 95% CIs, as presented in the study reports using the generic inverse variance method in Review Manager 5.3 (RevMan 2014). Where time-to-healing is analysed as a continuous measure, but it is not clear if all wounds healed, we will document use of the outcome in the study, but we will not summarise the data or use the data in any meta-analysis.

### 'Summary of findings' tables

We will present the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined and the sum of available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach. The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b). We plan to present the following outcomes in the 'Summary of findings' tables.

- Time-to-complete wound healing, when analysed using appropriate survival analysis methods.
- Proportion of wounds completely healing during the trial period.
- Changes in clinical infection status.
- Adverse events.

### Subgroup analysis and investigation of heterogeneity

When possible, we will perform subgroup analyses to explore the effect of interventions in children under the age of 18, in adults, and in older adults (aged over 65 years). When possible, we will also use subgroup analyses to assess the influence of burn size and depth on effect size. If there are sufficient data these analyses will assess whether there are differences in effect sizes for burns of different depths.

When possible, we will perform subgroup analyses to explore the influence of risk of bias on effect size. We will assess the influence of removing from meta-analyses studies classed as having high and unclear risk of bias. These analyses will include only studies that are assessed as having low risk of bias in all key domains, namely, adequate generation of the randomisation sequence, adequate allocation concealment, and blinding of outcome assessor for the estimates of treatment effect.

**Elements of this Methods section are based on the standard Cochrane Wounds Protocol Template.**

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* *Indicates the major publication for the study*

# APPENDICES

## Appendix 1. Assessment of risk of bias

**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.

**High risk of bias**

The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number.

**Unclear**

Insufficient information about the sequence generation process provided to permit a judgement of low or high risk of bias.

**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 non-opaque, or not sequentially-numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

**Unclear**

Insufficient information provided to permit a 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 and the outcome or outcome measurement is likely to be influenced by lack of blinding.
- Either participants or some key study personnel were not blinded, and the non-blinding 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 was 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 was 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 prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).

**High risk of bias**

Any one of the following.

- Not all of the study's prespecified primary outcomes have been reported.
- One or more primary outcomes are reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified.
- One or more reported primary outcomes of the study were not prespecified (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 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 additional risk of bias. For example, the study:

- had a potential source of bias related to the specific study design used; or
- has been claimed to have been fraudulent; or
- had some other problem.

**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.

## Appendix 2. Risk of bias in cluster-randomised trials

In cluster-randomised trials, particular biases to consider include:
- recruitment bias;
- baseline imbalance;
- loss of clusters;
- incorrect analysis; and
- comparability with individually-randomised trials.

**Recruitment bias:** can occur when individuals are recruited to the trial after the clusters have been randomised, as the knowledge of whether each cluster is an 'intervention' or 'control' cluster could affect the types of participants recruited.
**Baseline imbalance:** cluster-randomised trials often randomise all clusters at once, so lack of concealment of an allocation sequence should not usually be an issue. However, because small numbers of clusters are randomised, there is a possibility of chance baseline imbalance between the randomised groups, in terms of either the clusters or the individuals. Although this is not a form of bias as such, the risk of baseline differences can be reduced by using stratified or pair-matched randomisation of clusters. Reporting of the baseline comparability of clusters, or statistical adjustment for baseline characteristics, can help reduce concern about the effects of baseline imbalance.
**Loss of clusters:** occasionally complete clusters are lost from a trial, and have to be omitted from the analysis. Just as for missing outcome data in individually-randomised trials, this may lead to bias. In addition, missing outcomes for individuals within clusters may also lead to a risk of bias in cluster-randomised trials.
**Incorrect analysis:** many cluster-randomised trials are analysed by incorrect statistical methods that do not take the clustering into account. Such analyses create a 'unit of analysis error' and produce over-precise results (the standard error of the estimated intervention effect is too small) and P values that are too small. They do not lead to biased estimates of effect. However, if they remain uncorrected, they will receive too much weight in a meta-analysis.
**Comparability with individually-randomised trials:** in a meta-analysis that includes both cluster-randomised and individually-randomised trials, or includes cluster-randomised trials with different types of clusters, possible differences between the intervention effects being estimated need to be considered. For example, in a vaccine trial of infectious diseases, a vaccine applied to all individuals in a community would be expected to be more effective than a vaccine applied to only half the people. Another example is provided by discussion of a Cochrane review of hip protectors (Hahn 2005), where cluster trials showed a large positive effect, whereas individually-randomised trials did not show any clear benefit. One possibility is that there was a 'herd effect' in the cluster-randomised trials (which were often performed in nursing homes, where compliance with using the protectors may have been enhanced). In general, such 'contamination' would lead to underestimates of effect. Thus, if an intervention effect is still demonstrated despite contamination in those trials that were not cluster-randomised, a confident conclusion about the presence of an effect can be drawn. However, the size of the effect is likely to be underestimated. Contamination and 'herd effects' may be different for different types of cluster.

# CONTRIBUTIONS OF AUTHORS

Janice Christie: edited and advised on the protocol, made an intellectual contribution to the protocol and approved the protocol prior to submission.

Jo Dumville: secured funding, conceived the review question, developed the protocol and co-ordinated its development, wrote part of the protocol edited and advised on the protocol, approved the protocol prior to submission and is a guarantor of the protocol.

Jacky Edwards: edited and advised on the protocol, made an intellectual contribution to the protocol and approved the protocol prior to submission.

Ibrahim Hassan: edited and advised on the protocol, made an intellectual contribution to the proto and approved the protocol prior to submission.

DeviPrasad Mohapatra: edited and advised on the protocol, made an intellectual contribution to the proto and approved the protocol prior to submission.

Gill Norman: developed the protocol, completed the first draft of the protocol, edited the protocol, approved the protocol prior to submission and is a guarantor of the protocol.

**Contributions of editorial base:**

Andrea Nelson, Editor: approved the final protocol prior to submission.
Sally Bell-Syer: coordinated the editorial process. Advised on methodology, interpretation and content. Edited the protocol.
Rocio Rodriguez-Lopez: designed the search strategy and edited the search methods section.

## DECLARATIONS OF INTEREST

Janice Christie: None known

Jo Dumville: None known

Jacky Edwards: None known

Ibrahim Hassan: None known

DeviPrasad Mohapatra: None known

Gill Norman: None known

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