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[Intervention Review]

Systemic antibiotics for treating malignant wounds

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ABSTRACT

Background

Malignant wounds are a devastating complication of cancer. They usually develop in the last six months of life, in the breast, chest wall or head and neck regions. They are very difficult to treat successfully, and the commonly associated symptoms of pain, exudate, malodour, and the risk of haemorrhage are extremely distressing for those with advanced cancer. Treatment and care of malignant wounds is primarily palliative, and focuses on alleviating pain, controlling infection and odour from the wound, managing exudate and protecting the surrounding skin from further deterioration. In malignant wounds, with tissue degradation and death, there is proliferation of both anaerobic and aerobic bacteria. The aim of antibiotic therapy is to successfully eliminate these bacteria, reduce associated symptoms, such as odour, and promote wound healing.

Objectives

To assess the effects of systemic antibiotics for treating malignant wounds.

Search methods

We searched the following electronic databases on 8 March 2017: the Cochrane Wounds Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL; the Cochrane Library, 2017, Issue 3), Ovid MEDLINE, Ovid Embase and EBSCO CINAHL Plus. We also searched the clinical trial registries of the World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch) and [ClinicalTrials.gov](https://clinicaltrials.gov) on 20 March 2017; and OpenSIGLE (to identify grey literature) and ProQuest Dissertations & Theses Global (to retrieve dissertation theses related to our topic of interest) on 13 March 2017.

Selection criteria

Randomised controlled trials that assessed the effects of any systemic antibiotics on malignant wounds were eligible for inclusion.

Data collection and analysis

Two review authors independently screened and selected trials for inclusion, assessed risk of bias and extracted study data. A third reviewer checked extracted data for accuracy prior to analysis.

Main results

We identified only one study for inclusion in this review. This study was a prospective, double-blind cross-over trial that compared the effect of systemic metronidazole with a placebo on odour in malignant wounds. Nine participants with a fungating wound and for whom the smell was troublesome were recruited and six of these completed both the intervention and control (placebo) stages of the trial. Each stage lasted fourteen days, with a fourteen day gap (washout period) between administration of the metronidazole and the placebo.

The study, in comparing metronidazole and placebo, reported on two of this review's pre-specified primary outcomes (malodour and adverse effects of the treatment) and on none of the review's pre-specified secondary outcomes.

Malodour

The mean malodour (smell) scores for the metronidazole group was 1.17 (standard deviation (SD) 1.60) and the mean for the placebo group was 3.33 (SD 0.82). It is unclear if systemic antibiotics were associated with a difference in malodour (1 study with 6 participants; MD -2.16, 95% CI -3.6 to -0.72) as the quality of the evidence (GRADE) was very low for this outcome. The study was downgraded due to high risk of attrition bias (33% loss to follow-up) and very serious imprecision due to the small sample size.

Adverse effects

No adverse effects of the treatment were reported in either the intervention or control group by the trial authors.

Authors' conclusions

It is uncertain whether systemic metronidazole leads to a reduction in malodour in patients with malignant wounds. This is because we were only able to include a single study at high risk of bias with a very small sample size, which focused only on patients with breast cancer. More research is needed to substantiate these findings and to investigate the effects of systemic metronidazole and other antibiotics on quality of life, pain relief, exudate and tumour containment in patients with malignant wounds.

PLAIN LANGUAGE SUMMARY

Systemic antibiotics for treating malignant wounds

Review question

We reviewed the evidence about the effect of systemic antibiotics on malignant wounds. We were looking for evidence relating to possible side effects of this treatment, and the impact on quality of life and other symptoms.

Background

Malignant wounds occur in people who have advanced cancer. They usually develop in the last six months of life, at or near the site of a tumour. They occur when a tumour spreads and invades surrounding skin and blood vessels, causing them to break down. The area loses nourishment due to poor blood flow, and eventually the tissues die, resulting in a malignant wound. This type of wound can be very painful, can smell, and can bleed or ooze fluid. These symptoms can be very difficult for people with advanced cancer. Treatment for malignant wounds does not normally aim to heal the wound, but to limit symptoms that affect people's quality of life.

Antibiotics are medicines that fight bacterial infections. Systemic antibiotics affect the whole body. They can be given by mouth in tablet form, or in other ways such as via injections. We looked for evidence as to whether systemic antibiotics can prevent malignant wounds from getting worse, and help reduce the smell, pain and other complications associated with these wounds.

Study characteristics

In March 2017 we searched for randomised controlled trials looking at the effects of systemic antibiotics on malignant wounds. We found only one trial, dating from 1984, which compared the effectiveness of the antibiotic metronidazole with a placebo (sugar pill) on six participants with malignant wounds resulting from breast cancer. The trial was a cross-over trial which means that participants receive both the treatment being tested and the comparison treatment, at different time-points, with a break between the treatments to ensure that the effects of the first treatment have worn off before the second treatment is taken. This is called the 'washout' period. In the one trial in this review, half the participants took the antibiotic first, for 14 days, and half took the placebo. Both groups then had 14 days with no medication before swapping over (cross-over) and trying the alternative treatment for 14 days.

Key results

It is unclear if metronidazole reduces the smell of malignant wounds when taken orally (by mouth) in tablet form, without any side effects occurring. Its effectiveness in relation to other outcomes such as pain or quality of life was not measured in this trial. No change in the size or appearance of participants' tumours was reported.

Quality of the evidence

It is uncertain whether metronidazole reduces the smell of malignant wounds when taken orally in tablet form because the quality of the evidence is very low. This evidence came from a very small study with serious study design flaws, and more research is needed involving more people with different types of cancer. Trials looking at how antibiotics can affect other outcomes, such as quality of life, pain relief and reducing any bleeding or ooze from the wound are also needed.

This plain language summary is up to date as of March 2017.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Metronidazole compared to Placebo for treating malignant wounds

Metronidazole compared to Placebo for treating malignant wounds

Patient or population: treating malignant wounds

Setting: hospital

Intervention: metronidazole

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with Metronidazole				
Malodour (smell score measured on a scale of 0 to 3 with higher scores indicating a more offensive smell)	The mean malodour (smell score) was 3.33 (range 2.0 to 4.0)	MD 2.16 lower (3.60 to 0.72 lower)	-	6 (1 RCT)	⊕⊕⊕⊕ very low ¹	It is uncertain whether metronidazole leads to a reduction in malodour because the quality of the evidence is very low
Adverse effects	Study population		not estimable	6 (1 RCT)	NA	
	0 per 1000	0 per 1000 (0 to 0)				

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio; **MD:** mean difference.

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

¹ Downgraded 3 levels: serious limitation — insufficient details provided to make clear judgements on random sequence generation and allocation concealment. There was also a 33% loss to follow-up; very serious imprecision; a small sample size of 6 participants.

² Smell was independently assessed at each visit by the patient, doctor, and nurse, who graded the smell as "absent" (0), "not offensive" (1), "offensive but tolerable" (2), or "offensive and intolerable" (3), and an amalgamated score calculated.

BACKGROUND

Description of the condition

Malignant wounds, which are also referred to as fungating wounds, ulcerating tumours or neoplastic (new growth) lesions ([Adderley 2014](#)), are a devastating complication of cancer that most often arises in the last six months of life ([McDonald 2006](#)). These wounds arise when tumour cells infiltrate the skin and its blood and lymph vessels from a local or distant primary tumour. Carcinomas of the breast in women and lung cancer in men are the most common sources of primary tumours that lead to these cutaneous (skin) metastases. They are also caused by primary cutaneous tumours, or by direct invasion of a primary tumour into the cutaneous structure ([Alexander 2009](#)). Globally, malignant wounds occur most frequently on the breast or chest wall (39% to 62%), with head and neck (24% to 33.8%), back, trunk or abdomen (1% to 3%), axilla or groin (3% to 7%) and genitals (3% to 5%) also being common sites ([McDonald 2006](#)). Although accurate statistics on, or reports of, their prevalence are not available, it is estimated that malignant wounds are present in 5% to 10% of people with cancer ([Seaman 2006](#)).

Malignant wounds present a particularly challenging clinical scenario, as they are very difficult to treat successfully. [Alexander 2009](#) claims that reports of healed malignant wounds are very rare. In addition, the commonly associated symptoms of pain, copious exudate, malodour, and the risk of haemorrhage are extremely distressing for people with advanced cancer.

Initial presentation varies depending on whether tumour invasion is as a result of the extension of a local tumour to the skin surface or as a metastasis (spread) of a primary tumour. In the former, inflammation with induration (hardening), and redness or tenderness — or both — may be present. When skin is affected as a result of metastasis, well-defined nodules that vary in size, colour and consistency but are generally painless, become visible. These nodules may be fixed to underlying tissue. In both cases, as the tumour spreads and extends above the skin surface, further tissue destruction occurs. The wound takes on an erosive and ulcerative appearance, or a fungus/cauliflower-like appearance, or both ([McDonald 2006](#)). These wounds are thought to interfere with oxygenation of the tissues, lymphatic drainage and haemostasis (maintenance of the healthy state of tissue). Tissue hypoxia (low oxygen levels) leads to lack of oxygen in the local cells, which sometimes leads to cell death ([Adderley 2014](#); [Mortimer 2003](#)). The resulting wound bed can vary in colour from pale to pink, with the tissue being very friable (easily torn, fragmented or made to bleed) or necrotic (dead cells or tissue), or a combination of both ([Seaman 2006](#)). The surrounding skin can be macerated (i.e. softened and broken down due to prolonged exposure to wetness), fragile and very tender to the touch.

The necrotic tissue of the wound bed becomes an ideal medium for anaerobic bacteria, which grow and flourish in areas of low oxygen concentrations. Their metabolic activities may account, in part, for the odour that patients find extremely distressing. Cell growth in malignant wounds can be very rapid and may affect the pH of extracellular fluid ([Adderley 2014](#)). This interferes with coagulation of blood, and vessel occlusion and necrosis may result. Disruption of the lymphatic system can lead to vascular collapse, hypoxia, necrosis, build-up of waste and oedema (fluid retention). Excessive wound exudate, which can amount to over a litre per day in some

individuals, results from a combination of vascular, bacterial and lymphatic factors.

Unless the underlying malignancy can be treated effectively, medically or surgically, the fungation in a malignant wound will continue to grow; and, through loss of vascularity, proliferative growth and ulceration, further damage to the surrounding skin occurs ([EONS 2015](#)). Wound-related symptoms commonly include odour, haemorrhage, pain and exudate, with odour, pain and exudate, in particular, presenting significant challenges for wound management ([Gethin 2014](#)). Care and treatment of these wounds is primarily palliative, with care and management focusing on problem solving to control and reduce the overall impact of wound symptoms and provision of physical, psychosocial and psychological support to patients and their families ([EONS 2015](#)). There is currently a lack of evidence, overall, to direct the clinical management of wound odour and local colonisation, with a 'trial and error' approach most frequently adopted ([Gethin 2014](#)). Nonetheless, a recent publication by the European Oncology Nursing Society recommends that wound cleansing and irrigation, debridement (non-surgical), metronidazole topically or orally, activated charcoal and antimicrobial (silver) dressings, frequent dressing changes (twice a day) and the use of opiates for pain management can help with effectively managing the most distressing symptoms ([EONS 2015](#)).

Description of the intervention

Antibiotics are agents that are used to kill or prevent the growth of disease-causing micro-organisms without causing damage to the host (patient). This selective toxicity depends on targeting differences between the host cell and that of the infecting micro-organism. While the term 'micro-organisms' includes bacteria, viruses and fungi, bacteria account for most infectious disease. Most antibiotics work by exploiting differences between bacterial and host cells — such as synthesis of proteins, DNA, RNA (ribonucleic acid), and peptidoglycan in bacterial cell walls ([Rang 2003](#)).

Systemic antibiotics, which affect the whole body, can be used to improve symptom management, reduce further deterioration and improve quality of life for those with malignant wounds ([Alexander 2009](#)). Systemic administration of antibiotic agents, rather than topical (surface) application to the infected area, can take place through a variety of routes. The route selected for systemic administration depends on factors relating to the infection, drugs and the patient.

Systemic antibiotics can be administered orally, rectally, transdermally (through the skin), sublingually (under the tongue) and via the buccal route (between gums and inner face of the cheek). In addition they can be delivered parenterally directly into veins, muscles and joints (intravenous, intramuscular and intra-articular routes, respectively). Topical antibiotics are applied to the wound site, acting directly on the site of application. Thus use of topical antibiotics will not lead to blood or tissue drug concentration levels. In this sense, topical agents are 'surface' agents rather than systemic agents. Transdermal antibiotics are applied to intact skin away from the wound site, and are absorbed into the body through the skin and mucous membranes, leading to drug levels in circulating blood. They are intended to act on an area of the body away from the site of application. The most common routes of administration for systemic antibiotics are the

oral, intravenous, intramuscular and rectal routes. The oral route is suitable for well-absorbed drugs, and is generally used for less severe infections; it is suitable if the patient can swallow and has no vomiting, nausea or gastrointestinal contraindications (conditions that would make the drug or route unsuitable). Generally, more severe infections require intravenous treatment. The intravenous route is also used if the drug is poorly absorbed when taken orally. If a patient cannot swallow or is vomiting, then parenteral or rectal routes of administration may be more suitable ([British National Formulary 2017](#)).

How the intervention might work

In malignant wounds, tissue degradation can lead to proliferation of both anaerobic and aerobic bacteria. Successful elimination of bacteria may reduce associated symptoms, such as odour, and promote wound healing. Antibiotics may be described as bacteriostatic (halting the growth of bacteria) or bactericidal (toxic to bacteria). Antibiotics achieve this effect by exploiting differences between the structure and biochemistry of microbial cells and human cells.

Anaerobic proliferation (rapid increase in bacteria that do not grow or live when oxygen is present) is common in malignant wounds and, although many antibiotics target anaerobic bacteria, metronidazole — a bactericidal antibiotic — is the most commonly used topical antibiotic for these wounds. It may also be used systemically against these bacteria, and appears to be the antibiotic of choice. When given systemically, it is reduced to its active form, which binds to bacterial DNA, inactivating it and preventing DNA synthesis. Metronidazole is highly active against anaerobic bacteria ([Löfmark 2010](#)), the growth of which may be facilitated by tissue hypoxia (deficiency in oxygen) in wounds. Metronidazole is used systemically by the oral, intravenous and rectal routes. Adverse reactions to metronidazole include nausea, vomiting, anorexia (loss of appetite) and oral mucositis (inflammation of the lining of the digestive tract). It interacts with other drugs including alcohol, warfarin and phenytoin. It should be used with caution in those with hepatic impairment ([British National Formulary 2017](#)). Other antibiotics may also be used systemically, depending on the type of bacteria present in the wound.

In malignant wounds, loss of vascularity (blood supply) and subsequent necrosis (death of the tissue) caused by tumour invasion may compromise the distribution, penetration and efficacy of systemic antibiotics such as metronidazole ([Grocott 2001a](#)).

Why it is important to do this review

A Cochrane Review on malignant wounds, titled ‘Topical agents and dressings for fungating wounds’, concluded that there was weak evidence to suggest that a 6% solution of miltefosine might slow progression of small, superficial fungating wounds on the breast, but that ultimately more research was needed in this area ([Adderley 2014](#)). Systemic treatments for malignant wounds have focused on various regimens of antibiotics, primarily metronidazole, aimed at slowing disease progression, alleviating symptoms and optimising the quality of life of the patient. We hoped that this review would expand the current evidence base regarding treatment options and, ideally, contribute to clinical decision making for those with malignant wounds and potentially identify the most effective treatment and management regime.

OBJECTIVES

To assess the effects of systemic antibiotics for treating malignant wounds.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) that assessed the effects of systemic antibiotics on malignant wounds were eligible for inclusion. In the absence of RCTs, we would have considered including controlled clinical trials (CCTs) that assessed the effects of systemic antibiotics in the treatment of malignant wounds, with a concurrent control group and prospective baseline assessment of the malignant wound in the review, but no eligible CCTs were identified.

Types of participants

Studies involving people of any age with a clinically diagnosed malignant wound resulting from any type of cancer were eligible for inclusion. Where differences in the definitions of a malignant wound existed, we accepted the study authors’ diagnosis as definitive.

Types of interventions

Studies evaluating the effects of any systemic antibiotic used in the treatment of any type of malignant wound were eligible for inclusion. This would have involved including studies that compared systemic antibiotics with a placebo, no treatment, or a topical antibiotic; and studies that compared one systemic antibiotic with another systemic antibiotic.

Types of outcome measures

Primary outcomes

- Malodour (measured by a validated assessment tool, e.g. the TELER system ([Grocott 2001b](#)) which assesses malignant wounds using a 0 to 5 ordinal scale on a number of indicators, for example skin condition, wound exudate and odour. For odour, a score of 0 indicates odour that is obvious in the house/hospital ward. A score of 5 indicates no odour).
- Adverse effects of treatment (e.g. nausea, vomiting, rash or any other adverse effect as reported by the trial authors).

Secondary outcomes

- Health-related quality of life (measured using a standardised generic questionnaire such as EQ-5D ([Brooks 1996](#)), SF-36 ([Jenkinson 1996](#)), or a disease-specific questionnaire).
- Exudate/haemorrhage (number of dressing changes).
- Pain relief (measured using visual analogue scale or other validated pain-measuring scale).
- Cost (including measurements of resource use, where reported).
- Malignant tumour containment or regression as measured by time to progression ([WHO 1979](#)).

Search methods for identification of studies

Electronic searches

We searched the following electronic databases to identify reports of relevant clinical trials:

- the Cochrane Wounds Specialised Register (searched 8 March 2017);
- the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 3) in the Cochrane Library (searched 8 March 2017);
- MEDLINE Ovid including In-Process & Other Non-Indexed Citations (1946 to 8 March 2017);
- Embase Ovid (1974 to 8 March 2017);
- CINAHL EBSCO Plus (Cumulative Index to Nursing and Allied Health Literature; 1937 to 8 March 2017).

The search strategies for the Cochrane Wounds Specialised Register, CENTRAL, Ovid MEDLINE, Ovid Embase and EBSCO CINAHL Plus can be found in [Appendix 1](#). We combined 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 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 2017](#)). There were no restrictions with respect to language, date of publication or study setting. We also searched the following clinical trials registries:

- ClinicalTrials.gov (www.clinicaltrials.gov) (searched 20 March 2017);
- World Health Organization (WHO) International Clinical Trials Registry Platform (<http://apps.who.int/trialsearch/Default.aspx>) (searched 20 March 2017).

Search strategies for clinical trial registries can be found in [Appendix 1](#).

Searching other resources

We reviewed the reference lists of all included papers to identify any additional potentially eligible studies that were not captured by the electronic searches as well as relevant systematic reviews, meta-analyses and Health Technology Assessment reports. We searched the OpenSIGLE database to identify grey literature and the ProQuest Dissertations & Theses Global database to retrieve dissertation theses related to our topic of interest. We also contacted experts in the field to identify any unpublished studies. We searched for conference abstracts or publications from the European Wound Management Association (1991 to 2016), the European Wound Management Association Journal since its inception in 2001, the Wound Care UK (www.wounds-uk.com) website and journal (2005 to 2016) and the International Conference on Wound Management (1999 to 2016).

Data collection and analysis

We carried out data collection and analysis according to methods stated in the published protocol ([Ramasubbu 2015](#)), which are based on methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)).

Selection of studies

Independently, two review authors (DR and PC) assessed the titles and abstracts of citations identified by the search strategy. The review authors were not blinded to the study authors or to the name of the publication. Full reports of all potentially relevant studies were retrieved for further assessment of eligibility based on the inclusion criteria. Had any disagreements occurred, we had planned to resolve them through discussion and consensus, or, where necessary, in consultation with a third review author (VS); however, this was not required.

Data extraction and management

Two review authors (DR and PC) extracted data independently using a pre-designed agreed data extraction form. A third review author (VS) checked the extracted data for accuracy. Where information regarding data was unclear (one study), we contacted the lead author of the original trial report for further details; however, we did not receive a response.

Assessment of risk of bias in included studies

Independently, two review authors (DR and PC) assessed risk of bias using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011b](#)). This tool addresses six specific domains, namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other biases (e.g. extreme baseline imbalance; see [Appendix 2](#) for details of criteria on which the judgement was based). Blinding and completeness of outcome data were assessed for each outcome separately. We completed a 'Risk of bias' table for the included study. We had planned to discuss any disagreements amongst all review authors to achieve a consensus should they have arisen; however, this was not required. We present the assessment of risk of bias using a 'Risk of bias' summary figure that presents the judgements for each risk of bias criterion.

Measures of treatment effect

Dichotomous data

For dichotomous data, (e.g. specific adverse events that are present or absent), we planned to present the results as summary risk ratio (RR) with 95% confidence intervals (CI).

Continuous data

For continuous data, we present the results as mean difference (MD) with 95% CI. When pooling data across studies, we had planned to estimate the MD if the outcome(s) were measured in the same way between trials, and use the standardised mean difference (SMD) to combine trials that measured the same outcome, but used different methods. However, as only one trial was included in the review, this was not applicable.

Time-to-event data

For time-to-event data such as time to wound progression, we had planned to use methods of survival analysis and present the results as a hazard ratio (HR) with 95% CI. As time-to-event data were not reported in the one included study in the review, this was not applicable.

Unit of analysis issues

Multiple ulcers in the same participant

Where included studies evaluated the effect of the treatment on multiple ulcers in the same participant we had planned to seek further statistical advice on how to handle and analyse these data; or, where we were unable to include these data in a meta-analysis, we would have reported the results using narrative synthesis. As one trial only was included in the review and focused on one wound per participant only, this was not applicable. We will consider this in future updates of the review, if indicated.

Dealing with missing data

We noted the levels of attrition for the included study. Using sensitivity analysis, we had planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect. For all outcomes we planned to carry out analyses as far as possible on an intention-to-treat basis. For dichotomous data, where participant outcome data were missing, we had planned to make an assumption that the outcome concerned was likely not to have occurred. For continuous outcome data (e.g. quality of life), the denominator for each outcome in each trial would have been the number randomised minus any participants whose outcomes were known to be missing; we had planned to use the numbers reported in the study. Dealing with missing data was not necessary in the review; we will consider this, if indicated, in future updates.

Assessment of heterogeneity

Had more than one study been included in this review, we would have assessed statistical heterogeneity in each meta-analysis, where performed, using the I^2 statistic (Higgins 2011b). We planned to interpret the I^2 statistic according to the following thresholds:

- 0% to 40%: might not be important;
- 40% to 60%: may represent moderate heterogeneity;
- more than 60%: may represent substantial heterogeneity.

We will apply this interpretation to future updates should additional studies be included in future meta-analyses.

We had planned to explore identified heterogeneity visually using forest plots and analytically using sub-group analyses (e.g. for clinical variation such as type of cancer) and random-effects meta-analyses; we will apply this, if indicated, in future updates.

Assessment of reporting biases

To address the potential for publication of positive, statistically significant results, we searched the grey literature comprehensively for unpublished data; however, no additional unpublished studies meeting the review's inclusion criteria were found. Had data from unpublished studies been identified, we would have included this data cautiously, recognising unpublished reports as a possible source of bias, and would have contacted the original trialists for further information as necessary; we will consider this, if indicated, in future updates.

Data synthesis

We carried out statistical analysis using Review Manager 5 software (Review Manager 2014). Had more than one study been included in the review, we would have synthesised data only where we thought

it was appropriate to do so, that is where trials were examining similar interventions, with similar populations and methods. We would have used a fixed-effect approach for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: that is where trials were examining the same intervention, and the trials' populations and methods were sufficiently similar. Where there was clinical or methodological heterogeneity between studies sufficient to suggest that treatment effects may have differed between trials, random-effects meta-analysis would have been used; we will apply this data synthesis plan to future updates.

Subgroup analysis and investigation of heterogeneity

If sufficient studies on diverse populations had been identified as eligible for inclusion, we would have attempted to conduct the following subgroup analyses for systematic antibiotics for malignant wounds according to:

- organ affected by cancer;
- drug used;
- dose of drug;
- duration of treatment with drug.

We will continue to consider these subgroup analyses in future updates.

Sensitivity analysis

Had more than one study been included in the review, we would have carried out sensitivity analyses to explore whether analysing studies stratified by quality (low risk of bias and high risk of bias) produces similar or different results. We would have carried out a sensitivity analysis by excluding those studies at an overall high risk of bias from the meta-analysis (as defined in [Assessment of risk of bias in included studies](#)); we will consider this analysis, if indicated, in future updates.

'Summary of findings' tables

We assessed the quality of the results for the primary outcomes of the review in a 'Summary of findings' table ([Summary of findings for the main comparison](#)). A 'Summary of findings' table presents 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' table also includes an overall grading of the evidence related to each of the main outcomes using the GRADE 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 presented the following outcomes in the 'Summary of findings' table:

- malodour
- adverse effects of the treatment.

RESULTS

Description of studies

See [Characteristics of included studies](#) table

Results of the search

The search yielded a total of 470 citations (467 from database searching and 3 from searching of additional sources), of which 415 were excluded on the basis of title or title and abstract as they did not investigate the use of systemic antibiotics in the treatment of malignant wounds ([Figure 1](#)). This resulted in the retrieval of five full-text reports for possible inclusion in the review ([Ashford 1984](#); [Dankert 1981](#); [De Castro 2015](#); [McGregor 1982](#); [Sparrow 1980](#)).

Figure 1. Study flow diagram.

Included studies

One study only met the inclusion criteria ([Ashford 1984](#)). This study was a prospective, double-blind cross-over trial that compared the effect of systemic metronidazole with a placebo on odour in malignant wounds. Nine participants with a fungating wound and for whom the smell was troublesome were recruited and six of these completed both the intervention and control (placebo) stages of the trial. Each stage lasted fourteen days, with a fourteen day gap (washout period) between administration of the metronidazole and the placebo. Swabs of the tumour were taken before and after each treatment stage, and tumour odour was assessed independently by the participant, a doctor and a nurse using an ordinal grading scale of 0 (no smell) to 3 (offensive and intolerable). All of the six participants that completed the trial stages had recurrent breast cancer and completed the trial with little change in tumour appearance, but had a reduction in malodour and

anaerobic (in the absence of air) isolates (level of bacteria that grew in a laboratory test from a swab of the wound). Although it is not entirely clear where the research took place, the researchers, who were clinical oncologists, worked in a hospital in London at the time of the study. Details of study funding are also not provided in the study report; however, it is noted that the placebo was provided by a pharmaceutical company.

Excluded studies

Three studies were excluded as they were not RCTs or CCTs ([Dankert 1981](#); [De Castro 2015](#); [Sparrow 1980](#)); and one study was excluded as it evaluated treatment of surgical rather than malignant wounds ([McGregor 1982](#)). See [Characteristics of excluded studies](#) table.

Risk of bias in included studies

The included study had high risk of bias. See [Figure 2](#), [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

The included study was described as a cross-over, double-blind randomised trial (Ashford 1984). The authors did not report the method of allocation concealment or how the randomisation sequence was generated, and the trial was assessed as unclear risk of bias on allocation.

Blinding

The trial was described as double blind, whereby both participants and personnel were blind to the intervention and control through the use of 'identical tablets'.

Incomplete outcome data

Three participants withdrew from the study. The reasons for withdrawal are provided by the authors in the study report: one participant died; a second required antibiotics for septicaemia; and a third responded unexpectedly to radiotherapy. This loss of three participants represents a loss of one-third of the total study participants, with six only remaining for data analysis. For this

reason, other potential sources of bias were assessed as high risk of bias.

Selective reporting

Trial registration was not available and because the outcomes of interest were not clearly specified, only inferred, we assessed the risk of bias for selective reporting as unclear.

Other potential sources of bias

The cross-over design was considered suitable because of the difficulty of recruitment in this population. The wash-out period of 14 days was deemed appropriate to eliminate the carry-over effect and was not considered a potential source of bias in the study.

Data from the six patients who completed both arms of the trial were presented.

The analysis of the available data was appropriate given that smell scores were available for each patient in each arm of the trial.

Effects of interventions

See: [Summary of findings for the main comparison Metronidazole compared to Placebo for treating malignant wounds](#)

The results are reported with reference to the review's pre-specified outcome measures.

Metronidazole versus placebo

Primary Outcomes

Malodour

It is unclear if systemic antibiotics are associated with a difference in malodour (MD -2.16 , 95% CI -3.60 to -0.72 , 1 study, 6

participants, see (Figure 4)). Malodour (smell scores) was graded on a 0 to 3 scale with higher values indicating a more offensive and intolerable smell. The mean smell scores for the metronidazole group was 1.17 (SD 1.60) and the mean for the placebo group was 3.33 (SD 0.82). The results for all six participants from both phases of the cross-over trial were included in the analysis, rather than the results from the first treatment phase only. We did this because only one study was included, the numbers of participants were small, and the washout period of 14 days was considered clinically sufficient to eliminate any potential effects from 'carry-over'. The quality of the evidence (GRADE) was assessed as very low for this outcome ([Summary of findings for the main comparison](#)).

Figure 4. Forest plot of comparison: 1 Metronidazole versus Placebo, outcome: 1.1 Malodour (Smell Score).

Adverse effects

No adverse effects of the treatment were reported in either the intervention or control group by the trial authors.

Secondary Outcomes

The one included study did not report on any of the review's pre-specified secondary outcomes of health-related quality of life, pain, exudate/haemorrhage (number of dressing changes), cost, or malignant tumour containment or regression.

DISCUSSION

Summary of main results

Overall, the results of this review highlight the lack of research in this area with very little evidence to direct clinical practice in the treatment of fungating malignant wounds with systemic antibiotics. We identified only one study that met the inclusion criteria for the review, and very few participants (six) were included in this study (Ashford 1984). Due to the very low quality evidence on the primary outcome of malodour, it is uncertain whether systematic metronidazole leads to a reduction in malodour when compared to the use of a placebo. No adverse outcomes of the treatment were reported in either of the groups by the trial authors.

Overall completeness and applicability of evidence

The evidence presented by the one included study is directly relevant to the review question as it addressed the use of systemic antibiotics in the treatment of malignant wounds. The study compared metronidazole with a placebo. Metronidazole is the antibiotic of choice for targeting the anaerobic bacteria commonly found in malignant wounds. The participants had malignant wounds associated with recurrent breast cancer, with this type of cancer being most commonly associated with the development of malignant wounds. Moreover, the study addressed the review's primary outcomes of malodour and adverse effects of the treatment; however, it did not assess any of the review's secondary outcomes. However, while the included study is relevant

to answering the review question, the final small sample of six who completed both arms of the trial renders negligible the overall completeness and applicability of the findings of this review for informing clinical practice.

Quality of the evidence

The results of the review show a positive outcome for the use of systemic metronidazole in reducing odour in malignant wounds but the quality of the evidence is very low. We downgraded the evidence for serious limitations as a third of the participants withdrew from the study, resulting in attrition bias. Due to the small sample size, we further downgraded the evidence for very serious imprecision; the lack of research in this area has been highlighted. The body of evidence on the use of systemic antibiotics in the treatment of malignant wounds is currently limited and further high-quality studies are required. We did not downgrade the evidence for inconsistency or publication bias due to insufficient data. We did not downgrade for indirectness as the evidence is in agreement with the review question.

Potential biases in the review process

A systematic review was undertaken with a predefined and peer-reviewed research question, search terms, and criteria for inclusion of studies. A comprehensive search strategy was developed and undertaken, including searching of multiple databases. Furthermore, two independent review authors reviewed the results of the search and independently identified studies to be included and excluded. The decision to include both periods of the cross-over trial may have introduced bias; however, given that the 14-day washout period in Ashford 1984 was considered a clinically sufficient period of time for washout, this was not considered to be a source of concern. For these reasons, we believe potential biases in the review process are minimal.

Agreements and disagreements with other studies or reviews

A systematic review by [De Castro 2015](#) investigated the effect of metronidazole on the management of odour in patients with fungating wounds, and three trials analysing topical metronidazole preparations met the criteria for inclusion. The authors concluded that these studies supported the use of metronidazole topically but were limited in terms of their methodology. [Adderley 2014](#) additionally systematically reviewed the evidence on topical preparations for the treatment of malignant wounds. No current systematic reviews exist on the use of systemic antibiotics for the treatment of malignant wounds. This review, although providing limited evidence, adds to the overall body of evidence on treatment options in people with malignant wounds.

AUTHORS' CONCLUSIONS

Implications for practice

It is uncertain whether metronidazole leads to a reduction in malodour, in particular in those with recurrent breast cancer. The quality of the evidence is very low as it is based on one small study at high risk of bias involving six participants only. Further studies are required to substantiate the findings from this one study before

systematic metronidazole is advised for the widespread treatment of malignant wounds in clinical practice.

Implications for research

There is limited evidence on the use of systemic antibiotics for treating malignant wounds. The only included study in the review was published in 1984. Evidence from large trials in this area could contribute to clinical improvements in the lives of patients who suffer from this distressing complication. Further well-designed studies are urgently needed to assess this important aspect of clinical care, especially on outcomes related to quality of life, pain and cost-effectiveness. Further studies involving larger sample sizes, with clearly specified methods of randomisation, adequate blinding and objective reporting of sufficient outcome measures, are required.

ACKNOWLEDGEMENTS

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ashford 1984

Methods	Randomised, double-blind, cross-over trial that explored the use of metronidazole for controlling the smell from fungating wounds in patients with breast cancer, using a placebo for comparison. Care setting and location: not clearly stated; however, the authors worked in hospitals in London, UK.
Participants	People with breast cancer, and a fungating wound which had a troublesome smell and was unlikely to respond to irradiation or chemotherapy. Six of the nine who were recruited to the trial participated and completed both arms of the study. Mean age and sex were not reported.
Interventions	Intervention: metronidazole 200 milligram tablets given orally three times daily (TDS) for 14 days; and placebo tablets TDS given orally for 14 days. Participants acting as their own controls.
Outcomes	Smell scores and anaerobe culture results were reported. Smell was graded 0 to 3 with 0 indicating the smell was 'absent', 1 being 'not offensive', 2 being 'offensive but tolerable' and 3 being 'offensive and intolerable'. Anaerobe culture results were reported as '-', '+', '++' and '+++'.
Notes	Funding source was not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated that "a randomised, double-blind, cross-over design" was used (p1232) but detail on how the random sequence was generated was not provided.

Ashford 1984 (Continued)

Allocation concealment (selection bias)	Unclear risk	No detail about sequence generation or allocation concealment was provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was described as double blind whereby both participants and personnel were blind to the intervention and control through the use of "identical tablets".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	It was stated that the participant, nurse and doctor independently assessed smell at each visit; "double-blind" implied that participant and personnel were unaware of which treatment is being dispensed at any particular time.
Incomplete outcome data (attrition bias) All outcomes	High risk	Original sample size was 9 but 3 participants were withdrawn; results are presented for 6 (2/3rds of the original sample). This is a small sample size that is likely to have impacted on the results.
Selective reporting (reporting bias)	Unclear risk	Trial registration was not available, and because the outcomes of interest were not clearly specified, only inferred, we assessed the risk of bias for selective reporting as unclear.
Other bias	Unclear risk	Limited information on participant characteristics (e.g. age) and study setting.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Dankert 1981	This study was not a trial (RCT or CCT) but was a case report on 4 participants with fungating gynaecological tumours treated with metronidazole.
De Castro 2015	This study was not a trial (RCT or CCT) but was a systematic review of the use of metronidazole (topical application) for odour control in malignant fungating wounds.
McGregor 1982	This study was a double-blind trial of 8 participants who received tinidazole (8 g over 7 days) pre- and post-operatively for prevention of infection in people with oropharyngeal tumours and not for treatment of malignant wounds.
Sparrow 1980	This study was not a trial (RCT or CCT) but was an observational study of 9 participants with fungating breast carcinoma and treated with metronidazole 400 milligrams three times daily.

DATA AND ANALYSES

Comparison 1. Metronidazole versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Malodour (Smell Score)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Metronidazole versus Placebo, Outcome 1 Malodour (Smell Score).

Study or subgroup	Metronidazole		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Ashford 1984	6	1.2 (1.6)	6	3.3 (0.8)		-2.16[-3.6,-0.72]

APPENDICES

Appendix 1. Central search strategy

Cochrane Wounds Specialised Register

- 1 MESH DESCRIPTOR Skin Ulcer EXPLODE ALL AND INREGISTER
- 2 MESH DESCRIPTOR Neoplasms EXPLODE ALL AND INREGISTER
- 3 #1 AND #2
- 4 MESH DESCRIPTOR Ulcer EXPLODE ALL AND INREGISTER
- 5 MESH DESCRIPTOR Skin Neoplasms EXPLODE ALL AND INREGISTER
- 6 #4 AND #5
- 7 (fungat* near3 (wound* or tumor* or tumour* or lesion* or ulcer*)) AND INREGISTER
- 8 (ulcera* near3 (tumor* or tumour*)) AND INREGISTER
- 9 (malodorous near3 (wound* or tumor* or tumour* or ulcer*)) AND INREGISTER
- 10 (smelly near3 (wound* or tumor* or tumour* or ulcer*)) AND INREGISTER
- 11 ((malignant or tumoral or neoplas* or cancer) near3 wound*) AND INREGISTER
- 12 ((melanoma or carcinoma or sarcoma or metasta*) near5 ulcer*) AND INREGISTER
- 13 #3 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
- 14 MESH DESCRIPTOR Anti-Infective Agents EXPLODE ALL AND INREGISTER
- 15 MESH DESCRIPTOR Antibiotic Prophylaxis EXPLODE ALL AND INREGISTER
- 16 MESH DESCRIPTOR Nitroimidazoles EXPLODE ALL AND INREGISTER
- 17 (Antibiotic* or Nitroimidazole* or Dimetridazole or Etanidazole or Iprnidazole or Metronidazole or Misonidazole or Nimorazole or Ornidazole or Ronidazole or Tinidazole) AND INREGISTER
- 18 MESH DESCRIPTOR Tetracyclines EXPLODE ALL AND INREGISTER
- 19 (Tetracycline* or Chlortetracycline or Demeclocycline or Doxycycline or Lymecycline or Methacycline or Minocycline or Oxytetracycline or Rolitetracycline) AND INREGISTER
- 20 (Erythromycin or Clindamycin or Ciprofloxacin) AND INREGISTER
- 21 (Spiramycin or Azithromycin or Roxithromicin or Roxithromycin) AND INREGISTER
- 22 MESH DESCRIPTOR Penicillins EXPLODE ALL AND INREGISTER
- 23 (Penicillin* or Phenoxyethylpenicillin or Amoxicillin or Ampicillin or Flucloxacillin or Amoxiclav) AND INREGISTER
- 24 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
- 25 #13 AND #24

The Cochrane Central Register of Controlled Clinical Trials (CENTRAL)

- #1 MeSH descriptor: [Skin Ulcer] explode all trees
- #2 MeSH descriptor: [Neoplasms] explode all trees
- #3 #1 and #2
- #4 MeSH descriptor: [Ulcer] explode all trees
- #5 MeSH descriptor: [Skin Neoplasms] explode all trees
- #6 #4 and #5
- #7 (fungat* near/3 (wound* or tumor* or tumour* or lesion* or ulcer*)):ti,ab
- #8 (ulcera* near/3 (tumor* or tumour*)):ti,ab
- #9 (malodorous near/3 (wound* or tumor* or tumour* or ulcer*)):ti,ab
- #10 (smelly near/3 (wound* or tumor* or tumour* or ulcer*)):ti,ab
- #11 ((malignant or tumoral or neoplas* or cancer) near/3 wound*):ti,ab
- #12 ((melanoma or carcinoma or sarcoma or metasta*) near/5 ulcer*) .ti,ab.
- #13 #3 or #6 or #7 or #8 or #9 or #10 or #11 or #12
- #14 MeSH descriptor: [Anti-Infective Agents] explode all trees
- #15 MeSH descriptor: [Antibiotic Prophylaxis] explode all trees
- #16 MeSH descriptor: [Nitroimidazoles] explode all trees

Systemic antibiotics for treating malignant wounds (Review)

#17 (Antibiotic* or Nitroimidazole* or Dimetridazole or Etanidazole or Ipronidazole or Metronidazole or Misonidazole or Nimorazole or Ornidazole or Ronidazole or Tinidazole):ti,ab
 #18 MeSH descriptor: [Tetracyclines] explode all trees
 #19 (Tetracycline* or Chlortetracycline or Demeclocycline or Doxycycline or Lymecycline or Methacycline or Minocycline or Oxytetracycline or Rolitetracycline):ti,ab
 #20 (Erythromycin or Clindamycin or Ciprofloxacin):ti,ab
 #21 (Spiramycin or Azithromycin or Roxithromicin or Roxithromycin):ti,ab
 #22 MeSH descriptor: [Penicillins] explode all trees
 #23 (Penicillin* or Phenoxymethylpenicillin or Amoxicillin or Ampicillin or Flucloxacillin or Amoxiclav):ti,ab
 #24 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
 #25 #13 and #24

Ovid MEDLINE

1 exp Skin Ulcer/ and exp Neoplasms/
 2 Ulcer/ and exp Skin Neoplasms/
 3 (fungat* adj3 (wound* or tumor* or tumour* or lesion* or ulcer*)):tw.
 4 (ulcera* adj3 (tumor* or tumour*)):tw.
 5 (smelly adj3 (wound* or tumor* or tumour* or ulcer*)):tw.
 6 (malodorous adj3 (wound* or tumor* or tumour* or ulcer*)):tw.
 7 ((malignant or tumoral or neoplas* or cancer) adj3 wound*):tw.
 8 ((melanoma or carcinoma or sarcoma or metasta*) adj5 ulcer*):tw.
 9 or/1-8
 10 exp Anti-Infective Agents/
 11 Antibiotic Prophylaxis/
 12 exp Nitroimidazoles/
 13 (Antibiotic* or Nitroimidazole* or Dimetridazole or Etanidazole or Ipronidazole or Metronidazole or Misonidazole or Nimorazole or Ornidazole or Ronidazole or Tinidazole):ti,ab,rn.
 14 exp Tetracyclines/
 15 (Tetracycline* or Chlortetracycline or Demeclocycline or Doxycycline or Lymecycline or Methacycline or Minocycline or Oxytetracycline or Rolitetracycline):ti,ab,rn.
 16 (Erythromycin or Clindamycin or Ciprofloxacin):ti,ab,rn.
 17 (Spiramycin or Azithromycin or Roxithromicin or Roxithromycin):ti,ab,rn.
 18 exp Penicillins/
 19 (Penicillin* or Phenoxymethylpenicillin or Amoxicillin or Ampicillin or Flucloxacillin or Amoxiclav):ti,ab,rn.
 20 or/10-19
 21 and/9,20
 22 randomized controlled trial.pt.
 23 controlled clinical trial.pt.
 24 randomi?ed.ab.
 25 placebo.ab.
 26 clinical trials as topic.sh.
 27 randomly.ab.
 28 trial.ti.
 29 or/22-28
 30 exp animals/ not humans.sh.
 31 29 not 30
 32 21 and 31

Ovid Embase

1 exp skin ulcer/ and exp neoplasm/
 2 (ulcer/ or exp nose ulcer/ or ulcer healing/ or exp urogenital ulcer/) and exp skin tumor/
 3 (fungat* adj3 (wound* or tumor* or tumour* or lesion* or ulcer*)):tw.
 4 (ulcera* adj3 (tumor* or tumour*)):tw.
 5 (malodorous adj3 (wound* or tumor* or tumour* or ulcer*)):tw.
 6 (smelly adj3 (wound* or tumor* or tumour* or ulcer*)):tw.
 7 ((malignant or tumoral or neoplas* or cancer) adj3 wound*):tw.
 8 ((melanoma or carcinoma or sarcoma or metasta*) adj5 ulcer*):tw.
 9 or/1-8
 10 exp antiinfective agent/
 11 antibiotic prophylaxis/
 12 exp nitroimidazole derivative/

Systemic antibiotics for treating malignant wounds (Review)

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13 (Antibiotic* or Nitroimidazole* or Dimetridazole or Etanidazole or Ipronidazole or Metronidazole or Misonidazole or Nimorazole or Ornidazole or Ronidazole or Tinidazole).ti,ab,rn.
14 exp tetracycline derivative/
15 (Tetracycline* or Chlortetracycline or Demeclocycline or Doxycycline or Lymecycline or Methacycline or Minocycline or Oxytetracycline or Rolitetracycline).ti,ab,rn.
16 (Erythromycin or Clindamycin or Ciprofloxacin).ti,ab,rn.
17 (Spiramycin or Azithromycin or Roxithromicin or Roxithromycin).ti,ab,rn.
18 exp Penicillins/
19 (Penicillin* or Phenoxymethylpenicillin or Amoxicillin or Ampicillin or Flucloxacillin or Amoxiclav).ti,ab,rn.
20 or/10-19
21 and/9,20
22 Randomized controlled trials/
23 Single-Blind Method/
24 Double-Blind Method/
25 Crossover Procedure/
26 (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or assign* or allocat* or volunteer*).ti,ab.
27 (doubl* adj blind*).ti,ab.
28 (singl* adj blind*).ti,ab.
29 or/22-28
30 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
31 human/ or human cell/
32 and/30-31
33 30 not 32
34 29 not 33
35 21 and 34

EBSCO CINAHL Plus

S32 S18 AND S31
S31 S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30
S30 TI allocat* random* or AB allocat* random*
S29 MH "Quantitative Studies"
S28 TI placebo* or AB placebo*
S27 MH "Placebos"
S26 TI random* allocat* or AB random* allocat*
S25 MH "Random Assignment"
S24 TI randomi?ed control* trial* or AB randomi?ed control* trial*
S23 AB (singl* or doubl* or trebl* or tripl*) and AB (blind* or mask*)
S22 TI (singl* or doubl* or trebl* or tripl*) and TI (blind* or mask*)
S21 TI clinic* N1 trial* or AB clinic* N1 trial*
S20 PT Clinical trial
S19 MH "Clinical Trials+"
S18 S7 AND S17
S17 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16
S16 TX (Penicillin* or Phenoxymethylpenicillin or Amoxicillin or Ampicillin or Flucloxacillin or Amoxiclav)
S15 (MH "Penicillins+")
S14 TX (Spiramycin or Azithromycin or Roxithromicin)
S13 TX (Erythromycin or Clindamycin or Ciprofloxacin)
S12 TX (Tetracycline* or Chlortetracycline or Demeclocycline or Doxycycline or Lymecycline or Methacycline or Minocycline or Oxytetracycline or Rolitetracycline or Tetracycline)
S11 (MH "Tetracyclines+")
S10 TX (Antibiotic* or Nitroimidazole* or Dimetridazole or Etanidazole or Ipronidazole or Metronidazole or Misonidazole or Nimorazole or Ornidazole or Ronidazole or Tinidazole)
S9 (MH "Antibiotic Prophylaxis")
S8 (MH "Antiinfective Agents+")
S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6
S6 TX ((melanoma or carcinoma or sarcoma or metasta*) N5 ulcer*)
S5 TX ((malignant or tumoral or neoplas* or cancer) N3 wound*)
S4 TX (ulcera* N3 (tumor* or tumour*))
S3 TX (fungat* N3 (wound* or tumor* or tumour* or lesion* or ulcer*)) OR TX (smelly N3 (wound* or tumor* or tumour* or lesion* or ulcer*))
OR TX (malodorous N3 (wound* or tumor* or tumour* or lesion* or ulcer*))
S2 (MH "Ulcer") AND (MH "Skin Neoplasms+")

S1 (MH "Skin Ulcer+") AND (MH "Neoplasms+")

US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov)

("malignant wound" OR "fungating wound") AND ("neoplasm" OR "cancer" OR "carcinoma" OR "tumor" OR "tumour")

World Health Organization International Clinical Trials Registry Platform

("malignant wound" OR "fungating wound") AND ("neoplasm" OR "cancer" OR "carcinoma" OR "tumor" OR "tumour")

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.

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 available to permit 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: use of an open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. envelopes were unsealed, non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

Unclear

Insufficient information available 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 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 likely to introduce bias.

Unclear

Either of the following.

- Insufficient information available to permit 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 is 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 is 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 is 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 is 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 is 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 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. sub-scales) 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 available 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 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.

CONTRIBUTIONS OF AUTHORS

Darshini Ramasubbu: conceived, designed and coordinated the review; extracted data; checked the quality of data extraction; checked quality assessment; produced the first draft of the review; contributed to writing and editing the review; made an intellectual contribution to the review; performed previous work that was the foundation of the current review; wrote to study author/experts/companies; provided data; performed economic analysis; performed translations; approved the final review prior to submission and is a guarantor of the review.

Valerie Smith: conceived and designed the review; checked the quality of data extraction; analysed or interpreted data; undertook and checked quality assessment; performed statistical analysis; checked the quality of the statistical analysis; produced the first draft of the review; contributed to writing or editing the review; made an intellectual contribution to the review; advised on the review and approved the final review prior to submission.

Fiona Hayden: made an intellectual contribution to the review; advised on the review and approved the final review prior to submission.

Patricia Cronin: conceived, designed and coordinated the review; extracted data; checked the quality of data extraction; analysed or interpreted data; undertook quality assessment; performed statistical analysis; produced the first draft of the review; contributed to writing or editing the review; made an intellectual contribution to the review; performed previous work that was the foundation of the current review; wrote to study author/experts/companies and approved the final review prior to submission.

Contributions of editorial base:

Andrea Nelson (Editor): edited the protocol; advised on methodology interpretation and content; approved the final protocol prior to submission.

Gill Norman (Editor): edited the review; advised on methodology interpretation and content; approved the final review prior to submission.

Gill Rizzello and **Sally Bell-Syer** (Managing Editors): co-ordinated the editorial process; advised on interpretation and content; edited the protocol and the review.

Zipporah Iheozor-Ejiofor (Methodologist): advised on methodology in the review.

Reetu Child and **Naomi Shaw** (Information Specialists): designed the search strategy, edited the search methods section and ran the searches for the review.

Ursula Gonthier (Editorial Assistant): edited the plain language summary and reference sections of the review.

DECLARATIONS OF INTEREST

Darshini Ramasubbu: none known.

Valerie Smith: none known.

Fiona Hayden: none known.

Patricia Cronin: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We updated our search strategies adding terms for smelly and malodorous tumours.

INDEX TERMS

Medical Subject Headings (MeSH)

*Odorants; Anti-Bacterial Agents [*therapeutic use]; Anti-Infective Agents [*therapeutic use]; Double-Blind Method; Metronidazole [*therapeutic use]; Neoplasms [*complications]; Prospective Studies; Soft Tissue Injuries [drug therapy] [etiology]; Wounds and Injuries [*drug therapy] [etiology]

MeSH check words

Humans