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[Intervention Review]

Dressings and topical agents for treating pressure ulcers

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ABSTRACT

Background

Pressure ulcers, also known as bedsores, decubitus ulcers and pressure injuries, are localised areas of injury to the skin or the underlying tissue, or both. Dressings are widely used to treat pressure ulcers and promote healing, and there are many options to choose from including alginate, hydrocolloid and protease-modulating dressings. Topical agents have also been used as alternatives to dressings in order to promote healing.

A clear and current overview of all the evidence is required to facilitate decision-making regarding the use of dressings or topical agents for the treatment of pressure ulcers. Such a review would ideally help people with pressure ulcers and health professionals assess the best treatment options. This review is a network meta-analysis (NMA) which assesses the probability of complete ulcer healing associated with alternative dressings and topical agents.

Objectives

To assess the effects of dressings and topical agents for healing pressure ulcers in any care setting. We aimed to examine this evidence base as a whole, determining probabilities that each treatment is the best, with full assessment of uncertainty and evidence quality.

Search methods

In July 2016 we searched the Cochrane Wounds Specialised Register; the Cochrane Central Register of Controlled Trials (CENTRAL); Ovid MEDLINE; Ovid MEDLINE (In-Process & Other Non-Indexed Citations); Ovid Embase and EBSCO CINAHL Plus. We also searched clinical trials registries for ongoing and unpublished studies, and scanned reference lists of relevant included studies as well as reviews, meta-analyses, guidelines and health technology reports to identify additional studies. There were no restrictions with respect to language, date of publication or study setting.

Selection criteria

Published or unpublished randomised controlled trials (RCTs) comparing the effects of at least one of the following interventions with any other intervention in the treatment of pressure ulcers (Stage 2 or above): any dressing, or any topical agent applied directly to an open pressure ulcer and left in situ. We excluded from this review dressings attached to external devices such as negative pressure wound therapies, skin grafts, growth factor treatments, platelet gels and larval therapy.

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Data collection and analysis

Two review authors independently performed study selection, risk of bias assessment and data extraction. We conducted network meta-analysis using frequentist mega-regression methods for the efficacy outcome, probability of complete healing. We modelled the relative effectiveness of any two treatments as a function of each treatment relative to the reference treatment (saline gauze). We assumed that treatment effects were similar within dressings classes (e.g. hydrocolloid, foam). We present estimates of effect with their 95% confidence intervals for individual treatments compared with every other, and we report ranking probabilities for each intervention (probability of being the best, second best, etc treatment). We assessed the certainty (quality) of the body of evidence using GRADE for each network comparison and for the network as whole.

Main results

We included 51 studies (2947 participants) in this review and carried out NMA in a network of linked interventions for the sole outcome of probability of complete healing. The network included 21 different interventions (13 dressings, 6 topical agents and 2 supplementary linking interventions) and was informed by 39 studies in 2127 participants, of whom 783 had completely healed wounds.

We judged the network to be sparse: overall, there were relatively few participants, with few events, both for the number of interventions and the number of mixed treatment contrasts; most studies were small or very small. The consequence of this sparseness is high imprecision in the evidence, and this, coupled with the (mainly) high risk of bias in the studies informing the network, means that we judged the vast majority of the evidence to be of low or very low certainty. We have no confidence in the findings regarding the rank order of interventions in this review (very low-certainty evidence), but we report here a summary of results for some comparisons of interventions compared with saline gauze. We present here only the findings from evidence which we did not consider to be very low certainty, but these reported results should still be interpreted in the context of the very low certainty of the network as a whole.

It is not clear whether regimens involving protease-modulating dressings increase the probability of pressure ulcer healing compared with saline gauze (risk ratio (RR) 1.65, 95% confidence interval (CI) 0.92 to 2.94) (moderate-certainty evidence: low risk of bias, downgraded for imprecision). This risk ratio of 1.65 corresponds to an absolute difference of 102 more people healed with protease modulating dressings per 1000 people treated than with saline gauze alone (95% CI 13 fewer to 302 more). It is unclear whether the following interventions increase the probability of healing compared with saline gauze (low-certainty evidence): collagenase ointment (RR 2.12, 95% CI 1.06 to 4.22); foam dressings (RR 1.52, 95% CI 1.03 to 2.26); basic wound contact dressings (RR 1.30, 95% CI 0.65 to 2.58) and polyvinylpyrrolidone plus zinc oxide (RR 1.31, 95% CI 0.37 to 4.62); the latter two interventions both had confidence intervals consistent with both a clinically important benefit and a clinically important harm, and the former two interventions each had high risk of bias as well as imprecision.

Authors' conclusions

A network meta-analysis (NMA) of data from 39 studies (evaluating 21 dressings and topical agents for pressure ulcers) is sparse and the evidence is of low or very low certainty (due mainly to risk of bias and imprecision). Consequently we are unable to determine which dressings or topical agents are the most likely to heal pressure ulcers, and it is generally unclear whether the treatments examined are more effective than saline gauze.

More research is needed to determine whether particular dressings or topical agents improve the probability of healing of pressure ulcers. The NMA is uninformative regarding which interventions might best be included in a large trial, and it may be that research is directed towards prevention, leaving clinicians to decide which treatment to use on the basis of wound symptoms, clinical experience, patient preference and cost.

PLAIN LANGUAGE SUMMARY

Which dressings or topical agents are the most effective for healing pressure ulcers?

Dressings and topical agents for treating pressure ulcers

Review question

We reviewed the evidence about the effects of dressings and topical agents (such as ointments, creams and gels) on pressure ulcer healing. There are many different dressings and topical agents available, and we wanted to find out which were the most effective.

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Background

Pressure ulcers, also known as bedsores, decubitus ulcers and pressure injuries, are wounds involving the skin and sometimes the tissue that lies underneath. Pressure ulcers can be painful, may become infected and affect people's quality of life. People at risk of developing pressure ulcers include those with limited mobility - such as older people and people with short-term or long-term medical conditions - and people with spinal cord injuries. In 2004 the total yearly cost of treating pressure ulcers in the UK was estimated as being GBP 1.4 to 2.1 billion, which was equivalent to 4% of the total National Health Service expenditure.

Topical agents such as ointments, creams or gels are applied to unhealed pressure ulcers and left in place to treat the wound; they may be covered with a dressing. Some of these treatments have been compared with each other in trials, usually comparing two treatments at a time. We used a method called 'network meta-analysis' to bring together all the trial results of different treatments in a reliable way. We hoped that this method, which compares all treatment options, would help us find out which was the best treatment for healing pressure ulcers.

Study characteristics

In July 2016 we searched for randomised controlled trials looking at dressings and topical agents for treating pressure ulcers and that gave results for complete wound healing. We found 51 studies involving a total of 2947 people. Thirty-nine of these studies, involving 2127 people, gave results we could bring together in a network meta-analysis comparing 21 different treatments. Most participants in the trials were older people; three of the 39 trials involved participants with spinal cord injuries.

Key results

Generally, the studies we found did not have many participants and results were often inconclusive. This problem carried over into the network meta-analysis and made the findings unclear. As a result, it was unclear whether one topical agent or dressing was better than another. Some findings for individual comparisons may be slightly more reliable. Protease-modulating dressings, foam dressings or collagenase ointment may be better at healing than gauze; but even this evidence is not certain enough to be an adequate guide for treatment choices.

Certainty of the evidence

We judged the certainty of the evidence to be very low or low. The next step might be to do more research of better quality to see which dressings or topical agents could best heal pressure ulcers.

This plain language summary is up to date as of July 2016.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

NMA evidence for individual network: proportion with complete healing - interventions versus saline gauze

Patient or population: people with pressure ulcers
Intervention: dressing or topical agent
Comparator: saline gauze
Settings: hospital, community or care home, or combinations

Contrasts: interventions versus saline gauze	Relative effect (95% CI)	Anticipated absolute effects* (95% CI) - from median of saline gauze control groups in direct evidence		Certainty (quality) of the evidence (GRADE)
		Median CGR	With interventions	
Alginate dressings	RR 1.09 (0.11 to 10.57)	157 per 1000	171 per 1000 (17 to 1000)	⊕◯◯◯ Very low[1]
		14 more people healed per 1000 (140 fewer to 1000 more)		
Sequential hydrocolloid alginate dressings	RR 0.50 (0.12 to 1.98)	157 per 1000	78 per 1000 (1.9 to 31.2)	⊕◯◯◯ Very low[1]
		79 fewer people healed per 1000 (138 fewer to 155 more)		
Basic wound contact dressings	RR 1.30 (0.65 to 2.58)	157 per 1000	204 per 1000 (102 to 407)	⊕⊕◯◯ Low[2]
		47 more people healed per 1000 (55 fewer to 250 more)		
Collagenase ointment	RR 2.12 (1.06 to 4.22)	157 per 1000	333 per 1000 (166 to 663)	⊕⊕◯◯ Low[3]
		176 more people healed per 1000 (9 more to 506 more)		
Dextranomer	RR 4.76 (0.86 to 26.39)	157 per 1000	747 per 1000 (135 to 1000)	⊕◯◯◯ Very low[4]

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		590 more people healed per 1000 (22 fewer to 1000 more)		
Foam dressings	RR 1.52 (1.03 to 2.26)	157 per 1000	239 per 1,000 (162 to 353)	⊕⊕◯◯ Low[5]
		82 more people healed per 1,000 (5 more to 196 more)		
Hydrocolloid dressing with/without alginate	RR 1.22 (0.06 to 24.74)	157 per 1000	**192 per 1,000 (9 to 1000)**	⊕◯◯◯ Very low[1]
		35 more people healed per 1,000 (148 fewer to 1000 more)		
Hydrocolloid dressings	RR 1.43 (1.00 to 2.05)	157 per 1000	225 per 1000 (157 to 322)	⊕◯◯◯ Very low[6]
		68 more people healed per 1000 (from 0 fewer to 165 more)		
Hydrogel	RR 1.55 (1.02 to 2.36)	157 per 1000	243 per 1000 (160 to 371)	⊕◯◯◯ Very low[6]
		86 more people healed per 1000 (from 3 more to 214 more)		
Iodine-containing dressings	RR 1.08 (0.58 to 2.03)	157 per 1000	170 per 1000 (91 to 316)	⊕◯◯◯ Very low[1]
		13 more people healed per 1000 (from 66 fewer to 159 more)		
Phenytoin	RR 1.27 (0.58 to 2.80)	157 per 1000	199 per 1000 (91 to 440)	⊕◯◯◯ Very low[7]
		42 more people healed per 1000 (from 66 fewer to 283 more)		
Protease-modulating dressings	RR 1.65 (0.92 to 2.94)	157 per 1000	259 per 1,000 (144 to 462)	⊕⊕⊕◯ Moderate[8]

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		102 more people healed per 1000 (from 13 fewer to 305 more)		
Polyvinylpyrrolidone + zinc oxide	RR 1.31 (0.37 to 4.62)	157 per 1000	206 per 1,000 (58 to 732)	⊕⊕◯◯ Low[2]
		49 more people healed per 1000 (from 99 fewer to 575 more)		
Combination silicone foam dressings	RR 1.93 (0.38 to 9.98)	157 per 1000	303 per 1,000 (60 to 1,000)	⊕◯◯◯ Very low[1]
		146 more people healed per 1000 (from 97 fewer to 1,000 more)		
Soft polymer dressings	RR 1.35 (0.55 to 3.27)	157 per 1000	212 per 1,000 (86 to 517)	⊕◯◯◯ Very low[1]
		55 more people healed per 1000 (from 71 fewer to 360 more)		
Sugar + egg white	RR 0.70 (0.03 to 15.62)	157 per 1000	110 per 1000 (5 to 1,000)	⊕◯◯◯ Very low[1]
		47 fewer people healed per 1000 (from 152 fewer to 1000 more)		
Tripeptide copper gel	RR 3.90 (1.04 to 14.63)	157 per 1000	612 per 1000 (163 to 1000)	⊕◯◯◯ Very low[9]
		455 more people healed per 1000 (6 more to 1000 more)		
Vapour-permeable dressings	RR 1.45 (0.74 to 2.81)	157 per 1000	228 per 1000 (118 to 440)	⊕◯◯◯ Very low[1]
		71 more people healed per 1000 (from 39 fewer to 283 more)		

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparator group and the __relative effect__ of the intervention (and its 95% CI).

CGR: control group risk; **CI:** confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty (quality): we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty (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 certainty (quality): our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty (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]Majority of evidence at high risk of bias (downgraded once); imprecision: very wide CI (crosses 0.75 and 1.25) (downgraded twice).
[2]Imprecision: very wide CI (crosses 0.75 and 1.25) (downgraded twice).
[3]Majority of evidence at high risk of bias (downgraded once); imprecision: wide CI and direct evidence on collagenase from three studies, 11 events (downgraded once).
[4]Majority of evidence at high risk of bias (downgraded once): imprecision: wide CI (crosses 1.25) and direct evidence on dextranomer from one study, seven participants and four events (downgraded twice).
[5]Majority of evidence at high risk of bias (downgraded once); imprecision: wide CI (downgraded once).
[6]Majority of evidence at high risk of bias (downgraded once); inconsistency: heterogeneity in direct evidence (downgraded once); imprecision: wide CI (downgraded once).
[7]Majority of evidence at high risk of bias (downgraded once); inconsistency: significant difference between direct and indirect estimates (downgraded once); imprecision: very wide CI (crossed 0.75 and 1.25).
[8]Imprecision: wide CI (crosses 1.25); (direct evidence for protease-modulating dressing: four studies, 76 participants, 31 events) (downgraded once).
[9]Majority of evidence at high risk of bias (downgraded once): imprecision: wide CI (crosses 1.25) and direct evidence on tripeptide copper gel from one study, six participants and five events (downgraded twice).

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BACKGROUND

Description of the condition

Pressure ulcers, also known as pressure injuries, bedsores, decubitus ulcers or pressure sores, are localised areas of injury to the skin, the underlying tissue or both. They often occur over bony prominences such as the sacrum (base of the spine) and heel (Vanderwee 2007), and are caused by external forces such as pressure, or shear, or a combination of both (EPUAP-NPUAP-PPPIA 2014; NPUAP 2016; Dumville 2015a; Dumville 2015b; Keogh 2013; Walker 2014).

Risk factors for pressure ulcer development have been summarised into three main categories: a lack of mobility; poor perfusion (e.g. diabetes and vascular disease) and low skin status (Coleman 2013); the latter category includes the presence of stage 1 pressure ulcers or incontinence or both, which also increases the risk of ulceration by producing a detrimental environment for the skin (Brandeis 1994).

Pressure ulcers vary in severity. One of the most widely recognised systems for categorising pressure ulcers is that of the National Pressure Ulcer Advisory Panel (NPUAP). Their international classification recognises four categories or stages of pressure ulcer and two categories of unclassifiable pressure injury. Stage 1 ulcers involve intact skin, but Stages 2 to 4 describe progressively deeper wounds with larger degrees of skin and tissue loss: Stage 2 pressure ulcers have partial-thickness skin loss and exposed dermis; Stage 3 refers to full-thickness skin loss and exposed fat tissue; and Stage 4 ulcers have full-thickness skin and tissue loss, with exposed fascia, muscle, tendon, ligament, cartilage or bone. The two categories of unclassifiable pressure injury are reserved for wounds for which wound depth or extent, or both, cannot be accurately determined; unclassifiable pressure ulcers are generally severe and would be grouped clinically with Stage 3 or Stage 4 ulcers (EPUAP-NPUAP-PPPIA 2014) (see Appendix 1 for further details of grading).

Prevalence

Pressure ulcers are one of the most common types of complex wound. Prevalence estimates differ according to the type of population assessed, the data collection methods used and period of data collection and whether Stage 1 ulcers were included).

One large European study estimated a hospital pressure ulcer prevalence (Stage 2 and above) of 10.5% (Vanderwee 2007) whilst a US study estimated a prevalence of 9.0% (Stage 2 and above) across acute-care, long-term care and rehabilitation settings (the highest prevalence of 26% was in long-term acute-care settings (VanGilder 2009)). In the UK, national pressure ulcer data are collected across community and acute settings (although data collection is not yet universal) as part of the National Health Service (NHS) Safety Thermometer initiative (Power 2012). About 4.4% of patients across these settings were estimated to have a pressure ulcer (Stage 2 to Stage 4) in November 2014 (NHS Quality Observatory 2015).

We note that all the prevalence figures quoted above are for at-risk populations currently receiving medical care. The point prevalence of pressure ulceration in the total adult population was recently estimated as 0.31 per 1000 population (including Stage 1) (Hall 2014).

Treatments for pressure ulcers

There are two main strategies in the treatment of pressure ulcers, namely relief of pressure - commonly using specialist support surfaces (McInnes 2011; NICE 2014) - together with management of the wound environment using wound dressings. Other general strategies include patient education, pain management, optimising circulation/perfusion, optimising nutrition and the treatment of clinical infection (EPUAP-NPUAP-PPPIA 2014; NICE 2014). Pressure ulcers are normally expected to show signs of healing within two weeks, but this may not occur and there can be deterioration (EPUAP-NPUAP-PPPIA 2014).

Impact of pressure ulcers on patients and financial costs

Pressure ulcers have a large impact on those affected; the ulcers can be painful, and may become seriously infected or malodorous. It has been shown that after adjustment for age, sex and co-morbidities people with pressure ulcers have a lower health-related quality of life than those without pressure ulcers (Essex 2009).

The financial cost of treating pressure ulcers in the UK has been estimated to range from GBP 1214 for a Stage 1 ulcer to GBP 14,108 for a Stage 4 ulcer. Costs are mainly dominated by health professional time, and for more severe ulcers, by the incidence of complications including hospital admission/length of stay (Dealey 2012). In 2004, the total annual cost of treating pressure ulcers in the UK was estimated as GBP 1.4 to 2.1 billion, which was equivalent to 4% of the total NHS expenditure (Bennett 2004). Pressure ulcers have been shown to increase length of hospital stay and associated hospital costs (Allman 1999). Figures from the USA suggest that for half a million hospital stays in 2006, 'pressure ulcer' was noted as a diagnosis; for adults, the total hospital cost for these stays was USD 11 billion (Russo 2008). Costs to the Australian healthcare system for treating pressure ulceration have been estimated at AUD 285 million annually (Graves 2005).

Description of the intervention

This review includes RCTs of any dressings or topical agents applied directly onto or into wounds and left in situ, as opposed to products used to irrigate, wash or cleanse wounds and those that are only in contact with wounds for a short period.

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Dressings

The classification of dressings usually depends on the key material used in their construction, and whether additional substances are added to the dressing. Several attributes of an ideal wound dressing have been described (BNF 2016; Bradley 1999), including the ability of the dressing to:

- absorb and contain exudate without leakage or strike-through, in order to maintain a wound that is moist but not macerated;
- achieve freedom from particulate contaminants or toxic chemicals left in the wound;
- provide thermal insulation, in order to maintain the optimum temperature for healing;
- allow permeability to water, but not bacteria;
- optimise the pH of the wound;
- minimise wound infection and avoid excessive slough;
- avoid wound trauma on dressing removal;
- accommodate the need for frequent dressing changes;
- provide pain relief; and
- be comfortable.

There are numerous and diverse dressings available for treating pressure ulcers and their properties are described below.

Absorbent dressings are applied directly to the wound and may be used as secondary absorbent layers in the management of heavily exuding wounds. Examples include Primapore (Smith & Nephew), Mepore (Mölnlycke) and absorbent cotton gauze (BP 1988).

Alginate dressings are highly absorbent fabrics/yarns that come in the form of calcium alginate or calcium sodium alginate and can be combined with collagen. The alginate forms a gel when in contact with the wound surface; this can be lifted off at dressing removal, or rinsed away with sterile saline. Bonding to a secondary viscose pad increases absorbency. Examples include: Curasorb (Covidien), SeaSorb (Coloplast) and Sorbsan (Unomedical).

Capillary-action dressings consist of an absorbent core of hydrophilic fibres held between two low-adherent contact layers. Examples include: Advadraw (Advancis) and Vacutex (Protex).

Films, i.e. permeable film and membrane dressings are permeable to water vapour and oxygen, but not to water or micro-organisms. Examples include Tegaderm (3M) and OpSite (Smith & Nephew).

Foam dressings contain hydrophilic polyurethane foam and are designed to absorb wound exudate and maintain a moist wound surface. There are a variety of versions and some include additional absorbent materials, such as viscose and acrylate fibres, or particles of superabsorbent polyacrylate, which are silicone-coated for non-traumatic removal. Examples include: Allevyn (Smith & Nephew), Biatain (Coloplast) and Tegaderm (3M).

Honey-impregnated dressings contain medical-grade honey that is purported to have antimicrobial and anti-inflammatory properties and can be used for acute or chronic wounds. Examples include: Medihoney (Medihoney) and Activon Tulle (Advancis).

Hydrocolloid dressings are usually composed of an absorbent hydrocolloid matrix on a vapour-permeable film or foam backing. Examples include: Granuflex (ConvaTec) and NU DERM (Systagenix). Fibrous alternatives that resemble alginates and are not occlusive have also been developed: Aquacel (ConvaTec).

Iodine-impregnated dressings release free iodine, which is thought to act as a wound antiseptic when exposed to wound exudate. Examples include Iodoflex (Smith & Nephew) and Iodozyme (Insense).

Low-adherence dressings and **wound contact materials** usually consist of cotton pads that are placed directly in contact with the wound. They can be non-medicated (e.g. paraffin gauze dressing, saline gauze dressing) or medicated (e.g. containing povidone iodine or chlorhexidine). Examples include paraffin gauze dressing, BP 1993 and Xeroform (Covidien) dressing - a non-adherent petrolatum blend with 3% bismuth tribromophenate on fine mesh gauze.

Odour-absorbent dressings contain charcoal and are used to absorb wound odour. Often this type of wound dressing is used in conjunction with a secondary dressing to improve absorbency. An example is CarboFLEX (ConvaTec).

Other antimicrobial dressings are composed of a gauze or low-adherent dressing impregnated with an ointment thought to have antimicrobial properties. Examples include: chlorhexidine gauze dressing (Smith & Nephew) and Cutimed Sorbact (BSN Medical).

Protease-modulating matrix dressings alter the activity of proteolytic enzymes in chronic wounds. Examples include: Promogran (Systagenix).

Silver-impregnated dressings are used to treat infected wounds, as silver ions are thought to have antimicrobial properties. Silver versions of most dressing types are available, including silver impregnated dressings (e.g. silver hydrocolloid etc). Examples include: Acticoat (Smith & Nephew) and Urgosorb Silver (Urgo).

Soft polymer dressings are composed of a soft silicone polymer held in a non-adherent layer; these are moderately absorbent. Examples include: Mepitel (Mölnlycke) and Urgotul (Urgo).

Topical agents

Topical agents are defined as hydrogels. ointments and creams that are placed in contact with the wound and left in situ; they may be covered with a secondary dressing.The following types of topical agents are considered as interventions in this review:

Cadexomer-iodine paste consists of a water-soluble, modified starch polymer containing iodine. It releases free iodine when exposed to wound exudate. The free iodine acts as an antiseptic on the wound surface, and the cadexomer absorbs wound exudate and encourages de-sloughing. Examples include: Iodosorb (Smith & Nephew) ointment and powder.

Collagenase-containing ointment is an enzymatic debriding ointment. Collagenase is thought to digest collagen in necrotic tissue and to contribute to granulation and epithelisation.

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Hydrogels consist of a starch polymer and up to 96% water. They can absorb wound exudate or rehydrate a wound depending on the wound moisture levels. Hydrogels are often considered to be dressings, but are also topical in nature. They are supplied in either flat sheets, an amorphous hydrogel or as beads. Examples include: ActiformCool (Activa and Aquaflo (Covidien).

Phenytoin topical is thought to promote wound healing by a number of mechanisms, including stimulation of fibroblast proliferation, facilitation of collagen deposition and antibacterial activity.

Silver sulfadiazine cream is a topical antimicrobial cream that is used to treat and prevent infection in wounds by damaging bacterial cell membranes. Examples include Flamazine (Smith & Nephew) and Silvadene (Pfizer).

Products containing **growth factors**, **platelet-rich plasma** or other **platelet-derived products** and **colony-stimulating factors** are outside the scope of this review.

How the intervention might work

Animal experiments conducted over 40 years ago suggested that acute wounds heal more quickly when their surfaces are kept moist rather than left to dry and scab (Winter 1962; Winter 1963a; Winter 1963b). A moist environment is thought to provide optimal conditions for the cells involved in the healing process, as well as allowing autolytic debridement (removal of dead tissue by natural processes), which is thought to be an important part of the healing pathway (Cardinal 2009).

The desire to maintain a moist wound environment is a key driver for the use of wound dressings and related topical agents. Whilst a moist environment at the wound site has been shown to aid the rate of epithelialisation in superficial wounds, excess moisture at the wound site can cause maceration of the surrounding skin (Cutting 2002), and it has also been suggested that dressings that permit fluid to accumulate might predispose wounds to infection (Hutchinson 1991). Wound treatments vary in their level of absorbency, so that a very wet wound can be treated with an absorbent dressing (such as a foam dressing) to draw excess moisture away and avoid skin damage, whilst a drier wound can be treated with a more occlusive dressing or a hydrogel to maintain a moist environment.

Some dressings are now also formulated with an 'active' ingredient (e.g. silver, honey or protease modulators).

Why it is important to do this review

The diversity of dressings and related materials available to health professionals for treating pressure ulcers makes evidence-based decision-making difficult when determining the optimum treatment regimen for a particular patient (Gillespie 2012; NICE 2014). With increasingly sophisticated technology being applied to wound care, practitioners need to know the relative effectiveness and cost-effectiveness of these sometimes expensive dressings. Even where cost is not an issue, the most effective treatment may not be available (e.g. in some developing countries) or may be difficult or to use, so that information on the second and third best treatments is important too (Salanti 2011).

Current evidence syntheses include four Cochrane Reviews (Dumville 2015a; Dumville 2015b; Keogh 2013; Walker 2014), two other systematic reviews (Reddy 2008; Smith 2013), and two recent clinical guidelines (EPUAP-NPUAP-PPPIA 2014; NICE 2014). Each of these consists of a series of pairwise comparisons. No review finds clear evidence of any effect of one dressing compared to another in terms of assessed outcome measures, including complete wound healing.

In the absence of an overview or network meta-analysis, decision-makers have to consider the findings of multiple pairwise randomised controlled trials (RCTs) simultaneously and qualitatively to judge, in the face of uncertainty, which dressing they might decide to use. It is extremely difficult to do this effectively, and this difficulty is compounded when the evidence comprises single small trials, about which decision-makers may have little confidence.

Network meta-analysis (NMA) is the simultaneous comparison of linked, multiple, competing treatments in a single statistical model (Caldwell 2005; Chaimani 2013a; Lu 2004; Salanti 2008). NMA utilises evidence from 'direct' (head-to-head or 'pairwise') comparisons (e.g. trials directly comparing treatments A and B), 'indirect' comparisons (e.g. the combination of trials comparing A with C and trials comparing B with C), and a synthesis of both when available. When pooling relative effect estimates, NMAs preserve within-trial randomisation (Grant 2013; Thorlund 2012; Tu 2012).

Where there are relevant common comparators across trials that allow treatments to be linked and form a network of evidence, NMA produces a set of effect estimates for each treatment relative to every other, whether or not they have been compared in head-to-head trials. In this way NMA allows us to obtain estimates for comparisons for which there is no (direct) trial evidence. Even when direct evidence is available there may not be much of it, so pooling it with data from indirect comparisons generally gives more robust evidence and reduces uncertainty in the estimates of effect (Higgins 1996; Thorlund 2012). From the NMA analysis, it is possible to evaluate the probability of each treatment being the best for a specific outcome: these probabilities reflect the precision surrounding the effect estimates (Caldwell 2014; Salanti 2011). A glossary of NMA terms is given in Appendix 2.

This review comprised a network meta-analysis (NMA) for the outcome of pressure ulcer healing, for alternative dressings and topical agents for the treatment of pressure ulcers of Stage 2 and above. The NMA enabled us to compare pairs of dressings/topical agents, taking into account direct and indirect evidence simultaneously, and explicitly determining the uncertainty in effect esti-

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mates. The ranking process allowed us to examine the evidence base as a whole, identifying the support of the evidence for each treatment, having consideration for indirect evidence (where it existed) and fully reflecting evidence uncertainties. We also explored assumptions made in the analysis.

OBJECTIVES

To assess the effects of dressings and topical agents for healing pressure ulcers in any care setting. We aimed to examine this evidence base as a whole, determining probabilities that each treatment is the best, with full assessment of uncertainty and evidence quality.

METHODS

Criteria for considering studies for this review

Types of studies

We included published and unpublished randomised controlled trials (RCTs), irrespective of language of report. We did not identify any cross-over trials, but we would have included them only if they reported outcome data at the end of the first treatment period and prior to cross-over. We excluded studies using quasi-random methods of allocation (such as alternation). We highlighted trials in which three or more interventions were randomised.

Types of participants

We included studies that recruited people with a diagnosis of pressure ulcer, Stage 2 and above (EPUAP-NPUAP-PPPIA 2014), managed in any care setting. We excluded studies that only recruited people with Stage 1 ulcers as these are not open wounds requiring dressings.

We accepted study authors' definitions of what they classed as Stage 2 or above, unless it was clear that they included wounds with unbroken skin. Where authors used grading scales other than NPUAP, we attempted to map to the NPUAP scale.

We included studies that recruited participants with pressure ulcers of Stage 2 severity or higher alongside people with Stage 1 pressure ulcers or other types of complex wound (e.g. leg and/or foot ulcers), or both, provided the allocation of participants was stratified by type of wound or pressure ulcer severity at randomisation and provided the results for people with eligible pressure ulcers (that is Stage 2 or higher) were presented separately (or became available from the study authors). Where studies included participants with Stage 1 ulcers or other types of complex wounds, but these made up 25% or less of the total study population we included all study data.

Types of interventions

Interventions of direct interest (decision set)

The interventions in this section were all those that can be directly applied as dressings or topical agents to open pressure ulcers. We presented results for these interventions and included them in summary tables. In the context of a network of competing treatments, there are no 'comparators'.

We considered trials for which at least one of the interventions was (1) any dressing, including impregnated dressings or saline-moistened dressings or combination dressings or (2) any topical agent applied directly to an open pressure ulcer and left in situ. Combination dressings are when two or more dressings are applied sequentially over time (e.g., hydrocolloid for four weeks followed by alginate for four weeks), or a product contains two or more types of dressing material (e.g., a multilayer product comprising silicone polymer and hydrocolloid). The treatment of interest had to be the only systematic difference between treatment groups. We did not take into account secondary dressings.

Some of the interventions we considered were as follows:

- Basic wound contact dressings (includes low-adherence (including paraffin gauze) or absorbent dressings (of any absorbency))
- Saline-moistened gauze (all degrees of moistness)
- Hydrogel dressing (includes hydrogel sheet or hydrogel application (amorphous) or sodium hyaluronate)
- Vapour-permeable films and membranes (includes adhesive film (semi-permeable) or adhesive film with absorbent pad)
- Soft polymer dressings (with/without absorbent pad or cellulose)
- Hydrocolloid dressing (with/without adhesive border or matrix hydrocolloid)
- Fibrous (spun) hydrocolloid
- Foam dressings (all absorbencies)
- Alginate dressings
- Capillary action dressings
- Alginate dressing with charcoal
- Other charcoal-containing dressing
- Honey sheet dressing or topical honey
- Cadexomer iodine ointments
- Iodine-containing dressings
- Soft polymer dressing (with silver)
- Hydrocolloid (with silver)
- Foam dressings (with silver)
- Alginate dressings (with silver)
- Silver sulfadiazine cream
- Protease-modulating matrix dressings
- Collagenase-containing ointment
- Topical phenytoin
- Topical zinc oxide
- No dressing (wound left exposed)

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- Other treatments considered by the review team (with additional clinical advice where required) to be dressings or topical agents applied directly to the wound and left in-situ.

The following interventions were not part of the decision set: treatments in which dressings are attached to external devices such as negative pressure wound therapies, skin grafts, growth factor treatments, platelet gels and larval therapy.
We grouped together dressings in the same class (e.g. alginates) (BNF 2016). This was regardless of a particular brand's stated absorbency, size, concentration of active component or the degree of moistness. Thus, where studies only compared two dressings from the same class (for example, two alginates or two foam dressings), we excluded such studies from the review as they contributed no information about the effectiveness of the class.
We included any RCT in which other concurrent therapies were given (e.g. antibiotics, debridement), provided that these treatments were delivered in a standardised way across the trial arms of the individual trial (such that the treatment of interest was the only systematic difference). We did not treat separately comparisons with and without concurrent therapies, that is, we considered intervention 1 + concurrent therapy versus intervention 2 + concurrent therapy to be the same as intervention 1 versus intervention 2.
One of the assumptions underpinning NMA is that interventions in the network are exchangeable, that is, participants in the network could, in principle, be randomised to any of the treatments being compared. For example, a person with a pressure ulcer could be equally likely to be randomised to an alginate dressing, a polyurethane foam dressing, honey or saline gauze. Depending on the wound requirements for the dressing (e.g. highly absorbent), this may not always be a good assumption for individual wounds, but across the population in the trials may be reasonable.

Supplementary intervention set

Some of the trial interventions were not included in the decision set (see above) but were included in a supplementary intervention set if they linked two or more decision set interventions: such supplementary interventions were of value solely because they allowed inferences to be drawn about the treatments of interest. In our individual network, the supplementary intervention set included radiant heat and skin substitute.

Terminology

For the rest of this review, we use the term 'comparison' to mean two interventions compared in a single study or in a pairwise meta-analysis of direct data. We use the term 'contrast' to mean two interventions compared across all studies in an NMA. This may be either direct or indirect evidence or both. We use the following terms: 'direct contrast' for interventions linked directly in the network; 'indirect contrast' when the two interventions are linked solely via indirect NMA evidence; and 'mixed treatment contrast' when either direct or indirect evidence or both are involved. Direct evidence may be informed by more than one study comparing the two interventions. Indirect estimates may be calculated using a 'node-splitting' approach, in which the NMA is run after excluding the direct evidence for a particular contrast.
We also use the term 'core intervention' to mean interventions that form part of at least one loop and 'peripheral interventions' to mean interventions that are not part of a loop and are only connected in a peripheral way.

Types of outcome measures

We reported outcome measures at the last time point available (assumed to be length of follow-up if not specified) or the time point specified in the methods as being of primary interest (if this was different from the latest time point available). Initially, we noted when studies reported results at other time points or whether they included Kaplan-Meier plots, or both.

Primary outcomes

The primary outcome for this review was complete wound healing. We regarded the following as providing the most relevant measures of outcome for the analyses:

- the proportion of wounds healed (frequency of complete healing: arm-level data);
- time to complete healing (survival data: study-level data).

We accepted authors' definitions of what constituted a healed wound.

Secondary outcomes

We did not consider any secondary outcomes, however they are reported in other relevant reviews (Dumville 2015a; Dumville 2015b; Keogh 2013; Walker 2014).

Search methods for identification of studies

Four existing Cochrane Reviews were relevant to this NMA (Dumville 2015a; Dumville 2015b; Keogh 2013; Walker 2014), and the protocol for this NMA complemented the protocols for these four reviews (an author on these four reviews is also a review author here). We automatically included trials from these reviews in this NMA if they reported complete healing outcomes; we planned to use the extracted data from these reviews where possible, supplementing if necessary which was required as some reviews had not been completed.
We conducted searches to identify relevant trials not covered by the four Cochrane Reviews as well as recently published trials. We cross-checked the identified trials against those in the 2014 NICE guideline and the 2013 US Agency for Healthcare Research and

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Quality (AHRQ) guideline on treating pressure ulcers to further locate any additional trials (AHRQ 2013; NICE 2014); we also checked the references of 24 systematic reviews identified by our search.

Electronic searches

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

- the Cochrane Wounds Specialised Register (searched 12 July 2016);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (in the Cochrane Library) (2016, Issue 6);
- Ovid MEDILINE (1946 to 12 July 2016);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations) (12 July 2016);
- Ovid Embase (1974 to 12 July 2016);
- EBSCO CINAHL Plus (1937 to 12 July 2016).

The search strategies for CENTRAL, Ovid MEDLINE, Ovid Embase and EBSCO CINAHL Plus can be found in Appendix 3. 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 randomised trials filter terms developed by the UK Cochrane Centre (Lefebvre 2011). We combined the CINAHL search with the randomised trials filter terms 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)
- WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/Default.aspx)
- EU Clinical Trials Register (www.clinicaltrialsregister.eu/).

Searching other resources

We searched for other potentially eligible trials or ancillary publications in the reference lists of retrieved included studies as well as relevant systematic reviews, meta-analyses, guidelines and health technology assessment reports.

Data collection and analysis

Data collection and analysis were carried out according to methods stated in the published protocol (Westby 2015), which were based on the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011a).

Selection of studies

Two review authors independently assessed the titles and abstracts of the citations retrieved by the searches for relevance. After this initial assessment, we obtained full-text copies of all studies considered to be potentially relevant. Two review authors independently checked the full papers for eligibility; disagreements were resolved by discussion and, where required, the input of a third review author. We did not contact study authors. We recorded all reasons for exclusion of the studies for which we had obtained full copies. We completed a PRISMA flowchart to summarise this process (Liberati 2009).

Where studies were reported in multiple publications/reports we obtained all publications. Such a study was included only once in the review, but we extracted data from all reports to ensure maximal relevant data were obtained.

Data extraction and management

We extracted the following information from each included study:

- interventions being compared, including any ineligible interventions randomised to additional trial groups;
- duration of the intervention;
- details of any co-interventions;
- the unit of randomisation (e.g. participant or ulcer);
- the number of ulcers per person;
- the unit of analysis (including any selection methods for people with multiple ulcers);
- the number of participants in each arm;
- the hazard ratio and its 95% confidence interval (CI) (or any data that would allow its calculation (Tierney 2007)) for comparisons between arms);
- the number of participants that healed in each arm, both at the latest time point or (if different) at another time specified as of primary interest in the study's methods section;
- all other follow-up times reported;
- we noted if a Kaplan Meier plot was displayed;
- missing data rates per arm, and reasons for 'missingness', including the number of people dying.

Data on potential effect modifiers

We were not aware of any population-specific effect modifiers for this research question: there was no existing evidence to suggest that one type of dressing worked better than another for certain subgroups, for example, people with different depths of tissue damage.

However, we extracted data that allowed us to determine for each included study factors that may act as effect modifiers (in this context):

- type of funding (e.g. industry, academic, government); this was dichotomised into non-for-profit and other;
- risk of bias (see Assessment of risk of bias in included studies).

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Other data

We also extracted the following data regarding patient and study characteristics at baseline for each intervention arm if possible:

- care setting;
- age of participants;
- duration of pressure ulcer(s);
- severity/grade of pressure ulcer;
- nature of pressure ulcer wounds (e.g. sloughy, necrotic, infected);
- size of pressure ulcer(s).

Assessment of risk of bias in included studies

Cochrane risk of bias assessment

We assessed risk of bias for each included study for the complete healing outcome. There is only one outcome in this review (complete wound healing) and so risk of bias assessments at the outcome level apply to the whole study.

Two review authors independently assessed included studies using the Cochrane risk of bias tool (Higgins 2011b) with involvement of a third author where consensus could not be reached. We also determined an all-domain risk of bias (see below).

Additionally, we reported separately an overall risk of bias for each direct comparison meta-analysis and for each contrast in the NMA (see next section).

Overall risk of bias and linking to GRADE assessment

In order to link these Cochrane ratings to the GRADE assessment for risk of bias of the evidence (downgrading 0, 1 or 2 times), we used a two-stage process. Firstly, we obtained an all-domain risk of bias for each study and then used this to produce an overall risk of bias for each comparison.

All-domain risk of bias for each study

We summarised data for each of the key domains of selection bias, detection bias, attrition bias, reporting bias and other bias, assigning one of four ratings: low, unclear, high and very high. For example, selection bias was informed by sequence generation, allocation concealment and comparability of baseline characteristics. In an adaption of the GRADE approach (Guyatt 2011a), we produced an all-domain risk of bias, with four ratings defined as:

- 'very high' - two or more key domains with a high risk of bias or a single domain with very high levels of uncertainty (e.g. very high degree of differential missing data);
- 'high' - high risk of bias for any one domain or we judged the risk of bias to be 'almost high' across more than one domain;
- 'low' - low risk of bias for each of the key domains;
- 'unclear' - insufficient information for at least one key domain (with the other domains being at low risk of bias).

Then we grouped together the low and unclear all-domain risk-of-bias ratings.

We included this all-domain risk of bias in the summary 'Risk of bias' figure, by adding two further columns: red in both of the last two columns indicated 'very high' all-domain risk of bias; red in the penultimate column (but not the last column) indicated 'high' risk of bias; and the combined low/unclear group was marked green in the penultimate column, with the last column remaining blank.

Overall risk of bias for a direct comparison

Wherever more than one study was pooled in a pairwise meta-analysis, we assigned an overall risk of bias for that comparison, by calculating a weighted average all-domain risk of bias across studies; weights were those produced in the meta-analysis (based on the inverse variance). We assigned numerical values to the all-domain ratings for each study: low/unclear (1), high (2) and very high (3) and calculated the weighted average.

We used the weighted average to give a rating of overall risk of bias for that comparison: low, high and very high, and aligned these ratings respectively with the GRADE categories of no limitations (not downgraded on risk of bias), serious limitations (downgraded once) and very serious limitations (downgraded twice) (Guyatt 2011a; Salanti 2014).

We superimposed the overall risk of bias for each direct comparison (on the basis of the direct meta-analysis) on the network diagram, using colours to represent different ratings. We used these overall risks of bias to calculate the risk of bias for each mixed treatment contrast (see below).

Overall risk of bias for each mixed treatment contrast in the network

An NMA comprises a set of interventions linked via a series of comparisons ('direct contrasts'). Each direct contrast contributes data to the evidence for all other contrasts in the network to which that contrast is linked indirectly (and becomes indirect evidence). The contribution of each piece of indirect evidence to a mixed treatment contrast depends on its point estimate, precision and relative location within the network, and on that of any direct evidence or other indirect evidence (Chaimani 2013b; Salanti 2014). A recently published tool, Krahn 2013, allows such contributions to be determined for each contrast in the network informed by direct and indirect evidence. We summarised the percentage contribution of each direct contrast to each network estimate in a matrix with columns and rows corresponding to the direct and mixed treatment contrasts respectively.

The overall risk of bias for each mixed treatment contrast is a composite measure of the risks of bias for all the contributing direct contrasts (that is, the sum of the all-domain risks of bias for all the direct contrasts, each weighted by their percentage contributions to the mixed treatment contrast).

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We calculated the overall risk of bias for the entire network using percentage contributions to the whole network for each direct contrast.

Measures of treatment effect

Relative treatment effects

For each contrast in the NMA, we presented the risk ratio with its 95% CI. We used raw data from individual studies, taking the number of ulcers healed at the latest time point, unless otherwise stated.

We also recorded separately the time-to-healing outcome for studies that reported this.

Relative treatment ranking

We presented the relative treatment ranking as a cumulative probability at each rank and as a **S**urface **U**nder the **C**umulative **RA**nking (SUCRA) value for each treatment (see Data synthesis - methods for indirect and mixed comparisons and Appendix 2).

Unit of analysis issues

We expected the main unit of analysis issues to occur when participants had more than one wound per person. In these cases, we treated the participant as the unit of analysis when the number of wounds assessed appeared to be equal to the number of participants (e.g. one wound per person). This included studies in which participants were randomised to treatments and there was more than one wound per person, but results were reported for one selected wound; we considered whether there was risk of bias in the selection process.

Where studies randomised at the participant level, used the allocated treatment on multiple wounds per participant, and measured and analysed outcomes at the wound level (e.g. wound healing), we expected there to be unit of analysis issues if the data were not correctly analysed. In practice, there was insufficient information to approximate the correct analyses (in accordance with Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions*, using information adapted from Higgins 2011c), so we assessed risk of unit-of-analysis bias, taking into account the number of people randomly assigned to each intervention; and the average (mean) number of wounds per person.

Dealing with missing data

It is common to have data missing from trial reports. Excluding participants post-randomisation, or ignoring those participants who withdrew from the trial or were lost to follow-up, compromises the randomisation and potentially introduces bias into the trial. Where data were missing for the primary outcome of proportion of ulcers healed, we assumed participants did not have the outcome (i.e. they were considered in the denominator but not the numerator). We examined this assumption in a sensitivity analysis, using a complete case analysis instead.

Assessment of heterogeneity

Assessment of clinical and methodological heterogeneity within treatment comparisons

We assessed the presence of clinical heterogeneity within each pairwise direct comparison (i.e. the degree to which studies varied in terms of participant, intervention and outcome characteristics) by comparing information extracted for included studies.

Assessment of transitivity across treatment contrasts

'Transitivity' refers to the situation in which an intervention effect measured using an indirect contrast is valid and equivalent to the intervention effect measured using a direct contrast. Where there are differences in (known or unknown) effect modifiers across contrasts, the transitivity assumption may not be met which may generate statistical inconsistency in the network (Grant 2013; Jansen 2013). We did not identify any potential effect modifiers from the literature, so there was no evidence that the transitivity assumption was not met. There were also limited underlying theoretical reasons to consider effect modification for these treatments.

If we had had sufficient data we planned to explore the effect of the funding source and differences in risk of bias as possible effect modifiers across the network. However, there was insufficient variation in these factors.

Assessment of reporting biases

We assessed for the presence of publication bias using a contour-enhanced funnel plot, provided there were at least 10 included studies (Peters 2008; Salanti 2014).

Data synthesis

General methods

We performed analyses in a frequentist framework using the statistical software STATA (STATA 2013). This is a change from the protocol, in which we had proposed a Bayesian framework using the statistical software WinBUGS for most of the analyses (Dias 2016; Lunn 2000; Lunn 2009; Spiegelhalter 2003; WinBUGS 2015), and STATA to calculate contributions of direct contrasts to the NMA results. One major advantage of the Bayesian framework would have been to confer flexibility by explicitly considering the duration of follow-up across studies by modelling the hazard function (Dias 2016; Saramago 2014; Soares 2014). However, there was insufficient variation in follow-up duration and fewer than

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20% of the studies reported time-to-event data, in six contrasts without loops, so we could not justify modelling the outcome data in this way. We therefore conducted analyses using the proportion healed, and we pooled risk ratios, ignoring differences in follow-up, This lack of need to model time, together with recent software developments in STATA for NMA (especially the contributions matrix routine, important for GRADE analysis), led to a decision to use a frequentist approach in STATA for all analyses (Chaimani 2013a; Chaimani 2013b; Chaimani 2015; Gasparrini 2015; Salanti 2014).

We have given a brief description of the STATA analytical routines used in Appendix 4, together with routines that enabled us to display the output visually (Chaimani 2013b). Where there were zero events in any one arm of a trial, we added 0.5 to the numerator and 1 to the denominator for each arm in the trial, in accordance with the general approach taken by STATA.

Methods for standard meta-analysis

We performed pairwise meta-analyses in a frequentist framework, both within the STATA software and also using Review Manager 5 (RevMan 5) (RevMan 2014) for convenience in producing forest plots. For RevMan, we used both inverse variance weighting and a random-effects model (for consistency with the NMA methods). Results for the two sets of software were compared and found to be identical in most cases; where there were differences we reported both sets of results. Differences were due to how zero cells are dealt with.

Methods for network meta-analysis

We initially used the STATA software to produce a network diagram based on all included studies in order to inform the analysis plan (Chaimani 2013b). We then excluded from the analysis two-arm studies in which one of the interventions could be described as 'standard care' or 'mixed care' involving the choice of more than one treatment because they crossed intervention categories. We also excluded from the analysis studies that had one intervention of direct interest (e.g. hydrocolloid) compared with one ineligible intervention (e.g. radiant heat), unless we found, after examining the network diagram, that the ineligible intervention linked two or more interventions of direct interest.

We performed multivariate network meta-analysis using STATA routines. This took into account correlations between the effect sizes from multi-arm studies (Chaimani 2013a; Chaimani 2013b; White 2012). We used a consistency model (which assumes that there is agreement between direct and indirect sources of evidence) and assumed a random-effects model. The NMA results were reported for 'mixed treatment contrasts', which means the evidence synthesis involved both direct evidence and indirect evidence from across the whole network. The output was reported as pooled risk ratios, with their 95% CIs.

We evaluated the surface under the cumulative ranking curve (SUCRA) and obtained mean ranks (Salanti 2011) for each treatment. Both these measures are based on an assessment of the probability of each treatment being best, second best, etc. In general, the probability that a particular treatment ranks best represents the likelihood of it being considered the most effective (within the pool of treatments analysed) reflecting the evidence of effectiveness and the precision surrounding the estimates. It is expressed as a proportion, where a value of 1 means that the evidence determines that a particular treatment is the best with certainty and 0 is the certainty that it is not the best. The SUCRA is a numerical summary of the distribution of ranks for each treatment (probability of being best, second best, etc) and provides a hierarchy of the treatments that accounts both for the location and the variance of all relative treatment effects. The larger the SUCRA value, the better the rank of the treatment.

We conducted two NMAs: one for individual treatments and one in which dressings interventions were grouped in broader categories, with clinical guidance. We had planned the second (grouped) network as a sensitivity analysis at the protocol stage, but later decided to conduct this analysis in parallel with the individual treatment NMA, because we expected the group analysis to provide valuable and complementary clinical information. The results of the group analysis are presented in Appendix 5.

Assessment of statistical heterogeneity

We assessed statistically the presence of heterogeneity within each pairwise comparison using the I^2 (Higgins 2003) and tau^2 statistics from the RevMan 5 analyses; I^2 measures the percentage of variability that cannot be attributed to random error and tau^2 measures the extent of heterogeneity among the intervention effects observed in different studies. We also took into account the overlap of CIs and the variability in the point estimates.

Assessment of statistical inconsistency

We assessed inconsistency in two main ways: determining local inconsistencies (around particular contrasts in the network) and assessing inconsistency for the network as a whole. These tests are often underpowered so we assessed at the 90% significance level.

Local approaches to evaluating inconsistency

To evaluate the presence of inconsistency locally we considered two main approaches.

Firstly, we used a loop-specific approach. This method evaluated the consistency assumption in each closed loop of the network separately as the difference between direct and indirect estimates for a specific contrast in the loop (inconsistency factor: IF). We assumed a common heterogeneity estimate within each loop. We report results as the ratio of risk ratios (RoRR) with its 90% CI - the natural logarithm of the RoRR is the same as IF (Appendix 2).

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The magnitude and 90% CIs were used to draw inferences about the presence of inconsistency in each loop. If the CI excluded 1, statistically there was significant inconsistency. We also considered whether the CI included 2 or more (or 0.5 or less). This means that the direct estimate could be twice as large (half as big) as the indirect estimate, which is an indication of potential inconsistency (Chaimani 2013b). We also report the IF assuming a common heterogeneity estimate for the whole network (Veroniki 2013).
Secondly, we considered a "node splitting" approach (Dias 2010; Salanti 2014) This method was applied, singly, to each direct contrast (called a "node" by Dias 2010). The STATA routine calculated an indirect estimate using the rest of the network, by running the NMA after excluding the direct evidence for that contrast. The indirect estimates were then compared with the respective direct estimates, again calculating a RoRR with its 90% CI for each contrast.
Finally, we compared NMA results using inconsistency versus consistency assumptions for each contrast.

Global approaches to evaluating inconsistency

We evaluated consistency in the entire network simultaneously, by extending the analysis to include an inconsistency model that omitted consistency equations (Dias 2013). The latter used a design-by-treatment interaction model, which allowed for different designs (2-arm trials (A-X); 2-arm trials without A, and 3-arm trials, where A is the base treatment). This approach produced a set of inconsistency parameters. After fitting the inconsistency model, the null hypothesis of consistency is tested for the set of inconsistency parameters using a global Wald test. This test may lack power and we considered a significance level of $P < 0.1$ (Higgins 2012; White 2012).

Investigation of heterogeneity and inconsistency

If there had been sufficient studies available, we would have performed network meta-regression or subgroup analyses using funding source and risk of bias as possible sources of inconsistency or heterogeneity, or both. This was not possible.

Sensitivity analysis

We had intended to re-analyse the network with studies removed that were considered to be at high risk of bias for any one or more of selection, attrition or detection bias, however, due to the sparseness of the data available and the generally poor methodological quality of the studies, this analysis had to be restricted to removing studies with two or more domains at high risk of bias ("very high risk of bias") (Appendix 6).
We conducted a sensitivity analysis to assess the impact of imputing missing outcome data on the network estimates, via assessment of risk of attrition bias (as defined in Appendix 6), testing the assumption of imputation of no event for missing data by conducting a complete case analysis.

Quality assessment of evidence (GRADE) generated from the NMA and 'Summary of findings' table

We summarise the findings according to GRADE principles (Schünemann 2011a; Schünemann 2011b).
The quality of the data included in any synthesis model is key to determining the validity of the results and of inferences made. We explored the application of GRADE methodology to network meta-analysis, focusing on the approach of Salanti 2014. We assessed evidence quality (certainty) in two main ways, firstly, for each contrast and secondly, for the network as a whole, in order to assess the quality of the ranking order. We assessed GRADE factors as follows:

- Risk of bias: we considered contributions for each particular contrast, and used them to assess the overall risk of bias for that contrast (see Assessment of risk of bias in included studies section, Risk of bias for each contrast in the network). We assessed overall risk of bias per contrast and also for the network as a whole.
- Indirectness: we defined this as without limitations in GRADE because we had not identified any effect modifiers.
- Inconsistency:
  - **At the level of the contrast**, inconsistency could only be assessed where there was both direct and indirect evidence. We took into consideration heterogeneity in the direct evidence for that contrast (see Data synthesis, Assessment of statistical heterogeneity) and inconsistency, as described above (see Data synthesis, Local approaches to evaluating inconsistency). We assessed GRADE inconsistency as 'serious limitations' if there was heterogeneity in the direct estimate or inconsistency in the network with respect to that contrast. We attributed 'very serious limitations' to the contrast if there was severe heterogeneity or severe inconsistency or limitations with both heterogeneity and inconsistency, as agreed by two review authors.
  - **At the level of the network,** we considered the global Wald test for inconsistency (see Data synthesis, Assessment of statistical inconsistency). Tests of this nature are typically underpowered, so a P value less than 0.1 was considered significant. Additionally, if several contrasts showed direct and indirect results that would have led to different clinical decisions, we assigned inconsistency.
- Imprecision: currently, NMA GRADE methods do not consider the optimal information size (OIS) approaches used for systematic reviews of pairwise interventions (Guyatt 2011b) and imprecision is based solely on the CI in relation to minimum important difference (MID) values or the null (Salanti 2014), or both. However, in the type of sparse networks typically found in wounds research, the small sample size and ensuing Type I and Type II errors are potentially more of an issue (Dumville 2012; Soares 2014). We firstly considered whether the network was sparse, taking into account the total number of participants, the total number of events and the number of interventions and contrasts in the NMA. If we considered the network not to be

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sparse, we applied the methods of Salanti 2014. If we considered the network to be sparse, we used the following approach adapted from the Salanti 2014 guidance:

- **At the level of the contrast** - we considered the CI for the individual contrast in relation to the GRADE 'default' minimum important difference (MID) values of RR = 1.25 and 0.75. If the CI crossed both of these MIDs, we downgraded twice for imprecision. If the CI crossed one MID, we downgraded once, regardless of whether the null was crossed. For contrasts involving peripheral interventions, for which large effects were found, we additionally took into account the amount of direct evidence involving this intervention, considering (in an analogous way to simple meta-analysis) whether the evidence was 'fragile' because of small numbers of events (Guyatt 2011b).
- **At the level of the network**, we took into consideration the overlap of the rankograms/the magnitude of the SUCRA estimates and the sparseness of the network.

- We assessed publication bias by plotting a contour-enhanced funnel plot, which allowed visual assessment of asymmetry for either a particular contrast (all one colour) or for the network as a whole. We did this for the former only if there were 10 studies or more.

We have presented the main results of the review in a 'Summary of findings' table, reporting the results for a representative set of contrasts, with one row for each intervention versus saline gauze. Such tables present key information concerning the certainty (formerly, quality) of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data (Schünemann 2011a). 'Summary of findings' tables also include an overall grading of the evidence using the GRADE approach. The GRADE approach defines the certainty 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. For calculating absolute risk differences for the probability of healing we used a 'control group risk', calculated as the median of the probability of healing for saline gauze across all studies with these interventions.

RESULTS

Description of studies

Results of the search

The search generated 1038 records: we obtained 381 full papers Figure 1); 305 studies were excluded with reasons (Characteristics of excluded studies). We included 51 studies described in 74 reports. Two protocols of studies were also identified (ISRCTN57842461; ChiCTR-TRC-13003959), which appear to be ongoing (see Characteristics of ongoing studies).

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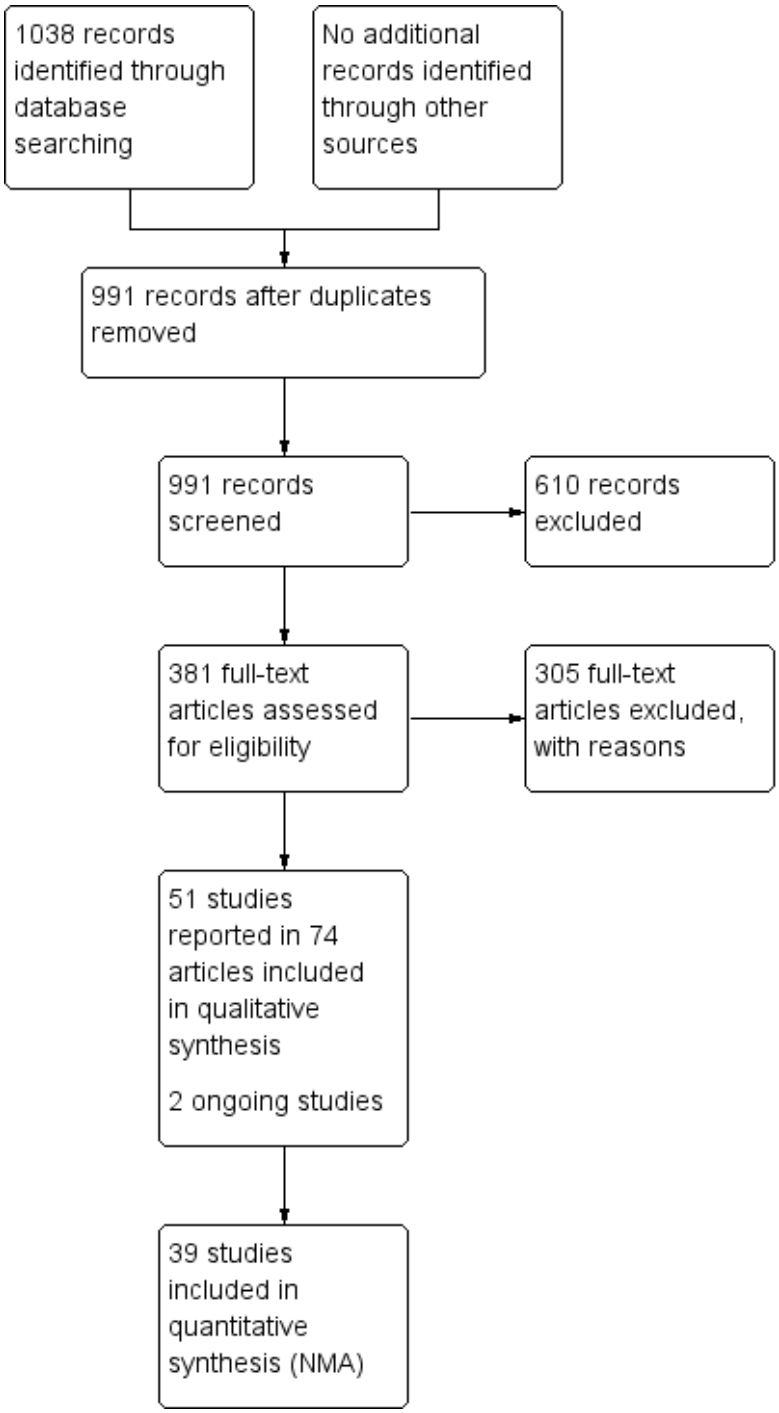
Figure 1. Study flow diagram



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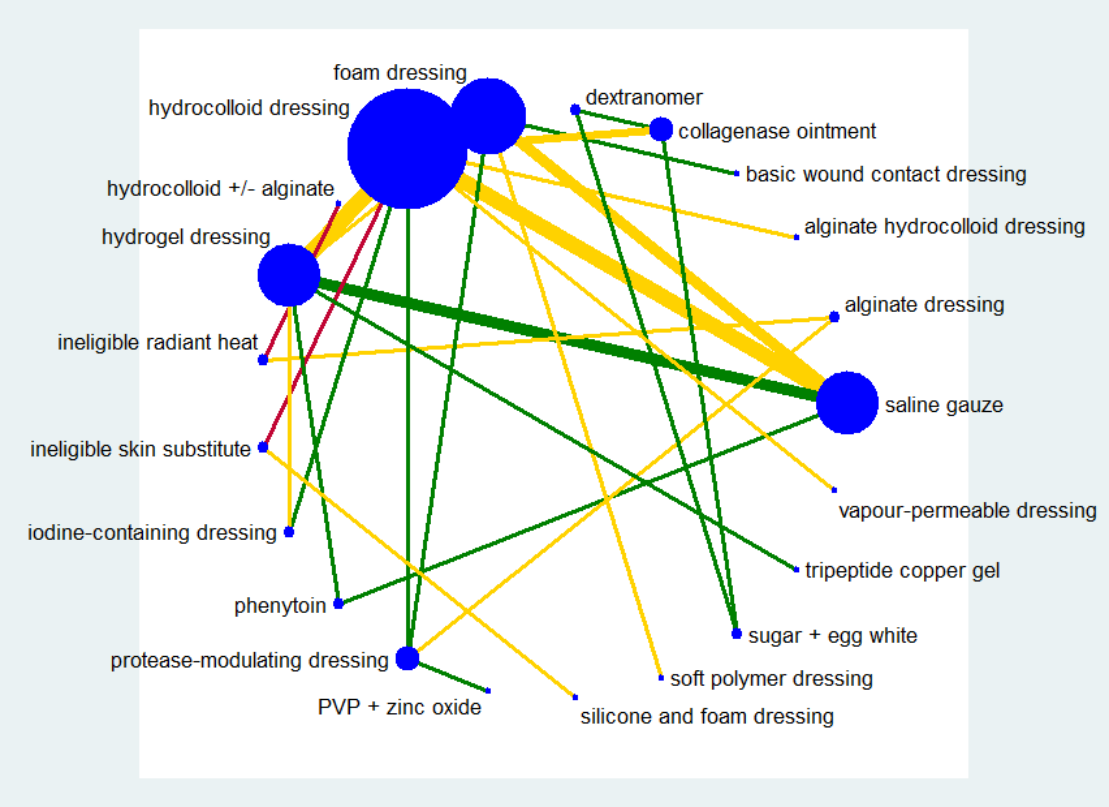
We also searched reference lists from identified systematic reviews and for two recent guidelines, but found no extra studies outside the electronic searching.

Included studies

This review distinguishes three sets of included studies: (i) all studies that meet the inclusion criteria ('all included studies'); (ii) the subset of (i) for which all studies have interventions that are joined into the network ('the individual network') (see Effects of interventions) and (iii) the subset of (i) for which all studies are joined in a network in which interventions are grouped ('the group network') (see Appendix 5). In this section we have given a brief summary for the individual network. Further details of each set of included studies are given in Table 1.

Fifty-one studies, involving 2947 participants, met the inclusion criteria for the whole review. Most of these studies could be linked to form a network of interventions, but 12 were not linked into the network; further details, and the results for the comparisons reported in these 12 studies are given in Appendix 7. The joined network (Figure 2) included 39 studies (Aguilo Sanchez 2002; Alm 1989; Bale 1997a; Banks 1994b; Banks 1994a; Banks 1994c; Barrois 1992; Belmin 2002; Brod 1990; Brown-Etris 1996; Brown-Etris 1997; Brown-Etris 2008; Burgos 2000b; Colwell 1993; Darkovich 1990; Graumlich 2003; Hollisaz 2004; Hondé 1994; Kaya 2005; Kraft 1993; Matzen 1999; Meaume 2003; Motta 1999; Muller 2001; Neill 1989a; Oleske 1986; Parish 1979; Payne 2009; Piatkowski 2012; Price 2000; Romanelli 2001; Seeley 1999; Serena 2010; Sopata 2002; Thomas 1997a; Thomas 1998; Thomas 2005; Xakellis 1992; Zeron 2007). The median (range) study size was 41 (10 to 168).

Figure 2. Network diagram - individual interventions, by risk of bias (3 categories)Key: green = low/unclear; yellow = high; red = very high overall risk of bias for the contrast. The number of studies for each contrast is given in .



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The majority of the 39 studies had only two randomised interventions (37), randomised people rather than ulcers or clusters (34), included at least some of the participants from a hospital setting (20), and were not funded by industry (7) or funding was not stated (17). The median follow-up time was eight weeks; range 10 days to 6 months. Most studies included participants with a mean age more than 65 years (33) and had ulcers that were mainly Stage 2 (15), Stage 3 (10) or Stages 2 and 3 (7). Sixteen studies included participants with ulcers of less than three months' duration; two had more than three months' duration and the rest (21) were unclear on duration. Further details are given in Table 1. We considered the clinical characteristics to be sufficiently similar across the studies to combine in the analysis, particularly since we had not defined clinical effect modifiers.

Excluded studies

We excluded 305 studies from this review (see Characteristics of excluded studies) The most common reasons for exclusion were 67 with a non-RCT study design; ineligible outcomes in 120 studies (including 64 with healing outcomes that were not reported as the time to complete healing or the probability of complete healing) and 57 had an ineligible patient population. Eleven studies were excluded because they had two interventions in the same class and 36 other studies had ineligible interventions in both randomised arms, or had treatments that could not be classified as a single intervention.

Risk of bias in included studies

Risk of bias for all included studies is summarised in Figure 3. In order to represent 'very high' risk of bias, we have used two columns - so very high risk of bias occurs when the cell is red in the final column (see Assessment of risk of bias in included studies).

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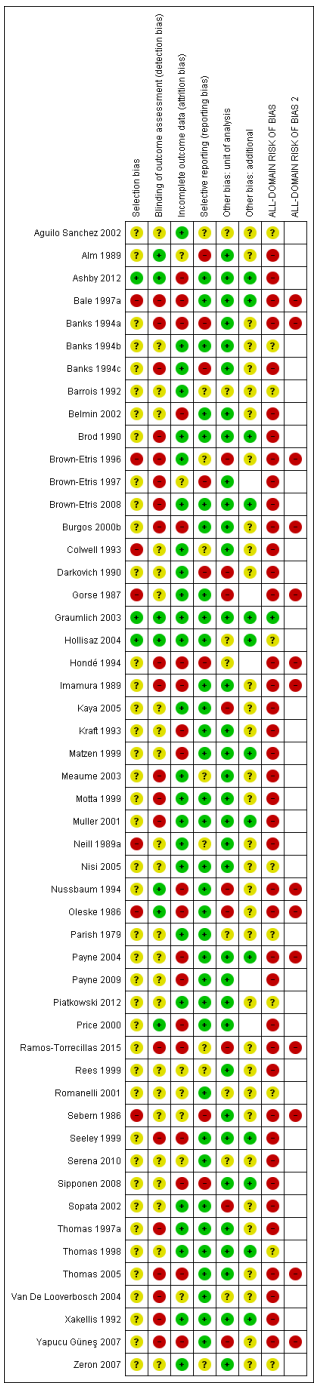
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



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We judged only one of the 51 studies (2%) to be at low risk of bias (Graumlich 2003) and ten (20%) to have unclear risk of bias (Aguilo Sanchez 2002; Banks 1994b; Barrois 1992; Hollisaz 2004; Nisi 2005*; Parish 1979; Piatkowski 2012; Romanelli 2001; Thomas 1998; Zeron 2007). We judged 14 (27%) studies to be at very high risk of bias, that is, to have high risk of bias for two or more domains (Bale 1997a; Banks 1994a; Brown-Etris 1996; Burgos 2000b; Gorse 1987*; Hondé 1994; Imamura 1989*; Nussbaum 1994*; Oleske 1986; Payne 2004*; Ramos-Torrecillas 2015*; Sebern 1986*; Thomas 2005; Yapucu Güne 2007*). We assessed the rest of the studies at high risk of bias. We grouped the low and unclear categories together.

*Studies marked with an asterisk were not included in the individual network.

Effects of interventions

See: **Summary of findings for the main comparison** NMA evidence for individual network: proportion with complete healing - interventions versus saline gauze

In this section, we present the results for the individual NMA. Results for the group network are given in Appendix 5.

We report the results in two ways. Firstly, we give risk ratios (RR) with their 95% CIs for each intervention compared with every other intervention in the network (NMA effect estimates); all results are presented in a forest plot, but we focus on a representative set of comparisons versus a reference intervention (saline gauze for the individual network). Secondly, we summarise findings for the network as a whole, giving the rank order for all the interventions in the network and the probability that a particular intervention is the best, second best, etc treatment.

We report the results alongside the assessment of evidence quality. To do this we applied various statistical techniques and tests, including methods for determining risk of bias in the whole network, examining whether the results for each comparison in the network were consistent with one another, and considering the uncertainty in various measures (e.g. the CI around the RR). For the latter, we downgraded evidence twice if the 95% CI crossed both of the two GRADE 'default' values (RR = 1.25 and RR = 0.75) and once if the 95% CI crossed one of these values. Additionally, if there was a large effect and there were very few events in the direct evidence for a particular intervention, we downgraded the evidence further ('fragility'; see Data synthesis, Quality assessment). We also conducted some sensitivity analyses to test assumptions made in the analysis. Much of the assessment of evidence quality is reported in Appendices, but is summarised in 'Summary of findings' tables for the comparisons with the reference intervention.

Interventions and comparisons

The individual network comprised 21 interventions: 13 eligible dressings (foam, hydrocolloid, alginate, protease-modulating, iodine-containing, soft polymer, vapour-permeable, silicone-foam combination, two alginate-hydrocolloid combination or sequential dressings, saline gauze, polyvinylpyrrolidone plus zinc oxide and basic wound contact); six topical agents (hydrogel, dextranomer, collagenase ointment, phenytoin, tripeptide copper gel, and sugar plus egg white) and two supplementary linking interventions (skin substitute and radiant heat dressing).

Two studies were three-arm trials: Hollisaz 2004 (hydrogel, phenytoin and saline gauze); and Parish 1979 (dextranomer, collagenase ointment, and sugar plus egg white). The total number of comparisons was 43, encompassing a total of 2127 participants, who experienced a total of 783 events (complete healing) - this is 72% of the participants included in all studies in the review before we excluded studies for not fitting into the network. There were 27 different direct contrasts and eight triangular loops, including one that was exclusive to one of the three-arm trials (Parish 1979).

In the network diagram (Figure 2), node (circle) size reflects weighting according to the number of studies reporting each intervention and the thickness of the edge lines reflects weighting according to the inverse variance of the direct treatment effect estimates for the particular contrast (Chaimani 2013b). We identified seven interventions as 'core interventions' (i.e. part of at least one loop: foam dressing, hydrocolloid dressing, hydrogel, iodine-containing dressing, phenytoin, protease-modulating dressing and saline gauze). The other interventions were only connected in a peripheral way.

Risk of bias for the individual network

We report risk of bias in three ways (see Methods: Assessment of risk of bias in included studies):

1. For each study, as the all-domain risk of bias - taking into account selection bias, detection bias, attrition bias, reporting bias and other bias
2. For each direct comparison of two interventions, as an overall risk of bias - taking into account the all-domain risk of bias for the studies (1 above) and the weighting in the meta-analysis for that comparison
3. For each contrast in the network (any pair of interventions in the network) as the overall risk of bias - taking into account the risk of bias for each direct comparison (2 above) and their percentage contributions to the network estimate. We also calculated the overall risk of bias in the network as a whole.

All-domain risk of bias for each study is shown in Figure 3. We judged one study to be at low risk of bias (Graumlich 2003) and nine at unclear risk of bias (Aguilo Sanchez 2002; Banks 1994b; Barrois 1992; Hollisaz 2004; Parish 1979; Piatkowski 2012; Romanelli 2001; Thomas 1998; Zeron 2007). Seven were at very high risk of bias (Bale 1997a; Banks 1994a; Brown-Etris

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1996; Burgos 2000b; Hondé 1994; Oleske 1986; Thomas 2005) and the rest we assessed to be at high risk of bias. We grouped the low and unclear categories together.

We have indicated the overall risk of bias for each direct comparison in Figure 2, using colour for three risk of bias ratings: low/unclear (green), high (yellow), very high (red). There is a relatively large amount of direct evidence at high or very high risk of bias.

For each contrast in the network, we calculated the overall risk of bias as described in Appendix 8, and the 'Risk of bias' ratings are shown beside the results in Figure 4.

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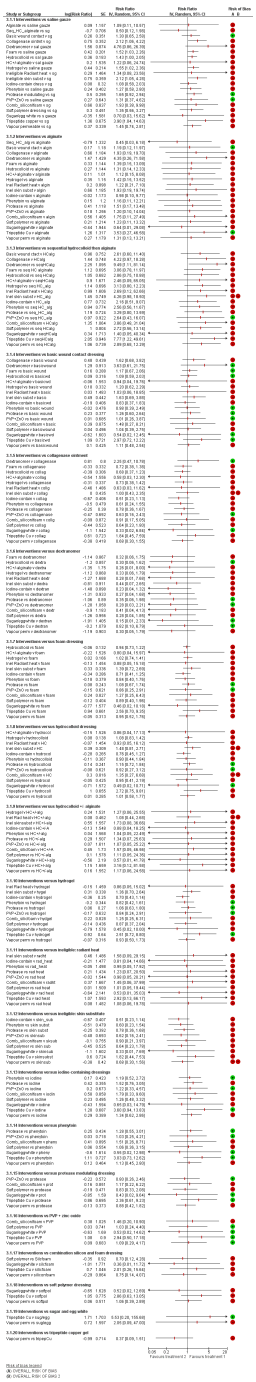
Figure 4. NMA results: individual intervention 1 versus individual intervention 2Key for overall risk of bias for the contrast: green = low/unclear; one red = high; two reds = very high



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Network meta-analysis results

The NMA generated results for 210 mixed treatment contrasts (i.e. all possible pairwise combinations of the interventions). The data were sparse and there was much uncertainty.

Figure 4 shows all NMA results, with the all-domain risk of bias shown alongside the forest plot contrasts.

As a consequence of the sparseness in the network, no contrast had precise estimates, all CIs were wide or very wide and we downgraded all evidence at least once for imprecision, some because of 'fragility' (Figure 4). The majority of the evidence for each contrast was informed by studies at high or very high risk of bias. Across all the mixed treatment contrasts, there was only one that we assessed to have moderate-certainty evidence (downgraded once only): protease-modulating dressing versus saline gauze. Evidence for all other contrasts was of low or very low certainty, and the moderate-certainty evidence should also be interpreted in the light of the very low-certainty evidence for the network from which it was derived.

As a summary, we presented the evidence for the individual mixed treatment contrasts using a representative set of each intervention versus saline gauze (Summary of findings for the main comparison) and Figure 4, first subgroup of results); we did not include the ineligible interventions (radiant heat and skin substitute) in the 'Summary of findings' table. Further details of information used for GRADE assessment can be found in Appendix 8 and Appendix 9).

It is not clear whether protease-modulating dressings increase the probability of pressure ulcer healing, compared with saline gauze dressings (RR 1.65; 95% CI 0.92 to 2.94, moderate certainty evidence). This corresponds to an absolute risk difference of 102 more people healed per 1000 (95% CI 13 fewer to 305 more), for a saline gauze median probability of healing of 157 per 1000. We downgraded the evidence once for imprecision (low risk of bias).

For each of four contrasts, it is unclear whether the intervention increases the probability of healing compared with saline gauze dressings: collagenase ointment (RR 2.12; 95% CI 1.06 to 4.22); foam dressing (RR 1.52; 95% CI 1.03 to 2.26); basic wound contact dressing (RR 1.30; 95% CI 0.65 to 2.58) and polyvinylpyrrolidone (PVP) plus zinc oxide (RR 1.31; 95% CI 0.37 to 4.62) (Figure 4). In each of these four contrasts, the evidence was graded as low certainty; downgraded either once for imprecision and once for risk of bias (collagenase ointment and foam dressing) or twice for imprecision and not for risk of bias (basic wound contact dressing and PVP plus zinc oxide).

It is unclear whether there is a difference in the probability of healing associated with the following interventions compared with saline gauze for the remaining 13 contrasts because the evidence is of very low certainty (downgraded mainly for risk of bias (once) and imprecision (twice)): alginate dressings, sequential hydrocolloid alginate dressings, dextranomer, hydrocolloid dressing with/without alginate filler (given if the wound was highly exudative), hydrocolloid dressings, hydrogel, iodine-containing dressings, phenytoin, silicone-foam dressings, soft polymer dressings, sugar plus egg white, tripeptide copper gel and vapour-permeable dressings. Two contrasts were informed by very few participants in the direct evidence, with seven participants (4 events) receiving dextranomer and six participants (5 events) receiving tripeptide copper gel; we therefore downgraded imprecision twice to allow for the fragility this invoked. There was also heterogeneity or inconsistency, or both, for some contrasts.

Ranking of treatments

The NMA produced a large number of estimates. An alternative way of presenting and interpreting data from the whole NMA was to summarise using rankograms: data for each intervention were shown as the probability that each intervention is the best, second best, third best treatment, etc. These probabilities are based on uncertainty, reflecting the effectiveness from the network contrasts and the precision around the estimates. The closer the probability of a rank to 100% (or 0%) and the narrower the distribution across different ranks, the greater the confidence in the ranking. Results are given in Figure 5 and Appendix 10 and summarised here, but must be interpreted in the light of the considerable uncertainty and sparseness in the network and the individual estimates, giving potentially misleading results (see quality assessment below). Numerically, dextranomer and tripeptide copper gel had the highest probabilities of being the best treatments (41% and 25%, respectively), and the sequential hydrocolloid alginate dressings and sugar plus egg white were most likely to be the worst treatments (35% and 32%, respectively). No intervention had more than 50% probability of being the best treatment and the rankograms for each treatment show considerable overlap. However, these rankings are likely to be artificially high: the direct evidence for dextranomer and tripeptide copper involves one study each with, respectively, seven participants (4 events) and six participants (5 events). The NMA results for these peripheral interventions have wide CIs and large point estimates. Consequently, these interventions have a finite probability of having a very large effect estimate (at their upper confidence limit), in turn leading to an artificially high probability of being the best treatment.

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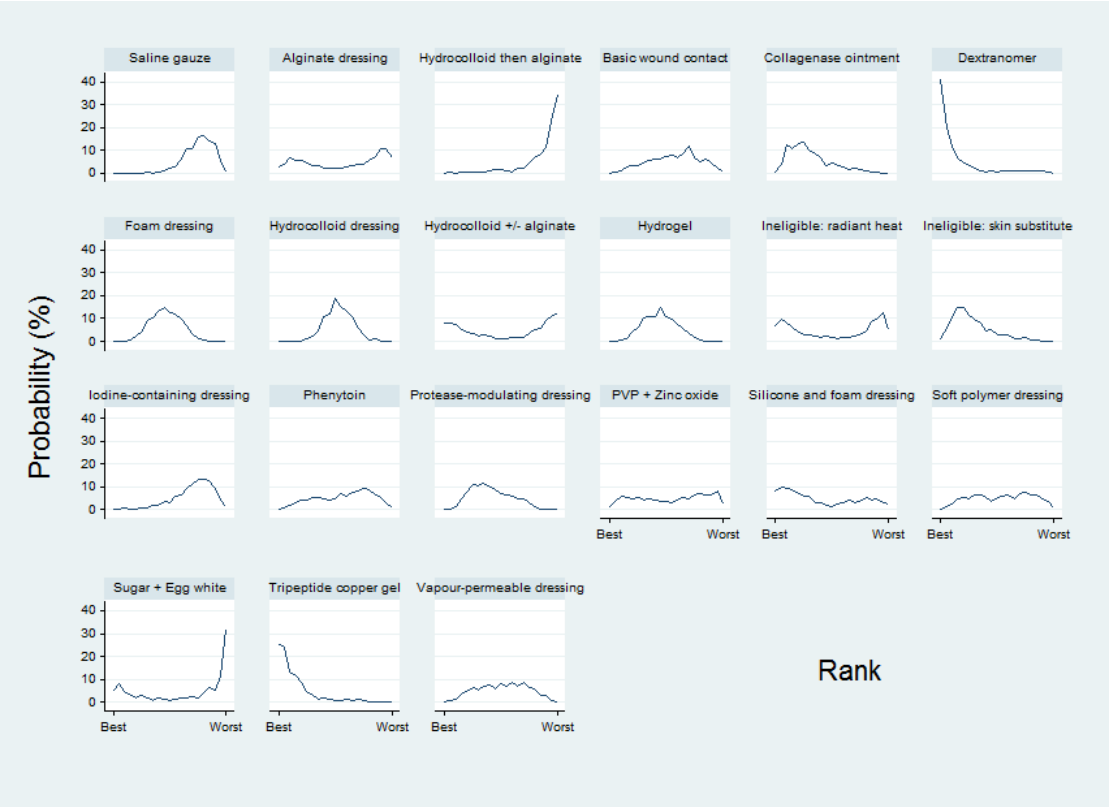
Figure 5. Rankograms for each intervention - individual network



Comparison of results from standard meta-analysis with NMA findings

We compared the NMA results with the direct comparison (pairwise) results for the proportion completely healed for the 27 different comparisons informing the individual network (Table 2). Six of these comparisons had two or more direct comparison studies (Analysis 1.1; Analysis 1.2). The direct comparison evidence shows heterogeneity for the comparisons of hydrocolloid dressing versus saline gauze dressing; hydrogel versus saline gauze dressing and hydrogel versus hydrocolloid dressing. Direct comparison evidence results for the time-to-healing outcome are reported in Appendix 11 for six comparisons in seven studies. The results for the direct comparison evidence and the NMA are shown in Table 2: there is too much uncertainty (wide CIs) to determine whether there are differences.

Certainty/quality assessment of the evidence across the whole network

The weighted average risk of bias across the network was high (Appendix 8). There did not appear to be much inconsistency in the network (see Appendix 9) and there were relatively few contrasts with conflicting results for direct and indirect or NMA estimates, so across the network we did not downgrade for inconsistency. We downgraded the evidence twice for imprecision: in addition to the sparseness (and probably as a consequence of it), there is substantial overlap of the individual rankograms (see Appendix 10); the mean rank was no smaller than 3.6 and no larger than 18.6 (out of 21) for any intervention, with no SUCRA value being zero or 1 (indicating uncertainty). A contour-enhanced funnel plot is shown in Figure 6. There may be a small studies effect, but this was too unclear for downgrading. Overall, we classed the evidence for the whole network as being of very low certainty (downgraded once on risk of bias and twice on imprecision).

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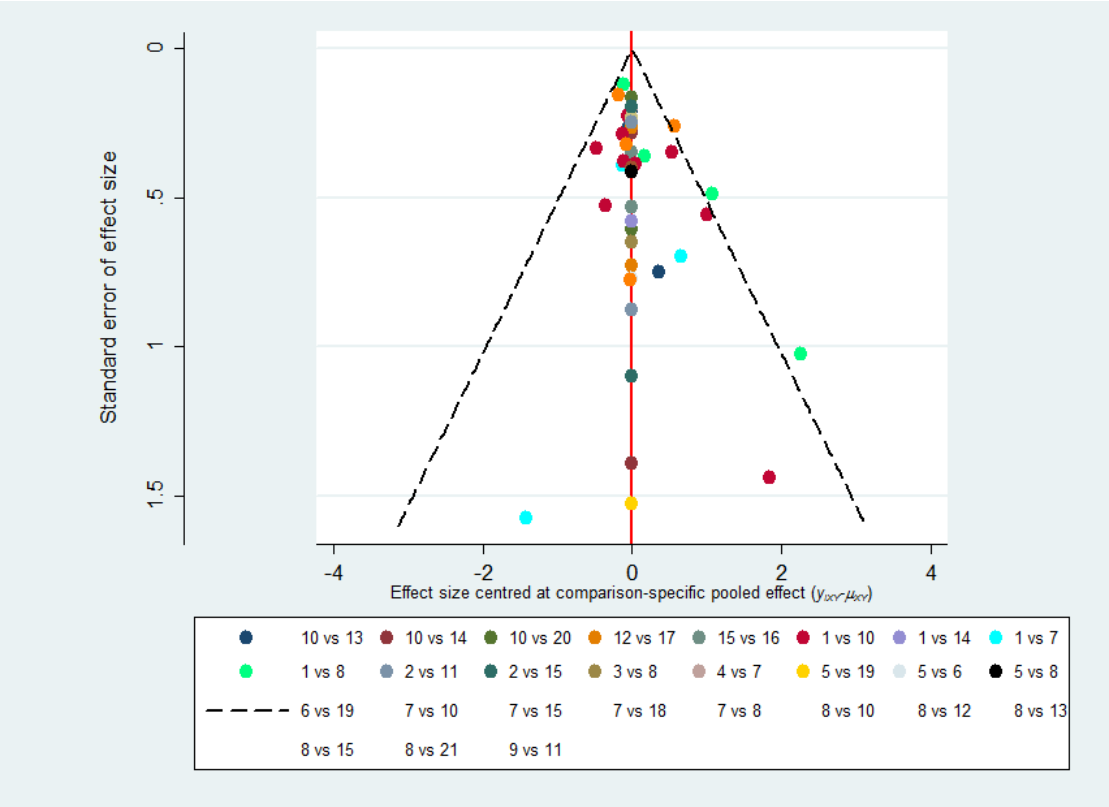
Figure 6. Funnel plot - individual networkKey to interventions: 1: saline gauze; 2: alginate dressing; 3: sequential hydrocolloid alginate dressings; 4: basic wound contact dressing; 5: collagenase ointment; 6: dextranomer; 7: foam dressing; 8: hydrocolloid dressing; 9: hydrocolloid +/- alginate (hydrocolloid dressing with/without alginate filler); 10: hydrogel dressing; 11: ineligible radiant heat; 12: ineligible skin substitute; 13: iodine-containing dressing; 14: phenytoin; 15: protease-modulating dressing; 16: PVP + zinc oxide 17: silicone + foam dressing; 18: soft polymer dressing; 19: sugar + egg white; 20: tripeptide copper gel; 21: vapour-permeable dressing



Overall, we have little confidence in the findings in this network, either in terms of the effect estimates or in the ranking of interventions.

Sensitivity analyses

We carried out the following pre-specified sensitivity analyses to examine the above inconsistencies: excluding studies at very high risk of bias; and assuming an available case analysis rather than imputing no event for missing values. The sensitivity analyses are discussed in Appendix 12. Neither sensitivity analysis had much impact on the effect estimates or the rankograms. There appeared to be less inconsistency in the sensitivity analysis that excluded studies at very high risk of bias, but this possible improvement was at the expense of precision and resulted a smaller network, and so the original analysis was preserved. An additional post-hoc sensitivity analysis (Appendix 12) examined the original assumption of combining topical agents and dressings in the same NMA, by restricting the network to studies comparing any two eligible dressings - similar results were found for the contrasts versus saline gauze, and the imprecision in the overall network continued to give uncertainty.

Group network findings

We mapped individual interventions onto the group categories (Appendix 5), grouping together dressings into the following pre-specified categories: basic wound dressings, advanced dressings and antimicrobial dressings (as described in the BNF 2016), and keeping specialist dressings (e.g. protease-modulating matrix dressings)

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and the different topical agents as separate categories. The group network included 22 studies (of 51 included) in 946 participants, encompassing 10 different interventions in 12 direct contrasts and these informed 45 mixed treatment contrasts. The median (range) study size was 38.5 (10 to 100). We had hoped that grouping interventions might increase the power in the network, but fewer than half of the included studies formed the group network (see Appendix 5) and only 32% of the participants were involved; only three contrasts were informed by more than one study.

The group NMA generated results for 45 mixed treatment contrasts. The network was dominated by the advanced dressing versus basic dressing contrast and the rest of the data were sparse. Figure 7 shows all group NMA results, with the all-domain risk of bias shown alongside the forest plot contrasts. The results and the certainty of the evidence are summarised for a representative set of contrasts (each intervention versus basic dressing) in Table 3. Evidence was of low or very low certainty, with the exception of one contrast, for which we assessed the evidence to be of moderate certainty. As for the individual network, this moderate-certainty evidence should be interpreted in the light of the very low-certainty evidence for the network as a whole.

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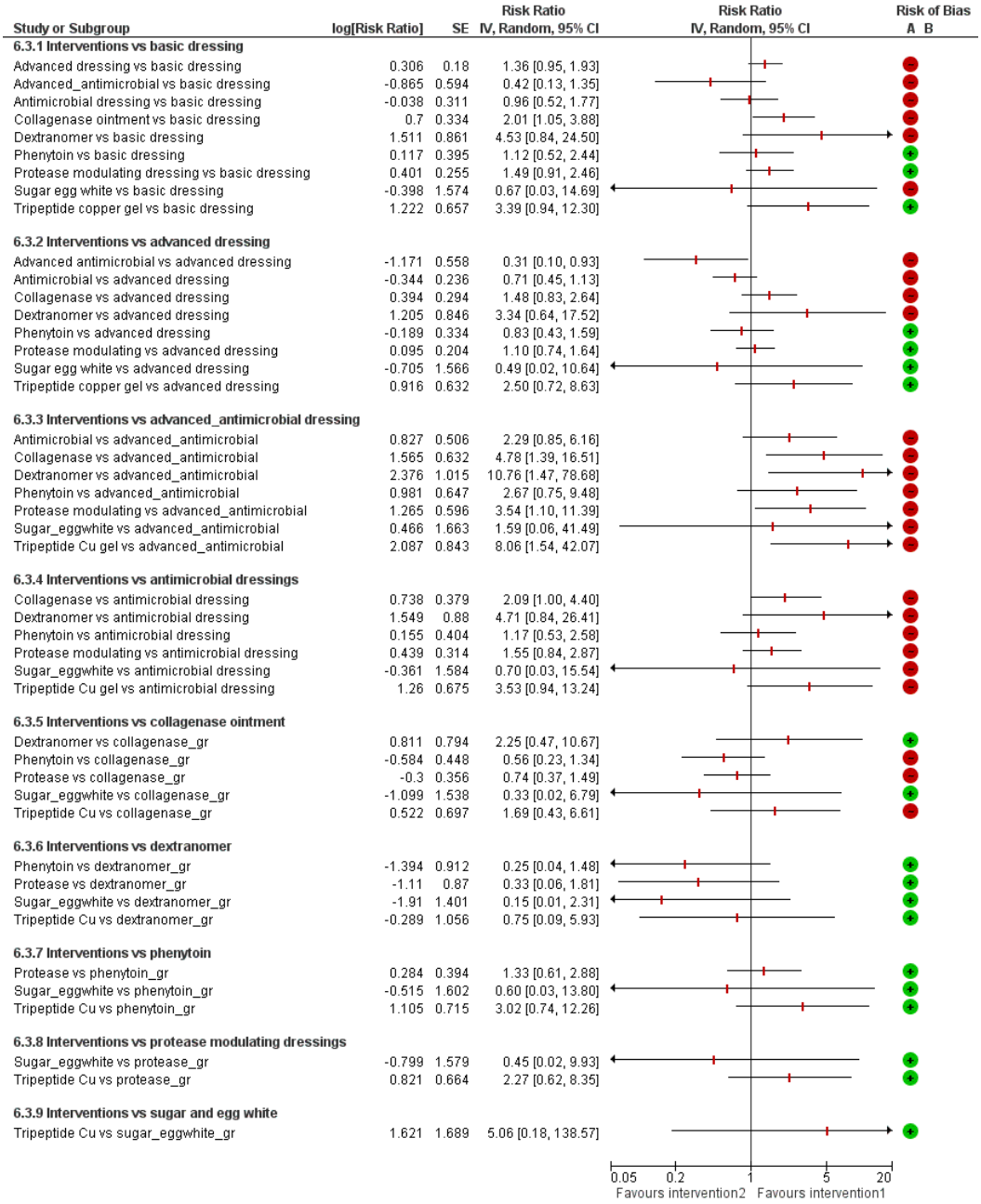
Figure 7. Intervention 1 versus intervention 2 - group networkKey for overall risk of bias for the contrast: green = low/unclear; one red = high; two reds = very high



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Rankograms for the group network are shown in Figure 8. There was more of a distinction between interventions, but still overlap of rankograms and the improvement in precision came at the expense of increased inconsistency and possible publication bias (Figure 9). Overall we downgraded the evidence certainty three times for the network as a whole, because of risk of bias (once), imprecision (once) and inconsistency and publication bias (once). As in the individual network, dextranomer and tripeptide copper had high ranks and this was again likely to be an artificial result. Further details of the group network are given in Appendix 5.

Figure 8. Rankograms combined - group network

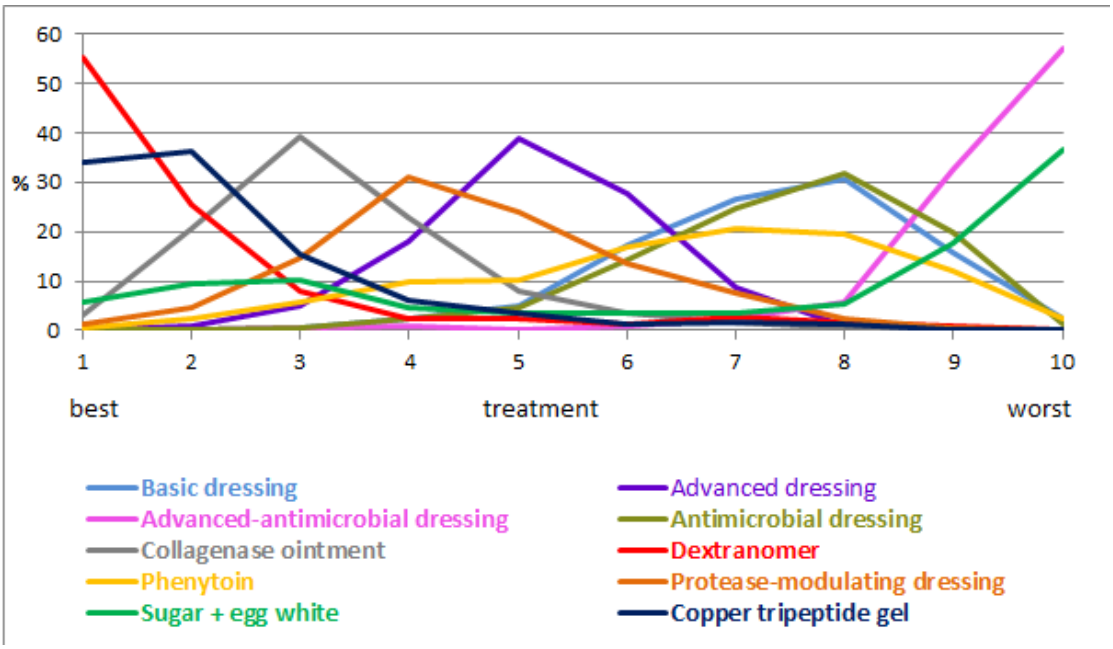

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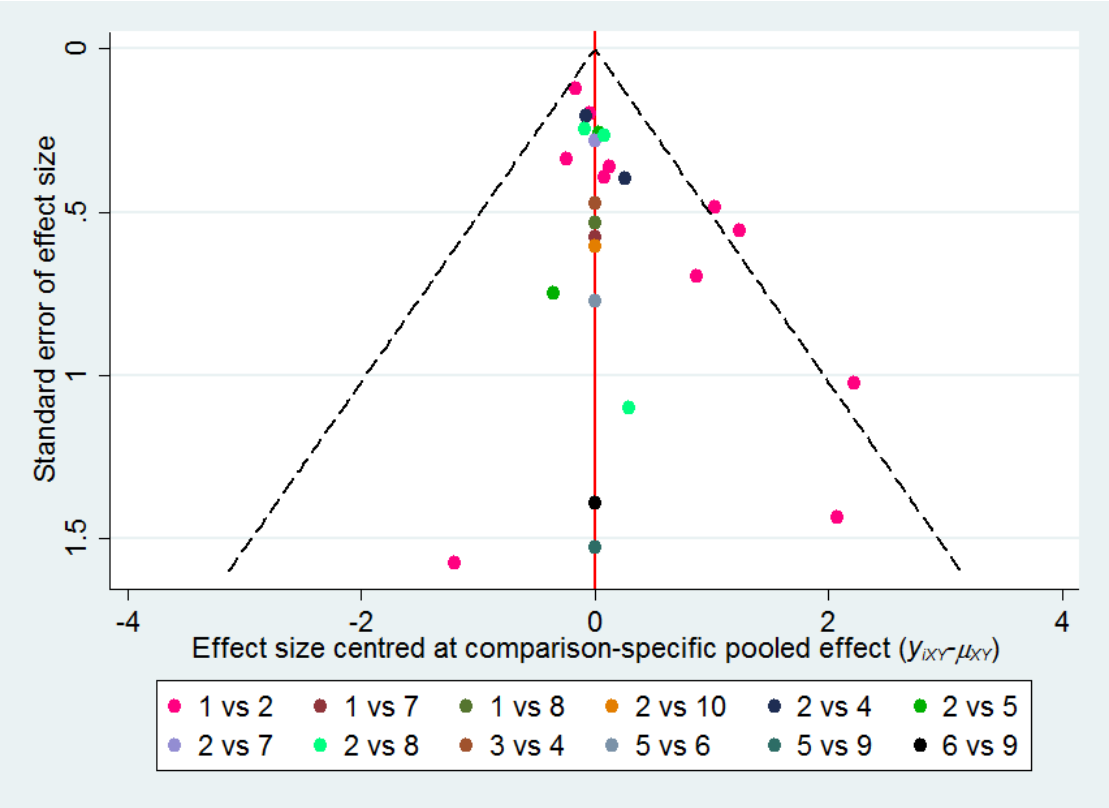
Figure 9. Funnel plot - group networkKey to interventions: 1: basic dressing; 2: advanced dressing; 3: advanced or antimicrobial dressing; 4: antimicrobial dressing;5: collagenase ointment; 6: dextranomer; 7: phenytoin; 8: protease-modulating dressing; 9: sugar + egg white; 10: tripeptide copper gel



DISCUSSION

Summary of main results

We have successfully conducted a network meta-analysis of dressings and topical agents for healing pressure ulcers. Alongside the analysis we have applied a new method of GRADE assessment (Salanti 2014), which allows us to view the results in the light of our certainty in their findings. Using this approach, we found the majority of the evidence to be of low or very low certainty, and was mainly downgraded for risk of bias and imprecision (see Quality of the evidence). This level of uncertainty within the totality of the dataset impacts on all subsequent interpretation of its outputs.

This review includes 51 RCTs involving a total of 2964 participants, comparing 39 different dressings or topical agents for the healing of pressure ulcers. Most of the studies were in older participants, but four included participants with spinal cord injuries and one was in younger people said to be chronically ill or physically disabled. Seventeen (33%) studies included participants mainly with Stage 2 pressure ulcers and 15 (29%) mainly had Stage 3 pressure ulcers; 13 studies investigated treatment of ulcers with a mean duration of less than three months.

We treated each topical agent as a separate intervention, but initially grouped dressings by class as described in the BNF 2016 (e.g. alginates, hydrocolloids). The network involved 39 studies in 2116 participants, encompassing 21 different interventions in 27 direct contrasts and these informed 210 mixed treatment contrasts.

We reported the evidence in two ways, firstly, as effect estimates for each of 210 NMA mixed treatment contrasts , and secondly as rank order of interventions. We summarised the set of effect estimates using contrasts versus saline gauze.

Overall findings reflect the uncertainty of the component evidence and the sparseness of the network, and even moderate ratings should be interpreted in the context of the network uncer-

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tainty. For network contrasts involving saline gauze, it is not clear whether protease-modulating dressings result in more healing (RR 1.65, 95% CI 0.92 to 2.94; moderate certainty evidence). It is unclear whether four interventions increase the probability of healing compared with saline gauze dressings: collagenase ointment RR 2.12 (95% CI 1.06 to 4.22); foam dressing RR 1.52 (95% CI 1.03 to 2.26); basic wound contact dressing RR 1.30 (95% CI 0.65 to 2.58) and PVP plus zinc oxide RR 1.31 (95% CI 0.37 to 4.62) (all low certainty evidence). It is worth noting that the contrasts for the latter two interventions had CIs consistent with both a clinically important benefit and a clinically important harm, and the other two contrasts had both high risk of bias and some imprecision. The remaining contrasts were all very low-certainty evidence, with all being imprecise, often with CIs consistent with both a clinically important increase and a clinically important decrease in the probability of healing.

Relative to the median control group risk (probability) (CGR) of healing for saline gauze of 157 per 1000, the absolute risk differences for the above comparisons in the individual network were: protease-modulating dressings: 102 more people healed per 1000 (13 fewer to 305 more); foam dressings: 82 more per 1000 (5 more to 196 more); collagenase ointment 176 more per 1000 (9 more to 506 more); basic wound contact dressing: 47 more per 1000 (55 fewer to 250 more); polyvinylpyrrolidone plus zinc oxide: 49 more per 1000 (99 fewer to 575 more). Thus, uncertainty notwithstanding, the effect is relatively small and fairly large numbers of wounds remain unhealed.

For the network as a whole, the evidence was of very low certainty, reflecting the general uncertainty surrounding the mixed treatment contrasts, as described above. There was considerable uncertainty in the ranking of interventions and no intervention had more than 50% probability of being the best treatment.

Overall completeness and applicability of evidence

The network is sparse, in terms of the total number of participants, the total number of wounds healed, the number of studies per contrast, the size of the constituent studies and the duration of follow-up: 21 of 27 direct contrasts were informed by only one study and the average number of events per mixed treatment contrast was around four. The median (range) study size was 41 (10 to 168) and several studies had zero events. The duration of follow-up was relatively short for most studies (median 8 weeks): only 3/39 studies in the network had a follow-up duration of 16 weeks or more.

In parallel we conducted a second NMA, grouping together some classes of dressings. We had hoped that the group network would provide more power in the analysis, but in practice too many data were excluded from the network, and the network was also unbalanced, being dominated by the advanced dressing versus basic dressing contrast, which involved about 55% of the participants in the group network. The group network provided equally uncertain evidence and the findings are not discussed further here, but are reported in Appendix 5 for the interested reader.

There may have been small-study effects, and the contour-enhanced funnel plot appeared to show some asymmetry. The Chaimani 2013b methodological paper demonstrated that small-study effects can materially affect the rank order of effectiveness. STATA code is available to adjust for small-study effects in ranking, however, we did not investigate this approach because the evidence was of such low certainty for reasons of risk of bias, imprecision and inconsistency. Additionally, Kibret 2014 suggested in a simulation study in a Bayesian setting that an unequal number of studies per comparison may result in biased estimates of treatment rank probabilities.

In the absence of evidence for effect modifiers, we can make observations about the population covered and the trial duration, only approximating the applicability of the evidence. In particular, there were eight studies with a follow-up time of less than six weeks, which may be too short to properly investigate healing, and the reporting of time-to-event data was insufficient to understand how the hazard of healing changes over time. Whilst treatments may have impacted on the speed of wound healing as well as the number of healing events per se, this requires further exploration, which would be better supported by increased collection and analysis of time-to-healing data in wound care trials. We note that the two small three-arm trials, which may have shown some incongruent results, were in younger people with spinal cord injuries or chronic illnesses/physical disabilities. Overall, our view is that the results can probably be applied more generally, within the constraints of the uncertainty of the evidence and also the comparisons for which trial data exist. There are many different dressing and topical treatment choices and, whilst several key treatments are represented by trial data, others are addressed only in pilot studies and there may be treatments that are yet to be evaluated in a trial or for which data remain unpublished. We could only assess publication bias in a limited way.

The NMA focused on complete wound healing as the key outcome - this has repeatedly been found to be the most important outcome to patients and health professionals (Cullum 2016; Kelly 2015). Dressings and topical agents are generally low risk treatments so we did not consider adverse events. Other outcomes that might have been useful include those related to the management properties of dressings such as ease of use, exudate management and pain on removal. We did not consider these in the NMA for practical reasons: such outcomes are reported inconsistently with data that rarely allow meta-analysis. Given that the quality assessment of healing data was based on study-level issues like small samples and flawed methodology, we can suppose the quality of other outcome data would have been equally sparse and likely uncertain.

Quality of the evidence

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We have explored the application of a new approach to GRADE analysis, alongside NMA in STATA (Chaimani 2013b; Salanti 2014). We applied the GRADE approach separately to effect estimates for different contrasts and to the ranking of interventions, but the two aspects are closely inter-related and, in this review, are a consequence of the sparse network and the high risk of bias through much of the network. The effect estimates were exemplified by contrasts of interventions versus saline gauze.

For the effect estimates' assessment, most of the evidence was of very low certainty (very low quality). The GRADE meaning of 'low-certainty evidence' is that "our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect". 'Very low-certainty evidence' means "We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect". 'Moderate-certainty evidence' means "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" (Balshem 2011). Exceptions to an assignment of very low certainty were found for contrasts with protease-modulating dressings (moderate certainty); collagenase ointment, basic wound contact dressing, foam dressing and PVP plus zinc oxide (low-certainty evidence), We downgraded evidence certainty mainly because of risk of bias and imprecision, although there was inconsistency for the contrasts hydrogel and hydrocolloid versus saline gauze and phenytoin versus saline gauze. Having said this, we are uncertain about the inconsistency assessment because of wide CIs around the test parameters. The majority of the comparisons with saline gauze had high risk of bias. However, a few contrasts had evidence solely downgraded on the basis of wide confidence intervals, that is, random error (protease-modulating dressings, basic wound contact dressing and PVP plus zinc oxide, each in comparisons with saline gauze). The sparseness of the network led to widespread imprecision in the effect estimates. Although we rated the evidence for one contrast as moderate-certainty, this result should be interpreted in the context of the network as a whole and not taken as an implication for practice.

Across the network as a whole, the evidence was of very low certainty. There was overall high risk of bias and overlap of the ranking probability distributions, and no clearcut results. The evidence was of such poor quality that we consider it inappropriate to focus on which treatments had the highest probabilities of healing (see also Potential biases in the review process).

Potential biases in the review process

This was a sparse network and there may have been small-study effects which impacted on the network (see Overall completeness and applicability of evidence). The STATA routines have largely been developed for and tested on larger networks, and our work has contributed to modifications for sparse networks in the netweight routine. Other STATA routines can be modified by the user to take into account small-study effects, but we did not explore these approaches because there was too much uncertainty in the network for us to be confident of interpreting the results. Instead, we used the standard routines for NMA and adapted the recent approach to GRADE (Salanti 2014) to bring in sparseness when assessing evidence certainty.

The recent GRADE approach has not been applied in many NMA reviews so far, and so could give potential for bias. We judge that it is a useful approach for many of the GRADE factors, however, there is one area in which we consider imprecision is underestimated: the GRADE method does not currently have a way of assessing optimum information size and 'fragility' of the confidence intervals when there are large effect estimates with wide CIs; such effects can result when the direct evidence for a particular intervention derives from very small studies peripheral to the network. Wide CIs can lead some interventions to have a finite probability of having a very large effect estimate, in turn leading to an artificially high probability of being the best treatment. For example, there were only seven participants who actually received dextranomer, yet this intervention was the most highly ranked, and effect estimates versus other treatments were largest for dextranomer. Numerically, when we consider the direct evidence for dextranomer versus collagenase ointment, for example, a missed healing diagnosis for just one person treated with collagenase could change the risk ratio by 50%. This, in turn, could affect the ranking and effect estimates of other contrasts with dextranomer. It was important to capture this potential bias in the review process, and we therefore produced a modification to the GRADE process to enable the 'sample size' of the direct evidence to be considered in a way analogous to the GRADE 'fragility' effects in pairwise meta-analysis (Guyatt 2011b). Our approach does not change the magnitude of the effect estimate or ranking order, rather it allows us to represent our uncertainty around these values.

A further effect of the sparseness of the network may have been to hide any inconsistencies. The various statistical tests for inconsistency were generally not significant, but this may have been due to a lack of sensitivity of the tests and the wide CIs around the measures. Despite this, we found inconsistencies in the network for contrasts involving phenytoin. We cannot be sure that there are no other inconsistencies, but this may not matter given the already identified large uncertainties.

We have made some assumptions: firstly, to include dressings and topical agents of various types in the same NMA. This implies that dressings and topical agents fulfil the same role and are exchangeable (i.e. that the participants/wounds receiving topical agents are similar to those receiving dressings). We did a post-hoc sensitivity analysis, which included only trials comparing two dressings, to investigate this assumption. It gave similar effect estimates and CIs for individual contrasts.

Finally, application of the GRADE approach to this NMA has given a rating of moderate-certainty evidence for only one contrast in the whole NMA, and we recognise that by using a representa-

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tive set of comparisons and by applying GRADE rules of thumb, however carefully, we may have inadvertently emphasised the importance of one intervention. This is a limitation of the approach. Instead the evidence on protease-modulating dressings should be set in the context of the uncertainty in the network as a whole.

Agreements and disagreements with other studies or reviews

We have been unable to identify any network meta-analyses directed at healing pressure ulcers and incorporating both dressings and topical agents. The AHRQ guideline reviewed the evidence for dressings in a series of pairwise comparisons and stated that overall, they did not find substantial evidence to support certain local wound applications over others (AHRQ 2013). The most recent NICE guideline on the prevention and management of pressure ulcers (NICE 2014) considered all RCT evidence on dressings and separately all RCT evidence on topical agents. NICE recommendations are to not use saline gauze dressings and for the health professional and adult to discuss the type of dressing to use, taking into account pain and tolerance, position of the ulcer, amount of exudate and frequency of dressing change. These recommendations rely heavily on consensus decisions, weakly supported by the evidence, and as such, agree with the findings of this review.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently insufficient evidence to judge whether any one dressing or topical treatment increases the probability of pressure ulcer healing compared with others (and neither is there sufficient evidence to judge whether there is a negative relative impact on wound healing or no relative impact). None of the interventions with moderate- or low-quality evidence appear to result in a higher proportion of wounds healed. It is important to note that many trials in this review were small and at high risk of bias. Based on current evidence, decision-makers may wish to make wound dressing choices on the basis of wound symptoms, clinical experience, patient preference and cost.

Implications for research

There is a lack of high-quality research evidence regarding whether particular wound dressings or topical treatments have a beneficial impact on wound healing, even compared with basic dressings. This lack of evidence is disturbing in view of the high personal and health service burden of pressure ulcers (and indeed several other types of wounds), and also in view of the many potential participants who could be invited to take part in trials. The network meta-analysis (NMA) exposes the generally poor quality of randomised controlled trials of pressure ulcer dressings, suggesting a need for radical improvements in the planning and conduct of trials in this field.

Given the high uncertainty across several competing interventions, any investment in future research must maximise its value to decision-makers. Any future evaluation of interventions for healing pressure ulcers could focus on the dressings or topical agents that health professionals use most widely, with consideration given to protease-modulating dressings. Any future research should consider time to healing: quicker healing may be as important to people with pressure ulcers as whether healing occurs.

There may be value in asking decision-makers (including people with pressure ulcers) what they feel are the most important issues, for example, type of dressing, purpose of the dressing/topical agent (including possible evaluation of broader groups of dressings e.g. advanced or basic), or duration that a dressing remains in situ, as well as which outcomes are most important. At a more fundamental level, decision-makers and funders should decide where research resources are best invested, for example, pressure ulcer treatment or prevention. Such planning means that research resources can be focused to address priorities. Where trials are conducted, good practice guidelines must be followed in their design, implementation and reporting, in particular outcome assessors should be blinded. Studies should be adequately powered and have sufficient follow-up time to allow healing to occur.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Aguilo Sanchez 2002

Methods	RCT; unit of randomisation unclear (unclear if > 1 wound per person) Funding: not stated. Setting: not stated Duration of follow-up about 7 weeks Unit of analysis: unclear
Participants	~24 participants with pressure ulcers. PU Stage: not stated (PU classification: not stated) Age: not stated. Duration of ulcer: not stated. Ulcer size: not stated Wound characteristics at baseline: infection not reported; slough not reported; necrosis not reported; exudate not reported Comment: PU grade not stated
Interventions	Group 1: hydrocolloid dressing - Comfeel Plus: hydrocolloid-alginate, combination of 2 groups randomised to treatment in the debridement and granulation phases; n = 12 (probably). Grouped intervention category: advanced dressing Group 2: foam dressing - Biatain Adhesive (combination of 2 groups randomised to treatment in the debridement and granulation phases); n = 12 (probably). Grouped intervention category: advanced dressing
Outcomes	Primary outcomes: proportion completely healed at about 7 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability unclear - no information. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: unclear who the outcome assessor was
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - none. Group 2 - none - i.e. no missing data
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias unit of analysis	Unclear risk	Unit of randomisation unclear and unit of analysis unclear - assumed the participant

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Aguilo Sanchez 2002 (*Continued*)

		was analysed ("cases"); no details on the ratio of ulcers:participants
Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists
ALL-DOMAIN RISK OF BIAS	Unclear risk	Rating: unclear Reasons: unclear selection bias; unclear blinding; unclear unit of analysis; unclear subgroup Comments: unclear risk of bias on unit of analysis; time to event may have been reported - unclear

Alm 1989

Methods	RCT; ulcers randomised (> 1 wound per person, all followed) Funding: not stated. Setting: hospital inpatients Duration of follow-up 6 weeks (also reported at 12 for time to event weeks) Unit of analysis: ulcer
Participants	50 participants with pressure ulcers. PU Stage: not stated and no indication apart from mean depth (PU classification: not stated) Age: mean 83.6 (SD 9.2) and 83.4 (SD 9.4). Duration of ulcer: 4.6 (SD10.9) and 4.8 (SD 6.5). Ulcer size: median (range?) 2.02 (0.95, 3.10) and 2.44 (0.97, 3 .24) Wound characteristics at baseline: no wounds infected; slough not reported; necrosis not reported; exudate not reported Comment: "considerable amount of debris"
Interventions	Group 1: hydrocolloid dressing - Comfeel Ulcus (not in BNF): 1 week washout with saline gauze; then hydrocolloid sheet and, if appropriate, hydrocolloid paste (7) and powder (1 ulcer); dressings changed when necessary; n = total 50 (number per group not reported). Grouped intervention category: advanced dressing Group 2: gauze saline dressing - saline wet (1 week washout with saline gauze; then saline gauze changed twice/day); n = total 50 (number per group not reported). Grouped intervention category: basic dressing
Outcomes	Primary outcomes: complete healing not reported; time to complete healing reported (Kaplan Meier plot included)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear

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Alm 1989 (*Continued*)

		- no information on allocation concealment. Baseline comparability unclear - baseline difference but of unclear importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded to interventions (clear description)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data: not reported by group and very unclear overall - possibly 9/50 (18%) missing (1 died, 2 protocol violations, 2 results missing, 3 discontinued for surgery, 1 adverse event)
Selective reporting (reporting bias)	High risk	Inadequate - reported incompletely (e.g. P value > 0.05)
Other bias unit of analysis	Low risk	Unit of randomisation ulcer and unit of analysis ulcer - 6/50 participants had 2 pressure ulcers (2 participants had 1 ulcer assigned to each group); ulcer:person = 60/56 overall = 1.12
Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Reasons: unclear selection bias; unclear missing data; unclear if PU grade sufficient; main outcome results estimated Comments: very poorly reported study; PU stage not stated; main outcomes estimated; ulcers randomised and analysed, so no unit of analysis errors; stated to be some baseline differences in ulcer duration, but degree and importance unclear

Ashby 2012

Methods	RCT; participants randomised (> 1 wound per person, other selection of wound) Funding: non-industry funding - MRC grant. NPWT units supplied by Kinetic Concepts Inc, but they had no input to the trial. Setting: hospital and community Duration of follow = up to 26 weeks (6 months) Unit of analysis: person (1 ulcer/person)
Participants	12 participants with pressure ulcers. PU Stage: 3 (n = 7); 4 (n = 5) overall; data per group not stated (PU classification: NPUAP)

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	Age: median (IQR) 67.5 (54.5 to 82.0) years. Duration of ulcer: median (IQR): overall - 4.0 months (2.2 to 28.5). Ulcer size: median: 3.0 cm wide x 5.0 cm long x 4 cm deep (overall) Wound characteristics at baseline: no wounds infected; slough not reported; necrosis not reported; exudate not reported Comment: deepest wound selected if more than 1 per person (but not stated if this occurred)
Interventions	Group 1: standard care (all advanced dressings): hydrocolloid (fibrous hydrocolloid) dressing, a foam dressing or an alginate dressing (all non-silver); n = 6. Grouped intervention category: advanced dressing Group 2: ineligible intervention - negative pressure wound therapy (PU was filled with either VAC WhiteFoamW or Granufoam dressings and VAC applied); n = 6). Grouped intervention category: ineligible - NPWT
Outcomes	Primary outcomes: proportion completely healed at 26 (6 months) weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Low risk	Sequence generation adequate - computer-generated. Allocation concealment adequate - central randomisation with contact details or list held independently. Baseline comparability unclear - baseline difference but unclear of importance. Rating: low
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded to interventions (clear description)
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data: Group 1 - 1/6 (17%) withdrew from treatment and received other treatment; 0/6 died (PU slow to heal). Group 2 - 6/6 (100%) withdrew from treatment and received other treatment. 2/6 (33%) died during the trial (1 recurrence of black slough, 1 ulcer too small to continue treatment, 1 foam embedded in granulation tissue, 1 deterioration, 1 participant refusal, 1 difficulty with applying treatment) i.e. differential missing data rates; high differential rate - likely to change effect estimate

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Ashby 2012 (*Continued*)

Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person)
Other bias additional	Low risk	The study appears to be free of other sources of bias
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Reasons: differential missing data due to death; also differential switching to other treatments Comments: attrition bias (death); small trial, but more comorbidities in NPWT group

Bale 1997a

Methods	RCT; participants randomised (only 1 wound per person) Funding: not stated. Setting: hospital inpatients Duration of follow-up 4 (30 days) weeks Unit of analysis: person (1 ulcer/person)
Participants	60 participants with pressure ulcers. PU Stage: II/III (acceptable); 71% and 79% Stage II (PU classification: Stirling) Age: median 74 years and 73 years. Duration of ulcer: not stated. Ulcer size: < 5 cm^2 (32% and 48%), 5 to < 10 (19% and 21%), 10 to < 20 (29% and 14%), > 20 (19% and 17%) Wound characteristics at baseline: no wounds infected; slough not reported; necrosis not reported; exudate low-moderate levels Comment: same number of ulcers as participants in table; exudate: none (32% and 28%) , slight (58% and 31%), moderate (10% and 41%); 5-centre trial
Interventions	Group 1: hydrocolloid dressing - Granuflex; n = 31. Grouped intervention category: advanced dressing Group 2: foam dressing - Allevyn Adhesive; n = 29. Grouped intervention category: advanced dressing
Outcomes	Primary outcomes: proportion completely healed at 4 (30 days) weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Bale 1997a (*Continued*)

Selection bias	High risk	Sequence generation unclear - not stated. Allocation concealment inadequate - evidence that researchers knew the sequence. Baseline comparability inadequate - baseline characteristics different between arms. Rating: high
Blinding of outcome assessment (detection bias) All outcomes	High risk	Other evidence for no blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data: Group 1 - 22/31 (71%) withdrew (8 discharged, 2 died, 2 adverse incident, 2 participant request, 2 dressing unsuitable, 2 wound deteriorated, 1 lack of progress, 2 dressing rolling). Group 2 - 18/29 withdrew (62%) (5 discharged, 6 died, 3 adverse incident, 2 participant request, 1 dressing unsuitable, 1 wound deteriorated) i.e. similar rate missing in both groups; high rate - more than control event rate
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person)
Other bias additional	Low risk	The study appears to be free of other sources of bias
ALL-DOMAIN RISK OF BIAS	High risk	Rating: very high Comments: allocation concealment inadequate - "allocated sequentially using an open randomisation list"; ulcer size larger for hydrocolloid group. Not blinded: performance assessed at dressing change; attrition bias
ALL-DOMAIN RISK OF BIAS 2	High risk	

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Banks 1994a

Methods	RCT; participants randomised (only 1 wound per person) Funding: industry funded - CV Laboratories Ltd (foam manufacturer) and Calgon Vestal Laboratories (HC manufacturer). Setting: community Duration of follow-up 6 weeks Unit of analysis: person (1 ulcer/person)
Participants	40 participants with pressure ulcers. PU Stage: II and III (Stages I, IV, V excluded); proportions not stated (PU classification: not stated) Age: median (range): 73 (46-93) years and 71 (40-100) years. Duration of ulcer: median (range): 21 (5-252) days and 56 (3-365) days; P < 0.08. Ulcer size: median (range): 0.74 (0.16-8.19) cm^2 and 0.67 (0.03-9.7) cm^2; mean 1.51 (SD1.86) cm^2 and 1.47 (SD 2.26) cm^2 Wound characteristics at baseline: no wounds infected; slough not reported; no wounds necrotic; exudate unclear Comment: exuding wounds but level not stated. Inclusion criteria: shallow/moist pressure sore involving loss of skin tissue
Interventions	Group 1: hydrocolloid dressing - Granuflex: concurrent standard pressure-relieving devices and cushions in community as appropriate; n = 20. Grouped intervention category: advanced dressing Group 2: foam dressing - Spyrosorb (not in BNF) (necessary by the treating health professional); n = 20). Grouped intervention category: advanced dressing
Outcomes	Primary outcomes: proportion completely healed at 6 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation adequate - computer-generated. Allocation concealment unclear - no information on allocation concealment. Baseline comparability unclear - baseline difference but of unclear importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded ('open label') and no evidence that outcome assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data: Group 1 - 10/20 (50%) withdrawn (2 wound deteriorated, 2 overgranulation, 2 discomfort, 4 unrelated to wound (2 died, 2 had respite care)). Group 2 - 2/20 (10%) (2 for reasons unrelated to wound (1 died, 1 admitted to hospital))

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Banks 1994a (*Continued*)

		i.e. differential missing data rates; high differential rate - likely to change effect estimate
Selective reporting (reporting bias)	High risk	Inadequate - outcome included in methods section but not results
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person)
Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists
ALL-DOMAIN RISK OF BIAS	High risk	Rating: very high Reasons: unclear selection bias, not blinded, attrition bias Comments: some difference in duration of ulcers; time-to-event data reported only as not significant; Grade II assumed to be acceptable (loss of skin tissue)
ALL-DOMAIN RISK OF BIAS 2	High risk	

Banks 1994b

Methods	RCT; participants randomised (> 1 wound per person, unclear how assessed) Funding: unclear - authors at wound healing research unit. Setting: hospital and community Duration of follow-up 12 weeks (also reported at 1, 2, 6 weeks) Unit of analysis: person (unclear if > 1 ulcer analysed)
Participants	50 participants with pressure ulcers. PU Stage: II (non-blanching erythema +/- superficial damage) and III (PU classification: Torrance) Age: 68% over 75 years. Duration of ulcer: ascertained but not reported. Not available for 28%. Ulcer size: 16 and 19 $\leq$ 1 cm², 3 and 3 > 1 cm² and $\leq$ 2.5 cm²; 7 and 2 > 2.5 cm² Wound characteristics at baseline: no wounds infected; not reported; no wounds necrotic; exudate not reported Comment: number ulcers/person not stated, but some had > 1 ulcer
Interventions	Group 1: foam dressing - Lyofoam; n = 26. Grouped intervention category: advanced dressing Group 2: basic wound contact dressing - N-A Dressing; n = 24). Grouped intervention category: basic dressing
Outcomes	Primary outcomes: proportion completely healed at 12 weeks; time to complete healing not reported

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Banks 1994b (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment adequate - independent 3rd party allocates and retains schedule. Baseline comparability unclear - baseline difference but unclear of importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear - vague
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - 7/26 (27%) (2 died, 5 withdrew; 2 reasons NS, 2 improved, 1 deteriorated). Group 2 - 9/24 (38%) (2 died, 7 withdrew, 2 reason NS, 1 improved, 4 deteriorated) i.e. similar rate missing in both groups; low rate - less than control event rate
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (unclear if > 1 ulcer analysed) - stated that protocol allowed > 1 per wound person, but no evidence that this happened
Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists
ALL-DOMAIN RISK OF BIAS	Unclear risk	Rating: unclear Comments: trial co-ordinator was outcome assessor, unclear if blinded; imbalance at baseline - not clear if problem. More large ulcers for intervention 1

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Banks 1994c

Methods	RCT; participants randomised (only 1 wound per person) Funding: industry funded - CV Laboratories Ltd (foam manufacturer) and Calgon Vestal Laboratories (HC manufacturer). Setting: hospital inpatients Duration of follow-up 6 weeks Unit of analysis: person (1 ulcer/person)
Participants	29 participants with pressure ulcers. PU Stage: II and III (involving loss of skin) proportions not stated (PU classification: not stated) Age: median (range): 74 (40-95) years and 73 (40-88) years. Duration of ulcer: median (range): 5.5 (2-365) days and 7 (2-14) days. Ulcer size: median (range): 2.4 (0.1-25.8) and 1.4 (0.5-14.3) cm^2 Wound characteristics at baseline: no wounds infected; slough not reported; no wounds necrotic; exudate moderate levels
Interventions	Group 1: hydrocolloid dressing - Granuflex: Granuflex E; additional support therapy for immobile participants; n = 16. Grouped intervention category: advanced dressing Group 2: foam dressing - Spyrosorb (not in BNF) (additional support therapy for immobile participants); n = 13). Grouped intervention category: advanced dressing
Outcomes	Primary outcomes: proportion completely healed at 6 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability unclear - baseline difference but unclear of importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded ('open label') and no evidence that outcome assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - 4/16 (25%) (3 wound deterioration, 1 wound/dressing-related problems). Group 2 - 3/13 (23%) (1 wound deterioration, 1 wound/dressing-related problems, 1 discharged from hospital) i.e. similar rate missing in both groups; low rate - less than control event rate

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Banks 1994c (*Continued*)

Selective reporting (reporting bias)	High risk	Inadequate - outcome included in methods section but not results
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person)
Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Reasons: unclear selection bias, not blinded, baseline differences Comments: wound area showed no significant difference, but median 2.4 versus 1.4; Grade II assumed to be acceptable (loss of skin tissue)

Barrois 1992

Methods	RCT (abstract); participants randomised (unclear if > 1 wound per person) Funding: not stated. Setting: not stated Duration of follow-up 8 weeks Unit of analysis: person (unclear if > 1 ulcer analysed)	
Participants	76 participants with pressure ulcers. PU Stage: not stated (PU classification: not stated) Age: not stated. Duration of ulcer: not stated. Ulcer size: mean 15 cm^2 overall Wound characteristics at baseline: infection not reported; slough not reported; all wounds necrotic; exudate not reported Comment: implies 1 ulcer per person; "multicentre good practice trial"	
Interventions	Group 1: hydrocolloid dressing - Granuflex; n = 38. Grouped intervention category: advanced dressing Group 2: iodine containing dressing - povidone iodine soaked gauze (tulle impregnated with PI); n = 38. Grouped intervention category: antimicrobial dressing	
Outcomes	Primary outcomes: proportion completely healed at 8 weeks; time to complete healing not reported	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability unclear - no

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Barrois 1992 (*Continued*)

		information. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who outcome assessor was
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - 2/38 (5%) (2 dropped out due to deterioration). Group 2 - 5/38 (13%) (5 dropped out due to deterioration in the wound) i.e. similar rate missing in both groups; low rate - less than control event rate
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias unit of analysis	Unclear risk	Unit of randomisation person and unit of analysis person (unclear if > 1 ulcer analysed) - probably 1 ulcer per person
Other bias additional	Unclear risk	PU classification unclear
ALL-DOMAIN RISK OF BIAS	Unclear risk	Rating: unclear Comments: unclear selection bias, unclear whether ulcer or person is unit of analysis. Grade of PU not stated (but open necrotic pressure sores/ulceration)

Belmin 2002

Methods	RCT; participants randomised (> 1 wound per person, other selection of wound) Funding: industry funded - Urgo (manufacturers of intervention 2). Setting: hospital inpatients Duration of follow-up 8 weeks Unit of analysis: person (selected ulcer)
Participants	110 participants with pressure ulcers. PU Stage: III and IV; stage III proportions = group 1: 82.7% and group 2: 71.4% (PU classification: Yarkony) Age: 82.2 (SD 7.9) years and 84.8 (SD 7.1) years . Duration of ulcer: 7.7 weeks and 7.2 weeks. Ulcer size: mean 12.6 (SD 8.0) cm^2 and 14.7 (SD 10.4) cm^2 (NS) Wound characteristics at baseline: no wounds infected; slough not reported; necrosis not reported; exudate not reported
Interventions	Group 1: hydrocolloid dressing - DuoDERM Extra Thin: note different HC; hydrocolloid paste for deep ulcers. Prior treatment with mainly HC; n = 53. Grouped intervention category: advanced dressing Group 2: sequential dressing - hydrocolloid-alginate (Urgosorb (4 weeks) then Algoplaque (4 weeks); hydrocolloid paste for deep ulcers in first 4 weeks only. Prior treatment mainly HC); n = 57. Grouped intervention category: advanced dressing

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Outcomes	Primary outcomes: proportion completely healed at 8 weeks; time to complete healing not reported	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - other. Baseline comparability unclear - baseline difference but unclear of importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who outcome assessor was
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data: Group 1 - all analysed, though 16/53 (30%) did not complete treatment (8 died and 8 withdrew (2 transfer to another unit, 3 local infection, 3 PU impairment)). Group 2 - all analysed, though 17/57 (30%) did not complete treatment (11 died and 6 withdrew (1 transfer to another unit, 1 worsening health status, 1 local infection, 3 PU impairment)) i.e. all analysed but non-completers - similar rate in each group; high rate - more than control event rate
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (selected ulcer) - one ulcer selected
Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Comments: unclear selection bias (block randomised), different hydrocolloids and pastes used; unclear who assessed healing - nurses not blinded, assessor of wound area was blinded; baseline differences: dia-

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		betes, hypertension significantly higher for sequential; proportion of grade IV ulcers higher in sequential

Brod 1990

Methods	RCT (letter to journal); participants randomised (unclear if > 1 wound per person) Funding: industry funded - Acme/Chaston division, National Patent Development Corp (manufacturer poly HEMA). Setting: care home Duration of follow-up 8 weeks Unit of analysis: person (unclear if > 1 ulcer analysed)
Participants	43 participants with pressure ulcers. PU Stage: II and III (description available); stratified then randomised; proportions not stated (PU classification: not stated) Age: median 86 years and 82 years. Duration of ulcer: not stated, but comparable. Ulcer size: median 2.5 cm^2 and 1.9 cm^2 (P = 0.09) Wound characteristics at baseline: infection not reported; slough not reported; some wounds necrotic; exudate not reported Comment: if necrosis, wounds were debrided first
Interventions	Group 1: hydrogel dressing - poly HEMA: Hydron dressing; n = 27. Grouped intervention category: advanced dressing Group 2: hydrocolloid dressing - DuoDERM; n = 16. Grouped intervention category: advanced dressing
Outcomes	Primary outcomes: proportion completely healed at 8 weeks; time to complete healing reported (Kaplan Meier plot included)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability adequate - no suggestion of problems. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded to interventions - clear description
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - 2/27 (7%) (both died). Group 2 - 3/16 (19%) (1 died, 2 did not complete treatment (1 poor response, 1 adverse event))

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Brod 1990 (*Continued*)

		i.e. differential missing data rates; low differential rate - unlikely to change effect estimate
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (unclear if > 1 ulcer analysed) - one ulcer implied (e.g. "52% of group 1 had complete healing of the study ulcer")
Other bias additional	Low risk	Adequate - no suggestion of problems
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Reasons: unclear selection bias, not blinded Comments: unblinded research nurse who had no clinical responsibilities

Brown-Etris 1996

Methods	RCT; ulcers randomised (> 1 wound per person, other selection of wound) Funding: not stated. Setting: care home and hospital and community Duration of follow-up 10 weeks Unit of analysis: person (1 ulcer/person)
Participants	
Interventions	Group 1: hydrogel dressing - Transorbent dressing; n = 77. Grouped intervention category: advanced dressing Group 2: hydrocolloid dressing - DuoDERM CGF (not BNF); n = 63. Grouped intervention category: advanced dressing
Outcomes	Primary outcomes: proportion completely healed at 10 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	High risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability inadequate - baseline characteristics different between

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		arms. Rating: high
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded ('open label') and no evidence that outcome assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - 19/77 (25%) (11 unable to follow, 5 died, 3 other; overall 19 participants did not complete first 3 weeks of trial or missed 2 sequential visits). Group 2 - 12/63 (19%) (4 unable to follow, 5 died, 3 other; overall 19 participants did not complete first 3 weeks of trial or missed 2 sequential visits) i.e. similar rate missing in both groups; low rate - less than control event rate
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias unit of analysis	High risk	Unit of randomisation ulcer and unit of analysis person (1 ulcer/person) - ulcers randomised (stratified), but one II, III or IV ulcer was selected (implied at the beginning), at the discretion of the (unblinded) investigator at each centre
Other bias additional	Unclear risk	Some discrepancy between text and table in the number of participants
ALL-DOMAIN RISK OF BIAS	High risk	Rating: very high Reasons: selection bias (baseline differences), not blinded, ulcer selected by investigator Comments: allocation concealment - each centre randomised independently. Says wounds randomised and stratified by surface area and stage, but later says one ulcer was selected (implied at the beginning), at the discretion of the investigator. Baseline differences in the proportion with Grade III/IV ulcers (more in foam group) and duration of ulcer shorter in hydrocolloid group. Some discrepancy between text and table in the number of participants
ALL-DOMAIN RISK OF BIAS 2	High risk	

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Brown-Etris 1997

Methods	RCT (abstract); participants randomised (unclear if > 1 wound per person) Funding: non-industry funding - authors worked for health care agency. Setting: unclear Duration of follow-up 8 weeks Unit of analysis: person (unclear if > 1 ulcer analysed)
Participants	36 participants with pressure ulcers. PU Stage: II, III and IV (proportions not stated) (PU classification: not stated) Age: not stated. Duration of ulcer: not stated. Ulcer size: not stated Wound characteristics at baseline: infection not reported; slough not reported; necrosis not reported; exudate not reported Comment: few details (abstract)
Interventions	Group 1: protease-modulating dressing - Fibracol (90% collagen, 10% alginate (from suppliers' website)); n = 24. Grouped intervention category: protease-modulating dressing Group 2: alginate dressing - Kaltostat; n = 12. Grouped intervention category: advanced dressing
Outcomes	Primary outcomes: proportion completely healed at 8 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability unclear - no information. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded ('open label') and no evidence that outcome assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data: Group 1 - 116 total enrolled, 80 evaluable and interim analysis on 36 (not stated). Group 2 - 116 total enrolled, 80 evaluable and interim analysis on 36 (not stated) i.e. missing data, but unclear
Selective reporting (reporting bias)	High risk	Inadequate - outcome included in methods section but not results
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (unclear if > 1 ulcer anal-

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Brown-Etris 1997 (*Continued*)

		ysed) - one ulcer implied (e.g. "participants stratified before randomisation according to pressure ulcer location and size")
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Reasons: unclear selection bias, not blinded Comments: interim analysis - but planned, so acceptable

Brown-Etris 2008

Methods	RCT; participants randomised (> 1 wound per person, other selection of wound) Funding: industry funded - 3M grant (manufacturers of Tegaderm). Setting: care home and community Duration of follow-up 8 weeks Unit of analysis: person (1 ulcer/person)
Participants	72 participants with pressure ulcers. PU Stage: II (59.5% and 65%; P = 0.59), and shallow III (PU classification: not stated) Age: mean 72.7 (SD 18.61) years and 78.3 (SD 14.70) years. Duration of ulcer: median (range): 32.0 days (2-635) and 21.0 days (1-291); P = 0.169. Ulcer size: mean (SD): 2.5 (4.86) and 1.5 (1.69) cm^2 Wound characteristics at baseline: no wounds infected; slough not reported; some wounds necrotic; exudate low-moderate levels Comment: < 25% necrotic
Interventions	Group 1: hydrocolloid dressing - DuoDERM CGF; n = 37. Grouped intervention category: advanced dressing Group 2: vapour-permeable dressing - Tegaderm Absorbent Clear; n = 35). Grouped intervention category: advanced dressing
Outcomes	Primary outcomes: proportion completely healed at 8 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability adequate - no suggestion of problems. Rating: unclear
Blinding of outcome assessment (detection bias)	High risk	Not blinded ('open label') and no evidence that outcome assessor was blinded

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Brown-Etris 2008 (*Continued*)

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - none. Group 2 - none i.e. no missing data (no details)
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person) - if > 1, authors selected highest grade PU then largest ulcer
Other bias additional	Low risk	Adequate - no suggestion of problems
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Reasons: unclear selection bias, not blinded

Burgos 2000b

Methods	RCT; participants randomised (only 1 wound per person) Funding: industry funded - supported by Laboratorios Knoll (manufacturer of collagenase ointment). Setting: hospital inpatients Duration of follow-up 12 weeks Unit of analysis: person (1 ulcer/person)
Participants	37 participants with pressure ulcers. PU Stage: III only (PU classification: not stated) Age: mean 78.6 (SD 10.4) years and 81.9 (SD 12.7) years. Duration of ulcer: 2.6 (SD 1.9) months and 3.2 (SD 2.0) months P = 0.44; 89% and 83% previously treated. Ulcer size: approx 22 and 20.5 cm^2 (estimated from graph) Wound characteristics at baseline: no wounds infected; slough not reported; necrosis not reported; exudate not reported Comment: same number of ulcers as participants in table
Interventions	Group 1: hydrocolloid dressing - Varihesive (not in BNF): ulcers cleaned with saline; Varihesive paste used for deep ulcers/high exudate for HC group only; n = 19. Grouped intervention category: advanced dressing Group 2: collagenase-containing ointment - Iruxol (not BNF) (ulcers cleaned with saline); n = 18. Grouped intervention category: collagenase ointment
Outcomes	Primary outcomes: proportion completely healed at 12 weeks; time to complete healing not reported
Notes	
Risk of bias	

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Burgos 2000b (*Continued*)

Bias	Authors' judgement	Support for judgement
Selection bias	Unclear risk	Sequence generation adequate - computer-generated. Allocation concealment unclear - other. Baseline comparability adequate - no suggestion of problems. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	High risk	Other evidence for no blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data: 6 participants excluded overall (4 protocol violations) - not given by group. Additionally, discontinuations: Group 1: 6 (32%) (because of death due to unrelated cause, deterioration in general condition, discharge from hospital, protocol violations, lack of efficacy). Group 2: 8 (44%) (because of deaths due to unrelated cause, discharge from hospital, transfer to another centre), i.e. similar rate missing in both groups; high rate - more than control event rate "Eight (44.4%) and six (31.6%) patients in the collagenase and hydrocolloid groups, respectively, discontinued the study prematurely. Reasons for discontinuation in the collagenase group were: death due to unrelated cause (n = 3), discharge from the hospital (n = 3) and transfer to another centre (n = 3). Reasons for discontinuation in the hydrocolloid group included death due to unrelated cause (n = 1), deterioration of the patient's general condition (n = 1), discharge from the hospital (n = 1), protocol violation (n = 2) and lack of efficacy (n = 1)", i.e. discrepancy between total number missing and sum of reasons for group 2 - but 44% corresponds to 8 participants
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person) - same number of ulcers as participants in table
Other bias additional	Unclear risk	Paste used for hydrocolloid group only

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Burgos 2000b (*Continued*)

ALL-DOMAIN RISK OF BIAS	High risk	Rating: very high Comments: randomisation conducted by department of biometry of sponsor; said to be not blinded; paste used for hydrocolloid group only; difference between interventions for people leaving study prematurely
ALL-DOMAIN RISK OF BIAS 2	High risk	

Colwell 1993

Methods	RCT; ulcers randomised (> 1 wound per person, all followed) Funding: industry funded - Convatec (manufacturer of hydrocolloid). Setting: hospital inpatients Duration of follow-up 12 weeks Unit of analysis: ulcer
Participants	70 participants with pressure ulcers. PU stage: II (69% and 44%) and III (PU classification: NS). Age: mean (range): 68 (18-100) years and 68 (29-92) years. Duration of ulcer: 55% and 59% < 1 month; 45% and 41% 1-3 months. Ulcer size: surface area: 2.29 cm^2 and 2.37 cm^2 Wound characteristics at baseline: no wounds infected; slough not reported; necrosis not reported; exudate not reported Comment: tertiary care centre; "each patient's ulcers were randomised to 1 of 2 treatments" and discussion states ulcers randomised. 94 participants enrolled, but analysis on 70 participants with 97 ulcers
Interventions	Group 1: hydrocolloid dressing - DuoDERM CGF (not BNF); n = 33. Grouped intervention category: advanced dressing Group 2: gauze saline dressing - saline moist; n = 37. Grouped intervention category: basic dressing
Outcomes	Primary outcomes: proportion completely healed at 12 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	High risk	Sequence generation unclear - not stated. Allocation concealment unclear - no information on allocation concealment. Baseline comparability inadequate - baseline characteristics different between arms. Rating: high

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Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who outcome assessor was
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - Overall 24/94 (26%) (12 died from causes unrelated to PU, 5 discharged from hospital, 5 lost to follow-up, 1 colonised with MRSA, 1 participant's ulcer progressed to Stage 4. Equivalent number dropped from each group). Group 2 - Overall 24/94 (26%) (12 died from causes unrelated to PU, 5 discharged from hospital, 5 lost to follow-up, 1 colonised with MRSA, 1 participant's ulcer progressed to Stage 4. Equivalent number dropped from each group) i.e. overall rate only; low rate - less than control event rate
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias unit of analysis	Low risk	Unit of randomisation ulcer and unit of analysis ulcer - approx 1.5 ulcer:person ratio = 48/33 and 49/37
Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Reasons: selection bias (baseline imbalance), available case only, baseline imbalance Comments: results and number of ulcers not reported for those that dropped out of the study, so available case analysis only. Significantly more grade III ulcers for the saline gauze dressing vs hydrocolloid (56% vs 31%). Ulcers randomised and analysed so no unit of analysis issues

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Darkovich 1990

Methods	RCT; unit of randomisation unclear (> 1 wound per person, all followed) Funding: not stated. Setting: hospital and care home Duration of follow-up 8.5 (60 days) weeks Unit of analysis: ulcer
Participants	90 participants with pressure ulcers. PU Stage: I and II (54% and 56%) (results separate) ; stage I is ulceration or skin breakdown limited to superficial epidermal and dermal layer - probably corresponds to grade II? (PU classification: Enis and Sarmiento). Age: overall mean: 75 years (range 30-98); mean in acute care 69 years, in care homes 83 years. Duration of ulcer: not stated. Ulcer size: hydrogel: mean 11.0 (range 0.2-100) cm^2; hydrocolloid: mean 9.2 (0.4-63.75) cm^2 Wound characteristics at baseline: no wounds infected; slough not reported; necrosis not reported; exudate not reported Comment: it says wounds randomised, but also says people with multiple wounds had same treatments; 67/49 (1.4) and 62/41 (1.5) wounds per person
Interventions	Group 1: hydrocolloid dressing - DuoDERM; n = 49 overall. Grouped intervention category: advanced dressing Group 2: hydrogel dressing - Biofilm (not in BNF); n = 41 overall. Grouped intervention category: advanced dressing
Outcomes	Primary outcomes: proportion completely healed at 8.5 (60 days) weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability unclear - baseline difference but unclear of importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear - no information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - 4/67 (6%) excluded from the authors' analysis (3 wounds' size increased by more than 10% per day and 1 decreased by more than 25% per day). Group 2 - 2/62 (3%) excluded from the authors' analysis (1 wound's size increased by more than 10% per day and 1 decreased by more than 25% per day).

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Darkovich 1990 (*Continued*)

		i.e. similar rate missing in both groups; low rate - less than control event rate
Selective reporting (reporting bias)	High risk	Inadequate - reported incompletely
Other bias unit of analysis	High risk	Unit of randomisation unclear and unit of analysis ulcer - Overall ulcer:person ratio = 67/49 and 62/41 (1.52)
Other bias additional	Unclear risk	Extraction from a graph
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high/very high Reasons: unclear selection bias, unit of analysis issues; extraction from a graph Comments: baseline difference: 11.0 versus 9.2 cm^2 mean wound area; number of ulcers reported for grade II only on graph. May be best to report overall (see definition of stage I). Unit of analysis issues; 6/90 participants excluded as outliers

Gorse 1987

Methods	RCT; wards randomised (> 1 wound per person, all followed) Funding: not stated. Setting: hospital inpatients Duration of follow-up approx 11 (assumed from mean + SD) weeks Unit of analysis: ulcer
Participants	52 participants with pressure ulcers. PU Stage: II (87% and 79%) and III (with acceptable definition) (PU classification: not stated) Age: mean (SD): 72.0 (12.8) years and 68.4 (13.5) years; proportion ≥ 65 years: 75% and 56%. Duration of ulcer: not stated. Ulcer size: not stated Wound characteristics at baseline: some wounds infected; slough not reported; some wounds necrotic; exudate not reported Comment: infection at baseline: 9% and 23%; proportion with necrotic wounds not stated
Interventions	Group 1: hydrocolloid dressing - DuoDERM; n = 27. Grouped intervention category: advanced dressing Group 2: ineligible intervention - whirlpool + chloramine dressing (gauze dampened with Dakin's solution + whirlpool hydrotherapy 3 times/week); n = 25. Grouped intervention category: ineligible - whirlpool
Outcomes	Primary outcomes: proportion completely healed at approx 11 (assumed from mean + SD) weeks; time to complete healing not reported
Notes	

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Gorse 1987 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Selection bias	High risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability inadequate - baseline characteristics different between arms. Rating: high
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who outcome assessor was
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - none. Group 2 - none i.e. no missing data (clearly stated)
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	High risk	Unit of randomisation ward and unit of analysis ulcer - each ward assigned one or other treatment regimen
ALL-DOMAIN RISK OF BIAS	High risk	Rating: very high Reasons: selection bias (large baseline differences); unit of analysis issues - ward randomised, ulcer analysed; unclear blinding Comments: baseline differences for: proportion of ulcers in over 65 age group (greater for hydrocolloid), proportion of grade II ulcers (87% and 79%), proportion infected ulcers (9% and 23%)
ALL-DOMAIN RISK OF BIAS 2	High risk	

Graumlich 2003

Methods	RCT; participants randomised (only 1 wound per person) Funding: mixed industry and non-industry - Biocore Medical Technologies supplied the collagen + grant from Retirement Research Foundation. Setting: care home Duration of follow-up 8 weeks (also reported at 1 and 4 weeks) Unit of analysis: person (1 ulcer/person)
Participants	65 participants with pressure ulcers. PU Stage: 2 (77% and 83%) and 3 (PU classification: NPUAP) Age: 80.6 (SD 12.2) years and 82.0 (SD 9.9) years. Duration of ulcer: median (IQR):

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	6.5 (2.0, 12.0) weeks and 3.0 (1.6, 8.0) weeks (not statistically significant). Ulcer size: median (IQR) 1.74 (0.5, 4.36) and 1.21 (0.63, 3.38); not statistically significant Wound characteristics at baseline: infection not reported; no wounds sloughy; no wounds necrotic; exudate not reported Comment: wounds with eschar (not slough) or necrosis excluded (but re-included after debridement)
Interventions	Group 1: hydrocolloid dressing - DuoDERM: twice-weekly. Standard nursing care. No ancillary non-protocol treatments; n = 30. Grouped intervention category: advanced dressing Group 2: protease-modulating dressing (cleansed with saline then sprinkled with collagen particles in thin continuous layer; covered with dry gauze. Standard nursing care. No ancillary non-protocol treatments); n = 35. Grouped intervention category: protease-modulating dressing
Outcomes	Primary outcomes: proportion completely healed at 8 weeks; time to complete healing reported (Kaplan Meier plot included)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Low risk	Sequence generation adequate - computer-generated. Allocation concealment adequate - central randomisation with contact details or list held independently. Baseline comparability adequate - no suggestion of problems. Rating: low
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded to interventions (clear description)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - 5/30 (17%) (1 withdrew consent, 3 died, 2 hospitalised) . Group 2 - 6/35 (17%) (2 died, 1 hospitalised, 2loss to follow-up). i.e. similar rate missing in both groups; low rate - less than control event rate
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person)
Other bias additional	Low risk	Adequate - well-conducted study

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Graumlich 2003 (*Continued*)

ALL-DOMAIN RISK OF BIAS	Low risk	Rating: low Comments: some differences at baseline (size and duration) but not statistically significant

Hollisaz 2004

Methods	RCT; participants randomised (> 1 wound per person, all followed) Funding: non-industry funding - Jaonbazan Medical and Engineering Research Center (Iranian government body for spinal chord injury war victims). Setting: care home and community with spinal injury Duration of follow-up 8 weeks Unit of analysis: ulcer
Participants	52 participants with pressure ulcers. PU Stage: I (33%; 36%) and II (58%, 64%) (stratified and results separate). Shea I defined as "Limited to epidermis, exposing dermis; includes a red area" (PU classification: Shea). Age: for all participants (mixed wounds): mean 36.6 (SD 6.0) years - no difference between groups. Duration of ulcer: for all participants (mixed wounds): 7.6 (SD 5.6) weeks, 5.8 (SD 8.0) weeks, 5.3 (SD 5.4) weeks; P > 0.10. Ulcer size: for all participants (mixed wounds): mean 7.26 cm^2 (SD 15.4), 5.12 cm^2 (SD 3.63), 10.27 cm^2 (SD 15.32); P > 0.10. Wound characteristics at baseline: infection not reported; slough not reported; no wounds necrotic; exudate not reported Comment: spinal chord injury; all male and young war victims; wounds debrided first if necessary
Interventions	Group 1: hydrogel dressing - hydrocolloid adhesive dressing (description "hydrocolloid adhesive dressings absorb water and low molecular weight components from ulcer secretions, so they swell to produce a jelly"). No concomitant antibiotic, steroid or antisuppressant treatments allowed. No debridement needed during treatment. All other concomitant treatments the same; n = 16. Grouped intervention category: advanced dressing Group 2: phenytoin topical - phenytoin topical (no concomitant antibiotic, steroid or antisuppressant treatments allowed. No debridement needed during treatment. All other concomitant treatments the same); n = 19. Grouped intervention category: phenytoin topical Group 3: saline wet - no concomitant antibiotic, steroid or antisuppressant treatments allowed. No debridement needed during treatment. All other concomitant treatments the same (no concomitant antibiotic, steroid or antisuppressant treatments allowed. No debridement needed during treatment. All other concomitant treatments the same; n = 17. Grouped intervention category: basic dressing
Outcomes	Primary outcomes: proportion completely healed at 8 weeks; time to complete healing not reported
Notes	

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Hollisaz 2004 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Low risk	Sequence generation adequate - random number tables. Allocation concealment adequate - central randomisation with contact details or list held independently. Baseline comparability adequate - no suggestion of problems. Rating: low
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded to interventions (clear description)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - none. Group 2 - none. Group 3 - none i.e. no missing data (clearly stated)
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Unclear risk	Unit of randomisation person and unit of analysis ulcer - probably participants randomised; if > 1 ulcer then same treatment within participant; < 1.2 ulcer:person = 18/16, 21/19 and 19/17
Other bias additional	Low risk	Adequate - no suggestion of problems
ALL-DOMAIN RISK OF BIAS	Unclear risk	Rating: unclear/low Reasons: unit of analysis issues (small) Comments: slight unit of analysis issues (but number of ulcers very close to number of participants)

Hondé 1994

Methods	RCT; participants randomised (> 1 wound per person, other selection of wound) Funding: industry funded - funded by Synthelabo Recherche (manufacturers of Inerpan) . Setting: hospital inpatients Duration of follow-up 8 weeks Unit of analysis: person (1 ulcer/person)
Participants	168 participants with pressure ulcers. PU Stage: 1 grade I (excluded from analysis), 187 II to IV (II: 54% and 64%; III: 40% and 30%; IV: 5.7% and 6.2%) (PU classification: Shea) Age: mean 83.5 (SD 7.8; range 64-101) years and mean 80.4 (SD 8.2, range 63-98)

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	years. Duration of ulcer: not stated. Ulcer size: mean surface area: 6.85 cm² and 8.99 cm² Wound characteristics at baseline: infection not reported; slough not reported; unclear necrotic; exudate unclear Comment: study says, "in cases of multiple ulcers, only one sore per patient was evaluated"
Interventions	Group 1: hydrocolloid dressing - Comfeel (unspecified); n = 88. Grouped intervention category: advanced dressing Group 2: ineligible intervention - skin substitute (amino acid copolymer (leucine and methyl glutamate) - Interpam); n = 80. Grouped intervention category: ineligible intervention - skin substitute
Outcomes	Primary outcomes: proportion completely healed at 8 weeks; time to complete healing not reported (Kaplan Meier plot included)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation adequate - computer-generated. Allocation concealment unclear - vague statement about central randomisation. Baseline comparability unclear - baseline difference but unclear of importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded ('open label') and no evidence that outcome assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data: Group 1 - 24/88 (27%) (6 withdrew because of local complications (mainly necrosis), 18 withdrew for reasons unconnected with treatment (mainly death, transfer to another ward, discharge from hospital)). Group 2 - 14/80 (17.5%) (4 withdrew because of local complications (mainly necrosis), 10 withdrew for reasons unconnected with treatment (mainly death, transfer to another ward, discharge from hospital)) i.e. differential missing data rates; high differential rate - likely to change effect estimate
Selective reporting (reporting bias)	High risk	Inadequate - analysis methods differed from those of other trials

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Hondé 1994 (*Continued*)

Other bias unit of analysis	Unclear risk	Unit of randomisation person and unit of analysis person (1 ulcer/person) - study says, "in cases of multiple ulcers, only one sore per patient was evaluated". Not stated how many this applied to
ALL-DOMAIN RISK OF BIAS	High risk	Rating: very high Reasons: not blinded, attrition bias, unclear selection bias Comments: allocation concealment: according to a randomisation list prepared by Biometry group (does not say what happened to list). Open label trial, "investigators asked to give an assessment of treatment performance (healed)". Time to event analysis using Wilcoxon. Age and grade of PU differences at baseline
ALL-DOMAIN RISK OF BIAS 2	High risk	

Imamura 1989

Methods	RCT (translation); participants randomised (only 1 wound per person) Funding: unclear. Setting: hospital inpatients Duration of follow-up 8 weeks (also reported at 1, 2, 4, 6 weeks) Unit of analysis: person (1 ulcer/person)
Participants	141 participants with pressure ulcers. PU Stage: I (23% and 21%), II and III (44% and 38%) and IV (34% and 41%) (PU classification: not stated) Age: not stated/translated. Duration of ulcer: not stated/translated. Ulcer size: not stated Wound characteristics at baseline: unclear infection; slough not reported; necrosis not reported; exudate not reported Comment: number with change in infection status reported, but unclear what sort of change
Interventions	Group 1: topical - sugar plus povidone iodine: sugar 70 g/100 g and povidone iodine 3 g/100 g; ointment applied directly on the wound or applied on a sheet of gauze and then applied on the wound once or twice a day; n = 72. Grouped intervention category: sugar plus povidone iodine Group 2: other topical - lysozyme ointment (5 g/100 g ointment applied directly on the wound or on a sheet of gauze and then on the wound once or twice a day); n = 69. Grouped intervention category: lysosyme ointment
Outcomes	Primary outcomes: complete healing not reported; time to complete healing not reported
Notes	
Risk of bias	

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Imamura 1989 (*Continued*)

Bias	Authors' judgement	Support for judgement
Selection bias	Unclear risk	Sequence generation adequate - random number tables. Allocation concealment adequate - central randomisation with contact details or list held independently. Baseline comparability unclear - baseline difference but unclear of importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	High risk	Other evidence for no blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data: Group 1 - 27/72 (38%) (withdrew (1 because of adverse effects)). Group 2 - 29/69 (42%) (withdrew (1 because of adverse effects)). i.e. similar rate missing in both groups; high rate - more than control event rate
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person)
Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists
ALL-DOMAIN RISK OF BIAS	High risk	Rating: very high Comments: unclear selection bias: baseline differences for proportion of Stage 4 ulcers (34% vs 41%); translated as 'not blinded'; attrition bias
ALL-DOMAIN RISK OF BIAS 2	High risk	

Kaya 2005

Methods	RCT; participants randomised (> 1 wound per person, all followed) Funding: non-industry funding - declaration of interest: none. Setting: hospital with spinal chord injury Duration of follow-up unclear weeks Unit of analysis: ulcer
Participants	27 participants with pressure ulcers. PU Stage: 1 (24% and 25% of ulcers), 2 (68% and 71%) and 3 (results separate, but best to combine) (PU classification: NPUAP) Age: mean (SD): 35.3 (14.6), range 16-56 years and 29.7 (6.4), range 17-39 years.

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	Duration of ulcer: not stated. Ulcer size: mean (SD): 4.13 (2.73; range: 2-13) cm^2; reporting of control group unclear: range 2-35 cm^2 Wound characteristics at baseline: no wounds infected; slough not reported; necrosis not reported; exudate not reported Comment: spinal chord injury (78% complete, 22% incomplete SCI); 15 participants/25 ulcers and 12 participants/24 ulcers
Interventions	Group 1: hydrogel dressing - Elastogel (not in BNF); n = 15. Grouped intervention category: advanced dressing Group 2: iodine containing dressing - povidone iodine soaked gauze; n = 12. Grouped intervention category: antimicrobial dressing
Outcomes	Primary outcomes: complete healing not reported; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability adequate - no suggestion of problems. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear - no information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - 0. Group 2 - 0; i.e. no missing data (no details)
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	High risk	Unit of randomisation person and unit of analysis ulcer - for combination of stages I and II and III, ulcer:person ratio = 25/15 (1.7) and 24/12 (2.0)
Other bias additional	Unclear risk	Adequate - no suggestion of problems
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Comments: unclear selection bias, unclear blinding; unit of analysis issues

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Kraft 1993

Methods	RCT; participants randomised (only 1 wound per person) Funding: industry funded - Calgon Vestal Laboratories, manufacturer of foam dressing. Setting: hospital and care home with spinal injury Duration of follow-up 24 weeks (also reported at 3, 6, 12 (graph) weeks) Unit of analysis: person (1 ulcer/person)
Participants	38 participants with pressure ulcers. PU Stage: II (58% overall) and III (PU classification: Enterstomal Therapy) Age: overall mean: 76, range 28-78 years. Duration of ulcer: 58% for 2 months or less; range 0-5 years. Ulcer size: not stated Wound characteristics at baseline: no wounds infected; slough not reported; necrosis not reported; exudate not reported Comment: 33/38 were people with spinal chord injury
Interventions	Group 1: foam dressing - Epi-Lock (not in BNF); n = 24. Grouped intervention category: advanced dressing Group 2: gauze saline dressing - saline moist; n = 14. Grouped intervention category: basic dressing
Outcomes	Primary outcomes: proportion completely healed at 24 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias	Unclear risk	Sequence generation unclear - not stated. Allocation concealment unclear - no information on allocation concealment. Baseline comparability unclear - no information. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who outcome assessor was
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data: Group 1 - 11/24 (45%) and (5 staff-requested removal, 1 participant-requested removal, 1 special bed treatment, 4 reactions to treatment). Group 2 - 6/14 (43%) (2 died, 1 staff-requested removal, 1 participant-requested removal, 1 surgery, 1 reaction to treatment). i.e. similar rate missing in both groups; high rate - more than control event rate
Selective reporting (reporting bias)	Low risk	Adequate - full results reported

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Kraft 1993 (*Continued*)

Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person)
Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Reasons: unclear selection bias, attrition bias Comments: all assessed by same rater (a registered nurse), but no information on what she knew

Matzen 1999

Methods	RCT; participants randomised (only 1 wound per person) Funding: not stated. Setting: community Duration of follow-up 12 weeks Unit of analysis: person (1 ulcer/person)
Participants	32 participants with pressure ulcers. PU Stage: III and IV: median for both groups was IV (PU classification: not stated) Age: median (range): 82 (32-97) years and 84 (46-89) years. Duration of ulcer: not stated. Ulcer size: not stated Wound characteristics at baseline: no wounds infected; slough not reported; unclear necrotic; exudate not reported
Interventions	Group 1: hydrogel dressing - amorphous hydrocolloid (hydrogel, Coloplast) - in Cochrane Review as hydrogel; n = 17. Grouped intervention category: advanced dressing Group 2: gauze saline dressing - saline gauze; n = 15. Grouped intervention category: basic dressing
Outcomes	Primary outcomes: proportion completely healed at 12 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability adequate - no suggestion of problems. Rating: unclear

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Matzen 1999 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who outcome assessor was
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data: Group 1 - 9/17 (53%) (5 other illness, 2 deaths, 1 missing schedule, 1 wish to cease participation). Group 2 - 11/15 (73%) (6 insufficient effect of treatment, 3 other illness, 1 death, 1 wish to cease participation) i.e. differential missing data rates; high differential rate - likely to change effect estimate
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person)
Other bias additional	Low risk	Adequate - no suggestion of problems
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Comments: unclear selection bias, attrition bias; unlikely that outcome assessor blinded, but not clear who it was

Meaume 2003

Methods	RCT; participants randomised (unclear if > 1 wound per person) Funding: not stated. Setting: care home Duration of follow-up 8 weeks Unit of analysis: person (unclear if > 1 ulcer analysed)
Participants	38 participants with pressure ulcers. PU Stage: 2 (PU classification: EPUAP) Age: mean age 83.8 years, range 74.9-95.1 and 82.5 years, range 66.4-91.9 . Duration of ulcer: at least 4 weeks; NICE guideline: mean (range) 8.3 (1-24) weeks and 13.0 (1-52) weeks. Ulcer size: not reported (table 2 missing); NICE guideline: mean 4.9 (0.7-25.3) cm^2 and 5.4 (0.2-26.0) Wound characteristics at baseline: no wounds infected; some wounds sloughy; no wounds necrotic; exudate not reported Comment: red-yellow wounds in the red-yellow-black system (no necrosis, but some slough)
Interventions	Group 1: soft polymer dressing - Mepilex Border; n = 18. Grouped intervention category: advanced dressing Group 2: foam dressing - Tielle; n = 20. Grouped intervention category: advanced dressing

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Outcomes	Primary outcomes: proportion completely healed at 8 weeks; time to complete healing not reported	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation adequate - computer-generated. Allocation concealment unclear - envelopes not said to be opaque. Baseline comparability unclear - no information. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded to interventions - clear description
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - 1/18 ? (6%) (unclear if other withdrawals) (1 died during the study (so missing), 1 had hip fracture). Group 2 - 1/20? (5%) (unclear about withdrawals) (1 died (but unclear when and not listed by authors as missing); 1 developed symptoms of heart disorder). i.e. similar rate missing in both groups; low rate - less than control event rate
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (unclear if > 1 ulcer analysed) - implies 1 per person
Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Comments: unclear selection bias - allocation concealment: envelopes not said to be opaque; also says block size unknown to investigators and predetermined list; not blinded; unclear re missing data and appropriate tables not available

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Motta 1999

Methods	RCT; participants randomised (only 1 wound per person) Funding: industry funded - educational grant from Acryl Med (manufacturer of hydrogel). Setting: community Duration of follow-up 8 weeks Unit of analysis: person (1 ulcer/person)
Participants	10 participants with pressure ulcers. PU Stage: II (30%) and III (PU classification: not stated) Age: 'average' 60 (range 34-76) years. Duration of ulcer: 'average' 49.8 days. Ulcer size: Group 1 IPD: mean (SD) area 10.2 cm^2 (SD 10.6), median 6.67 cm^2 (range 0.75-24); Group 2: mean(SD) 1.94 cm^2 (SD 1.48), median 2 cm^2 Wound characteristics at baseline: infection not reported; slough not reported; necrosis not reported; exudate low-moderate levels Comment: exudate levels assumed from text
Interventions	Group 1: hydrogel dressing - Flexigel (not in BNF); n = 5. Grouped intervention category: advanced dressing Group 2: hydrocolloid dressing - DuoDERM CGF (not BNF); n = 5. Grouped intervention category: advanced dressing
Outcomes	Primary outcomes: proportion completely healed at 8 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability unclear - baseline difference but unclear of importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	High risk	Other evidence for no blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - 0. Group 2 - 0. i.e. no missing data (no details)
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person)

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Motta 1999 (*Continued*)

Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Comments: circumstantial evidence for lack of blinding (e.g. parameters relating to dressing performance scored at each dressing change, and participants receiving wound care treatment in a home health-care environment); hydrogel group had 4/5 grade III ulcers and hydrocolloid had 2/5; ulcer area: mean 10.2 cm^2 and 1.9 cm^2

Muller 2001

Methods	RCT; participants randomised (> 1 wound per person, all followed) Funding: non-industry funding - cost effectiveness study stated to have an unrestricted grant from Knoll AG (manufacturers of collagenase); original trial states no support from either manufacturer. Setting: hospital inpatients Duration of follow-up probably 16 weeks Unit of analysis: person (all ulcers analysed as a whole)
Participants	24 participants with pressure ulcers. PU Stage: IV (PU classification: not stated) Age: mean (range) 72.4 (65-78) years and 74.6 (68-79) years. Duration of ulcer: not stated. Ulcer size: not stated Wound characteristics at baseline: infection not reported; slough not reported; no wounds necrotic; exudate not reported Comment: debridement to remove all necrotic tissue; 2/24 participants had 2 ulcers i.e. approx 1 ulcer/person. All participants were female. Heel ulcers only
Interventions	Group 1: hydrocolloid dressing - DuoDERM: complete debridement first. New necrosis led to a change to alginate or collagenase (4/12; 33%); n = 12. Grouped intervention category: advanced dressing Group 2: collagenase-containing ointment - Novuxol (not BNF) (Novuxol + paraffin gauze secondary dressing. Complete debridement first. New necrosis led to a change to alginate or collagenase (1/12; 8%)); n = 12. Grouped intervention category: collagenase ointment
Outcomes	Primary outcomes: proportion completely healed at probably 16 weeks; time to complete healing reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Muller 2001 (*Continued*)

Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability adequate - no suggestion of problems. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded to interventions - clear description
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - 1/12 (8%); 4/12 (33%) changed treatment (1 failed to comply with weekly inspection, so dropped; changed treatment for new necrosis). Group 2 - 1/12 (8%) changed treatment (changed treatment for new necrosis) i.e. differential switching data rates; switching rate low - less than control event rate
Selective reporting (reporting bias)	Low risk	Adequate - reported incompletely as 'significant' or P value < 0.05
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (all ulcers analysed as a whole) - 2/24 (8%) participants had 2 ulcers - but participants analysed; ratio ulcers: participants = 13/12 (1.08) in each group
Other bias additional	Low risk	Adequate - no suggestion of problems
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high/very high Comments: not blinded; outcome assessor was 'physician each week', who also oversaw the changing of dressings (so not blinded)

Neill 1989a

Methods	RCT; ulcers randomised (> 1 wound per person, all followed) Funding: industry funded - 3M Company. Setting: hospital and care home Duration of follow-up 8 weeks Unit of analysis: ulcer
Participants	87 participants with pressure ulcers. PU Stage: II (60% and 76%) and III (% of available cases) (PU classification: Shea) Age: not stated. Duration of ulcer: not stated. Ulcer size: mean (SD): 8.3 (9.9), range 0.4-43.9 cm^2 and 7.6 (8.6), range 0.2-35.2 cm^2

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	Wound characteristics at baseline: some wounds infected; some wounds sloughy; some wounds necrotic; exudate not reported Comment: 32/42 (76%) and 32/45 (71%) had infected wounds at baseline. Initially 81% and 62% wounds necrotic but treated before randomised treatments given
Interventions	Group 1: hydrocolloid dressing - Tegasorb (not in BNF): dressing scheduled to be changed every 7 days; if there was necrotic tissue it was debrided; n = 100 ulcers randomised (total), number of participants not stated, but available cases 87 total. Grouped intervention category: advanced dressing Group 2: gauze saline dressing - saline wet-to-damp (dressing scheduled to be changed every 8 h; if there was necrotic tissue it was debrided); n = 100 ulcers randomised (total) , number of participants not stated, but available cases 87 total. Grouped intervention category: basic dressing
Outcomes	Primary outcomes: proportion completely healed at 8 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	High risk	Sequence generation unclear - "randomised". Allocation concealment inadequate - alternation. Baseline comparability inadequate - baseline characteristics different between arms. Rating: high
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who outcome assessor was
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - overall 13/100 (13%) ulcers excluded from the analysis (intercurrent medical events (n = 11) and 2 had protocol violations). Group 2 - overall 13/100 (13%) ulcers excluded from the analysis (intercurrent medical events (n = 11) and 2 had protocol violations) i.e. overall rate only; low rate - less than control event rate
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias unit of analysis	Low risk	Unit of randomisation ulcer and unit of analysis ulcer - 22/87 (25%) participants had 2 ulcers

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Neill 1989a (*Continued*)

Other bias additional	Unclear risk	25% had 2 ulcers - not treated as paired data
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high/very high Reasons: high selection bias; unclear blinding, some unit of analysis issues Comments: some baseline differences in grade of ulcer 60% and 76% grade II and HC size was larger, with more necrotic tissue; if participants had 2 ulcers, then alternation; blinding not stated, overall 13/100 missing data; number of ulcers per group not stated, so available case used; 25% had 2 ulcers - not treated as paired data

Nisi 2005

Methods	RCT; participants randomised (only 1 wound per person) Funding: not stated. Setting: hospital inpatients Duration of follow-up 8 weeks Unit of analysis: person (1 ulcer/person)
Participants	80 participants with pressure ulcers. PU Stage: 2-4 (proportion not stated) (PU classification: NPUAP) Age: mean 45 (range 35-85) years, overall. Duration of ulcer: not stated. Ulcer size: not stated Wound characteristics at baseline: no wounds infected; slough not reported; no wounds necrotic; exudate unclear Comment: debridement to remove infection and necrosis; some exudate but level not stated
Interventions	Group 1: protease-modulating dressing - Promogran: hydropolymer secondary dressing; preparation phase included hydrogel; n = 40. Grouped intervention category: protease modulating dressing Group 2: ineligible intervention - povidone iodine + paraffin-soaked gauze (50% povidone iodine wash then viscose-rayon gauze soaked in white Vaseline + hydropolymer secondary dressing; phase 1 included hydrogel); n = 40. Grouped intervention category: ineligible - basic dressing + antiseptic
Outcomes	Primary outcomes: proportion completely healed at 8 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Nisi 2005 (*Continued*)

Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability unclear - no information. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who outcome assessor was
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - 0 (all appear to be covered). Group 2 - 0 i.e. no missing data (no details)
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person)
Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists
ALL-DOMAIN RISK OF BIAS	Unclear risk	Rating: unclear Reasons: unclear selection bias, unclear blinding Comments: times of healing given, so potential for time to event, but not reported

Nussbaum 1994

Methods	RCT; participants randomised (> 1 wound per person, all followed) Funding: non-industry funding - study was funded by the John Labatt Seed Fund Award. Setting: hospital with spinal chord injury Duration of follow-up could choose (IPD) e.g. Results given at 8 (reviewer choice) weeks (also reported at various times from IPD graph weeks). Unit of analysis: ulcer
Participants	20 participants with pressure ulcers. PU Stage: not stated (PU classification: not stated) Age: mean (range): 36 (15-46) years; 42.2 (26-59) years; 42 (30-61) years. Duration of ulcer: > 6 weeks 67%, 100%, 100%, < 1 week 33%, 0%, 0%. Ulcer size: not stated Wound characteristics at baseline: infection not reported; slough not reported; necrosis not reported; exudate not reported Comment: people with spinal chord injury (younger people)
Interventions	Group 1: basic wound contact dressing - paraffin gauze (Jelonet); n = 9. Grouped intervention category: basic dressing Group 2: ineligible intervention - ultrasound + UV (US/UV + Jelonet); n = 5. Grouped intervention category: ineligible - ultrasound + UV

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	Group 3: laser - laser + Jelonet (laser + Jelonet; n = 6). Grouped intervention category: ineligible - laser	
Outcomes	Primary outcomes: proportion completely healed at could choose (IPD) e.g. Results given at 8 (reviewer choice) weeks; time to complete healing reported (Kaplan Meier plot included)	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability unclear - baseline difference but unclear of importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded to interventions (clear description)
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data: Group 1 - 3/9 (33%) (2 elected to have wounds surgically repaired and withdrew; 1 transferred to acute hospital). Group 2 - 0. Group 3 - 1/6 (17%) (1 transferred to acute hospital). i.e. differential missing data rates; high differential rate - likely to change effect estimate
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	High risk	Unit of randomisation person and unit of analysis ulcer - IPD reported per ulcer (but only 2/16 (12.5%) participants had 2 ulcers); ≤ 1.2 ulcer:person = 9/9, 6/5 and 7/6
Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists
ALL-DOMAIN RISK OF BIAS	High risk	Rating: very high Reasons: unclear selection bias, attrition bias, unit of analysis issues Comments: PU grade not reported. Baseline characteristics: laser group had 2/6

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Nussbaum 1994 (*Continued*)

		deeper ulcers (6-10 mm), other ulcers all shallower; control group had 2/6 acute ulcers
ALL-DOMAIN RISK OF BIAS 2	High risk	

Oleske 1986

Methods	RCT; nursing module (cluster)s randomised (> 1 wound per person, all followed) Funding: non-industry funding - supported by Rush-Presbyterian-St Lukes Medical Center and Chicago Community Trust. Setting: hospital inpatients Duration of follow-up 1.5 (12 days) weeks Unit of analysis: ulcer
Participants	15 participants with pressure ulcers. PU Stage: I (22% and 50%) and II, results separately for II. Inclusion criteria state all should have break in skin (PU classification: Enis and Sarmiento) Age: overall mean (SD): 69 (6), range 52-93 years. Duration of ulcer: not stated. Ulcer size: mean 3.5 (SD 1.2), range 1.7-5.0 cm^2; mean 7.9 (SD 7.3), range 1.2-22.7cm^2 Wound characteristics at baseline: no wounds infected; slough not reported; necrosis not reported; exudate not reported Comment: nursing modules on 4 participating units were randomised (no info on cluster size)
Interventions	Group 1: foam dressing - self adhesive PU dressing; n = 7 (5 grade II). Grouped intervention category: advanced dressing Group 2: gauze saline dressing - other (normal saline dressing); n = 8 (5 grade II). Grouped intervention category: basic dressing
Outcomes	Primary outcomes: proportion completely healed at 1.5 (12 days) weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	High risk	Sequence generation unclear - other. Allocation concealment unclear - no information on allocation concealment. Baseline comparability inadequate - baseline characteristics different between arms. Rating: high
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded to interventions (clear description)

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Oleske 1986 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data: Group 1 - 1/16 dropped from analysis but group unclear (1 unanticipated transfer to nursing home). Group 2 - 1/16 dropped from analysis but group unclear (1 unanticipated transfer to nursing home). i.e. overall rate only; high rate - comparable with control event rate
Selective reporting (reporting bias)	Low risk	Inadequate - reported incompletely (e.g. P value > 0.05)
Other bias unit of analysis	High risk	Unit of randomisation nursing module (cluster) and unit of analysis ulcer - 4/15 (27%) participants had 2 ulcers each (2 participants had different treatments for their 2 ulcers); < 1.3 ulcer:person ratio = 9/7 and 10/8
Other bias additional	Unclear risk	Results not adjusted for clustering. Unclear if grades I and II are subgroups in this classification
ALL-DOMAIN RISK OF BIAS	High risk	Rating: very high Reasons: inadequate selection bias (baseline characteristics), attrition bias, unit of analysis issues Comments: results not adjusted for clustering. Unclear if grades I and II are subgroups in this classification. Differences at baseline in proportion grade II (7/9 and 5/10 ulcers) and size of PU (mean 3.5 and 7.9 cm^2)
ALL-DOMAIN RISK OF BIAS 2	High risk	

Parish 1979

Methods	RCT; participants randomised (> 1 wound per person, all followed) Funding: not stated. Setting: care home Duration of follow-up 4 weeks Unit of analysis: results for both people and ulcers
Participants	17 participants with pressure ulcers. PU Stage: not stated (PU classification: not stated) Age: range 28-59 years, 29-57 years and 32-70 years. Duration of ulcer: not stated. Ulcer size: collagenase: 10.24 cm^2; dextranomer: 20.25 cm^2 and sugar + egg white 5.76 cm^2 Wound characteristics at baseline: infection not reported; slough not reported; necrosis not reported; exudate not reported Comment: assumed that all ulcers in a participant had to heal before a participant was

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Parish 1979 (*Continued*)

	healed
Interventions	Group 1: collagenase-containing ointment - collaganese: ointment applied with wooden applicator and covered with a dry dressing; n = 5. Grouped intervention category: collagenase ointment Group 2: dextranomer - dextranomer (dextranomer beads poured into the ulcer and covered with dry dressing); n = 7. Grouped intervention category: dextranomer Group 3: sugar + egg white - sugar + egg white applied to the area 4 times/d (sugar + egg white applied to the area 4 times/d; n = 5. Grouped intervention category: sugar + egg white
Outcomes	Primary outcomes: proportion completely healed at 4 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability unclear - baseline difference but unclear of importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who outcome assessor was
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - none. Group 2 - none. Group 3 - none i.e. no missing data (no details)
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Unclear risk	Unit of randomisation person and unit of analysis results for both people and ulcers - we used the results for the participants, but unclear what was meant by healing => unclear risk of bias
Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists
ALL-DOMAIN RISK OF BIAS	Unclear risk	Rating: unclear Reasons: unclear selection bias, unclear unit of analysis issues

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Parish 1979 (*Continued*)

		Comments: says participants and investigators were blinded and nurses looked after participants => implies outcome assessors were investigators. Baseline differences said to be not statistically significant in area of ulcer

Payne 2004

Methods	RCT; participants randomised (> 1 wound per person, largest selected) Funding: industry funded - sponsored by Smith & Nephew Inc, makers of Dermagraft. Setting: community outpatients Duration of follow-up 26 weeks (also reported at 12 weeks) Unit of analysis: person (1 ulcer/person)
Participants	34 participants with pressure ulcers. PU Stage: III (PU classification: not stated) Age: mean (SD): 69.1 (18.5) years and 69.4 (16.5) years. Duration of ulcer: mean (range) : 29.2 (4.0-104.0) weeks and 30.2 (6-95.3) weeks. Ulcer size: mean (range): 21.1 (3.5-1.2) and 19.8 (5.2-60.7) cm^2 Wound characteristics at baseline: no wounds infected; slough not reported; no wounds necrotic; exudate not reported Comment: after debridement, no infection or necrotic tissue
Interventions	Group 1: combination intervention - other: non-adherent + saline gauze + foam (Allevyn) dressing; n = 16. Grouped intervention category: mixed advanced and basic dressings Group 2: ineligible intervention - graft + conventional dressing (Dermagraft + intervention 1 dressings); n = 18. Grouped intervention category: ineligible - graft + basic and advanced
Outcomes	Primary outcomes: proportion completely healed at 26 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation adequate - computer-generated. Allocation concealment unclear - "sealed envelopes". Baseline comparability adequate - no suggestion of problems. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who outcome assessor was

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Payne 2004 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data: Group 1 - 11/16 (69%) (1 death due to unrelated cause, other withdrawals related to morbidity). Group 2 - 13/18 (72%) (3 deaths due to unrelated causes, other withdrawals related to morbidity) i.e. similar rate missing in both groups; high rate - more than control event rate
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person) - largest ulcer selected
Other bias additional	Low risk	Adequate - no suggestion of problems
ALL-DOMAIN RISK OF BIAS	High risk	Rating: very high Reasons: unclear selection bias, high attrition bias Comments: high levels of missing data (70%). Says it was single blind, so this could be the outcome assessor
ALL-DOMAIN RISK OF BIAS 2	High risk	

Payne 2009

Methods	RCT; participants randomised (> 1 wound per person, largest selected) Funding: industry funded - funded by Smith & Nephew (manufacturers of PU foam). Setting: care home and hospital and community Duration of follow-up 4 weeks Unit of analysis: person (1 ulcer/person)
Participants	36 participants with pressure ulcers. PU Stage: 2 (PU classification: NPUAP) Age: median 74.0 years and 71.5 years; mean (SD): 72.5 (14.3) years and 73.3 (12.4) years. Duration of ulcer: median 3.5 weeks and 2.0 weeks. Ulcer size: median 1.8 cm^2 and 1.4 cm^2 Wound characteristics at baseline: no wounds infected; slough not reported; necrosis not reported; exudate low-moderate levels Comment: multicentre (2 hospital inpatient wards, 1 hospital outpatients, 1 community, 1 care home)
Interventions	Group 1: foam dressing - Allevyn Thin: no secondary dressing; n = 20. Grouped intervention category: advanced dressing Group 2: gauze saline dressing - saline soaked (secondary dressing as required); n = 16. Grouped intervention category: basic dressing

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Outcomes	Primary outcomes: proportion completely healed at 4 weeks; time to complete healing reported	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation unclear - other. Allocation concealment unclear - no information on allocation concealment. Baseline comparability unclear - baseline difference but unclear of importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear - vague
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data: Group 1 - 6/20 (30%) (3 died, 1 developed wound infection, 1 developed an abscess unrelated to the study wound, 1 ineligible for other reasons). Group 2 - 3/16 (19%) (2 died, 1 asked to be discharged) i.e. differential missing data rates; high differential rate - likely to change effect estimate
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person) - largest ulcer selected
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Reasons: unclear selection bias, attrition bias Comments: "randomisation schedule"; may be a difference in duration of wound at baseline (3.5 and 2.0 weeks)

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Piatkowski 2012

Methods	RCT; participants randomised (> 1 wound per person, largest selected) Funding: industry funded - educational grant from Lohmann & Rauscher GmbH (manufacturer of both interventions). Author employee. Setting: hospital inpatients Duration of follow-up 3 weeks (also reported at 2 weeks) Unit of analysis: person (1 ulcer/person)
Participants	10 participants with pressure ulcers. PU Stage: 3 (PU classification: EPUAP) Age: mean (range): 67.0 (59-71) years and 63.0 (52-68) years. Duration of ulcer: at least 4 weeks . Ulcer size: median (range) diameter: 11.4 (5.2-19.6) cm and 9.3 (4.3-21.0) cm. Wound characteristics at baseline: no wounds infected; no wounds sloughy; no wounds necrotic; exudate not reported
Interventions	Group 1: protease-modulating dressing - Suprasorb C: with Suprasorb P as secondary dressing; n = 5. Grouped intervention category: protease-modulating dressing Group 2: foam dressing - Suprasorb P (not in BNF); n = 5. Grouped intervention category: advanced dressing
Outcomes	Primary outcomes: proportion completely healed at 3 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation adequate - computer-generated. Allocation concealment unclear - no information on allocation concealment. Baseline comparability unclear - baseline difference but unclear of importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who outcome assessor was
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - 0. Group 2 - 0 i.e. no missing data (clearly stated)
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person) - largest ulcer selected
Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists

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Piatkowski 2012 (*Continued*)

ALL-DOMAIN RISK OF BIAS	Unclear risk	Rating: unclear Reasons: unclear selection bias Comments: differences at baseline probably unimportant - slightly bigger diameter for the collagen group

Price 2000

Methods	RCT; participants randomised (only 1 wound per person) Funding: not stated - clear statement of no funding. Setting: hospital and community Duration of follow-up 6 weeks Unit of analysis: person (1 ulcer/person)
Participants	58 participants with pressure ulcers. PU Stage: III (92% and 80%) and IV (PU classification: not stated) Age: mean (SD): 69.76 (16.2) years and 75.72 (16.8) years. Duration of ulcer: not stated. Ulcer size: mean (SD): 9.8 (12.0) cm^2 and 7.3 (7.0) cm^2, median 4.18 cm^2 and 5.10 cm^2 Wound characteristics at baseline: no wounds infected; slough not reported; necrosis not reported; exudate not reported Comment: range of settings from hospitals to their own homes. Same number of ulcers as participants in tables 1 and 2
Interventions	Group 1: alginate dressing - type not stated (standard care); n = 26 (missing data added) . Grouped intervention category: advanced dressing Group 2: ineligible intervention - radiant heat; n = 32 (missing data added). Grouped intervention category: ineligible - radiant heat
Outcomes	Primary outcomes: proportion completely healed at 6 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation adequate - computer-generated. Allocation concealment adequate - serially-numbered opaque sealed envelopes. Baseline comparability unclear - baseline difference but unclear of importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded to interventions (clear description)

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Price 2000 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data: Group 1 - 1/26 (4%); Group 2 - 7/32 (22%). Reasons for 'missingness' across both groups: 3 died, 3 experienced general deterioration, 1 experienced device-related deterioration and 1 asked to withdraw: i.e. differential missing data rates; high differential rate - likely to change effect estimate
Selective reporting (reporting bias)	Low risk	Adequate - outcome measured but not necessarily analysed for a good reason
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person)
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Reasons: unclear selection bias (baseline differences); attrition bias Comments: time to event recorded for 75%, 50%, 25% healed but not 100% - probably available, but few events. Differences at baseline in diabetes, urinary incontinence, neurological disorders, BMI (direction not stated), proportion of stage III (92% and 80%)

Ramos-Torrecillas 2015

Methods	RCT; participants randomised (> 1 wound per person, all followed) Funding: non-industry funding. Setting: hospital inpatients Duration of follow-up 5 (36 days) weeks Unit of analysis: ulcer
Participants	124 ulcers, participants with pressure ulcers. PU Stage: 2 and 3 (control: 96%, group A: 85.3%, group B: 100% and group C: 60%) (PU classification: EPUAP) Age: overall mean (SD): 82.5 (4.7) years, range 64-90 years. Duration of ulcer: mean (SD): control 6.2 (1.5) months; group A 4.8 (1.1) months, group B 5.0 (1.6) months and group C 4 (1.1) months. Ulcer size: not stated Wound characteristics at baseline: no wounds infected; slough not reported; no wounds necrotic; exudate not reported Comment: one long-stay hospital and 3 'geriatric centres' in Granada, Spain
Interventions	Group 1: hydrogel dressing - Intrasite Gel: saline cleansing, hydrogel and PU (secondary) dressing; n = 25 ulcers. Grouped intervention category: advanced dressing Group 2: ineligible intervention - growth factor gel (combining 2 GF groups (1 and 2 doses) + hydrogel; % estimated from graph (8% and 32% respectively); n = 59 ulcers. Grouped intervention category: ineligible - growth factor gel Group 3: growth factor gel + hyaluronic acid - platelet GF + HA + hydrogel (platelet

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	GF + HA + hydrogel; n = 40 ulcers;. Grouped intervention category: ineligible - growth factor gel + HA	
Outcomes	Primary outcomes: proportion completely healed at 5 (36 days) weeks; time to complete healing not reported	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation adequate - computer-generated. Allocation concealment unclear - no information on allocation concealment. Baseline comparability unclear - baseline difference but unclear of importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded ('open label') and no evidence that outcome assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data: Group 1 - 15/115 (13%) overall (loss to follow-up). Group 2 - 15/115 (13%) overall (loss to follow-up). Group 3 - 15/115 (13%) overall (loss to follow-up). i.e. overall rate only; high rate - comparable with control event rate
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias unit of analysis	High risk	Unit of randomisation person and unit of analysis ulcer - multiple PUs per person treated with the same interventions. 140 ulcers in 100 persons across both groups. Unit of analysis issue
Other bias additional	Unclear risk	Data extracted from graph
ALL-DOMAIN RISK OF BIAS	High risk	Rating: very high Reasons: unclear selection bias, not blinded, unit of analysis issues, data extracted from graph Comments: some baseline differences (e.g. group C had more Grade II ulcers)

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ALL-DOMAIN RISK OF BIAS 2	High risk	

Rees 1999

Methods	RCT; participants randomised (> 1 wound per person, likely slowest healing wound selected) Funding: industry funded - funded by Johnson & Johnson Inc. Setting: unclear Duration of follow-up 16 weeks Unit of analysis: person (1 ulcer/person)
Participants	124 participants with pressure ulcers. PU Stage: 3 and 4 (PU classification: NPUAP) Age: mean (SD) group 1: 50 (13.6) years; group 2: 48 (13.1) years; group 3: 49 (12.5) years and group 4: 51 (18.3) years. Duration of ulcer: median (IQR) Group 1: 30 (43) weeks; group 2: 22 (32) weeks; group 3: 33 (40) weeks and group 4: 22 (52) weeks. Ulcer size: ulcer volume median (IQR): group 1: 19.6 (21.9) cm^2; group 2: 16.6 (15.1) cm^2; group 3: 17.2 (19.7) cm^2 and group 4: 17.6 (33.8) cm^2 Wound characteristics at baseline: no wounds infected; no wounds sloughy; no wounds necrotic; exudate not reported Comment: probably a community-based study; ulcer selected that was likely to be the slowest healing; debridement to remove necrotic material and fibrin (slough)
Interventions	Group 1: hydrogel dressing - carboxymethylcellulose vehicle gel (as placebo) + saline gauze; n = 31. Grouped intervention category: advanced dressing Group 2: ineligible intervention - 100 µg / g of growth factor in sodium carboxymethylcellulose vehicle gel + saline gauze Group 3: ineligible intervention - 300 µg / g of growth factor in vehicle gel + saline gauze Group 4: ineligible intervention - 100 µg / g of growth factor in vehicle gel, twice daily + saline gauze Results available separately - numbers calculated from % - but results from groups 2-4 were combined (n = 93). Grouped intervention category: ineligible - growth factor gel
Outcomes	Primary outcomes: proportion completely healed at 16 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability unclear - baseline difference but unclear of importance. Rating: unclear

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Rees 1999 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who outcome assessor was
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data: Group 1 - unclear but may be 0. Group 2 - unclear but may be 1 (1 participant with 100 microg bid discontinued) . i.e. similar rate missing in both groups; unclear rate
Selective reporting (reporting bias)	Unclear risk	Unclear reporting
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person) - ulcer selected that was likely to be the slowest healing
Other bias additional	Unclear risk	Results calculated from percentages
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Reasons: unclear selection bias; results calculated from percentages Comments: number of missing data unclear, assumed 0. Slight differences in duration of ulcer

Romanelli 2001

Methods	RCT (abstract); participants randomised (unclear if > 1 wound per person) Funding: not stated. Setting: not stated Duration of follow-up 8 weeks Unit of analysis: unclear
Participants	12 participants with pressure ulcers. PU Stage: 2 and 3 (proportions not stated) (PU classification: EPUAP) Age: not stated. Duration of ulcer: not stated. Ulcer size: not stated Wound characteristics at baseline: infection not reported; slough not reported; necrosis not reported; exudate not reported
Interventions	Group 1: hydrogel dressing - DuoDERM Hydrogel (not in BNF): with OpSite Flexigrid secondary dressing; n = 6. Grouped intervention category: advanced dressing Group 2: topical - tripeptide-copper gel + OpSite; n = 6. Grouped intervention category: tripeptide-copper
Outcomes	Primary outcomes: proportion completely healed at 8 weeks; time to complete healing not reported

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Romanelli 2001 (*Continued*)

Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability unclear - no information. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who outcome assessor was
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data: Group 1 - 0 (implied). Group 2 - 0 (implied) i.e. unclear if data missing; unclear rate
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Unclear risk	Unit of randomisation person and unit of analysis unclear - 1 ulcer per person implied
Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists
ALL-DOMAIN RISK OF BIAS	Unclear risk	Rating: unclear Reasons: unclear selection bias, unclear attrition, unclear blinding (abstract); preliminary results Comments: abstract - few details

Sebern 1986

Methods	RCT; ulcers randomised (> 1 wound per person, all followed) Funding: mixed industry and non-industry - part supported by Research Grant Award to the University Nursing dept from Sigma Theta Tau and part funded by 3M Medical Division. Setting: home care population Duration of follow-up 8 weeks Unit of analysis: ulcer
Participants	48 participants with pressure ulcers. PU Stage: II and III (41% and 70% grade III) (PU classification: Shea). All participants had chronic illness (focal cerebral disorders, spinal chord disorders, neurological disorders, cardiac disease, diabetes) Age - mean (SD): group 1: 76.3 (SD 17.6) years; group 2: 72.4 (SD 17.8) years. Duration of ulcer: not stated. Ulcer size: group 1: grade II median (range) 1.9 (0.1-32.9) cm^2;

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	grade III 6.1 (0.3-33.0) cm². Group 2: grade II 3.4 (0.6-23.9) cm², grade III 4.5 (0.5-47.1) cm²
Interventions	Group 1: vapour-permeable dressing: polyurethane adhesive dressing; vapour-permeable; n = unclear number randomised, but overall 48 participants in analysed population. Grouped intervention category: advanced dressing Group 2: gauze saline dressing - wet-to-dry; n = unclear number randomised, but overall 48 participants in analysed population. Grouped intervention category: basic dressing
Outcomes	Primary outcomes: complete healing not reported; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	High risk	Sequence generation unclear - "randomised". Allocation concealment unclear - other. Baseline comparability inadequate - baseline characteristics different between arms. Rating: high
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear - vague
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data: Group 1 - 13/50 (26%) ulcers missing (number participants missing not reported) (Overall, the "Most frequent causes of dropout were: death, hospitalisation, and inability to comply with protocol for pressure relief" - no more information). Group 2 - 10/50 (20%) ulcers missing (number participants missing not reported) (Overall, the "Most frequent causes of dropout were: death, hospitalisation, and inability to comply with protocol for pressure relief" - no more information) i.e. similar rate missing in both groups; unclear rate
Selective reporting (reporting bias)	High risk	Comment: inadequate - reported incompletely (results given only for grade II ulcers and "not significantly different" for grade III ulcers)

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Sebern 1986 (*Continued*)

Other bias unit of analysis	Low risk	Unit of randomisation ulcer and unit of analysis ulcer; > 6 people had 2 or more ulcers; 6 people had 2 ulcers assigned to different treatments; 77/48 (1.6) ulcers: people in available case analysis
Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists
ALL-DOMAIN RISK OF BIAS	High risk	Rating: very high Reasons: selection bias (baseline differences), unit of analysis issues; selective outcome reporting bias Comments: sequential list of 100 random numbers was used to assign the treatment: unclear where list kept. Outcome assessor was project director who made weekly visits to assess the wound and review the protocol for wound care - implies not blinded; baseline differences: proportion of stage II different (59% vs 30%) and size of ulcer differences but numbers only reported for stage II
ALL-DOMAIN RISK OF BIAS 2	High risk	

Seeley 1999

Methods	RCT; participants randomised (> 1 wound per person, largest selected) Funding: not stated. Setting: care home and outpatients Duration of follow-up 8 weeks Unit of analysis: person (selected ulcer)
Participants	40 participants with pressure ulcers. PU Stage: II (11 and 15%) and III (PU classification: AHCPR) Age: mean (SD): 76.7 (19.5) years and 75.7 (18.6) years. Duration of ulcer: median: 10 weeks and 9 weeks. Ulcer size: mean(SD): 4.61 (5.56) cm^2 and 6.84 (8.19) cm^2 Wound characteristics at baseline: no wounds infected; some wounds sloughy; necrosis not reported; exudate not reported Comment: slough: 4/19 (21%) and 5/20 (25%)
Interventions	Group 1: hydrocolloid dressing - DuoDERM CGF (not BNF); n = 20. Grouped intervention category: advanced dressing Group 2: foam dressing - Allevyn Adhesive; n = 20. Grouped intervention category: advanced dressing

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Seeley 1999 (*Continued*)

Outcomes	Primary outcomes: proportion completely healed at 8 weeks; time to complete healing not reported	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation adequate - computer-generated. Allocation concealment unclear - no information on allocation concealment. Baseline comparability adequate - no suggestion of problems. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	High risk	Other evidence for no blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data: Group 1 - 6/20 (30%) (2 adverse effects (both due to dressing), 1 death, 2 increased ulcer size, 1 unable to tolerate dressing). Group 2 - 8/20 (40%) (1 participant request, 3 loss to follow-up, 2 adverse effects (1 related to dressing), 1 death, 1 infection). i.e. similar rate missing in both groups; high rate - comparable with control event rate
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (selected ulcer) - largest ulcer selected
Other bias additional	Low risk	Adequate - no suggestion of problems
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Reasons: unclear selection bias, not blinded, some attrition bias Comments: stratified randomisation (by size); unlikely to be blinded - assessors were clinical investigators who changed dressings. Attrition bias borderline high (because of reasons for missingness)

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Serena 2010

Methods	RCT (abstract); not stated randomised (unclear if > 1 wound per person) Funding: not stated. Setting: not stated Duration of follow-up 12 weeks Unit of analysis: person (unclear if > 1 ulcer analysed)
Participants	74 participants with pressure ulcers. PU Stage: 3 (PU classification: NPUAP) Age: not stated. Duration of ulcer: mean (SD): 71 (59) weeks and 84 (139) weeks. Ulcer size: mean (SD): 8.1 (76.1) cm^2 and 9.8 (12.5) cm^2 Wound characteristics at baseline: infection not reported; slough not reported; necrosis not reported; exudate not reported Comment: debridement throughout trial
Interventions	Group 1: combination intervention - "primary nonadherent silicone dressing and foam dressing"; n = 44. Grouped intervention category: advanced dressing Group 2: ineligible intervention - skin substitute (Apligraf (bilayered living cell-based treatment)); n = 30. Grouped intervention category: ineligible - skin substitute
Outcomes	Primary outcomes: proportion completely healed at 12 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability unclear - baseline difference but unclear of importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who outcome assessor was
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data: Group 1 - none stated. Group 2 - none stated i.e. unclear if data missing; unclear rate
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Unclear risk	Unit of randomisation not stated and unit of analysis person (unclear if > 1 ulcer analysed) - implies 1 per person
Other bias additional	Unclear risk	Unclear if the trial was stopped early because of the results

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ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Reasons: unclear selection bias, possibly terminated early, unclear blinding and attrition - abstract. Comments: conclusions say "although this study was terminated early… trials of longer duration are required". It is unclear if this means the trial was stopped early because of the results. Baseline difference in ulcer size and duration (larger for the bilayer)

Sipponen 2008

Methods	RCT; participants randomised (> 1 wound per person, all followed) Funding: industry funded - study authors have now founded a company to manufacturer intervention 1. Setting: hospital inpatients Duration of follow-up 26 weeks (6 months) Unit of analysis: results for both people and ulcers
Participants	37 participants with pressure ulcers. PU Stage: 2 (39% and 45%), 3 (50% and 45%) and 4 (11% and 9%) (PU classification: EPUAP) Age: per protocol: mean (SD) 80 (10) years and 74 (8) years; range 58-98 years and 60-88 years. Duration of ulcer: not stated. Ulcer size: width mean(SD): 3.2 (2.4) cm and 4.2 (2.8) cm Wound characteristics at baseline: some wounds infected; slough not reported; necrosis not reported; exudate not reported Comment: 27/21 and 18/16 ulcers per person (18 (86%) and 14 (88%) participants had only 1 ulcer); number of ulcers infected not stated
Interventions	Group 1: resin salve - resin salve: Norway spruce salve mixed with butter between gauze; n = 21. Grouped intervention category: antimicrobial Group 2: hydrocolloid or hydrocolloid silver dressing - Aquacel + Aquacel Ag (Aquacel Ag if infected wounds (NS proportion)); n = 16). Grouped intervention category: advanced - antimicrobial
Outcomes	Primary outcomes: proportion completely healed at 26 (6 months) weeks; time to complete healing reported (Kaplan Meier plot included)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation unclear - other. Allocation concealment unclear - other. Baseline comparability unclear - baseline dif-

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		ference but unclear of importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear - vague
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data: Group 1 - 8/21 (38%) (3 deaths, 2 admissions to operative treatment, 1 allergic skin reaction, 1 misdiagnosis, 1 participant-based refusal without any specific cause). Group 2 - 7/16 (44%) (4 deaths, 2 participant-based refusal without any specific cause, 1 participant-based refusal because of randomisation to control group) i.e. similar rate missing in both groups; high rate - more than control event rate
Selective reporting (reporting bias)	High risk	Inadequate - other. Time to event outcome excluded dropouts
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis results for both people and ulcers - 3/21 (14%) and 2/16 (12.5%) participants had > 1 ulcer; study analysis seemed to require that all ulcers in a person should heal; ulcers:person ratio = 27/21 (1.3) and 18/16 (1.1)
Other bias additional	Low risk	Adequate - no suggestion of problems
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Reasons: unclear selection bias, attrition bias, time to event outcome excluded drop outs, so risk of outcome reporting bias for that outcome only Comments: randomisation in permuted blocks of 4. Randomisation list in closed envelopes. Independent physicians in each hospital assessed wound - this is probably enough for blinding. Time to event outcome excluded dropouts

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Sopata 2002

Methods	RCT; participants randomised (> 1 wound per person, all followed) Funding: non-industry funding - declaration of interest: none. Setting: hospital inpatients Duration of follow-up 8 weeks Unit of analysis: ulcer
Participants	34 participants with pressure ulcers. PU Stage: II (non-blanching erythema and superficial damage - may be closer to NPUAP I; 33% and 30%) and III (PU classification: Torrance) Age: mean (SD): 58.7 (14.1) years and 58.5 (16.9) years. Range overall: 24-88 years. Duration of ulcer: mean (SD): 2.45 (1.60) weeks and 2.46 (0.24) weeks. Ulcer size: mean (SD): 8.28 (13.90) cm^2 and 11.04 (11.65) cm^2. Range: 0.41-98.78 and 0.68-51.05 cm^2 Wound characteristics at baseline: some wounds infected; slough not reported; no wounds necrotic; exudate not reported Comment: participants were people with advanced cancer in palliative care department; 38/34 ulcers per person; 9/17 (53%) and 10/17 (59%) participants had infected wounds
Interventions	Group 1: hydrogel dressing - Aquagel (not in BNF); n = 17. Grouped intervention category: advanced dressing Group 2: foam dressing - Lyofoam; n = 17. Grouped intervention category: advanced dressing
Outcomes	Primary outcomes: proportion completely healed at 8 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation adequate - computer-generated. Allocation concealment unclear - no information on allocation concealment. Baseline comparability unclear - baseline difference but unclear of importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who outcome assessor was
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - 3/17 (18%) (3 died). Group 2 - 2/17 (12%) (2 died) i.e. similar rate missing in both groups; low rate - less than control event rate
Selective reporting (reporting bias)	Low risk	Adequate - full results reported

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Sopata 2002 (*Continued*)

Other bias unit of analysis	High risk	Unit of randomisation person and unit of analysis ulcer - ulcer:person ratio = 20/17 (1.2) and 18/17 (1.1)
Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Comments: unclear selection bias, unclear subgroup - grade II Torrance may be closer to NPUAP stage I, could be subgroup issue. Slightly larger wounds for foam. Slight unit of analysis issue

Thomas 1997a

Methods	RCT; participants randomised (only 1 wound per person) Funding: not stated. Setting: community Duration of follow-up 6 weeks Unit of analysis: person (1 ulcer/person)
Participants	99 participants stratified by wound. PU Stage: II and III (61% and 54% grade II) (PU classification: Stirling) Age: 78.6 (SD 14.3) years, 80.1 (SD 10.2) years. Duration of ulcer: 9 and 8 at < 1 month; 18 and 21 at 1-3 months, 21 and 20 at > 3 months. Ulcer size: not stated Wound characteristics at baseline: no wounds infected; slough not reported; necrosis not reported; exudate not reported Comment: text says "for each wound type, patients were allocated to 2 treatment groups" => implied stratification
Interventions	Group 1: hydrocolloid dressing - Granuflex: cleansed using 0.9% saline as necessary; n = 49. Grouped intervention category: advanced dressing Group 2: foam dressing - Tielle (cleansed using 0.9% saline as necessary); n = 50. Grouped intervention category: advanced dressing
Outcomes	Primary outcomes: proportion completely healed at 6 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - "sealed envelopes". Baseline comparabil-

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Thomas 1997a (*Continued*)

		ity unclear - baseline difference but unclear of importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded ('open label') and no evidence that outcome assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - 1/49 (2%) and some may have died (reason not stated; overall 5 participants died). Group 2 - 2/50 (4%) and some may have died (reason not stated; overall 5 participants died) i.e. similar rate missing in both groups; low rate - less than control event rate
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person)
Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Reasons: unclear selection bias, not blinded Comments: difference in proportion of grade II ulcers (61% and 54%)

Thomas 1998

Methods	RCT; participants randomised (> 1 wound per person, other selection of wound) Funding: industry funded - grant from Carrington labs Inc (hydrogel manufacturers). Setting: care home and community Duration of follow-up 10 weeks Unit of analysis: person (1 ulcer/person)
Participants	41 participants with pressure ulcers. PU Stage: II (50% and 43%), III (38% and 50%) and IV (13% and 7%) (PU classification: not stated) Age: mean (SD): 79 (9) years and 72 (13) years. Duration of ulcer: not stated. Ulcer size: mean (SD): 8.9 (9.3) cm^2 and 5.9 (6.0) cm^2 Wound characteristics at baseline: no wounds infected; slough not reported; necrosis not reported; exudate not reported
Interventions	Group 1: hydrogel dressing - Carrosyn Gel Wound Dressing (contains Acemannan hydrogel - from aloe vera); n = 22. Grouped intervention category: advanced dressing Group 2: gauze saline dressing - saline moist; n = 19. Grouped intervention category: basic dressing

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Thomas 1998 (*Continued*)

Outcomes	Primary outcomes: proportion completely healed at 10 weeks; time to complete healing not reported	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability unclear - baseline difference but unclear of importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear - vague
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - 6/22 (27%) (4 died (not attributed to treatment), 1 showed deterioration and was terminated from study, 1 participant hospitalised). Group 2 - 5/19 (26%) (2 died (not attributed to treatment), 1 showed deterioration and was terminated from study, 1 participant hospitalised, 1 protocol violation) i.e. similar rate missing in both groups; low rate - less than control event rate
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person) - 1 per person; NS how selected
Other bias additional	Low risk	Adequate - no suggestion of problems
ALL-DOMAIN RISK OF BIAS	Unclear risk	Rating: unclear Reasons: unclear selection bias; unclear blinding Comments: baseline difference in ulcer size (8.9 cm^2 and 5.9 cm^2, but not significant) ; unclear if outcome assessors were blinded - "study nurses who evaluated weekly"

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Thomas 2005

Methods	RCT; participants randomised (only 1 wound per person) Funding: not stated. Setting: care home and outpatients Duration of follow-up 12 weeks Unit of analysis: person (1 ulcer/person)
Participants	41 participants with pressure ulcers. PU Stage: III (55% and 52%) or IV (PU classification: not stated) Age: mean (SD): 77.0 (11.5) years and 74.1 (13.8) years. Duration of ulcer: not stated. Ulcer size: mean (SD): 12.1 (18.2) cm^2 and 11.0 (9.5) cm^2 Wound characteristics at baseline: no wounds infected; slough not reported; necrosis not reported; exudate not reported Comment: one ulcer evaluated per person
Interventions	Group 1: hydrocolloid with or without alginate - DuoDERM with or without Sorbasan: calcium alginate filler given as needed if the wound was highly exudative. Dressing changed every 7 d; n = 20. Grouped intervention category: advanced dressing Group 2: ineligible intervention - radiant heat (dressing change every 7 d); n = 21. Grouped intervention category: ineligible - radiant heat
Outcomes	Primary outcomes: proportion completely healed at 12 weeks; time to complete healing reported (Kaplan Meier plot included)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation adequate - computer-generated. Allocation concealment unclear - "opaque envelopes". Baseline comparability adequate - no suggestion of problems. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded to interventions - deduced from interventions
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data: Group 1 - 4/20 (20%) (1 died, 3 hospitalised). Group 2 - 6/21 (29%) (2 died, 2 hospitalised, 2 dropped out for non-study-related reasons) i.e. similar rate missing in both groups; high rate - comparable with control event rate
Selective reporting (reporting bias)	Low risk	Adequate - full results reported

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Thomas 2005 (*Continued*)

Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person) - unclear if selected
Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists
ALL-DOMAIN RISK OF BIAS	High risk	Rating: very high Reasons: unclear selection bias, not blinded, attrition bias Comments: outcome assessed at each visit after removing dressing - not blinded
ALL-DOMAIN RISK OF BIAS 2	High risk	

Van De Looverbosch 2004

Methods	RCT (abstract); participants randomised (unclear if > 1 wound per person) Funding: industry funded - Molnlycke Health Care sponsored the study. Setting: not stated Duration of follow-up 8 weeks Unit of analysis: person (unclear if > 1 ulcer analysed)
Participants	11 participants with pressure ulcers. PU Stage: II only (no subcutaneous involvement) (PU classification: not stated) Age: mean 87.7 years and 88.2 years; 75 years and over. Duration of ulcer: more than 1 month. Ulcer size: not stated Wound characteristics at baseline: infection not reported; slough not reported; necrosis not reported; exudate not reported
Interventions	Group 1: topical - enamel matrix protein; n = 6. Grouped intervention category: enamel matrix protein Group 2: topical - propylene glycol alginate (vehicle - propylene glycol alginate); n = 5. Grouped intervention category: propylene glycol alginate
Outcomes	Primary outcomes: proportion completely healed at 8 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability unclear -

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		baseline difference but unclear of importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded ("open label") and no evidence that outcome assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data: Group 1 - none stated. Group 2 - none stated i.e. unclear if data missing; unclear rate
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Unclear risk	Unit of randomisation person and unit of analysis person (unclear if > 1 ulcer analysed) - implies 1 per person
Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Reasons: unclear selection bias, not blinded Comments: comparable in age, more women in control group

Xakellis 1992

Methods	RCT; participants randomised (> 1 wound per person, ulcer chosen at random) Funding: non-industry funding - explicit statement that not industry funded. Supported by The Family Health Foundation of America. Setting: care home Duration of follow-up 26 weeks (6 months) protocol Unit of analysis: person (1 ulcer/person)
Participants	39 participants with pressure ulcers. PU Stage: II (100% and 90%) and III (Shea - must have a break in the skin for inclusion) (PU classification: Shea) Age: mean (SD): 77.3 (16.9) years and 83.5 (10.6) years. Duration of ulcer: not stated. Ulcer size: median (range): 0.66 (0.12-13.4) cm^2 and 0.38 (0.04-24.6) cm^2 Wound characteristics at baseline: infection not reported; slough not reported; some wounds necrotic; exudate mixed levels Comment: necrotic tissue: 2/18 (11%) and 7/21 (33%) but debridement used before and throughout, so unclear whether successful. Exudate: level not stated, but 9/18 (50%) and 7/21 (33%) had exudate at baseline. Exudate and necrosis were independent predictors of healing
Interventions	Group 1: hydrocolloid dressing - DuoDERM; n = 18. Grouped intervention category: advanced dressing Group 2: gauze saline dressing - saline wet-to-moist; n = 21. Grouped intervention category: basic dressing

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Xakellis 1992 (*Continued*)

Outcomes	Primary outcomes: proportion completely healed at 26 weeks (6 months); time to complete healing reported (Kaplan Meier plot included)	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation unclear - "randomised". Allocation concealment unclear - no information on allocation concealment. Baseline comparability adequate - no suggestion of problems. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded to interventions - clear description
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - 2/18 (11%) (1 hospitalised, 1 withdrew consent). Group 2 - 3/21 (14%) (3 died) i.e. similar rate missing in both groups; low rate - unlikely to alter the effect estimate
Selective reporting (reporting bias)	Low risk	Adequate - full results reported
Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person) - ulcer chosen at random (by coin toss)
Other bias additional	Low risk	Adequate - no suggestion of problems
ALL-DOMAIN RISK OF BIAS	High risk	Rating: high Reasons: unclear selection bias, not blinded

Yapucu Güne 2007

Methods	RCT; participants randomised (> 1 wound per person, all followed) Funding: not stated. Setting: hospital inpatients Duration of follow-up 5 weeks Unit of analysis: ulcer
Participants	27 participants with pressure ulcers. PU Stage: II and III (96% III in both groups) (PU classification: AHCRQ) Age: mean (SD): 65.80 (6.30) years and 66.56 (5.53) years. Duration of ulcer: not stated. Ulcer size: not stated

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	Wound characteristics at baseline: unclear infection; slough not reported; necrosis not reported; exudate not reported Comment: staging used AHRQ guidelines (probably NPUAP). Infection implied (control said to be a treatment for infected ulcers). 50+ ulcers (1 participant excluded and not stated no. of ulcers), 27 participants; all ulcers assessed
Interventions	Group 1: honey - unprocessed gauze impregnated (dressing): semi-permeable adhesive secondary dressing; n = 15. Grouped intervention category: antimicrobial Group 2: combination dressing - ethoxy-diaminoacridine plus nitrofurazone dressings; n = 12. Grouped intervention category: antimicrobial
Outcomes	Primary outcomes: proportion completely healed at 5 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation adequate - computer-generated. Allocation concealment unclear - no information on allocation concealment. Baseline comparability adequate - no suggestion of problems. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded to interventions - clear description
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data: Group 1 - 0. Group 2 - 1/12 (8%) (1 died) i.e. similar rate missing in both groups; high rate - comparable with control event rate
Selective reporting (reporting bias)	Low risk	Adequate - reported incompletely as 'significant' or P value < 0.05
Other bias unit of analysis	High risk	Unit of randomisation person and unit of analysis ulcer - ulcer:person ratio: 25/15 (1.7) and 26/12 (2.2)
Other bias additional	Unclear risk	Only available case analysis reported
ALL-DOMAIN RISK OF BIAS	High risk	Rating: very high Reasons: unclear selection bias, not blinded, attrition bias, unit of analysis issues

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Yapucu Güne 2007 (*Continued*)

ALL-DOMAIN RISK OF BIAS 2	High risk	

Zeron 2007

Methods	RCT; participants randomised (only 1 wound per person) Funding: unclear - product supplied by Aspid. Setting: hospital inpatients Duration of follow-up 3 weeks Unit of analysis: person (1 ulcer/person)
Participants	24 participants with pressure ulcers. PU Stage: 2 and 3 (PU classification: NPUAP) Age: mean 79.8 years and 78.3 years. Duration of ulcer: not stated. Ulcer size: diameter mean (SD): 3.4 (1.2) cm and 2.9 (1.3) cm Wound characteristics at baseline: infection not reported; slough not reported; necrosis not reported; exudate not reported Comment: IPD reported
Interventions	Group 1: protease-modulating dressing - Fibroquel: collagen plus polyvinylpyrrolidone + zinc oxide paste cleansing; n = 12. Grouped intervention category: protease-modulating dressing Group 2: polyvinylpyrrolidone (PVP + zinc oxide paste cleansing); n = 12. Grouped intervention category: basic dressing
Outcomes	Primary outcomes: proportion completely healed at 3 weeks; time to complete healing not reported
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection bias	Unclear risk	Sequence generation adequate - random number tables. Allocation concealment unclear - no information on allocation concealment. Baseline comparability unclear - baseline difference but unclear of importance. Rating: unclear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who outcome assessor was
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data: Group 1 - none. Group 2 - none. i.e. no missing data (clearly stated)
Selective reporting (reporting bias)	Unclear risk	Unclear reporting

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Zeron 2007 (*Continued*)

Other bias unit of analysis	Low risk	Unit of randomisation person and unit of analysis person (1 ulcer/person)
Other bias additional	Unclear risk	Insufficient information to assess whether an important risk of bias exists
ALL-DOMAIN RISK OF BIAS	Unclear risk	Rating: unclear Reasons: unclear selection bias, unclear who outcome assessor was, unclear reporting of numbers healed (but not a problem) Comments: healing data not reported explicitly, but deduced from IPD on ulcer size (number with zero size)

AHRQ: US Agency for Healthcare Research and Quality
BNF: British National Formulary
HC: hydrocolloid
IPD: individual participant data
NPWT: negative pressure wound therapy
NS: not stated
RCT: randomized controlled trial
UV: ultraviolet

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

Study	Reason for exclusion
Abbott 1968	Ineligible outcomes
Agren 1985	Ineligible outcomes
Ahmad 2008	Ineligible intervention
Alvarez 1999	Ineligible outcomes
Alvarez 2000a	Ineligible outcomes
Alvarez 2000b	Ineligible outcomes
Alvarez 2002	Ineligible outcomes
Alvarez Vázquez 2014	Ineligible patient population

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(*Continued*)

Aminian 1999	Ineligible type of healing outcome
Amione 2005	Comparison of two interventions in the same class
Anitua 2008	Ineligible patient population
Anonymous 1982	Ineligible study design
Anonymous 2000	Ineligible study design
Anzai 1989	Ineligible patient population
Avanzi 1998a	Ineligible outcomes
Avanzi 1998b	Ineligible outcomes
Avanzi 2000a	Ineligible outcomes
Avanzi 2000b	Ineligible outcomes
Avanzi 2000c	Ineligible outcomes
Avanzi 2001	Ineligible outcomes
Baade 1965	Ineligible intervention
Baatenburg de Jong 2004	Ineligible patient population
Baker 1981	Ineligible study design
Bale 1997b	Ineligible outcomes
Bale 1997c	Comparison of two interventions in the same class
Bale 1998a	Ineligible patient population
Bale 1998b	Ineligible outcomes
Bale 2004	Ineligible outcomes
Banks 1997a	Ineligible outcomes
Banks 1997b	Ineligible indication
Barnes 1992	Comparison of two interventions in the same class

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(*Continued*)

Bazzigaluppi 1991	Ineligible study design
Becker 1984	Ineligible type of healing outcome
Beele 2010	Ineligible patient population
Berard 1986	Ineligible study design
Bigolari 1991	Ineligible patient population
Bito 2012	Mixed intervention
Blanco Blanco 2002	Ineligible indication
Blum 1973	Ineligible patient population
Boxer 1969	Ineligible outcomes
Boykin 1989	Ineligible study design
Brady 1987	Ineligible study design
Brem 2000	Ineligible study design
Brett 2003	Ineligible outcomes
Brown-Etris 1999a	Ineligible type of healing outcome
Brown-Etris 1999b	Mixed intervention
Burgos 2000	Comparison of two interventions in the same class
Burke 1998	Ineligible type of healing outcome
Capillas Pérez 2000	Ineligible patient population
Carusone 2001	Ineligible indication
Casali 1997	Ineligible study design
Chang 1998	Ineligible outcomes
Chen 2004	Ineligible intervention
Cheneworth 1994	Ineligible study design
Chirwa 2010	Ineligible patient population

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Chuangsuwanich 2011a	Ineligible type of healing outcome
Chuangsuwanich 2011b	Ineligible outcomes
Chuangsuwanich 2013	Ineligible outcomes
Colin 1996a	Ineligible type of healing outcome
Colin 1996b	Ineligible type of healing outcome
Colonna 2004	Ineligible study design
Cooper 2008	Ineligible patient population
Coutts 2000	Ineligible outcomes
D'Aniello 1998	Ineligible outcomes
Dat 2014	Ineligible study design
Day 1995	Comparison of two interventions in the same class
De Laat 2005	Ineligible outcomes
De Laat 2011	Ineligible type of healing outcome
Dealey 1997	Ineligible outcomes
Dealey 1998	Ineligible study design
Dealey 2008	Editorial
Dierick 2004a	Ineligible outcomes
Dierick 2004b	Ineligible type of healing outcome
Dobrzanski 1990	Comparison of two interventions in the same class
Durovic 2008	Ineligible type of healing outcome
Dwivedi 2016	Ineligible type of healing outcome
El Zayat 1989	Ineligible study design
Ellis 2002	Ineligible type of healing outcome

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(*Continued*)

Ellis 2003	Ineligible type of healing outcome
Engdahl 1980	Ineligible study design
Esch 1989	Ineligible type of healing outcome
Farsaei 2014	Ineligible patient population
Fear 1992	Ineligible outcomes
Feldman 2005	Ineligible type of healing outcome
Felzani 2011	Ineligible type of healing outcome
Flanagan 1995	Ineligible study design
Ford 2002	Mixed intervention
Fowler 1983	Ineligible study design
Franek 2011	Mixed intervention
Franek 2012	Mixed intervention
Franken 1999	Ineligible type of healing outcome
Fulco 2015	Ineligible type of healing outcome
Fønnebø 2008	Ineligible study design
García González 2002	Ineligible outcomes
Garrett 1969	Ineligible outcomes
Gerding 1992	Ineligible patient population
Gilligan 2014	Ineligible intervention
Goldmeier 1997	Ineligible type of healing outcome
Gostishchev 1983	Ineligible study design
Greer 1999	Ineligible type of healing outcome
Gregory 1997	Ineligible intervention
Guthrie 1989	Ineligible type of healing outcome

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Hamilton Hislop 1962	Ineligible study design
Hampton 1998	Ineligible patient population
Harada 1996	Ineligible type of healing outcome
Harding 1996	Ineligible outcomes
Harding 2000	Ineligible study design
Helaly 1988	Ineligible patient population
Heuckeroth 2013	Ineligible study design
Heyer 2013	Ineligible study design
Hinz 1986	Ineligible patient population
Hirshberg 2001	Ineligible intervention
Hock 1997	Comparison of two interventions in the same class
Hofman 1994	Ineligible type of healing outcome
Horch 2005	Ineligible study design
Hsu 2000	Ineligible study design
Hu 2009	Ineligible patient population
Ishibashi 1991	Ineligible patient population
Ishibashi 1996	Ineligible patient population
Janssen 1989	Ineligible patient population
Jercinovic 1994	Ineligible intervention
Johnson 1992	Mixed intervention
Kallianinen 2000	Ineligible intervention
Karap 2008	Ineligible outcomes
Kerihuel 2010	Ineligible type of healing outcome

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(*Continued*)

Kerstein 2004	Ineligible study design
Kim 1996	Ineligible patient population
Kloth 2000a	Mixed intervention
Kloth 2000b	Ineligible study design
Kloth 2001	Mixed intervention
Kloth 2002	Mixed intervention
Knudsen 1982	Ineligible type of healing outcome
Kohr 2000	Ineligible outcomes
Kordestani 2008	Ineligible study design
Kucan 1981	Ineligible outcomes
Kuflik 2001	Ineligible patient population
Kuisma 1987	Ineligible indication
Kukita 1990	Ineligible type of healing outcome
Kurring 1994	Ineligible study design
Kurzuk-Howard 1985	Ineligible study design
Landi 2003	Ineligible intervention
Langer 1996	Ineligible intervention
Lazareth 2012	Ineligible patient population
Lechner 1991	No results
Lee 1975	Ineligible type of healing outcome
Lee 2014	Ineligible patient population
LeVasseur 1991	Ineligible study design
Li 2016	Dressings/topical agents not the only difference between interventions (nursing care was also different)
Lin 1997	Ineligible study design

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(*Continued*)

Lindsay 2011	Ineligible study design
Lingner 1984	Ineligible study design
Liu 2012	Ineligible type of healing outcome
Liu 2013	Ineligible study design
Ljungberg 1998	Ineligible type of healing outcome
Llewellyn 1996	Ineligible outcomes
Lopez-Jimenez 2003	Ineligible outcomes
Lum 1996	Ineligible type of healing outcome
Macario 2002	Ineligible study design
Manzanero-Lopez 2004	Protocol only and review still not published
Martin 1996	Ineligible outcomes
Meaume 1996a	Ineligible type of healing outcome
Meaume 1996b	Ineligible type of healing outcome
Meaume 2005	Ineligible patient population
Mian 1992	Ineligible study design
Milne 2012	Confounded - selection into phase 2 of trial on basis of results
Mizuhara 2012	Mixed intervention
Mo 2015	Ineligible patient population
Moberg 1983	Mixed intervention
Mody 2008	Ineligible type of healing outcome
Moody 1991	Ineligible study design
Moody 2002	Ineligible study design
Moore 2011	Ineligible patient population

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(*Continued*)

Morimoto 2015	Ineligible study design
Motta 1991	Ineligible study design
Motta 2004	Ineligible patient population
Mouës 2004	Ineligible patient population
Mouës 2007	Ineligible patient population
Mulder 1989a	Ineligible patient population
Mulder 1989b	Ineligible patient population
Mulder 1993a	Ineligible type of healing outcome
Mulder 1993b	Ineligible type of healing outcome
Mustoe 1994	Ineligible intervention
Myers 1990	Ineligible type of healing outcome
Münter 2006	Ineligible patient population
Nasar 1982	Ineligible type of healing outcome
NCT02299557	Ineligible patient population
Neill 1989b	Ineligible study design
Niezgoda 2004	Ineligible type of healing outcome
Niimura 1990	Ineligible patient population
Niimura 1991	Ineligible patient population
Nixon 1998	Ineligible intervention
Ohura 2004	Mixed intervention
Olivar 1999	Ineligible intervention
Ovington 1999	Ineligible study design
Ozdemir 2011	Ineligible type of healing outcome

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(*Continued*)

Panahi 2015	Ineligible patient population
Payne 2001	Ineligible intervention
Perez 2000	Ineligible type of healing outcome
Peschardt 1997	Ineligible type of healing outcome
Picard 2015	Ineligible patient population
Pierce 1994	Ineligible outcomes
Pullen 2002	Ineligible outcomes
Quelard 1985	Ineligible intervention
Ramsay 1979	Ineligible study design
Rhodes 1979	Ineligible study design
Rhodes 2001	Ineligible type of healing outcome
Roberts 1959	Ineligible indication
Robson 1992a	Ineligible type of healing outcome
Robson 1992b	Ineligible intervention
Robson 1992c	Ineligible intervention
Robson 1994	Ineligible intervention
Romanelli 2008	Ineligible patient population
Romanelli 2009	Ineligible patient population
Rooman 1991	Ineligible patient population
Routkovsky-Norval 1996	Comparison of two interventions in the same class
Saha 2012	Ineligible type of healing outcome
Saidkhani 2016	Ineligible study design
Sayag 1996	Ineligible type of healing outcome

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(*Continued*)

Saydak 1990	Ineligible study design
Scevola 2010	Ineligible outcomes
Scott 1999	Ineligible study design
Seaman 2000	Comparison of two interventions in the same class
Sebern 1989	Ineligible outcomes
Serra 2005	Ineligible study design
Settel 1969	Ineligible type of healing outcome
Shamimi Nouri 2008	Ineligible outcomes
Shannon 1988	Ineligible study design
Sherman 2000	Ineligible study design
Shirakawa 2005	Ineligible study design
Shojaei 2008	Ineligible outcomes
Shrivastava 2011	Ineligible patient population
Sibbald 2011	Ineligible patient population
Small 2002	Mixed intervention
Smietanka 1981	Ineligible study design
Souliotis 2016	Ineligible type of healing outcome
Stepan 2014	Ineligible study design
Stephen 2016	Ineligible type of healing outcome
Stoker 1990	Ineligible study design
Strong 1985	Ineligible type of healing outcome
Subbanna 2007	Ineligible type of healing outcome
Takahashi 2006	Ineligible study design

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(*Continued*)

Teot 2008	Ineligible outcomes
Teot 1997	Ineligible type of healing outcome
Tewes 1993	Ineligible study design
Thomas 1993	Ineligible outcomes
Thomas 1997b	Ineligible outcomes
Toba 1997	Ineligible type of healing outcome
Tolentino 2011	Ineligible study design
Toriyabe 2004	Ineligible study design
Torra i Bou 1999	Ineligible outcomes
Trial 2010	Ineligible outcomes
Tricco 2015	Ineligible study design
Unglaub 2004	Ineligible type of healing outcome
Valentini 2015	Ineligible type of healing outcome
Van Leen 2004	Ineligible study design
Varma 1973	Ineligible outcomes
Vernassiere 2005	Ineligible patient population
Wagstaff 2014	Comparison of two interventions in the same class
Wallace 2009	Ineligible study design
Wang 2014	Ineligible intervention
Wanner 2003	Ineligible type of healing outcome
Watts 1994	Ineligible outcomes
Waycaster 2011	Ineligible type of healing outcome
Waycaster 2013	Confounded - selection into phase 2 of trial on basis of results

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(*Continued*)

Weheida 1991	Ineligible patient population
Weststrate 1999	Ineligible study design
Whitney 1999	Mixed intervention
Whitney 2001	Mixed intervention
Wild 2009	Ineligible outcomes
Wild 2012	Ineligible outcomes
Winter 1990	Ineligible patient population
Woo 2009	Ineligible outcomes
Worsley 1991	Ineligible patient population
Yastrub 2004	Ineligible type of healing outcome
Yastrub 2005	Ineligible type of healing outcome
Young 1973	Ineligible study design
Young 1997	Ineligible type of healing outcome
Yura 1984	Ineligible patient population
Zhou 2001	Ineligible intervention
Zuloff-Shani 2010	Ineligible study design

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

ChiCTR-TRC-13003959

Trial name or title	ChiCTR-TRC-13003959
Methods	RCT pilot study; Duration 3 months
Participants	30 eligible participants with pressure ulcers randomised in a ratio of 1:1
Interventions	Treatment group: indirect moxibustion for 30 min before application of a dressing, 1 session daily, 5 sessions weekly for 4 weeks Control group will only receive a dressing, applied in the same way as in the treatment group

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ChiCTR-TRC-13003959 (*Continued*)

Outcomes	Primary outcomes: wound surface area (WSA) and proportion of ulcers healed within trial period
Starting date	registered 7/12/2013
Contact information	
Notes	Protocol only

ISRCTN57842461

Trial name or title	ISCRCTN57842461 study reported to be registered
Methods	RCT; participants randomised Duration 8 weeks
Participants	820 participants with at least 1 grade II pressure ulcer will be recruited from primary health care and home care centres
Interventions	Polyurethane foam and hydrocolloid dressings
Outcomes	Primary outcome: percentage of wounds healed after 8 weeks. Secondary outcomes will include cost-effectiveness, as evaluated by cost per healed ulcer and cost per treated participant and safety evaluated by adverse events
Starting date	Not stated
Contact information	
Notes	Protocol only; trial not on ClinicalTrials.gov

RCT: randomised controlled trial

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DATA AND ANALYSES

Comparison 1. Direct evidence: individual interventions, number with complete healing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Interventions vs saline gauze	10		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1 Hydrocolloid vs saline gauze	4	279	Risk Ratio (IV, Random, 95% CI)	1.89 [0.91, 3.93]
1.2 Hydrogel vs saline gauze	3	110	Risk Ratio (IV, Random, 95% CI)	2.44 [0.64, 9.27]
1.3 Foam vs saline gauze	3	93	Risk Ratio (IV, Random, 95% CI)	1.51 [0.78, 2.90]
2 Interventions vs hydrocolloid	13		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.1 Hydrogel vs hydrocolloid	4	322	Risk Ratio (IV, Random, 95% CI)	1.11 [0.74, 1.67]
2.2 Foam vs hydrocolloid	6	292	Risk Ratio (IV, Random, 95% CI)	1.05 [0.81, 1.36]
2.3 Collagenase ointment vs hydrocolloid	2	61	Risk Ratio (IV, Random, 95% CI)	1.51 [0.93, 2.43]
2.4 Protease-modulating dressing vs hydrocolloid	1	65	Risk Ratio (IV, Random, 95% CI)	1.03 [0.64, 1.66]

Comparison 2. Direct evidence group intervention, number with complete healing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Intervention 1 vs intervention 2	18		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1 Advanced dressing vs basic dressing	11	532	Risk Ratio (IV, Random, 95% CI)	1.55 [1.10, 2.19]
1.2 Antimicrobial dressing vs advanced dressing	2	125	Risk Ratio (IV, Random, 95% CI)	0.69 [0.48, 0.99]
1.3 Collagenase ointment vs advanced dressing	2	61	Risk Ratio (IV, Random, 95% CI)	1.51 [0.93, 2.43]
1.4 Protease-modulating dressing vs advanced dressing	3	112	Risk Ratio (IV, Random, 95% CI)	1.13 [0.80, 1.60]

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Comparison 3. Direct evidence: individual interventions, time-to-healing data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time-to-healing (survival analysis)	7		Hazard Ratio (Fixed, 95% CI)	Subtotals only
1.1 Hydrocolloid versus saline gauze	2	95	Hazard Ratio (Fixed, 95% CI)	1.75 [1.00, 3.05]
1.2 Hydrogel versus hydrocolloid	1	43	Hazard Ratio (Fixed, 95% CI)	1.30 [0.54, 3.13]
1.3 Protease-modulating versus hydrocolloid	1	65	Hazard Ratio (Fixed, 95% CI)	1.34 [0.67, 2.65]
1.4 Collagenase ointment versus hydrocolloid	1	24	Hazard Ratio (Fixed, 95% CI)	2.59 [1.01, 6.62]
1.5 Foam versus saline gauze	1	36	Hazard Ratio (Fixed, 95% CI)	1.13 [0.42, 3.00]
1.6 Hydrocolloid +/- alginate versus ineligible: radiant heat	1	41	Hazard Ratio (Fixed, 95% CI)	0.64 [0.23, 1.77]

Comparison 4. Direct evidence: group interventions, time-to-healing data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time-to-healing (survival analysis)	5		Hazard Ratio (Fixed, 95% CI)	Subtotals only
1.1 Advanced dressing versus basic dressing	3		Hazard Ratio (Fixed, 95% CI)	1.57 [0.97, 2.55]
1.2 Protease-modulating dressing versus advanced dressing	1		Hazard Ratio (Fixed, 95% CI)	1.34 [0.67, 2.65]
1.3 Advanced dressings versus collagenase ointment	1		Hazard Ratio (Fixed, 95% CI)	0.27 [0.11, 0.67]

Comparison 5. Direct evidence - non-network comparisons

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Intervention 1 vs intervention 2	4		Risk Ratio (IV, Random, 95% CI)	Totals not selected
1.1 Sugar + povidone iodine vs lysosyme	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Enamel matrix protein vs propylene glycol alginate	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

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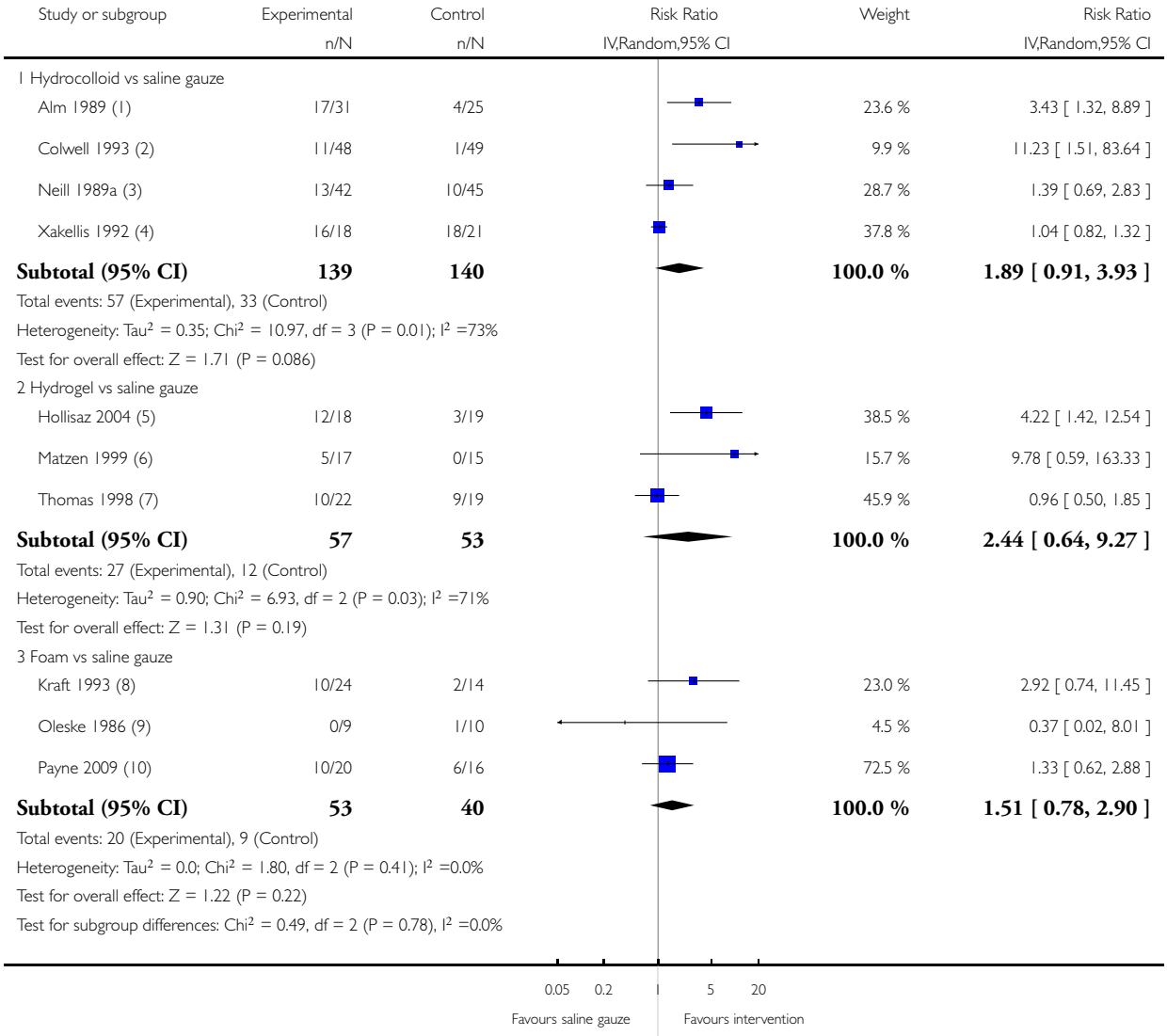
1.3 Honey vs ethoxy-diaminoacridine +nitrofurazone dressings	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 Resin salve vs hydrocolloid or hydrocolloid silver dressing	1	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Direct evidence: individual interventions, number with complete healing, Outcome 1 Interventions vs saline gauze.

Review: Dressings and topical agents for treating pressure ulcers

Comparison: 1 Direct evidence: individual interventions, number with complete healing

Outcome: 1 Interventions vs saline gauze



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(1) 6 weeks follow-up

(2) 4 weeks follow-up

(3) 8 weeks follow-up

(4) 26 weeks (6 months) follow-up; missing data added to denominator

(5) 8 weeks follow-up

(6) 11 weeks follow-up

(7) 8 weeks follow-up

(8) 24 weeks follow-up

(9) 11 weeks follow-up

(10) 4 weeks follow-up

Analysis 1.2. Comparison 1 Direct evidence: individual interventions, number with complete healing, Outcome 2 Interventions vs hydrocolloid.

Review: Dressings and topical agents for treating pressure ulcers

Comparison: 1 Direct evidence: individual interventions, number with complete healing

Outcome: 2 Interventions vs hydrocolloid

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Hydrogel vs hydrocolloid					
Brod 1990 (1)	13/27	8/16		23.7 %	0.96 [0.51, 1.80]
Brown-Etris 1996 (2)	39/77	37/63		41.0 %	0.86 [0.64, 1.17]
Darkovich 1990 (3)	27/62	16/67		28.9 %	1.82 [1.09, 3.05]
Motta 1999 (4)	2/5	2/5		6.4 %	1.00 [0.22, 4.56]
Subtotal (95% CI)	**171**	**151**		**100.0 %**	**1.11 [0.74, 1.67]**
Total events: 81 (Experimental), 63 (Control)					
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 6.13$, df = 3 (P = 0.11); $I^2 = 51\%$					
Test for overall effect: Z = 0.50 (P = 0.62)					
2 Foam vs hydrocolloid					
Aguilo Sanchez 2002 (5)	7/12	6/12		12.3 %	1.17 [0.56, 2.45]
Bale 1997a (6)	7/29	5/31		6.4 %	1.50 [0.53, 4.19]

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Study or subgroup	Experimental n/N	Control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Banks 1994a (7)	12/20	10/20		21.1 %	1.20 [0.68, 2.11]
Banks 1994c (8)	10/13	11/16		34.1 %	1.12 [0.72, 1.75]
Seeley 1999 (9)	8/20	8/20		11.7 %	1.00 [0.47, 2.14]
Thomas 1997a (10)	10/50	16/49		14.4 %	0.61 [0.31, 1.21]
Subtotal (95% CI)	**144**	**148**		**100.0 %**	**1.05 [0.81, 1.36]**
Total events: 54 (Experimental), 56 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.22, df = 5 (P = 0.67); I^2 =0.0%					
Test for overall effect: Z = 0.38 (P = 0.70)					
3 Collagenase ointment vs hydrocolloid					
Burgos 2000b (11)	3/18	3/19		10.7 %	1.06 [0.24, 4.57]
Muller 2001 (12)	11/12	7/12		89.3 %	1.57 [0.95, 2.61]
Subtotal (95% CI)	**30**	**31**		**100.0 %**	**1.51 [0.93, 2.43]**
Total events: 14 (Experimental), 10 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.25, df = 1 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 1.67 (P = 0.094)					
4 Protease-modulating dressing vs hydrocolloid					
Graumlich 2003	18/35	15/30		100.0 %	1.03 [0.64, 1.66]
Subtotal (95% CI)	**35**	**30**		**100.0 %**	**1.03 [0.64, 1.66]**
Total events: 18 (Experimental), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.11 (P = 0.91)					
Test for subgroup differences: Chi^2 = 1.81, df = 3 (P = 0.61), I^2 =0.0%					

(1) 8 weeks follow-up

(2) 10 weeks follow-up

(3) 8.5 weeks follow-up

(4) 8 weeks follow-up

(5) Estimated 7 weeks follow-up

(6) 4 weeks follow-up

(7) 6 weeks follow-up

(8) 6 weeks follow-up

(9) 8 weeks follow-up

(10) 5 weeks follow-up

(11) 7 weeks follow-up

(12) 16 weeks follow-up (assumed)

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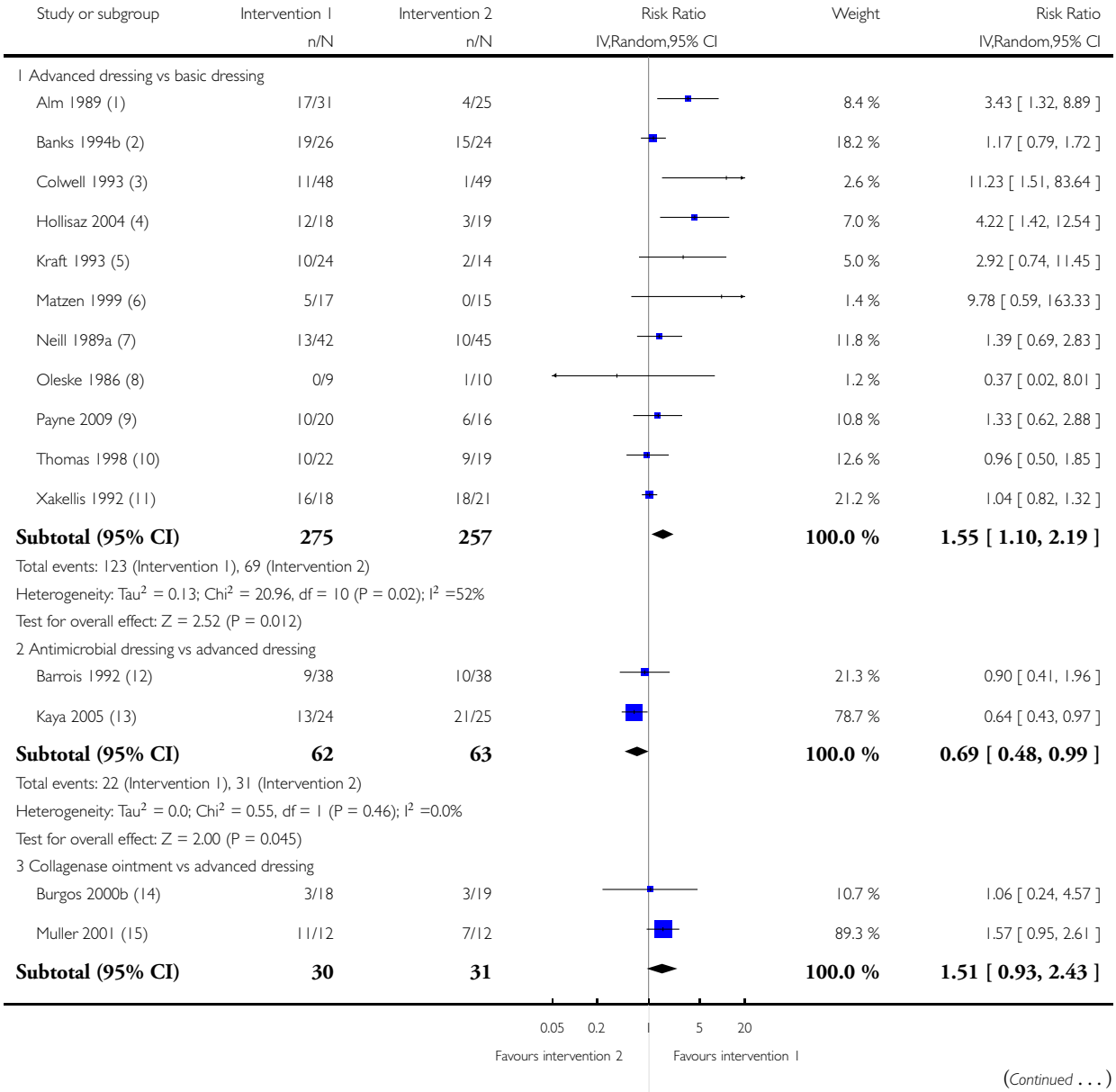
Analysis 2.1. Comparison 2 Direct evidence group intervention, number with complete healing, Outcome 1 Intervention 1 vs intervention 2.

Review: Dressings and topical agents for treating pressure ulcers

Comparison: 2 Direct evidence group intervention, number with complete healing

Outcome: 1 Intervention 1 vs intervention 2



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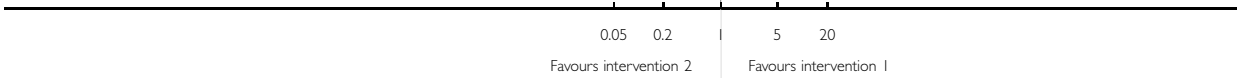
Study or subgroup	Intervention 1 n/N	Intervention 2 n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Total events: 14 (Intervention 1), 10 (Intervention 2)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.25, df = 1 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 1.67 (P = 0.094)					
4 Protease-modulating dressing vs advanced dressing					
Brown-Etris 1997	3/24	1/12		2.6 %	1.50 [0.17, 12.94]
Graumlich 2003	18/35	15/30		51.1 %	1.03 [0.64, 1.66]
Piatkowski 2012	6/6	4/5		46.3 %	1.24 [0.75, 2.05]
Subtotal (95% CI)	**65**	**47**		**100.0 %**	**1.13 [0.80, 1.60]**
Total events: 27 (Intervention 1), 20 (Intervention 2)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.34, df = 2 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 0.70 (P = 0.48)					
Test for subgroup differences: Chi^2 = 11.80, df = 3 (P = 0.01), I^2 =75%					



(1) 6 weeks follow-up

(2) 12 weeks follow up

(3) 4 weeks follow-up

(4) 8 weeks follow-up

(5) 24 weeks follow-up

(6) 11 weeks follow-up

(7) 8 weeks follow-up

(8) 11 weeks follow-up

(9) 4 weeks follow-up

(10) 8 weeks follow-up

(11) 26 weeks (6 months) follow-up; missing data added to denominator

(12) 8 weeks follow-up

(13) unclear follow-up

(14) 7 weeks follow-up

(15) 16 weeks follow-up (assumed)

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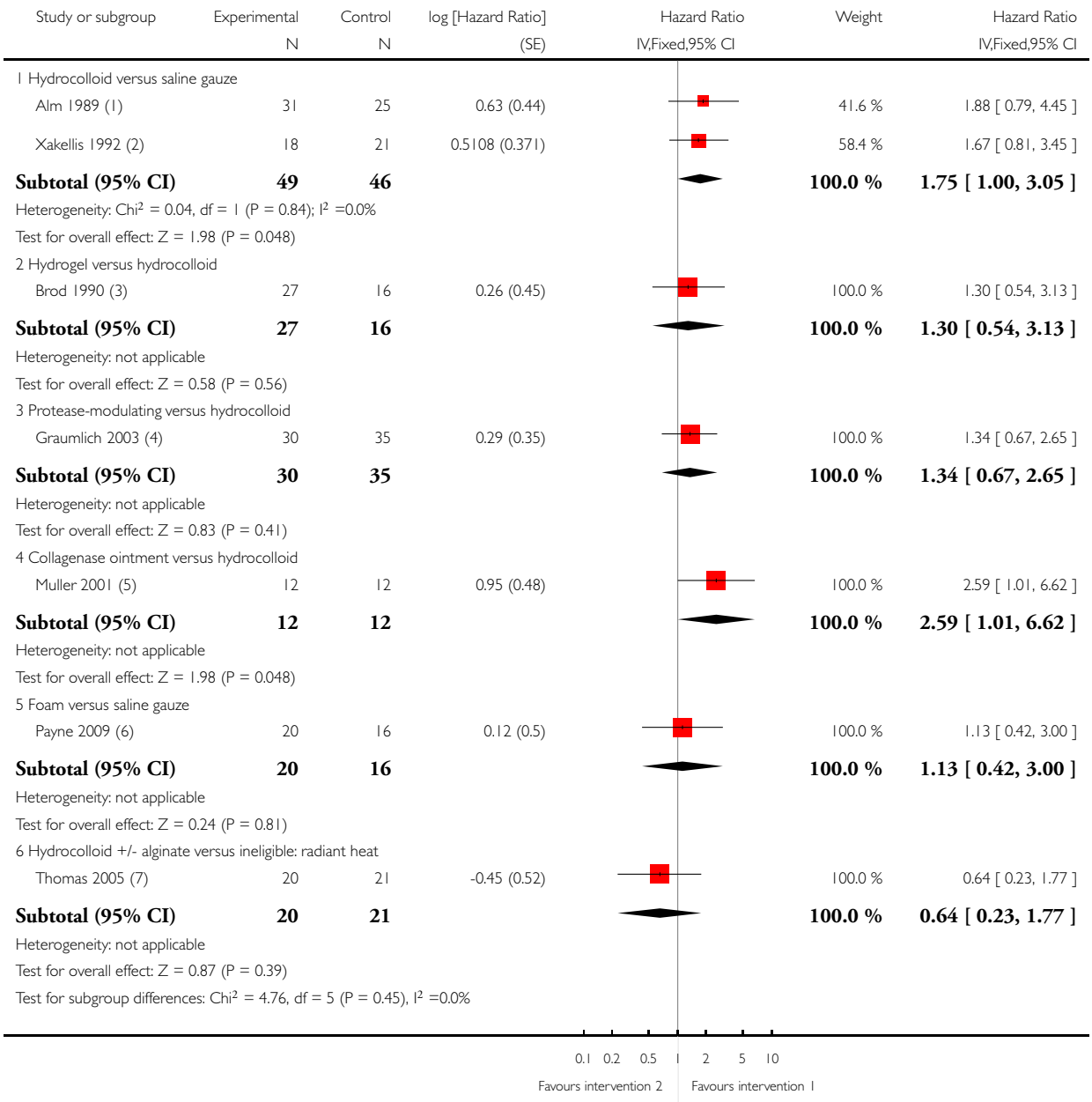
Analysis 3.1. Comparison 3 Direct evidence: individual interventions, time-to-healing data, Outcome 1 Time-to-healing (survival analysis).

Review: Dressings and topical agents for treating pressure ulcers

Comparison: 3 Direct evidence: individual interventions, time-to-healing data

Outcome: 1 Time-to-healing (survival analysis)



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(1) HR calculated using estimated number of events and logrank p-value (0.15)

(2) HR (adjusted for exudate) reported

(3) HR calculated using number of events and p-value from K-M plot (0.56)

(4) HR calculated using number of events and logrank p-value (0.409, unadjusted)

(5) HR calculated usingnumber of events and logrank p-value (<0.005)

(6) HR calculated number of events and logrank p-value (0.817)

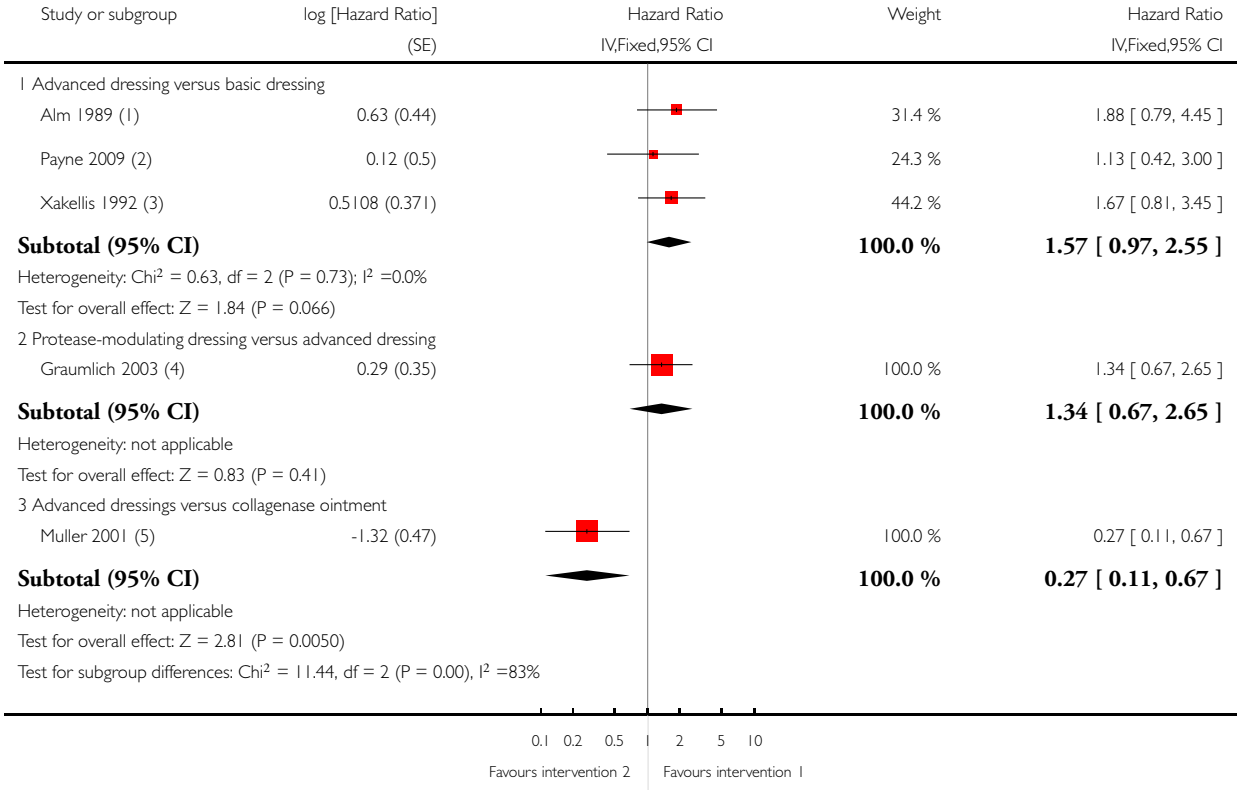
(7) HR calculated usingnumber of events and logrank p-value (0.38)

Analysis 4.1. Comparison 4 Direct evidence: group interventions, time-to-healing data, Outcome 1 Time-to-healing (survival analysis).

Review: Dressings and topical agents for treating pressure ulcers

Comparison: 4 Direct evidence: group interventions, time-to-healing data

Outcome: 1 Time-to-healing (survival analysis)



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(1) HR calculated using estimated number of events and logrank p-value (0.15)

(2) HR calculated number of events and logrank p-value (0.817)

(3) HR (adjusted for exudate) reported

(4) HR calculated using number of events and logrank p-value (0.409, unadjusted)

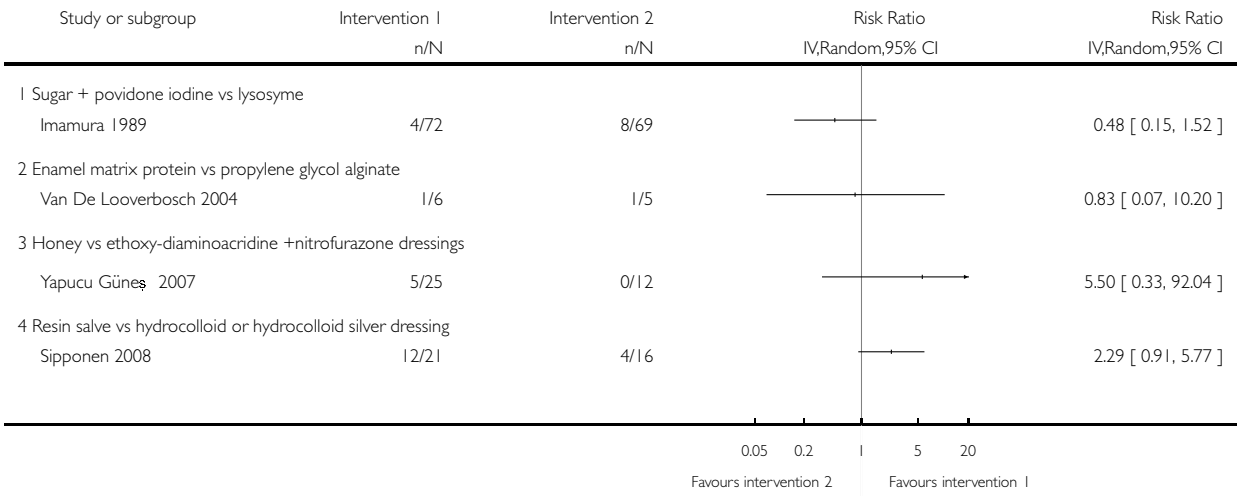
(5) HR calculated usingnumber of events and logrank p-value (<0.005)

Analysis 5.1. Comparison 5 Direct evidence - non-network comparisons, Outcome 1 Intervention 1 vs intervention 2.

Review: Dressings and topical agents for treating pressure ulcers

Comparison: 5 Direct evidence - non-network comparisons

Outcome: 1 Intervention 1 vs intervention 2



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ADDITIONAL TABLES

Table 1. Summary characteristics of included studies

Study characteristic		Studies in the individual network only	Studies in both individual and group networks	Studies in the group network only	Studies included in neither network
Publication (all others were full published papers)	**Conference abstracts (5)**	Serena 2010	Barrois 1992; Brown-Etris 1997; Romanelli 2001		Van De Looverbosch 2004
Multiple interventions	**> 2 arms (4)**		Hollisaz 2004; Parish 1979		Nussbaum 1994; Ramos-Torrecillas 2015 (4 arms)
Unit of randomisation (all other studies randomised individuals)	**Ulcers randomised (5)**	Brown-Etris 1996	Alm 1989; Colwell 1993; Neill 1989a		Sebern 1986
	Cluster-randomised (2)		Oleske 1986		Gorse 1987
	not stated (3)	Aguilo Sanchez 2002; Darkovich 1990; Serena 2010			
Funding	**Industry funding (18)**	Banks 1994c; Belmin 2002; Brod 1990; Brown-Etris 2008; Hondé 1994; Motta 1999	Banks 1994a; Burgos 2000b; Colwell 1993; Kraft 1993; Neill 1989a; Payne 2009; Piatkowski 2012; Thomas 1998	Sipponen 2008	Payne 2004; Rees 1999; Van De Looverbosch 2004
	Mixed industry and non industry (2)		Graumlich 2003		Sebern 1986
	Non industry (10)	Sopata 2002	Brown-Etris 1997; Hollisaz 2004; Kaya 2005; Muller 2001; Oleske 1986; Xakellis 1992		Ashby 2012; Nussbaum 1994; Ramos-Torrecillas 2015
	Not stated (21)	Aguilo Sanchez 2002; Bale 1997a; Brown-Etris 1996; Darkovich 1990; Meaume 2003; Price 2000; Seeley 1999; Seeley 1999; Thomas 1997a;	Alm 1989; Banks 1994b; Barrois 1992; Matzen 1999; Parish 1979; Romanelli 2001; Zeron 2007		Gorse 1987; Imamura 1989; Nisi 2005; Yapucu Güne 2007

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Table 1. Summary characteristics of included studies (*Continued*)

		Thomas 2005			
Setting	**Community only (6)**	Motta 1999; Thomas 1997a	Banks 1994a; Matzen 1999		Payne 2004; Sebern 1986
	Hospital only (20)	Bale 1997a; Banks 1994c; Belmin 2002; Hondé 1994; Sopata 2002	Alm 1989; Burgos 2000b; Colwell 1993; Kaya 2005; Muller 2001; Oleske 1986; Piatkowski 2012; Zeron 2007	Sipponen 2008;	Gorse 1987; Imamura 1989; Nisi 2005; Nussbaum 1994; Ramos-Torrecillas 2015; Yapucu Güne 2007
	Hospital and other setting (7)	Price 2000 (hospital and community); Darkovich 1990 (hospital and care home); Brown-Etris 1996 (hospital and community and care home)	Banks 1994b (hospital and community); Kraft 1993; Neill 1989a (hospital and care home); Payne 2009 (hospital and community and care home)		Ashby 2012 (hospital and community)
	Care home and community (5)	Brown-Etris 2008; Seeley 1999; Thomas 2005	Hollisaz 2004; Thomas 1998		
	Care home only (5)	Brod 1990; Meaume 2003	Graumlich 2003; Parish 1979; Xakellis 1992		
	Not stated (7)	Aguilo Sanchez 2002; Serena 2010	Barrois 1992; Brown-Etris 1997; Romanelli 2001		Rees 1999; Van De Looverbosch 2004
Follow-up time	**< 6 weeks (8)**	Bale 1997a	Oleske 1986; Parish 1979; Payne 2009; Piatkowski 2012; Zeron 2007		Ramos-Torrecillas 2015; Yapucu Güne 2007
	6 to 8 weeks (25)	Aguilo Sanchez 2002; Banks 1994c; Belmin 2002; Brod 1990; Brown-Etris 2008; Hondé 1994; Meaume 2003; Motta 1999; Price 2000; Seeley 1999; Sopata 2002; Thomas 1997a;	Alm 1989; Banks 1994a; Barrois 1992; Brown-Etris 1997; Graumlich 2003; Hollisaz 2004; Neill 1989a; Romanelli 2001		Imamura 1989; Nisi 2005; Nussbaum 1994; Sebern 1986; Van De Looverbosch 2004

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Table 1. Summary characteristics of included studies (*Continued*)

	> 8 to 12 weeks (10)	Brown-Etris 1996; Darkovich 1990; Serena 2010; Thomas 2005	Banks 1994b; Burgos 2000b; Colwell 1993; Matzen 1999; Thomas 1998		Gorse 1987
	≥ 16 weeks (7)		Kraft 1993; Muller 2001; Xakellis 1992	Sipponen 2008	Ashby 2012; Payne 2004; Rees 1999
	Unclear (1)		Kaya 2005		
Mean age (other studies mean ≥ 65 years	**< 65 years (8)**	Motta 1999; Sopata 2002	Hollisaz 2004; Kaya 2005; Parish 1979		Nisi 2005; Nussbaum 1994; Rees 1999
	Not stated (1)	Serena 2010			
Physical conditions	**Spinal cord injuries (4)**		Hollisaz 2004; Kaya 2005; Kraft 1993		Nussbaum 1994
	Other (2)	Sopata 2002 (advanced cancer)	Parish 1979 ("chronically ill or physically disabled")		
Ulcer grade	**Mainly Stage 2 (17)**	Bale 1997a; Thomas 1997a (Stirling); Brown-Etris 2008 (classification not stated); Darkovich 1990 (Enis and Sarmiento); Hondé 1994 (Shea); Meaume 2003 (EUPAP)	Colwell 1993 (classification not stated); Graumlich 2003; Kaya 2005; Payne 2009 (NPUAP); Hollisaz 2004; Neill 1989a; Xakellis 1992 (Shea); Kraft 1993 (Enterstomal Therapy); Oleske 1986 (Enis and Sarmiento)		Gorse 1987; Van De Looverbosch 2004 (classification not stated)
	Mainly Stage 3 (15)	Belmin 2002 (Yarkony); Seeley 1999 (AHCPR); Thomas 1997a (Stirling); Serena 2010 (NPUAP); Brown-Etris 1996; Motta 1999; Price 2000; Thomas 2005 (classification not stated)	Burgos 2000b (classification not stated); Piatkowski 2012 (EPUAP)	Sipponen 2008 (EPUAP)	Ashby 2012; Ramos-Torrecillas 2015; (EPUAP classification); Yapucu Güne 2007 (AHCRQ); Payne 2004 (classification not stated)

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Table 1. Summary characteristics of included studies (*Continued*)

	Mainly Stage 4 (2)		Matzen 1999; Muller 2001 (classification not stated)		
	Other (12)	Banks 1994c (II/III); Sopata 2002 II/III (Torrance); Brod 1990 (II/III) (classification not stated)	Banks 1994a (II/III); Brown-Etris 1997 (II/III/IV) (classification not stated); Banks 1994b (Torrance II/III); Romanelli 2001 (II/III); Zeron 2007(2/3) (NPUAP)		Nisi 2005 (2-4); Rees 1999 (3/4) (NPUAP); Sebern 1986 (II/III) (Shea); Imamura 1989 (II/III/IV) (classification not stated)
	Not stated (5)	Aguilo Sanchez 2002	Alm 1989; Barrois 1992; Parish 1979		Nussbaum 1994
Ulcer duration (other studies had ≥ 3 months)	**< 3 months (16)**	Banks 1994c (median 7 days); Belmin 2002; Brown-Etris 1996; Brown-Etris 2008; Meaume 2003; Motta 1999; Seeley 1999; Sopata 2002 (mean 2.5 weeks); Thomas 1997a	Banks 1994a; Burgos 2000b; Colwell 1993; Graumlich 2003; Hollisaz 2004; Kraft 1993; Payne 2009		
	≥ 3 months (6)	Serena 2010	Alm 1989		Ashby 2012; Payne 2004; Ramos-Torrecillas 2015; Rees 1999
	Not stated/unclear (29)	Aguilo Sanchez 2002; Bale 1997a; Brod 1990; Darkovich 1990; Hondé 1994; Price 2000; Thomas 2005	Banks 1994b; Barrois 1992; Brown-Etris 1997; Kaya 2005; Matzen 1999; Muller 2001; Neill 1989a; Oleske 1986; Parish 1979; Piatkowski 2012 (> 4 weeks); Romanelli 2001; Thomas 1998; Xakellis 1992; Zeron 2007	Sipponen 2008	Gorse 1987; Imamura 1989; Nisi 2005; Nussbaum 1994 (> 6 weeks); Sebern 1986; Van De Looverbosch 2004 (> 1 month); Yapucu Güne 2007

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Table 2. Direct comparisons for individual interventions - proportion healed - compared with NMA results

Contrast/comparison	Number of studies (participants)	RR (95% CI) direct evidence Random-effects (inverse variance) Heterogeneity statistics	NMA results (consistency assumption) RR (95% CI)
Hydrocolloid dressing versus saline gauze dressing (Alm 1989; Colwell 1993; Neill 1989a; Xakellis 1992)	4 (279)	1.89 (0.91 to 3.93) $Tau^2 = 0.35$; P = 0.01; $I^2 = 73\%$	1.43 (1.00 to 2.05)
Hydrogel versus saline gauze dressing (Hollisaz 2004; Matzen 1999; Thomas 1998)	3 (110)	2.44 (0.64 to 9.27) $Tau^2 = 0.90$; P = 0.03; $I^2 = 71\%$	1.55 (1.02 to 2.36)
Foam dressings versus saline gauze dressing (Kraft 1993; Oleske 1986; Payne 2009)	3 (93)	1.51 (0.78 to 2.90) P = 0.41; $I^2 = 0\%$	1.52 (1.03 to 2.26)
Phenytoin versus saline gauze dressing (Hollisaz 2004)	1 (40)	3.02 (0.97 to 9.35)	1.27 (0.58 to 2.80)
Hydrogel versus hydrocolloid dressings (Brod 1990; Brown-Etris 1996; Darkovich 1990; Motta 1999)	4 (322)	1.11 (0.74 to 1.67) $Tau^2 = 0.08$; P = 0.11; $I^2 = 51\%$	1.08 (0.83 to 1.42)
Foam dressing versus hydrocolloid dressing (Aguilo Sanchez 2002; Bale 1997a; Banks 1994a; Banks 1994c; Seeley 1999; Thomas 1997a)	6 (292)	1.05 (0.81 to 1.36) $Tau^2 = 0.00$; P = 0.67; $I^2 = 0\%$ (Stata: 1.05 (0.73 to 1.23))	1.07 (0.82 to 1.38)
Collagenase ointment versus hydrocolloid dressing (Burgos 2000b; Muller 2001)	2 (61)	1.51 (0.93 to 2.43) P = 0.61; $I^2 = 0\%$	1.48 (0.81 to 2.69)
Iodine-containing dressing versus hydrocolloid dressing (Barrois 1992)	1 (76)	0.90 (0.41 to 1.96)	0.76 (0.45 to 1.27)
Protease-modulating dressing versus hydrocolloid dressing (Graumlich 2003)	1 (65)	1.03 (0.64 to 1.66)	1.15 (0.72 to 1.84)

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Table 2. Direct comparisons for individual interventions - proportion healed - compared with NMA results (*Continued*)

Vapour-permeable dressing versus hydrocolloid dressing (Brown-Etris 2008)	1 (72)	1.01 (0.69 to 1.47)	1.01 (0.58 to 1.77)
Hydrocolloid dressing 4 weeks then alginate dressing 4 weeks versus hydrocolloid dressing (Belmin 2002)	1 (110)	0.35 (0.10 to 1.25)	0.35 (0.09 to 1.33)
Ineligible intervention: skin substitute versus hydrocolloid dressing (Hondé 1994)	1 (168)	1.48 (0.95 to 2.32)	1.48 (0.81 to 2.71)
Foam dressing versus hydrogel (Sopata 2002)	1 (38)	1.11 (0.80 to 1.54)	0.98 (0.71 to 1.36)
Tripeptide copper versus hydrogel (Romanelli 2001)	1 (12)	2.50 (0.76 to 8.19)	2.51 (0.72 to 8.80)
Iodine-containing dressing versus hydrogel (Kaya 2005)	1 (49)	0.64 (0.43 to 0.97)	0.70 (0.43 to 1.14)
Phenytoin versus hydrogel (Hollisaz 2004)	1 (39)	0.71 (0.41 to 1.24)	0.82 (0.42 to 1.61)
Foam dressing versus protease-modulating dressing (Piatkowski 2012)	1 (10)	0.82 (0.49 to 1.38)	0.93 (0.57 to 1.49)
Alginate dressing versus protease-modulating dressing (Brown-Etris 1997)	1 (36)	0.67 (0.08 to 5.75)	0.30 (0.07 to 1.25)
PVP + zinc oxide versus protease-modulating dressing (Zeron 2007)	1 (24)	0.80 (0.28 to 2.27)	0.80 (0.26 to 2.46)
Soft polymer dressing versus foam dressing (Meaume 2003)	1 (38)	0.89 (0.45 to 1.75)	0.89 (0.40 to 1.96)
Combination silicone-foam dressing versus ineligible intervention: skin substitute (Serena 2010)	1 (74)	0.91 (0.22 to 3.77)	0.90 (0.21 to 3.97)

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Table 2. Direct comparisons for individual interventions - proportion healed - compared with NMA results (*Continued*)

Hydrocolloid with/without alginate filler versus ineligible intervention: radiant heat (Thomas 2005)	1 (41)	0.92 (0.41 to 2.06)	0.92 (0.37 to 2.27)
Collagenase ointment versus dextranomer (Parish 1979)	1 (12)	0.35 (0.05 to 2.26) (Stata 0.44 (0.10 to 2.02))	0.44 (0.09 to 2.13)
Collagenase ointment versus sugar + egg white (Parish 1979)	1 (10)	3.00 (0.15 to 59.89) (Stata 3.00 (0.15 to 59.79))	3.00 (0.15 to 61.59)
Dextranomer versus sugar + egg white (Parish 1979)	1 (12)	6.75 (0.44 to 102.80)	6.75 (0.43 to 105.99)
Foam dressing versus basic wound contact dressing (Banks 1994b)	1 (50)	1.17 (0.79 to 1.72)	1.17 (0.67 to 2.06)
Alginate dressing versus ineligible intervention: radiant heat (Price 2000)	1 (58)	0.82 (0.15 to 4.55)	0.82 (0.14 to 4.77)

Table 3. NMA evidence for group network: proportion with complete healing - interventions versus basic dressings

NMA evidence for group network: proportion with complete healing - interventions versus basic dressings				
Patient or population: people with pressure ulcers **Intervention:** dressing or topical agent **Comparison:** basic dressing **Settings:** hospital, community or care home, or combinations				
Contrasts: interventions versus basic dressing	**Relative effect (95% CI)**	**Anticipated absolute effects* (95% CI) - from median of basic dressing control groups in direct evidence**		**Certainty (quality) of the evidence (GRADE)**
		Median CGR	**With interventions**	
Advanced dressings versus basic dressing	RR 1.36 (0.95 to 1.93)	191 per 1000	260 per 1000 (181 to 369)	⊕◯◯◯ Very low[1]
		69 more people healed per 1000 (from 10 fewer to 178 more)		

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Table 3. NMA evidence for group network: proportion with complete healing - interventions versus basic dressings (*Continued*)

Advanced + antimicrobial dressing versus basic dressing	RR 0.42 (0.13 to 1.35)	191 per 1000	80 per 1000 (25 to 258)	⊕◯◯◯ Very low[2]
		111 fewer people healed per 1000 (from 67 more to 166 fewer)		
Antimicrobial dressing versus basic dressing	RR 0.96 (0.52 to 1.77)	191 per 1000	183 per 1000 (99 to 338)	⊕◯◯◯ Very low[2]
		8 fewer people healed per 1000 (from 92 fewer to 147 more)		
Collagenase ointment versus basic dressing	RR 2.01 (1.05 to 3.88)	191 per 1000	384 per 1000 (201 to 741)	⊕⊕◯◯ Low[3]
		193 more people healed per 1000 (from 10 more to 550 more)		
Dextranomer versus basic dressing	RR 4.53 (0.84 to 24.50)	191 per 1000	865 per 1000 (160 to 1000)	⊕◯◯◯ Very low[4]
		674 more people healed per 1000 (from 31 fewer to 1,000 more)		
Phenytoin versus basic dressing	RR 1.12 (0.52 to 2.44)	191 per 1000	214 per 1000 (99 to 466)	⊕◯◯◯ Very low[5]
		23 more people healed per 1000 (from 92 fewer to 275 more)		
Protease-modulating dressing versus basic dressing	RR 1.49 (0.91 to 2.46)	191 per 1000	285 per 1000 (174 to 470)	⊕⊕⊕◯ Moderate[6]
		94 more people healed per 1000 (from 17 fewer to 279 more)		
Sugar + egg white versus basic dressing	RR 0.67 (0.03 to 14.69)	191 per 1000	128 per 1000 (6 to 1000)	⊕◯◯◯ Very low[2]
		63 fewer people healed per 1000 (from 185 fewer to 1000 more)		
Tripeptide copper gel versus basic dressing	RR 3.39 (0.94 to 12.30)	191 per 1000	647 per 1000 (180 to 1000)	⊕⊕◯◯ Low[7]
		456 more people healed per 1000 (from 11 fewer to 1000 more)		

*__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).

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Table 3. NMA evidence for group network: proportion with complete healing - interventions versus basic dressings (*Continued*)

CGR: control group risk; **CI:** confidence interval; **RR:** risk ratio
GRADE Working Group grades of evidence **High certainty (quality):** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate certainty (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 certainty (quality):** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low certainty (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]Majority of evidence at high risk of bias (downgraded once); inconsistency: heterogeneity in direct evidence (downgraded once); imprecision: wide CI (downgraded once).
[2]Majority of evidence at high risk of bias (downgraded once); imprecision: very wide CI (crosses 0.75 and 1.25) (downgraded twice).
[3]Majority of evidence at high risk of bias (downgraded once); imprecision: wide CI (crosses 1.25) and direct evidence on collagenase from three studies, 11 events (downgraded once).
[4]Majority of evidence at high risk of bias (downgraded once): imprecision: wide CI (crosses 1.25) and direct evidence on dextranomer from one study, seven participants and four events (downgraded twice).
[5]Inconsistency: significant difference between direct and indirect estimates (downgraded once); imprecision: very wide CI (crossed 0.75 and 1.25).
[6]Imprecision: wide CI (crosses 1.25) (downgraded once).
[7]Imprecision: wide CI (crosses 1.25) and direct evidence on tripeptide copper gel from one study, six participants and five events (downgraded twice).

Table 4. Direct evidence for grouped interventions - proportion healed

Contrast/comparison	Number of studies (participants)	RR (95% CI) direct evidence Random-effects (inverse variance) Heterogeneity statistics	NMA results (consistency assumption) RR (95% CI)
Advanced dressings versus basic dressings (Alm 1989; Banks 1994b; Colwell 1993; Hollisaz 2004; Kraft 1993; Matzen 1999; Neill 1989a; Oleske 1986; Payne 2009; Thomas 1998; Xakellis 1992)	11 (532)	1.55 (1.10 to 2.19) Tau² = 0.13; P = 0.02; I² = 52%	1.36 (0.95 to 1.93)
Phenytoin versus basic dressing (Hollisaz 2004)	1 (40)	3.02 (0.97 to 9.35)	1.12 (0.52 to 2.44)
Protease-modulating dressing versus	1 (24)	1.25 (0.44 to 3.55)	1.49 (0.91 to 2.46)

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Table 4. Direct evidence for grouped interventions - proportion healed (*Continued*)

basic dressing (Zeron 2007)			
Antimicrobial dressings versus advanced dressings (Barrois 1992; Kaya 2005)	2 (125)	0.69 (0.48 to 0.99) Tau² = 0.00; P = 0.46; I² = 0%	0.71 (0.45 to 1.13)
Collagenase ointment versus advanced dressings (Burgos 2000b; Muller 2001)	2 (61)	1.51 (0.93 to 2.43) Tau² = 0.00; P = 0.61 ; I² = 0%	1.48 (0.83 to 2.64)
Phenytoin versus advanced dressing (Hollisaz 2004)	1 (39)	0.71 (0.41 to 1.24)	0.83 (0.43 to 1.59)
Protease-modulating dressing versus advanced dressing (Brown-Etris 1997; Graumlich 2003; Piatkowski 2012)	3 (112)	1.13 (0.80 to 1.60) Tau² = 0.00; P = 0.84 ; I² = 0% (Stata: 1.12 (0.79 to 1.59))	1.10 (0.74 to 1.64)
Tripeptide copper gel versus advanced dressing (Romanelli 2001)	1 (12)	2.50 (0.76 to 8.19)	2.50 (0.72 to 8.63)
Antimicrobial dressing versus advanced antimicrobial dressing (Sipponen 2008)	1 (37)	2.29 (0.91 to 5.77)	2.29 (0.85 to 6.16)
Collagenase versus dextranomer (part of 3-arm trial) (Parish 1979)	1 (12)	0.35 (0.05 to 2.26) (Stata 0.44 (0.10 to 2.02))	0.44 (0.09 to 2.11)
Collagenase ointment versus sugar + egg white (part of 3-arm trial) (Parish 1979)	1 (10)	3.00 (0.15 to 59.89) (Stata 3.00 (0.15 to 59.79))	3.00 (0.15 to 61.18)
Dextranomer versus sugar + egg white (part of 3-arm trial) (Parish 1979)	1 (12)	6.75 (0.44 to 102.80)	6.75 (0.43 to 105.22)
TOTAL	22 (959)		

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Table 5. Mapping from individual to group interventions

Individual intervention	Group intervention (studies in final network)
Basic wound contact dressing	Basic dressing (12 studies)
Saline gauze dressing	
Polyvinylpyrrolidone	
Hydrocolloid dressing	Advanced dressing (19 studies)
Foam dressing	
Hydrogel dressing	
Soft polymer dressing	
Alginate dressing	
Vapour-permeable dressing	
Combination silicone foam dressing	
Hydrocolloid with/without alginate	
Standard care as described in Ashby 2012	
Honey	Antimicrobial dressing (3 studies)
Iodine-containing dressing	
Ethoxy diaminoacridine + nitrofurazone dressing	
Resin salve	
Hydrocolloid or hydrocolloid silver dressing	Advanced or antimicrobial dressing (1 study)
Protease-modulating dressing	Protease-modulating dressing (4 studies)
Collagenase ointment	Collagenase ointment (3 studies)
Dextranomer	Dextranomer (1 study)

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Table 5. Mapping from individual to group interventions (*Continued*)

Phenytoin topical	Phenytoin topical (1 study)
Sugar + egg white	Sugar + egg white (1 study)
Tripeptide copper gel	Tripeptide copper gel (1 study)

Table 6. Ranks of interventions - group network

Group intervention	Mean rank	SUCRA	Probability at maximum	Rank at maximum probability
Basic dressing	7.3	0.3	30.6	8
Advanced dressing	5.2	0.5	38.8	5
Advanced - antimicrobial dressing	9.4	0.1	57.0	10
Antimicrobial dressing	7.4	0.3	31.9	8
Collagenase ointment	3.3	0.7	39.4	3
Dextranomer	2	0.9	55.3	1
Phenytoin	6.5	0.4	20.5	7
Protease-modulating dressing	4.6	0.6	31.2	4
Sugar + egg white	7	0.3	36.5	10
Tripeptide copper gel	2.3	0.9	36.2	2

Table 7. Interventions in the included studies

Intervention	Number of included studies	Number of participants in included studies	In joined network?	Number of studies in joined individual network	Number of participants in joined individual network

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Table 7. Interventions in the included studies (*Continued*)

Alginate dressings	2	38	Y	2	38
Basic wound contact dressings	2	33	Y	1	24
Collagenase-containing ointment	3	35	Y	3	35
Combination dressing: non-adherent + saline gauze + foam	1	16	N		
Combination dressing: silicone + foam	1	44	Y	1	44
Dextranomer	1	7	Y	1	7
Enamel matrix protein	1	6	N		
Ethoxy-diaminoacridine plus nitrofurazone dressing	1	26	N		
Foam dressings	13	266	Y	13	266
Gauze saline dressings	11	245	Y	10	233
Honey	1	25	N		
Hydrocolloid dressings	22	791	Y	21	715
Hydrocolloid or hydrocolloid silver dressing	1	16	N		
Hydrocolloid with or without alginate filler (hydrocolloid +/- alginate)	1	20	Y	1	20
Hydrocolloid-alginate sequential dressings	1	57	Y	1	57

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Table 7. Interventions in the included studies (*Continued*)

Hydrogel	12	335	Y	10	279
Ineligible intervention: graft + conventional dressing	1	18	N		
Ineligible intervention: growth factor + hyaluronic acid	1	40	N		
Ineligible intervention: growth factor	2	152	N		
Ineligible intervention laser	1	7	N		
Ineligible intervention: NPWT (only included in group analysis)	1	6	N		
Ineligible intervention: povidone iodine + paraffin soaked gauze	1	40	N		
Ineligible intervention: radiant heat	2	53	Y	2	53
Ineligible intervention: skin substitute	2	110	Y	2	110
Ineligible intervention: ultrasound + ultraviolet	1	6	N		
Ineligible intervention: whirlpool + chloramine dressing	1	52	N		
Iodine-containing dressings	2	62	Y	2	62
Lysosyme ointment	1	69	N		
Phenytoin topical	1	21	Y	1	21

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Table 7. Interventions in the included studies (*Continued*)

Polyvinylpyrrolidone + zinc oxide	1	12	Y	1	12
Propylene glycol alginate	1	5	N		
Protease-modulating dressings	5	116	Y	4	76
Resin salve	1	16	N		
Soft polymer dressing	1	18	Y	1	18
Standard care (only included in group analysis)	1	6	N		
Sugar + egg white	1	5	Y	1	5
Sugar + povidone iodine	1	72	N		
Tripeptide copper + Opsite	1	6	Y	1	6
Vapour-permeable dressings	2	57	Y	1	35

Table 8. Contributions matrix - group network

NMA Contrasts	Contributions from each direct evidence contrast	Overall risk of bias
1 vs 2	74.5% **1 vs 2** + 5.5% **1 vs 7** + 7.2% **1 vs 8** + 5.5% **2 vs 7** + 7.2% **2 vs 8**	high
1 vs 3	27.1% **1 vs 2** + 2.0% **1 vs 7** + 2.6% **1 vs 8** + 31.8% **2 vs 4** + 2.0% **2 vs 7** + 2.6% **2 vs 8** + 31.8% **3 vs 4**	high
1 vs 4	39.8% **1 vs 2** + 2.9% **1 vs 7** + 3.9% **1 vs 8** + 46.6% **2 vs 4** + 2.9% **2 vs 7** + 3.9% **2 vs 8**	high

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Table 8. Contributions matrix - group network (*Continued*)

1 vs 5	39.8% **1 vs 2** + 2.9% **1 vs 7** + 3.9% **1 vs 8** + 46.6% **2 vs 5** + 2.9% **2 vs 7** + 3.9% **2 vs 8**	high
1 vs 6	26.1% **1 vs 2** + 1.9% **1 vs 7** + 2.5% **1 vs 8** + 30.6% **2 vs 5** + 1.9% **2 vs 7** + 2.5% **2 vs 8** + 26.8% **5 vs 6** + 3.8% **5 vs 9** + 3.8% **6 vs 9**	high
1 vs 7	37.8% **1 vs 2** + 13.4% **1 vs 7** + 3.7% **1 vs 8** + 41.4% **2 vs 7** + 3.7% **2 vs 8**	low
1 vs 8	40.8% **1 vs 2** + 3.0% **1 vs 7** + 9.3% **1 vs 8** + 3.0% **2 vs 7** + 43.8% **2 vs 8**	low
1 vs 9	23.6% **1 vs 2** + 1.7% **1 vs 7** + 2.3% **1 vs 8** + 27.6% **2 vs 5** + 1.7% **2 vs 7** + 2.3% **2 vs 8** + 13.2% **5 vs 6** + 14.3% **5 vs 9** + 13.2% **6 vs 9**	high
1 vs 10	39.8% **1 vs 2** + 2.9% **1 vs 7** + 3.9% **1 vs 8** + 2.9% **2 vs 7** + 3.9% **2 vs 8** + 46.9% **2 vs 10**	low
Whole network	**8.7% 1 vs 2 + 2.1% 1 vs 7 + 1.6% 1 vs 8 + 14.9% 2 vs 4 + 19.6% 2 vs 5 + 7.3% 2 vs 7 + 8.2% 2 vs 8 + 8.4% 2 vs 10 + 8.4% 3 vs 4 + 10.5% 5 vs 6 + 5.2% 5 vs 9 + 5.1% 6 vs 9**	**high**

Key to interventions: 1 = basic dressing; 2 = advanced dressing; 3 = advanced +/- antimicrobial dressing; 4 = antimicrobial dressing; 5 = collagenase ointment; 6 = dextranomer; 7 = phenytoin; 8 = protease-modulating dressing; 9 = sugar + egg white; 10 = tripeptide copper gel
Risk of bias for direct contrasts: Low - 1 vs 7; 1 vs 8; 2 vs 7; 2 vs 8; 2 vs 10; 5 vs 6; 5 vs 9; 6 vs 9.
High risk of bias: 1 vs 2; 2 vs 4; 2 vs 5; 3 vs 4

Table 9. Inconsistency factors - individual network

	Common heterogeneity estimate within each loop			**Common heterogeneity estimate for network: tau² (network) = 0.0435**	
Loop	**Ratio of RR (90% CI)**	**P value**	**Loop heterogeneity tau² (loop)**	**Ratio of RR (90% CI)**	**P value**
Saline gauze - hydrogel - phenytoin	3.90 (1.19 to 12.77)	0.059	0.000	3.75 (90%CI 1.14 to 12.29)	0.067

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Table 9. Inconsistency factors - individual network (*Continued*)

Saline gauze - foam - hydrogel	1.64 (0.27 to 9.99)	0.651	0.512	1.21 (90%CI 0.56 to 2.63)	0.682
Hydrocolloid - hydrogel - iodine containing dressing	1.26 (0.44 to 3.61)	0.721	0.084	1.28 (90%CI 0.59 to 2.75)	0.602
Foam - hydrocolloid - protease-modulating	1.25 (0.66 to 2.35)	0.562	0	1.24 (90%CI 0.66 to 2.35)	0.572
Foam - hydrocolloid - hydrogel	1.13 (0.7 to 1.83)	0.675	0.016	1.16 (90%CI 0.77 to 1.75)	0.548
Saline gauze - foam - hydrocolloid	1.04 (0.45 to 2.41)	0.936	0.084	1.04 (90%CI 0.55 to 1.96)	0.919
Saline gauze - hydrocolloid - hydrogel	1.01 (0.33 to 3.11)	0.993	0.244	1.09 (90%CI 0.62 to 1.89)	0.808

Table 10. Inconsistency: node splitting - individual network

Contrast	Direct evidence RR (95% CI)	Indirect evidence RR (95% CI)	RR direct/RR indirect (90% CI)	P value	tau²
Foam versus saline gauze	1.52 (0.73 to 3.16)	1.54 (0.95 to 2.49)	0.99 (90% CI 0.47 to 2.05)	0.973	0.22
Hydrocolloid versus saline gauze	1.41 (0.88 to 2.26)	1.49 (0.87 to 2.56)	0.95 (90% CI 0.53 to 1.69)	0.876	0.22
Hydrogel versus saline gauze	1.67 (0.86 to 3.22)	1.52 (0.91 to 2.54)	1.10 (90% CI 0.57 to 2.12)	0.820	0.22
Phenytoin versus saline gauze	3.01 (0.93 to 9.71)	0.29 (0.05 to 1.51)	10.06 (90% CI 1.35 to 75.13)	0.059	0.15
Hydrocolloid versus foam	0.95 (0.68 to 1.32)	0.91 (0.57 to 1.44)	1.04 (90% CI 0.65 to 1.68)	0.881	0.23
Hydrogel versus foam	0.90 (0.51 to 1.58)	1.10 (0.72 to 1.68)	0.81 (90% CI 0.45 to 1.47)	0.568	0.23

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Table 10. Inconsistency: node splitting - individual network (*Continued*)

Protease-modulating dressing versus foam	1.22 (0.61 to 2.41)	0.94 (0.46 to 1.92)	1.29 (90% CI 0.56 to 2.94)	0.614	0.22
Hydrogel versus hydrocolloid	1.10 (0.76 to 1.59)	1.07 (0.68 to 1.68)	1.02 (90% CI 0.63 to 1.67)	0.935	0.24
Iodine-containing dressing versus hydrocolloid	0.90 (0.36 to 2.19)	0.68 (0.35 to 1.33)	1.31 (90% CI 0.51 to 3.32)	0.638	0.22
Protease-modulating dressing versus hydrocolloid	1.02 (0.53 to 1.97)	1.32 (0.63 to 2.76)	0.78 (90% CI 0.34 to 1.77)	0.614	0.22
Iodine-containing dressing versus hydrogel	0.64 (0.35 to 1.16)	0.84 (0.32 to 2.15)	0.77 (90% CI 0.30 to 1.95)	0.639	0.22
Phenytoin versus hydrogel	0.71 (0.38 to 1.34)	7.18 (0.68 to 75.47)	0.10 (90% CI 0.01 to 0.74)	0.059	0.15

Table 11. Inconsistency and consistency NMA results

Contrast	**Design 1 (pairwise)**	**NMA results for design 1 Inconsistency assumption RR (95% CI)**	**Design 2 (3-arm)**	**(NMA results for design 2 Inconsistency assumption RR (95% CI)**	**NMA results Consistency assumption RR (95% CI)**
Foam versus saline gauze	7 vs 1 (3 studies)	1.53 (0.71 to 2.22)	NA	NA	1.52 (1.03 to 1.85)
Hydrocolloid versus saline gauze	8 vs 1 (4 studies)	1.50 (0.9 to 1.92)	NA	NA	1.43 (1.00 to 1.70)
Hydrogel versus saline gauze	10 vs 1 (2 studies; heterogeneity)	1.16 (0.51 to 1.73)	10 vs 1 vs 14 (one 3-arm study)	4.22 (1.26 to 7.65)	1.55 (1.02 to 1.91)
Phenytoin versus saline gauze	NA	NA	14 vs 1 vs 10 (one 3-arm study)	3.02 (0.86 to 5.56)	1.28 (0.58 to 1.88)
Hydrocolloid versus collagenase	8 vs 5 (2 studies)	0.68 (0.35 to 0.95)	NA	NA	0.68 (0.37 to 0.91)

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Table 11. Inconsistency and consistency NMA results (*Continued*)

Hydrocolloid versus foam	8 vs 7 (6 studies)	0.96 (0.67 to 1.13)	NA	NA	0.94 (0.73 to 1.07)
Hydrogel versus foam	10 vs 7 (1 study)	0.90 (0.48 to 1.22)	NA	NA	1.02 (0.74 to 1.2)
Protease-modulating versus foam	15 vs 7 (1 study)	1.22 (0.58 to 1.76)	NA	NA	1.08 (0.67 to 1.36)
Hydrogel versus hydrocolloid	10 vs 8 (4 studies)	1.11 (0.74 to 1.35)	NA	NA	1.09 (0.83 to 1.24)
Iodine-containing dressing versus hydrocolloid	13 vs 8 (1 study)	0.90 (0.35 to 1.43)	NA	NA	0.76 (0.45 to 0.97)
Protease-modulating versus hydrocolloid	15 vs 8 (1 study)	1.03 (0.5 to 1.46)	NA	NA	1.15 (0.72 to 1.45)
Iodine-containing dressing versus hydrogel	13 vs 10 (1 study)	0.64 (0.33 to 0.9)	NA	NA	0.70 (0.43 to 0.88)
Phenytoin versus hydrogel	NA	NA	14 vs 10 vs 1 (one 3-arm study)	0.71 (0.33 to 1.04)	0.82 (0.42 to 1.14)

Table 12. Inconsistency factors - group network

Loop	Ratio of RR (90% CI)	P value	Loop heterogeneity - tau²
Basic dressing - advanced dressing - phenytoin	3.04 (0.71 to 13.06)	0.210	0.085
Basic dressing - advanced dressing - protease-modulating dressing	1.36 (0.39 to 4.73)	0.682	0.091

Table 13. Inconsistency: node splitting - group network

Contrast	Direct evidence RR (95% CI)	Indirect evidence RR (95% CI)	RR direct/RR indirect (90% CI)	P value	Tau²
Advanced dressing versus basic dressing	1.41 (0.96 to 2.09)	1.10 (0.33 to 3.73)	1.28 (90% CI 0.44 to 3.76)	0.705	0.221791

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Table 13. Inconsistency: node splitting - group network (*Continued*)

Phenytoin versus basic dressing	3.02 (0.97 to 9.38)	0.24 (0.06 to 1.02)	12.51 (90% CI 1.87 to 83.55)	0.029	0.048414
Protease-modulating dressing versus basic dressing	1.25 (0.4 to 3.87)	1.60 (0.87 to 2.95)	0.78 (90% CI 0.27 to 2.3)	0.707	0.221734
Phenytoin versus advanced dressing	0.71 (0.41 to 1.25)	8.94 (0.96 to 83.43)	0.08 (90% CI 0.01 to 0.53)	0.029	0.048424
Protease-modulating dressing versus advanced dressing	1.13 (0.71 to 1.79)	0.88 (0.27 to 2.92)	1.28 (90% CI 0.44 to 3.76)	0.706	0.221781

Table 14. Inconsistency and consistency NMA results - group network

Contrast	Design 1 (pairwise)	NMA results for design 1 Inconsistency assumption RR (95% CI)	Design 2 (3-arm)	NMA results for design 2 Inconsistency assumption RR (95% CI)	NMA results Consistency assumption RR (95% CI)
Advanced dressing versus basic dressing	2 vs 1 (10 studies; heterogeneity)	1.21 (0.88 to 1.67)	2 vs 1 vs 7 (1 study)	4.22 (1.41 to 12.68)	1.36 (0.95 to 1.93)
Phenytoin versus basic dressing	NA	NA	7 vs 1 vs 2 (1 study)	3.02 (0.96 to 9.44)	1.12 (0.52 to 2.44)
Protease-modulating dressing versus basic dressing	8 vs 1 (1 study)	1.25 (0.44 to 3.59)	NA	NA	1.49 (0.91 to 2.46)
Phenytoin versus advanced dressing	NA	NA	7 vs 2 vs 1 (1 study)	0.71 (0.4 to 1.27)	0.83 (0.43 to 1.59)
Protease-modulating dressing versus advanced dressing	8 vs 2 (3 studies)	1.12 (0.78 to 1.62)	NA	NA	1.10 (0.74 to 1.64)

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Table 15. Ranks of interventions - individual network

Intervention	Mean rank	SUCRA	Probability at maximum	Rank at maximum probability
Saline gauze	16.3	0.2	16.2	17
Alginate dressing	12.4	0.4	10.8	19
Sequential hydrocolloid alginate dressings	18.6	0.1	34.6	21
Basic wound contact dressing	12.4	0.4	11.6	15
Collagenase ointment	6.9	0.7	13.5	6
Dextranomer	3.5	0.9	40.8	1
Foam dressing	10.3	0.5	15.0	10
Hydrocolloid dressing	11.6	0.5	18.6	11
Hydrocolloid with/ without alginate filler	11.9	0.5	12.4	21
Hydrogel	9.9	0.6	14.9	10
Ineligible intervention - radiant heat	11.4	0.5	12.8	20
Ineligible intervention - skin substitute	6.6	0.7	15.0	4
Iodine-containing dressing	15.3	0.3	13.4	17
Phenytoin	12.6	0.4	9.4	16
Protease-modulating dressing	9.3	0.6	11.8	8
PVP + zinc oxide	11.8	0.5	8.1	20
Silicone + foam dressing	8.9	0.6	10.0	2
Soft polymer dressing	11.9	0.5	7.7	16
Sugar + egg white	14.4	0.3	31.8	21

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Table 15. Ranks of interventions - individual network (*Continued*)

Tripeptide copper gel	3.7	0.9	25.3	1
Vapour-permeable dressing	11.4	0.5	8.9	13

Table 16. Direct evidence: comparison of time-to-event outcomes and dichotomous data

Contrast	Study	Risk ratio (95% CI)	Hazard ratio (95% CI)	Median times to healing
Hydrocolloid versus saline gauze	Alm 1989 (6 weeks)	3.43 (1.32 to 8.89)	1.88 (0.80 to 4.45)	
	Xakellis 1992 (26 weeks)	1.04 (0.82 to 1.32)	1.67 (0.81 to 3.45)	9 days versus 11 days (P = 0.12; unadjusted); hydrocolloid time to healing consistently shorter across time period
	Meta-analysis of 2 studies in 95 participants (Alm 1989; Xakellis 1992) - selected	Meta-analysis: 1.72 (0.54 to 5.47) I^2 = 82%, P = 0.02	Meta-analysis: 1.75 (95% CI 1.00 to 3.05 I^2 = 0%, P = 0.84	
Hydrogel versus hydrocolloid	Brod 1990 (43 participants) (8 weeks)	1.11 (0.74 to 1.67)	1.30 (0.54 to 3.13)	32 days versus 42 days (P = 0.56); Kaplan-Meier curves crossing
Protease-modulating dressing versus hydrocolloid	Graumlich 2003 (65 participants) (8 weeks)	1.03 (0.64 to 1.66)	1.34 (0.67 to 2.65)	4 weeks and 7 weeks (estimated from Kaplan-Meier plot); protease-modulating dressing had more healing from 5 weeks
Collagenase ointment versus hydrocolloid	Muller 2001 (24 participants) (16 weeks - probably)	1.57 (0.95 to 2.61)	2.58 (1.00 to 6.65)	
Hydrocolloid +/- alginate versus ineligible: radiant heat	Thomas 2005 (41 participants) (12 weeks)	0.92 (0.41 to 2.06)	0.64 (0.23 to 1.77)	> 90 days and 70 days (estimated from Kaplan-Meier plot); radiant heat had consistently more healing at all time points

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Table 16. Direct evidence: comparison of time-to-event outcomes and dichotomous data (*Continued*)

Foam versus saline gauze	Payne 2009 (36 participants) (4 weeks)	1.33 (0.62 to 2.88)	1.12 (0.42 to 3.01)	

Table 17. NMA results and ranks for original and sensitivity analyses

	Risk ratio (95% CI) intervention versus saline gauze			**Mean rank (of 21 interventions unless otherwise stated)**		
Intervention	**Original**	**Sensitivity analysis 1. Very high risk of bias studies excluded**	**Sensitivity analysis 2. Complete case**	**Original saline 16.3**	**Sensitivity analysis 1. Very high risk of bias excluded (rank of 18) saline = 14.1**	**Sensitivity analysis 2. Complete case saline = 16.3**
Alginate dressing	1.10 (0.11 to 10.57)	1.14 (0.11 to 11.45)	1.08 (0.11 to 10.69)	12.4	11	12.6
Sequential hydrocolloid alginate dressing	s0.50 (0.12 to 1.99)	0.52 (0.12 to 2.20)	0.51 (0.12 to 2.1)	18.6	15.8	18.5
Basic wound contact dressing	1.30 (0.65 to 2.59)	1.33 (0.61 to 2.93)	1.44 (0.76 to 2.73)	12.4	10.6	11.1
Collagenase ointment	2.11 (1.06 to 4.21)	2.35 (1.02 to 5.44)	2.01 (0.98 to 4.12)	6.9	5.2	7.4
Dextranomer	4.75 (0.86 to 26.34)	5.29 (0.87 to 32.26)	4.51 (0.79 to 25.88)	3.5	2.9	3.8
Foam dressing	1.52 (1.03 to 2.26)	1.56 (1 to 2.43)	1.45 (0.97 to 2.15)	10.3	9	11.2
Hydrocolloid dressing	1.43 (1 to 2.05)	1.50 (0.99 to 2.26)	1.47 (1.02 to 2.12)	11.6	9.7	11.1
Hydrocolloid with/without alginate filler	1.23 (0.06 to 24.86)	not in network	1.33 (0.06 to 27.37)	11.9	not in network	11.5
Hydrogel dressing	1.55 (1.02 to 2.36)	1.74 (1.09 to 2.77)	1.56 (1.02 to 2.37)	9.9	7.5	9.8

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Table 17. NMA results and ranks for original and sensitivity analyses (*Continued*)

Ineligible: radiant heat	1.34 (0.08 to 23.53)	1.39 (0.07 to 25.76)	1.62 (0.09 to 29.28)	11.4	not in network	10.2
Ineligible: skin substitute	2.12 (1.05 to 4.28)	not in network	1.92 (0.91 to 4.02)	6.6	9.8	7.6
Iodine-containing dressing	1.08 (0.58 to 2.02)	1.19 (0.6 to 2.38)	1.13 (0.58 to 2.18)	15.3	12.1	14.7
Phenytoin	1.28 (0.58 to 2.81)	1.66 (0.71 to 3.89)	1.3 (0.57 to 2.96)	12.6	8.6	12.4
Protease-modulating dressing	1.64 (0.92 to 2.93)	1.71 (0.89 to 3.26)	1.63 (0.89 to 2.97)	9.3	7.9	9.4
PVP + ZnO	1.32 (0.37 to 4.64)	1.37 (0.36 to 5.19)	1.30 (0.35 to 4.78)	11.8	10.2	11.9
Combined silicone foam dressing	1.93 (0.37 to 9.92)	not in network	1.74 (0.33 to 9.32)	8.9	not in network	9.7
Soft polymer dressing	1.35 (0.56 to 3.27)	1.39 (0.53 to 3.63)	1.29 (0.52 to 3.23)	11.9	10.2	12.3
Sugar + egg white	0.70 (0.03 to 15.6)	0.78 (0.03 to 18.33)	0.67 (0.03 to 15.11)	14.4	12	14.6
Tripeptide copper gel	3.88 (1.03 to 14.56)	2.78 (0.90 to 8.58)	3.89 (1.01 to 15)	3.7	4.8	3.8
Vapour-permeable dressing	1.44 (0.74 to 2.8)	1.51 (0.70 to 3.25)	1.48 (0.72 to 3.04)	11.4	9.5	11

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APPENDICES

Appendix 1. Pressure ulcer grading

One of the most widely recognised systems for categorising pressure ulcers is that of the National Pressure Ulcer Advisory Panel (NPUAP). Their international classification recognises four categories or stages of pressure ulcer and two categories of unclassifiable pressure injury, in which wound depth and/or extent, or both, cannot be accurately determined; unclassifiable pressure ulcers are generally severe and would be grouped clinically with Stage 3 or Stage 4 ulcers (EPUAP-NPUAP-PPPIA 2014; NPUAP 2016):

- **Category/Stage 1: Non-blanchable erythema of intact skin:** Intact skin with a localized area of non-blanchable erythema, which may appear differently in darkly pigmented skin. Presence of blanchable erythema or changes in sensation, temperature, or firmness may precede visual changes. Color changes do not include purple or maroon discoloration; these may indicate deep tissue pressure injury.
- **Category/Stage 2: Partial-thickness skin loss with exposed dermis:** Partial-thickness loss of skin with exposed dermis. The wound bed is viable, pink or red, moist, and may also present as an intact or ruptured serum-filled blister. Adipose (fat) is not visible and deeper tissues are not visible. Granulation tissue, slough and eschar are not present. These injuries commonly result from adverse microclimate and shear in the skin over the pelvis and shear in the heel. This stage should not be used to describe moisture associated skin damage (MASD) including incontinence associated dermatitis (IAD), intertriginous dermatitis (ITD), medical adhesive related skin injury (MARSI), or traumatic wounds (skin tears, burns, abrasions).
- **Category/Stage 3: Full-thickness skin loss:** Full-thickness loss of skin, in which adipose (fat) is visible in the ulcer and granulation tissue and epibole (rolled wound edges) are often present. Slough and/or eschar may be visible. The depth of tissue damage varies by anatomical location; areas of significant adiposity can develop deep wounds. Undermining and tunneling may occur. Fascia, muscle, tendon, ligament, cartilage and/or bone are not exposed. If slough or eschar obscures the extent of tissue loss this is an Unstageable Pressure Injury.
- **Category/Stage 4: Full-thickness skin and tissue loss:** Full-thickness skin and tissue loss with exposed or directly palpable fascia, muscle, tendon, ligament, cartilage or bone in the ulcer. Slough and/or eschar may be visible. Epibole (rolled edges), undermining and/or tunneling often occur. Depth varies by anatomical location. If slough or eschar obscures the extent of tissue loss this is an Unstageable Pressure Injury.

The two additional categories of unclassifiable wounds are:

- **Unstageable/unclassified - Obscured full-thickness skin and tissue loss:** Full-thickness skin and tissue loss in which the extent of tissue damage within the ulcer cannot be confirmed because it is obscured by slough or eschar. If slough or eschar is removed, a Stage 3 or Stage 4 pressure injury will be revealed. Stable eschar (i.e. dry, adherent, intact without erythema or fluctuance) on the heel or ischemic limb should not be softened or removed.

- **Deep Tissue Pressure Injury - Persistent non-blanchable deep red, maroon or purple discoloration:** Intact or non-intact skin with localized area of persistent non-blanchable deep red, maroon, purple discoloration or epidermal separation revealing a dark wound bed or blood filled blister. Pain and temperature change often precede skin color changes. Discoloration may appear differently in darkly pigmented skin. This injury results from intense and/or prolonged pressure and shear forces at the bone-muscle interface. The wound may evolve rapidly to reveal the actual extent of tissue injury, or may resolve without tissue loss. If necrotic tissue, subcutaneous tissue, granulation tissue, fascia, muscle or other underlying structures are visible, this indicates a full thickness pressure injury (Unstageable, Stage 3 or Stage 4). Do not use DTPI to describe vascular, traumatic, neuropathic, or dermatologic conditions.

Photographs of the different PU stages are included in the US Agency for Healthcare Research and Quality guideline (AHRQ 2013).

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Appendix 2. Glossary of NMA terms

Arm-specific outcomes/arm-level data: raw outcome data (e.g. mean (SD) or risk) for each arm of the trial (see treatment **contrast**).
Assumptions for NMA: in common with all meta-analysis, the true treatment effect across trials is assumed to be described by a **fixed-effect** or **random-effects** model**.** Additionally, **transitivity** is assumed and, concurrently, **exchangeability** and **consistency**.
Baseline risk: the absolute risk of the outcome in the 'control' group. This is affected by the presence of **prognostic factors**. Some authors have used the baseline risk as a proxy **effect modifier**, but in general the effect estimate (RR/OR/HR) is independent of the baseline risk; on the other hand, the absolute risk difference depends on baseline risk.
Bayesian approach: the explicit quantitative use of external evidence in the design, monitoring, analysis, interpretation of a health-care evaluation. In the Bayesian paradigm, prior beliefs about parameters in the models are specified and factored into the estimation. Posterior distributions of model parameters are then derived from the prior information and the observed data. In NMA, it is common to use non-informative priors for effect estimates.
Coherence/consistency: the direct effect estimate (e.g. mean difference or log odds ratio) is the same as the sum of the indirect effect estimates.
Connected network: a group of linked interventions, such that every trial in the network has at least one intervention in common with at least one other trial. Sometimes individual comparisons are not connected to the rest of the network (disconnected network) and can sometimes be joined in by extending the network to include **supplementary** interventions.
Contour-enhanced funnel plot: contour-enhanced funnel plots show areas of statistical significance, and they can help in distinguishing publication bias from other possible reasons for asymmetry. In a network of interventions, each study estimates the relative effect of *different* interventions, so asymmetry in the funnel plot cannot be judged. To account for this, an adaptation of the funnel plot can be used, in which the standard error is plotted against an adjusted effect size for each study: the adjusted effect size for a comparison is the study-specific effect size minus the mean for the meta-analysis for that comparison.
Contrast/comparison/study-level data: outcome data for the comparison (e.g. mean difference, odds ratio).
Credible interval (CrI): the 95% credible interval is the range within which the mean value lies with posterior probability of 95%.
Decision space/decision set: the interventions in the decision set are the focal treatments of interest to systematic review authors.
Direct evidence/direct comparison/direct contrast: head-to-head comparison of two treatments, for example, A versus B (see **indirect evidence**).
Edge: line representing a direct contrast on a **network diagram**.
Effect modifier: effect modification occurs when the effect of A versus B (as the RR/OR/HR for binary outcomes) is significantly different in two or more subgroups, and this leads to **heterogeneity**, either within trials or between trials, or both. Factors that give rise to subgroup effects are called effect modifiers, and it is important to identify potential effect modifiers and allow for them in the analysis. The identification of significant effect modifiers may lead to stratification (separate analyses for each subgroup) or to a decision not to combine data from different trials in a meta-analysis. In general, trials have different distributions of effect modifiers (e.g. proportion of people with and without diabetes), leading to **inconsistency** between trials in the treatment effect. This is often magnified when there is a network of different contrasts.
Exchangeability: it is assumed that treatments in a NMA are exchangeable, so, if treatment B had been given to participants in the indirect A versus C trials and if A had been given in the B versus C indirect trials, then the true AB differences in these indirect studies would be identical to the true AB difference in direct A versus B trials, or at least from the same common distribution. Furthermore, if participants in other trials within the wider linked network (e.g. D versus E trials) were given A and B, the AB differences would also be the same or from the same distribution. This assumption breaks down when there are **effect modifiers**.
Fixed-effect: the true treatment effect is assumed to be constant across trials (fixed-effect) - see also **random-effects** and **transitivity**.
Global inconsistency: inconsistency across a network is described as global inconsistency. It can be evaluated statistically by fitting models that allow and do not allow for inconsistency. See also: **Inconsistency/incoherence:**
Heterogeneity in a NMA: participants are not randomised to different trials. Therefore, there may be systematic differences in study characteristics or the distribution of participant characteristics across trials. If these characteristics influence the treatment effects (i.e. are **effect modifiers**), then there are systematic differences in treatment effects across trials, which is called between-trial heterogeneity. There may also be within-trial heterogeneity if there are subgroups of an effect modifier for which results are reported separately. In a NMA, the term, '**heterogeneity**' applies to variation in effect modifiers *within* a single contrast (e.g. A versus B); the term, '**inconsistency**' refers to the imbalance in effect modifiers *between* contrasts.
Heterogeneity variance parameter (tau²): in a **random-effects** model we assume there is heterogeneity for each pairwise comparison (e.g. A versus B) with variance (tau^2_{AB}), but in a NMA we often assume that there is a common heterogeneity amongst all the contrasts in the network; this common heterogeneity has a variance (tau²), which is called the 'heterogeneity variance parameter'. It can be compared with empirical distributions of heterogeneity values typically found in meta-analyses (Salanti 2014; Turner 2012).

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Inconsistency/incoherence: this occurs when the effect estimate derived from an indirect contrast is not the same as the effect estimate derived from a direct contrast. For example, in a network of three interventions, there is inconsistency if d_{AB}(direct) d_{AB}(indirect), where d_{AB}(indirect) = d_{AC}(direct) - d_{BC}(direct); the effect estimates are given as mean differences or log(odds ratios/risk ratios/hazard ratios). Note that in order to investigate inconsistency there must be both indirect and direct evidence (loops in the network). See also **global inconsistency**.

Inconsistency factor: this is the absolute difference between the direct and indirect estimates on the log scale (or the logarithm of the ratio of the two odds/hazard ratios) for one of the contrasts in a **loop**. A statistically low powered z-test and a 90% or 95% confidence interval (CI) of the inconsistency is computed to determine whether this difference is significant.

Indirect evidence/indirect comparison/indirect contrast: comparison of two treatments, for example, A versus B, obtained from combinations of other comparisons (e.g. trials comparing A versus C and trials comparing B with C) (see **direct evidence**).

Indirect comparison meta-analysis: meta-analysis of a set of treatments that are linked via common comparator(s), but none are compared directly; evidence is combined in a single internally consistent model.

Leverage: this is the effective number of parameters of the model, which is calculated differently for fixed-effect and random-effects models, with the latter having greater complexity.

Likelihood (function): the likelihood function is a tool for inferring the underlying distribution of the observed data. To do this, we propose a **model** to represent the data - often a parametric distribution is assumed (e.g. binomial) - and unknown parameters of that distribution are determined, given the data, by maximising the likelihood (the larger the likelihood, the closer the model fit).

Loop (of evidence): combination of direct and indirect evidence, such that the interventions in the network diagram can be linked to form a closed loop.

Meta-analysis: a statistical synthesis of the results from two or more separate studies. Methods involve calculating a weighted average of effect estimates from the separate studies.

Mixed treatment comparison meta-analysis: another name for **network meta-analysis**.

Model: a statistical model is a (simplified) mathematical representation of the system we wish to learn about, and which generates our observed data. The model will usually depend on some known factors, such as other variables measured alongside the data, and some unknown parameters that we wish to determine. Then having determined the unknown parameters, the model should be able to simulate data that are an approximation of the real data, allowing us to make inferences from the data.

Multi-arm trial: individual trial that compares more than two interventions.

Network: trials must be linked in a network of interventions, such that every trial in the network has at least one intervention in common with at least one other trial.

Network diagram: graphical representation of the interventions in the network. It consists of **nodes** representing the interventions and **edges** representing the contrasts. The amount of available information can be presented by 'weighting' the nodes and edges using different node sizes and line thicknesses according to the number of studies reporting that treatment or contrast respectively. Other types of weighting are discussed in Chaimani 2013b.

Network meta-analysis (NMA): NMA is the simultaneous combination of data from randomised comparisons of multiple competing treatments (A versus B, A versus C, A versus D, B versus D, and so on), to deliver an internally consistent set of estimates while respecting the randomisation in the evidence. The use of indirect estimates can provide information on contrasts for which no trials exist. It can also improve the precision of the direct estimate by reducing the width of the CIs compared with the direct evidence alone.

Node: intervention represented on a network diagram, usually by a circle of weighted size.

Node splitting: a method of assessing inconsistency. A 'leave-one comparison-out' approach, often called 'node splitting,' is applied, with each direct contrast being excluded from the network and then estimating the difference between this direct evidence and the indirect evidence from the network.

Pairwise meta-analysis: meta-analysis of one or more trials of direct comparisons (e.g. A versus B) - see **direct evidence**.

Prognostic factors: population or study characteristics that affect the risk of the outcome. In a sufficiently large randomised trial that is free from bias, prognostic factors are distributed evenly between intervention groups and do not affect the effect estimate (RR/OR/HR for binary outcomes) unless they are **effect modifiers**, but they do affect the **baseline risk** and absolute risk difference.

Random-effects: trial-specific treatment differences are assumed to be from a common distribution - see also **fixed-effect** and **transitivity**.

Ranking: ordering of treatments according to their relative effectiveness.

Rankogram: graph of probability versus rank order for a particular treatment. Rankograms are based on the uncertainty in the effect estimates. So if two treatments A and B are each compared with the reference intervention and the CIs for the effect overlap, then each treatment will have some probability of being the most effective. If there is no overlap and A is better than B, then the probability of A being the best will be 1.

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Sparse data: data with wide CIs because of few events as a consequence of small studies or short follow-up periods.
Study-level data: see **contrast**.
SUCRA: Surface Under the Cumulative RAnking. This is a measure of the probability that the given treatment is the best. Thus, a SUCRA would be 1 (or 100%) when a treatment was certain to be the best and 0 (0%) when a treatment was certain to be the worst.
Supplementary set (of interventions): interventions added to the network to provide additional evidence on relative treatment effects of the **decision set**. This may be to connect an otherwise unconnected network of treatments, to increase the precision of the treatment effect estimates or to help address between-trial heterogeneity.
Transitivity: NMA requires a transitivity assumption, such that there is no imbalance in the distribution of **effect modifiers** across the different types of treatment contrasts (see also **exchangeability**).
'Unadjusted' meta-analysis: meta-analysis of all the treatment arms for a particular treatment (e.g. all A arms). This breaks the randomisation and should not be done.
References include: Caldwell 2005; Caldwell 2014; Chaimani 2013a; Chaimani 2013b; Cipriani 2013; Dias 2013; Dias 2016; Grant 2013; Jansen 2013; Lu 2004; Salanti 2008; Salanti 2011; Salanti 2014; Soares 2014; Thorlund 2012; Tu 2012; White 2012.

Appendix 3. Search strategies

The Cochrane Central Register of Controlled Trials (CENTRAL)
#1MeSH descriptor: [Bandages] explode all trees
#2MeSH descriptor: [Alginates] explode all trees
#3MeSH descriptor: [Hydrogels] explode all trees
#4MeSH descriptor: [Honey] explode all trees
#5MeSH descriptor: [Silver] explode all trees
#6MeSH descriptor: [Silver Sulfadiazine] explode all trees
#7MeSH descriptor: [Charcoal] explode all trees
#8MeSH descriptor: [Silicones] explode all trees
#9(dressing* or pad or pads or gauze or tulle or film or bead or foam* or non-adherent or "non adherent" or hydrocolloid* or "sodium hyaluronate" or alginat* or hydrogel* or silver* or honey* or matrix or iodine* or "protease modulat*" or "capillary action" or charcoal or silicon* or polymer*):ti,ab,kw
#10((odour or odor) near/3 absorb*):ti,ab,kw
#11(primapore or curasorb or seasorb or sorbsan or advadraw or vacutex or tegaderm or opsite or allevyn or biatain or medihoney or activon tulle or granuflex or "nu derm" or aquacel or iodoflex or iodozyme or xeroform or carboflex or cutimed sorbact or promogran or acticoat or "urgosorb silver" or mepitel or urgotul):ti,ab,kw
#12{or #1-#11}
#13MeSH descriptor: [Metronidazole] explode all trees
#14metronidazole:ti,ab,kw
#15MeSH descriptor: [Anti-Bacterial Agents] explode all trees
#16MeSH descriptor: [Administration, Topical] explode all trees
#17{and #15-#16}
#18(topical near/2 (antibiotic* or antimicrobial* or antibacterial*)):ti,ab,kw
#19MeSH descriptor: [Iodophors] explode all trees
#20{and #16, #19}
#21((topical near/2 iodin*) or ("cadexomer iodine")):ti,ab,kw
#22MeSH descriptor: [Collagenases] explode all trees
#23{and #16, #22}
#24(topical near/2 collagen*):ti,ab,kw
#25MeSH descriptor: [Phenytoin] explode all trees
#26{and #16, #25}
#27(topical near/2 phenytoin):ti,ab,kw
#28MeSH descriptor: [Zinc Oxide] explode all trees
#29{and #16, #28}
#30(topical near/2 zinc):ti,ab,kw
#31(iodosorb or actiformcool or aquaflo or flamazine or silvadene):ti,ab,kw

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#32MeSH descriptor: [Ointments] explode all trees
#33(ointment* or lotion* or cream* or powder* or gel or gels):ti,ab,kw
#34(topical next (agent* or preparation* or therap* or treatment*)):ti,ab,kw
#35{or #13-#14, #17-#18, #20-#21, #23-#24, #26-#27, #29-#34}
#36{or #12, #35}
#37MeSH descriptor: [Pressure Ulcer] explode all trees
#38(pressure next (ulcer* or sore* or injur*)):ti,ab,kw
#39(decubitus next (ulcer* or sore*)):ti,ab,kw
#40((bed next sore*) or bedsore*):ti,ab,kw
#41{or #37-#40}
#42{and #36, #41} in Trials

Ovid MEDLINE

1 exp Bandages/
2 exp Alginates/
3 exp Hydrogels/
4 exp Honey/
5 exp Silver/
6 exp Silver Sulfadiazine/
7 exp Charcoal/
8 exp Silicones/
9 (dressing* or pad or pads or gauze or tulle or film or bead or foam* or non-adherent or "non adherent" or hydrocolloid* or "sodium hyaluronate" or alginat* or hydrogel* or silver* or honey* or matrix or iodine* or "protease modulat*" or "capillary action" or charcoal or silicon* or polymer*).tw.
10 ((odour or odor) adj3 absorb*).tw.
11 (primapore or curasorb or seasorb or sorbsan or advadraw or vacutex or tegaderm or opsite or allevyn or biatain or medihoney or activon tulle or granuflex or "nu derm" or aquacel or iodoflex or iodozyme or xeroform or carboflex or cutimed sorbact or promogran or acticoat or "urgosorb silver" or mepitel or urgotul).tw.
12 or/1-11
13 exp Metronidazole/
14 metronidazole.tw.
15 exp Administration, Topical/
16 exp Anti-Bacterial Agents/
17 and/15-16
18 (topical adj2 (antibiotic* or antimicrobial* or antibacterial*)).tw.
19 exp Iodophors/
20 and/15,19
21 ((topical adj2 iodin*) or "cadexomer iodine").tw.
22 exp Collagenases/
23 and/15,22
24 (topical adj2 collagen*).tw.
25 exp Phenytoin/
26 and/15,25
27 (topical adj2 phenytoin).tw.
28 exp Zinc Oxide/
29 and/15,28
30 (topical adj2 zinc).tw.
31 (iodosorb or actiformcool or aquaflo or flamazine or silvadene).tw.
32 exp Ointments/
33 (ointment* or lotion* or cream* or powder* or gel or gels).tw.
34 (topical adj (agent* or preparation* or therap* or treatment*)).tw.
35 or/13-14,17-18,20-21,23-24,26-27,29-34
36 or/12,35
37 exp Pressure Ulcer/

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38 (pressure adj (ulcer* or sore* or injur*)).tw.
39 (decubitus adj (ulcer* or sore*)).tw.
40 (bedsore* or bed sore*).tw.
41 or/37-40
42 and/36,41
43 randomized controlled trial.pt.
44 controlled clinical trial.pt.
45 randomi?ed.ab.
46 placebo.ab.
47 clinical trials as topic.sh.
48 randomly.ab.
49 trial.ti.
50 or/43-49
51 exp animals/ not humans.sh.
52 50 not 51
53 and/42,52

Ovid Embase

1 exp "bandages and dressings"/
2 exp honey/
3 exp hydrogel/
4 exp Calcium Alginate/
5 (dressing* or pad or pads or gauze or tulle or film or bead or foam* or non-adherent or "non adherent" or hydrocolloid* or "sodium hyaluronate" or alginat* or hydrogel* or silver* or honey* or matrix or iodine* or "protease modulat*" or "capillary action" or charcoal or silicon* or polymer*).ti,ab.
6 ((odour or odor) adj3 absorb*).ti,ab.
7 (primapore or curasorb or seasorb or sorbsan or advadraw or vacutex or tegaderm or opsite or allevyn or biatain or medihoney or activon tulle or granuflex or "nu derm" or aquacel or iodoflex or iodozyme or xeroform or carboflex or cutimed sorbact or promogran or acticoat or "urgosorb silver" or mepitel or urgotul).ti,ab.
8 or/1-7
9 exp metronidazole/
10 metronidazole.ti,ab.
11 topical drug administration/
12 exp Antibiotic Agent/
13 and/11-12
14 (topical adj2 (antibiotic* or antimicrobial* or antibacterial*)).ti,ab.
15 exp cadexomer iodine/
16 and/11,15
17 "cadexomer iodine".ti,ab.
18 exp silver/ or exp sulfadiazine silver/
19 and/11,18
20 exp collagenase/
21 and/11,20
22 (topical adj2 collagen*).ti,ab.
23 phenytoin/
24 and/11,23
25 (topical adj2 phenytoin).ti,ab.
26 exp zinc oxide/
27 and/11,26
28 (topical adj2 zinc).ti,ab.
29 (iodosorb or actiformcool or aquaflo or flamazine or silvadene).ti,ab.
30 exp ointment/
31 (ointment* or lotion* or cream* or powder* or gel or gels).ti,ab.
32 (topical adj (agent* or preparation* or therap* or treatment*)).ti,ab.

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33 or/9-10,13-14,16-17,19,21-22,24-25,27-32
34 or/8,33
35 exp decubitus/
36 (pressure adj (ulcer* or sore* or injur*)).tw.
37 (decubitus adj (ulcer* or sore*)).tw.
38 (bedsore* or bed sore*).tw.
39 or/35-38
40 and/34,39
41 Randomized controlled trials/
42 Single-Blind Method/
43 Double-Blind Method/
44 Crossover Procedure/
45 (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or assign* or allocat* or volunteer*).ti,ab.
46 (doubl* adj blind*).ti,ab.
47 (singl* adj blind*).ti,ab.
48 or/41-47
49 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
50 human/ or human cell/
51 and/49-50
52 49 not 51
53 48 not 52
54 and/40,53

EBSCO CINAHL Plus

S57 S43 AND S56
S56 S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55
S55 TI allocat* random* or AB allocat* random*
S54 MH "Quantitative Studies"
S53 TI placebo* or AB placebo*
S52 MH "Placebos"
S51 TI random* allocat* or AB random* allocat*
S50 MH "Random Assignment"
S49 TI randomi?ed control* trial* or AB randomi?ed control* trial*
S48 AB (singl* or doubl* or trebl* or tripl*) and AB (blind* or mask*)
S47 TI (singl* or doubl* or trebl* or tripl*) and TI (blind* or mask*)
S46 TI clinic* N1 trial* or AB clinic* N1 trial*
S45 PT Clinical trial
S44 MH "Clinical Trials+"
S43 S37 AND S42
S42 S38 OR S39 OR S40 OR S41
S41 TI decubitus or AB decubitus
S40 TI (bed sore* or bedsore*) or AB (bed sore* or bedsore*)
S39 TI (pressure ulcer* or pressure sore*) or AB (pressure ulcer* or pressure sore*)
S38 (MH "Pressure Ulcer+")
S37 S13 OR S36
S36 S14 OR S15 OR S18 OR S19 OR S21 OR S22 OR S24 OR S25 OR S27 OR S28 OR S30 OR S31 OR S33 OR S34 OR S35
S35 TI (topical N3 agent* or topical N3 preparation* or topical N3 therap* and topical N3 treatment*) OR AB (topical N3 agent* or topical N3 preparation* or topical N3 therap* and topical N3 treatment*)
S34 TI (ointment* or lotion* or cream* or powder* or gel or gels) OR AB (ointment* or lotion* or cream* or powder* or gel or gels)
S33 (MH "Ointments")
S32 TI (iodosorb or actiformcool or aquaflo or flamazine or silvadene) OR AB (iodosorb or actiformcool or aquaflo or flamazine or silvadene)
S31 TI (topical N2 zinc) OR AB (topical N2 zinc)
S30 S16 AND S29

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S29(MH "Zinc Oxide")
S28TI (topical N2 phenytoin) OR AB (topical N2 phenytoin)
S27S16 AND S26
S26(MH "Phenytoin+")
S25 TI (topical N2 collagen*) OR AB (topical N2 collagen*)
S24 S16 AND S23
S23 (MH "Collagen")
S22 TI "cadexomer iodine" OR AB "cadexomer iodine"
S21 S16 AND S20
S20 (MH "Iodophors+")
S19 TI (topical N2 (antibiotic* or antimicrobial* or antibacterial*)) OR AB (topical N2 (antibiotic* or antimicrobial* or antibacterial*))
S18 S16 AND S17
S17 (MH "Antiinfective Agents+")
S16 (MH "Administration, Topical+")
S15 TI metronidazole OR AB metronidazole
S14 (MH "Metronidazole")
S13 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12
S12 AB (primapore or curasorb or seasorb or sorbsan or advadraw or vacutex or tegaderm or opsite or allevyn or biatain or medihoney or activon tulle or granuflex or "nu derm" or aquacel or iodoflex or iodozyme or xeroform or carboflex or cutimed sorbact or promogran or acticoat or "urgosorb silver" or mepitel or urgotul)
S11 TI (primapore or curasorb or seasorb or sorbsan or advadraw or vacutex or tegaderm or opsite or allevyn or biatain or medihoney or activon tulle or granuflex or "nu derm" or aquacel or iodoflex or iodozyme or xeroform or carboflex or cutimed sorbact or promogran or acticoat or "urgosorb silver" or mepitel or urgotul)
S10 TI odor N3 absorb* or AB odor N3 absorb*
S9 TI odour N3 absorb* or AB odour N3 absorb*
S8 AB (dressing* or pad or pads or gauze or tulle or film or bead or foam* or non-adherent or "non adherent" or hydrocolloid* or "sodium hyaluronate" or alginat* or hydrogel* or silver* or honey* or matrix or iodine* or "protease modulat*" or "capillary action" or charcoal or silicon* or polymer*)
S7 TI (dressing* or pad or pads or gauze or tulle or film or bead or foam* or non-adherent or "non adherent" or hydrocolloid* or "sodium hyaluronate" or alginat* or hydrogel* or silver* or honey* or matrix or iodine* or "protease modulat*" or "capillary action" or charcoal or silicon* or polymer*)
S6 (MH "Silver") or (MH "Silver Sulfadiazine")
S5 (MH "Honey")
S4 (MH "Charcoal")
S3 (MH "Silicones")
S2 (MH "Alginates")
S1 (MH "Bandages and Dressings+")

Appendix 4. STATA routines

We used the following specialist NMA STATA routines in addition to the standard STATA meta-analysis routines of **metan** and **mvmeta.**

- **network meta consistency** - a multivariate network meta-analysis routine; 'consistency' means assuming the heterogeneity variance is the same for all contrasts
- **network meta inconsistency** - multivariate network meta-analysis routine: 'inconsistency' means account is taken of different study designs (e.g. pairwise/3-arm trials) - heterogeneity is assumed to be different amongst contrasts
- **intervalplot** - output of all NMA results (follows network meta routines)
- **netleague -** gives a 'league table' of results (follows network meta routines)
- **network rank** - produces ranking of interventions (follows network meta routines)
- **netweight** - calculates all direct pairwise summary effect sizes with their variances, creates the design matrix, and estimates the percentage contribution of each direct comparison to the network summary estimates and in the entire network.

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- **ifplot** - identifies all triangular and quadratic loops in a network of interventions and estimates the respective inconsistency factors and their uncertainties

We also used STATA routines to visually display the data

- **network plot** - produces a network diagram, can be modified to add risk of bias
- **network rank** - produces rankograms
- **network forest** - plots results grouped by study design
- **netfunnel** - plots a comparison-adjusted funnel plot for assessing small-study effects within a network of interventions

Appendix 5. Group Network

Studies included in the group network

Individual interventions were mapped onto the group categories as shown in Table 5. Based on an assumption that dressings within certain categories can be used interchangeably, we grouped the individual interventions into the following pre-specified categories: basic wound dressings, advanced dressings and antimicrobial dressings (as described in the BNF 2016), and we kept the different types of specialist dressings (e.g. protease-modulating matrix dressings) and the different topical agents as separate categories.

We excluded 15 of the 51 included studies from the group analysis because they compared interventions in the same group: 14 had advanced dressings in both arms (Aguilo Sanchez 2002; Bale 1997a; Banks 1994a; Banks 1994c; Belmin 2002; Brod 1990; Brown-Etris 1996; Brown-Etris 2008; Darkovich 1990; Motta 1999; Muller 2001; Seeley 1999; Sopata 2002; Thomas 1997a); and one had two antimicrobial dressings (Yapucu Güne 2007). Three additional studies not joined into the individual network were also isolated from the group network (Imamura 1989; Payne 2004; Van De Looverbosch 2004). Two studies previously excluded from the individual network were included initially in the group network (Ashby 2012; Sipponen 2008), but only the Sipponen 2008 study was included in the network. We excluded the Ashby 2012 study and nine others from the network because they were joined to an ineligible intervention that did not link two or more interventions in the network (Gorse 1987; Hondé 1994; Nisi 2005; Nussbaum 1994; Price 2000; Ramos-Torrecillas 2015; Rees 1999; Serena 2010; Thomas 2005). We also excluded the Sebern 1986 study from the group network, as for the individual network.

Interventions and comparisons

The group network comprised 22 studies (which is less than half of the 51 included studies) (Alm 1989; Banks 1994b; Barrois 1992; Brown-Etris 1997; Burgos 2000b; Colwell 1993; Graumlich 2003; Hollisaz 2004; Kaya 2005; Kraft 1993; Matzen 1999; Muller 2001; Neill 1989a; Oleske 1986; Parish 1979; Payne 2009; Piatkowski 2012; Romanelli 2001; Sipponen 2008; Thomas 1998; Xakellis 1992; Zeron 2007), The median (range) study size was 38.5 (10 to 100). Only three contrasts were informed by more than one study.

The network comprised 10 interventions. Two studies were three-arm trials (Hollisaz 2004; Parish 1979), so the total number of comparisons was 26, encompassing a total of 959 participants, experiencing 362 events (complete healing). There were eight direct contrasts and three triangular loops (one of which was exclusive to the Parish 1979 study). This is only 32.5% of the participants in the 51 included studies. The network diagram is shown in Figure 10. Only three contrasts were informed by more than one study: advanced dressing versus basic dressing (11 studies); antimicrobial dressing versus advanced dressing (2); and collagenase ointment versus advanced dressing (2).

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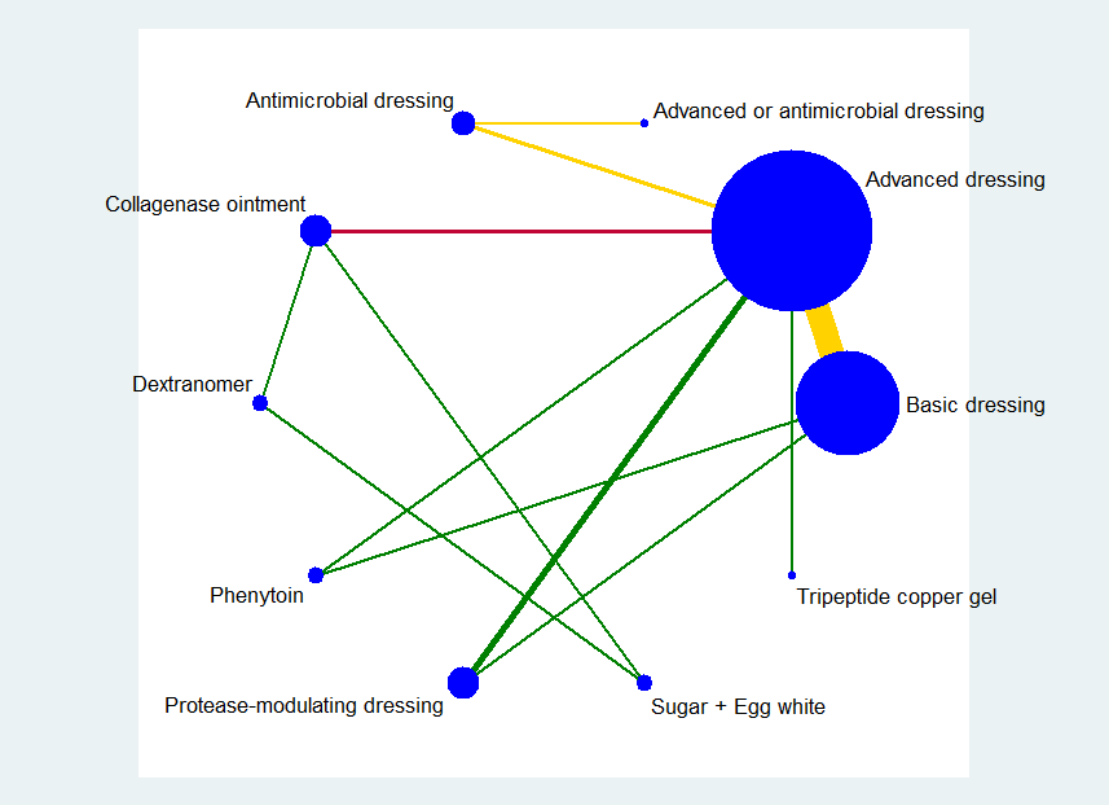
Figure 10. Key: green = low/unclear risk of bias; yellow = high risk of bias; red = very high overall risk of bias for the contrast. The number of studies for each contrast is given in .



The characteristics of studies and participants in the group network are described in Table 1.

Risk of bias

We have summarised the all-domain risk of bias for each study in the group network in Figure 11. We judged one study to be at low risk of bias (Graumlich 2003) and eight at unclear risk of bias (Banks 1994b; Barrois 1992; Hollisaz 2004; Parish 1979; Piatkowski 2012; Romanelli 2001; Thomas 1998; Zeron 2007). We judged three studies to be at very high risk of bias, that is, to have high risk of bias for two or more domains (Banks 1994a; Burgos 2000b; Oleske 1986). The rest of the studies we assessed to be at high risk of bias. We grouped the low and unclear categories together in the network.

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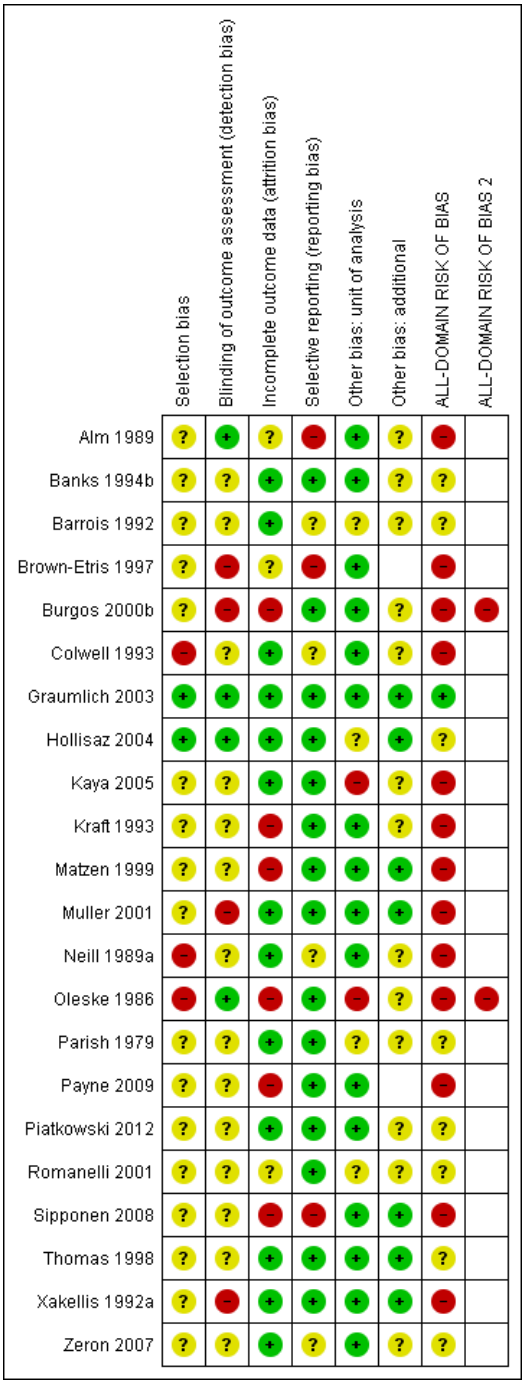
Figure 11. Risk of bias summary - group network: review authors' judgements about each risk of bias item for each included study



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For each direct comparison, the overall risk of bias is shown colour coded in Figure 10. There is a relatively large amount of evidence at high or very high risk of bias.
For each contrast in the network, we calculated the overall risk of bias as described in Appendix 8, and the risk of bias ratings are also shown beside the results in Figure 7.

Network meta-analysis results

The group NMA generated results for 45 mixed treatment contrasts. The network was dominated by the contrast advanced dressing versus basic dressing and the rest of the data were sparse.
Figure 7 shows all NMA results, with the all-domain risk of bias shown alongside the forest plot contrasts.
As in the individual network, the evidence for the majority of contrasts was informed by studies at high risk of bias, and CIs were wide or very wide, such that we downgraded all evidence at least once for imprecision. There was also heterogeneity or inconsistency, or both, for some contrasts. Consequently, evidence was of low or very low certainty, with the exception of one contrast, for which we assessed the evidence to be of moderate certainty. As for the individual network, this moderate-certainty evidence should be interpreted in the light of the very low-certainty evidence for the network as a whole.
We report the representative set of contrasts of each intervention versus basic dressings (Table 3 and Figure 7 first subgroup). Further details of the GRADE assessment can be found in Appendix 8 and Appendix 9.
It is not clear whether protease-modulating dressings increase the probability of healing compared with basic dressings (RR 1.49; 95% CI 0.91 to 2.46, moderate quality evidence). This corresponds to an absolute risk difference of 94 more people healed per 1000 (95% CI 17 fewer to 279 more). We downgraded the evidence once for imprecision (low risk of bias).
For each of two contrasts (collagenase ointment and tripeptide copper gel) it is unclear whether the intervention increases the probability of healing compared with basic dressings (collagenase: RR 2.01, 95% CI 1.05 to 3.88 and tripeptide copper gel: RR 3.39, 95% CI 0.94 to 12.30); Figure 7). This was low certainty evidence, downgraded once for risk of bias and once for imprecision for collagenase ointment, and twice for imprecision for tripeptide copper gel (for which the direct evidence involved only six participants experiencing five events (complete healing)).
It is unclear whether the remaining six interventions affect the probability of healing compared with basic dressings (advanced dressings, advanced and antimicrobial dressings; antimicrobial dressings, dextranomer, phenytoin and sugar plus egg white) because the evidence is of very low certainty (downgraded mainly for risk of bias (once) and imprecision (twice), although two contrasts (phenytoin and advanced dressings versus basic dressings) had inconsistency.

Ranking of treatments

The rank probability data are shown in Figure 12 and Table 6. The rankograms have maximum probabilities more sharply defined in the group network compared with the individual network for the treatments advanced dressings, advanced-antimicrobial dressings, collagenase ointment and dextranomer, but there is still overlap of the rankograms for different treatments (Figure 8). The mean rank was 2.0 for dextranomer and 2.3 for tripeptide copper gel, and two treatments had a mean rank of 10 (out of 10): advanced-antimicrobial dressings and sugar plus egg white. However, no SUCRA value was 0 or 1, indicating uncertainty in the group network.

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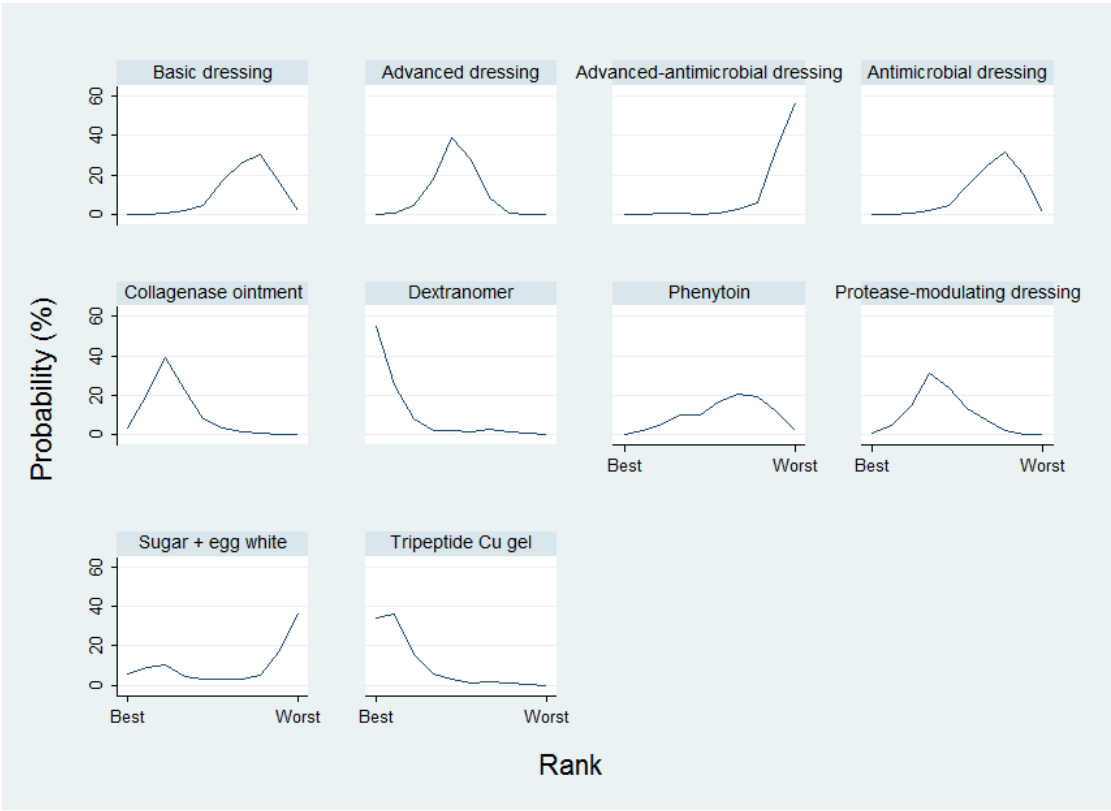
Figure 12. Group network - rankograms



As with the individual network, the results must be interpreted in the light of the considerable uncertainty in the network and individual estimates, which can give misleading results. Numerically, dextranomer and tripeptide copper gel had the highest probabilities of being the best treatments (55% and 34%, respectively), but these high rankings are likely to be an artificial result. . Across all treatments there was very low certainty in the ranking of interventions (see quality assessment below).

Comparison of results from standard meta-analysis versus NMA findings

We compared the NMA results with the direct comparison (pairwise) results for the proportion completely healed for the eight different comparisons informing the group network (Table 4). Three comparisons had two or more direct comparison studies (Analysis 2.1). The direct evidence shows some heterogeneity for the comparison of advanced dressing versus basic dressing (I^2 = 52%, P = 0.02 and some variation in the point estimates). Appendix 11 shows direct evidence results for the time-to-healing outcome for three comparisons in five studies.

Certainty/quality assessment of the network

Overall we downgraded the evidence certainty three times for the network as a whole, because of risk of bias (once), imprecision (once) and inconsistency and publication bias (once): the weighted average risk of bias across the network was high (Appendix 8). For inconsistency, the global Wald test was borderline significant at the 90% significance level (P value was 0.095) (see Appendix 9), however, there were relatively few contrasts with conflicting results for direct and indirect estimates. We downgraded the evidence once for imprecision: there is some overlap of the individual rankograms and no SUCRA value was zero or 1, suggesting uncertainty around treatment estimates and ranking in this network. A contour-enhanced funnel plot (Figure 9) suggested there may be some asymmetry in the plot (which may be a consequence of publication bias).

Overall, we have little confidence in the findings in this group network, either in terms of the effect estimates or in the ranking of interventions.

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Sensitivity analyses - group network

We did not pre-specify sensitivity analyses for the group network, mainly because the group network itself is based on the assumption that a variety of dressings can be grouped as advanced dressings or basic dressings (as defined by the BNF 2016). We attempted to investigate this assumption by examining the network contrasts for the individual network that compared two advanced dressings, expecting the effect estimates to be close to 1 if the assumption was valid. Results can be seen in Figure 4. Most point estimates were fairly close to 1, but CIs were usually wide or very wide around the estimates. Without exception, the risk of bias for each contrast was either high or very high, and the CI crossed at least one GRADE default MID. Thus, there is no clear evidence either to support or refute the group assumption.

A post-hoc sensitivity analysis (Appendix 12) examined the original assumption of combining topical agents and dressings in the same NMA, by restricting the group NMA to dressings. There may have been less imprecision in the network as a whole, but results for the contrasts with basic dressings were similar to those in the full group network.

Appendix 6. Assessment of risk of bias

1. Was the allocation sequence randomly generated? (Part of 'Selection bias')

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? (Part of 'Selection bias')

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? (Performance bias for blinding of participants and caregivers; detection bias for outcome assessors)

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.

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- 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? (Attrition bias)

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? (Outcome reporting bias)

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 are reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified.
- One or more reported primary outcomes of the study 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

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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 7. Studies included in the individual network

The 51 included studies compared 39 different interventions in 59 comparisons, summarised in Table 7.

One study (Ashby 2012) had a range of advanced dressings as the comparator, so was ineligible for the individual intervention NMA (but was eligible for the group NMA). Thus there were 50 eligible studies for the individual NMA, comparing 37 different interventions in 58 comparisons with 2952 participants.There were nine interventions eligible for the individual network, which, on their own, did not meet the inclusion criteria of the review, but were compared with interventions that did meet the inclusion criteria - we have called these 'ineligible interventions'.

The network diagram for all interventions in the individual NMA is shown in Figure 13. Ten interventions (including one ineligible intervention) were isolated from the network and are shown in red in Figure 13. Two further ineligible interventions (radiant heat and skin substitute) linked two of the eligible interventions and so were included in the joined network; the other six ineligible interventions (shown in blue) did not link eligible interventions and their studies were therefore omitted from thejoined network. Two of these omitted studies were three-arm trials each with two ineligible interventions (Nussbaum 1994; Ramos-Torrecillas 2015). Therefore, ten studies could not be included in the joined network (Gorse 1987; Imamura 1989; Nisi 2005; Nussbaum 1994; Payne 2004; Ramos-Torrecillas 2015; Rees 1999; Sipponen 2008; Van De Looverbosch 2004; Yapucu Güne 2007). The results for the isolated studies in which both interventions were eligible are reported in Analysis 5.1. Another study (Sebern 1986) only partially reported their results and was not considered further.

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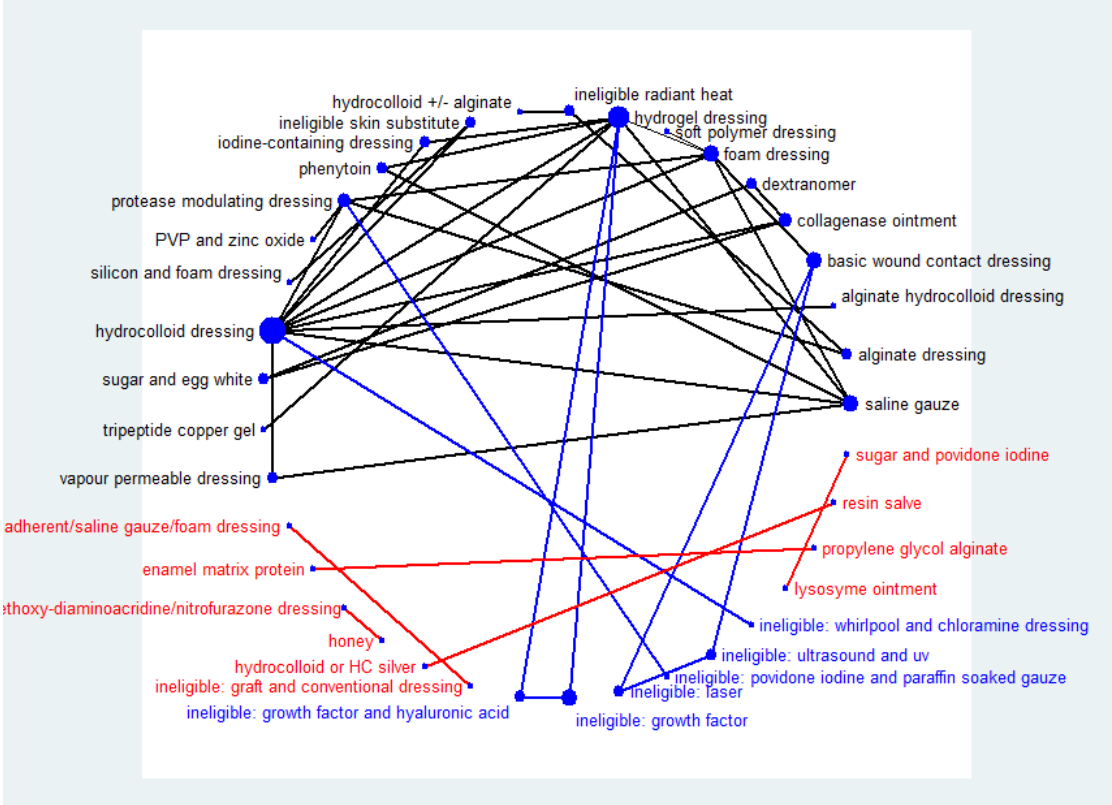
Figure 13. Network diagram - all interventionsKey: red = isolated interventions; blue = ineligible interventions joined to only one eligible intervention. Line and node weights not to scale



Thus 39 studies were included in the individual network (Aguilo Sanchez 2002; Alm 1989; Bale 1997a; Banks 1994b; Banks 1994a; Banks 1994c; Barrois 1992; Belmin 2002; Brod 1990; Brown-Etris 1996; Brown-Etris 1997; Brown-Etris 2008; Burgos 2000b; Colwell 1993; Darkovich 1990; Graumlich 2003; Hollisaz 2004; Hondé 1994; Kaya 2005; Kraft 1993; Matzen 1999; Meaume 2003; Motta 1999; Muller 2001; Neill 1989a; Oleske 1986; Parish 1979; Payne 2009; Piatkowski 2012; Price 2000; Romanelli 2001; Seeley 1999; Serena 2010; Sopata 2002; Thomas 1997a; Thomas 1998; Thomas 2005; Xakellis 1992; Zeron 2007).

Appendix 8. Contributions and risk of bias in the individual and group networks

7.1. Individual network

The percentage contributions to the mixed treatment contrasts from each direct contrast are shown in Figure 14 for the individual network contrasts versus saline gauze. We calculated the risk of bias for each contrast in the NMA and results for each mixed treatment contrast are shown in the last column of the table in Figure 14 and represented on the forest plot (see Assessment of risk of bias in included studies).

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Figure 14. Contributions matrix - interventions versus saline gauze (independent network)Key: 1 = saline gauze dressing; 2 = alginate dressing; 3 = sequential hydrocolloid alginate dressings; 4 = basic wound contact dressing; 5 = collagenase ointment; 6 = dextranomer; 7 = foam dressing; 8 = hydrocolloid dressing; 9 = hydrocolloid +/- alginate (hydrocolloid with/without alginate filler); 10 = hydrogel dressing; 11 = ineligible intervention: radiant heat; 12 = ineligible intervention: skin substitute; 13 = iodine-containing dressing; 14 = phenytoin; 15 = protease-modulating dressing; 16 = PVP + zinc oxide; 17 = silicone + foam dressing; 18 = soft polymer dressing; 19 = sugar + egg white; 20 = tripeptide copper gel; 21 = vapour-permeable dressing.

NMA contrasts ↓	1 vs 7	1 vs 8	1 vs 10	1 vs 14	2 vs 11	2 vs 15	3 vs 8	4 vs 7	5 vs 6	5 vs 8	5 vs 19	6 vs 19	7 vs 8	7 vs 10	7 vs 15	7 vs 18	8 vs 10	8 vs 12	8 vs 13	8 vs 15	8 vs 21	9 vs 11	10 vs 13	10 vs 14	10 vs 20	12 vs 17	15 vs 16	Overall risk of bias
Risk of bias (direct) →	High	High	Low	Low	High	High	High	Low	Low	High	Low	Low	High	High	Low	High	High	Very high	Low	Low	High	Very high	High	Low	Low	High	Low	
1 vs 2	12.7	10.5	2.9	3.3	0.1	29.2							1.9	2.9	13.7		2.6		0.6	15.5		0.1	0.6	3.2				high
1 vs 3	14.5	13.4	3.5	3.9			35.3						13.3	0.5	1.8		5.6		1.2	1.8			1.2	3.9				high
1 vs 4	17.0	12.3	3.6	4.1				37.0					11.1	7.4	1.5		0.3		0.1	1.5			0.1	4.1				low
1 vs 5	14.5	13.4	3.5	3.9						35.3			13.3	0.5	1.8		5.6		1.2	1.8			1.2	3.9				high
1 vs 6	10.4	9.6	2.5	2.8					22.2	25.3	3.1	3.1	9.5	0.4	1.3		4.0		0.9	1.3			0.9	2.8				high
1 vs 7	27.0	19.5	5.8	6.5									17.6	11.8	2.4		0.4		0.1	2.4			0.1	6.5				high
1 vs 8	22.5	20.7	5.4	6.0									20.5	0.8	2.8		8.7		1.9	2.8			1.9	6.0				high
1 vs 9	8.1	6.6	1.8	2.1	18.4	18.4							1.2	1.8	8.6		1.6		0.4	9.8		18.5	0.4	2.0				high
1 vs 10	21.1	16.9	6.4	7.1									0.3	21.4			13.6		3.0				3.0	7.1				high
1 vs 11	9.9	8.1	2.2	2.5	22.6	22.6							1.5	2.3	10.6		2.0		0.4	12.0		0.1	0.5	2.5				high
1 vs 12	14.5	13.4	3.5	3.9									13.3	0.5	1.8		5.6	35.3	1.2	1.8			1.2	3.9				high
1 vs 13	15.0	12.5	4.3	4.9									2.8	11.9	0.4		6.4		9.2	0.4			27.5	4.9				high
1 vs 14	14.1	11.3	4.3	13.1									0.2	14.3			9.1		2.0				2.0	29.7				high
1 vs 15	18.0	14.9	4.1	4.6									2.7	4.2	19.5		3.7		0.8	22.1			0.8	4.6				low
1 vs 16	12.7	10.5	2.9	3.2									1.9	2.9	13.8		2.6		0.6	15.6			0.6	3.2			29.4	low
1 vs 17	10.8	9.9	2.6	2.9									9.8	0.4	1.3		4.2	26.1	0.9	1.3			0.9	2.9		26.1		high
1 vs 18	17.0	12.3	3.6	4.1									11.1	7.4	1.5	37.0	0.3		0.1	1.5			0.1	4.1				high
1 vs 19	9.6	8.8	2.3	2.6					11.1	23.2	12.1	11.1	8.7	0.3	1.2		3.7		0.8	1.2			0.8	2.6				high
1 vs 20	13.9	11.2	4.2	4.7									0.2	14.1			9.0		2.0				2.0	4.7	34.0			high
1 vs 21	14.5	13.4	3.5	3.9									13.3	0.5	1.8		5.6		1.2	1.8	35.3		1.2	3.9				high
whole network	**1.9**	**1.8**	**0.5**	**1.1**	**5.4**	**7.6**	**2.9**	**2.9**	**3.7**	**7.7**	**1.8**	**1.7**	**7.9**	**5.9**	**5.8**	**2.9**	**4.6**	**5.4**	**1.6**	**6.9**	**2.9**	**2.9**	**3.0**	**2.8**	**2.9**	**2.9**	**2.9**	**high**

The contributions to the whole network from each direct contrast are given in the last row of the table in Figure 14. The overall risk of bias was high and the largest contributions to the network were from the direct contrasts: foam versus hydrocolloid; collagenase ointment versus sugar plus egg white; and protease-modulating dressings versus alginate dressings (but all contributions were still 10% or less).

7.2. Group network

The percentage contributions to the mixed treatment contrasts from each direct contrast are shown in Table 8 for the group network contrasts versus basic dressings. We calculated the risk of bias for each contrast in the NMA and results for each mixed treatment contrast are shown in the last column of Table 8.

Contributions to the whole network are given in the last row. The overall risk of bias was high and the largest contributions to the network were for the direct contrasts: collagenase ointment versus advanced dressings (19.6%); antimicrobial dressings versus advanced dressings (14.9%) and dextranomer versus collagenase ointment (10.5%).

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Appendix 9. Inconsistency

8.1 Individual network

8.1.1. Inconsistency for each contrast (local inconsistency)

Firstly, we examined inconsistency factors, comparing results from the direct evidence with those from the indirect evidence for each contrast informed by a loop. We reported results as the ratio of risk ratios (RoRR), with its 90% confidence interval (CI) for the seven loops (Table 9), assuming a common heterogeneity estimate within each loop. At the 90% significance level, there appeared to be inconsistency in the saline gauze-hydrogel-phenytoin loop (RoRR 3.90, 90% CI 1,19 to 12.77). The results also suggested some non-significant potential inconsistency in all other loops (because the 90% CI crosses 2 or 0.5), except for the loop comprising foam, hydrocolloid and hydrogel. In particular, the loop comprising saline gauze-foam-hydrogel had potential inconsistency (RoRR 1.64, 90% CI 0.27 to 9.99); this loop also had a fairly high tau² (0.512), suggesting heterogeneity within that loop. We also examined inconsistency factors using the assumption of a common heterogeneity estimate across the network (Veroniki 2013) (Table 9): for the individual network, tau² (network) was 0.043, and the RoRR for the saline gauze-hydrogel-phenytoin loop was 3.75 (90% CI 1.14 to 12.29), that is, similar to the original assumption. For this analysis, the 90% CI crossed 0.5 or 2.0 for all loops except foam-hydrocolloid-hydrogel.

– Secondly, a node-splitting approach was taken. The results following node-splitting for indirect and direct NMA estimates are shown in Table 10, together with the ratio of risk ratios (RoRR) (indirect/direct) with its 90% CI (the 90% significance level was chosen for this test because of its lack of power). The 'indirect' estimate is the result when the NMA is run in the absence of the direct evidence for that contrast. This is only meaningful if the two interventions in the contrast are joined indirectly through the rest of the network; therefore, we report node splitting results for only 12 (of 27) direct contrasts. We made the following observations:

- Results for two contrasts suggested inconsistency at the 90% confidence level: phenytoin versus saline gauze (RoRR 10.06, 90% CI 1.35 to 75.13) and phenytoin versus hydrogel (RoRR 0.10, 90% CI 0.01 to 0.74). However, the CIs were wide.
- There was potential for inconsistency for four other contrasts (with the CI including either 0.5 or 2, but not both): hydrogel versus foam (RoRR 0.81, 90% CI 0.45 to 1.47); protease-modulating dressing versus foam (RoRR 1.29, 90% CI 0.56 to 2.94); protease-modulating dressing versus hydrocolloid (RoRR 0.78, 90% CI 0.34 to 1.77) and iodine-containing dressing versus hydrogel (RoRR 0.77, 90% CI 0.30 to 1.95).

However, all the CIs were wide and there was uncertainty around whether there was inconsistency or not.
We also compared inconsistency versus consistency assumptions for each contrast, examining any differences between different designs (3-arm and 2-arm), and between inconsistency and consistency NMA results (Table 11). We reported results only for contrasts with two 'core' interventions; there were no differences between models for 'peripheral' contrasts. Only one contrast had more than one type of design (hydrogel versus saline gauze) and there appeared to be large non-significant differences in the results for different designs. One contrast had non-significant differences between the NMA results using inconsistency and consistency assumptions (phenytoin versus saline gauze).

8.1.2. Inconsistency in the network as a whole

We conducted both consistency and inconsistency analyses. The latter showed that the six inconsistency parameters (IP) for the individual network were as follows:
(1) IP = 0: design is the 3-arm trial comparing saline gauze versus hydrogel versus phenytoin
(2) IP = 0: design is 2-arm trials comparing foam and hydrocolloid
(3) IP = 0: design is 2-arm trials comparing foam and hydrogel
(4) IP = 0: design is 2-arm trials comparing hydrocolloid and hydrogel
(5) IP = 0: design is 2-arm trials comparing hydrogel and protease-modulating dressings
(6) IP = 0: design is 2-arm trials comparing hydrogel and iodine-containing dressings

The global Wald test for inconsistency gave: $Chi^2(6) = 3.59$ and P value 0.7314.

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8.2 Group network

8.2.1. Inconsistency for each contrast (local inconsistency)

Inconsistency factors are reported as the RoRR with its 90% CI in Table 12. There are two loops, basic dressing - advanced dressing - phenytoin; and basic dressing - advanced dressing - protease-modulating dressing. At the 90% significance level, there did not appear to be inconsistency in these loops, but the results suggested some non-significant potential inconsistency in both loops (because the 90% CI crossed 2): for the loop containing phenytoin, the RoRR was 3.04 (0.71 to 13.06) and for the loop containing protease-modulating dressing the RoRR was 1.36 (0.39 to 4.73).

The results following node-splitting are shown in Table 13 for five (of 11) direct contrasts. The results suggested that there may be inconsistency at the 90% confidence level for two contrasts: phenytoin versus basic dressing (RoRR 12.51, 90% CI 1.87 to 83.55; P = 0.029) and phenytoin versus advanced dressing (RoRR 0.08, 90% CI 0.01 to 0.53; P = 0.029). However, the CIs were wide.

We also compared inconsistency versus consistency assumptions for each contrast, examining any differences between different designs (3-arm and 2-arm), and between inconsistency and consistency NMA results (Table 14). Results were reported only for contrasts with two 'core' interventions; there were no differences between models for 'peripheral' contrasts. Only one contrast had more than one type of design (advanced dressings versus basic dressings) and there appeared to be large non-significant differences in the results for different designs. One contrast had non-significant differences between the NMA results using inconsistency and consistency assumptions (phenytoin versus basic dressings).

8.2.2. Inconsistency in the network as a whole

There were two inconsistency parameters (IP) for the group network:

IP = 0: design is the 3-arm trial comparing basic dressing, advanced dressing and phenytoin

IP = 0: design is the 2-arm trial comparing advanced dressing and protease-modulating dressing

The global Wald test for inconsistency gave: $Chi^2(2) = 4.66$ and P-value 0.0975. This is borderline significant at the 90% confidence level.

Appendix 10. Ranking interventions

Data for each intervention were shown as the probability that each intervention is the best, second best, third best treatment, etc. (see Figure 5, and Table 15). There was substantial overlap of the individual rankograms, illustrated in Figure 15, which intentionally shows the confusion, together with some indication that dextranomer and tripeptide copper gel may be the best treatments and that the worst treatments may be the sequential hydrocolloid-alginate dressings and sugar plus egg white. Across all treatments there was considerable uncertainty in the ranking of interventions and no intervention had more than 50% probability of being the best treatment. This, together with the mean rank being no higher than 3.6 and no lower than 18.6 (out of 21), and no SUCRA value being 0 or 1, reinforces our view of the considerable uncertainty around treatment estimates in this network.

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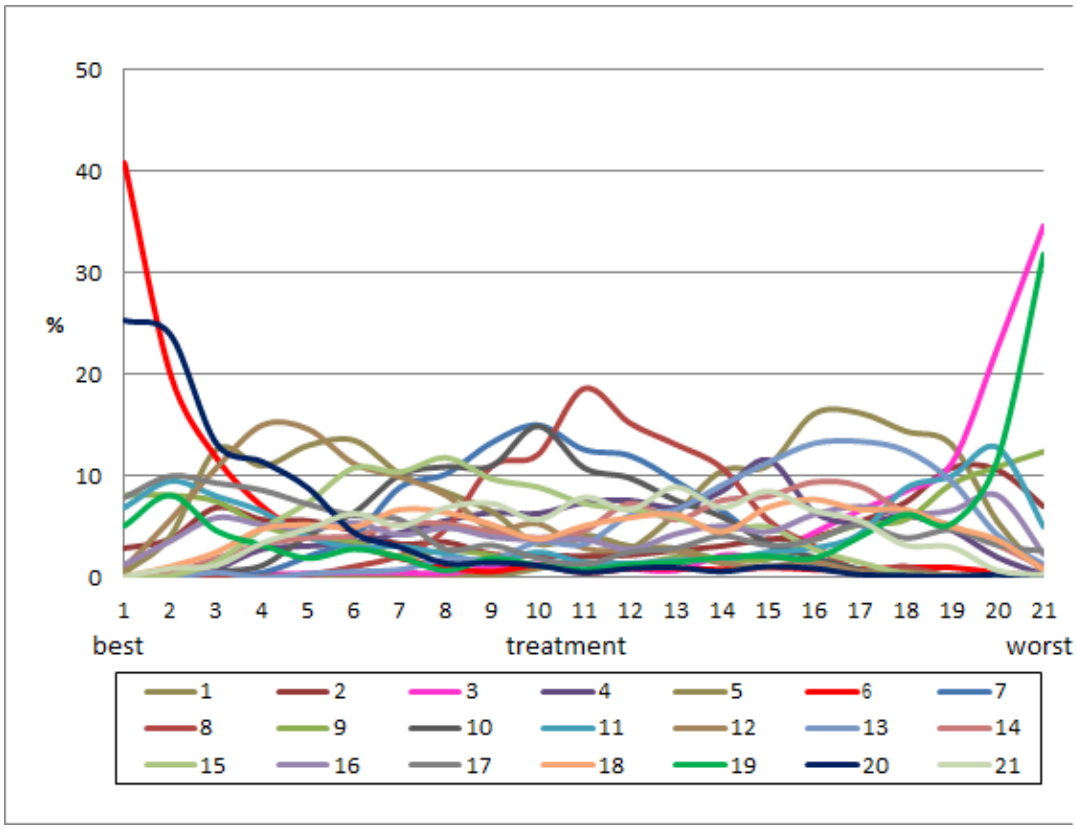
Figure 15. Rankograms combined - individual networkKey to interventions: 1: saline gauze; 2: alginate dressing; 3: sequential hydrocolloid alginate dressings; 4: basic wound contact dressing; 5: collagenase ointment; 6: dextranomer; 7: foam dressing; 8: hydrocolloid dressing; 9: hydrocolloid +/- alginate (hydrocolloid dressing with/without alginate filler); 10: hydrogel dressing; 11: ineligible radiant heat; 12: ineligible skin substitute; 13: iodine-containing dressing; 14: phenytoin; 15: protease-modulating dressing; 16: PVP + zinc oxide17: silicone + foam dressing; 18: soft polymer dressing; 19: sugar + egg white; 20: tripeptide copper gel; 21: vapour-permeable dressing



Appendix 11. Time to event data: direct evidence

The duration of follow-up ranged from 3 to 26 weeks, but the distribution was insufficient to allow modelling of time dependence in the network.

Seven studies (Alm 1989; Brod 1990; Graumlich 2003; Muller 2001; Payne 2009; Thomas 2005; Xakellis 1992) reported time-to-event data. We calculated the hazard ratio using the method and spreadsheet from Tierney 2007; one study (Xakellis 1992) reported the hazard ratio directly, adjusted for exudate level. The time-to-healing data are shown in Analysis 3.1 and summary statistics for the time-to-healing and the proportion healed are compared in Table 16 for the studies that report both healing outcomes.

In the individual network, two studies in 95 participants suggested that the time to healing may have been quicker for hydrocolloid versus saline gauze (HR 1.75, 95% CI 1.00 to 3.05); there was no heterogeneity (unlike the risk ratio). One study in 24 participants suggested healing may have been quicker for collagenase ointment compared with hydrocolloid (HR 2.58, 95% CI 1.00 to 2.65). In the other studies, the CI showed much uncertainty.

There was some suggestion of a time dependent effect because there were qualitative and quantitative differences between the HR and the RR: for shorter studies (4-6 weeks), the HR gave a smaller effect than the RR, but for the medium and longer term studies the HR gave a larger effect than the RR, suggesting that wounds that heal do so relatively quickly.

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For the group network, time-to-healing data are shown in Analysis 4.1. Three studies in 131 participants suggested that the time to healing may have been quicker for advanced dressing versus basic dressing (HR 1.57, 95% CI 0.97 to 2.55); there was no heterogeneity. This compared with the same three studies analysed as the proportion healed: RR (random-effects) 1.48 (95% CI 0.79 to 2.77); I^2 = 66%, P = 0.05.

Appendix 12. Sensitivity analyses

We conducted pre-specified sensitivity analyses for the individual network and a post-hoc sensitivity analysis for both networks.

11.1. Sensitivity analysis by risk of bias (individual network)

The planned sensitivity analysis for risk of bias was to restrict the network to those studies at low or unclear risk of bias. Only 12 studies with 13 interventions remained and these formed three isolated loops.

Instead we conducted a sensitivity analysis which excluded studies that had high risk of bias for two or more domains (very high risk of bias) - we excluded seven studies from the joined network (Bale 1997a; Banks 1994a; Brown-Etris 1996; Burgos 2000b; Payne 2004; Ramos-Torrecillas 2015; Thomas 2005); one further study (Serena 2010) was no longer joined into the network. This left 31 studies with 35 comparisons, including 18 interventions and 1513 participants (i.e. 51% of the participants in the full network and 72% of the joined network participants).

The NMA results for interventions versus saline gauze are shown in Table 17 alongside the original data. There were only minor differences. The mean rank order was similar to the original data (Table 17) and the rankograms similarly indicated much imprecision. The global Wald test for inconsistency was not significant - the P value was 0.761, which was very similar to the original analysis (P = 0.731). The point estimates for node splitting gave smaller ratios of RRs than the original for the contrasts previously showing inconsistencies: phenytoin versus saline gauze RoRR 1.97 (90% CI 0.33 to 11.87) and phenytoin versus hydrogel RoRR 0.96 (95% CI 0.47 to 1.94). These RoRRs were no longer significant at the 90% confidence level.

11.2. Sensitivity analysis by missing data assumption (individual network)

We conducted a sensitivity analysis using a different assumption regarding missing data: the original assumption was an intention-to-treat analysis with imputation that missing data had no event. This sensitivity analysis used an available case analysis assumption: data were reported for 22 of the 39 studies (Bale 1997a; Banks 1994b; Banks 1994a; Banks 1994c; Barrois 1992; Brod 1990; Brown-Etris 1996; Darkovich 1990; Graumlich 2003; Hondé 1994; Kraft 1993; Matzen 1999; Meaume 2003; Muller 2001; Payne 2009; Price 2000; Seeley 1999; Sopata 2002; Thomas 1997a; Thomas 1998; Thomas 2005; Xakellis 1992). For this analysis, the 39 studies had data on 1838 participants (i.e. 87%).

The NMA results for the sensitivity analysis are shown in Table 17 alongside the original data. Differences were only small. The mean rank order was similar to the original data (Table 17). The Wald test for inconsistency was not significant - the P value was 0.638, which was similar to the original analysis (P = 0.731).

The global Wald test for inconsistency was not significant - the P value was 0.638, which was similar to the original analysis (P = 0.731). The point estimates for node splitting gave similar RoRRs.

11.3 Post-hoc sensitivity analysis - dressings only (both individual and group networks)

For the individual network, we also investigated, post-hoc, our original assumption that topical agents could be used in place of dressings, by examining only the network of studies involving two or more dressings (or hydrogel). There were no three-arm trials remaining and the 30 studies compared 12 interventions in a total of 1627 participants experiencing 641 events, with 16 direct contrasts and 66 mixed treatment contrasts. The NMA rankings were similarly imprecise (data not shown).

For the group network, 17 studies compared five interventions in a total of 798 participants experiencing 304 events, with five direct contrasts and 10 mixed treatment contrasts. This network was still sparse in terms of total participants, but, on average, there were more events per contrast. The post-hoc sensitivity analysis had less overlap of rankograms (data not shown) than the full group network, and the mean rank was closer to a whole number; one SUCRA value was 0 and another was 0.9. The mean ranks were: protease-modulating 1.4; advanced 1.9; basic 3.1; antimicrobial 3.7: advanced-antimicrobial 4.9. For the comparisons with basic dressing, effect estimates were similar to those in Table 3 but CIs were still wide.

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CONTRIBUTIONS OF AUTHORS

Maggie Westby: designed and coordinated the review; extracted data; checked the quality of data extraction; analysed and 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 and editing the review; made an intellectual contribution to the review; contacted an expert statistician; approved the final review prior to submission and is a guarantor of the review.

Jo Dumville: conceived, designed and coordinated the review; analysed and interpreted data; checked quality assessment; contributed to writing and editing the review; made an intellectual contribution to the review; approved the final review prior to submission; secured funding; and performed previous work that was the foundation of the current review.

Marta Soares: analysed and interpreted data; performed statistical analysis; checked the quality of the statistical analysis; contributed to writing or editing the review; made an intellectual contribution to the review; advised on the review; approved the final review prior to submission and performed previous work that was the foundation of the current review.

Nikki Stubbs: 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.

Gill Norman: extracted data; checked the quality of data extraction; undertook and checked quality assessment; contributed to writing and editing the review; made an intellectual contribution to the review and approved the final review prior to submission.

Contributions of the editorial base

Nicky Cullum (Co-ordinating Editor): edited the protocol and the review; advised on methodology, interpretation and content; approved the final protocol and review prior to submission.
Gill Rizzello (Managing Editor): co-ordinated the editorial process, advised on content; edited the protocol and the review.
Reetu Child (Information Specialist): designed the search strategy and ran the search; edited the search methods section.
Ursula Gonthier (Editorial Assistant): edited the plain language summary and reference sections.

DECLARATIONS OF INTEREST

Maggie Westby: my employment at the University of Manchester is funded by National Institute for Health Research (NIHR) and focuses on high priority Cochrane Reviews in the prevention and treatment of wounds.

Jo Dumville: I receive research funding from the National Institute for Health Research (NIHR) for the production of systematic reviews focusing on high priority Cochrane Reviews in the prevention and treatment of wounds. This work was also partly funded by the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care (NIHR CLAHRC) Greater Manchester.

Marta Soares: none known.

Nikki Stubbs: funding from pharmaceutical companies has supported training and educational events, and payments have been received by the author for non-product-related educational sessions. These have been unrelated to the subject matter of the review and have never been in support or in pursuit of the promotion of products.

Gill Norman: my employment at the University of Manchester is funded by the National Institute for Health Research (NIHR) and focuses on high priority Cochrane Reviews in the prevention and treatment of wounds.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol states that where studies have 25% or fewer Stage 1 ulcers, or 25% or fewer other complex wound types, we would include all study data initially and test the assumption in sensitivity analysis. However, we decided that it was more appropriate to exclude these studies. We also planned to carry out a sensitivity analysis in the absence of studies for which there were more than 75% but less than 100% of eligible ulcers. However, this sensitivity analysis was not done. A post-hoc subgroup analysis was added, restricting the interventions to dressings (and hydrogel).

The major change from the protocol was to analyse the data in a frequentist rather than Bayesian framework, so STATA was used for all analyses rather than WinBUGS, as we originally proposed.

We did not contact study authors.

INDEX TERMS

Medical Subject Headings (MeSH)

*Bandages; *Wound Healing; Alginates [therapeutic use]; Bandages, Hydrocolloid; Collagenases [therapeutic use]; Dermatologic Agents [*therapeutic use]; Egg White; Gels [therapeutic use]; Glucuronic Acid [therapeutic use]; Hexuronic Acids [therapeutic use]; Network Meta-Analysis; Ointments [therapeutic use]; Pharmaceutic Aids [therapeutic use]; Phenytoin [therapeutic use]; Povidone [therapeutic use]; Pressure Ulcer [*therapy]; Randomized Controlled Trials as Topic; Zinc Oxide [therapeutic use]

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MeSH check words

Humans

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