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Hydrocolloid dressings for healing diabetic foot ulcers

Jo C Dumville , Sohan Deshpande, Susan O'Meara, Katharine Speak

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Abstract

Background

Foot ulcers in people with diabetes are a prevalent and serious global health issue. Wound dressings are regarded as important components of ulcer treatment, with clinicians and patients having many different types to choose from including hydrocolloid dressings. There is a range of different hydrocolloids available including fibrous-hydrocolloid and hydrocolloid (matrix) dressings. A clear and current overview of current evidence is required to facilitate decision-making regarding dressing use.

Objectives

To compare the effects of hydrocolloid wound dressings with no dressing or alternative dressings on the healing of foot ulcers in people with diabetes.

Search methods

For this first update, in April 2013, we searched the following databases the Cochrane Wounds Group Specialised Register; The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*); Ovid MEDLINE; Ovid MEDLINE (In-Process & Other Non-Indexed Citations); Ovid EMBASE; and EBSCO CINAHL. There were no restrictions based on language or date of publication.

Selection criteria

Published or unpublished randomised controlled trials (RCTs) that have compared the effects on ulcer healing of hydrocolloid with alternative wound treatments in the treatment of foot ulcers in people with diabetes.

Data collection and analysis

Two review authors independently performed study selection, risk of bias assessment and data extraction.

Main results

We included five studies (535 participants) in the review: these compared hydrocolloids with basic wound contact dressings, foam dressings, alginate dressings and a topical treatment. Meta-analysis of two studies indicated no statistically significant difference in ulcer healing between fibrous-hydrocolloids and basic wound contact dressings: risk ratio 1.01 (95% CI 0.74 to 1.38). One of these studies found that a basic wound contact dressing was more cost-effective than a fibrous-hydrocolloid dressing. One study compared a hydrocolloid-matrix dressing with a foam dressing and found no statistically significant difference in the number of ulcers healed. There was no statistically significant difference in healing between an antimicrobial (silver) fibrous-hydrocolloid dressing and standard alginate dressing; an antimicrobial dressing (iodine-impregnated) and a standard fibrous hydrocolloid dressing or a standard fibrous hydrocolloid dressing and a topical cream containing plant extracts.

Authors' conclusions

Currently there is no research evidence to suggest that any type of hydrocolloid wound dressing is more effective in healing diabetic foot ulcers than other types of dressing or a topical cream containing plant extracts. Decision makers may wish to consider aspects such as dressing cost and the wound management properties offered by each dressing type e.g. exudate management.

Plain language summary

English

Hydrocolloid dressings to promote foot ulcer healing in people with diabetes when compared with other dressing types

Diabetes, a condition which leads to high blood glucose concentrations, is a common condition with around 2.8 million people affected in the UK (approximately 4.3% of the population). Dressings are commonly used to treat foot ulcers in people with diabetes. There are many types of dressings that can be used, which also vary considerably in cost.This review (four studies involving a total of 511 participants) identified no research evidence to suggest that any type of hydrocolloid wound dressing is more effective in healing diabetic foot ulcers than other types of dressing.

Summary of findings (Explanation)

Summary of findings for the main comparison. Fibrous-hydrocolloid (hydrofibre) dressing compared to basic wound contact dressing for healing diabetic foot ulcers

Fibrous-hydrocolloid (hydrofibre) dressing compared to basic wound contact dressing for healing diabetic foot ulcers						
Patient or population: patients with healing diabetic foot ulcers **Settings:** Any **Intervention:** Fibrous-hydrocolloid (hydrofibre) dressing **Comparison:** basic wound contact dressing						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Basic wound contact dressing	**Fibrous-hydrocolloid (hydrofibre) dressing**				
Number of ulcers healed	**Low**[1]		**RR 1.01** (0.74 to 1.38)	229 (2 studies)	⊕⊕⊕⊖ **moderate**[2]	
	340 per 1000	**343 per 1000** (252 to 469)				

[1] Baseline risk of healing obtained from external source in which data from 27,630 patients with a diabetic neuropathic foot ulcer was used to develop a simple prognostic model to predict likelihood of ulcer healing (Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers: predicting which ones will not heal. Am J Med. 2003;115:627-31). It is important to note that given an outcome of ulcer healing, low risk refers to a low risk of healing and thus reflects the most severe patient populations. Conversely high risk refers to a high risk of healing.

[2] 108 participants achieved the endpoint of healing in the two studies, this is an underpowered comparison. The confidence interval around the estimate of relative risk is consistent with a 26% relative reduction in healing with hydrocolloid and a 38% relative increase in healing with hydrocolloid.

	Moderate[1] **530 per 1000** **High**[1] **650 per 1000**	**535 per 1000** (392 to 731) **657 per 1000** (481 to 897)				
HRQoL	See comment	See comment	Not estimable	0 (0)	See comment	One study measured HRQoL at 24 weeks follow-up. Data from several domains are presented in the report, with no statistically significant difference observed.
Adverse events	See comment	See comment	Not estimable	0 (0)	See comment	AEs for two studies - very similar numbers in each arms. Data not analysed here as not independent - that is one person could have multiple events or due to limited data.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate

[1] Baseline risk of healing obtained from external source in which data from 27,630 patients with a diabetic neuropathic foot ulcer was used to develop a simple prognostic model to predict likelihood of ulcer healing (Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers: predicting which ones will not heal. Am J Med. 2003;115:627-31). It is important to note that given an outcome of ulcer healing, low risk refers to a low risk of healing and thus reflects the most severe patient populations. Conversely high risk refers to a high risk of healing.
[2] 108 participants achieved the endpoint of healing in the two studies, this is an underpowered comparison. The confidence interval around the estimate of relative risk is consistent with a 26% relative reduction in healing with hydrocolloid and a 38% relative increase in healing with hydrocolloid.

of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Baseline risk of healing obtained from external source in which data from 27,630 patients with a diabetic neuropathic foot ulcer was used to develop a simple prognostic model to predict likelihood of ulcer healing (Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers: predicting which ones will not heal. Am J Med. 2003;115:627-31). It is important to note that given an outcome of ulcer healing, low risk refers to a low risk of healing and thus reflects the most severe patient populations. Conversely high risk refers to a high risk of healing.
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Background

Description of the condition

Diabetes, a condition which leads to high blood glucose concentrations is common and affects around 2.8 million people in the UK (approximately 4.3% of the population) (Diabetes UK 2011). This number is set to increase over the next 25 years as the incidence of diabetes increases rapidly (WHO 2005). Global projections suggest that the worldwide prevalence of diabetes is expected to rise to 4.4% by 2030, meaning that approximately 366 million people will be affected (Wild 2004).

Success in treating people with diabetes has improved their life expectancy. However, the increased prevalence of diabetes coupled with the extended time people live with the disease has led to a rise in the number of diabetes-related complications, such as neuropathy and peripheral arterial disease (PAD). It is estimated that lower extremity disease (defined as lower-extremity PAD, lower-extremity peripheral neuropathy or history of foot ulcer or lower-extremity amputations) is twice as common in people with diabetes compared with people without (Gregg 2004). Both neuropathy and PAD are risk factors for diabetic foot ulceration (Pecoraro 1990; Reiber 1999), which is a problem reported to affect 15% or more of the diabetic population at some time in their lives (Reiber 1996; Singh 2005). Around 1% to 4% of people with diabetes have foot ulcers at any given time (Abbott 2002; Kumar 1994). An ulcer forms as a result of damage to the epidermis and subsequent loss of underlying tissue. Specifically, the International Consensus on the Diabetic Foot defines a foot ulcer as a wound extending through the full thickness of the skin below the level of the ankle (Apelqvist 2000a). This is irrespective of duration and the ulcer can extend to muscle, tendon and bone. The Wagner wound classification system is well established and widely used for grading diabetic foot ulcers. The system assesses ulcer depth and the presence of osteomyelitis or gangrene in the following grades: grade 0 (pre- or post-ulcerative lesion), grade 1 (partial/full thickness ulcer), grade 2 (probing to tendon or capsule), grade 3 (deep with osteitis), grade 4 (partial foot gangrene) and grade 5 (whole foot gangrene) (Wagner 1981). However, newer grading systems, such as the PEDIS system (Schaper 2004) and the University of Texas Wound Classification System (Oyibo 2001) have been developed.

PAD and neuropathy can occur separately (ischaemic foot and neuropathic foot) or in combination (in the neuroischaemic foot). The over-arching term 'diabetic neuropathy' refers to a number of neuropathic syndromes. Chronic distal sensorimotor symmetrical neuropathy (abbreviated to distal symmetrical neuropathy) is the most common, affecting around 28% of people with diabetes. It can lead to ulceration through the following route(s) (Tesfaye 1996).

- Sympathetic autonomic neuropathy leads to decreased sweating causing anhidrotic (dry) skin, which is prone to cracks and fissures causing a break in the dermal barrier (Tesfaye 1996).
- Motor neuropathy causes wasting of the small, intrinsic muscles of the foot by de-enervation. As the muscles waste they cause retraction of the toes and lead to a subsequent deformity. The abnormal foot shape can promote ulcer development due to an increase in plantar pressures (Murray 1996).
- Sensory neuropathy results in impaired sensation, making the patient unaware of potentially dangerous foreign bodies and injuries.

People with diabetes-related foot ulceration are treated in a variety of settings, for example community clinics, surgeries and their own homes, by a variety of practitioners; this can make data collection challenging. A UK study estimated that 2% of community-based diabetic patients develop new foot ulcers each year (Abbott 2002). In terms of healing, a meta-analysis of trials in which people with neuropathic ulcers received good wound care reported that 24% of ulcers attained complete healing by 12 weeks and 31% by 20 weeks (Margolis 1999). However, the risk of ulcer recurrence post-healing is high. Pound 2005 reported that 62% of ulcer patients (n = 231) became ulcer-free at some stage over a 31-month observation period. However, of the ulcer-free group 40% went on to develop a new or recurrent ulcer after a median of 126 days. The ulcer recurrence rate over five years can be as high as 70% (Dorresteijn 2010; Van Gils 1999).

Diabetic foot ulcers can seriously impact on an individual's quality of life and as many as 85% of foot-related amputations are preceded by ulceration (Apelqvist 2000b; Pecoraro 1990). Patients with diabetes have a 10 to 20-fold higher risk of losing a lower limb or part of a lower limb due to non-traumatic amputation than those without diabetes (Morris 1998; Wrobel 2001).

Diabetic foot ulcers represent a major use of health resources, incurring costs not only for dressings applied, but also staff costs (for podiatry, nurses, doctors), tests and investigations, antibiotics and specialist footwear. Currie 1998 estimated the cost of healing a foot ulcer in a patient with diabetes at around GBP 1451. Hospital admissions add further to the costs. Ten years ago the cost of diabetic foot ulceration to the UK National Health Service was believed to be about GBP 12.9 million per year (Spencer 2000) and this figure is likely to have increased significantly. The economic impact is also high in terms of the personal costs to patients and carers, for example costs associated with lost work time and productivity while the patient is non-weight bearing or hospitalised.

Description of the intervention

Broadly, the treatment of diabetic foot ulcers includes pressure relief (or off-loading) by resting the foot or wearing special footwear or shoe inserts (or both); the removal of dead cellular material from the surface of the wound (debridement or desloughing)(**Edwards 2010**); infection control (**Storm-Versloot 2007**); and the use of wound dressings (**Bergin 2006**; **Dumville 2011a**; **Dumville 2011b**; **Dumville 2012**). Other general strategies in the treatment of diabetic foot ulcers include: patient education (**Dorresteijn 2010**; **Dorresteijn 2001**); optimisation of blood glucose control; correction (where possible) of arterial insufficiency; and surgical interventions (debridement, drainage of pus, revascularisation, amputation).

Dressings are widely used in wound care, both to protect the wound and to promote healing. Classification of a dressing normally depends on the key material used. Several attributes of an ideal wound dressing have been described (**BNF 2010**), including:

- the ability of the dressing to absorb and contain exudate without leakage or strike-through;
- lack of particulate contaminants left in the wound by the dressing;
- thermal insulation;
- permeability to water and bacteria;
- avoidance of wound trauma on dressing removal;
- frequency with which the dressing needs to be changed;
- provision of pain relief; and
- comfort.

There is a vast choice of dressings available to treat chronic wounds such as diabetic foot ulcers. For ease of comparison this review has categorised dressings according to the British National Formulary 2010 (**BNF 2010**) which is freely available via the Internet, although there are alternative classifications. We will use 'generic' names where possible, also providing UK trade names and manufacturers where these are available to allow cross-referencing with the BNF. However, it is important to note that the way dressings are categorised as well as dressing names, manufacturers and distributors may vary from country to country, so these are provided as a guide only. Below is a description of all categories of dressings and includes the category of dressing (hydrocolloid) which is the focus of this review:

Basic wound contact dressings

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

Absorbent dressings: applied directly to the wound or 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).

Advanced wound dressings

Hydrocolloid dressings: are occlusive dressings usually composed of a hydrocolloid matrix bonded onto a vapour-permeable film or foam backing. When in contact with the wound surface this matrix forms a gel to provide a moist environment. Examples are: Granuflex (ConvaTec) and Duoderm (Smith and Nephew). Fibrous hydrocolloids have been developed which resemble alginates and are not occlusive but which are more absorbant than standard hydrocolloid dressings: Aquacel (ConvaTec).

Hydrogel dressings: consist of a cross-linked insoluable polymers (i.e. starch or carboxymethylcellulose) and up to 96% water. These dressings are designed to absorb wound exudate or rehydrate a wound depending on the wound moisture levels. They are supplied in either flat sheets, an amorphous hydrogel or as beads. Examples are: ActiformCool (Activa) and Aquaflo (Covidien)

Films - permeable film and membrane dressings: permeable to water vapour and oxygen but not to water or microorganisms. Examples are Tegaderm (3M) and Opsite (Smith & Nephew).

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

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

Alginate dressings: highly absorbent and 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 which can be lifted off with dressing removal or rinsed away with sterile saline. Bonding to a secondary viscose pad increases absorbency. Examples are: 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 are: Advadraw (Advancis) and Vacutx (Protex).

Odour-absorbent dressings: dressings that contain charcoal and are used to absorb wound odour. Often these types of wound dressings are used in conjunction with a secondary dressing to improve absorbency. Example: CarboFLEX (ConvaTec).

Antimicrobial dressings

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

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

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

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

Specialist dressings

Protease-modulating matrix dressings: alter the activity of proteolytic enzymes in chronic wounds. Examples are: Promogran (Systagenix) and Sorbion (H & R).

The diversity of dressings available to clinicians (including variation within each type listed above) makes evidence-based decision-making difficult when deciding the best treatment regimen for the patient. In a UK survey undertaken to determine treatments used for debriding diabetic foot ulcers, a diversity of treatments was reported (Smith 2003). It is possible that a similar scenario is true for dressing choice. A survey of Diabetes Specialist Nurses found that low/non-adherent dressings, hydrocolloids and alginate dressings were the most popular for all wound types, despite a paucity of evidence for either of these dressing types (Fiskin 1996). However, several new dressing types have been made available and heavily promoted in recent years. Some dressings now have an 'active' ingredient such as silver that are promoted as dressing treatment options to reduce infection and thus possibly also promote healing in this way. With increasingly sophisticated technology being applied to wound care, practitioners need to know how effective these often expensive dressings are compared with more traditional dressings.

How the intervention might work

Animal experiments conducted over 40 years ago suggest that acute wounds heal more quickly when their surface is kept moist, rather than left to dry and scab (Winter 1963). A moist environment is thought to provide optimal conditions for the cells involved in the healing process as well as allowing autolytic debridement, 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. Different wound dressings 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 from the wound to avoid skin damage, whilst a drier wound can be treated with a more occlusive dressing to maintain a moist environment. Hydrocolloid dressings are composed of a layer of sodium carboxymethylcellulose (or similar material which forms a gel when wet) bounded onto a vapour-permeable film or foam pad. When in contact with the wound dressings form a gel whilst maintaining a moist wound environment. Fibrous-hydrocolloids are a sub-set of dressings that are designed for use in wounds with heavy exudate in lieu of alternate dressing types such as alginates.

Why it is important to do this review

Diabetic foot ulcers are a common consequence of diabetes internationally. Treatment with dressings forms a key part of the treatment pathway when caring for people with diabetic foot ulcers and there are many types of dressings that can be used, which also vary considerably in cost. Guidelines for the treatment of diabetic ulcer (e.g. Steed 2006) maintain that clinical judgement should be used to select a moist wound dressing.

However, previous reviews of the evidence for wound dressings as treatments for diabetic foot ulcers have not found evidence to support a specific dressing choice. Ten trials were eligible for inclusion in a UK Health Technology Assessment review of wound dressings published in 2000 (O'Meara 2000). The review included nine trials that investigated a dressing or topical treatment for healing diabetic foot ulcers. The review did not find any evidence to suggest that one dressing type was more or less effective in terms of treating diabetic foot ulcers. The methodological quality of trials was poor and all were small. Only one comparison was repeated in more than one trial. A further systematic review, conducted some years ago reported similar findings (Mason 1999). A more recent systematic review on the effectiveness of interventions to enhance the healing of chronic ulcers of the foot (Hinchliffe 2008) (search date December 2006) included only eight trials (randomised and non-randomised) did not identify any evidence that one dressing type was superior to another in terms of promoting ulcer healing. A Cochrane review of silver-based wound dressings and topical agents for treating diabetic foot ulcers (Bergin 2006; search date 2010) did not find any studies that met its inclusion criteria. Finally, a review of antimicrobial treatments for diabetic foot ulcers (Nelson 2006) included dressings and found that existing evidence was too weak to recommend any antimicrobial product.

This review is part of a suite of Cochrane Reviews investigating the use of dressings in the treatment of foot ulcers in people with diabetes. Each review will focus on a particular dressing type which in this review is the hydrocolloid dressing. These reviews will be summarised in an overview of reviews (Becker 2011) which will draw together all existing Cochrane review evidence regarding the use of dressings to treat foot ulcers in people with diabetes. Whilst other existing review evidence may also be included in this overview, following Cochrane guidance, this will only occur in the absence of a relevant Cochrane intervention review (Becker 2011).

Objectives

To compare the effects of all types of hydrocolloid wound dressings with no dressing or alternative dressings on the healing of foot ulcers in people with diabetes.

Methods

Criteria for considering studies for this review

Types of studies

Published or unpublished randomised controlled trials (RCTs) that evaluate the effects of any type of hydrocolloid wound dressing in the treatment of diabetic foot ulcers, irrespective of publication status or language.

Types of participants

Trials recruiting people with Type I or Type II diabetes, with an open foot ulcer. Since study-specific classifications of ulcer diagnosis were likely to be too restrictive, we accepted study authors' definitions of what was classed a diabetic foot ulcer. There was no restriction in relation to the aetiology of the ulcer; trials recruiting people with ulcers of neuropathic, ischaemic or neuroischaemic causes were all eligible for inclusion.

We included trials involving participants of any age. We excluded trials which included patients with a number of different wound aetiologies in addition to diabetic foot ulcers (e.g. pressure ulcers, mixed arterial/venous arterial) unless the results for the subgroup of patients with a diabetic foot ulcer were reported separately or available from authors on contact.

Types of interventions

The primary intervention was all types of hydrocolloid wound dressings (BNF 2010). We included any RCT in which the presence or absence of a hydrocolloid dressing was the only systematic difference between treatment groups. We anticipated that likely comparisons would include hydrocolloid dressings compared with other dressing types and/or other interventions (which could be non-dressing treatments, i.e. topical applications). We did not consider differences in timings of applications to be an issue thus where dressings or creams were applied at different frequencies e.g. once a day in one trial arm and twice a day in the other arm - studies were still included.

Types of outcome measures

Primary outcomes

- Time to ulcer healing.
- Number of ulcers completely healed within a specific time period (we assumed that the period of time in which healing occurred was the duration of the trial unless otherwise stated).

Secondary outcomes

- Health-related quality of life (measured using a standardised generic questionnaire such as EQ-5D, SF-36, SF-12 or SF-6 or disease-specific

questionnaire). We did not include ad-hoc measures of quality of life which are likely not to be validated and will not be common to multiple trials.

- Number and level of amputations.
- Adverse events, including infection and pain (measured using survey/questionnaire/data capture process or visual analogue scale).
- Cost (including measurements of resource use such as number of dressing changes and nurse time).
- Ulcer recurrence.
- Change in ulcer area expressed as absolute changes (e.g. surface area changes in cm^2 since baseline) or relative changes (e.g. percentage change in area relative to baseline).

Search methods for identification of studies

For the search methods used in the original version of this review see Appendix 1

Electronic searches

For this first update we searched the following databases in April 2013:

- The Cochrane Wounds Group Specialised Register (searched 11 April 2013);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 3);
- Ovid MEDLINE (1950 to March Week 4 2013);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations, April 10, 2013);
- Ovid EMBASE (1980 to 2013 April 05);
- EBSCO CINAHL (1982 to 4 April 2013).

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) using the following exploded MeSH headings and keywords:

#1 MeSH descriptor Occlusive Dressings explode all trees
#2 MeSH descriptor Biological Dressings explode all trees
#3 MeSH descriptor Alginates explode all trees
#4 MeSH descriptor Hydrogels explode all trees
#5 MeSH descriptor Silver explode all trees
#6 MeSH descriptor Honey explode all trees
#7 (dressing* or alginate* or hydrogel* or "foam" or "bead" or "film" or "films" or tulle or gauze or non-adherent or "non adherent" or silver or honey or matrix):ti,ab,kw
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9 MeSH descriptor Foot Ulcer explode all trees
#10 MeSH descriptor Diabetic Foot explode all trees

#11 diabet* NEAR/3 ulcer*:ti,ab,kw
#12 diabet* NEAR/3 (foot or feet):ti,ab,kw
#13 diabet* NEAR/3 wound*:ti,ab,kw
#14 (#9 OR #10 OR #11 OR #12 OR #13)
#15 (#8 AND #14)

The search strategies used in Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL can be found in Appendix 2, Appendix 3 and Appendix 4 respectively. 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 also combined the EMBASE and CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network (**SIGN 2011**). There were no restrictions on the basis of date or language of publication.

Searching other resources

In the original version of this review we attempted to contact researchers to obtain any unpublished data when needed. We also searched the reference lists of the included studies and previous systematic reviews. We contacted appropriate manufacturers (Smith & Nephew, Convatec Ltd, Mölnlycke Health Care, 3M Healthcare, Coloplast Ltd) for details of any unpublished studies.

Data collection and analysis

Selection of studies

Two review authors independently assessed the titles and abstracts of retrieved studies for relevance. After this initial assessment, we obtained all studies felt to be potentially relevant, in full. Two review authors then independently checked the full papers for eligibility, with disagreements resolved by discussion and, where required, the input of a third review author. We recorded all reasons for exclusion.

Data extraction and management

We extracted and summarised details of the eligible studies using a data extraction sheet. Two review authors extracted data independently and resolved disagreements by discussion. Where data were missing from reports we attempted to contact the study authors to obtain the missing information. We included studies published in duplicate once but maximally extracted data. We extracted the following data:

- country of origin;
- type of ulcer;
- unit of investigation (per patient) - single ulcer or foot or patient or multiple ulcers on the same patient;
- care setting;
- number of participants randomised to each trial arm;

- eligibility criteria and key baseline participant data;
- details of the dressing/treatment regimen received by each group;
- details of any co-interventions;
- primary and secondary outcome(s) (with definitions);
- outcome data for primary and secondary outcomes (by group);
- duration of follow up;
- number of withdrawals (by group);
- adverse events, including amputation; and
- source of funding.

Assessment of risk of bias in included studies

Two review authors independently assessed each included study using the Cochrane Collaboration tool for assessing risk of bias (**Higgins 2011**). This tool addresses six specific domains, namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues (e.g. extreme baseline imbalance, issues with unit of investigation) (see Appendix 5 for details of the criteria on which the judgement was based). We assessed blinding and completeness of outcome data for each outcome separately. We completed a 'Risk of bias' table for each eligible study. We resolved disagreements about risk of bias assessment by discussion. Where a lack of reported information resulted in an unclear decision, where possible we contacted authors for clarification.

We have presented our assessment of risk of bias findings using a 'Risk of bias' summary figure, which presents all of the judgements in a cross-tabulation of study by entry. This display of internal validity indicates the weight the reader may give the results of each study. We also aimed to present this assessment in the narrative review.

We classified trials as being at high risk of bias if they are rated 'high' for any of three key criteria (randomisation sequence, allocation concealment and blinded outcome assessment).

Measures of treatment effect

Where possible, we present the outcome results for each trial with 95% confidence intervals (CI). We report estimates for dichotomous outcomes (e.g. ulcers healed during time period) as risk ratio (RR). We used the RR rather than odds ratio (OR), since ORs (when interpreted as RR) can give an inflated impression of the effect size when event rates are high, as is the case for many trials reporting healing of chronic wounds (**Deeks 2002**). We planned to report outcomes relating to continuous data (e.g. percentage change in ulcer area) as mean difference (MD) and overall effect size (with 95% CI calculated). Where a study reported time to healing data (the probability of healing over a consecutive time period) we planned to report and plot these data (where possible) using hazard ratio estimates. If studies reporting time-to-event data (e.g. time to healing) did not report a hazard ratio or reported these data incorrectly as a continuous variable then, where feasible, we planned to estimate this using

other reported outcomes such as the numbers of events through the application of available statistical methods (Tierney 2007).

Unit of analysis issues

We recorded whether trials measured outcomes in relation to an ulcer, a foot, a participant or whether multiple ulcers on the same participant were studied. We also recorded where multiple ulcers on a participant had been (incorrectly) treated as independent in a study, rather than within-patient analysis methods being applied. We have recorded this as part of the risk of bias assessment. Unless otherwise stated, where the number of wounds appeared to equal the number of participants we treated the ulcer as the unit of analysis in this review.

Dealing with missing data

Missing data are common in trial reports. Excluding participants post-randomisation from the analysis or ignoring those participants lost to follow up can, in effect, compromise the process of randomisation and thus potentially introduce bias into the trial. In individual studies, where "proportion of ulcers healed" data were presented, we assumed that where randomised participants were not included in an analysis, their wound did not heal (that is, they will be considered in the denominator but not the numerator). Where a trial did not specify participant group numbers prior to dropout, we planned to present only complete case data. We planned to present data for time to healing, area change and for all secondary outcomes as a complete case analysis.

Assessment of heterogeneity

We considered both clinical and statistical heterogeneity. Wherever appropriate, we pooled data using meta-analysis (conducted using RevMan 5.1 (RevMan 2011)), that is where studies appeared similar in terms of level of participants, intervention type and duration and outcome type. We assessed statistical heterogeneity using the Chi^2 test (a significance level of $P < 0.1$ was considered to indicate heterogeneity) and the I^2 statistic (Higgins 2003). The I^2 statistic examines the percentage of total variation across studies due to heterogeneity rather than to chance. Values of I^2 over 50% indicate a high level of heterogeneity. In the absence of clinical heterogeneity and in the presence of statistical heterogeneity (I^2 over 50%), we used a random-effects model. However, we did not pool studies where heterogeneity was substantial (I^2 over 75%). Where there was no clinical or statistical heterogeneity we envisaged using a fixed-effect model.

Data synthesis

We combined studies using a narrative overview with meta-analyses of outcome data where appropriate (in RevMan 5.1). The decision to include studies in a meta-analysis depended on the availability of treatment effect data and assessment of heterogeneity. For time-to-event data, we planned to plot log rank observed minus expected events estimates using a fixed-effect model (a random-effects model for time to event data is not available for this analysis in RevMan 5.1). Where relevant and possible we planned to conduct sensitivity analysis to investigate the potential impact of studies at high risk of bias on pooled results.

Results

Description of studies

See Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The systematic search yielded 346 abstracts which we screened for potential inclusion in the review. Of these, we obtained 103 reports (for 84 studies) for a more detailed assessment and four studies were eligible for inclusion in the review. No eligible studies were obtained from the five commercial companies that were contacted. The update search conducted in April 2013 yielded 116 citations of which two studies were obtained for further information (**Turns 2012**) (excluded) and **Kuo 2012** (included).

One study is awaiting translation from Turkish (**Ogce 2007**). We are not aware of any relevant ongoing studies (checked ISRCTN register 25 April 2013).

Included studies

Five studies (535 participants) were included in this review (**Clever 1995**; **Jeffcoate 2009**; **Jude 2007**; **Kuo 2012**; **Piaggesi 2001**). The dressings evaluated are detailed in Table 1 (three trials evaluated a fibrous hydrocolloid dressing, one a hydrocolloid-matrix dressing and one a silver fibrous-hydrocolloid dressing). Two studies were single-centred (**Kuo 2012**; **Piaggesi 2001**), two were multi-centred (**Jeffcoate 2009**; **Jude 2007**) and the remaining study did not detail the number of centres (**Clever 1995**). One study was undertaken in the UK (**Jeffcoate 2009**); one in Germany (**Clever 1995**); one in Italy (**Piaggesi 2001**); one in Taiwan (**Kuo 2012**) and one study was multi-national, taking place in Italy, France, Germany and Sweden (**Jude 2007**).

Table 1. Summary of studies

First author	Group A	Group B	Group C	Duration of follow up	% healed data
Clever 1995	Hydrocolloid (polyurethane matrix) dressing (Cutinova Hydro, S&N Hlth)	Foam dressing (Allevyn, S&N Hlth)		16 weeks	yes
Jeffcoate 2009	Fibrous-hydrocolloid (hydrofibre) dressing (Aquacel, ConvaTec)	Iodine-impregnated dressing (Inadine, Johnson & Johnson)	Non-adherent dressing (Johnson & Johnson)	24 weeks	yes
Jude 2007	Fibrous-hydrocolloid (hydrofibre) dressing with 1.2% ionic silver	Calcium-alginate dressing (Algosteril, S&N Hlth)		8 weeks	yes

	(Aquacel Ag, ConvaTec)			
Kuo 2012	Fibrous-hydrocolloid (hydrofibre) dressing (Aquacel, ConvaTec)	Cream contained extracts from two botanical raw materials, P. amboinicus and C. asiatica.(Active ingredient 1.25%)	2 weeks	No
Piaggesi 2001	Fibrous-hydrocolloid (Hydrofibre) dressing (Aquacel, ConvaTec)	Saline-moistened gauze	Not reported (maximum follow up was 350 days)	yes

All studies were undertaken in adults with diabetes, three studies specified that they included people with both Type 1 and Type 2 diabetes (Jeffcoate 2009;Kuo 2012 Piaggesi 2001). One study specified that it included only people with Wagner grade 1 or 2 ulcers (Jude 2007) and all four studies specified that they only included participants with ulcers that were neuropathic or neuroischaemic in origin and/or specified that participants had to have an ankle brachial pressure index (ABPI) above a certain value (Clever 1995; Jeffcoate 2009; Jude 2007; Piaggesi 2001). Three studies excluded participants that had infected, sloughy or deep ulcers (Clever 1995; Jeffcoate 2009; Piaggesi 2001). In general it seems that studies aimed to include participants with relatively non-complex diabetic foot ulcers although Kuo 2012 only included ulcers that were classified as Wagner stage 3. The duration of trial follow up ranged from two weeks (Kuo 2012) to approximately 350 days (Piaggesi 2001); full details are presented in Table 1. Of the five included studies, four were two-arm and one was three-armed (Jeffcoate 2009). For this three-armed trial, as each study group received a different intervention all relevant comparisons were included. Four studies reported the number of ulcers healed: only Kuo 2012 did not: the study had only two weeks follow up and after this time all ulcers were either skin grafted or closed surgically. Mean time to healing was reported in three studies (Clever 1995; Jeffcoate 2009; Piaggesi 2001), however, the use of mean vales can result in biased estimates since to calculate mean time to healing either all participants must have healed and/or assumptions need to be made about the shape of the survival curve. The more appropriate summary measure, median time to healing, was reported for one study only (Clever 1995). The reporting of secondary outcomes was limited. Adverse event reporting appeared systematic in three studies: Jeffcoate 2009; Jude 2007 and Kuo 2012. Only one study conducted a robust economic evaluation (Jeffcoate 2009).

Excluded studies

We excluded 80 studies from the review. The main reasons for exclusion were: the participants in the study were not randomised (n = 10), no single, identifiable dressing type was evaluated (n = 11); another intervention, not a dressing, differed between study groups (n = 27); the dressing(s) evaluated were not hydrocolloid (n = 26). Another reason was recorded for six studies.

Risk of bias in included studies

We classified studies rated 'High Risk' for any of three key domains: randomisation sequence, allocation concealment and blinded outcome assessment, as being at high risk of bias. (Characteristics of included studies; Figure 1; Figure 2). One study (**Jeffcoate 2009**) was regarded as being at low risk of bias for the three key domains. The remaining three studies were rated unclear for one or more key domains and hence we could not confidently judge them to be at high or low risk of bias.

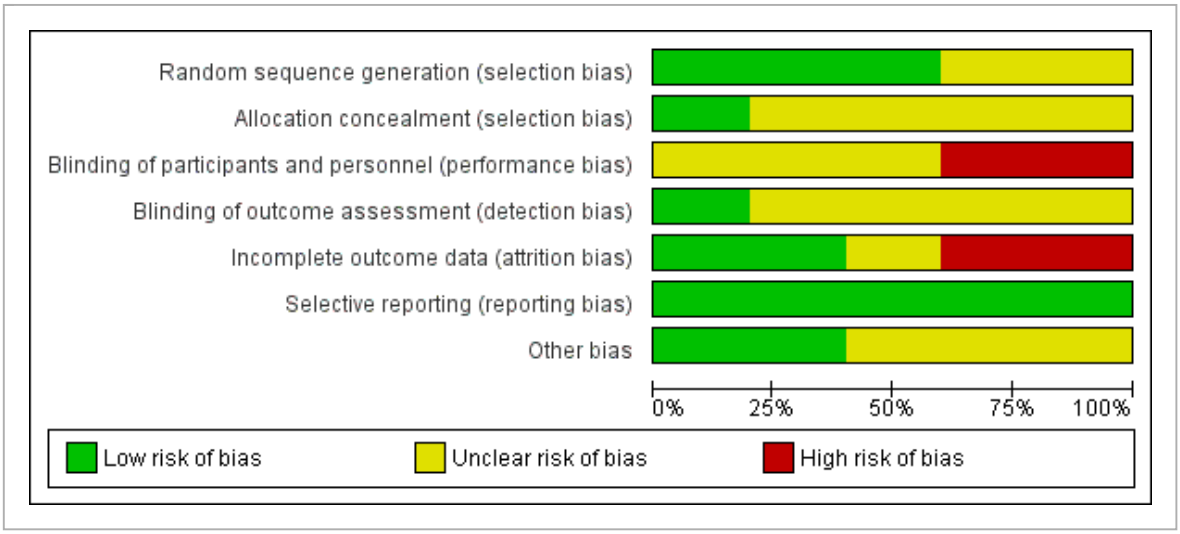

Figure 1.

Open in figure viewer

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

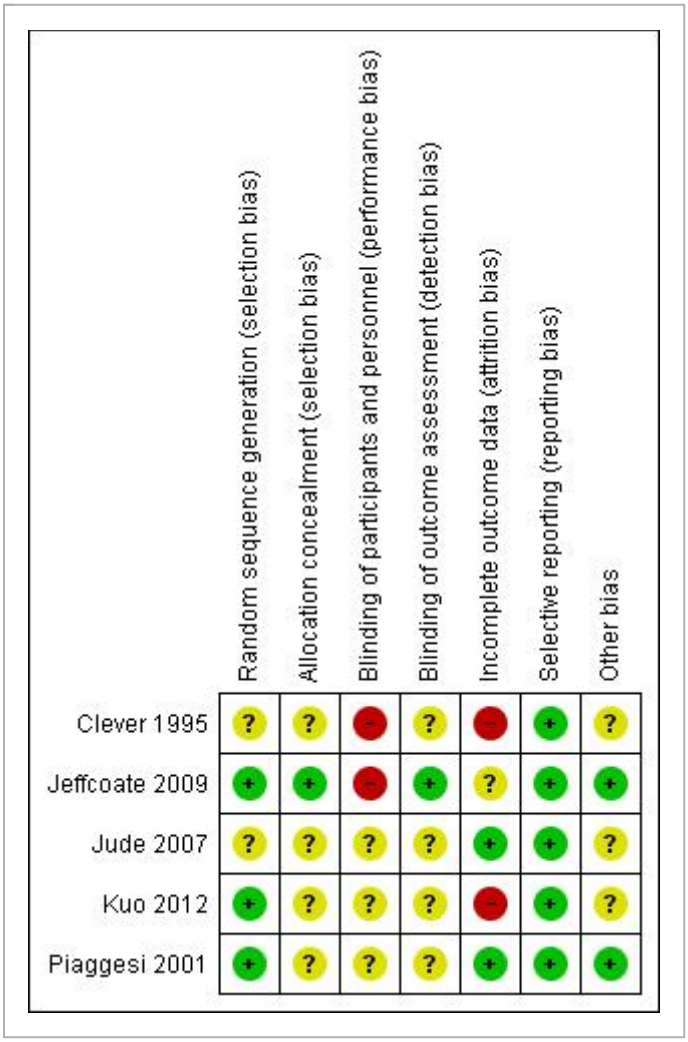

Figure 2.

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

Allocation

Adequacy of randomisation process

All five studies were described as "randomised" with three reporting the method used to generate randomisation sequence and hence judged to be at low risk of bias for this domain (Jeffcoate 2009; Kuo 2012; Piaggesi 2001). Piaggesi 2001 reported the use of computer-generated randomisation; Jeffcoate 2009 used a randomisation sequence created using SPSS (SPSS Inc., Version 14). Whilst Jude 2007 reported use of sealed envelopes the method of randomisation sequence generation remained unclear. The randomisation method was not reported in the remaining study (Clever 1995).

Allocation concealment

Jeffcoate 2009 utilised central office allocation and was the only included study to describe allocation concealment adequately. Jude 2007 reported the use of sealed envelopes for allocation, however, it was unclear if these envelopes were sequentially numbered and opaque. Likewise, the remaining studies did not clearly report the allocation concealment procedure such that we could assess the degree of concealment.

Blinding

Assessment of wound healing can be subjective and thus has the potential to be influenced if the outcome assessor is aware of the treatment allocation. In this review we focused on whether included studies had conducted blinded outcome assessment. One study (Jeffcoate 2009) reported adequate blinding of the outcome assessors and hence was judged to be at low risk of bias for this domain; the remaining four studies were judged to be at unclear risk of bias. Piaggesi 2001 reported blinding of outcome assessment for some trial outcomes, however, it was unclear if this included ulcer healing data and in Jude 2007; Kuo 2012 and Clever 1995 the blinding of outcome assessment was not explicitly mentioned.

Incomplete outcome data

Three studies were judged to have high loss to follow up (Clever 1995; Jeffcoate 2009; Kuo 2012). Clever 1995 reported six of 40 participants (15%) were lost to follow up; Jeffcoate 2009 reported that 88 of 317 (28%) participants were lost to follow up with significant differences between groups. And in Kuo 2012 3/24 randomised participants (12.5%) were not included in the analysis. In terms of conducting intention-to-treat (ITT) analysis, Clever 1995 stated that withdrawals were excluded from the final analyses and was hence deemed to be at high risk of bias for this domain. Jeffcoate 2009 conducted ITT analysis dealing with missing data using the last value carried forward method, which was judged to be at unclear risk of bias. This method is not a robust way of imputing missing data and has the potential to introduce bias (Moher 2010). Jude 2007 and Piaggesi 2001 were deemed to have conducted ITT analysis (thus at low risk of bias for this domain).

Selective reporting

All studies reported outcomes adequately and were deemed to be at low risk of bias. However, it is important to note that judgement for this domain may be of limited value given it was made at face value based on the reporting of outcomes in the results that were described in the methods. Study reports were not compared to study protocols, which were not actively sought out.

Other potential sources of bias

Two studies were funded by non-commercial organisations (Jeffcoate 2009; Piaggesi 2001) and two studies were funded by commercial organisations (Clever 1995; Jude 2007). Kuo 2012 did not report funding information.

Effects of interventions

See: **Summary of findings for the main comparison** Fibrous-hydrocolloid (hydrofibre) dressing compared to basic wound contact dressing for healing diabetic foot ulcers

Dressing compared with dressing

Advanced wound dressing compared with basic wound contact dressing

Comparison 1: fibrous-hydrocolloid dressing compared with basic wound contact dressing (two trials; 229 participants)

Two studies (**Jeffcoate 2009**; **Piaggesi 2001**) compared a fibrous-hydrocolloid dressing with a basic wound contact dressing. Both studies compared the same brand of fibrous-hydrocolloid dressing (Table 1) with either a dry, non-adherent dressing (**Jeffcoate 2009**) or saline-moistened gauze (**Piaggesi 2001**). **Jeffcoate 2009** was a three-armed study in which two groups were relevant to this comparison; in total 229 participants were included in this comparison, however only 20 of these participants were recruited in **Piaggesi 2001**.

Primary outcome: ulcer healing

Jeffcoate 2009 had a follow-up time of 24 weeks. There was no statistically significant difference in the number of ulcers healed in the fibrous-hydrocolloid-dressed group (46/103; 45%) compared with the basic wound contact dressed-group (41/106; 39%): risk ratio (RR) 1.15, 95% confidence interval (CI) 0.84 to 1.59 (Analysis 1.1). The mean time to healing was reported as 125.8 days (standard deviation (SD) 55.9) for the fibrous hydrocolloid-dressed group and 130.7 days (SD 52.4) for the basic wound contact-dressed group. The mean time to healing was obtained by fixing the maximum duration of trial involvement at 168 days. This trial reported a large number of losses to follow up (88 participants, 28% of total). ITT analysis was carried out by the trialists using the last value carried forward method to deal with missing data resulting from withdrawal of participants. It is important to note that this method of dealing with missing data is not robust and has the potential to bias treatment effects especially where loss of data is unequal between trial arms (**Moher 2010**).

Piaggesi 2001 did not report the study follow-up time; the maximum period reported (graphically) in the study report was approximately 350 days. There was no statistically significant difference in the number of ulcers healed in the fibrous-hydrocolloid-dressed group (9/10; 90%) compared with the basic wound contact dressed-group (10/10; 100%): RR 0.90, 95% CI 0.69 to 1.18 (Analysis 1.1). Mean time to healing data were presented: 127 days (SD 46) in the fibrous-hydrocolloid-dressed group and 234 days (SD 61) in the basic wound contact-dressed group. The study authors analysed these data (log rank test) reporting a statistically different difference in time to healing ($p < 0.001$). Whilst it is usually incorrect to treat healing data as continuous since in most studies not all patients will heal and thus will not have a time to healing value from which to calculate the mean; in this small study 19 of the 20 participants did heal and one underwent an amputation (not clear if amputation date was used in calculation of mean healing values). However, such small participant numbers limit the conclusions that can be drawn from these data; although we note there was no apparent baseline imbalance for duration and size of ulcer.

We pooled ulcer healed data from Jeffcoate 2009 and Piaggesi 2001 using a random-effects model (Chi²: P = 0.14; I² = 54%) (Analysis 1.1). There was no statistically significant difference in the number of ulcers healed in the fibrous-hydrocolloid-dressed groups compared with the basic wound contact-dressed groups: RR 1.01 (95% CI 0.74 to 1.38). Thus, on average, there was no difference in treatment effect between fibrous-hydrocolloid and basic wound contact dressings although confidence intervals were wide. In terms of the source of heterogeneity, the two studies had different ankle brachial pressure index (ABPI) thresholds for study inclusion (> 0.7 in Jeffcoate 2009 and > 0.9 in Piaggesi 2001). Additionally the Piaggesi 2001 study was small with only 20 participants, compared with over 300 in Jeffcoate 2009 . Whilst this should not make a difference in terms of heterogeneity per se, the small number of participants could lead to differences between the study populations even though they had similar inclusion criteria. Comparing the baseline variables suggests that, on average, the patients in Piaggesi 2001 were slightly younger than in Jeffcoate 2009). Finally it is important to note that these trials had different follow-up times, with one (Piaggesi 2001) being twice as long as the other. This, as well as the participants having higher ABPI values, may explain the higher rates of healing in the Piaggesi 2001 study. Jeffcoate 2009 does not present information about ulcer duration and/or size at baseline so it is not clear if these characteristics differed between studies.

Secondary outcomes

Jeffcoate 2009: There were four amputations reported in the fibrous-hydrocolloid-dressed group compared with two amputations in the basic wound contact-dressed group. We did not analyse these data as it was not clear from the report if there was one amputation per person or if one person had undergone two amputations. The cost of generating a healed ulcer was estimated to be GBP 362 in the basic wound contact group, with the cost of an additional ulcer healed increasing to GBP 836 for the fibrous-hydrocolloid group. This increase in cost was likely due to the incremental mean cost difference in per patient dressing management (higher costs associated the with fibrous-hydrocolloid dressing) and the limited incremental difference in healing between the study groups. In terms of adverse events, both groups had similar numbers of serious (28 in the fibrous-hydrocolloid-dressed group compared with 35 in the basic wound contact-dressed group) and non-serious (227 in the fibrous-hydrocolloid-dressed group compared with 244 in the basic wound contact-dressed group) events. There was no difference in quality of life (disease-specific and generic) nor in recurrence rates.

Piaggesi 2001: There were five amputations in the fibrous-hydrocolloid-dressed group compared with three amputations in the basic wound contract-dressed group. Adverse events recording was minimal with two specific adverse events being reported for the fibrous-hydrocolloid group compared with five for the basic wound contact-dressed group. The average number of days between dressings changes was similar for both groups (2.1 compared with 2.4).

Summary: fibrous-hydrocolloid dressing compared with basic wound contact dressing

There was no statistically significant difference in the number of diabetic foot ulcers healed when treated with a fibrous-hydrocolloid dressing compared with basic wound contact dressings in these studies with good length of follow up. There was a statistically significant difference in mean time to healing reported in Piaggesi 2001 however the small size of this

study and potential issues with analysis mean that limited conclusions can be drawn. In terms of secondary outcome data, Jeffcoate 2009 suggests that the basic wound contact dressing was a more cost-effective treatment compared with a fibrous-hydrocolloid dressing. There did not appear to be any difference in the number of adverse events, the quality of life or ulcer recurrence between the groups.

Comparisons between alternative advanced dressings

Comparison 2: hydrocolloid (matrix) dressing compared with foam dressing (one trial; 40 participants)

Clever 1995 recruited 40 participants and compared a hydrocolloid-matrix dressing with a foam dressing (Table 1).

Primary outcome: ulcer healing

Clever 1995 had a maximum follow-up of 16 weeks. There was no statistically significant difference in the number of ulcers healed in the hydrocolloid-matrix-dressed group (16/20; 80%): compared with the foam-dressed group (14/20; 70%): RR 1.14, 95% CI 0.80 to 1.64 (Analysis 2.1). The median time to healing was similar in both groups: 15.5 (range 4 to 76) days in the hydrocolloid-matrix dressed group compared with 16.5 days (range 4 to 52) in the foam-dressed group.

Secondary outcomes

Clever 1995: There was limited reporting of adverse events, with one event reported in the hydrocolloid-matrix-dressed group and five events in the foam-dressed group. The mean number of dressing changes between clinical visits was similar for both groups: 2.23 changes in the hydrocolloid-matrix-dressed group compared with 2.37 changes in the foam-dressed group.

Summary: hydrocolloid (matrix) dressing compared with foam dressing

Limited data from one small study found no difference in healing between ulcers treated with hydrocolloid matrix and foam dressings.

Antimicrobial dressing compared with non antimicrobial dressing

Jude 2007 recruited 134 participants and compared a silver fibrous-hydrocolloid dressing with an alginate dressing (Table 1). Jeffcoate 2009 was a three-armed study with 317 participants, with two arms (number of participants 211) that compared an iodine-impregnated dressing with a fibrous-hydrocolloid dressing.

Comparison 3: silver-hydrocolloid dressing compared with an alginate dressing (one trial; 134 participants)

Primary outcome: ulcer healing

Jude 2007 had a follow-up period of eight weeks. There was no statistically significant difference in the number of ulcers healed in the silver fibrous-hydrocolloid-dressed group

(21/67; 31%) compared with the alginate-dressed group (15/67; 22%): RR 1.40, 95% CI 0.79 to 2.47 (Analysis 3.1). The mean time to healing was reported as 52.6 days (SD 1.8) in the silver fibrous-hydrocolloid-dressed group compared with 57.7 days (SD 1.7) in the alginate-dressed group.

Secondary outcomes

Jude 2007: 25 participants experienced one or more events in the silver fibrous-hydrocolloid-dressed group (including one death) compared with 26 participants in the alginate-dressed group (including one death). The mean number of dressing changes during study were similar for both group (21.9 for the silver fibrous-hydrocolloid-dressed group and 20.8 for the alginate-dressed group). There were more infections in the fibrous hydrocolloid group (14 versus 8).

Comparison 4: iodine-impregnated dressing compared with fibrous-hydrocolloid dressing (one trial; 211 participants)

Primary outcome: ulcer healing

Jeffcoate 2009 was a three-armed study, in which two groups were relevant to this comparison and had a follow-up time of 24 weeks. There was no statistically significant difference in the number of ulcers healed in the iodine-impregnated dressing group (48/108; 44%) compared with the fibrous-hydrocolloid group (46/103; 45%): RR 1.00, 95% CI 0.74 to 1.34 (Analysis 4.1). The mean time to healing was reported as 127.8 days (SD 54.2) for the iodine-dressed group and 125.8 days (SD 55.9) for the fibrous-hydrocolloid dressed-group. The mean time to healing was obtained by fixing the maximum duration of trial involvement at 168 days.

Secondary outcomes

There was one amputation in the iodine-dressed group compared with four amputations in the fibrous-hydrocolloid-dressed group. We did not analyse these data as it was not clear if it was the same people who had undergone amputation (thus introducing clustering). The cost of healing an additional ulcer healed was GBP 848 for the iodine-dressed group. In terms of adverse events, both groups had similar numbers of serious (37 in the iodine-dressed group compared with 28 in the fibrous-hydrocolloid-dressed group) and non-serious (239 in the iodine group compared with 227 in the fibrous-hydrocolloid dressed group) events. There was no difference in quality of life (disease-specific and generic) nor in recurrence rates. There was a possible difference in recurrence rates, more in iodine group (seven compared with three) but these numbers of events were small.

Given the different dressing type we did not pool these data in an antimicrobial compared with non-antimicrobial meta-analysis.

Summary: antimicrobial fibrous-hydrocolloid dressing compared with non-antimicrobial dressing

There was no statistically significant difference in the number of ulcers healed when treated with an antimicrobial (silver) fibrous-hydrocolloid dressing compared with a standard alginate dressings. Nor was there any statistically significant difference in ulcer healing between an antimicrobial (iodine impregnated)-dressed group when compared with a

standard fibrous hydrocolloid-dressed group. In terms of secondary outcome data, Jeffcoate 2009 conducted a detailed cost-effectiveness analysis and concluded that the costs of using fibrous-hydrocolloid and an iodine-impregnated dressing were similar. There did not appear to be any difference in the number of adverse events, the quality of life or ulcer recurrence between the groups, although number of recurrence events were small. This trial was of adequate statistical power and good methodological quality.

Dressing compared with topical treatment

Advanced wound dressing compared with plant-based topical treatment

Comparison 4: fibrous-hydrocolloid dressing compared with Plectranthus amboinicus and Centella asiatica Cream (one trial; 24 participants)

Primary outcome: ulcer healing

Kuo 2012 had a maximum follow-up of 2 weeks with all ulcers being treated surgically after this point (grafting or surgical closure for healing by primary intention). Number of ulcers healed was not reported however the median percent change in wound size (assume from baseline to 14 days) was reported. The median % change was reported as -22.64% in the hydrocolloid group and -27.18% in the topical treatment group. This difference was stated as not statistically significant in the trial report (p=0.673). Given the limited data reported we have not analysed further (Analysis 5.1)

Kuo 2012: It was reported that 5/12 (41.7%) participants in each group had one or more adverse events. No further analysis was undertaken (Analysis 5.1).

Summary of Findings Table

We have included a Summary of Findings table (Summary of findings for the main comparison) in this review for the comparisons informed by more than one trial (fibrous-hydrocolloid dressing compared with basic wound contact dressing): this aims to give a concise overview and synthesis of the volume and quality of the evidence for this comparison. The Summary of Findings table confirm our conclusion that the quality of evidence is of moderate quality and on balance there is no strong evidence of a benefit of using hydrocolloid dressings for healing foot ulcers in people with diabetes.

Discussion

Summary of main results

This review has identified, appraised and presented all available RCT evidence (Clever 1995; Jeffcoate 2009; Jude 2007; Kuo 2012; Piaggesi 2001) regarding the clinical and cost-effectiveness of all types of hydrocolloid wound dressings in the treatment of diabetic foot ulcers.

When data from two studies comparing fibrous-hydrocolloid and basic wound contact dressings were pooled, there was no statistically significant difference in ulcer healing

between the treatments. We also found no evidence of any difference in ulcer healing between a hydrocolloid-matrix dressing and a foam dressing. Similarly, there was no evidence of any difference in the number of diabetic foot ulcers healed when treated with an antimicrobial (silver) fibrous-hydrocolloid dressing compared with a standard alginate dressing; nor between an antimicrobial dressing (iodine-impregnated) and a standard fibrous-hydrocolloid dressing. One robust study with an adequate follow-up period (24 weeks) found that a basic wound contact dressing was more cost-effective in healing diabetic foot ulcers than a fibrous hydrocolloid (hydrofibre) dressing (Jeffcoate 2009). Four of the included studies (Clever 1995; Piaggesi 2001; Jude 2007; Kuo 2012) were small and therefore statistically underpowered to detect important treatment differences should they exist and one study did not follow wounds up to healing (Kuo 2012). However, the pooling of data from Piaggesi 2001 with the much larger Jeffcoate 2009 study increased the power of this comparison. We note that most included studies were evaluating treatments on people who appeared to have relatively non-complex foot ulcers. This means the body of literature presented may be of limited use to health professionals in the treatment of people with harder to heal foot ulcers as it is difficult to generalise from the included studies to people with more co-morbidities or complications; this is a limitation of the RCTs that have been undertaken in this field thus far.

Quality of the evidence

One included study in this review was of deemed to be at low risk of bias (Jeffcoate 2009); the remaining studies were at unclear risk of bias due to poor reporting since studies did not follow good practice conduct and reporting guidelines, e.g. CONSORT (Schulz 2010). Key areas of good practice are the robust generation of a randomisation sequence, for example, computer-generated, robust allocation concealment, the use of a telephone randomisation service and blinded outcome assessment where possible. All this information should be clearly stated in the study report as all trial authors should anticipate the inclusion of their trials in systematic reviews. In terms of analysis, where possible, data from all participants should be included, that is an intention-to-treat analysis is conducted. Steps should be taken during trial conduct to prevent missing data as far as is possible. Where missing data are an issue, imputation methods should be considered and clearly reported when implemented. Finally, where possible robust economic data should be collected.

Potential biases in the review process

The review considered as much evidence as it was possible to obtain, including studies that were not published in the English language. We contacted relevant pharmaceutical companies but did not receive any RCT data from them. There is the potential for publication bias, however, this is likely to be a limited issue in this review given the large number of negative findings that have been published. It is also important to note that two studies are awaiting assessment and may be included in future reviews.

Agreements and disagreements with other studies or reviews

The existing evidence-base to help clinicians in their decision-making processes suggests that there is no evidence to suggest that hydrocolloid dressings are better than alternative

dressings for diabetic foot ulcers. This agrees with the most recent systematic review in this area (Hinchliffe 2008), which did not find any evidence that any one dressing type was more effective than others in healing diabetic foot ulcers. However, we note that Hinchliffe 2008 included only one trial of hydrocolloid dressings, compared with the four studies included in this review .

Authors' conclusions

Implications for practice

Based on a comprehensive review of current evidence, fibrous-hydrocolloid dressings (with or without antimicrobial components) and hydrocolloid-matrix dressings do not appear to increase the healing rates of diabetic foot ulcers compared with alternative dressings. Practitioners may therefore elect to consider other characteristics such as costs and symptom management properties when choosing between alternatives. We note that most included studies were evaluating treatments on people who appeared to have relatively non-complex foot ulcers. This means the body of literature presented may be of limited use to health professionals in the treatment of people with harder to heal foot ulcers as it is difficult to generalise from the included studies to people with more co-morbidities or complications; this is a limitation of the RCTs that have been undertaken in this field thus far.

Implications for research

Current evidence suggests that there is no difference in ulcer healing between hydrocolloid dressings and alternatives; it is important to note that included studies have evaluated only fibrous-hydrocolloid and matrix hydrocolloid dressings. It is unclear if this is due to limited used of occlusive hydrocolloid dressings on diabetic foot ulcers due to the perceived (but untested) risk of increased infection risk from anaerobic micro-organisms with these treatments. The importance of including robust cost-effectiveness analyses is highlighted by Jeffcoate 2009, who did not find that treatment with advanced wound management dressings reduced the number of clinic visits. In terms of dressing choice, any investment in future research must maximise its value to decision-makers. Given the large number of dressing options, the design of future trials should be driven by the questions of high priority to patients and other decision makers. It is also important for research to ensure that the outcomes that are collected in research studies are those that matter to patients, carers and health

professionals. It may be that dressings should be viewed as management tools and that other treatments that address patient lifestyle issues deserve attention. Where trials are conducted, good practice guidelines must be followed in their design, implementation and reporting. Further reviews are being conducted to synthesise evidence regarding the effect of other dressings on the treatment of diabetic foot ulcers. It would then be useful to conduct further evidence synthesis (overviews of reviews, mixed treatment comparisons or both) to aid decision-making about the choice of dressings for diabetic foot ulcers across all dressing options.

Acknowledgements

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Data and analyses

Download statistical data

Comparison 1. Fibrous-hydrocolloid (hydrofibre) dressing compared with basic wound contact dressing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of ulcers healed	2	229	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.74, 1.38]

Comparison 2. Hydrocolloid (matrix) dressing compared with foam dressing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of ulcers healed	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 3. Silver hydrocolloid dressing compared with alginate dressing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of ulcers healed	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 4. Iodine-impregnated dressing compared with fibrous-hydrocolloid (hydrofibre) dressing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of ulcers healed	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 5. Trial data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Trial data			Other data	No numeric data

Appendices

Appendix 1. Search methods for the original version of the review - January 2011

Electronic searches

We searched the following databases:

- The Cochrane Wounds Group Specialised Register (searched 4 January 2012);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 4);
- Ovid MEDLINE (1950 to December Week 3 2011);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations, January 03, 2012);
- Ovid EMBASE (1980 to 2011 Week 52);
- EBSCO CINAHL (1982 to 30 December 2011).

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) using the following exploded MeSH headings and keywords:

#1 MeSH descriptor Occlusive Dressings explode all trees
#2 MeSH descriptor Biological Dressings explode all trees
#3 MeSH descriptor Alginates explode all trees
#4 MeSH descriptor Hydrogels explode all trees
#5 MeSH descriptor Silver explode all trees
#6 MeSH descriptor Honey explode all trees
#7 (dressing* or alginate* or hydrogel* or "foam" or "bead" or "film" or "films" or tulle or gauze or non-adherent or "non adherent" or silver or honey or matrix):ti,ab,kw
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9 MeSH descriptor Foot Ulcer explode all trees
#10 MeSH descriptor Diabetic Foot explode all trees
#11 diabet* NEAR/3 ulcer*:ti,ab,kw
#12 diabet* NEAR/3 (foot or feet):ti,ab,kw
#13 diabet* NEAR/3 wound*:ti,ab,kw
#14 (#9 OR #10 OR #11 OR #12 OR #13)
#15 (#8 AND #14)

The search strategies used in Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL can be found in Appendix 1, Appendix 2 and Appendix 3 respectively. 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 also combined the EMBASE and CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network (**SIGN 2011**). There were no restrictions on the basis of date or language of publication.

We searched for on-going studies on the ISRCTN register (http://www.controlled-trials.com/isrctn/) (last searched 22nd May 2011).

Searching other resources

We attempted to contact researchers to obtain any unpublished data when needed. We also searched the reference lists of the included studies and previous systematic reviews. We contacted appropriate manufacturers (Smith & Nephew, Convatec Ltd, Mölnlycke Health Care, 3M Healthcare, Coloplast Ltd) for details of any unpublished studies.

Appendix 2. Ovid MEDLINE search strategy

1 exp Occlusive Dressings/
2 exp Biological Dressings/
3 exp Alginates/
4 exp Hydrogels/
5 exp Silver/
6 exp Honey/
7 (dressing* or hydrocolloid* or alginate* or hydrogel* or foam or bead or film*1 or tulle or gauze or non-adherent or non adherent or silver or honey or matrix).tw.
8 or/1-7

9 exp Foot Ulcer/
10 exp Diabetic Foot/
11 (diabet* adj3 ulcer*).tw.
12 (diabet* adj3 (foot or feet)).tw.
13 (diabet* adj3 wound*).tw.
14 or/9-13
15 8 and 14

Appendix 3. Ovid EMBASE search strategy

1 exp wound dressing/
2 exp alginic acid/
3 exp hydrogel/
4 exp SILVER/
5 exp HONEY/
6 (dressing* or hydrocolloid* or alginate* or hydrogel* or foam or bead or film*1 or tulle or gauze or non-adherent or non adherent or silver or honey or matrix).tw.
7 or/1-6
8 exp foot ulcer/
9 exp diabetic foot/
10 (diabet* adj3 ulcer*).tw.
11 (diabet* adj3 (foot or feet)).tw.
12 (diabet* adj3 wound*).tw.
13 or/8-12
14 7 and 13

Appendix 4. EBSCO CINAHL search strategy

S11 S4 and S10
S10 S5 or S6 or S7 or S8 or S9
S9 TI diabet* N3 wound* or AB diabet* N3 wound*
S8 TI (diabet* N3 foot OR diabet* N3 feet) or AB (diabet* N3 foot OR diabet* N3 feet)
S7 TI diabet* N3 ulcer* or AB diabet* N3 ulcer*
S6 (MH "Foot Ulcer+")
S5 (MH "Diabetic Foot")
S4 S1 or S2 or S3
S3 TI (dressing* or alginate* or hydrogel* or foam or bead or film or films or tulle or gauze or non-adherent or non adherent or honey or silver or matrix) or AB (dressing* or alginate* or hydrogel* or foam or bead or film or films or tulle or gauze or non-adherent or non adherent or honey or silver or matrix)
S2 (MH "Honey")
S1 (MH "Bandages and Dressings+")

Appendix 5. Risk of bias criteria

1. Was the allocation sequence randomly generated?

Low risk of bias

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

High risk of bias

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

Unclear

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

2. Was the treatment allocation adequately concealed?

Low risk of bias

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

High risk of bias

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

Unclear

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

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

Low risk of bias

Any one of the following.

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

High risk of bias

Any one of the following.

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

Unclear

Any one of the following.

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

4. Were incomplete outcome data adequately addressed?

Low risk of bias

Any one of the following.

- No missing outcome data.
- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.

- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk 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 not enough to have a clinically relevant impact on observed effect size.
- Missing data have been imputed using appropriate methods.

High risk of bias

Any one of the following.

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

Unclear

Any one of the following.

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

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

Low risk of bias

Any of the following.

- The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.

- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

High risk of bias

Any one of the following.

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

Unclear

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

6. Other sources of potential bias

Low risk of bias

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

High risk of bias

There is at least one important risk of bias. For example, the study:

- had a potential source of bias related to the specific study design used; or
- had extreme baseline imbalance; 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.

What's new

Date	Event	Description
11 April 2013	New citation required but conclusions have not changed	One new study included (Kuo 2012), no change to conclusions.
11 April 2013	New search has been performed	First update, new search, summary of findings table added.

Contributions of authors

Jo Dumville developed the review and co-ordinated development, completed the first draft of the review, made an intellectual contribution, approved the final version prior to submission and is the guarantor of the review and the update.
Sohan Deshpande completed the first draft of the review, made an intellectual contribution and approved the final version of the review prior to submission.
Susan O'Meara edited the review, made an intellectual contribution and approved the final version of the review and the update prior to submission.
Katharine Speak made an intellectual contribution to the review, advised on the review and approved the final version prior to submission.

Contributions of editorial base:

Nicky Cullum: edited the protocol and review; advised on methodology, interpretation and content. Approved the final review prior to submission.
Joan Webster, Editor: approved the review update prior to submission.
Sally Bell-Syer: co-ordinated the editorial process. Advised on methodology, interpretation and content. Edited the review.
Ruth Foxlee: designed the search strategy and edited the search methods section.

Declarations of interest

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External sources

- NIHR Programme Grants for Applied Research, UK.
- NIHR/Department of Health (England), Cochrane Wounds Group, UK.

Characteristics of studies

Characteristics of included studies [ordered by study ID]

Clever 1995

Methods	RCT (not clear if single-centre or multi-centred) comparing a foam dressing (Allevyn, Smith & Nephew) with a hydrocolloid (polyurethane matrix) dressing (Cutinova Hydro, S&N Hlth, previously Beiersdorf) undertaken in Germany Duration of follow up: until healing occurred or for a maximum of 16 weeks
Participants	40 participants Inclusion criteria: patients aged 18 to 80 years with a pure neuropathic superficial ulcer 1 to 5 cm in diameter and with no clinical and radiological signs of osteomyelitis or tendon involvement Exclusion criteria: patients with an ankle-brachial pressure index < 0.8 (measured using doppler ultrasound) and with clinical or radiological signs of osteomyelitis or tendon involvement. Ulcers requiring topical treatment were also excluded, as were patients with know allergies to any product being used.
Interventions	Group A (n = 20): hydrocolloid (polyurethane matrix) dressing (Cutinova Hydro, Smith & Nephew) Group B (n = 20): foam dressing (Allevyn, Smith & Nephew) In both groups, dressing changes were performed as often as required but at least once a week Co-intervention: pressure relief comprising a half-shoe or so-called 'heal sandal', therapeutic footwear with cushioned insoles, and crutches as required to meet individual needs, infection control with systemic antibiotics if required, wound cleansing with Ringer's solution and debridement with removal of callus if needed
Outcomes	Primary outcome: ulcer healing (number of ulcers healed; mean time to healing; median time to healing; wound size)

	Secondary outcomes: adverse events (number); costs (mean number of dressing changes between clinical visits) Health-related quality of life; amputations and ulcer recurrence not reported
Notes	Trial data: Analysis 5.1 Funding source: Beiersdorf AG, Hamburg

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** *"Conducted an open, randomised, controlled study"* **Comment:** method of generation of random schedule not reported
Allocation concealment (selection bias)	Unclear risk	**Comment:** the process of randomising participants, including who did this is not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Quote:** " *Conducted an open, randomised, controlled study* " **Comment:** the trial was stated as being open-labelled. No other details in the text
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Quote:** *"Conducted an open, randomised, controlled study* " **Comment:** this was labelled an open trial not clear if blinded evaluation was conducted.
Incomplete outcome data (attrition bias) All outcomes	High risk	**Comment:** in total 6 participants were withdrawn, or 15% of the total study population. The study report also states that withdrawals were excluded from the analyses.
Selective reporting (reporting bias)	Low risk	**Comment:** based on paper only, protocol not obtained
Other bias	Unclear risk	**Comment:** funded by commercial organisation

Jeffcoate 2009

Methods	Three-armed RCT comparing an iodine-impregnated dressing (Inadine, Johnson and Johnson) and fibrous-hydrocolloid (hydrofibre) dressing (Aquacel, ConvaTec) with a non-adherent dressing, viscose filament gauze (Johnson & Johnson) undertaken in the UK Duration of follow up: ulcers once healed were followed bi-weekly for 4 weeks to ensure they remained healed. Ulcers that recurred within the 4 weeks were regarded as unhealed and continued in the study. All participants with healed ulcers were re-assessed by the clinicians in charge of their care 12 weeks after healing to assess for recurrence. Patients with persistent ulcers were assessed by

	clinicians in charge by 24 weeks and withdrawn from the intervention phase at that time. They did attend for a final assessment 36 weeks after recruitment.
Participants	317 participants Inclusion criteria: patients with Type 1 or 2 diabetes, aged 18 years or more having a foot ulcer present for at least 6 weeks. Ulcer cross-sectional area of between 25 and 2500 mm^2. Able and willing to give informed consent. Reasonably accessible by car to the hospital base and under routine review by the multidisciplinary clinic. If there was more than one ulcer on the foot, the largest ulcer that conformed to the inclusion criteria was selected as the index ulcer. Exclusion criteria: patients with a known allergy to any of the trial preparations (including iodine). Any ulcer on either foot extending to tendon, periosteum or bone. Patients with infection of the bone, soft tissue infection requiring treatment with systemic antibiotics. An ulcer on a limb being considered for revascularisation. Ulcers chosen for management with a non-removable cast without a dressing window. Gangrene on the affected foot. Eschar which was not removable by clinical debridement. Patients with evidence of a sinus or deep track. Patients in whom the hallux had been amputated on the affected side (preventing the measurement of toe pressure). Those with an ankle:brachial pressure index of less than 0.7 or toe systolic pressure less than 30 mmHg. Ulceration judged to be caused primarily by disease other than diabetes. Patients with any other serious disease likely to compromise the outcome of the trial. Patients with critical renal disease (creatinine greater than 300 mmol/l) and those receiving immunosuppressants, systemic corticosteroid therapy (other than by inhalation) or any other preparation which could, in the opinion of the supervising clinician, have interfered with wound healing. Patients living at such a distance (generally further than 10 miles) from the clinic as would have made frequent assessment visits inappropriately expensive and/or impractical. Patients who withheld consent.
Interventions	Group A (n = 103): fibrous-hydrocolloid (hydrofibre) dressing (Aquacel, ConvaTec) Group B (n = 108): iodine-impregnated dressing (Inadine, Systagenix) Group C (n = 106): non-adherent dressing, viscose filament gauze (Johnson & Johnson) For all groups, patients and carers were shown the dressing to be used and asked if they wished to change their own dressings (either entirely or just on some occasions), but with fortnightly monitoring by a trial nurse. Those who wished to do so received further training to ensure the dressings were applied correctly. Those who chose not to be responsible for this aspect of their care had their dressings changed by the district nurse or practice nurse, according to usual procedure, or by the trial nurse. Dressings were changed daily, on alternate days or 3 times a week according to need and/or availability of professional staff. Co-intervention: ulcer management was in line with current guidelines for good practice, including appropriate and regular use of debridement and with a removable fibreglass or polyester boot being recommended for off-loading. Participants were advised to have a bath or shower as often as they wished provided the ulcer could be redressed afterwards, and provided the ulcerated foot was not immersed in water for more than 5 minutes.
Outcomes	Primary outcome: ulcer healing (number of ulcers healed at 24 weeks; mean time to healing in days) Secondary outcomes: health-related quality of life (Mean Cardiff Wound Impact Schedule score); amputations (minor and major); adverse events (serious and non-serious); cost (cost per patient); ulcer recurrence
Notes	

	Trial data: Analysis 5.1 In total, 88 were withdrawn from this study. The study methods note that an ITT analysis for % healed was conducted using last entry carried forward, with participants only considered healed if this was confirmed after 4 weeks. Thus, the analysis assumed that those withdrawn did not heal (they are in denominator but not the numerator) Funding source: non-commercial organisation (United Kingdom National Health Service Health Technology Assessment Programme)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** *"Randomisation lists were created using SPSS (SPSS Inc., Version 14), using blinded dressing codes "* **Comment:** method of generation of random schedule reported
Allocation concealment (selection bias)	Low risk	**Quote:** *"using blinded dressing codes. The lists were held at Cardiff University and each recruiting centre telephoned a designated number during working hours"* **Comment:** central allocation using telephone
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Quote:** *"The nurse was not blinded to the randomisation and dressed the wound at the end of the visit"* **Comment:** no mention about blinding of participants. Healthcare providers were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** *"Dressings were removed prior to the examination by investigators who were not involved in the conduct of the trial and who were blind to the randomisation group."* **Comment:** outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Quote:** *"Intention to treat analysis was carried out using the last value carried forward method, with strict adherence to the protocol such that only those who attended for a healing verification visit and reported as still healed at 28 days have been coded as 'healed' for the outcome classification."* **Comment:** ITT analysis was done but imputing missing data due to withdrawal of trial participants due to adverse events and protocol violations
Selective reporting (reporting bias)	Low risk	**Comment:** based on full report, protocol not obtained
Other bias	Low risk	**Comment:** funded by non-commercial organisation (UK Health Technology Assessment Programme)

Jude 2007

Methods	Multi-centred, 2-armed trial, RCT comparing a fibrous-hydrocolloid (hydrofibre) dressing with 1.2% ionic silver (Aquacel Ag, ConvaTec) with a calcium-alginate dressing (Algosteril, Smith & Nephew) undertaken in the UK, France, Germany, Sweden Duration of follow up: 8 weeks
Participants	134 participants Inclusion criteria: patients with type 1 or type 2 diabetes mellitus (HbA1c ≤ 12%), serum creatinine ≤ 200 mol/l diabetic foot ulcers classed as Wagner grade 1 or 2 and of neuropathic or neuro-ischaemic aetiology. All wounds > 1 cm^2 in area. Exclusion criteria: patients with known allergies to dressings under study; if there was a known or suspected malignancy near ulcer. Also, if patient had been on systemic antibiotics > 7 days prior to enrolment or with inadequate arterial perfusion as defined by ankle-to-brachial index < 0.8, great toe systolic blood pressure < 40 mmHg or forefoot TcPO2 < 30 mmHg (subject supine) or < 40 mmHg (subject sitting)
Interventions	Group A (n = 67): fibrous-hydrocolloid (hydrofibre) dressing with 1.2% ionic silver (Aquacel® Ag, ConvaTec). Left in place and changed on leakage or at evaluation or every 7 days as indicated. Group B (n = 67): calcium-alginate dressing (Algosteril, Smith & Nephew). Manufacturers instructions were followed and the dressing was moistened before use on dry wounds and changed on leakage or at evaluation or every 7 days as indicated (except if the wound was infected when dressed changed daily). In both groups, ulcers were cleansed using sterile saline, each dressing was covered with a sterile, non-adherent foam dressing Co-intervention: accommodative footwear for non-plantar ulcers and off-loading for planter ulcers was delivered as required.
Outcomes	Primary outcome: ulcer healing (number of ulcers healed; velocity of healing; mean time in days to healing; reduction in ulcer area; reduction in ulcer depth) Secondary outcomes: adverse events (number); costs (mean number of dressing changes) Health-related quality of life; amputations and ulcer recurrence not reported
Notes	Trial data: Analysis 5.1 22 participants had clinically infected ulcers at baseline, 9 in Group A and 13 in Group B . On enrolment antibiotics were prescribed to 13 in Group A and 8 in Group B. Funding source: ConvaTec (Bristol Myers Squibb)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote:** *"Individuals were randomly assigned to receive either ** or ** dressings according to instructions in a sealed envelope and stratified according to whether or not systemic antibiotics were*

		being administered for treatment of the study ulcer" **Comment:** method of generation of random schedule not clear from this description
Allocation concealment (selection bias)	Unclear risk	**Comment:** not clear if envelopes were sequentially numbered, opaque and sealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	**Comment:** no mention of blinding in study report
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Comment:** no mention of blinding in study report
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** 21 participants recorded as discontinuing treatment, however, it does not seem like these were study withdrawals. All randomised included in the analysis.
Selective reporting (reporting bias)	Low risk	**Comment:** based on study report, protocol not obtained
Other bias	Unclear risk	**Comment:** funded by commercial organisation

Kuo 2012

Methods	2-arm trial, RCT comparing a fibrous-hydrocolloid (hydrofibre) dressing with a topical cream containing P. amboinicus (Lour.) Spreng. (Lamiaceae) and C. asiatica (L.) Urban (Umbelliferae) undertaken in Taiwan. Duration of follow up: 2 weeks. After two weeks, the wounds in both groups were all reconstructed by split-thickness skin graft or primary closure.
Participants	24 participants Inclusion criteria: Inclusion criteria were patients with type 1 or type 2 diabetes, aged 20 years or older, and having Wagner grade 3 foot ulcers postsurgical debridement. Wagner grade 3 was defined as “deep ulcer involving osteitis, abscess, or osteomyelitis”. Exclusion criteria: Patients with poor nutritional status (albumin <3 g/dL), poor diabetic control (HbA1c >10%), anaemia (hemoglobin <10 g/dL), and leukocyte counts <1,000/cu mm; presence of connective tissue disease; known or suspected malignancy local to the study ulcer; renal failure insufficiency (serum creatinine >1.5mg/dL) or abnormal liver function (AST, ALT >2.5 × upper limit of normal range); requiring treatment with immunosuppressive agents, corticosteroids, chemotherapy or radiotherapy; female patients with positive pregnancy test or breastfeeding or unwilling to use appropriate contraceptive

	methods during study; patients with known sensitivity to essential oils or lanolin cream.
Interventions	Group A (n = 12): fibrous-hydrocolloid (hydrofibre) dressing (Aquacel ConvaTec, Valencia, CA, USA). Hydrocolloid fiber dressing group and left in place for up to 7 days or changed earlier as clinically indicated. Group B (n = 12): cream contained extracts from two botanical raw materials, P. amboinicus and C. asiatica. The plants of P. amboinicus were collected on 2007 according to good agricultural and good collection practices. C. asiatica. extract was sourced commercially with certificate of analysis of the extract and herbal material. the most active fractions from P. amboinicus and from C. asiatica, were combined in a 1 : 4 ratio to form the drug substance. The final cream, contained 1.25% of drug substance in a cream base, 15 g per tube. The cream base contained cetostearyl alcohol, ireine, liquid petrolatum, methyl paraben propyl paraben, Span 60, Tween 60, white petrolatum, water, and pigments. The cream was applied topically twice daily in an amount to fully cover the ulcer area in a thin and even layer (not exceed 2 millimetres in thickness). In both groups, After applying cream or fibrous-hydrocolloid dressing, the wound was covered with a transparent, adhesive, waterproof dressing (Opsite, Smith & Nephew, Taipei, Taiwan). After two weeks, the wounds in both groups were all reconstructed by split-thickness skin graft or primary closure. Co-intervention: sharp surgical debridement (including resection of necrotic soft tissue and bone, sinus tracts, fistulae, undermined borders, callus) to form viable wound margins was performed before randomization and repeated as needed during the dosing period. Systemic antimicrobial agents were allowed for treatment of infections. Nonweight bearing or offloading was required for all subjects. Prohibited treatments during the study period included immunosuppressive agents, corticosteroids, chemotherapy and radiotherapy.
Outcomes	Primary outcome: Percent change in wound size Secondary outcomes: Adverse event (no. of participants with at least one adverse event).
Notes	Trial data: Analysis 5.1 Funding source: No details

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: Treatment allocation was performed before site initiation. Permuted-block treatment allocation was used to assign participants to each group. A list of sequential numbers was generated using a permuted-block randomization procedure with a block size of 4 in SAS 9.1, with each number randomly assigned to one group.

		Comment: Adequate
Allocation concealment (selection bias)	Unclear risk	Quote: " *Patients meeting the inclusion and exclusion criteria were randomly assigned in a 1:1 ratio to the WH-1 cream group or the hydrocolloid fiber dressing group according to a predefined randomization schedule* " Comment: No mention of how the randomisation sequence was implemented
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: No mention of blinding in report
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: No mention of blinding in report
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 24 participants were randomised and 21 were included in the analysis: the 3 exclusions represent 12.5% of the total sample size. Classed as high risk of bias.
Selective reporting (reporting bias)	Low risk	No evidence. Healed wounds were not planned in this study.
Other bias	Unclear risk	Possibility some baseline imbalance perhaps due to the small sample size.

Piaggesi 2001

Methods	Single-centred, 2-armed RCT comparing a fibrous-hydrocolloid (hydrofibre) dressing (Aquacel, ConvaTec) with saline moistened gauze undertaken in Italy Duration of follow up: patients were followed until complete re-epithelialisation occurred. Maximum calculated by review authors as approximately 350 days.
Participants	20 participants Inclusion criteria: diabetic patients (type 1 or type 2) for over 5 years, between age 18 to 75 years, foot ulcer more than 3 weeks, > 1 cm wide and 1 cm deep, good peripheral blood supply (palpable peripheral pulses or ABPI > 0.9). Ulcers were due to diabetic neuropathy, or surgical drainage of a previous

[a] ABPI: ankle brachial pressure index
ITT: intention-to-treat
RCT: randomised controlled trial

	infection or both. Exclusion criteria: active infection documented by clinical local (redness, swelling, tenderness, purulent discharge, odour) or systemic (fever, malaise, leukocytosis) and confirmed with culture exams. Serum creatinine > 2 mg/dl, recent episodes of ketoacidosis, malignancies and any systemic therapy or chronic pathology which could obstruct the healing process.
Interventions	Group A (n = 10): fibrous-hydrocolloid (hydrofibre) dressing (Aquacel, ConvaTec); dressing changed every second or third day, depending on the extent of wound exudate Group B (n = 10): saline-moistened gauze; dressing renewed twice a day with saline to prevent drying out Both trial dressings were covered by several layers of gauze Co-interventions: participants received special postoperative shoes to relieve the pressure from the ulcerated foot. Participants were trained to walk with crutches until there was satisfactory healing.
Outcomes	Primary outcome: ulcer healing (number of ulcers healed; healing time in days; median % reduction in lesion volume; median % of granulation tissue) Secondary outcomes: amputation; adverse events; cost/resource use (average number of days between dressings changes) Health-related quality of life and ulcer recurrence not reported
Notes	Trial data: Analysis 5.1 Study authors have also reported the results for healing time excluding the patients suffering from infection (NOT extracted) Funding source: grant from Italian health board (Ministero della Sanita: Ricerca Finalizzata 1999 - Convenzione no. RF 99.52). Dressing material and devices were supplied by the hospital during the study as part of the routine therapy: manufacturers were not involved in any part of the experiment.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote:** *"Patients were randomly sorted into two different groups using a computer -generated list".* **Comment:** method of generation of random schedule reported
Allocation concealment (selection bias)	Unclear risk	**Comment:** the process of randomising participants, including who did this is not reported
Blinding of participants and personnel	Unclear risk	**Comment:** no mention of blinding in study report

[a] ABPI: ankle brachial pressure index
ITT: intention-to-treat
RCT: randomised controlled trial

(performance bias) All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	**Quote:** *"After 8 weeks patients were blindly evaluated by one of the authors (M.R) for rate of RVL and rate of GT".* **Comment:** it is not clear if healing assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** no indication of incomplete outcome data in paper
Selective reporting (reporting bias)	Low risk	**Comment:** based on study report, protocol not obtained
Other bias	Low risk	**Comment:** funded by non-commercial organisation

[a] ABPI: ankle brachial pressure index
ITT: intention-to-treat
RCT: randomised controlled trial

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Agas 2006	Study did not randomise participants
Ahroni 1993	The dressing groups evaluated in this study were not hydrocolloid dressings
Altman 1993	No single, identifiable dressing type evaluated.
Alvarez 2003	The dressing groups evaluated in this study were not hydrocolloid dressings
Apelqvist 1990	Relevant outcome data are not reported: study outcome was limited to change in size of necrotic material on the wound. Study authors were unable to provide the original healing outcome data.
Apelqvist 1996	No single, identifiable dressing type evaluated.
Apelqvist 2004	No single, identifiable dressing type evaluated.
Armstrong 2004	No single, identifiable dressing type evaluated.
Baker 1993	The dressing groups evaluated in this study were not hydrocolloid dressings
Belcaro 2010	The dressing groups evaluated in this study were not hydrocolloid dressings

Study	Reason for exclusion
Blackman 1994	The dressing groups evaluated in this study were not hydrocolloid dressings
Bogaert 2004	Study did not randomise participants
Bradshaw 1989	Trial stopped after recruiting six participants. No data presented. Authors not contacted for healing data.
Caravaggi 2003	Other intervention, not dressings, differs between trial arms
Chang 2000	Study did not include diabetic foot ulcers
Chauhan 2003	Other intervention, not dressings, differ between trial arms
Chirwa 2010	Study did not randomise participants
Cuevas 2007	No single, identifiable dressing type evaluated.
D'Hemecourt 1998	The dressing groups evaluated in this study were not hydrocolloid dressings
Dash 2009	Other intervention, not dressings, differ between trial arms
Diehm 2005	Study did not randomise participants
Donaghue 1998	The dressing groups evaluated in this study were not hydrocolloid dressings
Driver 2006	Other intervention, not dressings, differs between trial arms
Edmonds 2009	Other intervention, not dressings, differs between trial arms
Eginton 2003	No single, identifiable dressing type evaluated.
Etoz 2003	Study did not randomise participants
Farac 1999	Author contacted: study not suitable for inclusion due to data quality issues
Foo 2004	The dressing groups evaluated in this study were not hydrocolloid dressings
Foster 1994	The dressing groups evaluated in this study were not hydrocolloid dressings
Foster 1999	Other intervention, not dressings, differs between trial arms
Gao 2007	Other intervention, not dressings, differs between trial arms
Gentzkow 1996	Other intervention, not dressings, differs between trial arms
Gottrup 2011	The dressing groups evaluated in this study were not hydrocolloid dressings
Hanft 2002	Other intervention, not dressings, differs between trial arms

Study	Reason for exclusion
Jeffery 2008	Study did not randomise participants
Jensen 1998	The dressing groups evaluated in this study were not hydrocolloid dressings
Kordestani 2008	The dressing groups evaluated in this study were not hydrocolloid dressings
Lalau 2002	The dressing groups evaluated in this study were not hydrocolloid dressings
Landsman 2010	Other intervention, not dressings, differs between trial arms
Lazaro-Martinez 2007	No single, identifiable dressing type evaluated.
Lipkin 2003	Other intervention, not dressings, differs between trial arms
Markevich 2000	The dressing groups evaluated in this study were not hydrocolloid dressings
Marston 2001	Other intervention, not dressings, differs between trial arms
Mazzone 1993	The dressing groups evaluated in this study were not hydrocolloid dressings
McCallon 2000	Study did not randomise participants
Mody 2008	Study did not include diabetic foot ulcers
Moretti 2009	Other intervention, not dressings, differs between trial arms
Mueller 1989	Other intervention, not dressings, differs between trial arms
Mulder 1994	The dressing groups evaluated in this study were not hydrocolloid dressings
Munter 2006	The dressing groups evaluated in this study were not hydrocolloid dressings
Novinscak 2010	No single, identifiable dressing type evaluated.
Palao i Domenech 2008	The dressing groups evaluated in this study were not hydrocolloid dressings
Parish 2009	Other intervention, not dressings, differs between trial arms
Pham 1999	Other intervention, not dressings, differs between trial arms
Piaggesi 1997	Study did not randomise participants
Reyzelman 2009	No single, identifiable dressing type evaluated.
Roberts 2001	The dressing groups evaluated in this study were not hydrocolloid dressings

Study	Reason for exclusion
Robson 2005	Other intervention, not dressings, differs between trial arms
Robson 2009	Study did not include diabetic foot ulcers
Sabolinski 2000	Other intervention, not dressings, differs between trial arms
Sabolinski 2001	Other intervention, not dressings, differs between trial arms
Shaw 2010	Other intervention, not dressings, differs between trial arms
Shukrimi 2008	Other intervention, not dressings, differs between trial arms
Sibbald 2011	The dressing groups evaluated in this study were not hydrocolloid dressings
Solway 2011	Study did not randomise participants
Steed 1992	Other intervention, not dressings, differs between trial arms
Steed 1995	Other intervention, not dressings, differs between trial arms
Steed 1996	Other intervention, not dressings, differs between trial arms
Subrahmanyam 1993	The dressing groups evaluated in this study were not hydrocolloid dressings
Trial 2010	The dressing groups evaluated in this study were not hydrocolloid dressings
Turns 2012	Study did not randomise participants
Urbaneie-Rovan 1999	No single, identifiable dressing type evaluated.
Vandeputte 1997	The dressing groups evaluated in this study were not hydrocolloid dressings
Varma 2006	No single, identifiable dressing type evaluated.
Veves 2001	Other intervention, not dressings, differs between trial arms
Veves 2002	The dressing groups evaluated in this study were not hydrocolloid dressings
Whalley 2001	The dressing groups evaluated in this study were not hydrocolloid dressings
Woo 2010	The dressing groups evaluated in this study were not hydrocolloid dressings
Yao 2007	Other intervention, not dressings, differs between trial arms
Zimny 2003	Other intervention, not dressings, differs between trial arms

Characteristics of studies awaiting assessment [ordered by study ID]

Ogce 2007

Methods	
Participants	
Interventions	
Outcomes	
Notes	Translation required

References

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