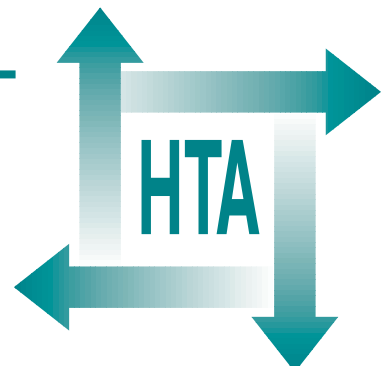


## **Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration**

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**Health Technology Assessment  
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# Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration

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# Contents

<b>Executive summary</b> .....	i	Cost-effectiveness .....	41
<b>Part 3: antimicrobial agents for chronic wounds</b> .....	1	<b>5 Conclusions</b> .....	43
<b>Contents to Part 3</b> .....	3	Clinical practice .....	43
<b>List of abbreviations</b> .....	5	Future research .....	43
<b>Executive summary to Part 3</b> .....	7	<b>Acknowledgements</b> .....	45
<b>1 Introduction</b> .....	9	<b>References</b> .....	47
The role of antimicrobials in wound healing .....	9	<b>Appendix 1</b> Databases searched and search strategies .....	53
The microbiology of chronic wounds .....	9	<b>Appendix 2</b> Advisory panel .....	57
Antimicrobials in current use .....	9	<b>Appendix 3</b> Hand-searching .....	59
Aim .....	10	<b>Appendix 4</b> Notes on the figures .....	61
<b>2 Methods</b> .....	11	<b>Appendix 5</b> Summary of included studies .....	63
Data sources .....	11	<b>Appendix 6</b> Quality assessment of included studies .....	99
Study selection .....	11	<b>Appendix 7</b> Summary of excluded studies .....	103
Decisions on study inclusion .....	12	<b>Part 4: diabetic foot ulceration</b> .....	109
Data extraction .....	12	<b>Contents to Part 4</b> .....	111
Quality assessment of included studies .....	12	<b>Glossary and list of abbreviations</b> .....	113
Data analysis and synthesis .....	12	<b>Executive summary to Part 4</b> .....	119
<b>3 Results</b> .....	13	<b>1 Introduction</b> .....	123
Literature search results .....	13	Aims .....	124
Excluded studies .....	13	<b>2 Methods</b> .....	125
Quality of included studies .....	13	Study inclusion criteria .....	125
Venous leg ulcers .....	13	Search strategy .....	125
Wounds of mixed aetiologies .....	15	Relevance and validity of primary studies .....	126
Pressure ulcers .....	17	Data extraction .....	126
Diabetic foot ulcers .....	19		
Pilonidal sinuses .....	20		
<b>4 Discussion</b> .....	33		
Systemic agents .....	33		
Topical agents .....	33		
Topical agents not included in this review .....	34		
Comparison with other systematic reviews .....	34		
Reporting of underlying factors in trials .....	35		
Outcome assessment in wound healing trials .....	36		
Wound microbiology and healing .....	39		

Data synthesis .....	126	<b>Appendix 2</b> Databases searched and search strategies .....	167
<b>3 Results</b> .....	127	<b>Appendix 3</b> Hand-searching .....	171
Studies excluded from the review .....	127	<b>Appendix 4</b> Advisory panel .....	173
Studies included in the review .....	127	<b>Appendix 5</b> Data extraction form .....	175
Prevention of diabetic foot ulceration .....	127	<b>Appendix 6</b> Summary of included studies .....	179
Treatment of diabetic foot ulceration .....	130	<b>Appendix 7</b> Quality assessment of included studies .....	213
<b>4 Discussion</b> .....	151	<b>Appendix 8</b> Summary of excluded studies .....	223
Prevention of diabetic foot ulceration .....	151	<b>Health Technology Assessment reports published to date</b> .....	229
Treatment of diabetic foot ulceration .....	151	<b>Health Technology Assessment panel membership</b> .....	233
Summary .....	152		
<b>5 Conclusions</b> .....	155		
Implications for future research .....	155		
<b>Acknowledgements</b> .....	157		
<b>References</b> .....	159		
<b>Appendix I</b> Wagner's system for the classification of diabetic feet .....	165		





## Executive summary

### Background

Chronic wounds, including pressure sores, leg ulcers, diabetic foot ulcers and other kinds of wounds, healing by secondary intention are common in both acute and community settings. The prevention and treatment of chronic wounds includes many strategies, including the use of various wound dressings, bandages, antimicrobial agents, footwear, physical therapies and educational strategies. This review is one of a series of reviews, and focuses on the prevention and treatment of diabetic foot ulcers and the role of antimicrobial agents in chronic wounds in general.

### Objectives

To assess the clinical- and cost-effectiveness of

- prevention and treatment strategies for diabetic foot ulcers and
- systemic and topical antimicrobial agents in the prevention and healing of chronic wounds.

### Methods

#### Data sources

Nineteen electronic databases were searched, including MEDLINE, CINAHL, Embase and the Cochrane Library. Relevant journals, conference proceedings and bibliographies of retrieved papers were hand-searched. An expert panel was consulted.

#### Study selection

Randomised and non-randomised trials with a concurrent control group, which evaluated any intervention for the prevention or treatment of diabetic foot ulcers, or systemic or topical antimicrobials for chronic wounds (diabetic foot ulcers, pressure ulcers, leg ulcers of various aetiologies, pilonidal sinuses, non-healing surgical wounds, and cavity wounds) and used objective measures of outcome such as:

- development or resolution of callus
- incidence of ulceration (for diabetic foot ulcer prevention studies)
- incidence of pressure sores (pressure sore prevention studies)

- any objective measure of wound healing (frequency of complete healing, change in wound size, time to healing, rate of healing)
- ulcer recurrence rates
- side-effects
- amputation rates (diabetic foot ulcer treatment studies)
- healing rates and recurrence of disease, among others, for pilonidal sinuses.

Studies reporting solely microbiological outcomes were excluded.

Decisions on the inclusion of primary studies were made independently by two reviewers. Disagreements were resolved through discussion. Data were extracted by one reviewer into structured summary tables. Data extraction was checked independently by a second reviewer and discrepancies resolved by discussion.

All included studies were assessed against a comprehensive checklist for methodological quality.

### Included studies

#### Diabetic foot ulcers

Thirty-nine trials which evaluated various prevention and treatment modalities for diabetic foot ulcers: footwear (2), hosiery (1), education (5), screening and foot protection programme (1); podiatry (1) for the prevention of diabetic foot ulcers; and footwear (1), skin replacement (2), hyperbaric oxygen (2), ketanserin (3), prostaglandins (3), growth factors (5), dressings and topical applications (9), debridement (2) and antibiotics (2) for the treatment of diabetic foot ulcers.

#### Antimicrobials

Thirty studies were included, 25 with a randomised design. There were nine evaluations of systemic antimicrobials and 21 of topical agents.

### Quality of studies

The methodological and reporting quality was generally poor. Commonly encountered problems

of reporting included lack of clarity about randomisation and outcome measurement procedures, and lack of baseline descriptive data. Common methodological weaknesses included: lack of blinded outcome assessment and lack of adjustment for baseline differences in important variables such as wound size; large loss to follow-up; and no intention-to-treat analysis.

## Results

### Prevention of diabetic foot ulcers

There is some evidence (1 large trial) that a screening and foot protection programme reduces the rate of major amputations. The evidence for special footwear (2 small trials) and educational programmes (5 trials) is equivocal. A single trial of podiatric care reported a significantly greater reduction in callus in patients receiving podiatric care.

### Treatment of diabetic foot ulcers

Total contact casting healed significantly more ulcers than did standard treatment in one study.

There is evidence from 5 trials of topical growth factors to suggest that these, particularly platelet-derived growth factor, may increase the healing rate of diabetic foot ulcers. Although these studies were of relatively good quality, the sample sizes were far too small to make any definitive conclusions, and growth factors should be compared with current standard treatments in large, multicentre studies.

Topical ketanserin increased ulcer healing rate in 2 studies, while systemic hyperbaric oxygen therapy reduced the rate of major amputations in 1 study.

Preliminary research into the effects of iloprost and prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) on diabetic foot ulcer healing suggests possible benefits. However, good quality, large-scale confirmatory research is needed.

Topical dimethyl sulphoxide (DMSO) (1 trial), glycyl-L-histidyl-L-lysine:copper (1 trial) and topical phenytoin (1 trial) were associated with increased healing. There is no good evidence in favour of any other dressing from 9 small trials, or for skin replacement dressings from 2 trials (the larger of which suffered substantial loss to follow-up).

### Antimicrobials

Thirty studies were included, 25 with a randomised design. There were nine evaluations of systemic antimicrobials and 21 of topical agents.

### Venous leg ulcers

DMSO powder produced significantly higher healing rates than placebo, but was equivalent to allopurinol powder. Results were conflicting for silver-based products (silver sulphadiazine and silver-impregnated activated charcoal dressing). There was no evidence in favour of systemic antibiotics, polynoxylin paste, mupirocin 2% impregnated dressing or povidone iodine 10%.

### Mixed aetiology wounds

Systemic ciprofloxacin added to a topical regimen produced increased healing rates in 1 trial. Levamisole (primarily used to treat roundworm infection) was associated with significantly higher healing rates than placebo (1 trial). The results for benzoyl peroxide were equivocal. 1% silver-zinc allantoinate cream was more effective than a variety of other topical preparations in a single small study. No differences were found between a hydrocolloid dressing and povidone iodine ointment for complete healing in patients with leg ulcers (aetiology unspecified) or pressure ulcers. No differences were found between an antiseptic spray (eosin 2% and chloroxylenol 0.3%) and an alternative preparation in patients with diabetic foot ulcers or pressure ulcers.

### Pressure ulcers

There is no evidence in favour of topical antimicrobials in pressure-sore prevention. Oxyquinoline ointment was significantly more effective than a standard emollient for treating pressure sores in 1 study. No significant difference was detected between a hydrocolloid dressing and povidone iodine ointment, or between a gentian violet preparation and povidone iodine/sugar ointment.

### Diabetic foot ulcers

No beneficial effect of topical or systemic antibiotics was identified.

### Pilonidal sinuses

Oral metronidazole given after excision resulted in significantly shorter healing time (1 study). Gentamicin-impregnated sponge produced significantly higher rates of primary healing than no sponge.

## Conclusions

Much uncertainty remains over the most effective interventions for the prevention and treatment of diabetic foot ulcers. Certain treatments (e.g. growth factors and off-loading techniques such as

total contact casting) show promise but need further, more rigorous evaluation.

There is no existing evidence to support the use of systemic antimicrobial agents for chronic wound healing. Even with interventions that appear to be promising, further, more rigorous evaluation is required before use becomes routine, as existing trials are generally small and many have other methodological problems. Several topical agents may be helpful, but again further research is required to establish effectiveness. Until improved data on relative effectiveness become available, considerations such as cost-minimisation may be used to guide decisions on the use of antimicrobial agents.

## **Implications for future research**

It is likely that most of the included trials have insufficient statistical power to detect a true treatment effect. Most of this research requires replication in larger, well-designed studies, with the incorporation of: adequate sample size, clear inclusion criteria, true randomisation, assessment of baseline comparability, blinded outcome assessment, objective outcome measurement, intention-to-treat protocol and detailed reporting of withdrawals. Details of concomitant interventions and an assessment of the adverse effects associated with interventions should be provided.



# **Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds**

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## Contents to Part 3

<b>List of abbreviations</b> .....	5	Topical agents not included in this review .....	34
<b>Executive summary to Part 3</b> .....	7	Comparison with other systematic reviews .....	34
<b>1 Introduction</b> .....	9	Reporting of underlying factors in trials .....	35
The role of antimicrobials in wound healing .....	9	Outcome assessment in wound healing trials .....	36
The microbiology of chronic wounds .....	9	Wound microbiology and healing .....	39
Antimicrobials in current use .....	9	Cost-effectiveness .....	41
Aim .....	10	<b>5 Conclusions</b> .....	43
<b>2 Methods</b> .....	11	Clinical practice .....	43
Data sources .....	11	Future research .....	43
Study selection .....	11	<b>Acknowledgements</b> .....	45
Decisions on study inclusion .....	12	<b>References</b> .....	47
Data extraction .....	12	<b>Appendix 1</b> Databases searched and search strategies .....	53
Quality assessment of included studies .....	12	<b>Appendix 2</b> Advisory panel .....	57
Data analysis and synthesis .....	12	<b>Appendix 3</b> Hand-searching .....	59
<b>3 Results</b> .....	13	<b>Appendix 4</b> Notes on the figures .....	61
Literature search results .....	13	<b>Appendix 5</b> Summary of included studies .....	63
Excluded studies .....	13	<b>Appendix 6</b> Quality assessment of included studies .....	99
Quality of included studies .....	13	<b>Appendix 7</b> Summary of excluded studies .....	103
Venous leg ulcers .....	13		
Wounds of mixed aetiologies .....	15		
Pressure ulcers .....	17		
Diabetic foot ulcers .....	19		
Pilonidal sinuses .....	20		
<b>4 Discussion</b> .....	33		
Systemic agents .....	33		
Topical agents .....	33		







## List of abbreviations

A&D	a standard emollient
AZAC 1%	1% silver zinc allantoinate cream
CCT	controlled clinical trial
CI	confidence interval
DMSO	dimethyl sulphoxide*
DVT	deep vein thrombosis*
ES	effect size
EUSOL	Edinburgh University Solution (chlorinated lime 1.25%, boric acid 1.25% in purified water)
HQ	healing quotient*
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
OR	odds ratio
RCT	randomised controlled trial
SD	standard deviation
SEM	standard error of the mean*

\* Used only in tables and figures



## Executive summary to Part 3

### Background

The role of antimicrobial agents in the management of chronic wounds is unclear. Systemic preparations include the penicillins, cephalosporins, aminoglycosides and quinolones. Topical agents include antibiotics, antiseptics and disinfectants.

### Objective

To assess systematically the clinical- and cost-effectiveness of systemic and topical antimicrobial agents in the prevention and healing of chronic wounds.

### Methods

#### Data sources

Eighteen electronic databases were searched. Relevant journals, conference proceedings and bibliographies of retrieved papers were hand-searched. An expert panel was consulted.

#### Study selection

##### *Design of primary studies*

Both randomised and non-randomised trials with a concurrent control group were included, with patients, limbs or lesions as the units of allocation.

##### *Participants*

People with diabetic foot ulcers, pressure ulcers, leg ulcers (various aetiologies), pilonidal sinuses, non-healing surgical wounds and chronic cavity wounds were included, as were patients at risk of developing pressure ulcers.

##### *Interventions*

Any systemic or topical agents with antimicrobial properties, including antibiotics, anti-fungal preparations, anti-viral agents and alternative approaches.

##### *Outcome measures*

The primary outcome was wound healing, assessed using an objective measurement such as change in ulcer size, rate of healing, frequency of complete healing or time to healing. For pilonidal sinuses outcomes included healing rates and recurrence of disease, and for pressure ulcer prevention outcomes

included the incidence of new lesions. Studies reporting solely microbiological outcomes were excluded.

##### *Study inclusion*

Decisions on the inclusion of primary studies were made independently by two reviewers. Disagreements were resolved through discussion.

##### *Data extraction*

Data were extracted by one reviewer into structured summary tables. Data extraction was checked independently by a second reviewer and discrepancies were resolved by discussion.

##### *Quality assessment*

All included studies were assessed against a comprehensive checklist for methodological quality.

##### *Data synthesis*

A narrative (qualitative) overview was conducted, with results grouped according to wound type. It was not appropriate to combine results quantitatively as studies were not sufficiently similar.

### Included studies

Thirty studies were included, 25 with a randomised design. There were nine evaluations of systemic antimicrobial agents and 21 of topical agents.

### Quality of studies

Several methodological problems were detected, the most common being inadequate sample size.

### Results

#### **Venous leg ulcers**

##### *Systemic agents (2 trials)*

For both trials, no statistically significant difference in healing was found when antibiotics plus topical care was compared with topical care alone.

##### *Topical agents (7 trials)*

Dimethyl sulphoxide powder produced significantly higher healing rates than placebo, but was equivalent to allopurinol powder. Results were

conflicting for silver based products (silver sulphadiazine and silver impregnated activated charcoal dressing). There was no evidence to promote the use of polynoxylin paste, mupirocin 2% impregnated dressing or povidone iodine 10%.

### **Wounds of mixed aetiologies**

#### **Systemic agents (2 trials)**

The addition of ciprofloxacin to a topical regimen may produce increased healing rates. Levamisole (primarily used to treat roundworm infection) was associated with significantly higher healing rates than was placebo.

#### **Topical agents (5 trials)**

A benzoyl peroxide-impregnated sponge produced greater reduction in wound area compared with a saline-impregnated sponge. However, other results showed that a benzoyl peroxide pack performed significantly less well compared with a collagen gel dressing for the same outcome. A very small study showed that 1% silver zinc allantoinate cream may be more effective than a variety of other topical preparations. No differences were found between a hydrocolloid dressing and povidone iodine ointment for complete healing in patients with leg ulcers (aetiology unspecified) or pressure ulcers. No differences were found between an antiseptic spray (eosin 2% and chloroxylenol 0.3%) and an alternative preparation in patients with diabetic foot ulcers or pressure ulcers.

### **Pressure ulcers**

#### **Systemic agents**

No trials of systemic agents were identified.

#### **Topical agents (5 trials)**

For prevention, no difference was found between a hexachlorophane lotion and an inert preparation or a cetrimide containing lotion. For treating existing lesions, an oxyquinoline ointment was significantly more effective than a standard emollient. No significant difference was detected between a hydrocolloid dressing and povidone iodine ointment, or between a gentian violet preparation and povidone iodine/sugar ointment.

### **Diabetic foot ulcers**

#### **Systemic agents (2 trials)**

No significant differences were detected between amoxicillin plus clavulanic acid versus placebo, or for clindamycin versus cephalexin, for complete healing and reduction of ulcer area.

#### **Topical agents (1 trial)**

A hydrogel dressing was significantly more effective than various systemic and topical antimicrobial preparations, for complete healing.

### **Pilonidal sinuses**

#### **Systemic agents (3 trials)**

Preoperative antibiotic prophylaxis (cefoxitin) achieved equivalent results for time to healing compared with surgery without antibiotic prophylaxis. When excision only, excision plus suture and excision plus suture and clindamycin were compared there were no significant differences between groups for rates of initial healing. However, primary closure may have been associated with faster healing. The addition of oral metronidazole after excision resulted in a significantly shorter healing time.

#### **Topical agents (3 trials)**

The postoperative application of a gentamicin-impregnated sponge produced significantly higher rates of primary healing than no sponge. Two trials evaluating silastic foam dressings did not show any difference between this and chlorhexidine or Eusol packs for time to healing. However, the use of the silastic dressing appeared to be associated with reduced nurse labour time.

## **Conclusions**

### **Implications for clinical practice**

There is no existing evidence to support the use of systemic antimicrobial agents for chronic-wound healing. Even with interventions that appear to be promising, further, more rigorous evaluation is required before use becomes routine, as existing trials are generally small and many have other methodological problems. Several topical agents may be helpful but, again, further research is required to establish effectiveness. Until improved data on relative effectiveness become available, considerations such as cost minimisation may be used to guide decisions on the use of antimicrobial agents.

### **Implications for future research**

It is likely that most of the included trials have insufficient statistical power to detect a true treatment effect. Most of this research requires replication in larger, well-designed studies, with incorporation of: adequate sample size, clear inclusion criteria, true randomisation, assessment of baseline comparability, blinded outcome assessment, objective outcome measurement, intention-to-treat protocol and detailed reporting of withdrawals. Details of concomitant interventions and an assessment of the adverse effects associated with interventions should be provided. The cost-effectiveness of antimicrobials needs to be established.

# Chapter I

## Introduction

This review is one of a series of eight systematic reviews of chronic wound care carried out by the NHS Centre for Reviews and Dissemination, and the Centre for Evidence Based Nursing, University of York. The series, commissioned by the NHS Health Technology Assessment Programme, aims to identify effective interventions for the prevention and treatment of chronic wounds. This review focuses specifically on the evidence of the effectiveness and cost-effectiveness of systemic and topical antimicrobial agents.

### The role of antimicrobials in wound healing

The role of antimicrobial agents in the healing of chronic wounds is unclear. The lack of clarity is due in part to uncertainty around the issue of whether bacterial presence is an important factor in wound healing. While the results from some studies indicate a positive association between higher bacterial counts and delayed wound healing,<sup>1,2</sup> others show no such association.<sup>3,4</sup> Clinicians may use systemic antibiotics as a last resort when topical interventions have failed to produce healing.<sup>5</sup> Wound type may also influence prescribing, particularly when the consequences of infection are potentially serious. For example, infected diabetic foot ulcers may result in gangrene, amputation or death,<sup>6,7</sup> and infection in pressure ulcers may lead to septicaemia or osteomyelitis.<sup>8</sup> Pressure ulcers may also be referred to as 'pressure sores' or 'decubitus ulcers', but in this review the term 'pressure ulcers' is used.

### The microbiology of chronic wounds

Moist chronic skin ulcers and sinuses are an ideal medium for bacterial growth, and a variety of micro-organisms can be cultured from these lesions. Studies have shown that over 80% of chronic leg ulcers may be contaminated with bacteria,<sup>2,9,10</sup> the commonest isolates being *Staphylococcus aureus* and *Pseudomonas aeruginosa*.<sup>2,11,12</sup> Pressure ulcers may have a varied bacterial flora, with aerobic organisms cultured more frequently than anaerobes. *Staph. aureus*,

*Streptococcus* species, *Proteus* species, *Escherichia coli*, *Pseudomonas*, *Klebsiella* and *Citrobacter* species are the most common isolates.<sup>8,13,14</sup> *P. aeruginosa* and anaerobes may be cultured from diabetic foot ulcers,<sup>11,15</sup> and anaerobes are often present in the discharge from chronic pilonidal sinuses.<sup>16</sup>

### Antimicrobials in current use

#### Systemic agents

Systemic agents fall into four main groups: penicillins, cephalosporins, aminoglycosides and quinolones. There are also several other drugs in use, including clindamycin, metronidazole and trimethoprim.

The penicillins work by interfering with the development of bacterial cell walls and cross-linkages. Broad-spectrum agents such as ampicillin and amoxycillin are active against certain Gram-positive and Gram-negative organisms, but are inactivated by penicillinases produced by *Staph. aureus* and *E. coli*.<sup>17</sup> Amoxycillin is sometimes used in combination with clavulanic acid.<sup>6</sup> This combination produces an increased range of activity and is effective against both *Staph. aureus* and *E. coli*.<sup>17</sup>

The cephalosporins have a similar action to the penicillins and have a wide range of activity against both Gram-negative and Gram-positive organisms.<sup>17</sup>

The aminoglycosides, such as gentamicin, act by interfering with normal protein synthesis. They have a wide range of action, but are potentially nephrotoxic and ototoxic, and serum levels should be monitored. They are active against the more resilient Gram-negative organisms. They are not absorbed from the gut and systemic administration is therefore by injection.<sup>17</sup>

The quinolones, such as ciprofloxacin, prevent the formation of DNA within the cell nucleus. They are active against both Gram-positive and Gram-negative organisms. Ciprofloxacin is licensed for skin and soft-tissue infections, but there is a high incidence of staphylococcal resistance and it is recommended that its use is avoided in methicillin-resistant *Staph. aureus* (MRSA) infections.<sup>17</sup>

Clindamycin is active against Gram-positive cocci, including penicillin-resistant staphylococci, and also against many anaerobes. It has an uncommon but serious and potentially fatal side-effect, namely antibiotic-associated colitis. Current prescribing guidelines state that therapy should be withdrawn immediately in any patient developing diarrhoea.<sup>17</sup> Metronidazole is active against anaerobic organisms,<sup>17</sup> and has sometimes been used in combination with other agents, such as ampicillin.<sup>18</sup> Trimethoprim is commonly used to treat urinary tract infections and respiratory tract infections,<sup>17</sup> and has been shown to be active against *E. coli* when used to treat these conditions.<sup>19</sup>

### Topical agents

Topical agents include antibiotics, antiseptics and disinfectants. Although various definitions exist for these terms, there appears to be a lack of consensus within the literature as to the characteristics of each type of preparation. It has been suggested that both antiseptics and disinfectants destroy micro-organisms or limit their growth in the non-spore or vegetative state. However, antiseptics are usually applied solely to living tissues, while disinfectants may also be applied to equipment and surfaces.<sup>20</sup>

Topical preparations may be divided into two categories, according to their function. One group consists of lotions with antimicrobial properties, used to irrigate or cleanse wounds. These usually have only a brief contact time with the wound surface, unless they are used as a pack or soak. They include the hypochlorites (e.g. Eusol<sup>®</sup>), hexachlorophane (a constituent of some soaps and other skin cleansers), and substances such as potassium permanganate and gentian violet (both used in solution for skin cleansing).

The second group consists of preparations designed to stay in contact with the wound surface for a longer period of time, ideally until the next dressing change. These include creams, ointments and impregnated dressings. Most topical antibiotics come into this category, and include mupirocin (available as 2% ointment), which has a wide range of activity, and fusidic acid (available as impregnated dressing, or ointment, cream or gel, all 2%) for staphylococcal infections. Neomycin sulphate, available as a cream (0.5%) or ointment (0.25%), is used to treat bacterial skin infections. If large areas of skin are treated, ototoxicity is a possible adverse effect.<sup>17</sup> Silver based products, such as silver sulphadiazine (1% cream and impregnated dressing), have a broad-spectrum action against both Gram-negative and Gram-positive organisms, and also yeasts and fungi.<sup>21</sup>

Some products that are available in different forms fall into both categories. These include povidone iodine (available as 10% solution, 10% ointment, 5% cream, 2.5% dry powder spray and impregnated dressing), chlorhexidine (available as 0.05% solution, 5% ointment and medicated tulle dressing; it is also a constituent of skin cleansers), benzoyl peroxide (available as lotions, creams and gels in various strengths) and hydrogen peroxide (available as 3% and 6% solutions and 1% cream).<sup>17</sup>

### Aim

To assess systematically the evidence for the clinical effectiveness and cost-effectiveness of systemic and topical antimicrobial agents in the prevention and healing of chronic wounds. These wounds include diabetic foot ulcers, pressure ulcers, chronic leg ulcers, pilonidal sinuses, non-healing surgical wounds and chronic cavity wounds.

# Chapter 2

## Methods

### Data sources

A comprehensive and sensitive search strategy was developed and used for all eight reviews in this series. Eighteen electronic databases, including MEDLINE and CINAHL were searched, with no restriction on date of study or language of the report (see appendix 1). The search strategies used for MEDLINE and CINAHL are listed in appendix 1. Search terms were adapted for the other databases used. Additional search terms used to identify economic studies are also listed in appendix 1. All databases were searched from their date of inception to January 2000.

Additional sources included the National Research Register and bibliographies of retrieved reviews and papers. An expert panel was also consulted (see appendix 2).

Five journals specialising in wound care and the proceedings from 12 specialist conferences were hand-searched to locate relevant studies. These are detailed in appendix 3, together with a list of sources hand-searched for economic papers.

### Study selection

#### Design

Both randomised controlled trials (RCTs) and non-randomised trials with a concurrent control group were included. In general, RCTs are considered to give the most reliable estimates of the effectiveness of interventions. This is because randomisation increases the likelihood that differences in outcomes are due to differences in the interventions received rather than to variations in other factors, such as patient characteristics. RCTs that incorporate single- or double-blinding procedures help to control for the biases in health outcomes brought about by the preconceived expectations of patients and assessors.<sup>22</sup>

It is also possible to obtain useful data from the results of non-RCTs, or controlled clinical trials (CCTs). However, groups may not be homogenous at baseline, and therefore these studies are considered to give less reliable information compared with RCTs. Only prospective CCTs with concurrent

control groups were included in this review. For both RCTs and CCTs, the units of allocation had to be patients, limbs or lesions. Studies in which wards or clinics were the units of allocation were excluded because of the possibility of non-comparability of standard care.

Both published and unpublished studies were included, with no restriction on date or language.

#### Participants

Studies that recruited people with diabetic foot ulcers, pressure ulcers, chronic leg ulcers (caused by venous, arterial or mixed insufficiency), pilonidal sinuses, non-healing surgical wounds and chronic cavity wounds were included. Patients considered to be at risk of developing pressure ulcers were also eligible. Patients with ulcers caused by leprosy, sickle cell disease, thalassaemia or scleroderma, or those having soft-tissue infections in the absence of a chronic lesion, were excluded, as were people with burns. Patients with pilonidal abscesses were excluded since these lesions are associated with the acute phase of disease. Studies recruiting patients with both pilonidal abscesses and pilonidal sinuses were included only if separate data were available for the patients with pilonidal sinuses. Animal studies were excluded.

#### Interventions

Evaluations of systemic or topical antimicrobial agents used for the prevention or healing of chronic wounds were included. Trials of antibiotics, antifungal and antiviral agents were all considered. Reports of antibiotic cover used with skin grafting of chronic wounds, and antimicrobials used in conjunction with debriding agents, were excluded.

#### Outcomes

The primary outcome was wound healing, or prevention of wound formation. Since some measures of wound healing can be subjective, studies had to incorporate an objective assessment, such as change in ulcer size, rate of healing, frequency of complete healing or time to complete healing, to be included in the review. Change in ulcer size may be presented as a percentage or absolute change over a period of time. Objective methods of measuring changes in wound size



include tracing the ulcer outline followed by counting grids on graph paper, weighing uniform-density tracing paper, planimetry or computerised image analysis. For evaluation of agents designed to prevent pressure ulcers, the primary outcome was the development of new lesions. For studies of pilonidal sinuses, outcomes of interest were healing rates, recurrence of disease, time to healing and incidence of surgical complications.

Many evaluations of antimicrobial agents focus on microbiological outcomes, such as wound cultures, sensitivities of micro-organisms, bacterial counts and bacterial eradication. Studies reporting only these types of results were excluded from this review since these intermediate outcomes have not been shown to be accurate and reliable indicators of healing. Studies have shown that the use of surrogate (intermediate) outcomes can be misleading and, in some cases, may be detrimental to patients.<sup>23</sup> Where studies reported both wound healing and microbiological outcomes, only the former were incorporated in the review. Where available, data concerning the adverse effects of interventions were included.

### **Decisions on study inclusion**

Decisions on the inclusion of primary studies were made independently by two reviewers, and disagreements were resolved through discussion.

### **Data extraction**

Data from included studies were extracted by one reviewer into structured summary tables. Data extraction was checked independently by a second reviewer and discrepancies were resolved by discussion. Where necessary, authors were contacted and requested to supply further details.

### **Quality assessment of included studies**

All included studies were assessed by one reviewer against a comprehensive checklist for methodological quality. The checklist covered the following: method of randomisation (for RCTs), criteria for selecting participants, baseline comparability of groups, sample size, outcome assessment, reporting of withdrawals and use of intention-to-treat analysis. Quality assessment was checked independently by a second reviewer and discrepancies were resolved by discussion.

### **Data analysis and synthesis**

A narrative (qualitative) overview of the studies was conducted. Statistical pooling of trials was not possible due to the lack of similarity between the included studies. The results were grouped according to different wound types.



# Chapter 3

## Results

### Literature search results

The search generated 400 references of possible relevance to this review. Once titles (and, where available, abstracts) had been assessed, hard copies of 150 papers were examined. Of these, 30 studies were included in the review.<sup>5-7,10,12,16,24-47</sup> Of the 30 studies included, 25 were RCTs<sup>5-7,10,12,16,24-34,36-38,41-43,45,47</sup> and five were CCTs.<sup>35,39,40,44,46</sup> There were nine evaluations of systemic antimicrobials,<sup>5-7,12,16,25,42-44</sup> and 21 of topical agents.<sup>10,24,26-41,45-47</sup> In terms of wound type, nine studies focused on venous leg ulcers,<sup>5,10,12,33-37,46</sup> seven on wounds of mixed aetiologies,<sup>38-43,45</sup> six on pilonidal sinuses,<sup>16,25-28,44</sup> five on pressure ulcers<sup>29-32,47</sup> and three on diabetic foot ulcers.<sup>6,7,24</sup> The years of publication represented by the included studies were within the range 1968–1997. Eight papers reported research originating from the UK,<sup>10,27,28,30,32,34,41,44</sup> four from the USA,<sup>7,29,33,39</sup> three each from Germany<sup>6,26,37</sup> and Belgium,<sup>24,42,46</sup> two each from Finland,<sup>5,43</sup> France<sup>31,40</sup> and Italy,<sup>12,45</sup> and one each from Denmark,<sup>16</sup> Sweden,<sup>38</sup> Norway,<sup>25</sup> Ireland,<sup>35</sup> Iraq<sup>36</sup> and Japan.<sup>47</sup> Four papers were published in languages other than English, and required translation.<sup>26,37,45,47</sup>

Details of the trials included are summarised in appendix 5, and study quality is presented in appendix 6. Forest plots representing the estimate effects of the individual evaluations are presented in the figures (collected together at the end of this chapter). The figures are a visual representation of estimated treatment effects, and should not be regarded as part of a meta-analysis. Wherever possible, odds ratios (ORs) and effect sizes (ESs) were calculated on an intention-to-treat basis. See appendix 4 for further details on the interpretation of the figures.

### Excluded studies

Although there is much available research in this area, many identified papers were not eligible for inclusion. Common reasons for exclusion were study design (non-comparative cohort), type of wound (not chronic) and outcome assessment (microbiological data only, or subjective measure

of wound healing). Studies that were closely considered for inclusion, but eventually excluded, are summarised in appendix 7.

### Quality of included studies

Details of study quality assessment are given in appendix 6. Sample size was highly variable between studies (range 10–319 patients) and only two studies reported an *a priori* sample-size power calculation.<sup>12,36</sup> Other aspects of study quality were also variable. Eight papers reported the method of treatment allocation as being truly randomised.<sup>6,10,12,24-26,36,47</sup> Six studies included an intention-to-treat analysis,<sup>10,24,35,36,41,42</sup> and in a further eight trials there were no withdrawals.<sup>25,27,28,39,40,43,45,47</sup> In 12 studies, the number of withdrawals per treatment arm was reported together with the reason for withdrawal,<sup>5,6,10,12,16,24,30,31,36,38,41,42</sup> six reported the number of withdrawals, but these were not broken down by either group or reason,<sup>7,32,33,35,37,46</sup> and four included no details at all on withdrawals.<sup>26,29,34,44</sup>

Eleven trials failed to provide clear inclusion and exclusion criteria for participants,<sup>25-28,35,38-42,44</sup> five studies provided no details of baseline comparability between groups,<sup>25,27,31,38,44</sup> five reported baseline data on wound size, but not on demographic characteristics,<sup>5,29,39,46,47</sup> and two failed to report baseline wound area, although other data were provided.<sup>41,45</sup> Twelve studies incorporated blinded outcome assessment.<sup>5-7,29,30,32-34,36,38,42,46</sup>

### Venous leg ulcers

Nine eligible studies were identified, of which two were trials of systemic agents<sup>5,12</sup> and seven were of topical agents.<sup>10,33-37,46</sup>

### Systemic agents used with venous leg ulcers

An Italian study compared a topical regimen, which included a pressure bandage, with the same regimen plus antibiotics (*Figure 1*).<sup>12</sup> The antibiotics included co-trimoxazole (trimethoprim and sulphamethoxazole combined), gentamicin or amikacin, prescribed according to sensitivities

determined from baseline ulcer surface swabs. Patients were excluded from the trial if there were clinical signs of wound infection and/or negative bacterial wound-surface cultures at baseline. There were no statistically significant differences in ulcer-healing rates, or the frequency of complete healing, after 20 days.

In a second study, the broad-spectrum agents ciprofloxacin and trimethoprim, and a placebo, were compared (*Figure 2*).<sup>5</sup> All patients received topical care consisting of zinc ointment and a support bandage. The presence of clinical infection or baseline bacterial colonisation of the wound were not mentioned as selection criteria for participants. However, bacterial cultures and sensitivities of the ulcer flora were taken at baseline, and subsequently every 4 weeks during the 12-week regimen. There was no statistically significant difference between study groups at 16 weeks in terms of complete healing or change in ulcer area. However, this was a very small study with only 12 participants per treatment arm, and therefore the possibility of type II error cannot be excluded.

### Topical agents used with venous leg ulcers

An early study examined the effectiveness of adding polynoxylin paste to lint dressing, compared with lint dressing alone, in female patients (*Figure 3*).<sup>35</sup> All patients received compression therapy combined with injection of sclerosant agents. Polynoxylin has been shown to have antimicrobial properties when applied to the skin,<sup>48</sup> and it is thought to be effective against both bacteria and fungi.<sup>20</sup> Participants were allocated to treatment groups on an alternating basis. Since the two groups were not comparable at baseline for mean ulcer area, analysis was carried out on 17 pairs of patients matched for baseline ulcer size. No statistically significant difference was found between the two groups for time to healing (mean values: 37 days for polynoxylin group, 34 days for control group). In addition, there was no statistically significant difference between the two groups for healing quotient, measured at intervals of 2 or 3 weeks. The healing quotient was defined as the mean rate of epithelialisation in square millimetres per day, calculated to the nearest 0.1 mm<sup>2</sup>/day. No details were given about whether the presence of signs of clinical infection or bacterial colonisation of the wound influenced selection of participants for the study.

A three-arm, double-blind RCT compared allopurinol with dimethyl sulphoxide and placebo (*Figure 4*).<sup>36</sup> All were applied in a topical powder form. Dimethyl sulphoxide increases local

microcirculation and enhances tissue oxygen saturation,<sup>49</sup> and is also thought to have antimicrobial properties.<sup>50</sup> All patients received a below-knee graduated compression bandage. The presence of signs of clinical infection (criteria for diagnosis not defined) was an exclusion criterion for participants. After 3 months both the active drugs achieved statistically significantly superior results compared to placebo in terms of frequency of complete healing and remaining ulcer area. However, no statistically significant difference was detected between the two active drugs. Four patients withdrew from the study due to local itching and erythema, one from the allopurinol group, two from the dimethyl sulphoxide group and one from the placebo group.

Another study compared the application of 2% mupirocin in a white soft paraffin tulle gras, with vehicle (*Figure 5*).<sup>34</sup> Mupirocin is active against Gram-positive organisms, but ineffective against *Pseudomonas* species. Resistant strains of *Staph. aureus* have been identified.<sup>17</sup> Both study groups received compression therapy. No statistically significant differences were reported at 12 weeks for mean percentage change in ulcer area or frequency of complete healing. The authors considered that compression therapy may have been the most important factor in healing. The presence of clinical infection and/or wound colonisation were not mentioned as selection criteria for participants.

A small study assessed the effect of povidone iodine solution (10%) used with a hydrocolloid dressing compared with hydrocolloid dressing alone (*Figure 6*).<sup>46</sup> All dressings were secured with elastic stockings. This was a CCT in which patients had at least two leg ulcers and acted as their own controls. No information was provided concerning the method used for allocating wounds to the povidone iodine plus hydrocolloid regimen; control ulcers were selected on the basis of being of similar size and location to those in the intervention group. Although ulcers in the povidone iodine group had statistically significantly higher healing indices relative to controls up to 7 weeks follow-up, the difference did not remain statistically significant at 8 weeks. The healing index was calculated by subtracting the initial ulcer area from the actual ulcer area, and then dividing this number by the initial wound perimeter. The presence of clinical infection and/or wound colonisation were not described as participant selection criteria. However, there were two withdrawals in the control group due to infection of ulcers. No details were given about adverse effects.

Three studies examined the effects of silver-based products.<sup>10,33,37</sup> A small German study randomised patients to receive either a silver impregnated activated charcoal dressing (Actisorb Plus<sup>®</sup>, Johnson & Johnson) or a control regimen (*Figure 7*).<sup>37</sup> Actisorb Plus consists of 100% pure activated charcoal cloth with silver enclosed within a porous nylon sleeve. The dressing works by absorbing bacteria, and helps to eliminate odour and reduce exudate.<sup>20</sup> The control treatment consisted of various topical agents targeted at different stages of wound healing, including mineral oil, sea-salt, povidone iodine paste, paraffin-impregnated gauze and a lotion containing panthenol. All patients received wound debridement. Although significant between-group differences in ulcer size were seen at 2 and 4 weeks in favour of Actisorb Plus, this was not maintained by the end of the 6-week trial, and there were no statistically significant differences for rates of complete healing at 6 weeks. Again, infection or colonisation of the wounds were not described as selection criteria.

Bishop and co-workers<sup>33</sup> compared the antibacterial agent silver sulphadiazine with tripeptide-copper complex and placebo in people with venous leg ulcers of at least 3 months duration (*Figure 8*). Silver sulphadiazine is active against Gram-positive and Gram-negative bacteria and yeasts,<sup>14</sup> and is thought to work by inhibiting bacterial growth. For all patients, the dressing was secured with an elastic bandage. Silver sulphadiazine proved to be significantly more effective than the other two preparations in terms of reducing ulcer area, but no statistically significant difference was detected between tripeptide-copper complex and placebo. There were no statistically significant differences between any of the agents in terms of complete healing. Only patients with lesions colonised with  $10^5$  or less bacteria per gram of ulcer tissue (detected by biopsy) were eligible to enter the study. For this reason, the authors suggested that silver sulphadiazine was effective through promoting epithelialisation rather than by its antimicrobial action. Patients with systemic or bone infection were also excluded from the trial.

The final study in this group compared the effectiveness of silver sulphadiazine with saline cleansing plus non-adherent dressing in patients with venous leg ulcers of up to 10 cm<sup>2</sup> surface area at baseline (*Figure 9*).<sup>10</sup> All patients received compression therapy. There were no statistically significant differences between groups for rates of complete healing or mean reduction in ulcer size. Four of 30 patients allocated to the silver

sulphadiazine arm experienced local adverse effects, such as erythema and pruritis, and had to discontinue treatment. No adverse effects were reported in the control group. The authors attributed healing to the compression therapy, and concluded that there was no benefit gained from the addition of silver sulphadiazine. Neither the presence of signs of clinical infection nor wound colonisation were mentioned as selection criteria for participants. However, all ulcers were contaminated at baseline, the most common isolates being *Staph. aureus* and  $\beta$ -haemolytic streptococcus, and rates of contamination were unchanged at the end of the study.

## Wounds of mixed aetiologies

Seven studies were identified that recruited participants with wounds of mixed aetiologies.<sup>38-43,45</sup> There tended to be a predominance of venous leg ulcers in the studies. There were two evaluations of systemic agents<sup>42,43</sup> and five of topical preparations.<sup>38-41,45</sup>

### Systemic agents used with wounds of mixed aetiologies

A Finnish study compared a topical regimen with the same regimen plus ciprofloxacin in patients with leg ulcers in whom the majority had a diagnosis of both venous and arterial insufficiency (*Figure 10*).<sup>43</sup> All patients in the control group had arterial disease ( $n = 8$ ) compared with 13 of 18 patients (72%) in the treatment group. Three patients in each group had diabetes mellitus. Patients had to have a leg ulcer with isolation of either *P. aeruginosa* or another Gram-negative rod sensitive to ciprofloxacin in order to be included in the trial.

The topical regimen consisted of cleansing with chlorhexidine or potassium permanganate solution. Necrotic tissue was removed by debridement and clean ulcers were covered with either dextranomer paste or a hydrocolloid dressing. No statistically significant differences were found between groups for significant reduction in ulcer size or frequency of complete healing after 3 months. When significant reduction and complete healing were combined as a single outcome, however, a statistically significant improvement was seen in the ciprofloxacin group ( $p < 0.05$ ). Significant reduction was defined as a 10% reduction in the sum of the maximum length and width of the ulcer. It is not stated whether ulcer measurement was blinded, and methods of data collection were not described. Three patients

in the ciprofloxacin group experienced mild and transient nausea, but none withdrew from the trial. The incidence of adverse events was not reported for the control group.

This was a very small study, with 18 participants in the antibiotic group and eight in the control group. In addition to the drug under study, all patients were allowed extra systemic antibiotics in cases of urinary tract infection, cellulitis or acute ulcer infection. This means that it is unclear whether wound healing may be attributed to the experimental therapy.

A Belgian study investigated the use of levamisole in patients with various types of leg ulcers (see *Figure 10*).<sup>42</sup> Diagnoses included venous, arterial and lymph insufficiency, and diabetes. Levamisole, a treatment for roundworm infestation,<sup>17</sup> is thought to have an antibacterial action in wounds.<sup>42,51</sup> At present it is available in the UK only on a named-patient basis.<sup>17</sup>

At the end of the 20-week trial, all patients in the levamisole group were cured, compared to 76% in the placebo group ( $p < 0.01$ ). However, the term 'cure' was not defined, and it is unclear whether this means complete closure of lesions. Three of 30 patients in the levamisole group experienced moderate gastric complaints, but did not withdraw from the trial. There were no adverse events in the control group.

The high cure rates in both treatment and control groups may have been partly attributable to the use of topical regimens such as compression therapy, which were not described in the paper. A further factor influencing healing outcomes could have been the long assessment period of 20 weeks. Since the details of the topical treatment and the comparability of provision between groups were not reported in the paper, the results are difficult to interpret. No details were given about whether the presence of signs of clinical infection or bacterial colonisation of the wound influenced selection of participants for the study.

### Topical agents used with wounds of mixed aetiologies

A small Swedish trial examined the effects of different dilutions of benzoyl peroxide lotion compared to saline, when both were used to impregnate a wound dressing sponge (*Figure 11*).<sup>38</sup> Benzoyl peroxide ointment is normally used for the treatment of acne vulgaris,<sup>17</sup> but the lotion, in various concentrations, can be used with chronic

wounds. It is considered to have antibacterial, antifungal and antipruritic properties. Other possible modes of action include stimulation of granulation and debridement.<sup>38</sup>

For all patients, dressings were secured using an elastic support bandage. Inclusion criteria were not clearly stated for this study. Most patients had leg ulcers of venous origin, but 4 of 28 patients had wounds caused by both venous and arterial incompetence. Each patient had at least two leg ulcers, and patients acted as their own controls. Benzoyl peroxide lotion in both 10% and 20% strengths proved to be significantly more effective than saline in reducing ulcer area ( $p < 0.01$  and  $p < 0.05$ , respectively). There was little difference in healing rates between the two strengths of the solution, implying that lower concentrations can be used with similar effect. Three patients developed severe local irritation from using the 10% concentration, and withdrew from the trial. The authors reported the difference in outcome between the vehicle of benzoyl peroxide lotion and saline as not statistically significant ( $p$  value not reported); however, in the figure this is shown as just achieving statistical significance. Neither the presence of signs of clinical infection nor bacterial colonisation of the wounds were mentioned as selection criteria for participants.

A second study compared a 20% benzoyl peroxide pack with collagen gel in patients with leg ulcers of various aetiologies.<sup>40</sup> Eight of the 20 patients recruited had venous insufficiency, three had arterial insufficiency and nine had both. In addition, eight patients had diabetes and 15 had arteriosclerosis. Prior to treatment allocation, all patients received topical trichlorocarbanilide solution and polymyxin in order to resolve any signs of infection. This was a CCT in which patients acted as their own controls; however, there was no information on the methods of treatment allocation. Only ulcers on the same leg were compared. The mean ulcer area appeared to be comparable at baseline. At 12 weeks, the percentage of baseline wound area remaining was significantly smaller in the group that received collagen gel compared with the group that received the benzoyl peroxide pack (0.5% versus 15.9%,  $p < 0.01$ ). There is no figure to go with this study as insufficient data were provided for calculation of the effect size with 95% confidence intervals (CIs).

An American study compared 1% silver zinc allantoinate cream (AZAC 1%) with various other topical regimens (0.5% silver nitrate, wet to dry saline dressing, nitrofurazone, bismuth



tribromophenate dressing, Unna's boot, compression bandaging and povidone iodine ointment) (Figure 12).<sup>39</sup> This was another CCT in which patients acted as their own controls. Ten patients were recruited for whom AZAC 1% was applied to ulcers on the left leg, and control treatments applied to ulcers on the right leg. This comparison was part of a larger uncontrolled case series, and baseline information pertained mostly to the main study, in which the majority of patients had leg ulcers of either venous or diabetic origin. With the exception of ulcer area, no baseline data were reported specifically for the comparative study. Infected ulcers could be included, but results were not stratified according to the presence of clinical infection at baseline. Analysis of the mean  $\pm$  standard deviation (SD) time to healing showed that there was a statistically significant difference between the two groups:  $45 \pm 21$  days for AZAC 1% compared with  $104 \pm 31$  days for control lesions ( $p < 0.001$ ).

In a small single-blind RCT recruiting patients with diabetic foot ulcers or pressure ulcers, an antiseptic spray containing eosin 2% and chloroxylenol 0.3% was compared with an alternative spray, which was not specified in the paper (see Figure 12).<sup>45</sup> Wounds were covered with gauze, but no details of the use of other concomitant interventions, such as pressure relief, were given. Healing progress was assessed every 5 days, using a wound-grading system: complete healing was graded as 3; more than 50% of the wound area healed (relative to baseline), 2; 25–50% of the initial area healed, 1; and less than 25% of the initial area healed, 'unsatisfactory'. No information was given about the methods of measuring wound area, how many assessors were involved or whether the assessment was blinded.

For diabetic foot ulcers, at 15 days complete healing had occurred in 82% of those in the antiseptic spray group and 50% in the alternative spray group. For pressure ulcers, the values were 20% and 10%, respectively. Tests of statistical significance were not reported in the paper, but the figure shows no significant difference between treatment groups, for either wound type. Four patients experienced a local burning sensation (three in the intervention group, and one in the control group) but did not withdraw from the trial. The presence of clinical infection and/or wound colonisation were not mentioned as selection criteria for participants.

The last study in this group involved the use of iodine as a topical agent for wound healing (see

Figure 12).<sup>41</sup> Iodine is thought to have a broad-spectrum antimicrobial activity<sup>52</sup> and several types of preparation are available. Concerns have been expressed about potentially toxic effects, both local and systemic,<sup>53</sup> but this may be more relevant to earlier products containing free iodine. More recent slow-release formulations, such as povidone iodine, are considered to be safer.<sup>20, 52, 54</sup> However, systemic absorption and toxicity may occur if povidone iodine is used in large open wounds.<sup>20</sup>

This study was an RCT in which patients with leg ulcers (aetiologies not specified) and pressure ulcers were recruited.<sup>41</sup> No details were given about whether the presence of signs of clinical infection or bacterial colonisation of the wound influenced selection of participants for the study. The effectiveness of a povidone iodine (10%) dressing was compared with a hydrocolloid (Comfeel<sup>®</sup>, Coloplast). Baseline information from the trial included a classification of the nutritional status of patients (good, reasonable or not stated), but there was no description of how this was assessed. There was no presentation of baseline wound size, only the relative frequencies of wound types within the two treatment groups.

At 12 weeks the two groups had achieved similar rates of complete healing. However, this was a small study ( $n = 27$ ), and a large proportion of patients withdrew (56%). In an analysis including all recruited patients, the authors drew attention to the fact that fewer dressing changes per week were needed in the hydrocolloid group compared with the povidone iodine group (mean  $\pm$  SD:  $3 \pm 1.38$  versus  $4.9 \pm 1.69$ , respectively,  $p < 0.005$ ). One patient in the hydrocolloid group withdrew because of an inability to tolerate further dressings. Few details of interventions or inclusion criteria for participants were reported. Co-interventions for pressure relief in patients with pressure ulcers, or other topical regimens for leg ulcer patients, such as compression bandaging, were not described.

## Pressure ulcers

Pressure ulcers are commonly treated with topical agents, but intervention with a broad-spectrum systemic agent may become necessary.<sup>13,14</sup> In serious cases, infected lesions can lead to osteomyelitis and septicaemia.<sup>13</sup> Pressure-relieving interventions are of importance in the management of these wounds.<sup>55</sup>

Seven eligible RCTs of pressure ulcers were identified.<sup>29–32,41,45,47</sup> Two of these trials recruited patients

with pressure ulcers as well as other types of wound, and have been described above.<sup>41,45</sup> All seven studies evaluated topical agents; no eligible trials of systemic antimicrobial agents used with pressure ulcers were identified.

### Topical agents used for the prevention of pressure ulcers

Two RCTs of the prevention of pressure ulcers were included (*Figure 13*).<sup>30,32</sup>

Green and co-workers<sup>30</sup> recruited patients in elderly care wards who had a Norton score of 14 or less. The patients received either Dermalex<sup>®</sup> lotion (contains hexachlorophane) or an inert lotion. All patients received bed cradles, 2-hourly turning and regular washing of pressure areas with re-application of lotion. Large-cell alternating pressure mattresses were used for patients with a Norton score of less than 10. Catheterisation was avoided if possible. There were no statistically significant differences between the groups in terms of the development of superficial lesions at 3 weeks, or the mean time to the development of new lesions (9.8 days for the Dermalex group versus 8.7 days for controls). Two patients in the Dermalex group withdrew from the study after developing an allergic rash, but there were no adverse events in the group receiving the inert lotion.

Initially, 319 participants were recruited to this trial, but the analysis was based on only 167 patients who remained at the 3-week assessment. This large withdrawal rate (48%), partly due to the fact that development of new ulcers was a criterion for withdrawal, combined with a failure to analyse by the intention-to-treat protocol, makes the results of this study difficult to interpret.

A later study recruited chair-bound patients with Norton scores of 5–14.<sup>32</sup> The patients were randomised to receive either Dermalex lotion or Prevasore<sup>®</sup> lotion (contains cetrimide). Existing pressure-relief regimens were continued for all patients, but these were not described. There was no statistically significant difference between the groups in terms of the change in skin condition at the end of the 3-week trial.

### Topical agents used for the treatment of pressure ulcers

Three RCTs were identified.<sup>29,31,47</sup> The first study compared DermaMend<sup>®</sup> ointment (contains oxyquinoline) with A&D ointment, a standard emollient (*Figure 14*).<sup>29</sup> There were no details of the use of other strategies to relieve pressure.

Oxyquinoline based preparations have been shown to have anti-infective properties when used on the skins of infants and animals.<sup>29,56</sup> The ointment is not currently licensed for use in the UK. The standard emollient soothes and hydrates the skin, but does not have antimicrobial properties. Lesions were graded as either stage I (erythema) or stage II (superficial breakdown), and results were presented according to this classification. In total, 137 lesions in 74 patients were studied; some patients had both stage I and stage II lesions. Patients was the unit of randomisation, but lesions was the unit of analysis.

For stage I lesions, the two groups lack comparability for mean baseline ulcer area (18.9 versus 4.3 cm<sup>2</sup>, DermaMend group versus A&D, respectively). Comparability was greater for stage II lesions (1.0 versus 1.2 cm<sup>2</sup>). The study was double blinded and the initial staging of skin lesions was checked by a second observer.

The percentage of completely resolved stage I lesions at 28 days was 59% in the DermaMend group and 57% in the A&D group. The percentage of improved lesions (completely or partially healed) was 90% and 72%, respectively (authors' reported *p* value = 0.05, shown as a non-significant difference in the figure). The number of days to complete healing was 6 versus 7 in the DermaMend and A&D groups, respectively (non-significant difference).

For stage II lesions at 28 days, 45% of patients in the DermaMend group had completely healed lesions compared with 22% in the A&D group (*p* < 0.05). The percentage of improved lesions was 87% and 57%, respectively (*p* < 0.03), and days to complete healing were 8 versus 13, respectively (*p* < 0.05).

A multicentre trial compared a hydrocolloid dressing (Granuflex<sup>®</sup>, ConvaTec) with a povidone iodine dressing in patients who had pressure ulcers staged as either 2 or 3 following debridement (see *Figure 14*).<sup>31</sup> Stage 2 was defined as loss of epidermal tissue and stage 3 as presence of slough, or the presence of slough or same with a loss of substance. No information was provided about general care for pressure relief.

At the end of the 56-day trial, 84% of patients receiving the hydrocolloid dressing had achieved either complete or partial healing, compared with 71% of patients in the povidone iodine group (non-significant difference). The mean rate of ulcer-area reduction per week was 10% for the hydrocolloid group and 7% for the povidone

iodine group (non-significant difference). When the mean number of dressings per week per patient were examined, a highly significant difference of 2.4 (hydrocolloid) versus 5.0 (povidone iodine) was demonstrated ( $p < 0.0001$ ). Although this may have implications for nursing labour time, the reliability of this finding depends on how effectively nursing staff were blinded to which dressing had been allocated. No adverse effects were reported for either group.

No details were given about whether the presence of signs of clinical infection or bacterial colonisation of the wounds influenced the selection of participants for either study.

In a third small RCT, eligible patients were stated to be elderly women with pressure ulcers contaminated with MRSA during the month preceding the trial (*Figure 15*).<sup>47</sup> However, it appeared that not all the wounds were infected with MRSA at baseline. The two largest wounds (area greater than 50 cm<sup>2</sup>) were in the experimental group. The experimental group was treated with GVCAMP (gentian violet 0.1% blended with dibutyl cAMP as an ointment) and control participants received povidone iodine (concentration not specified) and sugar ointment. No details were given about the use of concomitant pressure relief. The change in wound area was assessed every 2 weeks using photography. There was no statistically significant between-group difference for change in wound area at 14 weeks. No adverse effects were observed in either group.

## Diabetic foot ulcers

Three RCTs evaluated the effects of antimicrobial agents in the treatment of diabetic foot ulcers (*Figure 16*).<sup>6,7,24</sup> Two of these examined systemic antibiotics<sup>6,7</sup> and the third focused on topical agents.<sup>24</sup>

### Systemic agents used with diabetic foot ulcers

A placebo-controlled trial evaluated the effect of the broad-spectrum antibiotic amoxicillin in combination with the penicillinase inactivator clavulanic acid.<sup>6</sup> Patients with polyneuropathy and foot lesions graded between 1A and 2A on the Wagner and Harkness Scale were recruited.<sup>57</sup> The presence of wound-surface cultures unresponsive to test medication was an exclusion criterion for participants. The treatment lasted for 20 days and the drugs were given orally. There were no statistically significant differences for mean reduction of

ulcer radius or the proportion of patients with complete healing. On the figure, the difference in reduction in ulcer radius is shown as just achieving statistical significance. One patient in the active-treatment group experienced diarrhoea, but did not withdraw from the trial.

A second study compared the action of clindamycin with cephalexin, a first-generation cephalosporin.<sup>7</sup> In order to be included, patients had to have a clinically infected wound, defined as the recent development of purulence or at least two of the following: erythema, warmth, tenderness, induration, fluctuance or drainage. However, systemic infection, or infection that was immediately threatening to life or limb, were exclusion criteria. No difference in treatment outcome was found for complete healing. The outcome assessment for wound healing involved ulcers being graded as one of the following: healed, healing in progress or unimproved. Wound dimensions were measured in order to grade lesions, and outcome assessment was blinded. Three patients had mild gastrointestinal symptoms, but did not withdraw from the trial. Two of these patients were from the control group.

### Topical agents used with diabetic foot ulcers

The only study in this section involved the use of chlorhexidine within a topical regimen. Aqueous solutions of chlorhexidine are active against many Gram-positive and Gram-negative organisms. They are ineffective against acid-fast bacilli, bacterial spores, fungi and viruses, and have reduced efficacy in the presence of organic matter such as blood or pus. Chlorhexidine is considered to have a low toxicity in living tissue.<sup>58</sup>

An unpublished Belgian trial compared a hydrogel dressing with chlorhexidine cleansing plus dry gauze dressing in insulin-dependent diabetic patients.<sup>24</sup> Patients with infected ulcers were not excluded from the study. Although use of systemic antibiotics at entry to the study was an exclusion criterion, all patients were prescribed systemic or topical antibiotics, or topical antiseptics, if required, during the course of the trial. All patients in the chlorhexidine group ( $n = 14$ ) received other systemic or topical antibiotics, or topical antiseptic creams. Six of the 14 patients in this group were prescribed systemic antibiotics, the most commonly used topical preparation being povidone iodine ointment. One patient of 15 in the hydrogel group received systemic antibiotics, and none received topical preparations.

The overall healing rate was significantly higher in the hydrogel group (14/15 versus 7/14,  $p < 0.05$ ). One patient required toe amputation in the hydrogel group, compared with five in the control group (non-significant difference). The use of the hydrogel dressing was found to significantly reduce nursing labour time because it stayed *in situ* for longer, but rigorous blinding procedures would be required to ensure the reliability of this finding.

An additional trial recruiting patients with diabetic foot ulcers or pressure ulcers has been reviewed above.<sup>45</sup>

## Pilonidal sinuses

A sinus is an epithelial-lined, blind-ended track, extending from the skin surface to the subcutaneous tissues, which may form a cavity or abscess. Pilonidal sinuses are caused by an accumulation of coarse hair penetrating the skin via a crevice or follicle. The upper natal cleft is the most common site but there may be other locations, such as the umbilicus and axilla.<sup>21</sup> Young, dark, hirsute, overweight males are most at risk of developing the condition.<sup>59</sup> Typical isolates of pilonidal sinuses and cavities include *Staph. aureus* and anaerobes such as *Bacteroides*.<sup>16,59,60</sup>

Interventions currently in use include management of risk factors, phenol injection and surgical excision of the sinus, either with or without closure. Any of these may be combined with dressings and/or antimicrobial therapy.<sup>59</sup>

Five RCTs<sup>16,25–28</sup> and one CCT<sup>44</sup> evaluating interventions for pilonidal sinuses were included in the review. Three studies involved systemic antibiotics<sup>16,25,44</sup> and three involved topical agents.<sup>26–28</sup>

### Systemic agents used with pilonidal sinuses

One trial examined the effectiveness of antibiotic prophylaxis in surgery (*Figure 17*).<sup>25</sup> The cephamycin cefoxitin (2 g intravenously) was given prior to excision and primary suture, and this was compared with the same surgery without antibiotic prophylaxis. The presence of acute abscesses was an exclusion criterion for participants. The number of patients who had undergone previous surgery was not reported at baseline. There were no significant differences between groups for the initial time to healing, which was approximately 5 weeks in both groups, or in rates of postoperative complications. Patients were followed up for a period of 18–30 months.

A second trial recruited patients with chronic discharging pilonidal sinuses and allocated them to receive one of three interventions: excision only, excision and suture, or excision and suture plus clindamycin (*Figure 18*).<sup>16</sup> Patients were followed up for 3 years. There was no statistically significant difference between groups in terms of initial healing rates. The median time to healing was significantly different between excision only and excision and suture (64 versus 14 days,  $p < 0.001$ ) and between excision only and excision and suture plus clindamycin (64 versus 11 days). However, there were no statistically significant differences between excision and suture and excision and suture plus clindamycin (14 versus 11 days). The same levels of significance and time intervals also applied to patients who required revisional surgery. There were no statistically significant differences between groups in the recurrence of disease after 3 months and 3 years. No adverse effects were observed with the use of clindamycin. The results of this study suggested that primary closure may have been the factor that produced significantly shorter healing times, and the authors maintained that this intervention resulted in less requirement for community nurse care.

Another study showed that a prescription of oral metronidazole commencing 7–14 days after excision, resulted in faster healing compared with the same surgery without antibiotics (shown as just non-statistically significant on the figure) (*Figure 19*).<sup>44</sup> This was a CCT in which patients were allocated to treatment and control groups on an alternating basis. The presence of infection or wound colonisation were not mentioned as selection criteria for participants. Seven patients in the control group developed wound pockets postoperatively compared with none in the metronidazole group. Two patients in the control group were eventually referred for further surgery, but the corresponding number was not given for the treatment group. This was a small study, with no report of inclusion and exclusion criteria for participants, and no baseline information about patient characteristics.

### Topical agents used with pilonidal sinuses

One study assessed the effectiveness of topical gentamicin, applied postoperatively (*Figure 20*).<sup>26</sup> Gentamicin is effective against many Gram-positive and Gram-negative bacteria, including some penicillin-resistant strains.<sup>14</sup> All patients underwent surgical excision and any abscesses were lanced preoperatively. One group was randomised to receive insertion of a gentamicin-impregnated



collagen sponge into the excised area, and the other group did not receive a sponge. The numbers of patients who had undergone previous surgery were not reported. The rate of primary healing was significantly higher in the sponge group (86% versus 35%,  $p < 0.001$ ). However, since the other group did not receive any topical application, it is unclear whether the higher healing rates were due to the gentamicin, the sponge or both. Assessments at the 1-year follow-up showed no recurrence of disease in either group.

Two trials assessed the effectiveness of antiseptic packs compared with silastic foam dressing.<sup>27,28</sup> In the earlier study,<sup>28</sup> all patients underwent excision of sinuses followed by a 4-day pack with a flavine-emulsion-soaked gauze. Following this, patients were randomised to receive either daily packing using chlorhexidine-soaked gauze, or silastic foam dressing, to be re-made weekly to ensure a comfortable fit within the cavity. Patients appeared to be comparable for baseline wound volume. There were no statistically significant differences between groups for the number of days with the pack *in situ*, time to healing (see *Figure 20*), length of hospital stay or number of days lost from work. However, the authors drew attention to the mean difference in the number of home visits by community nurses (35.1 for the chlorhexidine pack, 4.6 for the silastic foam dressing).

The other study involved the use of hypochlorites.<sup>27</sup> Solutions of sodium hypochlorite have been in use for over 100 years. Various versions of the product are available, including Eusol, Chlorasol<sup>®</sup> and Dakin's solution. These products are active against both Gram-positive and Gram-negative bacteria, and also some spores and viruses. Although hypochlorites have traditionally been used for desloughing purposes, their safety has been

questioned more recently,<sup>20</sup> and expert consensus now dictates that they should not be used in slough-free wounds.<sup>61</sup> It has been suggested that their use may be associated with delayed healing and systemic adverse effects, including renal failure (Schwartzmann reaction) and hypernatraemia.<sup>20,58</sup> However, much of the relevant evidence is weak due to methodological flaws, and is taken from studies of clean wounds in animals.

In this study, patients underwent excision of pilonidal sinuses followed by insertion of a half-strength Eusol pack.<sup>27</sup> The Eusol pack was removed 48 hours postoperatively, and patients were randomly allocated to either a continuation of the Eusol dressing (twice daily initially, then once daily when the wound was clean) or to a silastic foam dressing (removed and washed twice daily, and re-made as required). No baseline information was given relating to wound characteristics or frequency of previous surgery. No statistically significant differences between groups were found for mean length of hospital stay or mean time to healing. However, as in the previous study, authors mentioned that the use of the silastic foam dressing was associated with less community nursing input following discharge. Patients allocated to the silastic foam group required two or three visits in total, for refashioning of the foam, while Eusol-treated patients required daily visits for up to 4 weeks. The impact of different dressings on nursing labour time and costs is an area that warrants further research. There is no figure to go with this study as insufficient data were provided to calculate effect size with 95% CIs.

No details were given about whether the presence of signs of clinical infection or bacterial colonisation of the wound influenced selection of participants for either of the latter two studies.<sup>27,28</sup>

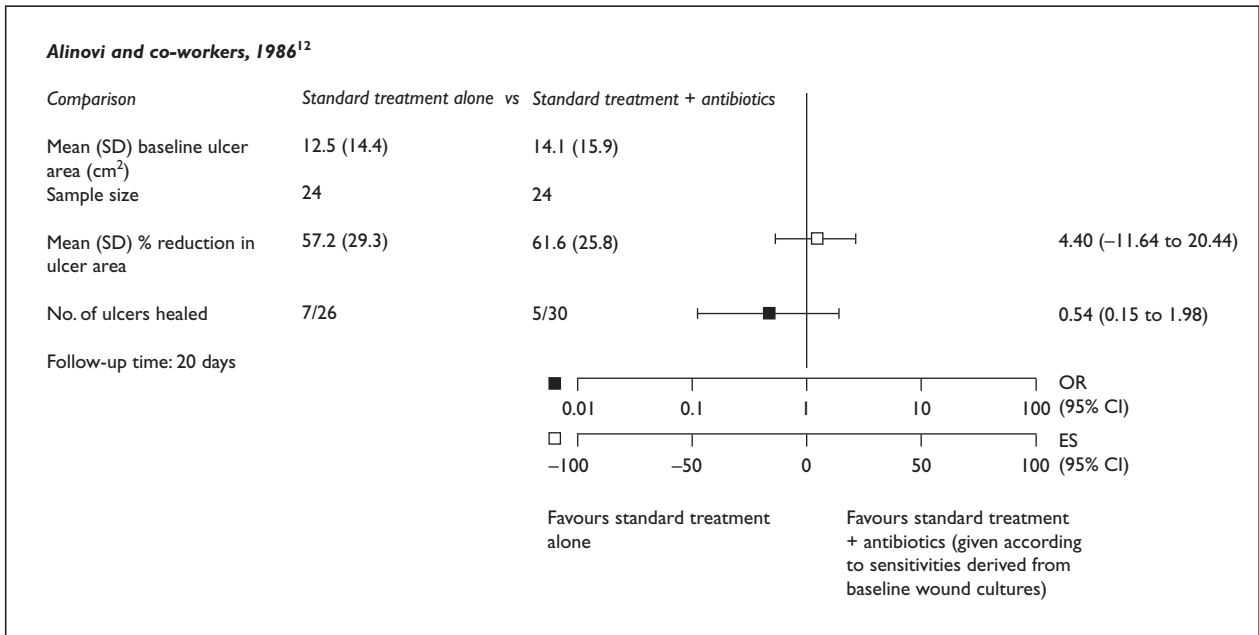


FIGURE 1 Systemic agents used for venous leg ulcers

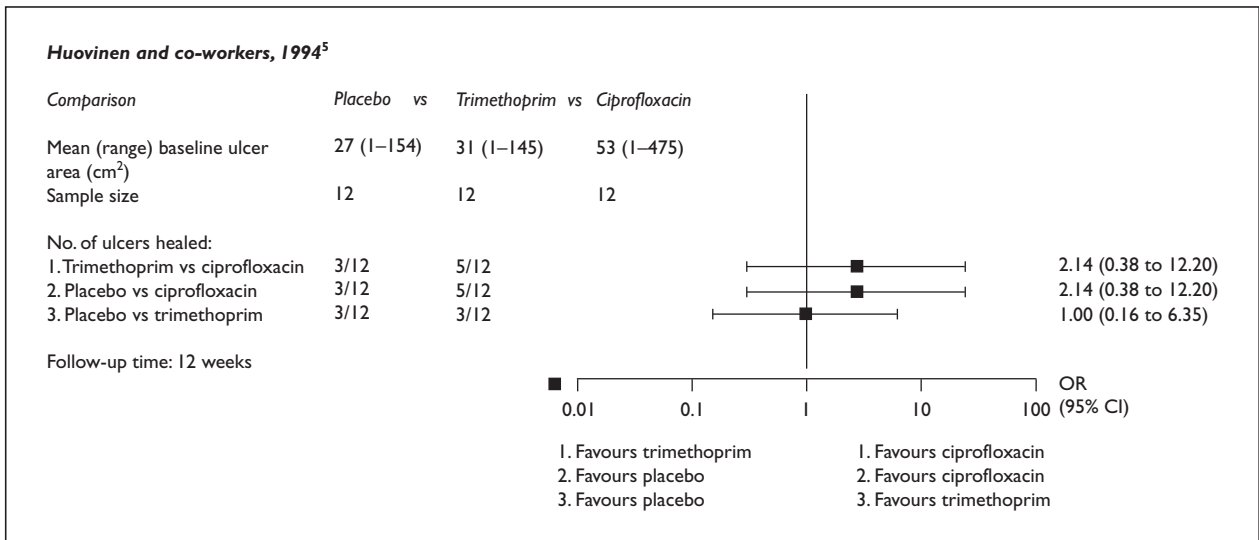
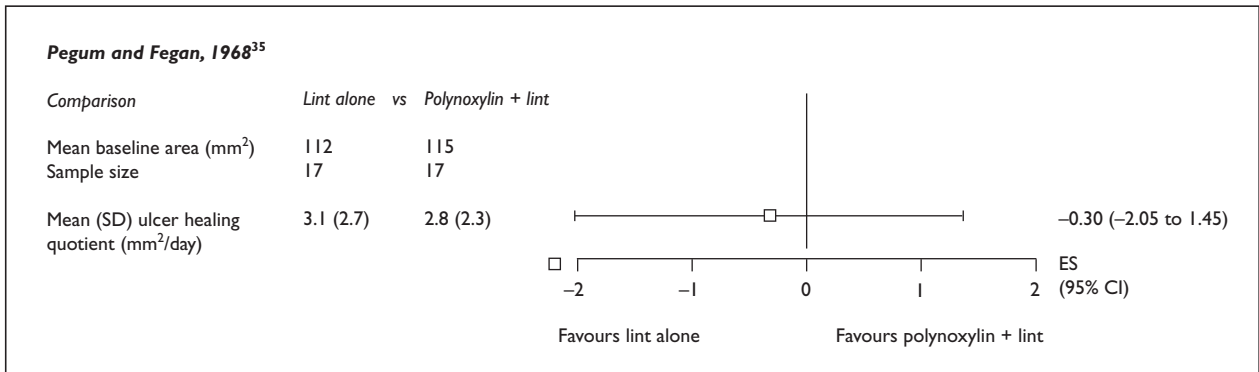
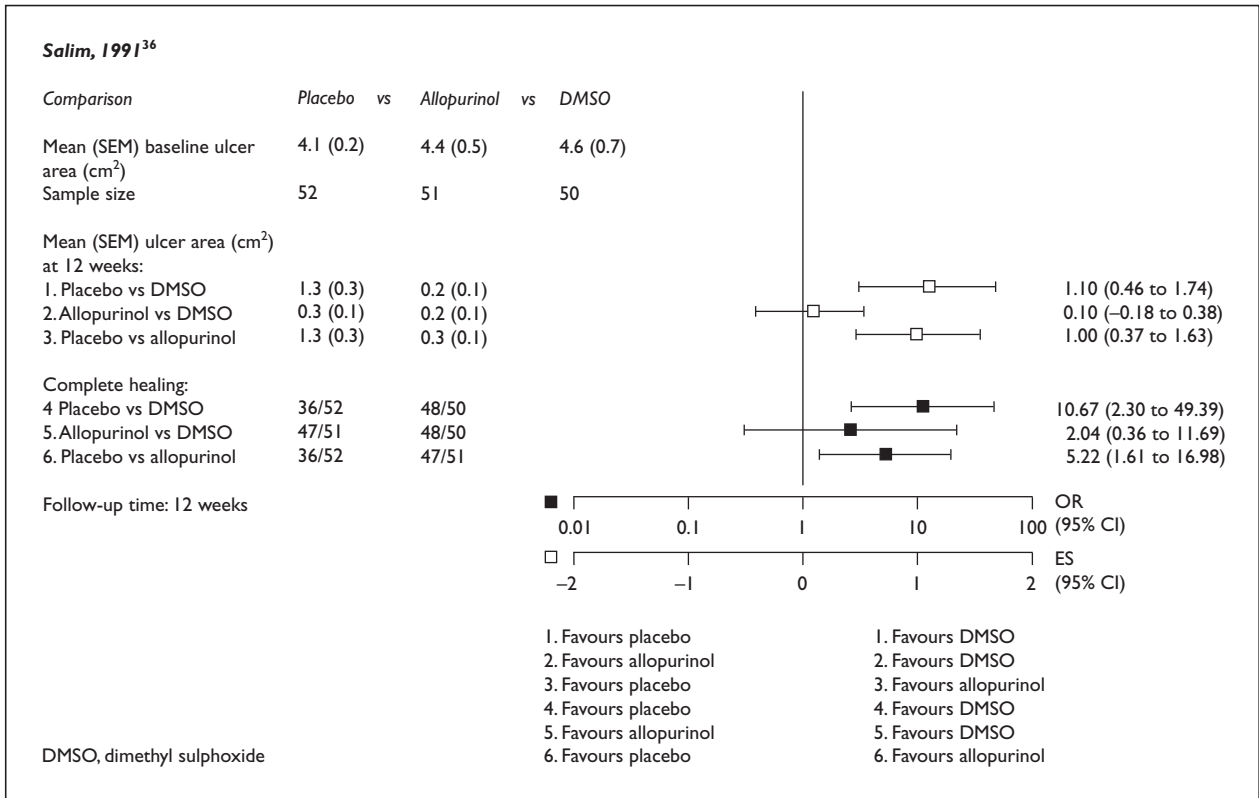


FIGURE 2 Systemic agents used for venous leg ulcers (see appendix 4)



**FIGURE 3** Topical agents used for venous leg ulcers



**FIGURE 4** Topical agents used for venous leg ulcers (see appendix 4)

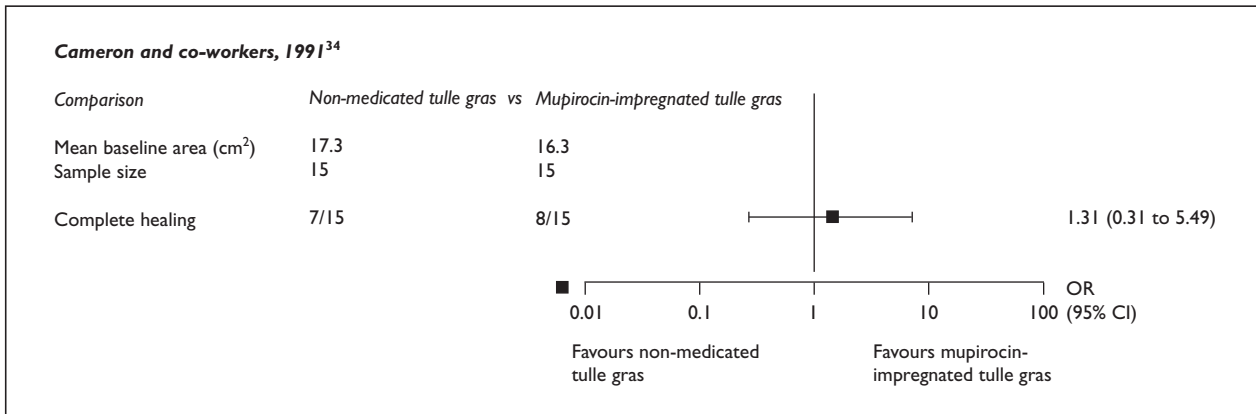


FIGURE 5 Topical agents used for venous leg ulcers

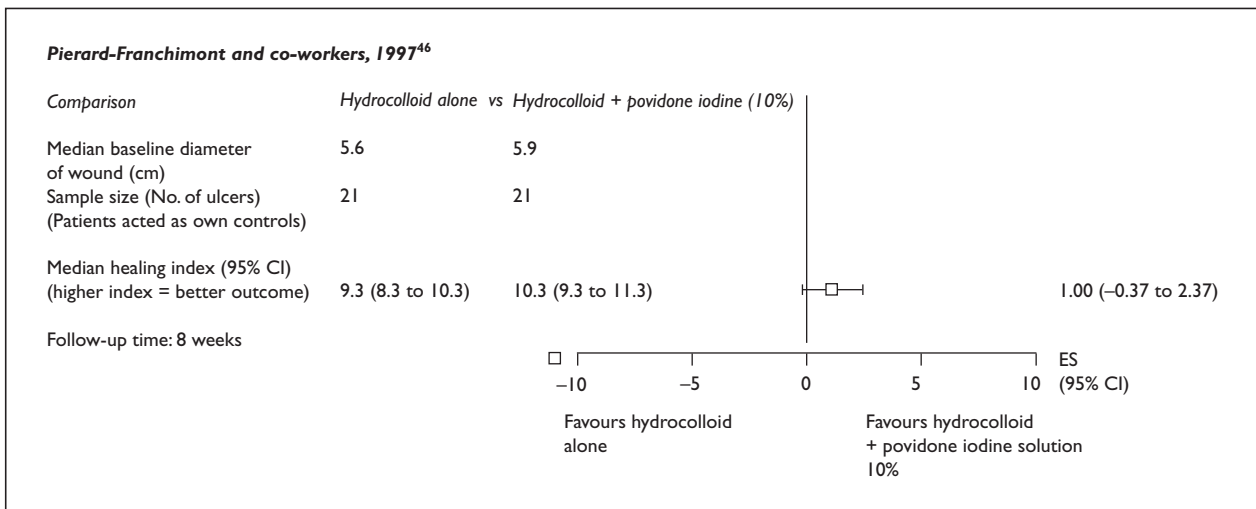


FIGURE 6 Topical agents used for venous leg ulcers

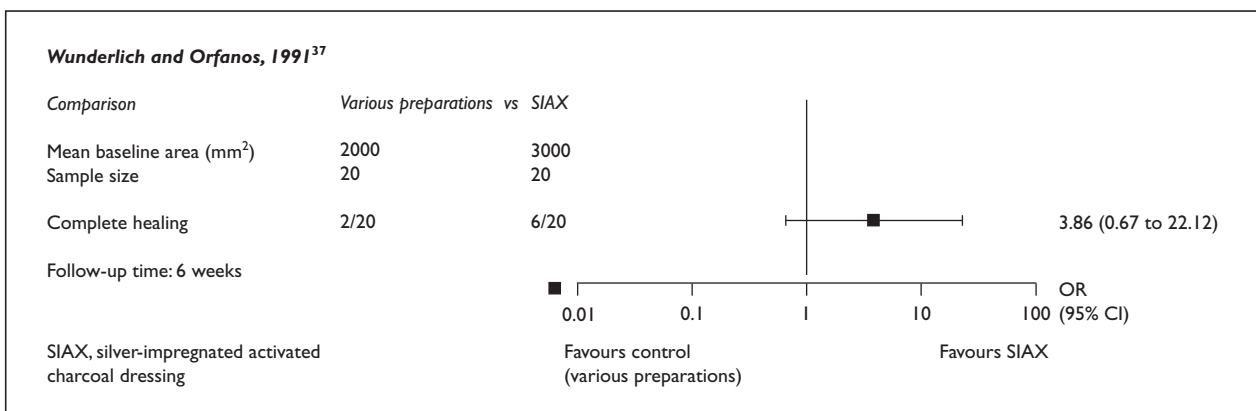


FIGURE 7 Silver-based topical agents used for venous leg ulcers

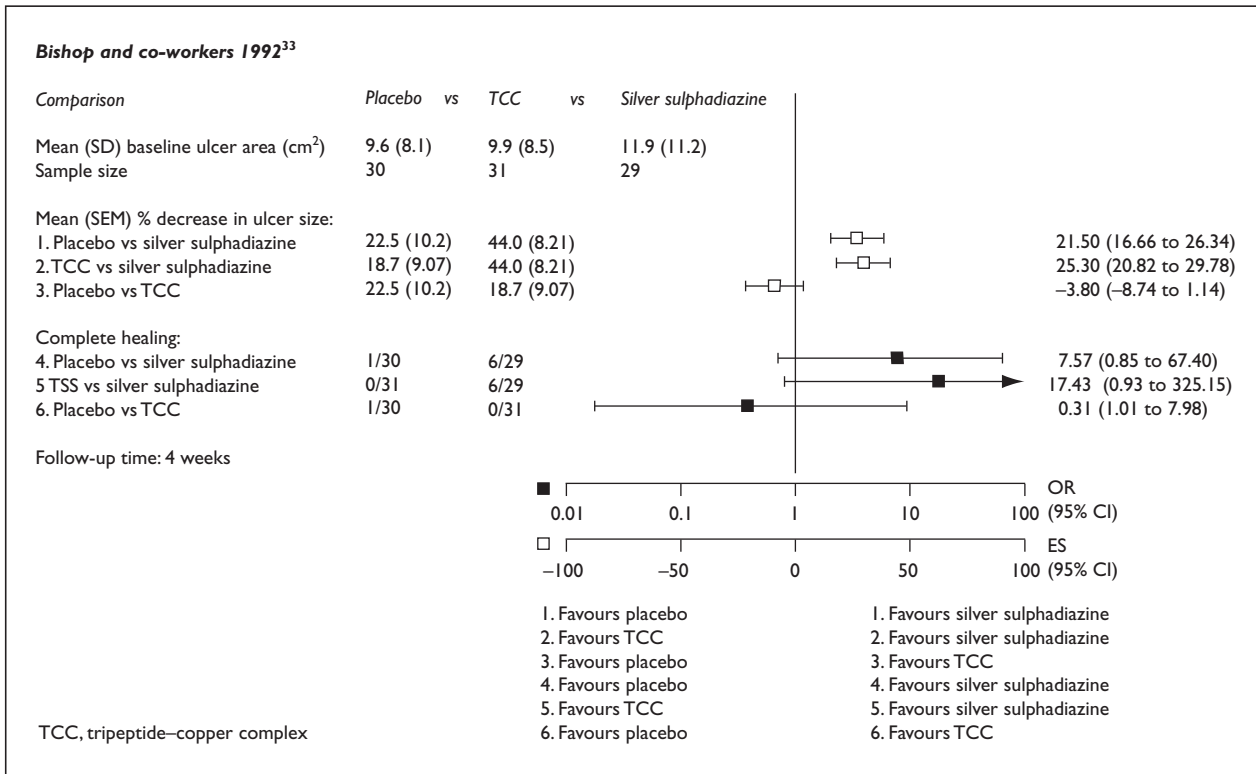


FIGURE 8 Silver-based topical agents used for venous leg ulcers (see appendix 4)

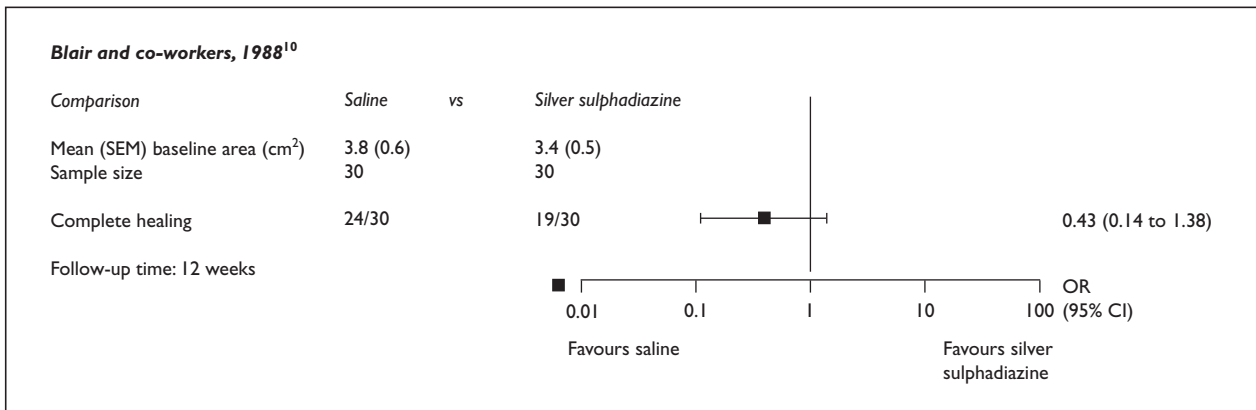
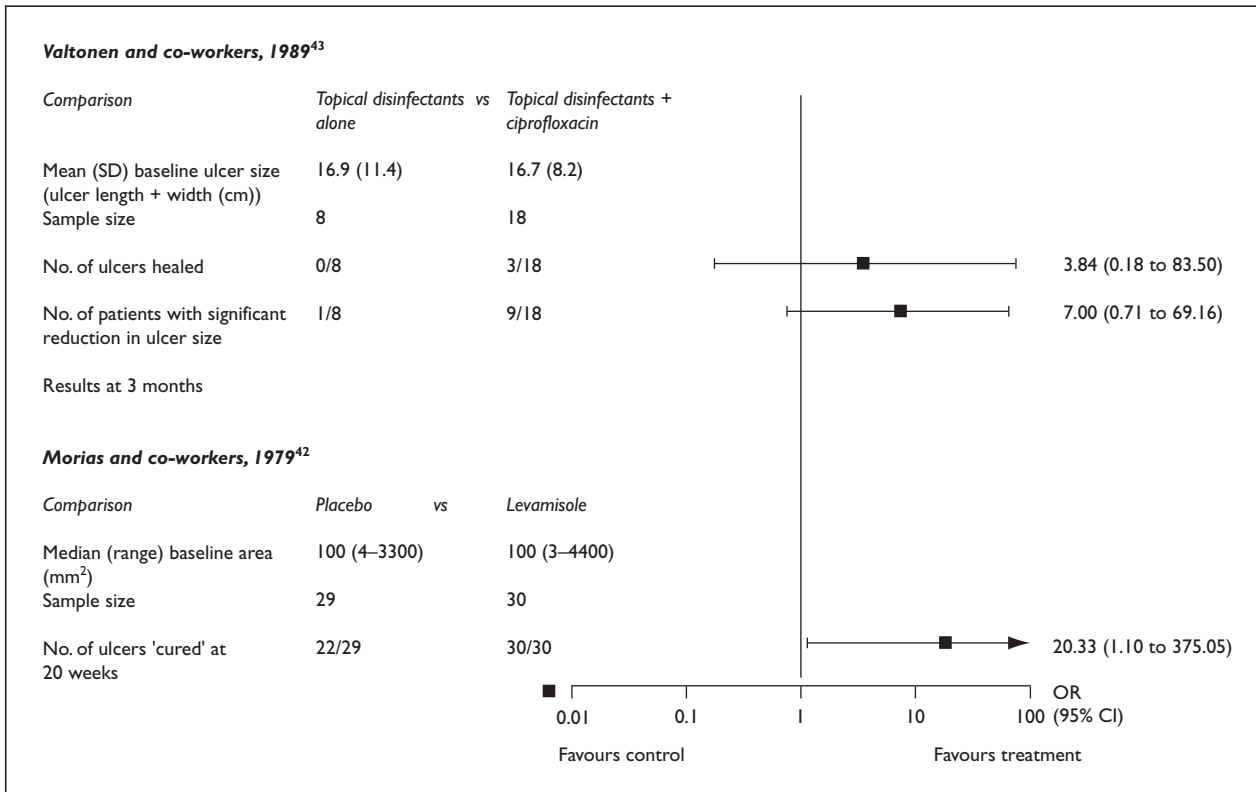
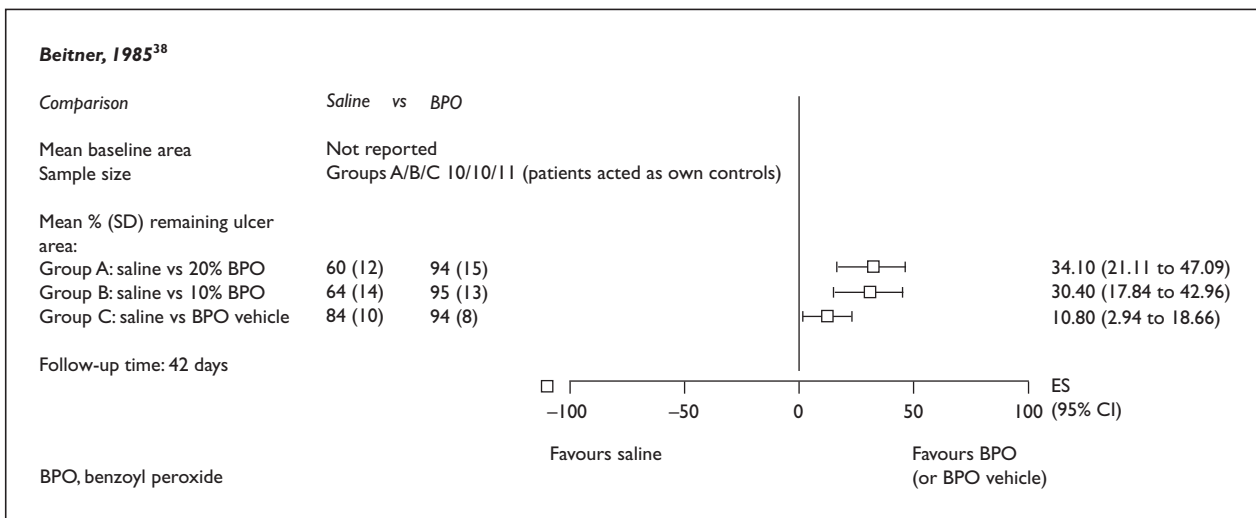


FIGURE 9 Silver-based topical agents used for venous leg ulcers



**FIGURE 10** Systemic agents used for leg ulcers of mixed aetiologies



**FIGURE 11** Topical agents used for leg ulcers of mixed aetiologies (see appendix 4)

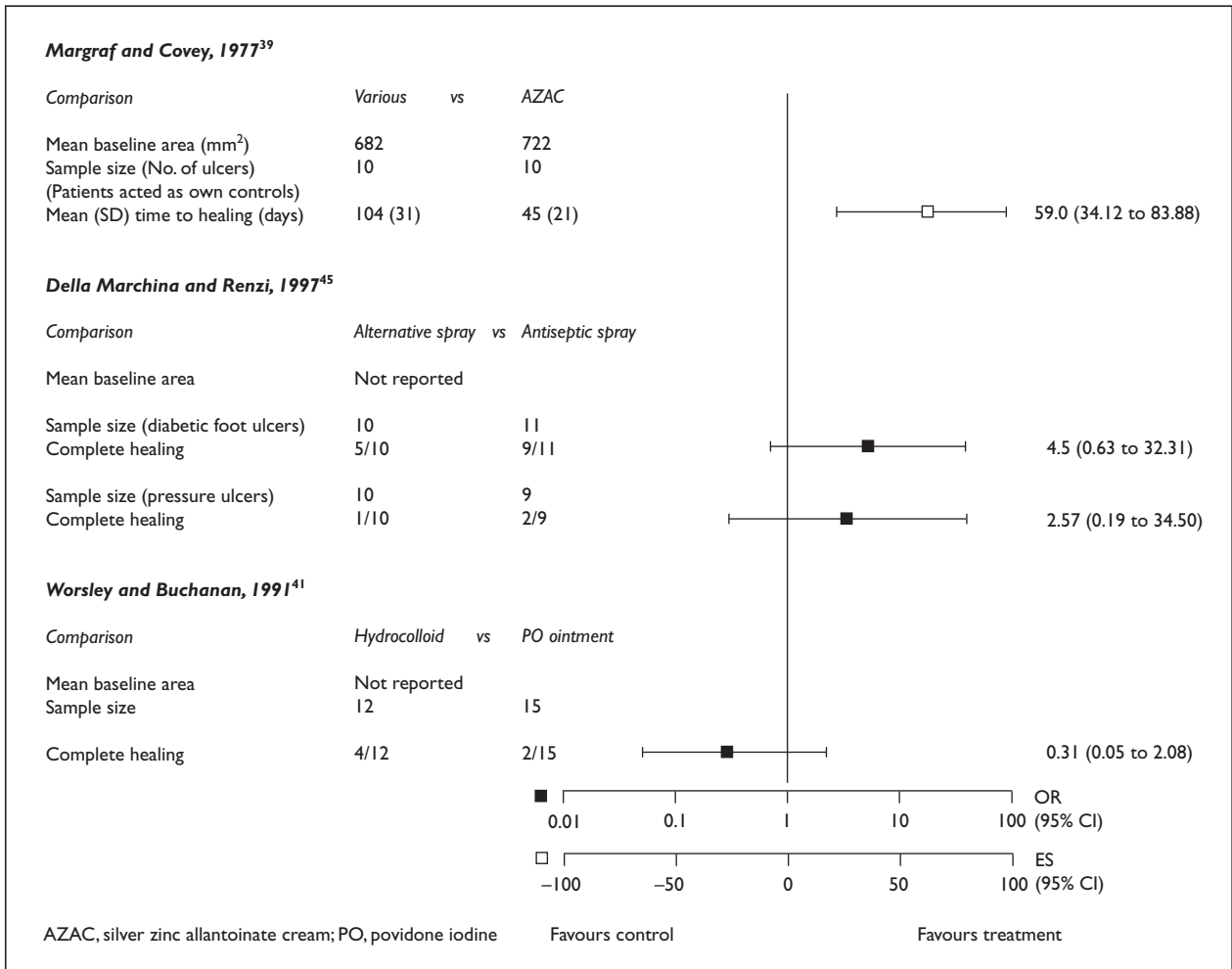
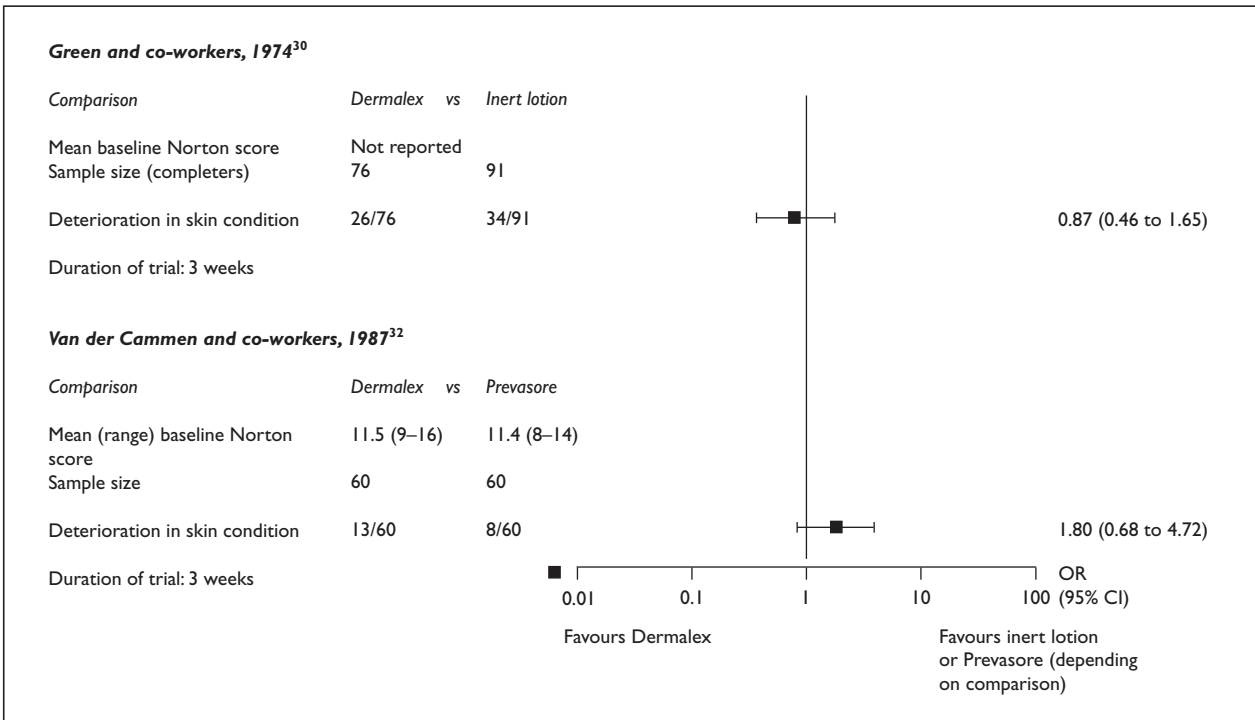
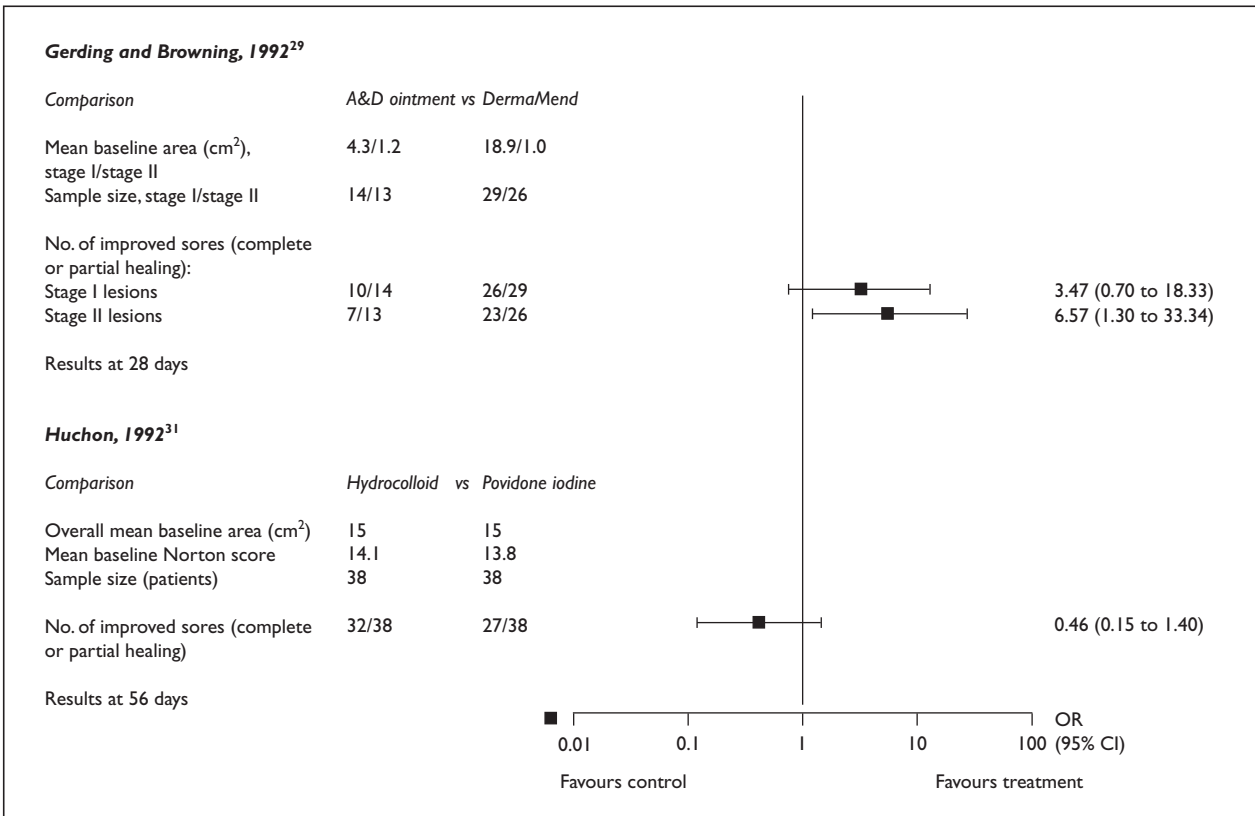


FIGURE 12 Topical agents used for wounds of mixed aetiologies



**FIGURE 13** Topical agents used for the prevention of pressure ulcers



**FIGURE 14** Topical agents used for the treatment of pressure ulcers



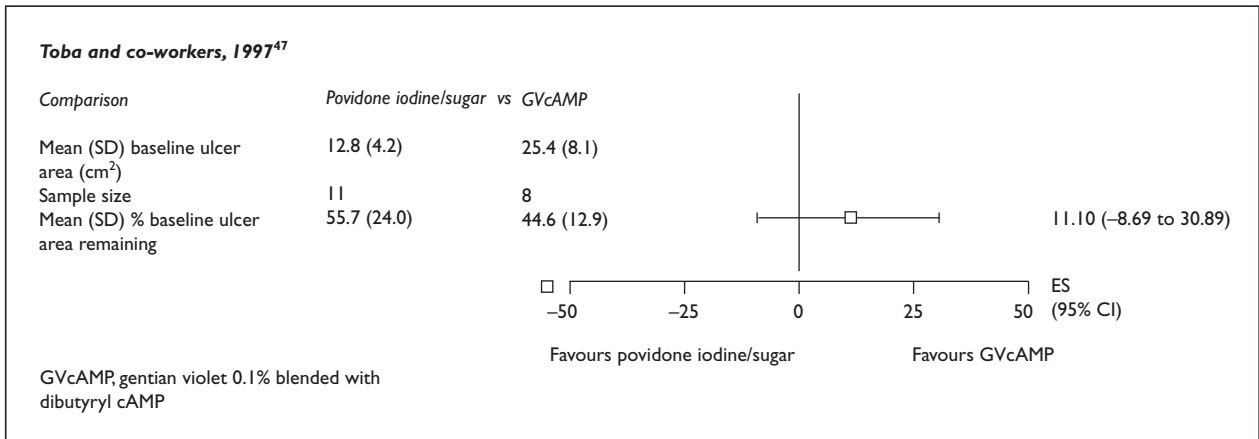


FIGURE 15 Topical agents used for the treatment of pressure ulcers

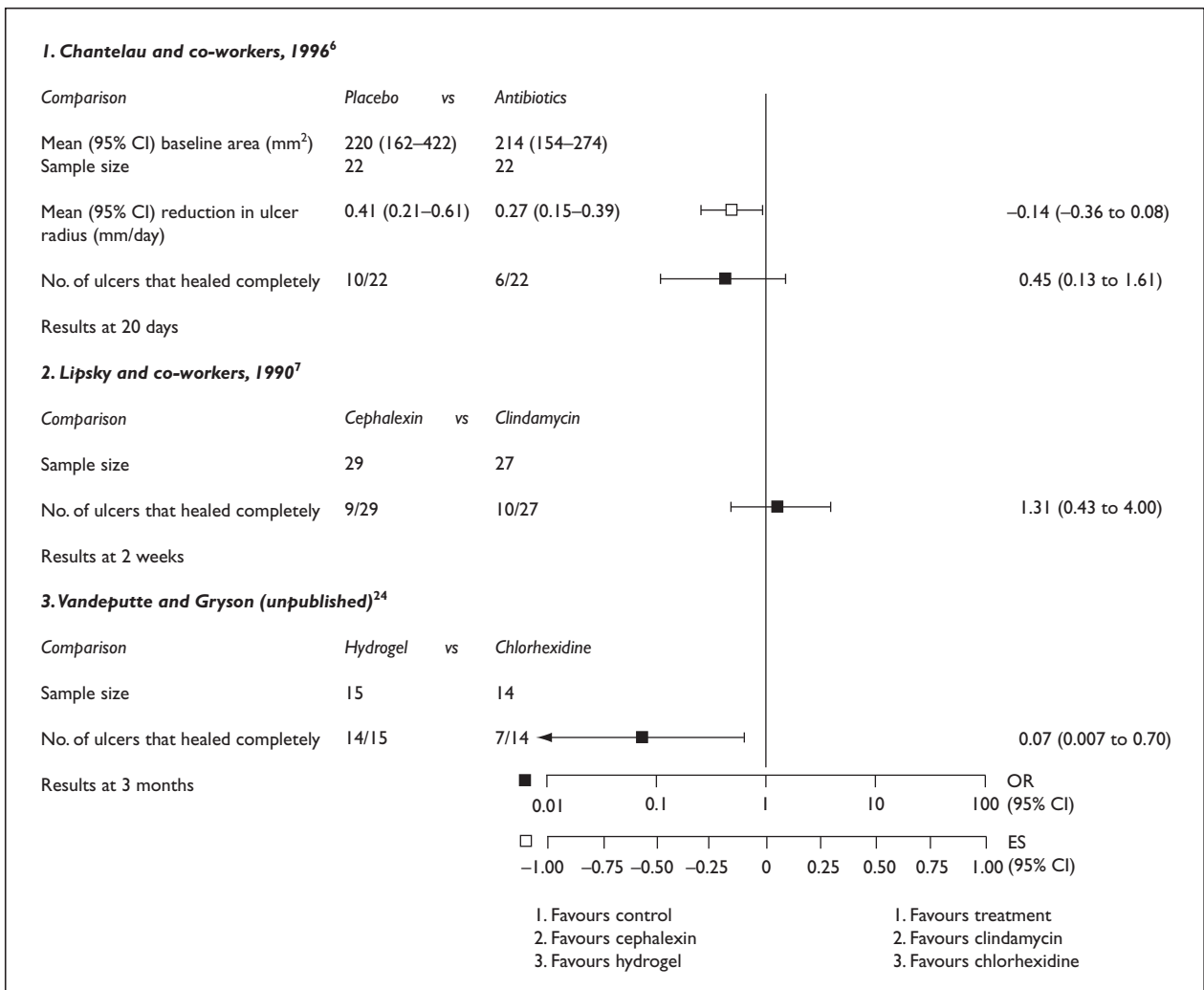


FIGURE 16 Treatment of diabetic foot ulcers

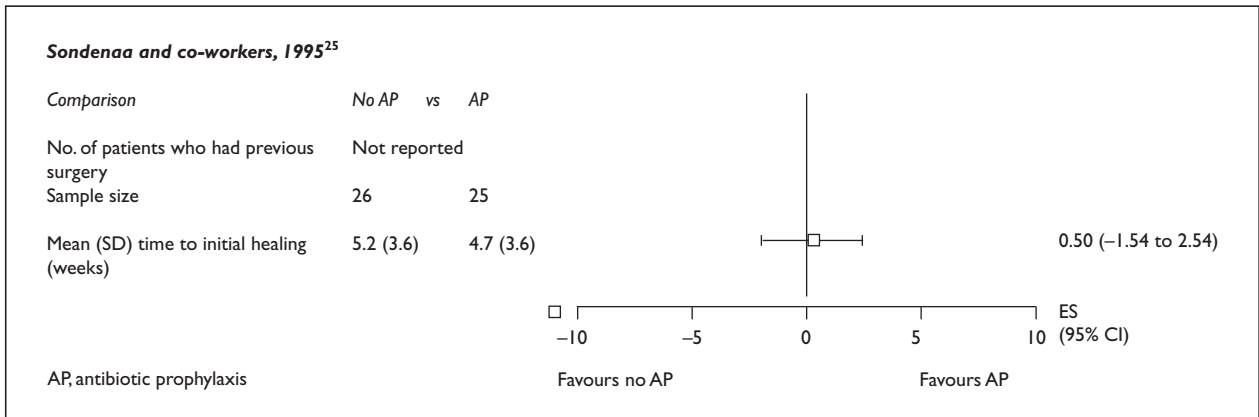


FIGURE 17 Systemic agents used for pilonidal sinuses

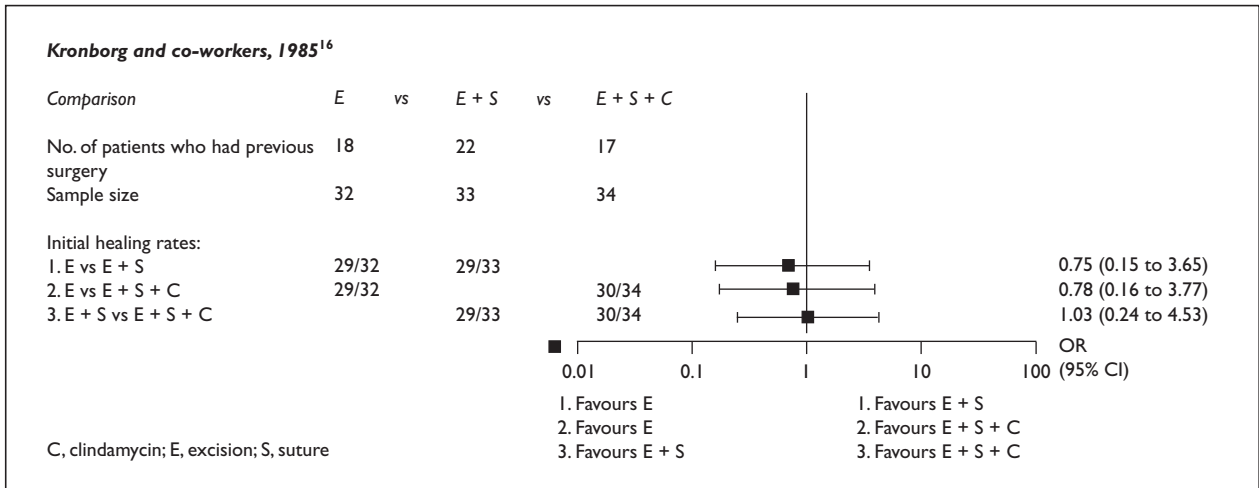


FIGURE 18 Systemic agents used for pilonidal sinuses (see appendix 4)

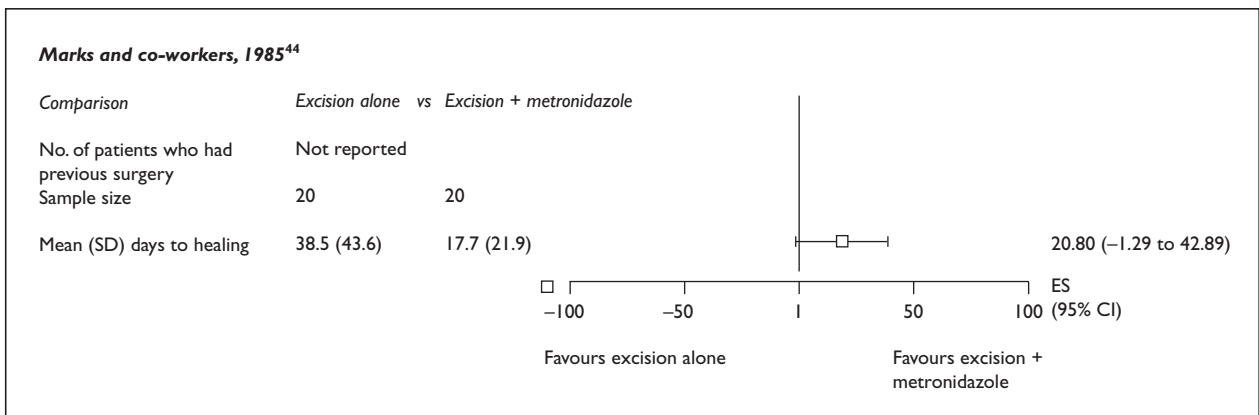
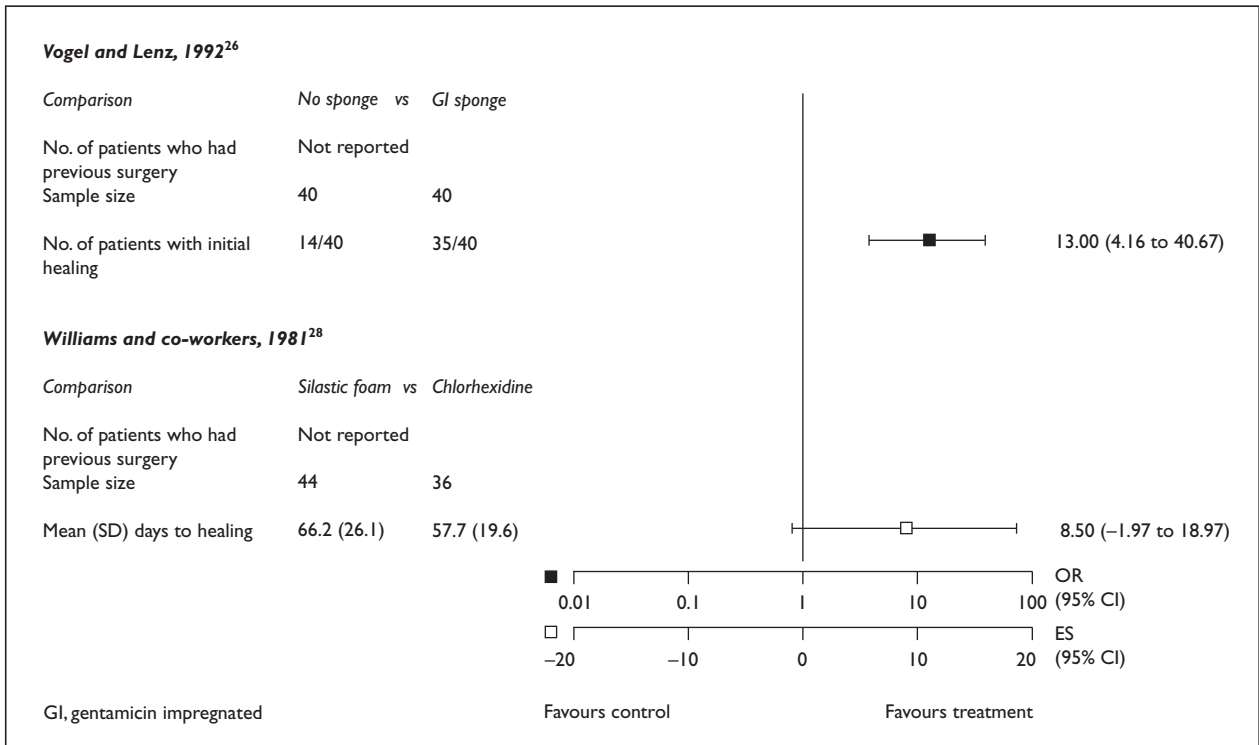


FIGURE 19 Systemic agents used for pilonidal sinuses



**FIGURE 20** Topical agents used for pilonidal sinuses



# Chapter 4

## Discussion

### Systemic agents

Existing evidence does not support the routine use of systemic antibiotics in patients with venous leg ulcers. However, this conclusion is based on findings from two small studies,<sup>5,12</sup> where the possibility of type II error could not be excluded. The role of antimicrobial agents used with leg ulcers of mixed aetiologies remains unclear due to methodological problems of the primary literature and lack of detail on baseline characteristics. It should be noted that current prescribing guidelines recommend the use of systemic antibiotics in cases of acute infection associated with leg ulcers, such as cellulitis.<sup>17</sup>

For diabetic foot ulcers, oral amoxicillin combined with clavulanic acid proved to be no better than placebo,<sup>6</sup> and another evaluation showed no statistically significant difference between clindamycin and cephalexin in terms of wound healing.<sup>7</sup> Again, both studies were small.

The role of antibiotics, both as prophylaxis in surgery<sup>25</sup> and as postoperative cover,<sup>16</sup> in pilonidal sinus disease remains unclear. In an evaluation involving clindamycin, primary closure may have been the most important factor for rapid healing.<sup>16</sup> However, a small trial showed that oral metronidazole used after excision may be beneficial.<sup>44</sup> No trials of systemic antimicrobials for pressure ulcer healing were identified.

The above results are all from small studies ( $n = 34$  in the largest treatment arm), and it is likely that evaluations on this scale lack the statistical power to detect true treatment effects. It would therefore be useful to replicate this research in larger, well-designed studies. A further problem is lack of detail relating to baseline characteristics, and scant presentation of inclusion and exclusion criteria. In trials of patients with wounds of mixed aetiologies, it is particularly important to have detailed reporting of baseline patient characteristics, and results should be presented according to aetiology. It is also important that details of concomitant care, such as compression bandaging, are reported.

### Topical agents

A range of topical agents has been reviewed, and the role of many of these in the management of chronic wounds remains unclear. For venous leg ulcers, it is possible that dimethyl sulphoxide powder<sup>36</sup> and silver-based products<sup>10,33,37</sup> may be beneficial in terms of healing. Further research is required to determine the best preparation of silver-based products and the type of patients most likely to benefit. There was no evidence to promote the use of polynoxylin paste,<sup>35</sup> mupirocin<sup>34</sup> or the addition of povidone iodine solution 10% to a hydrocolloid dressing.<sup>46</sup>

Results for benzoyl peroxide in patients with wounds of mixed aetiologies (mostly venous leg ulcers) were unclear,<sup>38,40</sup> and the same is true for AZAC 1% cream.<sup>39</sup> In a very small trial recruiting patients with leg ulcers (aetiology unspecified) or pressure ulcers, no differences were found between a hydrocolloid dressing and povidone iodine ointment for complete healing.<sup>41</sup> No statistically significant differences were found between an antiseptic spray (eosin 2% and chloroxylenol 0.3%) and an alternative spray (constituents not described) in a small Italian study.<sup>45</sup>

The effectiveness of preparations for the prevention of pressure ulcers is also yet to be established.<sup>30,32</sup> For the treatment of existing pressure ulcers, an oxyquinoline ointment may be more effective than a standard emollient,<sup>29</sup> but no significant differences were seen when a hydrocolloid dressing was compared with povidone iodine ointment,<sup>31</sup> or when a preparation based on gentian violet 0.1% was compared with a povidone iodine and sugar ointment.<sup>47</sup>

For diabetic foot ulcers, a hydrogel dressing was significantly more effective than various systemic and topical antimicrobial preparations in terms of complete healing.<sup>24</sup> However, the variety of preparations used in the control group makes the results difficult to interpret.

The postoperative application of a gentamicin-impregnated sponge may help promote healing in patients with pilonidal sinuses, but further research

is required.<sup>26</sup> Two trials evaluating silastic foam dressings showed that there was no difference between this and a chlorhexidine pack<sup>28</sup> or a Eusol pack<sup>27</sup> in terms of length of hospital stay and time to healing. However, the use of the silastic dressing appeared to be associated with less nurse labour time.

As is the case with evaluations of systemic antimicrobials, much of the research into topical agents requires replication on a larger scale. Attention should be paid to detailed baseline data collection and reporting, blinding of outcome assessors, reporting of withdrawals and the use of the intention-to-treat protocol. Rigorous methods of blinding for wound assessors are essential to establish the relationship between different types of product and changes in the nurse labour time required. Finally, concurrent interventions should be described in detail, and should cover compression bandaging for venous leg ulcers, pressure relief for pressure ulcers and diabetic foot ulcers, and surgical techniques for pilonidal sinuses.

## Topical agents not included in this review

Several topical agents are in use for which no eligible evaluations were identified for inclusion in this review. One such agent is hydrogen peroxide, which has traditionally been used with sloughy or necrotic wounds. Hydrogen peroxide has a caustic action that is dependent on the steady release of oxygen, and can sting when applied to wounds. Damage may also occur to surrounding healthy skin. Some sources suggest that air embolism may result from pressurised irrigation or use within an enclosed body cavity.<sup>8,20</sup> However, the frequency of such adverse effects is unclear. No evaluations of hydrogen peroxide were identified for inclusion in this review, but in one study it was part of the standard topical regimen.<sup>7</sup> In addition, no eligible evaluations were identified for topical preparations of fusidic acid or neomycin. Fusidic acid is used to treat staphylococcal skin infections, and neomycin is used for bacterial infections, but ototoxicity is a possible adverse effect.<sup>17</sup>

Certain alternative therapies purported to have antimicrobial properties may be useful in the management of wounds. These are usually in the form of topical applications, and include extract of marigold, honey, propolis and sugar.

Extracts of marigold are considered to have antimicrobial effects. The infused essential oil from the pot marigold (*Calendula officinalis*) is reputed

to have antifungal properties when applied to the skin.<sup>62</sup> One study was identified that compared a preparation based on extract of *C. officinalis* with the same extract combined with another plant extract, in various wounds including venous leg ulcers. This study was excluded from the review because insufficient methodological details were reported.<sup>63</sup>

The effects of the tincture of another type of marigold (*Tagetes patula*) added to a vehicle of white soft paraffin were studied in patients suffering from leprosy who had trophic ulcers (ulcers arising from damage to the nerve supply of the skin).<sup>64</sup> *T. patula* is stated to have both antibacterial and antifungal effects when applied to the skin.<sup>62</sup> The study was not eligible for inclusion due to the wound type and because insufficient details of the methodology and results were available.

Honey is considered have antibacterial properties,<sup>65</sup> and has been compared with silver sulphadiazine in the treatment of burns.<sup>66</sup> No evaluations were identified that could be included in this review. Granulated sugar,<sup>67</sup> sugar paste<sup>68</sup> and propolis (a sticky substance produced by bees to seal honeycomb cells)<sup>69</sup> are also reputed to be beneficial, but again no relevant studies were eligible for inclusion. Sugar was a component of a treatment regimen in one study, where it was combined with povidone iodine to make a blended ointment. However, the type of sugar used was not described.<sup>47</sup>

Alternative approaches may be beneficial, but their effectiveness and safety need to be established in well-designed comparative studies before any conclusions can be made about their role in the management of chronic wounds.

## Comparison with other systematic reviews

Four other systematic reviews concerned with the management of chronic wounds and that included sections on antimicrobial agents were identified.<sup>70-73</sup> Three of the reviews focused on leg ulcers,<sup>70-72</sup> and one on pressure ulcers.<sup>73</sup>

### Systematic reviews of the management of leg ulcers

A review of RCTs of various interventions for venous leg ulcers concluded by recommending neither systemic antibiotics nor antiseptics for

wound cleansing.<sup>70</sup> The only recommended topical application was silver sulphadiazine, as a result of evidence from one study (included in the current review).<sup>33</sup> The information relevant to systemic agents was based on one RCT (also included in the current review).<sup>12</sup> Some methodological problems were noted with this review. The search strategy was confined to MEDLINE, with a limited list of search terms, and only English-language reports were sought. There was no quality assessment of primary studies, and details of included material were sparse.

A second review reached similar conclusions, and stated that systemic and topical antimicrobials were not recommended for the routine treatment of venous leg ulcers.<sup>71</sup> Again, the search strategy was confined to MEDLINE, with a limited list of search terms. The inclusion criteria for primary studies were unclear, no assessment of study quality was presented, and it appeared that only English-language reports were selected. Two included studies overlap with the current review.<sup>12,33</sup>

The third leg ulcer review was concerned with community-based management.<sup>72</sup> This was a good quality review, with detailed reporting of the methodology and content of primary studies. This included a thorough review of the effects of microorganisms in ulcer healing and concluded that, although most chronic wounds are colonised, there is little evidence to suggest that this influences healing. Two studies included in the current review were assessed,<sup>12,43</sup> and the main criticism was that results from these trials were difficult to interpret since, in both cases, only some participants were followed up to complete healing.

### Systematic review of the management of pressure ulcers

A systematic review assessed different options for the management of pressure ulcers in the elderly, including general care, mattresses, pads, dressings and topical applications.<sup>73</sup> Two studies of antimicrobial topical agents used for prevention were included.<sup>32,74</sup> One of these studies was included in the current review,<sup>32</sup> but the other was excluded because the unit of allocation was wards as opposed to patients or lesions.<sup>74</sup> For therapeutic interventions, three studies assessing the effectiveness of topical agents with antimicrobial properties were included,<sup>75-77</sup> and also one evaluation of a systemic agent (oral metronidazole).<sup>78</sup> These studies were excluded from the current review due to use of a before/after study design,<sup>78</sup> wards as the unit of allocation,<sup>76</sup> absence of wound-healing outcomes<sup>77</sup> and confounding treatment regimens.<sup>75</sup>

The general conclusions were that the area of topical applications requires further research, and that a consensus in outcome measurement is needed. The search strategy was limited to MEDLINE and *Index Medicus*, for the periods 1980–1988 and 1979–1989, respectively, and only English-language articles were sought.

### Reporting of underlying factors in trials

A number of factors known to influence wound healing are seldom reported in primary studies. These factors include nutritional status, metabolic status, immunocompetence, vascular disease, level of mobility and continence. The impact of such factors is likely to differ for the various aetiologies covered in this review; for example, continence would be of less importance for leg ulcers than for pressure ulcers. Sparse data relating to these variables may make study findings difficult to interpret.

#### Nutritional status

Wound healing is affected by the intake of fluids, carbohydrates, lipids, protein, vitamins A, B<sub>6</sub>, B<sub>12</sub> and C, calcium, iron and zinc.<sup>8,79,80</sup> Deficiency may cause complications such as delayed healing and infection.<sup>79</sup>

One study in this review reported the nutritional status of participants at baseline, however it is unclear how this was assessed.<sup>41</sup> In another case, the authors stated that the two study groups had similar baseline nutritional status, but no further details were provided.<sup>47</sup> In a third study, low serum levels of zinc and iron were corrected prior to commencing the trial.<sup>38</sup>

#### Metabolic status

Diabetic patients have impaired glucose metabolism, which may result in delayed wound healing.<sup>79</sup> Studies sometimes report the type and duration of diabetes,<sup>6</sup> but individual differences in glycaemic control may confound findings, and this is not accounted for in the reporting of trials.

Diabetic patients who experience sensory loss through neuropathy are at greater risk of incurring new wounds and of inflicting further damage to existing ones. Therefore it is important to report the baseline prevalence of neuropathy in diabetic study groups. One of the three studies of diabetic foot ulcers included in this review reported this variable at baseline.<sup>24</sup>



### Immunocompetence

Patients with compromised immune systems have a diminished capacity for wound healing.<sup>80</sup> No data relating to baseline immunocompetence were reported in any of the included studies. However, immune-system depression was a criterion for exclusion in one case.<sup>6</sup>

### Vascular disease

Both venous and arterial insufficiency can impair healing due to the impeded supply of oxygen and nutrients to local tissue. Chronic leg ulcers may be caused by mixed arterial and venous insufficiency.<sup>80</sup> Of the seven trials of wounds of mixed aetiologies included in this review,<sup>38–43,45</sup> six recruited patients with leg ulcers.<sup>38–43</sup> Of these six, four reported the relative frequencies of venous and arterial insufficiency at baseline.<sup>38,40,42,43</sup> One study reported descriptively that venous disease was more common than arterial disease; however, numbers of patients were not provided.<sup>39</sup> It was also noted that this information related to a larger cohort, from which the comparative study group was sampled, and it is unclear to what extent the same information applied to the smaller group.<sup>39</sup> In the remaining study, the aetiologies of leg ulcers were not specified.<sup>41</sup>

### Level of mobility

Low levels of mobility are a risk factor for chronic wounds, especially those arising from pressure damage.<sup>81,82</sup> Three studies in this review provided details of levels of mobility at baseline for patients with, or at risk of developing, pressure ulcers.<sup>30–32</sup> Baseline data were also given in one study of diabetic patients<sup>24</sup> and in one study of venous leg ulcers.<sup>36</sup>

A related issue concerns the concurrent use of pressure-relief surfaces with topical applications for pressure ulcers. Results from another review in this series have shown that the use of such surfaces may be useful.<sup>55</sup> Of the seven trials involving pressure ulcers included in this review,<sup>29–32,41,45,47</sup> only one provided details of the use of concomitant therapy to relieve pressure.<sup>30</sup>

### Contenance

Faecal incontinence is a risk factor for the development of pressure ulcers.<sup>81–84</sup> Incontinence rates were reported in one paper on pressure ulcers.<sup>30</sup>

### Outcome assessment in wound healing trials

The primary outcome for this review was wound healing (or the incidence of new lesions for

prevention studies). Several methods are available to assess healing. The measurements of most interest were frequency of complete healing and mean change in ulcer size.

### Complete healing

The frequency, or rate, of complete healing is the proportion of participants achieving complete healing (in most studies this means lesion closure) relative to the total number in the treatment arm. Between-group comparisons are then made by looking for statistically significant differences between the proportions of healed lesions in each arm. While this can be a useful measure, the choice of follow-up time may influence outcomes, as complete healing is more likely to occur with longer follow-up, even in the absence of an intervention. Some studies resolved this issue through survival analysis. This involves the estimate, by regression, of the time taken for all ulcers to heal beyond the follow-up period, and is most reliable when it takes account of both frequency of healing and rate of healing.<sup>85</sup> None of the trials included in this review included survival analysis.

If time to healing is chosen as the primary outcome, a group that has a predominance of smaller ulcers is more likely to achieve better results, because larger ulcers take longer to close.<sup>86</sup> It is therefore important to match groups for ulcer size by using baseline wound size as a stratification variable.<sup>35,86</sup>

Other difficulties involve subjectivity of measurement and different definitions of complete healing. Subjectivity may be involved in the judgement of whether complete healing has occurred, and inter-rater reliability may be poor, even when assessors are experienced in wound management. Using definitions of complete healing per patient, per limb and per wound may give different results in cases where patients have more than one wound included in the study.

### Mean change in ulcer size

A between-group comparison of the mean change in ulcer size relative to baseline was used as an outcome in many of the included studies. The ulcer outline may be traced directly onto paper or acetate, or a photograph or slide may be used. If photographs or slides are used, the image can be calibrated by placing a centimetre scale at the side of the wound. The area within the tracing can then be calculated by counting grids on graph paper, weighing uniform-density tracing paper, planimetry or by using computerised image

analysis. Techniques such as computerised image analysis or the use of digitisers are not yet readily available.<sup>80</sup>

A comparison of different methods of wound measurement showed that direct acetate tracing produced more accurate wound measurement compared with photography combined with computerised image analysis.<sup>87</sup> Another study showed that the planimetric area of ulcers determined from photography used with a computerised ultrasonic digitiser correlates well with the product of two maximal perpendicular diameters of a wound. The latter is a more accurate measurement when a formula for calculating the area of an ellipse, rather than a rectangle, is used.<sup>86</sup>

One included study assessed the rate of reduction of ulcer area via planimetry with a millimetre grid, then transformed this into a circle area.<sup>6</sup> Changes in the circle radius (mm/day) over time were calculated, and taken to represent changes in ulcer surface area. This is a more reliable method of measurement than the change in ulcer area, because it estimates the linear healing rate of the ulcer over time through a one-dimensional measure and is independent of baseline ulcer size.

### Assessment of wound volume

Assessment of wound volume is important for deeper lesions, such as pressure ulcers, pilonidal sinuses and cavity wounds. However, three-dimensional assessments of wounds are rarely reported, perhaps because of the operational difficulties involved in measurement. Only one study included in this review reported a measurement of baseline wound volume, in patients with pilonidal sinuses. However, no details were provided about the techniques used.<sup>28</sup>

Several methods of assessing volume are available. These include three-dimensional probing and measurement, filling wound cavities with fluids, taking impressions using dental materials, stereophotogrammetry, ultrasonic surface scanners and structured light.<sup>21</sup>

The use of fluids to assess wound volume involves covering the wound with a semipermeable film dressing and injecting sterile water or saline into the space. The fluid is then drawn back and the volume measured from the syringe.<sup>21</sup> This method of measurement was used in a trial of ascorbic acid and ultrasound in the treatment of pressure ulcers. Leaking occurred in some cases, which influenced the accuracy of the measurements.<sup>88</sup>

Dental impression materials based on alginates<sup>89</sup> or silicon rubber<sup>90</sup> may also be used to calculate volume. Moulds can be weighed and the volume calculated, and the moulds can be helpful in providing a visual image of the shape of the wound.<sup>91</sup>

Stereophotogrammetry (or stereophotography) is a remote method of measurement using photography in conjunction with computerised data analysis. A three-dimensional image is produced from two photographs taken simultaneously from different angles.<sup>92</sup> Other sophisticated methods include ultrasonic surface scanners and structured light. Although these techniques are considered to be accurate, the equipment is expensive and specialised skills are required for their use, factors that are likely to limit access to them in many clinical areas.<sup>21</sup> Other practical issues to consider are the space required for the equipment and the fact that some patients may experience discomfort when lying with the wound exposed for some time while the photographs are being taken.

### Bias arising from ulcer size

Unless treatment groups are matched at baseline for ulcer size, bias may render results unreliable. This is because a group containing many smaller ulcers, which are likely to heal quickly, will be favoured if complete healing and time to healing are selected as study end-points. Groups with a predominance of small ulcers are also likely to achieve better treatment outcomes if the primary outcome is the percentage change in ulcer area. Conversely, a patient group with mainly large ulcers will appear to produce better healing outcomes if absolute change in ulcer area healed is the outcome of interest.<sup>86,93</sup> In evaluations of pressure ulcers, pilonidal sinuses and cavity wounds, the baseline comparability of wound volume should also be considered.

### Outcome measurement in included trials of pilonidal sinuses

The outcome measures used in trials of pilonidal sinuses differ from those seen in other studies of chronic wound management, because interventions are based on surgery. The fact that secondary or revisional surgery is often necessary in these patients, due to abscess formation or recurrence of disease, means that both primary and secondary healing rates should be reported. In addition to this, time to healing, complications of surgery and recurrence of disease are all outcomes of interest. Primary and secondary healing rates were reported in two studies,<sup>16,26</sup> time to healing was reported in

five studies,<sup>16,25,27,28,44</sup> complications of surgery in one study<sup>25</sup> and recurrence of disease in one study.<sup>16</sup>

### Outcome assessment in included trials of pressure ulcers

Four trials used a rating scale to assess skin condition, which could be prone to variation in interpretation between individual assessors.<sup>29–32</sup> One of the studies also assessed complete healing and time to healing,<sup>29</sup> and another based grading classification on measurement of ulcer area;<sup>31</sup> however, this was not described in detail. If researchers choose this type of rating scale, then the measurements should be independently verified by another observer and inter-rater reliability checks should be carried out. In two trials of wounds of mixed aetiologies that included pressure ulcers, complete healing was the primary outcome,<sup>41,45</sup> and in one case this was part of a more detailed skin grading system.<sup>45</sup> The final paper in this category reported the mean percentage change in baseline wound area per group as the primary outcome.<sup>47</sup>

### Outcome assessment in other included trials

Eleven studies included an objective measurement of ulcer area, which involved a tracing of the wound perimeter,<sup>5,6,10,12,33–38,40</sup> and six went on to calculate the ulcer area by planimetry.<sup>6,33–35,37,38</sup> One study reported the use of planimetry, but did not mention tracing the wound area prior to this.<sup>46</sup> In four studies, the traced area was cut out and the paper weighed.<sup>5,10,12,36</sup>

One study assessed ulcer size by multiplying the maximum length and width of the wound together and then graded the ulcer according to whether it had completely or partially healed.<sup>7</sup> This method of measurement has potential for bias from the subjective judgement involved in deciding the location of the maximum wound dimensions. An additional problem is that the product of the two measurements equates to the area of a rectangle, which is likely to be an overestimation of the wound area.<sup>86</sup>

Three studies did not present an objective assessment of change in ulcer area, but used frequency of complete healing as the primary outcome,<sup>24,42,43</sup> and one study used time to complete healing as the primary outcome.<sup>39</sup>

### Baseline comparability of groups

In evaluations of interventions for wound care, ulcer size is an important baseline variable. It is

likely that estimates from trials incorporating groups poorly matched for ulcer size at baseline will be biased because groups may predominantly include smaller or larger lesions. Larger RCTs (where randomisation is adequate) are more likely to produce comparability than are smaller trials, where groups may be non-equivalent by chance. However, a predominance of large or small wounds in a trial of any size will produce bias. Although the use of matched pairs or stratified randomisation helps to reduce bias, this review has identified that most studies in this area do not utilise such techniques.

Most of the included studies reported some sort of baseline data on wound size (not an appropriate assessment for pilonidal sinuses or pressure ulcer prevention).<sup>5,6,10,12,29,33–37,39,40,42,43,46,47</sup> However, only two took steps to help ensure comparability of treatment groups with respect to this variable.<sup>33,35</sup> In one study, a subset of matched pairs was selected for analysis, paired according to baseline ulcer area.<sup>35</sup> The other study incorporated stratified randomisation according to two categories of baseline ulcer size.<sup>33</sup> Another study did not stratify at baseline, but carried out stratified analysis with reference to two different levels of baseline pressure ulcer severity.<sup>29</sup> In one RCT, the possible difficulties of having two larger ulcers (wound area greater than 50 cm<sup>2</sup>) in the experimental group were highlighted.<sup>47</sup> The authors recommended better baseline matching for wound area in subsequent trials.

Since average baseline estimates of wound size within groups can mask the true distribution, and therefore heterogeneity, between groups, more detailed data on the relative frequencies of different categories of wound size per group are required. Other characteristics are also important, including aetiology (in trials of mixed wounds) and duration of wound. Demographic variables such as age, gender and ethnicity should also be reported. Likewise, details relating to the prevalence of factors known to influence wound healing should be provided. This has been discussed in more detail earlier in this chapter.

For certain types of chronic wound, such as pilonidal sinuses, baseline area is an inappropriate measure. In such trials detailed information should be given relating to the frequency of previous surgery and the associated recurrence of disease, the number of sinuses per patient, the location of the sinuses, the duration of disease, obesity and an estimate of hair growth. For studies of pressure ulcer prevention, an assessment of risk should be reported (e.g. Norton risk scale).

## Adverse events

Thirteen of the 30 trials included in this review reported data on adverse effects associated with treatments.<sup>6,7,10,16,30,31,36,38,41–43,45,47</sup> It is important that future research addresses this issue, as the incidence of adverse events may impact on the extent to which patients feel able to adhere with treatment regimens. In particular, localised skin reactions may be a problem for people using topical preparations, and gastrointestinal disturbances may occur with the administration of some systemic agents. Clindamycin should be withdrawn immediately in any patient developing diarrhoea.<sup>17</sup>

## Wound microbiology and healing

### Bacterial eradication and wound healing

The relationship between bacterial colonisation and wound healing remains unclear.<sup>1–4,94</sup> Although it has been proposed that higher bacterial counts may be associated with failure to heal,<sup>1,2,12</sup> some sources suggest that the presence of bacteria is unimportant.<sup>3,4</sup> However, other findings indicate that the presence of four or more bacterial groups may be associated with delayed healing.<sup>95</sup>

Results from some studies suggest that the presence of specific micro-organisms may be detrimental to wound healing. These include  $\beta$ -haemolytic streptococci and *Staph. aureus* in leg ulcers<sup>2</sup> and *Proteus mirabilis* and *P. aeruginosa* in pressure ulcers.<sup>96</sup> For chronic pilonidal disease, an association has been shown between the presence of *Bacteroides* species in sinuses and failure to heal following surgical excision.<sup>97</sup>

Different types of dressing may influence bacterial colonisation. Bacterial proliferation has been shown to be significantly lower under occlusive dressings, in cases where the use of such dressings was also associated with significantly better wound healing compared with gauze.<sup>94,98,99</sup>

### Culture methods

The research in the area of culture methods is difficult to interpret because of the variation in the sampling methods used for cultures. Results from specimens obtained by curettage or needle aspiration do not always match those obtained from superficial swabs,<sup>8,100</sup> and deep tissue cultures are thought to provide a more accurate bacterial profile compared to swabs of the wound surface.<sup>101</sup> Many sampling errors are associated with taking, transporting and plating out swabs.<sup>95</sup>

## Infection versus colonisation

Some of the variation in the study results may be due to the included trials not sharing common criteria for selecting participants on the basis of whether wounds were infected or colonised at baseline. Many included studies did not report any data relating to this variable.

In two studies the presence of signs of clinical infection was an inclusion criterion,<sup>7,16</sup> and in a further two infected wounds could be included, but results were not stratified according to the presence of baseline infection.<sup>24,39</sup> In two cases, the presence of clinical infection was an exclusion criterion,<sup>12,36</sup> and in another patients received a topical regimen designed to resolve signs of infection prior to treatment allocation.<sup>40</sup> For studies of pilonidal sinuses, presence of discharge was an inclusion criterion in one case,<sup>16</sup> in another the presence of acute abscesses was an exclusion criterion<sup>25</sup> and in a third any abscesses present at baseline had to be lanced prior to treatment.<sup>26</sup>

Several other studies specified selection criteria in connection with the bacterial colonisation (as opposed to clinical infection) of wounds at baseline. For three trials, positive bacterial wound surface cultures at baseline comprised a participant inclusion criterion.<sup>6,12,43</sup> For a fourth trial, eligible patients had pressure ulcers contaminated with MRSA during the month prior to the trial.<sup>47</sup> In another study, all ulcers were contaminated at baseline, but this was not specified as an inclusion criterion.<sup>10</sup> In another case, patients having more than  $10^5$  bacteria per gram of ulcer tissue detected by biopsy of lesion were excluded.<sup>33</sup>

Other studies did not mention the presence of infection or colonisation as selection criteria for participants.<sup>5,27–29,31,34,35,37,38,41,42,44–46</sup> However, in one of these studies, patients developing infected lesions during the trial period were withdrawn.<sup>46</sup>

Given this variation in selection criteria across the included studies, and given the differences between studies in other participant characteristics, wound types, interventions and outcome measurements, it is difficult to identify a pattern of healing and effectiveness of interventions in relation to presence of infection or colonisation at baseline. This could only be assessed if a group of more homogenous studies were available. A further difficulty with interpretation of results occurred in two studies where participants were allowed to receive additional antimicrobial agents, if required, during the study period.<sup>32,43</sup>



Four trials of venous leg ulcers included subgroup analyses in order to assess the impact of wound infection or bacterial colonisation on healing.<sup>5,10,12,36</sup> In one case, results indicated that ulcer infection had a significantly detrimental effect on healing.<sup>36</sup> For bacterial colonisation, one study showed a statistically significant association between positive post-treatment wound cultures and lower healing rates,<sup>12</sup> but other analyses suggested that bacterial contamination of ulcers (specifically *Staph. aureus* in one case)<sup>5</sup> did not appear to delay healing.<sup>5,10</sup> In an additional study of pressure ulcers, the presence of MRSA was significantly associated with a smaller reduction in baseline wound area at 14 weeks.<sup>47</sup> However, these results were not presented according to treatment arm. It should be noted that the numbers used for the analysis in each of these cases were small, and therefore these findings should be interpreted with caution.

Future studies should make inclusion and exclusion criteria clear with reference to infection and colonisation of wounds. In trials where the presence of infection does not exclude patients, the numbers of patients with and without the clinical signs of infection should be reported at baseline, and groups should be comparable for infection rates and types.

There do not appear to be universally accepted definitions of colonisation and infection within the literature. Colonisation may be defined as the multiplication of organisms in wounds, reaching numbers as high as  $10^6$  bacteria per gram of tissue, while the diagnosis of clinical infection also requires the presence of high bacterial counts,<sup>13,102</sup> and additionally the presence of local heat, redness, pain, swelling and purulence.<sup>102</sup> However, it is unclear to what extent these definitions may be reliably applied to chronic wounds. Many sources now recommend that the use of systemic antimicrobials in simple colonisation is inappropriate, and that they should be reserved for cases of clinically apparent infection, such as cellulitis.<sup>8,17,71,103</sup>

### Do antibiotics effectively reduce bacterial count?

There is uncertainty as to whether antimicrobials effectively reduce bacterial counts in wounds with identified colonisation.<sup>15,104</sup> One reason for this could be that therapeutic doses of systemic agents cannot easily reach affected areas in patients who have a poor local vascular supply. This implies a need for antimicrobials to be given in very large doses, which may pose problems with adverse effects.<sup>105</sup> One possible solution is to administer

antibiotics via venous retrograde perfusion, where the dose of an intravenous antibiotic is concentrated within the lower extremities by the use of tourniquets.<sup>106</sup> However, this method has yet to be evaluated in a well-controlled trial incorporating objective wound-healing outcomes.

The ability of certain topical agents to reduce bacterial count has also been questioned. In cases where lotions are used for wound cleansing only, it is possible that the product is not in contact with the wound for a sufficient length of time to exert any antimicrobial action. In addition, organic matter such as blood or pus is believed to inactivate the antibacterial effects of some preparations, such as chlorhexidine<sup>58</sup> and the hypochlorites.<sup>61</sup>

A further problem is that some topical agents may have more than one mode of action, and therefore it may be unclear whether to attribute an effect to the antimicrobial mechanism of the product. The results of one study included in this review showed that silver sulphadiazine proved to be significantly more effective than either placebo or a growth factor in terms of percentage decrease in ulcer size, in patients with venous leg ulcers.<sup>33</sup> Since a bacterial count of more than  $10^5$  bacteria per gram of ulcer tissue was an exclusion criterion for participants, the authors suggested that the healing action of silver sulphadiazine may have been due to promotion of epithelialisation rather than to an antimicrobial effect. Another example is iodine, where wound healing may arise from its antimicrobial action or other properties, such as the control of exudate and eschar.<sup>54</sup> Further research is required to establish more accurately the mechanism of action of topical applications in chronic wounds.

### Bacterial resistance

There is much concern about the development of resistance of micro-organisms to systemic antimicrobials, notorious examples being *Staph. aureus* and *P. aeruginosa*, both of which are common wound isolates. Bacterial resistance can come about in several ways. Micro-organisms vary in their sensitivity to antibiotics, especially penicillins, and the less sensitive bacteria will either survive or require larger doses for eradication. Another factor is the production of enzymes by certain bacteria (e.g. penicillinase, which can inactivate penicillin). Resistance to one antibiotic may be related to resistance to related products (e.g. the well-known cross-resistance between penicillin and the cephalosporins). However, some semisynthetic penicillins are not inactivated by such enzymes and so remain active against

penicillin-resistant organisms. Alternatively, micro-organisms may develop resistance by the transfer of genetic material between bacteria. This is thought to be the method by which many strains of *Staph. aureus* have acquired resistance.<sup>107</sup>

Resistance may occur through the inappropriate use of antibiotics for minor infections, or the use of broad-spectrum agents before the sensitivity of the invading organisms has been identified. This has led many hospitals to develop an antibiotics policy so that the indiscriminate use of these drugs is avoided.<sup>107</sup> This may have important implications for clinical audit, whereby prescribing standards and criteria may be monitored in order to identify inappropriate use of these drugs. Such policies could also be applied to the use of topical agents.

As with systemic agents, there is concern about the misuse of topical agents,<sup>108</sup> and bacterial resistance has occurred with longer term use of topical antibiotics. Current recommendations state that such agents should not be used for chronic wounds, such as leg ulcers, except in cases of defined infection, and that their prescription for bacterial colonisation is inappropriate.<sup>17</sup>

## Cost-effectiveness

The costs of wound care may be direct or indirect. Direct costs include costs of supplies, dressings, cleansing agents, topical applications, surgical interventions, medications, related investigations, inpatient care, formal and informal care-giver time, travel by care-giver or patient and disposal of wound-care material. Indirect costs include assistance with activities of daily living and the effects of days lost from work.<sup>109</sup>

There are very few data on the cost-effectiveness of antimicrobial agents in wound healing. Cost-effectiveness studies should be carried out in conjunction with rigorous evaluations of clinical effectiveness in order to determine the relative difference between the cost per unit of the clinical effects of two or more treatments. A cost-effectiveness or cost-utility analysis should include both a measure of the clinical benefit from a non-biased study, and a measure of the net resources used.<sup>110</sup> Data should be collected relating to both short- and long-term patterns of wound healing and recurrence.

Information from six studies included in this review suggests that certain treatments may be associated with reduced nurse labour time, but further research is required to establish this more reliably.<sup>16,24,27,28,31,41</sup> Hydrogel and hydrocolloid dressings require significantly fewer changes than do dressings using conventional antiseptics and wound coverings.<sup>24,31,41</sup> For two studies, there were equivalent results in terms of clinical effectiveness (wound healing),<sup>31,41</sup> but in a third the hydrogel dressing produced significantly greater healing rates compared with chlorhexidine combined with various antimicrobials.<sup>24</sup> For pilonidal sinuses, primary closure was associated with less need for community nurse care, and with significantly shorter healing times, compared with excision only (and healing by secondary intention).<sup>16</sup> In two other studies, the use of a postoperative silastic foam dressing was associated with less nursing labour time compared with a Eusol pack<sup>27</sup> and a chlorhexidine pack.<sup>28</sup> In both cases, clinical effectiveness (time to healing and length of hospital stay) were similar between the experimental and control regimens.



# Chapter 5

## Conclusions

### Clinical practice

At present, there is no existing evidence to support the routine use of systemic antimicrobial agents to promote healing in chronic wounds. However, the lack of reliable evidence means that it is not possible to recommend the discontinuation of any of the agents reviewed. It is possible that metronidazole may be effective following excision of pilonidal sinuses;<sup>44</sup> however, more rigorous evaluation is needed.

Several topical agents gave promising results in small studies, including dimethyl sulphoxide in venous leg ulcers.<sup>36</sup> There is conflicting evidence for the use of silver-based products in venous leg ulcers,<sup>10,33,37,39</sup> and for benzoyl peroxide in leg ulcers of mixed aetiologies.<sup>38,40</sup> Oxyquinoline ointment may help to heal stage I (erythema) and stage II (superficial breakdown) pressure ulcers,<sup>29</sup> but a hydrogel dressing was more effective than chlorhexidine plus other antimicrobials for diabetic foot ulcers.<sup>24</sup> Topical gentamicin may promote postoperative healing in pilonidal sinuses.<sup>26</sup> Again, further research is required before definitive conclusions can be made about the effectiveness of these products in chronic wound healing.

### Future research

Many of the results summarised in this review are based on findings from small trials with methodological problems. Therefore, much of the research requires replication in larger, well-designed studies. Future research should pay attention to the following: clearly defined and reported inclusion and exclusion criteria for participants, sample size with sufficient power to detect true treatment effects, clear reporting of *a priori* power calculations, use of true randomisation with allocation concealment (e.g. opaque, sequentially numbered sealed envelopes, computer-generated codes), clear reporting of the method of

randomisation, measures to help ensure comparability of treatment arms at baseline (e.g. stratification for ulcer size), detailed reporting of baseline characteristics (including underlying factors that may affect healing), blinded outcome assessment, use of objective outcome measurement and appropriate methods for data analysis (e.g. ulcer area, complete healing rates, survival analysis), use of the intention-to-treat protocol, incidence of adverse events, and detailed reporting of the numbers and characteristics of withdrawals from the treatment group.

Further research is required to clarify the relationship between healing and the colonisation or infection of wounds, and to clarify these definitions in terms of chronic wounds. Attention should also be paid to the potential development of resistance to antimicrobial agents, and follow-up should include an assessment of this. The mechanism of action of certain agents, such as silver sulphadiazine, needs elucidation. Future research should include detailed reporting of concomitant interventions, as these can exert important effects on healing. These include compression therapy in venous leg ulcers, pressure relief in pressure ulcers and different techniques for the excision, closure, debridement and packing in patients with pilonidal sinuses. As well as detailed descriptions of these interventions, it may be useful to evaluate their effectiveness both relative to, and combined with, antimicrobial agents. It would also be useful to carry out further comparisons between antimicrobials and occlusive dressings, such as the hydrocolloids, in order to evaluate both the relative effectiveness and the cost-effectiveness. The cost-effectiveness of both systemic and topical antimicrobials also needs to be established, taking into account the patterns of healing and recurrence that can occur with chronic wounds. Finally, it is important that future research includes both comparisons between antimicrobial agents and placebo, and comparisons involving combinations with other treatment strategies, since this is more likely to accurately reflect clinical practice.







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# Appendix I

## Databases searched and search strategies

### Databases searched

- ISI Science Citation Index (on BIDS)
- BIOSIS (on Silver Platter)
- British Diabetic Association Database (BDAD)
- CINAHL (on OVID CD-ROM)
- CISCOM, the database of the Research Council for Complementary Medicine
- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Wounds Group developing database
- Current Research in Britain (CRIB)
- Database of Abstracts of Reviews of Effectiveness (DARE) (NHS Centre for Reviews and Dissemination)
- Dissertation Abstracts
- DHSS Data (on Knight-Ridder Datastar)
- EconLit
- EMBASE (on Knight-Ridder Datastar)
- Index to Scientific and Technical Proceedings (searched on BIDS)
- MEDLINE (on OVID CD-ROM)
- NHS Economic Evaluation Database (NHS Centre for Reviews and Dissemination)
- Royal College of Nursing Database (CD-ROM)
- System for Information on Grey Literature in Europe (SIGLE – on Blaise Line)
- National Research Register

### MEDLINE search strategy

The MEDLINE search strategy used was as follows:

1. decubitus ulcer/ or foot ulcer/
2. leg ulcer/ or varicose ulcer/
3. pilonidal cyst/
4. skin ulcer/
5. diabetic foot/
6. ((plantar or diabetic or heel or venous or stasis or arterial) adj. Ulcer).tw.
7. ((decubitus or foot or diabetic or ischaemic or pressure) adj. Ulcer).two.
8. ((pressure or bed) adj. sore\$).tw.
9. ((pilonidal adj. cyst) or (pilonidal adj. sinus) or bedsore\$).tw.
10. ((diabetic adj foot) or (cavity adj wound)).tw.
11. ((varicose or leg or skin) adj ulcer\$).tw.
12. (decubitus or (chronic adj wound\$)).tw.
13. ((sinus adj wound\$) or (cavity adj wound\$)).tw.
14. or/1–13
15. debridement/ or biological dressings/ or bandages/
16. occlusive dressings/ or clothing/ or wound healing/
17. antibiotics/ or growth substances/ or platelet-derived growth factor/
18. fibroblast growth factor/ or electrical stimulation therapy.ti,ab,sh.
19. lasers/ or nutrition/ or surgery/ or surgery, plastic/
20. surgical flaps/ or skin transplantation/ or homeopathy/ or homeopathic/
21. acupuncture therapy/ or acupuncture/ or alternative medicine/
22. alternative medicine/ or massage/ or iloprost/ or alginates
23. zinc/ or zinc oxide/ or ointments/ or anti-infective agents/
24. dermatologic agents/ or colloids/ or cushions/ or wheelchairs/
25. beds/or wound dressings/
26. (debridement or dressing\$ or compress\$ or cream\$ or (growth adj factor\$)).tw.
27. (pressure-relie\$ or (recombinant adj protein\$) or bandag\$ or stocking\$).tw.
28. (antibiotic\$ or (electric adj therapy) or laser\$ or nutrition\$ or surg\$).tw.
29. (homeopath\$ or acupuncture or massage or reflexology or ultrasound).tw.
30. (iloprost or alginate\$ or zinc or paste\$ or ointment\$ or hydrocolloid\$).tw.
31. ((compression adj therapy) or (compression adj bandag\$) or wrap\$).tw.
32. (bed\$ or mattress\$ or wheelchair\$ or (wheel adj chair) or cushion\$).tw.
33. ((wound adj dressing\$) or vitamin\$ or bind\$ or gauze\$ or heals or healing).tw.
34. (diet or lotion\$ or infect\$ or reduc\$ or (wound adj healing)).tw.
35. (treat\$ or prevent\$ or epidemiol\$ or aetiol\$ or etiol\$ or therap\$ or prevalence or incidence).tw.
36. or/15–33
37. 14 and 36
38. random allocation/ or randomized controlled trials/

39. controlled clinical trials/ or clinical trials phase I/ or clinical trials phase II/
40. clinical trials phase III/ or clinical trials phase IV; or clinical trials overviews/
41. single-blind method/ or double-blind method/
42. publication bias/ or review/ or review, academic/
43. review tutorial/ or meta-analysis/ or systematic review/
44. ((random\$ adj controlled adj trial\$) or (prospective adj random\$)).tw.
45. ((random adj allocation) or random\$ or (clinical adj trial\$) or control\$).tw.
46. ((standard adj treatment) or compar\$ or single-blind\$ or double-blind\$).tw.
47. (blind\$ or placebo\$ or systematic\$ or (systematic adj review)).tw.
48. (randomised controlled trial or clinical trial).pt. or comparative study.tg.
49. or/38-48
50. 37-49
51. limit 50 to human
52. burns/ or wounds, gunshot/ or corneal ulcer/ or exp dentistry/
53. peptic ulcer/ or duodenal ulcer/ or stomach ulcer/
54. ((peptic adj ulcer) or (duodenal adj ulcer) or traum\$).tw.
55. ((aortocaval adj fistula) or (arteriovenous adj fistula)).tw.
56. (bite adj wound\$).tw.
57. or/52-56
58. 51 not 57

### CINAHL search strategy

1. pressure ulcer/ or foot ulcer/ or leg ulcer/ or skin ulcer/
2. diabetic foot/ or diabetic neuropathies/
3. diabetic angiopathies/ or diabetes mellitus/co
4. pilonidal cyst/ or surgical wound infection/
5. ((plantar or diabetic or heel or venous or stasis or arterial) adj. Ulcer).tw.
6. ((decubitus or foot or diabetic or ischaemic or pressure) adj. Ulcer).tw.
7. ((pressure or bed) adj. sore\$).tw.
8. ((pilonidal adj. cyst) or (pilonidal adj. sinus) or bedsore\$).tw.
9. ((diabetic adj foot) or (cavity adj wound)).tw.
10. ((varicose or leg or skin) adj ulcer\$).tw.
11. ((decubitus or (chronic adj wound\$)).tw.
12. ((sinus adj wound\$) or (cavity adj wound\$)).tw.
13. or/1-12
14. debridement/ or biological dressings/ or occlusive dressings/
15. (bandages.ti,sh,ab,it. and 'Bandages and Dressings'/) or compression garments/ or antibiotics/
16. electrical stimulation/ or Laser Surgery/ or lasers/th
17. lasers/ or Nutrition Care (Saba HHCC)/ or diet therapy/ or Nutrition Therapy (Iowa NIC)/
18. surgery, reconstructive/ or surgery, plastic/ or surgical flaps/
19. surgical stapling/ or skin transplantation/ or alternative therapies
20. acupuncture / or massage/ or zinc/ or ointments/
21. antiinfective agents, local/ or antibiotics/ or dermatologic agents/
22. dermatology nursing/ or colloids/ or beds and mattresses/
23. flotation beds/or wheelchairs/ or positioning: wheelchair/ or positioning:therapy/
24. patient positioning/ or positioning/ or wound care/ or wound healing/
25. (debridement or dressing\$ or compress\$ or cream\$).tw.
26. ((growth adj factor\$) or pressure relie\$ or (recombinant adj protein\$) or bandag\$).tw.
27. (stocking\$ or antibiotic\$ or (electric adj therapy) or laser\$ or nutrition\$ or surg\$).tw.
28. (iloprost or alginate\$ or zinc or paste\$ or ointment\$ or hydrocolloid\$).tw.
29. ((compression adj therapy) or (compression adj bandag\$) or wrap\$).tw.
30. (bed\$ or mattress\$ or wheelchair\$ or (wheel adj chair) or cushion\$).tw.
31. ((wound adj dressing\$) or vitamin\$ or bind\$ or gauze\$ or heals or healing).tw.
32. (diet or lotion\$ or infect\$ or reduc\$ or etiol\$ (wound adj healing)).tw.
33. (treat\$ or prevent\$ or epidemiol\$ or aetiol\$ or therap\$ or prevalence or incidence).tw.
34. 'Bandages and Dressings'/ or skin transplantation/ or homeopathy/ or ointment/ or 'beds and mattresses'/
35. or/14-34
36. 13 and 35
37. clinical trials/ or single-blind studies/ or double-blind studies/
38. control group/ or placebos/ or meta analysis/
39. ((random\$ adj clinical adj trial\$) or (prospective adj random\$)).tw.
40. ((random adj allocation) or random\$ or controlled clinical trial\$ or control).tw.
41. (comparison group\$ or (standard adj treatment) or compar\$).tw.

42. (single-blind\$ or (single adj blind) or double-blind or (double adj blind)).tw.
43. (blind\$ or placebo\$ or systematic or (systematic adj review)).tw.
44. (meta-analysis or meta-analysis).tw. or (trials or trial or prospective).tw.
45. (clinical trials).sh. or comparative studies.sh.
46. or/37-45
47. 36 and 46
48. burns/ or wounds, gunshot/ or corneal ulcer/ or exp dentistry/
49. peptic ulcer/ or duodenal ulcer/
50. ((peptic adj ulcer) or (duodenal adj ulcer) or trauma).tw.
51. (burn\$ or (gunshot adj wound\$) or (corneal adj ulcer) or dentist\$ or (bite adj wound)).tw.
52. or/48-51
53. 47 not 52

## Search terms for economic studies

Searches were based on the CRD Economic Search Strategy for MEDLINE. The search terms used were as follows:

exp Economics  
exp costs and cost analysis  
cost  
costs  
economics\*  
pharmacoeconomic\*  
cba  
cost benefit  
cea  
cost effectiveness  
cua  
health



## Appendix 2

### Advisory panel

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## Appendix 3

### Hand-searching

Several relevant nursing journals had already been hand-searched for RCTs, including the *Journal of Advanced Nursing* and the *International Journal of Nursing Studies*. In addition, the following are already indexed on MEDLINE or CINAHL: *Professional Nurse*, *Nursing Times* and the *Nursing Standard*. The following journals were hand-searched for relevant wound care studies:

- *CARE – Science and Practice*, 1979–1990
- *Decubitus*, 1987–present
- *Journal of Tissue Viability*, 1991–present
- *Journal of Wound Care*, 1991–present
- *Phlebology*, 1986–present.

In order to identify economic evaluations, bibliographic hand-searches were made of the following:

- *Health Economic Evaluation*, December 1992
- *Medical Care – Health Care Cost Benefit and Cost-Effectiveness Analysis*, 1979–1990.

- *Spilker's International Bibliography of Health Economics*, 1986
- *Department of Health Register of Cost-effectiveness Studies*, 1994.

The following conference proceedings were also hand-searched for references to trials. Where references were identified, authors were contacted to request a full report.

- 1st–5th European Conferences on Advances in Wound Management, 1991–1995
- 3rd–5th Annual Symposia on Advanced Wound Care, 1990–1992
- 1996 Symposium on Advanced Wound Care & Medical Research Forum on Wound Repair
- Going into the '90s: The Pharmacist and Wound Care, 1992
- Second Joint British/Swedish Angiology Meeting, 1991
- Societas Phlebologica Scandinavia Symposium on Venous Leg Ulcers 1985.





# Appendix 4

## Notes on the figures

### Odds ratios

The OR is a method of expressing the effect of an intervention with reference to dichotomous (count) data (e.g. frequency of complete healing). It may be defined as the ratio of the odds of an event (such as healing) in the treatment group (e.g. antibiotics) compared to the odds of the event happening in the control group (e.g. placebo, standard care).<sup>111</sup> The most frequently reported outcome of this type relevant to this review is complete healing. Other outcomes include numbers of patients with: significant reduction in ulcer size,<sup>43</sup> deterioration in skin condition,<sup>30,32</sup> improved skin condition<sup>29,31</sup> and primary healing after surgery.<sup>16,26</sup> Where possible, individual ORs were calculated on an intention-to-treat basis. This means that, when full data from primary studies were reported, participants were analysed according to the group to which they were initially allocated, regardless of whether or not they withdrew, and missing patients were regarded as treatment failures in order to avoid overestimation of the treatment effect.

### Effect sizes

The ES is used to present data arising from the measurement of continuous variables (reduction in wound size, time to healing) and may be defined as the difference in mean outcomes of the treatment and control groups. For two studies reporting continuous variables, there were insufficient data to calculate effect sizes.<sup>27,40</sup>

### Pooling data

ORs and ESs are presented for each study where they were available. These estimates have not been combined to produce pooled or overall results, due to significant variation between studies with regard to participants, interventions and outcome assessment (see appendix 5 and chapter 3 for further details).

### Interpreting the figures

The individual study point estimate effects are represented by the black (ORs) or white (ESs)

squares. The horizontal lines on either side of these represent the associated 95% CIs. When a square is on (or near) the central line, treatment effects are estimated as equivalent (or almost equivalent) between groups. When squares are to the right of the central vertical line, the treatment is estimated as being superior to the control, and when squares appear to the left of the line, control treatments are superior to interventions. (The exception to this is in *Figure 13*, where the outcome of interest is deterioration in skin condition, in evaluations of pressure ulcer prevention.) However, only when squares and horizontal lines are clear of the central line can differences between groups be considered as statistically significant. In cases where the CI crosses the central line, this represents an estimated difference that could be due to chance. Wide CIs indicate greater uncertainty around the estimated effect, while narrower intervals suggest greater confidence and a more precise estimate. See the notes below for trials with three arms.<sup>5,16,33,36,38</sup>

### Trials with three arms

#### Figure 2

The three arms in the trial by Huovinen and co-workers<sup>5</sup> were: ciprofloxacin, trimethoprim and placebo. Since the estimates of the ORs were based on data entered in a 2 × 2 contingency table, only two arms can be compared at a time. The first two point estimates located to the right of the central line, with 95% CIs crossing the line, indicate that there is no statistically significant difference between ciprofloxacin and trimethoprim, or between ciprofloxacin and placebo. The third point estimate, located on the central line, shows that the effect of trimethoprim and placebo were virtually identical in terms of the number of ulcers healed.

#### Figure 4

The three arms in the trial by Salim<sup>36</sup> were: dimethyl sulphoxide, allopurinol and placebo. Each point estimate in the figure was derived from a comparison between two of the three study groups. The 'control' group in the comparison may be either those receiving placebo or those receiving allopurinol, depending on the

comparison being made. Similarly, the 'treatment' group may be either those receiving dimethyl sulphoxide or those receiving allopurinol.

### Figure 8

The three arms in the trial by Bishop and co-workers<sup>33</sup> were: silver sulphadiazine, tripeptide–copper complex and placebo. Since the estimates of the ORs were based on the data entered in a  $2 \times 2$  contingency table, only two arms can be compared at a time. Similarly, estimates of the ES were based on the comparison between the means of two groups. Therefore, each point estimate on the figure was derived from a comparison between two of the three study groups. The 'control' group in the comparison may be either those receiving placebo or those receiving tripeptide–copper complex, depending on the comparison being made. Similarly, the 'treatment' group may be either those receiving silver sulphadiazine or those receiving tripeptide–copper complex.

### Figure 11

The study by Beitner<sup>38</sup> was not a three-arm trial, but a study comprising three different comparisons. A

separate sample of patients was recruited for each comparison. Each patient had at least two leg ulcers and acted as their own control. The control regimen in each case was saline. The experimental regimens were benzoyl peroxide 20%, benzoyl peroxide 10% and benzoyl peroxide vehicle only. All lotions were used to impregnate a sponge, which was used as part of the ulcer dressing.

### Figure 18

The three arms in the study by Kronborg and co-workers<sup>16</sup> were: excision + suture + clindamycin, excision + suture and excision alone. Since the estimates of the ORs were based on data entered in a  $2 \times 2$  contingency table, only two arms could be compared at a time. The first two point estimates located to the left of the central line, with 95% CIs crossing the line, indicate that there is no statistically significant difference between excision + suture + clindamycin and excision alone or between excision + suture and excision alone. The third point estimate, located on the central line, shows that the effects of excision + suture + clindamycin and excision + suture were almost identical in terms of healing rates.

# **Appendix 5**

## Summary of included studies

TABLE 1 Venous leg ulcers: systemic agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>Alinovi, 1986,<sup>12</sup> Italy</p> <p><b>Study design:</b> RCT</p> <p><b>Method of randomisation:</b> Sealed envelopes</p> <p><b>Unit of allocation:</b> Legs (when several ulcers were present, the largest ulcer was selected for study)</p> <p><b>Sample size:</b> Sample size was established to detect a 25% difference in mean ulcer healing rates between the 2 groups, with an <math>\alpha</math> error of 0.05, and a <math>\beta</math> error of 0.20</p> <p><b>Objective outcomes:</b></p> <ol style="list-style-type: none"> <li>1. Mean ulcer healing rates (ulcer outline traced onto transparent paper, which was then cut out and weighed). Calculated as initial area minus post-treatment area, divided by initial area</li> <li>2. Frequency of complete healing at 20 days following bandaging</li> <li>3. Relationship between ulcer healing rates and bacteriological results</li> </ol> <p><b>Setting and length of treatment:</b> Support bandages applied in an</p>	<p><b>Inclusion criteria:</b> Patients referred to University of Parma Dermatology Department because of venous leg ulcers</p> <p><b>Exclusion criteria:</b> Patients with ulcers having the following characteristics: &lt; 1 month duration, clinical signs of infection, negative bacteriological cultures, non-venous main cause. In addition, patients with diabetes, severe liver or kidney disease, or arterial insufficiency, were excluded</p>	<p><b>I (n = 24/30 patients/legs):</b> Standard treatment consisting of: merbromin 2% solution applied to ulcer surface, beta-methasone dipropionate 0.05% cream applied to rest of leg, zinc oxide and ichthammol-impregnated gauze bandage wrapped around leg, and elastic support bandage applied from toes to knee with gradually decreasing pressure. The bandages remained in place for 20 days. In addition, a 10-day course of systemic antibiotics (co-trimoxazole, gentamicin or amikacin, given according to sensitivities) was prescribed. Doses and routes of administration of the antibiotics not specified</p> <p><b>C (n = 24/26 patients/legs):</b> Standard treatment only, no antibiotics</p>	<p><b>Gender (male/female):</b> I: 13/10 (1 unknown) C: 11/13</p> <p><b>Mean (range) age:</b> I: 69 (46–85) years C: 67 (46–81) years</p> <p><b>Mean <math>\pm</math> SD ulcer area:</b> I: 14.1 <math>\pm</math> 15.9 cm<sup>2</sup> C: 12.5 <math>\pm</math> 14.4 cm<sup>2</sup></p> <p><b>Mean <math>\pm</math> SD number of ulcers per leg:</b> I: 2.1 <math>\pm</math> 0.8 C: 2.3 <math>\pm</math> 2.0</p> <p><b>Mean <math>\pm</math> SD ulcer duration:</b> I: 10.4 <math>\pm</math> 8.9 months C: 11.7 <math>\pm</math> 12.6 months</p> <p><b>Deep/superficial ulcers:</b> I: 10/19 (1 unknown) C: 9/17</p> <p>Method of assessment not stated</p> <p><b>Sclerosis of base present/absent:</b> I: 14/15 (1 unknown) C: 11/15</p> <p>Method of assessment not stated.</p> <p><b>Bacteriology:</b> Cultures reported at baseline, and the two groups were reported to be comparable</p>	<p>Results at 20 days after application of bandages</p> <p><b>Mean <math>\pm</math> SD ulcer-healing rate:</b> I: 61.6 <math>\pm</math> 25.8% C: 57.2 <math>\pm</math> 29.3% (<math>p = 0.56</math>, <math>t</math>-test for unpaired data)</p> <p><b>Complete healing:</b> I: 5/30 (17%) C: 7/26 (27%)</p> <p><b>Relationship between ulcer-healing rate (mean <math>\pm</math> SD) and bacteriology:</b> I (<math>n = 24</math>): positive post-treatment culture, 42.1 <math>\pm</math> 11.9; negative post-treatment culture, 76.6 <math>\pm</math> 13.6; <math>p = 0.00003</math> C (<math>n = 19</math>): positive post-treatment culture, 44.8 <math>\pm</math> 31.8; negative post-treatment culture, 70.8 <math>\pm</math> 19.4; <math>p = 0.04</math> Ulcers that healed completely were excluded from this analysis</p> <p><b>Bacteriology:</b> Post-treatment cultures were reported</p>	<p>One patient (with one ulcer) in the antibiotics group withdrew because of inability to tolerate the compression bandages</p>	
C, control group; I, intervention groups						
						continued

TABLE 1 contd Venous leg ulcers: systemic agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>inpatient setting, patients were discharged the following day and assessed at 20 days</p> <p>Huovinen, 1994,<sup>5</sup> Finland</p> <p><b>Study design:</b> RCT (double blinded)</p> <p><b>Method of randomisation:</b> Not stated</p> <p><b>Unit of allocation:</b> Patients</p> <p><b>Sample size:</b> No <i>a priori</i> power calculation reported</p> <p><b>Objective outcomes:</b></p> <p>1. Ulcer area (ulcer outline traced onto Opsite, which was then cut out and weighed)</p> <p>2. Complete healing</p> <p>3. Microbiology: cultures and sensitivities assessed at baseline, and at 4-week intervals thereafter</p> <p><b>Setting and length of treatment:</b> Outpatients, dressings done at home. Study duration 16 weeks (drugs given for 12 weeks)</p>	<p><b>Inclusion criteria:</b></p> <p>Outpatients with venous leg ulcers of &gt; 3 months duration, without significant healing, aged ≥ 18 years, body weight &gt; 50 kg, no antimicrobial treatment for 2 weeks prior to the trial, no current warfarin or theophylline treatment, no allergy to the antimicrobial agents to be used, able to dress wounds either unaided or with assistance</p> <p><b>Exclusion criteria:</b></p> <p>Patients with arteriosclerotic ulcers</p>	<p><b>I1:</b> Ciprofloxacin 750 mg orally, twice daily (n = 12)</p> <p><b>I2:</b> Trimethoprim 160 mg orally, twice daily (n = 12)</p> <p><b>C:</b> Placebo orally, twice daily (n = 12)</p> <p>All patients were encouraged to dress ulcers using zinc ointment and an elastic bandage.</p>	<p>Data are for the 31/36 patients who completed the trial:</p> <p>Male/female 5/26</p> <p>Age range 38–90 years</p> <p><i>Staph. aureus</i> present in 26/31 (84%) ulcers</p> <p>Average (range) ulcer duration:</p> <p>I1: 72 (3–216) months</p> <p>I2: 67 (4–252) months</p> <p>C: 29 (3–96) months</p> <p>Average (range) ulcer area:</p> <p>I1: 53 (1–475) cm<sup>2</sup></p> <p>I2: 31 (1–145) cm<sup>2</sup></p> <p>C: 27 (1–154) cm<sup>2</sup></p>	<p>Analysis: Kruskal–Wallis test (continuous variables); Fisher's table test (nominal-scale data); Fisher's exact test (2 × 2 tables)</p> <p>Results at 16 weeks:</p> <p>Complete healing:</p> <p>I1: 5/12 (42%)</p> <p>I2: 3/9 (33%)</p> <p>C: 3/10 (30%) (not significant)</p> <p>Average (range) change in ulcer size, calculated as % of original size:</p> <p>I1: –75 (+15 to –100)</p> <p>I2: –35 (+70 to –100)</p> <p>C (excluding outlier): –70 (+35, –100) (not significant)</p> <p>C (including outlier): –20 (+200 to –100)</p> <p>Figures taken from graph</p> <p>Presence of <i>Staph. aureus</i> in ulcers remaining open at end of trial:</p> <p>I1: 1/7</p> <p>I2: 5/6</p> <p>C: 7/7</p> <p>(p = 0.03, I1 vs I2)</p> <p>(p = 0.004, I1 vs C)</p>	<p>I1: personal reasons, 1</p> <p>I2: adverse effects (rash, mild vertigo and nausea, chest pain), 3</p> <p>C: development of osteitis, 1</p>	<p>This was a pilot study. No follow-up study was identified</p> <p>Cost of 12 weeks' treatment:</p> <p>Ciprofloxacin US\$600</p> <p>Trimethoprim US\$120</p> <p>(Finnish study, published in a US journal)</p>
C, control group; I1, I2, intervention groups						

continued

**TABLE 1 contd** Venous leg ulcers: systemic agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
				<p>Ulcer healing was not dependent on eradication of <i>Staph. aureus</i></p> <p><i>Other results:</i> Other microbiological results were presented, particularly in connection with the high rate of resistance to the two active drugs</p>		

TABLE 2 Venous leg ulcers: topical agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>Pegum and Fegan, 1968.<sup>35</sup> Ireland</p> <p><b>Study design:</b> CCT</p> <p><b>Method of treatment allocation:</b> Alternate</p> <p><b>Unit of allocation:</b> Patients. Where patients had 2 ulcers, both were treated similarly</p> <p><b>Sample size:</b> No <i>a priori</i> power calculation reported</p> <p><b>Objective outcomes:</b></p> <ol style="list-style-type: none"> <li>Ulcer area (ulcer photographed and area calculated by planimetry). This used to calculate the healing quotient (HQ, defined as the mean rate of epithelialisation in mm<sup>2</sup>/day, calculated to the nearest 0.1 mm<sup>2</sup>/day). Assessments made every 2–3 weeks</li> <li>Time to complete healing (defined as epithelium covering entire area of the former ulcer)</li> </ol> <p><b>Setting and length of treatment:</b> Outpatients at the Varicose Vein Clinic at Sir Patrick Dun's Hospital, Dublin. Patients were followed up to complete healing</p>	<p><b>Inclusion criteria:</b> Women with venous leg ulcers</p> <p><b>Exclusion criteria:</b> Not stated</p>	<p><b>I (n = 17):</b> Polynoxylin paste applied to ulcer and surrounding skin, covered with sterile lint</p> <p><b>C (n = 17):</b> Ulcer dressed with sterile lint only</p> <p><b>All patients:</b> Treated as outpatients using compression sclerotherapy (injection of a sclerosant at the sites of junction of incompetent perforating veins with the superficial veins, plus continuous compression at the injection sites using rubber pads, crepe bandages and elastic stockings; this maintained for at least 6 weeks). Each patient was instructed to walk for an hour outside every day and to avoid standing still. Obese patients were given a reducing diet</p>	<p>82/85 (patients/ulcers) entered the trial; all patients were female; a predominance of left-sided ulcers was noted</p> <p>Mean ulcer area: I: 437 mm<sup>2</sup> C: 371 mm<sup>2</sup></p> <p>The two groups were not comparable at baseline for mean ulcer area (larger ulcers have a higher HQ than smaller ones). Therefore, 17 matched pairs of patients were selected for analysis. In each case, the area of the control ulcer was within 10% of the area of the treated ulcer</p> <p>Mean ulcer area for 17 matched pairs: I: 115 mm<sup>2</sup> C: 112 mm<sup>2</sup></p>	<p>Results for 17 matched pairs: Mean <math>\pm</math> SD ulcer HQ: I: 2.8 <math>\pm</math> 2.3 mm<sup>2</sup>/day C: 3.1 <math>\pm</math> 2.7 mm<sup>2</sup>/day (not significant)</p> <p>Mean time to healing: I: 37 days C: 34 days</p>	<p>Of the 82 patients entering the trial, 6 were eliminated because it was not possible to photograph their ulcers</p> <p>Six patients with 7 ulcers ceased to attend the clinic before their ulcers had healed. Their HQ was calculated from the ulcer area of the last visit. (It is unclear whether these patients were among the 17 matched pairs)</p>	
						C, control group; I, intervention group

continued



TABLE 2 contd Venous leg ulcers: topical agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>Salim, 1991,<sup>36</sup> Iraq</p> <p><b>Study design:</b> RCT (double blinded)</p> <p><b>Method of randomisation:</b> Sealed envelopes</p> <p><b>Unit of allocation:</b> Patients</p> <p><b>Sample size:</b> Based on a two-tailed test, a sample size of 129 patients (43 per study arm) would detect a significant difference of 30% between the placebo and active-treatment groups (<math>p &lt; 0.05</math>), with a probability of 80% for the overall sample</p> <p><b>Objective outcomes:</b></p> <ol style="list-style-type: none"> <li>1. Ulcer area (outline traced onto cellophane, transferred to a card of known area/weight ratio, and ulcer area calculated from this); measured at weeks 2, 4, 8 and 12 of the trial</li> <li>2. Complete healing (defined as complete granulation and epithelialisation of ulcer)</li> </ol> <p><b>Setting and length of treatment:</b> Outpatients at the Venous Ulcer Clinic of the University Department of Surgery at the Medical City in Baghdad, Iraq. Trial duration 3 months</p>	<p><b>Inclusion criteria:</b> Patients with primary venous ulceration; non-circumferential unilateral ulceration on medial side of leg, <math>&lt; 10 \text{ cm}^2</math> in area; no previous treatment for venous ulcers; ulcer not infected or associated with gross leg oedema</p> <p><b>Exclusion criteria:</b> Evidence of previous treatment for venous ulceration; alcoholism; pregnancy; diabetes; hypertension; steroid or non-steroidal anti-inflammatory drug use over the previous year; regular medication use; hepatic or renal disorders; serious underlying disease; rheumatoid arthritis; collagen disease</p>	<p><b>All patients:</b> Devitalised skin around the ulcer was removed with warm olive oil; ulcer cleaned with normal saline and loose tissue removed; ulcer sprayed with powder (see below); non-adherent dressing, then gauze applied; propylene glycol monostearate applied to skin around the ulcer; then three-layer below-knee graduated compression bandage applied. Dressings were changed daily for 1 week, then weekly until healing or the end of study. Patients were advised to sleep with foot of bed raised, avoid long periods of standing, walk whenever possible and elevate the affected leg when sitting. After healing, patients were fitted with knee-length graduated elastic compression stockings, to be worn for at least 6 months, or permanently if any evidence of deep vein incompetence</p> <p><b>I1 (n = 51):</b> Allopurinol powder</p> <p><b>I2 (n = 50):</b> dimethyl sulphoxide (DMSO) powder</p>	<p>Results are for 133 evaluable patients</p> <p><i>Gender (male/female):</i> I1: 19/26 I2: 20/24 C: 18/26</p> <p><i>Mean (range) age:</i> I1: 57 (33–69) years I2: 58 (30–71) years C: 56 (29–71) years</p> <p><i>Mean <math>\pm</math> SEM ulcer area:</i> I1: <math>4.4 \pm 0.5 \text{ cm}^2</math> I2: <math>4.6 \pm 0.7 \text{ cm}^2</math> C: <math>4.1 \pm 0.2 \text{ cm}^2</math></p> <p><i>Mean ulcer duration:</i> I1: 24 months I2: 23 months C: 20 months</p> <p>Groups were comparable for all above baseline variables, and also for socio-economic status and occupation (particularly in relation to sedentary work)</p>	<p><b>Analysis:</b> Mann–Whitney <math>U</math>-test, and <math>\chi^2</math> test with Yates correction</p> <p>Results at 12 weeks:</p> <p><i>Complete healing:</i> I1: 93% I2: 95% C: 70% (<math>p &lt; 0.01</math> for I1 vs C and I2 vs C)</p> <p><i>Mean <math>\pm</math> SEM ulcer area:</i> I1: <math>0.3 \pm 0.1 \text{ cm}^2</math> I2: <math>0.2 \pm 0.1 \text{ cm}^2</math> C: <math>1.3 \pm 0.3 \text{ cm}^2</math> (<math>p &lt; 0.01</math> for I1 vs C and I2 vs C)</p> <p>Increasing duration of ulcer, previous DVT, increasing ulcer size and ulcer infection all had a significantly detrimental effect on healing (<math>p &lt; 0.01</math>). When these and all the non-significant variables were allowed for, treatment with allopurinol or DMSO continued to have a significantly beneficial effect on healing (<math>p &lt; 0.01</math>)</p> <p><b>Intention-to-treat analysis:</b> Assuming that excluded cases either healed within 12 weeks of treatment or</p>	<p>Patients were excluded from the analysis if they had ulcer infection and/or cellulitis, significant adverse effects to the study regimen or concomitant treatment during study. Decisions to exclude according to the above criteria were taken before breaking the treatment code. However, additional intention-to-treat analyses were done re-including such patients in order to determine if their exclusion had any effect on the results</p> <p><i>Unevaluable patients (I1/I2/C):</i> Ulcer infection 3/2/4 Adverse events 1/2/1 Concomitant treatment 1/0/0 Non-adherent with regimen 1/2/3</p>	<p>Treatment-related adverse effects included local itching and erythema. No systemic side-effects were noted. At the end of the study, all patients who had not yet healed had incompetent perforating and deep veins, with incompetent saphenous veins. All but one of these patients had a history of deep vein thrombosis (DVT). All the ulcers that remained in the allopurinol and DMSO groups at the end of the study were completely healed within 4 weeks of patients continuing their respective treatments</p>
C, control group; I1, I2, intervention groups						
continued						

TABLE 2 contd Venous leg ulcers: topical agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
Wunderlich and Orfanos, 1991, <sup>37</sup> Germany	<b>Inclusion criteria:</b> Venous leg ulcers	<b>C (n = 52):</b> Placebo powder	Data are for 38 patients Gender (male/female): I: 7/12 C: 4/15 Mean age: I: 74.3 years C: 72.9 years Mean ulcer duration: I: 7.6 years C: 7.9 years Mean ulcer area (values taken from graph): I: 3000 mm <sup>2</sup> C: 2000 mm <sup>2</sup>	remained ulcerated after 12 weeks, the two active drugs continued to have a significant advantage vs placebo ( $p < 0.01$ ). This advantage was not significant when only the placebo cases were assumed to have healed by 12 weeks	Two withdrawals (1 per group)	
<b>Study design:</b> RCT (open)	<b>Exclusion criteria:</b> Ulcers of origin other than venous insufficiency, corticosteroid therapy, other therapy delaying wound healing	<b>I (n = 20 patients):</b> A silver-impregnated, activated charcoal dressing (Actisorb Plus, Johnson & Johnson) was used for all stages of wound healing		Results at 6 weeks: Complete healing: I: 6/19 (32%) C: 2/19 (11%) (not significant) Mean ulcer size (values taken from graph): I: 1000 mm <sup>2</sup> C: 1000 mm <sup>2</sup> Relative reduction in ulcer area (values taken from graph): At 2 weeks: I, 40%; C, 15% ( $p < 0.05$ ) At 4 weeks: I, 60%; C, 40% ( $p < 0.05$ ) At 6 weeks: I, 75%; C, 60% (not significant)		
<b>Method of randomisation:</b> Not stated		<b>C (n = 20 patients):</b> Conventional therapy, using various topical agents for different stages of wound healing, including: mineral oil or mixture of sea salt and povidone iodine paste (granulation phase), parafin-impregnated gauze or oil-and-water emulsion with panthenol (epithelialisation phase), debridement continued as below				
<b>Unit of allocation:</b> Patients		<b>All patients:</b> Wounds were initially debrided mechanically, or by using enzymes, for 5 days. Debridement was also done intermittently				
<b>Sample size:</b> No <i>a priori</i> power calculation reported						
<b>Objective outcomes:</b>						
1. Ulcer size: assessed largest ulcer for each patient, used planimetry to calculate area						
2. Relative reduction of ulcer area						
<b>Setting and length of treatment:</b> Appears to be an inpatient setting. Trial duration 6 weeks						
C, control group; I, intervention group						continued

TABLE 2 contd Venous leg ulcers: topical agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
		during the trial (up to 4 times in 6 weeks) for large ulcers. No mention of using compression therapy				
<p>Piérard-Franchimont, 1997,<sup>46</sup> Belgium</p> <p><b>Study design:</b> CCT; patients with at least two leg ulcers; acted as own controls</p> <p><b>Method of treatment allocation:</b> No details about how intervention ulcers were selected. Control ulcers were selected on the basis of being of a similar size and location to those in the intervention group. Not stated whether the study was restricted to ulcers on the same limb</p> <p><b>Unit of allocation:</b> Ulcers</p> <p><b>Sample size:</b> No <i>a priori</i> power calculation reported</p> <p><b>Objective outcomes:</b> Healing rates assessed weekly using computerised planimetry; assessment was blinded. The healing index (in mm) was calculated for each ulcer using the</p>	<p><b>Inclusion criteria:</b> Women with long-standing venous leg ulcers, with at least two lesions. Ulcers had to have an area within the range 12–50 cm<sup>2</sup></p> <p><b>Exclusion criteria:</b> Ischaemic vascular disease, hypertension, insulin-dependent diabetes and terminal illness</p>	<p><b>I (n = 21):</b> Ulcers were irrigated daily with saline solution, dried with gauze, and painted with 10% povidone iodine solution. A hydrocolloid dressing was then applied to cover a minimum 2 cm rim of skin around each ulcer. The hydrocolloid dressing was changed twice weekly. Elastic stockings were worn during the daytime</p> <p><b>C (n = 21):</b> As intervention, but without povidone iodine solution</p>	<p>Age range: 57–73 years</p> <p>Initial circle diameter (median (95% CI)): I: 5.9 (4.2 to 6.3) cm C: 5.6 (5.3 to 6.3) cm</p> <p>It appears that the authors converted the ulcer area into a circle and then calculated the median diameter for each group of ulcers</p>	<p>Data are for 15 patients who completed the trial</p> <p>Ulcers in the intervention group had a statistically significantly higher healing index relative to those in the control group at 1, 2, 3, 4 and 7 weeks (<math>p &lt; 0.05</math>, Wilcoxon test). However, the difference did not remain significant at 8 weeks</p> <p>Healing index at 8 weeks (median (95% CI)): I: 10.3 (9.3 to 11.3) C: 9.3 (8.3 to 10.3) (not significant, Wilcoxon test)</p> <p>These figures were taken from the graph</p>	<p>Six withdrawals: infected ulcers (controls only), 2; protocol violation, 1; lost to follow-up, 3</p>	<p>This was a very small study with 6/42 (14%) patients withdrawing, and the analysis was not conducted on an intention-to-treat basis. Therefore, the results should be treated with caution, as it is possible that larger numbers would be required to demonstrate the true treatment effect. In addition, some values are given for the baseline status of wounds, but it is not entirely clear what these relate to or how they were calculated. Also, although the authors reported median values with 95% CIs, it is possible that they intended to report the median and range</p>
C, control group; I, I1, I2, intervention groups						
						continued

TABLE 2 contd Venous leg ulcers: topical agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>following formula, with a higher index indicating a better outcome: (actual ulcer area – initial ulcer area)/initial perimeter</p> <p><b>Setting and length of treatment:</b> All patients were managed at home by nurses. Lesions were followed up for a minimum of 8 weeks, unless the ulcer had healed or the patient was withdrawn from the trial</p>	<p><b>Inclusion criteria:</b> Age 21–90 years, venous leg ulcers of at least 3 months' duration, surface area of ulcers 3–50 cm<sup>2</sup>, not pregnant or planning conception</p> <p><b>Exclusion criteria:</b> Hypersensitivity to any components of the test medication, &gt; 10<sup>5</sup> bacteria/g of tissue in the ulcer (determined by biopsy of lesion), systemic sepsis or presence of bone infection, arm/ankle arterial perfusion index &lt; 0.5, hypercupraemia, systemic</p>	<p><b>All patients:</b> Dressings were performed once daily by the patient. The wound was cleaned with normal saline, and one of the study preparations was applied to the ulcer (see below). This was covered with a non-adherent dressing and elastic bandage. Patients remained ambulant but were instructed to elevate the affected limb when sitting</p> <p><b>I1 (n = 31 patients):</b> A growth factor was applied to the ulcer (0.4% tripeptide–copper complex, in a petrolatum based cream)</p>	<p>Information was given on the 86 patients who completed the study</p> <p>Gender (male/female): I1: 14/15 I2: 9/19 C: 20/9</p> <p>Mean ± SD age: I1: 58.2 ± 14.5 years I2: 58.2 ± 17.3 years C: 51.6 ± 14.6 years</p> <p>Race (white/black/other) I1: 20/8/1 I2: 16/10/2 C: 17/10/2</p>	<p>Results at 4 weeks</p> <p>Mean ± SD decrease in ulcer area: I1: 18.7 ± 9.07% I2: 44.0 ± 8.21% C: 22.5 ± 10.2%</p> <p>p = 0.03 for I1 vs I2 p = 0.05 for I2 vs C</p> <p>Not significant for I1 vs C</p> <p>Complete healing: I1: 0/29 (0%) I2: 6/28 (21%) C: 1/29 (3%)</p> <p>5/6 patients in I2 and the single patient in C maintained complete healing 1 year after the study was completed</p>	<p>Four withdrawals: I1, 2; I2, 1; C, 1</p>	<p><b>Authors' comment:</b> The effect of silver sulphadiazine cream was probably not due to its antibacterial properties since all included patients had to have a bacterial count of not more than 10<sup>5</sup> bacteria per gram of tissue, and this number of tissue bacteria has been shown not to interfere with wound healing. The silver sulphadiazine cream may promote wound healing by epithelialisation</p>
<p>Bishop, 1992,<sup>33</sup> USA</p> <p><b>Study design:</b> RCT (2 centres)</p> <p><b>Method of randomisation:</b> Not stated</p> <p><b>Unit of allocation:</b> Patients, stratified by ulcer size (3–20 or 21–50 cm<sup>2</sup>)</p> <p><b>Sample size:</b> No <i>a priori</i> power calculation reported</p> <p><b>Objective outcomes:</b></p> <p>I. Ulcer size (outline traced, photographed, and area calculated by digitised planimetry). Outcome assessment was blinded</p>	<p><b>Inclusion criteria:</b> Age 21–90 years, venous leg ulcers of at least 3 months' duration, surface area of ulcers 3–50 cm<sup>2</sup>, not pregnant or planning conception</p> <p><b>Exclusion criteria:</b> Hypersensitivity to any components of the test medication, &gt; 10<sup>5</sup> bacteria/g of tissue in the ulcer (determined by biopsy of lesion), systemic sepsis or presence of bone infection, arm/ankle arterial perfusion index &lt; 0.5, hypercupraemia, systemic</p>	<p><b>All patients:</b> Dressings were performed once daily by the patient. The wound was cleaned with normal saline, and one of the study preparations was applied to the ulcer (see below). This was covered with a non-adherent dressing and elastic bandage. Patients remained ambulant but were instructed to elevate the affected limb when sitting</p> <p><b>I1 (n = 31 patients):</b> A growth factor was applied to the ulcer (0.4% tripeptide–copper complex, in a petrolatum based cream)</p>	<p>Information was given on the 86 patients who completed the study</p> <p>Gender (male/female): I1: 14/15 I2: 9/19 C: 20/9</p> <p>Mean ± SD age: I1: 58.2 ± 14.5 years I2: 58.2 ± 17.3 years C: 51.6 ± 14.6 years</p> <p>Race (white/black/other) I1: 20/8/1 I2: 16/10/2 C: 17/10/2</p>	<p>Results at 4 weeks</p> <p>Mean ± SD decrease in ulcer area: I1: 18.7 ± 9.07% I2: 44.0 ± 8.21% C: 22.5 ± 10.2%</p> <p>p = 0.03 for I1 vs I2 p = 0.05 for I2 vs C</p> <p>Not significant for I1 vs C</p> <p>Complete healing: I1: 0/29 (0%) I2: 6/28 (21%) C: 1/29 (3%)</p> <p>5/6 patients in I2 and the single patient in C maintained complete healing 1 year after the study was completed</p>	<p>Four withdrawals: I1, 2; I2, 1; C, 1</p>	<p><b>Authors' comment:</b> The effect of silver sulphadiazine cream was probably not due to its antibacterial properties since all included patients had to have a bacterial count of not more than 10<sup>5</sup> bacteria per gram of tissue, and this number of tissue bacteria has been shown not to interfere with wound healing. The silver sulphadiazine cream may promote wound healing by epithelialisation</p>
<p>C, control group; I1, I2, intervention groups</p>						

continued

TABLE 2 contd Venous leg ulcers: topical agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>2. Frequency of complete healing</p> <p><b>Setting and length of treatment:</b> Outpatients attending the Plastic Surgery Clinics at the Universities of Texas and Washington. Patients were instructed in how to perform dressings. Trial duration 4 weeks, during which time patients were evaluated weekly</p>	<p>immunosuppressive or cytotoxic therapy, insulin-dependent diabetes mellitus</p>	<p><b>I2 (n = 29 patients):</b> 1% silver sulphadiazine cream applied to ulcer</p> <p><b>C (n = 30 patients):</b> Placebo preparation (petrolatum-based cream) applied to the ulcer</p>	<p><i>Diabetics treated with oral antidiabetic drugs:</i></p> <p>I1: 4 I2: 2 C: 2</p> <p><i>Mean ± SD ulcer area:</i></p> <p>I1: 9.9 ± 8.5 cm<sup>2</sup> I2: 11.9 ± 11.2 cm<sup>2</sup> C: 9.6 ± 8.1 cm<sup>2</sup></p> <p><i>Ulcer area &lt; 20 cm<sup>2</sup>:</i></p> <p>I1: 5 I2: 5 C: 4</p> <p><i>Mean ± SD ulcer duration:</i></p> <p>I1: 57.1 ± 94.9 months I2: 44.1 ± 58.0 months C: 38.0 ± 88.7 months</p>			
<p>Blair, 1988,<sup>10</sup> UK</p> <p><b>Study design:</b> RCT</p> <p><b>Method of randomisation:</b> Sealed envelopes, containing codes from a random-numbers table</p> <p><b>Unit of allocation:</b> Ulcers</p> <p><b>Sample size:</b> No <i>a priori</i> power calculation reported</p> <p><b>Objective outcomes:</b></p> <p>I. Complete healing. Ulcer area was measured weekly by tracing the outline onto cellophane, then transferring this onto card of known weight/area ratio</p>	<p><b>Inclusion criteria:</b> Venous leg ulcers ≤ 10 cm<sup>2</sup> in area</p> <p><b>Exclusion criteria:</b> Arterial insufficiency (ankle/brachial pressure index &lt; 0.8; Doppler)</p>	<p><b>I (n = 30):</b> Ulcers cleaned with saline, then a silver sulphadiazine dressing applied, followed by four-layer compression bandaging, aiming to produce a mean initial ankle pressure of 42 mmHg, to be sustained at a mean of 37 mmHg at 1 week</p> <p><b>C (n = 30):</b> Ulcers cleaned with saline, then a non-adherent dressing applied, followed by compression therapy as in the intervention group</p>	<p><i>Mean (range) age:</i></p> <p>I: 67 (36–86) years C: 70 (42–90) years</p> <p><i>Mean ± SEM ulcer area:</i></p> <p>I: 3.4 ± 0.5 cm<sup>2</sup> C: 3.8 ± 0.6 cm<sup>2</sup></p> <p><i>Mean ± SEM time since ulcer last healed:</i></p> <p>I: 33.4 ± 4.1 months C: 27.8 ± 3.4 months</p> <p><i>Microbiology:</i> All ulcers were contaminated at baseline (isolates listed in the paper)</p>	<p><i>Complete healing:</i></p> <p>I: 19/30 (63%) C: 24/30 (78%) (not significant)</p> <p><i>Mean reduction in ulcer area during weeks 1–6:</i></p> <p>I: 11% C: 12.8% (not significant)</p> <p><i>Mean reduction in ulcer area during weeks 7–12:</i></p> <p>I: 1.7% C: 2.5% (not significant)</p> <p><i>Microbiology:</i> Bacterial contamination continued for most ulcers, in both groups, throughout the</p>	<p><i>Adverse events:</i></p> <p>I: Treatment was discontinued in 4 (13%) patients who developed a local skin reaction with erythema and pruritis C: No adverse events</p> <p>The authors appear to have used the intention-to-treat protocol</p>	<p>The authors attribute the improved healing rates to the higher pressures achieved by the four-layer bandaging, and state that no further benefit was derived from using silver sulphadiazine</p>
C, control group; I, intervention group						

continued

TABLE 2 contd Venous leg ulcers: topical agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>2. Bacteriology: cultures taken (by swabbing) each fortnight</p> <p><b>Setting and length of treatment:</b> Outpatients, with dressings and bandages changed weekly in a venous ulcer clinic. Trial duration 12 weeks</p>	<p><b>Inclusion criteria:</b> Adults with venous leg ulcers and an ankle pressure index &gt; 0.8, measured using a non-invasive Doppler technique</p>	<p><b>I (n = 15):</b> 2% calcium mupirocin in a white, soft, paraffin tulle gras plus compression therapy, consisting of a viscopaste bandage with an outer elastic diachylon support bandage.</p> <p><b>C (n = 15):</b> White, soft, paraffin tulle gras plus compression therapy as for the intervention group</p> <p><b>All patients:</b> Patch testing was performed before and after the study, using a Standard European Battery, a Mupirocin Battery and relative medicaments</p>	<p>Gender (male/female): I: 2/13 C: 9/6</p> <p>Mean (range) age: I: 73 (57–88) years C: 70 (59–85) years</p> <p>Mean (range) ulcer duration: I: 2.7 years (6 months to 9 years) C: 6 years (1 month to 36 years)</p> <p>Mean baseline ulcer area: I: 16.3 cm<sup>2</sup> C: 17.3 cm<sup>2</sup></p>	<p>The presence of micro-organisms did not appear to delay healing. There was no significant difference in the number of organisms cultured between the two groups, either overall, or for any particular micro-organism</p> <p>Results at 12 weeks Mean (range) change in ulcer area: I: -50% (+55 to -100%) C: -68% (-35 to -100%) (not significant)</p> <p>Complete healing: I: 53% C: 46% (not significant)</p> <p>Other: Microbiological results also reported</p>	<p>None reported</p>	<p>Since there were no statistically significant differences between the two treatment groups, the compression therapy may have been the most important factor for wound healing</p>
<p>Cameron, 1991,<sup>34</sup> UK</p> <p><b>Study design:</b> RCT (double blinded)</p> <p><b>Method of randomisation:</b> Not stated</p> <p><b>Unit of allocation:</b> Patients</p> <p><b>Sample size:</b> No <i>a priori</i> power calculation reported</p> <p><b>Objective outcomes:</b> Healing rate of ulcers (assessed using photographs and computerised planimetry), clinical and bacteriological status of wounds</p> <p><b>Setting and length of treatment:</b> Setting not stated. Trial duration 12 weeks</p>						
C, control group; I, intervention group						

TABLE 3 Wounds of mixed aetiologies: systemic agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>Valtonen, 1989,<sup>43</sup> Finland</p> <p><b>Study design:</b> RCT (open design).</p> <p><b>Method of randomisation:</b> Not stated</p> <p><b>Unit of allocation:</b> Patients</p> <p><b>Sample size:</b> No <i>a priori</i> power calculation reported</p> <p><b>Objective outcomes:</b></p> <ol style="list-style-type: none"> <li>1. Complete healing (defined as total disappearance of ulcer)</li> <li>2. Significant decrease in ulcer size (defined as 10% reduction in the sum of the maximum length and width of ulcer)</li> <li>3. Microbiology (cultures and sensitivities)</li> </ol> <p><b>Setting and length of treatment:</b> Either in-patients or outpatients (according to clinical status) at the Department of Dermatology, Helsinki University Central Hospital, Helsinki, Finland. Trial duration 3 months</p>	<p><b>Inclusion criteria:</b> Adults with a leg ulcer of <math>\geq 2</math> months duration, isolation from ulcer of either <i>P. aeruginosa</i> or another aerobic Gram-negative rod sensitive to ciprofloxacin</p> <p><b>Exclusion criteria:</b> Ulcer flora resistant to ciprofloxacin</p>	<p><b>I (n = 18):</b> Ulcers bathed daily in disinfectant (chlorhexidine or potassium permanganate diluted in warm water); necrotic tissue removed both mechanically and with enzyme preparations (clostridial peptidase or streptokinase-streptodornase under wet compresses); no local antibiotic creams used; clean ulcers with granulation tissue coated with dextranomer paste or a hydrocolloid dressing. Ciprofloxacin 750 mg orally, twice daily, given for 3 months. Dose was later decreased in 7 patients to 250 or 500 mg twice daily in order to maintain a maximum serum level of 2–4 mg/l</p> <p><b>C (n = 8):</b> Treatment as above, but without ciprofloxacin</p> <p><b>All patients:</b> Given extra systemic antibiotics in cases of urinary tract infection, cellulitis and exacerbation of acute ulcer infection</p>	<p><b>Gender (male/female):</b> I: 2/16 C: 2/6</p> <p><b>Mean <math>\pm</math> SD age:</b> I: 74.1 <math>\pm</math> 13.7 years C: 74.9 <math>\pm</math> 9.2 years</p> <p><b>Mean <math>\pm</math> SD ulcer size (maximum length plus width of ulcer):</b> I: 16.7 <math>\pm</math> 8.2 cm C: 16.9 <math>\pm</math> 11.4 cm</p> <p><b>Range of ulcer duration:</b> I: 60.0–71.3 months C: 29.0–35.1 months</p> <p><b>Patients with diabetes mellitus:</b> I: 3/18 (17%) C: 3/8 (38%)</p> <p><b>Patients with arterial insufficiency:</b> I: 13/18 (72%) C: 8/8 (100%)</p> <p><b>Patients with venous insufficiency:</b> I: 16/18 (89%) C: 6/8 (75%)</p>	<p><b>Analysis:</b> t-test or Fisher's two-tailed exact test</p> <p><b>Complete healing:</b> I: 3/18 (17%) C: 0/8 (0%) (not significant)</p> <p><b>Patients with significant reduction in ulcer size:</b> I: 9/18 (50%) C: 1/8 (13%) (not significant)</p> <p><b>Patients with clinical improvement (complete healing and significant reduction combined):</b> I: 12/18 (67%) C: 1/8 (13%) (<math>p &lt; 0.05</math>)</p> <p><b>Patients needing extra antimicrobial treatment:</b> I: 3/18 (17%) C: 6/8 (75%) (<math>p &lt; 0.05</math>)</p> <p><b>Patients needing major surgery (amputation or skin graft):</b> I: 1/18 (6%) C: 3/8 (38%) (not significant)</p> <p><b>Adverse effects:</b> I: mild transient nausea in 3 patients; did not necessitate withdrawal C: not reported</p>	None	<p><b>Authors' comments:</b> The addition of ciprofloxacin to standard therapy was significantly more effective than standard therapy alone in reducing ulcer size</p> <p><b>Reviewers' comments:</b> The conventional local treatment is unusual in that, in this study, dextranomer was used for clean ulcers (usually recommended for sloughy ulcers), and the choice was between this and a hydrocolloid. Groups may not have been comparable for baseline ulcer duration. Results become statistically significant only when complete healing and significant reduction in ulcer size are combined to form a single outcome. The use of other systemic antibiotics in both the treatment and the control group makes the results of this small study difficult to interpret. No information was given about what the other antibiotics were</p>
C, control group; I, intervention group						
						continued



**TABLE 3 contd** Wounds of mixed aetiologies: systemic agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
				<i>Microbiology:</i> Bacterial growth, eradication and resistance to ciprofloxacin during the trial, were reported		
<p>Morias, 1979,<sup>42</sup> Belgium</p> <p><b>Study design:</b> RCT (double blinded)</p> <p><b>Method of randomisation:</b> Sequentially numbered medication bottles</p> <p><b>Unit of allocation:</b> Patients</p> <p><b>Sample size:</b> No <i>a priori</i> power calculation reported</p> <p><b>Objective outcomes:</b> Complete healing (assessed by measurement of ulcer area); treatment failure (no distinct observed improvement); adverse effects. Patients examined every 2 weeks</p> <p><b>Setting and length of treatment:</b> Outpatients. Trial duration 20 weeks</p>	<p><b>Inclusion criteria:</b> Outpatients with chronic leg ulcers</p> <p><b>Exclusion criteria:</b> Not stated</p>	<p><b>I (n = 30):</b> Levamisole 100–250 mg orally for 2 consecutive days each week until cure, failure or 20 weeks. Dose determined according to body weight</p> <p><b>C (n = 29):</b> Placebo (identical in appearance) regimen as intervention group</p> <p><b>All patients:</b> The authors state that previously used topical treatment continued throughout the trial, but no further details were provided</p>	<p><i>Gender (male/female):</i> I: 6/24 C: 7/22</p> <p><i>Median (range) age:</i> I: 60 (27–81) years C: 63 (36–82) years</p> <p><i>Predisposing factors (I/C):</i> Atherosclerosis or arteriosclerosis, 2/3 Hypertension, 13/9 Venous stasis, 21/24 Lymph stasis, 5/4 Diabetes, 1/1 Some patients had more than one predisposing factor</p> <p><i>Median (range) ulcer area:</i> I: 100 (3–4400) mm<sup>2</sup> C: 100 (4–3300) mm<sup>2</sup> Groups were comparable at baseline for the above characteristics, and also for use of topical agents</p>	<p><i>Cure rate at 20 weeks:</i> I: 100% C: 76% (<i>p</i> &lt; 0.01, Student's <i>t</i>-test) No correlation was found between predisposing factors and effect</p> <p><i>Adverse effects:</i> I: 3 (moderate gastric complaints, did not withdraw) C: None</p>	<p>10 withdrawals due to treatment failure at a median (range) duration of 8 (8–19) weeks: I, 2; C, 8 (<i>p</i> &lt; 0.05, Fisher's test)</p>	<p>It is unclear whether 'cure' means the same as 'complete healing', as no definition was given</p>
<p><i>C, control group; I, intervention group</i></p>						



TABLE 4 Wounds of mixed aetiologies: topical agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>Beitner, 1985,<sup>38</sup> Sweden</p> <p><b>Study design:</b> RCT</p> <p><b>Method of randomisation:</b> Not stated</p> <p><b>Unit of allocation:</b> Ulcers. The ulcer to be given the active treatment was randomised according to left or right leg, and most distal or proximal location. When ulcers were on the same level, medial or lateral location was randomised. All patients had at least 2 leg ulcers and served as their own controls. In each patient, only one ulcer was given the active treatment, and the remaining ulcer(s) served as controls</p> <p><b>Sample size:</b> No <i>a priori</i> power calculation reported</p> <p><b>Objective outcomes:</b></p> <ol style="list-style-type: none"> <li>1. Ulcer size (outline traced onto transparent paper and area calculated by planimetry)</li> <li>2. Adverse effects</li> </ol>	<p><b>Inclusion criteria:</b> People with at least 2 chronic leg ulcers</p>	<p><b>All patients:</b> Low serum zinc or iron levels were corrected prior to entering the study</p> <p><b>Benzoyl peroxide 20% (n = 10 patients):</b>  <b>I1:</b> A sterile sponge compress was cut into the exact shape of the ulcer and moistened with benzoyl peroxide lotion 20%. This was applied to the ulcer, covered with a pad and kept in place with a gauze stocking. The margins of the ulcer were protected with zinc ointment, and an elastic support bandage was applied. Dressings were changed 3 times per week, in the clinic  <b>C1:</b> Treatment as I1, except that the sponge was moistened with saline solution instead of benzoyl peroxide</p> <p><b>Benzoyl peroxide 10% (n = 10 patients):</b>  <b>I2:</b> Same regimen as I1, except that benzoyl peroxide 10% was used  <b>C2:</b> Saline used for control ulcers, as for C1</p>	<p>Data are for 28 completers. All patients had at least 2 leg ulcers</p> <p><b>Aetiology of leg ulcers:</b>  Venous incompetence, 22  Venous and arterial incompetence, 4  Rheumatoid arthritis, 1  Decubitus, 1</p> <p><b>Gender (male/female):</b>  14/14</p> <p><b>Age range:</b> 26–90 years</p> <p>No information was reported on baseline ulcer area, or duration of ulcers</p>	<p><b>Analysis:</b> paired t-test</p> <p><b>Results at 42 days:</b></p> <p><b>Mean ± SD remaining ulcer area, reported as % of baseline area:</b>  Benzoyl peroxide 20%: I1, 59.6 ± 12.3%; C1, 93.7 ± 15.2% (<i>p</i> &lt; 0.05)</p> <p>Benzoyl peroxide 10%: I2, 64.3 ± 14.0%; C2, 94.7 ± 12.7% (<i>p</i> &lt; 0.01)</p> <p>Vehicle: I3, 83.6 ± 9.6%; C3, 94.4 ± 8.0% (not significant)</p> <p>When I1 and I2 were combined and compared with their corresponding control ulcers, a significant difference was observed (<i>p</i> &lt; 0.01)</p> <p><b>Adverse effects:</b> Three patients in I2 experienced severe irritation</p>	<p>Three patients withdrew from I2 due to severe irritation</p>	
<p><i>C1, C2, C3, control groups; I1, I2, I3, intervention groups</i></p>						
						<p><i>continued</i></p>

TABLE 4 contd Wounds of mixed aetiologies: topical agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<b>Setting and length of treatment:</b> Outpatients. Treatment was conducted by staff not involved in the evaluation of results. Final assessment was made after 42 days of treatment		<b>Vehicle (n = 11 patients):</b> <b>I3:</b> Same regimen as I1, except that only the vehicle of benzoyl peroxide lotion was used <b>C3:</b> Saline used for control ulcers, as for C1				
Marzin and Rouveix, 1982, <sup>40</sup> France <b>Study design:</b> CCT <b>Method of treatment allocation:</b> Not stated <b>Unit of allocation:</b> Ulcers. Each patient acted as their own control, and only ulcers on the same leg were compared <b>Sample size:</b> No <i>a priori</i> power calculation reported <b>Objective outcomes:</b> Change in ulcer area (wound outline traced onto transparent film and surface area calculated). Outcome assessment was unblinded <b>Setting and length of treatment:</b> Inpatients. Trial duration 12 weeks	<b>Inclusion criteria:</b> Patients with leg ulcers	<b>All patients:</b> Prior to commencing treatment, all ulcers were dressed daily with trichlorocarbanilide solution and polymyxin, until there was no apparent infection <b>I (n = 20 ulcers):</b> Collagen gel was applied as a thick layer, and covered with a pad and bandage. Dressing changed every other day <b>C (n = 20 ulcers):</b> 20% benzoyl peroxide pack applied and covered with pad and bandage. Dressing changed daily	<b>Gender (male/female):</b> 7/13 <b>Mean (range) age:</b> 76 (66–90) years <b>Ulcer duration:</b> < 1 year: 8 > 1 year: 12 <b>Ulcer type:</b> Venous insufficiency, 8 Arterial insufficiency, 3 Mixed, 9 <b>Patients with diabetes:</b> 8 <b>Patients with arteriosclerosis:</b> 15 <b>Mean ± SD (range) ulcer area:</b> I: 22.2 ± 10.7 (5.9–47.0) cm <sup>2</sup> C: 21.0 ± 14.7 (4.6–64.5) cm <sup>2</sup> (calculated by reviewer) <b>Previous treatments</b> included zinc ointment, iron subcarbonate packs and/or compression bandage	Results at 12 weeks <b>Wound area remaining:</b> I: 0.5% C: 15.9% ( <i>p</i> < 0.01)	None	There is no information about how the treatments were allocated to the ulcers. Baseline information for individual ulcer size was available, and mean and SD values were calculated from this
C, C3, control groups; I, I3, intervention groups						
						continued

TABLE 4 contd Wounds of mixed aetiologies: topical agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>Margraf and Covey, 1977,<sup>39</sup> USA</p> <p><b>Study design:</b> Case series, incorporating smaller CCT, in which patients acted as their own controls</p> <p><b>Method of treatment allocation:</b> Not stated</p> <p><b>Unit of allocation:</b> Ulcers</p> <p><b>Sample size:</b> No <i>a priori</i> power calculation reported</p> <p><b>Objective outcomes:</b></p> <ol style="list-style-type: none"> <li>1. Complete healing (assessed using photography)</li> <li>2. Time to healing</li> <li>3. Microbiological cultures</li> </ol> <p><b>Setting and length of treatment:</b> Setting unclear. Patients followed up to complete healing</p>	<p><b>Inclusion criteria:</b> Patients with bilateral chronic leg ulcers of mixed aetiologies. Infected ulcers were included</p> <p><b>Exclusion criteria:</b> Not stated</p>	<p><b>I (n = 10 left-leg ulcers):</b> Wound cleansed by gentle washing or soaking using warm water and a mild, non-medicated soap, a thick layer of 1% silver zinc allantoinate cream (AZAC 1%) applied, then wound covered with gauze secured with paper surgical tape. In hot weather, or during intense activity, the dressing was secured with an elastic gauze bandage, and pressure bandages or support stockings. Dressings changed daily</p> <p><b>C (n = 10 right-leg ulcers):</b> Various treatments, including 0.5% silver nitrate, wet to dry saline dressing, nitrofurazone, bismuth tribromophenate dressing, Unna's boot, compression bandaging and povidone iodine ointment</p>	<p>Overall data for main study (no details available for smaller comparative study)</p> <p><i>Mean (range) age:</i> 51 (10–85) years</p> <p><i>Gender (male/female):</i> 30%/70%</p> <p><i>Range of ulcer duration:</i> 4 weeks to 20 years</p> <p><i>Ulcer aetiology:</i> Most patients had venous or diabetic ulcers. Less common were pressure ulcers, arterial ulcers, trophic ulcers, sickle cell anaemia and spider bites</p> <p><i>Mean (range) ulcer area for comparative study:</i> I: 722 (180–1800) mm<sup>2</sup> C: 682 (165–1860) mm<sup>2</sup></p>	<p>Results are for the comparative study</p> <p><i>Mean ± SD (range) time to healing:</i> I: 45 ± 21 (19–88) days C: 104 ± 31 (54–138) days (<i>p</i> &lt; 0.001, <i>t</i>-test for paired sample; calculated by reviewer)</p>	None for CCT	Very few data presented on the participants of the CCT
<p>Della Marchina and Renzi, 1997,<sup>45</sup> Italy</p> <p><b>Study design:</b> RCT (single blinded)</p> <p><b>Method of randomisation:</b> Not stated</p>	<p><b>Inclusion criteria:</b> Patients aged ≥ 65 years with diabetic foot ulcers, venous leg ulcers or pressure sores. Wounds had to be classified as first or second degree (not defined)</p>	<p><b>I (n = 20):</b> Wounds were cleaned with normal saline and dried with gauze. An antiseptic spray (2% eosin and 0.3% chloroxylenol in hydroglycolic solution) was applied to the wound surface using gauze. The</p>	<p><i>Gender (male/female):</i> I: 6/14 C: 8/12</p> <p><i>Mean ± SD (range) age:</i> I: 76.7 ± 5.2 (66–86) years C: 79.1 ± 6.4 (67–89) years</p>	<p>Results at 15 days</p> <p>Healing (3/2/1/unsatisfactory) – all wounds: I: 58%/12%/30%/0 C: 30%/40%/18%/12%</p> <p>Figures taken from graph</p>	No withdrawals	This was a small study. Larger numbers may be required to detect the true treatment effect. The baseline and end-point assessments of wound condition appear to be based on a subjective assessment. No details
C, control group; I, intervention group						
<i>continued</i>						

**TABLE 4 contd** Wounds of mixed aetiologies: topical agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p><b>Unit of allocation:</b> Patients</p> <p><b>Sample size:</b> No <i>a priori</i> power calculation reported</p> <p><b>Objective outcomes:</b> Healing progress was assessed at 5, 10 and 15 days. Wounds were graded as one of the following: complete healing, 3; &gt; 50% wound area healed relative to baseline, 2; 25–50% healed relative to baseline, 1; &lt; 25% healed relative to baseline, unsatisfactory. No information was given about the methods of measurement, or how many assessors were involved</p> <p><b>Setting and length of treatment:</b> Setting not stated. Trial duration 15 days</p>	<p><b>Exclusion criteria:</b> Sensitivity to test medication or receiving other treatment</p>	<p>wound was then covered with gauze. The dressing was changed 2 or 3 times per day. There were no details of the use of other interventions (e.g. pressure relief). Patients who were being treated with an antiseptic prior to the study had a 1-day washout period, during which the wound was cleaned 2 or 3 times with normal saline. During the study period, treatment with other antiseptics, healing medications, antibiotics, analgesics, absorbing agents and anti-inflammatory agents was discontinued</p> <p><b>C (n = 20):</b> As intervention group, except that an alternative spray was used (not described)</p>	<p><b>Wound type (pressure ulcer/diabetic foot):</b> I: 9/11 C: 10/10</p> <p><b>Wound condition (good/moderate/poor):</b> Pressure ulcers: I, 0/3/6; C, 0/3/7 Diabetic foot ulcers: I, 4/6/1; C, 3/7/0</p> <p>No information given on baseline wound area</p> <p><b>Other:</b> 38 patients presented other co-morbidities (e.g. diabetes mellitus, hypertension) and continued with usual medication during the study period</p>	<p><b>Healing (3/2/1/unsatisfactory) – diabetic foot ulcers only:</b> I: 82%/18%/0/0 C: 50%/50%/0/0 Figures taken from graph</p> <p><b>Healing (3/2/1/unsatisfactory) – pressure ulcers only:</b> I: 20%/10%/70%/0 C: 10%/30%/30%/30% Figures taken from graph</p> <p><b>Adverse effects (local burning sensation):</b> I: 3 patients C: 1 patient</p>		were given of independent assessments by more than one examiner, and blinding procedures were also unclear. The reliability of the results may therefore be questionable
<p>Worsley and Buchanan, 1991,<sup>41</sup> UK</p> <p><b>Study design:</b> RCT</p> <p><b>Method of randomisation:</b> Not stated</p>	<p><b>Inclusion criteria:</b> Patients with leg ulcers (aetiology not specified) or pressure ulcers</p> <p><b>Exclusion criteria:</b> Not stated</p>	<p><b>I (n = 12):</b> Hydrocolloid dressing applied (Comfeel, Coloplast); no other details given</p> <p><b>C (n = 15):</b> Wounds covered with 10% povidone iodine ointment,</p>	<p><b>Gender (male/female) – overall:</b> 4/23</p> <p><b>Mean age:</b> I: 75 years C: 80 years</p>	<p>Results at 12 weeks</p> <p><b>Complete healing:</b> I: 4/12 (33%) C: 2/15 (13%) (not significant)</p>	<p>15 (56%) withdrawals overall: I, 7/12 (58%); C, 8/15 (53%)</p> <p><b>Reasons for withdrawal (I/C):</b> Unable to tolerate further dressings, 1/0</p>	Although, data are not presented per wound type, the authors state that the patients with pressure ulcers tended to show greater improvement than those with leg ulcers, but this
C, control group; I, intervention group						
<i>continued</i>						

TABLE 4 contd Wounds of mixed aetiologies: topical agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p><b>Unit of allocation:</b> Patients</p> <p><b>Sample size:</b> No a priori power calculation reported</p> <p><b>Objective outcomes:</b> Change in ulcer area (calculated using computerised photographic techniques)</p> <p><b>Setting and length of treatment:</b> Setting not stated. Trial duration 12 weeks</p>		followed by non-adhering dressing and gauze	<p><i>Nutritional status (good/ reasonable/not stated):</i> I: 6/6/0 C: 4/10/1</p> <p><i>Wound type (leg ulcer/ pressure ulcer):</i> I: 6/6 C: 7/8</p>	<p><i>Wounds not healed:</i> I: 1/12 (8%) C: 5/15 (33%) (not significant)</p> <p><i>Mean ± SD (range) dressing changes per week (analysis of all patients):</i> I: 3 ± 1.38 (1–5) C: 4.9 ± 1.69 (3–7) (<i>p</i> &lt; 0.005)</p>	<p>Lack of progress, 2/3 Deterioration in condition, 1/0 Left area, 1/2 Took own discharge, 1/0 Died, 1/3</p>	<p>difference was not statistically significant. The small numbers recruited to the study, the large drop-out rate (56% overall) and the lack of data on baseline wound size make the results difficult to interpret. Few details were given of the interventions and inclusion/exclusion criteria for participants</p>
C, control group; I, intervention group						

TABLE 5 Pressure ulcers: prevention

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>Green, 1974,<sup>30</sup> UK</p> <p><b>Study design:</b> RCT (double blinded)</p> <p><b>Method of randomisation:</b> Not stated</p> <p><b>Unit of allocation:</b> Patients</p> <p><b>Sample size:</b> No <i>a priori</i> power calculation reported</p> <p><b>Objective outcomes:</b> Patients' skin graded as improved, unchanged or deteriorated, according to a five-point scale: no pressure ulcers; 0; persistent erythema; 1; localised superficial blistering; 2; deep localised ulcers or extensive superficial ulcers; 3; very extensive gangrenous ulcers; 4. Assessments were made at least 3 times weekly. Risk of pressure ulcer score and clinical findings were double checked</p> <p><b>Setting and length of treatment:</b> Multicentre trial. Participants were inpatients in elderly care wards of six London hospitals during a 6-month period (March–September 1972). Trial duration 3 weeks</p>	<p><b>Inclusion criteria:</b> Elderly care wards, judged to be at risk of developing pressure ulcers (Norton score <math>\leq 14</math>)</p> <p><b>Exclusion criteria:</b> Existing pressure ulcers, severe or terminal illness</p>	<p><b>I (n = 76 completers):</b> Dermalex lotion (contains hexachlorophene 0.5%, cosbiol 3%, allantoin 0.2%) applied to pressure areas (sacral, trochanteric, heel, shoulder, others as indicated), avoiding excessive friction</p> <p><b>C (n = 91 completers):</b> Inert lotion, similar in appearance and texture to that in the intervention and applied in the same way</p> <p><b>All patients:</b> Turned 2 hourly. Pressure areas washed with soap and water, and lotions reapplied every 6 hours, or more frequently in cases of incontinence. Catheterisation was avoided if possible, as were chlorhexidine-containing soaps and topical silicone preparations. Bed cradles were used for all patients. Large-cell alternating pressure mattresses were used for patients with a Norton score <math>&lt; 10</math>. In one hospital it was standard practice to nurse all elderly care admissions on such mattresses, but the authors state that this did not significantly affect the trial results</p>	<p>Erythema of pressure areas: 75% of the 319 patients entering the trial</p> <p>Mean age of the 167 completers: 81.5 years</p> <p>Gender (male/female): 40/127</p> <p>Other: For completers, groups were reported to be comparable for age, gender, build, month of admission, incontinence, general health, activity and mobility, site of ulcer, type of bed used and use of incontinence pads</p>	<p>Results for 167 completers at 3 weeks</p> <p>Deterioration of skin condition: I: 26/76 (34%) C: 34/91 (38%)</p> <p>No patients developed significant pressure ulcers</p> <p>Development of superficial ulcers (grade 2): I: 16% C: 24% (<math>p = 0.57</math>)</p> <p>Time to develop superficial ulcers: I: 9.8 days C: 8.7 days</p> <p>Skin condition unchanged: I: 32/76 (42%) C: 45/91 (49%)</p> <p>Improved skin condition: I: 18/76 (24%) C: 12/91 (13%) (<math>p &lt; 0.05</math>, baseline vs post-treatment scores for general comparison for improved/unchanged/deteriorated skin condition, I vs C, in favour of I)</p>	<p>Criteria for withdrawal: Discharge from ward, Norton score <math>&gt; 17</math>, development of pressure ulcers (excluding grades 1–2 on the assessment scale), non-adherence with protocol</p> <p>Total withdrawals: 152 patients</p> <p>Reasons for withdrawal (I/C): Death: 27/33 Discharges/transfers: 0/11 Norton score <math>&gt; 17</math>: 22/30 Allergic rash: 2/0</p> <p>Developed ulcers: I, 8 (9.5%), all patients died; C, 13 (12.5%), 6 patients died</p> <p>Other reasons: breach of trial protocol</p>	<p>The study validity was compromised by having a large number of withdrawals and no intention-to-treat protocol</p>
<p>C, control group; I, intervention group</p>						

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TABLE 5 contd Pressure ulcers: prevention

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>Van der Cammen, 1987,<sup>32</sup> UK</p> <p><b>Study design:</b> RCT (double blinded)</p> <p><b>Method of randomisation:</b> Not stated</p> <p><b>Unit of allocation:</b> Patients</p> <p><b>Sample size:</b> No calculation reported</p> <p><b>Objective outcomes:</b></p> <ol style="list-style-type: none"> <li>Norton score</li> <li>Skin condition grading, performed by a single assessor: normal, 0; mild persistent erythema, 1; moderate persistent erythema, 2; severe persistent erythema, 3; localised superficial blistering, 4; deep localised or extensive superficial blistering; 5</li> </ol> <p>Patients were examined weekly during the trial</p> <p><b>Setting and length of treatment:</b> Inpatients. Trial duration 3 weeks</p>	<p><b>Inclusion criteria:</b> Chair-bound patients with a Norton score of 5–14</p> <p><b>Exclusion criteria:</b> Existing pressure ulcers, severe or terminal illness, likely hospital stay of &lt; 3 weeks</p>	<p><b>I (n = 60):</b> Pressure-area care performed twice daily, or more frequently in cases of incontinence, as follows. Buttocks and sacrum were washed and dried, and Prevasore lotion (0.05% hexyl nicotinate, zinc stearate, isopropyl myristate, dimethicone 350, cetrimide and glycerol) applied. No other topical preparations were used. Existing routine procedures to prevent pressure ulcers were continued (not described). No vitamin C or zinc supplements to be given</p> <p><b>C (n = 60):</b> Treatment as intervention group, except that Dermalex (hexachlorophane, squalene, allantoin) lotion was used in place of Prevasore</p>	<p>Data are for 54/50 patients in the intervention and control groups</p> <p><b>Gender (male/female):</b> I: 14/40 C: 13/37</p> <p><b>Average (range) age:</b> I: 82.2 (53–98) years C: 82.9 (64–97) years</p> <p><b>Mean (range) Norton score:</b> I: 11.4 (8–14) C: 11.5 (9–16)</p> <p><b>Mean (range) skin score:</b> I: 0.5 (0–2) C: 0.5 (0–3)</p>	<p>Data are for 54/50 patients in the intervention and control groups at 3 weeks</p> <p><b>Mean (range) Norton score:</b> I: 13.4 (7–20) C: 13.9 (9–18) (not significant)</p> <p><b>Mean (range) skin score:</b> I: 0.4 (0–2) C: 0.6 (0–5) (not significant)</p> <p><b>No deterioration/improvement:</b> I: 87% C: 78% (not significant)</p> <p>Three patients in the control group showed a marked deterioration in skin condition during the study</p>	<p><b>Criteria for withdrawal:</b> Patients were withdrawn if their Norton score rose above 17</p> <p><b>Total withdrawals (I/C, 6/10):</b> Death: 8 Discharged: 6 Transferred: 1 Wet ulcer developed: 1</p>	<p><b>Reviewers' comments:</b> Inclusion of an intention-to-treat protocol would have strengthened the analysis of this study. The graded skin assessment scale is likely to produce low reliability, particularly in distinguishing between three different levels of persistent erythema. Assessment was carried out by a single investigator, with no report of reliability checks. Since the skin scores are ordinal numbers, it would have been more useful if median or mode values had been reported rather than mean scores</p>
C, control group; I, intervention group						

TABLE 6 Pressure ulcers: treatment

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>Gerding and Browning, 1992,<sup>29</sup> USA</p> <p><b>Study design:</b> RCT (double blinded)</p> <p><b>Method of randomisation:</b> Random allocation lists (unclear whether these were open lists)</p> <p><b>Unit of allocation:</b> Patients: Approximately twice as many patients were allocated to the intervention than to the control group, but it is unclear whether this was part of the study protocol. The unit of analysis was lesions</p> <p><b>Sample size:</b> No <i>a priori</i> power calculation reported</p> <p><b>Objective outcomes:</b> I. Complete healing, improvement, no change or worse. Lesions were assessed daily by a blinded assessor. The progression of healing was evaluated on the basis of change in lesion size, intensity and extent of surrounding erythema, the presence or</p>	<p><b>Inclusion criteria:</b> Geriatric residents of long-term care facilities, with one or more pressure ulcers, newly diagnosed as stage I or II (see below for definitions). Residents to be prescribed emollient as treatment for pressure ulcers</p> <p><b>Exclusion criteria:</b> Not reported</p> <p><b>Staging of lesions:</b> Stage I is defined as an area of erythema that persists for &gt; 30 minutes after pressure is relieved. No skin breakdown is evident, yet the affected area does not blanch or fade</p> <p>Stage II is defined as an area of superficial breakdown which involves the epidermis and/or dermis. It appears as an abrasion, a blister or a shallow crater</p>	<p>74 patients with 137 lesions were randomised</p> <p><b>I:</b> The area was washed with soap and water, and DermaMend (oxyquinoline ointment) applied. This was carried out at least 3 times per day, or whenever cleansing the area.</p> <p>Number of patients: stage I lesions, <i>n</i> = 29; stage II lesions, <i>n</i> = 26; some patients had both types of lesion</p> <p>Number of ulcers: overall, <i>n</i> = 86; stage I lesions, <i>n</i> = 41; stage II lesions, <i>n</i> = 45</p> <p><b>C:</b> The area was washed with soap and water and A&amp;D ointment (a standard emollient) was applied. This was carried out at least 3 times per day, or whenever cleansing the area</p> <p>Number of patients: stage I lesions, <i>n</i> = 14; stage II lesions, <i>n</i> = 13; some patients had both types of lesion</p> <p>Number of ulcers: overall, <i>n</i> = 51; stage I lesions, <i>n</i> = 28; stage II lesions, <i>n</i> = 23</p>	<p>Average ulcer area: Stage I lesions: 1, 18.9 cm<sup>2</sup>; C, 4.3 cm<sup>2</sup>                      Stage II lesions: 1, 1.0 cm<sup>2</sup>; C, 1.2 cm<sup>2</sup></p> <p>DermaMend-treated stage I lesions were 4.4 times larger than A&amp;D-treated lesions. No significant group difference in size of stage II lesions</p> <p>No details given of the demographic characteristics of participants</p>	<p>Results at 28 days</p> <p>% of lesions completely healed:</p> <p>Stage I lesions: 1, 58.5; C, 57.1 (not significant)</p> <p>Stage II lesions: 1, 44.5; C, 21.8 (<i>p</i> &lt; 0.05)</p> <p>% of improved lesions (excluding complete healing):</p> <p>Stage I lesions: 1, 31.7; C, 21.4 (not significant)</p> <p>Stage II lesions: 1, 42.2; C, 34.8 (not significant)</p> <p>% of lesions healed or improved:</p> <p>Stage I lesions: 1, 90; C, 72 (<i>p</i> = 0.05)</p> <p>Stage II lesions: 1, 87; C, 57 (<i>p</i> &lt; 0.03)</p> <p>% of lesions unchanged:</p> <p>Stage I lesions: 1, 9.8; C, 14.3 (not significant)</p> <p>Stage II lesions: 1, 11.1; C, 30.4 (not significant)</p> <p>% of deteriorated lesions:</p> <p>Stage I lesions: 1, 0; C, 7.2 (not significant)</p> <p>Stage II lesions: 1, 2.2; C, 13.0 (not significant)</p> <p>Days to complete healing:</p> <p>Stage I lesions: 1, 6.2; C, 7.3 (not significant)</p> <p>Stage II lesions: 1, 7.8; C, 13.0 (<i>p</i> &lt; 0.05)</p>	<p>No details given</p>	<p>Fewer applications of DermaMend were required for stage II lesions to heal (because the DermaMend-treated lesions healed more rapidly). The subjective (unblinded) impression of nurses was that DermaMend worked better (data collected by questionnaire). The units of allocation were stated to be patients, but the numbers allocated to each treatment are unclear (there was an overlap because some patients had both stage I and stage II lesions)</p>
<p>C, control group; I, intervention group</p>						

continued



TABLE 6 contd Pressure ulcers: treatment

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>absence of drainage, and the presence or absence of granulation</p> <p>2. Time to complete healing</p> <p>3. Nurses' preferences (unblinded) for the two treatments</p> <p><b>Setting and length of treatment:</b> Three long-term care institutions. Study duration 28 days or until resolution</p>		<p>No details were given about the extent to which the ointments were applied (to lesion only, or to lesion and surrounding skin), type of dressing applied, or the use of pressure-relieving surfaces</p>				
<p>Huchon, 1992,<sup>31</sup> France</p> <p><b>Study design:</b> RCT (multicentre, open)</p> <p><b>Method of randomisation:</b> Not stated</p> <p><b>Unit of allocation:</b> Patients</p> <p><b>Sample size:</b> No <i>a priori</i> power calculation reported</p> <p><b>Objective outcomes:</b></p> <p>1. Clinical assessment, classified into four stages: healing or re-epithelialisation of wound area, 1; improvement (reduction in wound</p>	<p><b>Inclusion criteria:</b></p> <p>Patients with pressure ulcers, which were graded, after debridement, as either: stage 2 (loss of epidermal tissue) or stage 3 (slough, or slough with loss of substance)</p> <p><b>Exclusion criteria:</b></p> <p>Diabetes; corticosteroid treatment</p>	<p><b>I (n = 38):</b> Lesions cleaned with saline, debrided with forceps if necessary, and a hydrocolloid dressing applied (Granuflex, ConvaTec). No anti-septics were used. Dressings were changed weekly, or more often in cases of excessive gel leakage</p> <p><b>C (n = 38):</b> Lesions cleaned with saline; debrided with forceps if necessary; lesions dressed with gauze impregnated with povidone iodine ointment. Dressings changed daily or every other day</p>	<p>76 patients entered the trial</p> <p>Groups were stated to be comparable for ulcer area, but data per group were not given. Overall mean ulcer area 15 cm<sup>2</sup>. Most wounds were necrotic</p> <p>Groups were stated to be comparable for age, gender distribution, body weight, development and duration of the pressure ulcer, and Norton score.</p> <p>Overall mean age: 81 years</p> <p>Mean Norton score:</p> <p>I: 14.1</p> <p>C: 13.8</p>	<p>Results at 56 days</p> <p><i>Number (%) of improved ulcers (number of ulcers completely or partially healed):</i></p> <p>I: 32/38 (84%) (10/22)</p> <p>C: 27/38 (71%) (9/18) (not significant)</p> <p><i>Mean rate of ulcer area reduction per week:</i></p> <p>I: 10%</p> <p>C: 7% (not significant)</p> <p><i>Adverse effects:</i> None</p> <p><i>Mean number of dressings per week per patient:</i></p> <p>I: 2.43</p> <p>C: 5.07 (p &lt; 0.0001)</p>	<p>Withdrawals due to deterioration in lesion (increase in area or slough): I, 2; C, 5</p>	<p>This is a duplicate publication. See Barrois (1991).<sup>112</sup> The use of Granuflex dressings may save nurse time because fewer changes are needed. Since the Norton score involves the use of ordinal values, it would have been more useful to have the median or mode reported at baseline, as opposed to the mean number. No details were given of the nursing-care protocols used in the different centres or of the different grades of pressure ulcers in each group</p>
C, control group; I, intervention group						
						continued

TABLE 6 contd Pressure ulcers: treatment

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>area or on-going granulation), 2; no change, 3; deterioration, 4</p> <p>2. Wound surface area (tracing onto acetate and photography)</p> <p><b>Setting and length of treatment:</b> The trial was carried out in six centres (one surgical, two functional rehabilitation, three elderly care). Trial duration 56 days or until healing</p>	<p>Pressure ulcers of the heel were predominant compared to other sites (sacrum, trochanter, malleolus)</p>	<p>Pressure ulcers of the heel were predominant compared to other sites (sacrum, trochanter, malleolus)</p>	<p>Pressure ulcers of the heel were predominant compared to other sites (sacrum, trochanter, malleolus)</p>	<p>Results at 14 weeks</p> <p>Change in wound area (mean <math>\pm</math> SD % of baseline area):</p> <p>I: 44.6 <math>\pm</math> 12.9</p> <p>C: 55.7 <math>\pm</math> 24.0 (not significant)</p> <p>Change in wound area: Positive culture for MRSA (n = 7): 93.2 <math>\pm</math> 23.7% of baseline area</p> <p>Negative culture for MRSA (n = 12): 26.5 <math>\pm</math> 7.3% of baseline area (p &lt; 0.01)</p> <p>Eradication rate of MRSA: I: 92.9%</p> <p>C: 74.3% (p &lt; 0.01)</p>	<p>No details reported, although it appears that there were no withdrawals</p>	<p>The trial was very small; larger numbers may be required to detect the true treatment effect. The authors considered that the non-significant difference for change in wound area may have been due to the two largest pressure ulcers (&gt; 50 cm<sup>2</sup>) being in the intervention group. They recommend better baseline matching for wound area in subsequent trials</p>
<p>Toba, 1997,<sup>47</sup> Japan</p> <p><b>Study design:</b> RCT</p> <p><b>Method of randomisation:</b> Random-number tables</p> <p><b>Unit of allocation:</b> Pressure ulcers</p> <p><b>Sample size:</b> No a priori power calculation reported</p> <p><b>Objective outcomes:</b></p> <p>I. Change in wound area, assessed fortnightly using photography. Method of calculating the percentage change in area relative to baseline not reported</p>	<p><b>Inclusion criteria:</b> Elderly women who had suffered a stroke, with pressure ulcers contaminated with MRSA during the month preceding the trial</p> <p><b>Exclusion criteria:</b> Diabetes, malignant tumour, respiratory disease, liver or kidney disease, patients taking prostaglandins, anticoagulants or steroids</p>	<p><b>I (n = 8 pressure ulcers):</b> An ointment containing gentian violet 0.1% was blended with dibutylcAMP ointment, in equal amounts, to produce a preparation called GVcAMP. Enough was applied to cover the pressure ulcer, every day. Other dressings and use of pressure relief not described</p> <p><b>C (n = 11 pressure ulcers):</b> Povidone iodine (concentration not stated) and sugar ointment applied to pressure ulcers every day. Other dressings and use of pressure relief not described</p>	<p>14 patients with 19 pressure ulcers were recruited. Mean <math>\pm</math> SD age for whole sample: 83.5 <math>\pm</math> 3.0 years</p> <p>It is stated that the prevalence of underlying disease and nutritional status, and age distribution, were similar between the two groups, but no detailed information was provided</p> <p>Pressure ulcer area: I: 25.4 <math>\pm</math> 8.1 cm<sup>2</sup></p> <p>C: 12.8 <math>\pm</math> 4.2 cm<sup>2</sup> (not significant)</p> <p>The intervention group included the two largest pressure sores of the sample (area &gt; 50 cm<sup>2</sup>)</p>	<p>Results at 14 weeks</p> <p>Change in wound area (mean <math>\pm</math> SD % of baseline area):</p> <p>I: 44.6 <math>\pm</math> 12.9</p> <p>C: 55.7 <math>\pm</math> 24.0 (not significant)</p> <p>Change in wound area: Positive culture for MRSA (n = 7): 93.2 <math>\pm</math> 23.7% of baseline area</p> <p>Negative culture for MRSA (n = 12): 26.5 <math>\pm</math> 7.3% of baseline area (p &lt; 0.01)</p> <p>Eradication rate of MRSA: I: 92.9%</p> <p>C: 74.3% (p &lt; 0.01)</p>	<p>No details reported, although it appears that there were no withdrawals</p>	<p>The trial was very small; larger numbers may be required to detect the true treatment effect. The authors considered that the non-significant difference for change in wound area may have been due to the two largest pressure ulcers (&gt; 50 cm<sup>2</sup>) being in the intervention group. They recommend better baseline matching for wound area in subsequent trials</p>
<p>C, control group; I, intervention group</p>						<p>continued</p>

TABLE 6 contd Pressure ulcers: treatment

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>2. Eradication of MRSA was assessed, using fortnightly cultures from the wound surface</p> <p><b>Setting and length of treatment:</b> Inpatients, single-centre trial. Treatment duration 14 weeks</p>				<p><i>Adverse effects:</i> No local or systemic adverse effects were observed in either group</p>		

TABLE 7 contd Diabetic foot ulcers: systemic agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>Chantrelau, 1996,<sup>6</sup> Germany</p> <p><b>Study design:</b> RCT (double blinded)</p> <p><b>Method of randomisation:</b> Computer-generated code</p> <p><b>Unit of allocation:</b> Patients</p> <p><b>Sample size:</b> No a priori power calculation reported</p> <p><b>Objective outcomes:</b></p> <ol style="list-style-type: none"> <li>Rate of reduction in ulcer size (surface area calculated by planimetry, transformed into a circle, changes in the circle radius over time were recorded)</li> <li>Frequency of complete healing (standardised photographs)</li> <li>Adverse effects</li> <li>Compliance with pressure relief (graded as optimal, sufficient or insufficient, according to clinical judgement)</li> <li>Bacteriology (cultures)</li> </ol> <p><b>Setting and length of treatment:</b> It appears that some patients were</p>	<p><b>Inclusion criteria:</b></p> <p>Diabetic patients with polyneuropathy, with skin and soft tissue lesions of the forefoot, and aged &gt; 18 years were included. Foot lesions were graded as IA to 2A, according to Wagner and Harkless classification (see below for definitions)</p> <p><b>Exclusion criteria:</b></p> <p>Known hypersensitivity to test medication, antibiotic treatment during the preceding 7 days, bilateral foot lesions, presence of osteomyelitis or peripheral vascular disease, pregnancy, serum creatinine level &gt; 130 µmol/l, immune depression due to underlying disease, prior organ transplantation, immunosuppressive drug therapy, micro-organisms unresponsive to test medication, inability to comply with protocol</p> <p><b>Wagner and Harkless classification of diabetic foot lesions:</b></p> <p>Grade IA: superficial, with or without cellulitis</p>	<p><b>I (n = 22 patients):</b></p> <p>Amoxicillin 500 mg plus clavulanic acid 125 mg, orally, three times daily</p> <p><b>C (n = 22 patients):</b></p> <p>Identical placebo</p> <p><b>All patients:</b> Mechanical debridement. The lesion was cleaned with a topical disinfectant (Dibromol solution) and dressed with cotton gauze and paraffinated non-adhering gauze. Pressure relief was provided through the use of a half-shoe, crutches and wheelchairs</p> <p>Outpatient treatment was carried out by a qualified nurse repeating the above wound-care procedure daily at the patient's home</p> <p>The study was stopped when the antibiotic proved unsuitable according to baseline cultures (at days 3 or 6), or if no clinical improvement was seen within 6 days, or if the study protocol was violated due to incomplete pressure relief or adverse effects of the medication</p>	<p>Mean (95% CI) ulcer area: I: 214 (154 to 274) mm<sup>2</sup> C: 220 (162 to 422) mm<sup>2</sup></p> <p>Mean (95% CI) diabetes duration: I: 22 (17 to 27) years C: 19 (14 to 24) years</p> <p>Insulin dependent: I: 11/22 (50%) C: 12/22 (55%)</p> <p>Gender (male/female): I: 16/6 C: 12/10</p> <p>Mean (95% CI) age: I: 58 (54 to 62) years C: 59 (55 to 63) years</p> <p>Bacteriology: Cultures presented</p>	<p>Results at 20 days</p> <p>Mean (95% CI) reduction in ulcer radius: I: 0.27 (0.15 to 0.39) mm/day C: 0.41 (0.21 to 0.61) mm/day (not significant)</p> <p>Complete healing: I: 6/22 (27%) C: 10/22 (45%) (not significant)</p> <p>Adverse effects: One case of diarrhoea in the antibiotic group, which did not require withdrawal</p> <p>Compliance rated as optimal: I: 16/19 (84%) patients C: 18/20 (90%) patients (not significant)</p>	<p>Five patients (I, 3; C, 2) were withdrawn within 6 days of the start of the trial due to non-compliance or bacteria unresponsive to the antibiotic</p>	<p>This was a small study, and possibly was not powerful enough to detect true treatment effects</p>
<p>C, control group; I, intervention group</p>						<p>continued</p>

TABLE 7 contd Diabetic foot ulcers: systemic agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
treated as inpatients and some as outpatients; however, no breakdown by numbers was given. Trial duration 20 days. Patients were assessed on days 3, 6, 14 and 20	Grade 2A: deeper, reaching to joints and tendons					
Lipsky, 1990, <sup>7</sup> USA <b>Study design:</b> RCT <b>Method of randomisation:</b> Not stated <b>Unit of allocation:</b> Patients <b>Sample size:</b> No calculation reported <b>Objective outcomes:</b> 1. Wound measurement (maximum width and length measured with ruler, photographs taken). Wound size graded as: healed (complete skin closure), 1; healing progress (lesions substantially smaller), 2; unimproved (lesions without healing), 3. Outcome assessment was blinded	<b>Inclusion criteria:</b> Diabetic outpatients referred to the Washington State Veterans Affairs Medical Center because of non-limb-threatening lower extremity infections. Clinically infected lesions were defined as the recent development of purulence or at least two of the following: erythema, warmth, tenderness, induration, fluctuance, drainage <b>Exclusion criteria:</b> Systemic or topical antimicrobial therapy within the preceding 2 weeks, presence of systemic toxicity, an infection that was immediately threatening to life or limb, patient unable to perform daily wound	<b>I (n = 27 patients):</b> Clindamycin 300 mg orally, four times daily for 2 weeks. <b>C (n = 29 patients):</b> Cephalexin 500 mg orally, four times daily for 2 weeks <b>All patients:</b> At the initial evaluation, lesions were cleaned with half-strength hydrogen peroxide, debrided mechanically and covered with a gauze dressing. Patients were instructed to elevate the affected limb and avoid unnecessary ambulation. Patients were also instructed to clean any open lesions twice daily with half-strength hydrogen peroxide and cover with gauze for the first few days. Dry and	60 male patients entered the study <i>Mean ± SEM age:</i> I: 59.4 ± 2.3 years C: 62.7 ± 2.4 years <i>Patients with an ulcerated lesion:</i> I: 24/27 (89%) C: 27/29 (93%)	Results at 2 weeks <i>Complete healing:</i> I: 10/25 (40%) C: 9/27 (33%) <i>Improved lesions:</i> I: 14/25 (56%) C: 18/27 (67%) <i>Lesions not improved:</i> I: 1/25 (4%) C: 0/27 (0%) <i>Adverse effects:</i> I: 1 patient had mild diarrhoea C: 2 patients had mild nausea and diarrhoea No tests of statistical significance reported	Osteomyelitis: 2 Requested hospitalisation during trial: 1 Non-adherence with study regimen: 1	
C, control group; I, intervention group						
						continued

TABLE 7 contd Diabetic foot ulcers: systemic agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>2. Microbiology (cultures)</p> <p><b>Setting and length of treatment:</b> Outpatients enrolled between October 1985 and March 1988. Trial duration 2 weeks, or until infection cleared</p>	<p>care, history of non-adherence with outpatient treatment, unwilling to return for outpatient visits, allergy to study drugs</p>	<p>epithelialising lesions were simply covered with gauze</p>				

TABLE 8 Diabetic foot ulcers: topical agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>Vandeputte and Gryson (unpublished),<sup>24</sup> Belgium</p> <p><b>Study design:</b> RCT</p> <p><b>Method of randomisation:</b> Pre-prepared random listing (unclear whether the list was open)</p> <p><b>Unit of allocation:</b> Patients</p> <p><b>Sample size:</b> No <i>a priori</i> power calculation reported</p> <p><b>Objective outcomes:</b> Overall wound healing (photography); amputation rates</p> <p><b>Setting and length of treatment:</b> Setting not stated. Trial duration 3 months</p>	<p><b>Inclusion criteria:</b> Diabetic people with foot ulcers. Ulcers could be neuropathic, necrotic or infected. Participants could already have toes amputated</p> <p><b>Exclusion criteria:</b> Patients taking systemic antibiotics</p>	<p><b>All patients:</b> Prescribed insulin and a diabetic diet. All could receive systemic antibiotics and topical antibiotics or antiseptics if necessary</p> <p><b>I (n = 15 patients):</b> Wounds cleaned with Flami-Clens<sup>®</sup> (saline and 8% vinegar acid as buffer) and covered with a hydrogel dressing. Wound cavities were filled with an alginate dressing. One patient received systemic antibiotics</p> <p><b>C (n = 14 patients):</b> Wounds were treated twice daily, irrigated with chlorhexidine 0.05% solution and covered with dry gauze. All patients received systemic or topical antibiotics or topical antiseptic creams. Six patients received systemic antibiotics. The most frequently used topical preparation was povidone iodine cream</p>	<p>All patients had insulin-dependent diabetes</p> <p><b>Gender (male/female):</b> I: 7/8 C: 6/8</p> <p><b>Mean ± SD age:</b> I: 62.6 ± 14.7 years C: 65.3 ± 14.3 years</p> <p><b>Completely mobile:</b> I: 12/15 (80%) C: 11/14 (79%)</p> <p><b>Neuropathy:</b> I: 9/15 (60%) C: 9/14 (64%)</p> <p><b>Infection present prior to trial:</b> I: 1/15 (7%) C: 1/14 (7%)</p>	<p><i>Need for systemic or topical antimicrobials during the trial:</i> I: 1/15 (7%) C: 14/14 (100%) (<i>p</i> &lt; 0.0001)</p> <p>One patient in the intervention group and six patients in the control group were given systemic antibiotics</p> <p><i>Toe amputation during trial:</i> I: 1/15 (7%) C: 5/14 (36%) (<i>p</i> = 0.053)</p> <p><i>Complete healing at 3 months:</i> I: 14/15 (93%) C: 7/14 (50%) (<i>p</i> &lt; 0.05)</p> <p><i>No improvement:</i> I: 4/15 (27%) C: 1/14 (7%)</p> <p><i>Slight improvement:</i> I: 1/15 (7%) C: 0/14 (0%)</p> <p><i>Died during trial:</i> I: 0/15 (0%) C: 2/14 (14%)</p>	<p>Two patients died during the trial, both were in the control group</p>	<p>The use of the hydrogel dressing was found to significantly reduce nursing labour time because it stayed <i>in situ</i> for over 5 days</p>
C, control group; I, intervention group						

TABLE 9 Pilonidal sinuses: systemic agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>Søndena, 1995,<sup>25</sup> Norway</p> <p><b>Study design:</b> RCT</p> <p><b>Method of randomisation:</b> Sealed envelopes, opened prior to anaesthesia</p> <p><b>Unit of allocation:</b> Patients, allocated by randomised blocks of 5</p> <p><b>Sample size:</b> No <i>a priori</i> power calculation reported</p> <p><b>Objective outcomes:</b></p> <ol style="list-style-type: none"> <li>1. Time to healing (healing defined as a dry wound with closure of wound edges)</li> <li>2. Wound complications, recurrence of disease</li> <li>3. Microbiology: cultures and sensitivities of material from sinuses taken perioperatively. Cultures were also taken from wounds with post-operative infection</li> </ol> <p><b>Setting and length of treatment:</b> Department of Surgery, Rogaland Central Hospital, Stavanger, Norway, 1991–1992. Follow-up 18–30 months</p>	<p><b>Inclusion criteria:</b> Chronic pilonidal sinus disease</p> <p><b>Exclusion criteria:</b> Acute abscess</p>	<p><b>I (n = 25):</b> Antibiotic prophylaxis (Cefoxitin 2 g intravenously) given preoperatively. Surgery consisted of excision and primary suture (gauze roll wrapped in non-adhering dressing with affinity for bacteria was used with retention sutures). Gauze roll and retention sutures removed 1 week post-operatively. Skin sutures removed after 14 days, and wound examined by surgeon. Patients then allowed to return to work, but physical activity was restricted for another 2 weeks</p> <p><b>C (n = 26):</b> Treatment as for intervention group, but with no antibiotic prophylaxis</p>	<p>Characteristics for whole sample (no breakdown by group given)</p> <p>Gender (male/female): 35/16</p> <p>Median (range) age: Males: 29 (14–63) years Females: 21 (16–52) years</p> <p>Four patients had recurrent disease after previous surgery</p>	<p>Analysis: <math>\chi^2</math> test with Yates correction used to compare frequencies</p> <p>Mean/median (range) initial time to healing: I: 4.7/4.0 (1.9–12.6) weeks (95% CI 3.3 to 6.1) C: 5.2/3.9 (1.9–11.1) weeks (95% CI 3.8 to 6.6)</p> <p>Complications (patients (%), I/C): Wound infection: 11(44)/13(50) Discharge or pus: 14(56)/13(50) Wound rupture: 13(52)/13(50) Wound dehiscence: 1(4)/1(4) Haematoma: 4(16)/1(4) Wound incised: 4(16)/8(31) New infection: 0/0 Recurrent disease: 0/0 Repeat surgery: 4(16)/4(15)</p> <p>Some patients had more than one complication</p> <p>Microbiological results are given</p> <p>Preoperative presence of bacteria was not significantly associated with wound complications</p>	<p>None (all patients were followed-up for at least 1 year)</p>	
C, control group; I, intervention group						

continued



TABLE 9 contd Pilonidal sinuses: systemic agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>Kronborg, 1985,<sup>16</sup> Denmark</p> <p><b>Study design:</b> RCT</p> <p><b>Method of randomisation:</b> Balanced randomisation</p> <p><b>Unit of allocation:</b> Patients</p> <p><b>Sample size:</b> No <i>a priori</i> power calculation reported</p> <p><b>Objective outcomes:</b> Healing rates, time to healing, recurrence rates. Follow-up was at 3, 6, 12, 24 and 36 months postoperatively</p> <p><b>Setting and length of treatment:</b> Surgical in-patients admitted between 1978 and 1981. Surgical study with 3-year postoperative follow-up</p>	<p><b>Inclusion criteria:</b> Patients with chronic discharging pilonidal sinuses, able to receive any of the three treatments</p> <p><b>Exclusion criteria:</b> Multiple sinuses over a wide area, making suture impossible</p>	<p><b>I1: Excision only (n = 32).</b> Conservative excision performed. Wound packed with petroleum gauze covered by a T-shaped dressing. Wound changed daily by community nurse; patients seen weekly in clinic until full healing occurred</p> <p><b>I2: Excision + suture (n = 33).</b> Conservative excision, cavity closed with deep and superficial sutures. Deep sutures removed after 7 days bed-rest, superficial sutures removed after 10 days</p> <p><b>I3: Excision + suture + clindamycin (n = 34).</b> Surgery/sutures as for I2 plus clindamycin 600 mg intramuscularly pre-operatively, then 150 mg orally, four times daily for 4 days</p> <p><b>All patients:</b> Treatment involved 1 week of inpatient care. Patients were instructed to shave natal cleft area every 4 weeks during follow-up</p>	<p><b>Gender(male/female):</b> I1: 27/5 I2: 25/8 I3: 28/6</p> <p><b>Median age (range):</b> I1: 28 (16–47) years I2: 23 (15–45) years I3: 25 (16–52) years</p> <p><b>Previous surgery:</b> I1: 18/32 (56%) patients I2: 22/33 (67%) patients I3: 17/34 (50%) patients</p> <p>The number and length of sinuses was similar in all three groups. Two-thirds of patients had more than one sinus</p>	<p><b>Healing rates (number of patients) (I1/I2/I3):</b> With no further surgery: 29/29/30 With revisional surgery: 2/3/1 Healing with development of new sinuses (subsequently treated by excision): 1/0/3 Failure to heal: 0/1/0 (all above non-significant, <math>\chi^2</math>)</p> <p><b>Median (range) days to healing without revisional surgery:</b> I1: 64 (17–157) I2: 14 (9–203) I3: 11 (7–102) (<math>p &lt; 0.001</math> for I1 vs I2 and I1 vs I3, not significant for I2 vs I3)</p> <p><b>Median (range) days to healing including revisional surgery:</b> I1: 66 (17–157) I2: 22 (9–203) I3: 11 (7–102) (<math>p &lt; 0.001</math> for I1 vs I2, not significant for I2 vs I3)</p> <p><b>Recurrence (number of patients) after 3 months/3 years:</b> I1: 0/4 I2: 4/4 I3, 3/3 (not significant)</p>	<p>One patient (I2) was withdrawn who failed to heal despite reconstructive surgery, different antiseptics and antibiotics, and radiotherapy</p>	<p>No adverse effects observed with clindamycin use</p>
I, I1, I2, I3, intervention groups						
						continued

TABLE 9 contd Pilonidal sinuses: systemic agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>Marks, 1985.<sup>44</sup> UK</p> <p><b>Study design:</b> CCT</p> <p><b>Method of treatment allocation:</b> Alternate allocation</p> <p><b>Unit of allocation:</b> Patients</p> <p><b>Sample size:</b> No <i>a priori</i> power calculation reported</p> <p><b>Objective outcomes:</b></p> <p>I. Mean delay in healing (defined as the difference between the observed healing time and the time predicted from wound size, based on the regression line relating healing time to wound size from</p>	<p><b>Inclusion criteria:</b> Patients with pilonidal sinuses</p> <p><b>Exclusion criteria:</b> Pregnancy</p>	<p><b>I (n = 20 patients):</b> Excision of pilonidal sinuses, wound packed with gauze soaked in proflavine paraffin emulsion for 3 days post-operatively, then silastic foam dressing applied. Patients were instructed to bathe their wounds and disinfect the foam (using Hibitane) twice daily prior to discharge. They then attended the clinic weekly for assessment and renewal of foam. When the wound had filled and contracted,</p>	<p>No information given</p>	<p>There was no recurrence in 4 patients who had excision after initial healing for new sinuses. Neither revisional surgery nor previous surgery was a risk factor for recurrence</p> <p><i>Median (total) days spent in healing after initial surgery and excision of recurrences within 3 years:</i></p> <p>I1: 67 (2659)</p> <p>I2: 33 (1642)</p> <p>I3: 13 (1815)</p> <p>(<math>p &lt; 0.001</math> for I1 vs I2, not significant for I2 vs I3)</p>	<p>None reported</p>	<p>This paper reported three studies, only one of which was suitable for inclusion in this review. No data were given on the baseline characteristics of participants. Minimal inclusion and exclusion criteria reported</p>
<p>C, control group: I, I1, I2, I3, intervention groups</p>						
						<p>continued</p>

TABLE 9 contd Pilonidal sinuses: systemic agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>a reference group); development of pockets in wound base post-operatively</p> <p>2. Referral for further surgery</p> <p>3. Microbiology: swabs taken at intervals of 1 or 2 weeks</p> <p><b>Setting and length of treatment:</b> Inpatients initially, then managed as outpatients. Metronidazole given for 2 weeks. Followed up to complete healing or surgical referral</p>		<p>the foam was replaced with dry gauze. Poorly draining wound pockets were opened with forceps or a scalpel, and premature epithelial bridging was split by gentle distraction. Patients attended the clinic until healing or referral for further surgery because of failure to heal</p> <p>Patients in this group also received metronidazole, 400 mg orally, three times daily for 2 weeks, commencing at first clinic attendance (usually 7–14 days after surgery)</p> <p><b>C (n = 20 patients):</b> Treatment as for the intervention group, but without metronidazole</p>				
C, control group						

TABLE 10 Pilonidal sinuses: topical agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>Vogel and Lenz, 1992,<sup>26</sup> Germany</p> <p><b>Study design:</b> RCT</p> <p><b>Method of randomisation:</b> Random-numbers table</p> <p><b>Unit of allocation:</b> Patients</p> <p><b>Sample size:</b> No <i>a priori</i> power calculation reported</p> <p><b>Objective outcomes:</b> Incidence of postoperative abscess; secondary surgery; bacteriology</p> <p><b>Setting and length of treatment:</b> Inpatients. One-year postoperative follow-up (patients unable to come to hospital for examination were asked for reply by questionnaire)</p>	<p><b>Inclusion criteria:</b> Pilonidal sinuses</p> <p><b>Exclusion criteria:</b> Not stated</p>	<p><b>I (n = 40 patients):</b> Surgical excision of pilonidal sinuses, followed by insertion of collagen sponge impregnated with gentamicin (different sizes of sponge available, prescribed according to wound size), wound closed using subcutaneous sutures in 1 or 2 layers, then skin closed and pressure dressing applied</p> <p><b>C (n = 40 patients):</b> As intervention group, but without sponge</p> <p><b>All patients:</b></p> <p><i>Preoperative care:</i> abscesses were lanced, then wound packed and pressure dressing applied for 2 days</p> <p><i>Post-operative care:</i> daily dressing change was commenced on the second postoperative day, and sutures were removed on the ninth postoperative day</p>	<p>Few details were given per treatment arm. Groups stated to be comparable for size of excision, number of sinuses, presence of abscess preoperatively, duration of disease (range from &lt; 3 months to 1 year), hair growth and obesity</p>	<p><math>\chi^2</math> test used for comparisons</p> <p>Rate of primary healing: I: 87.5% C: 35% (<math>p &lt; 0.001</math>)</p> <p>Secondary healing (healing rates following secondary surgery): I: 5/40 (13%) C: 25/40 (63%)</p> <p>Reasons for secondary surgery: Abscess (23/80 patients): I, 7.5%; C, 50% Serum accumulation (cyst): I, C, 3 Haematoma: I, C, 2</p> <p>Follow-up data on 61/80 patients: 55 came to hospital; 6 went to GP for examination and to complete questionnaire</p> <p>No recurrence of disease in either group</p>	None	<p>For patients with pre-operative abscesses, there was less need for secondary surgery. Neither strong hair growth nor obesity was associated with recurrence after initial surgery</p>
C, control group; I, intervention group						
continued						

TABLE 10 contd Pilonidal sinuses: topical agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p>Williams, 1981,<sup>28</sup> UK</p> <p><b>Study design:</b> RCT (multicentre)</p> <p><b>Method of randomisation:</b> Not stated</p> <p><b>Unit of allocation:</b> Patients</p> <p><b>Sample size:</b> No a priori power calculation reported</p> <p><b>Objective outcomes:</b> Time to healing; length of hospital stay</p> <p><b>Setting and length of treatment:</b> Initially treated as inpatients, then as outpatients. All patients followed up to complete healing</p>	<p><b>Inclusion criteria:</b> Patients with pilonidal sinuses</p> <p><b>Exclusion criteria:</b> None stated</p>	<p><b>All patients:</b> Sinuses were excised, then packed for 4 days with a gauze roll soaked in flavine emulsion. When this was removed, the wound was measured, and the patient was randomised to receive one of the following</p> <p><b>I (n = 44):</b> Silastic foam dressing, refashioned at weekly intervals</p> <p><b>C (n = 36):</b> Daily packing with gauze soaked in a 0.5% aqueous solution of chlorhexidine</p>	<p><b>Mean ± SD wound volume:</b> I: 59 ± 57.7 ml C: 64 ± 74.5 ml The methods for assessing wound volume were not described</p>	<p><b>Mean ± SD time packed:</b> I: 41.5 ± 21.2 days C: 41.8 ± 26.7 days (not significant)</p> <p><b>Mean ± SD time to healing:</b> I: 66.2 ± 26.1 days C: 57.7 ± 19.6 days (not significant)</p> <p><b>Mean ± SD time in hospital:</b> I: 8.5 ± 12.3 days C: 7.3 ± 6.2 days (not significant)</p> <p><b>Mean ± SD work time lost:</b> I: 38.6 ± 24.9 work days C: 45.4 ± 19.9 work days (not significant)</p> <p><b>Mean ± SD number of home nursing visits:</b> I: 4.6 ± 1.5 C: 35.1 ± 17.4 (<i>p</i> &lt; 0.0001, unpaired <i>t</i>-test, calculated by reviewer)</p>	None	Data extracted from brief report
<p>Walker, 1991,<sup>27</sup> UK</p> <p><b>Study design:</b> RCT</p> <p><b>Method of randomisation:</b> Not stated</p> <p><b>Units of allocation:</b> Patients</p>	<p><b>Inclusion criteria:</b> Patients with pilonidal sinuses or pilonidal abscesses</p> <p><b>Exclusion criteria:</b> Not stated</p>	<p><b>All patients:</b> After excision of sinuses, the wound was dressed with 2.5 cm ribbon gauze soaked in half-strength Eusol. The dressing was removed 48 hours post-operatively, and patients were randomly allocated to one of the following</p>	<p><b>Gender:</b> The majority of patients were male</p> <p><b>Mean (range) age:</b> Men: 25 (18–33) years Women: 19 (16–23) years</p>	<p><b>Mean (range) stay in hospital:</b> I: 12.8 (6–20) days C: 15.2 (3–27) days (not significant)</p> <p><b>Mean (range) time to healing:</b> I: 30.0 (21–39) days C: 33.0 (20–46) days (not significant)</p>	None	The authors provided separate data for patients with pilonidal sinuses and pilonidal abscesses. For the purposes of this review, only data for patients with pilonidal sinuses have been tabulated
C, control group; I, intervention group						
						continued

TABLE 10 contd Pilonidal sinuses: topical agents

Study and design	Inclusion/exclusion criteria	Intervention details	Baseline characteristics	Results	Withdrawals	Comments
<p><b>Sample size:</b> No <i>a priori</i> power calculation reported</p> <p><b>Objective outcomes:</b> Length of hospital stay; time to healing</p> <p><b>Setting and length of treatment:</b> Participants were initially treated as inpatients, then as outpatients. All were followed up to complete healing</p>		<p><b>I (n = 17):</b> Patients were instructed on how to replace and manage the silastic foam dressing. The foam was removed and washed twice daily. A new sponge was made when it no longer fitted easily into the cavity. Patients were discharged when they were able to manage their own dressing</p> <p><b>C (n = 21):</b> Continued with half-strength Eusol solution in gauze wick. The dressing was changed twice daily initially, then once daily when the wound was considered to be clean. Patients were discharged when they required only daily dressings by the district nurse</p>				<p><b>Authors' statement:</b> After discharge, Silastic foam treated patients require 2–3 visits for refashioning of new foam dressings, whilst Eusol treated patients require daily visits for up to 4 weeks. This may have implications for costs and nursing labour times</p>
<p>C, control group; I, intervention group</p>						



## **Appendix 6**

### Quality assessment of included studies



TABLE 11 Quality assessment of included studies

Study	Clear inclusion and exclusion criteria	Overall sample size (No. of study arms)	A priori sample-size calculation	True randomisation	Comparability of groups reported at baseline	Blinded outcome assessment	Objective outcome measures	Withdrawals	Intention-to-treat analysis
Alinovi, 1986 <sup>12</sup>	✓	47/55 patients/legs (2)	✓	✓	✓	Not stated	✓	✓a	✗
Beitner, 1985 <sup>38</sup>	✗	31 patients (3)	✗	Not stated	✗	✓	✓	✓a	✗
Bishop, 1992 <sup>33</sup>	✓	90 patients (3)	✗	Not stated	✓	✓	✓	✓b	✗
Blair, 1988 <sup>10</sup>	✓	60 patients/ulcers (2)	✗	✓	✓	Not stated	✓	✓a	✓
Cameron, 1991 <sup>34</sup>	✓	30 patients (2)	✗	Not stated	✓	✓	✓	✗a	✗
Chantelau, 1996 <sup>6</sup>	✓	44 patients (2)	✗	✓	✓	✓	✓	✓a	✗
Della Marchina, 1997 <sup>45</sup>	✓	40 patients (2)	✗	Not stated	✓	Not stated	✓	None	None
Gerding, 1992 <sup>29</sup>	✓	74/137 patients/lesions (2)	✗	Not stated	✓ For ulcer size only, no demographic information	✓	✓	✗a	✗
Green, 1974 <sup>30</sup>	✓	319 patients (2)	✗	Not stated	✓	✓	✓	✓a	✗
Huchon, 1992 <sup>31</sup>	✓	76 patients (2)	✗	Not stated	✗	✗	✓	✓a	Not stated

✓, Yes; ✗, no; ✓a, withdrawals reported by group, with reason given; ✓b, withdrawals reported, but either not by group or with no reason given; ✗a, withdrawals not reported

*continued*

**TABLE 11 contd** Quality assessment of included studies

Study	Clear inclusion and exclusion criteria	Overall sample size (No. of study arms)	A priori sample-size calculation	True randomisation	Comparability of groups reported at baseline	Blinded outcome assessment	Objective outcome measures	Withdrawals	Intention-to-treat analysis
Huovinen, 1994 <sup>5</sup>	✓	36 patients (3)	✗	Not stated	✓ For ulcer size and duration only, not demographic information	✓	✓	✓a	✗
Kronborg, 1985 <sup>16</sup>	✓	99 patients (3)	✗	Not stated	✓	✗	✓	✓a	✗ (1 withdrawal only)
Lipsky, 1990 <sup>7</sup>	✓	60 patients (2)	✗	Not stated	✓	✓	✓	✓b	✗
Margraf, 1977 <sup>39</sup>	✗	20 ulcers (2)	✗	✗ (CCT)	✓ For ulcer area only	✗	✓	None	None
Marks, 1985 <sup>44</sup>	✗	40 patients (2)	✗	✗ (CCT)	✗	✗	✓	✗	✗
Marzin, 1982 <sup>40</sup>	✗	40 ulcers (2)	✗	✗ (CCT)	✓	✗	✓	None	None
Morias, 1979 <sup>42</sup>	✗	59 patients (2)	✗	Unclear	✓	✓	✓	✓a	✓
Pegum, 1968 <sup>35</sup>	✗	34 patients (2)	✗	✗ (CCT)	✓	Not stated	✓	✓b	✓
Piérard-Franchimont, 1997 <sup>46</sup>	✓	42 ulcers (2)	✗	✗ (CCT)	✓ For ulcer dimensions only	✓	✓	✓b	✗
Salim, 1991 <sup>36</sup>	✓	153 patients (3)	✓	✓	✓	✓	✓	✓a	✓
Søndenaa, 1995 <sup>25</sup>	✗	51 patients (2)	✗	✓	✗	Not stated	✓	None	None

✓, Yes; ✗, no; ✓a, withdrawals reported by group, with reason given; ✓b, withdrawals reported, but either not by group or with no reason given; ✗a, withdrawals not reported

*continued*

TABLE 11 contd Quality assessment of included studies

Study	Clear inclusion and exclusion criteria	Overall sample size (No. of study arms)	A priori sample-size calculation	True randomisation	Comparability of groups reported at baseline	Blinded outcome assessment	Objective outcome measures	Withdrawals	Intention-to-treat analysis
Toba, 1997 <sup>47</sup>	✓	19 wounds (2)	✗	✓	✓ For wound area only	Not stated	✓	None	None
Valtonen, 1989 <sup>43</sup>	✓	26 patients (2)	✗	Not stated	✓	✗	✓	None	None
Vandeputte, unpublished <sup>24</sup>	✓	29 patients (2)	✗	✓	✓	✗	✓	✓a	✓
Van der Cammen, 1987 <sup>32</sup>	✓	120 patients (2)	✗	Not stated	✓	✓	✓	✓b	✗
Vogel, 1992 <sup>26</sup>	✗	80 patients (2)	✗	✓	✓	✗	✓	✗a	✗
Walker, 1991 <sup>27</sup>	✗	38 patients (2)	✗	Not stated	✗	✗	✓	None	None
Williams, 1981 <sup>28</sup>	✗	80 patients (2)	✗	Not stated	✓	✗	✓	None	None
Worsley, 1991 <sup>41</sup>	✗	27 patients (2)	✗	Not stated	✓ For some data, but baseline wound area not reported	✗	✓	✓a	✓
Wunderlich, 1991 <sup>37</sup>	✓	40 patients (2)	✗	Not stated	✓	✗	✓	✓b	✗

✓, Yes; ✗, no; ✓a, withdrawals reported by group, with reason given; ✓b, withdrawals reported, but either not by group or with no reason given; ✗a, withdrawals not reported

# **Appendix 7**

## Summary of excluded studies

TABLE 12 Excluded studies

Study	Participants/wounds	Interventions	Reasons for exclusion
Acevedo, 1990 <sup>113</sup>	Diabetic foot lesions	Regional intravenous antibiotic therapy vs conventional systemic antibiotic therapy	Historical controls
Akova, 1996 <sup>114</sup>	Diabetic patients with osteomyelitis or soft-tissue infection	Sulbactam–ampicillin	Non-comparative cohort
Altman, 1976 <sup>105</sup>	Patients with chronic leg ulcers and gangrenous lesions	Triiodide solution vs control (antibiotics, ointments, creams, debriding enzymes, wet dressings, Unna's boot)	Patients were permitted to switch treatments if ulcer did not improve or became larger
Anania, 1987 <sup>115</sup>	Diabetic foot lesions	Ceftizoxime	Non-comparative cohort
Arnold, 1994 <sup>116</sup>	Venous leg ulcers	Duoderm vs either paraffin gauze or betadine dressing	No separate data given for betadine patients
Baker, 1981 <sup>78</sup>	Pressure ulcers	Metronidazole vs usual care	Before–after study
Bassetti, 1970 <sup>117</sup>	Leg ulcers	Bendazolic acid vs placebo	No objective wound-healing outcomes
Baum, 1987 <sup>118</sup>	Leg ulcers	Topical antimicrobial therapy vs saline	Participants had leg ulcers of sickle cell origin
Beam, 1989 <sup>119</sup>	Diabetic patients with osteomyelitis or soft-tissue infection	Ciprofloxacin	Non-comparative cohort
Bendy, 1964 <sup>77</sup>	Pressure ulcers	Gentamicin cream vs standard regimen	No objective wound-healing outcomes
Bradsher, 1984 <sup>120</sup>	Patients with bacterial infection of skin and soft tissue	Ceftriaxone vs cefazolin	No objective wound-healing outcomes
Calandra, 1987 <sup>121</sup>	Diabetic patients with skin and soft-tissue infections of the lower extremities	Imipenem/cilastatin	Non-comparative cohort
Cooper, 1993 <sup>122</sup>	Surgical wounds, some from surgery for pilonidal sinuses	Postoperative stent disinfection using hibitane at 12-hour intervals vs same at 48-hour intervals	Not all the wounds were chronic, and no separate data were given for patients with pilonidal sinuses
Daltrey, 1981 <sup>123</sup>	Leg ulcers	Benzoyl peroxide 20% vs Eusol and liquid paraffin	Microbiological outcomes only
Danielsen, 1992 <sup>124</sup>	Patients with chronic leg ulcers undergoing surgery (vein ligation, excision of tissue or skin grafts)	Postoperative dressings: Comfeel vs chlorhexidine cream	No objective wound-healing outcomes
Danziger, 1988 <sup>125</sup>	Patients with soft-tissue or intra-abdominal infection	Imipenem + cilastatin vs clindamycin + gentamicin	Not chronic wounds
File, 1983 <sup>126</sup>	Patients with wounds of mixed aetiologies	Amdinocillin + cefoxitin vs cefoxitin alone	Patients had soft-tissue infections, not chronic wounds; microbiological outcomes only

*continued*

TABLE 12 contd Excluded studies

Study	Participants/wounds	Interventions	Reasons for exclusion
Gorse, 1987 <sup>76</sup>	Inpatients with pressure ulcers	Hydrocolloid dressing vs Dakin's solution soaked wet-to-dry dressings	The unit of allocation was wards (this allocation is likely to produce heterogeneous treatment groups)
Grayson, 1994 <sup>127</sup>	Diabetic foot ulcers	Imipenem + cilastatin vs ampicillin plus sulbactam	Microbiological outcomes only
Hughes, 1987 <sup>128</sup>	Patients with diabetes and/or peripheral vascular disease	Cefoxitin vs ceftizoxime	Microbiological outcomes only
Huizinga, 1986 <sup>129</sup>	Septic surgical wounds, ulcers, septic burns, infected civilian wounds	Augmentin vs placebo	No objective wound-healing outcomes
Hutchinson, 1991 <sup>130</sup>	Patients with venous leg ulcers, burns and skin-graft donor sites	Jelonet vs granuflex vs granuflex over silver sulphadiazine cream	No separate data for leg ulcers; microbiological outcomes only
Jorge Neto, 1996 <sup>63</sup>	Various types of wound, including venous leg ulcers	Calendula (marigold extract) alone vs calendula + barbadetiman (another plant extract)	Insufficient methodological information available
Kartikayan, 1990 <sup>64</sup>	Patients with leprosy with trophic ulcers	Calendula ointment vs neomycin vs paraffin	Patients with leprosy ulcers excluded from the review. Also, insufficient details available for methodology and results
Katellaris, 1987 <sup>131</sup>	Venous leg ulcers	Povidone iodine + electrode therapy vs povidone iodine alone vs saline + electrode therapy vs saline alone	Insufficient methodological details available
Kucan, 1981 <sup>132</sup>	Infected pressure ulcers	Silver sulphadiazine cream vs povidone iodine vs saline	Microbiological outcomes and subjective assessment of wounds
LeFrock, 1983 <sup>133</sup>	Diabetic patients with soft-tissue, skeletal or joint infections	Cefoxitin	Non-comparative cohort
Lipsky, 1997 <sup>134</sup>	Diabetic patients with foot infection (some had infected ulcers)	Ofloxacin vs aminopenicillin	No separate data for patients with ulcers; no objective wound-healing outcomes
Lishner, 1985 <sup>49</sup>	Diabetic patients with perforating foot ulcers	DMSO + conventional treatment vs conventional treatment alone	No objective wound-healing outcomes
Lookingbill, 1978 <sup>1</sup>	Chronic leg ulcers	Benzoyl peroxide lotion (10%) vs placebo lotion	No objective wound-healing outcomes
Lundhus, 1989, <sup>18</sup> 1993 <sup>135</sup> (the second study is a follow-up report)	Perianal and pilonidal abscesses	Primary closure of abscesses with 1-day antibiotic cover vs primary closure with 4-day cover	Patients had abscesses, not sinuses
Magana Lozano, 1980 <sup>136</sup>	Patients with leg ulcers	Bromelin alone vs bromelin and tetracycline vs placebo	No objective wound-healing outcomes

continued

TABLE 12 contd Excluded studies

Study	Participants/wounds	Interventions	Reasons for exclusion
Mehtar, 1988 <sup>137</sup>	Patients with infected leg ulcers	Mupirocin vs ointment base	No objective wound-healing outcomes
Milward, 1991, <sup>138</sup> Chaloner, 1991 <sup>139</sup> (duplicate publications)	Patients with leg ulcers	Activated charcoal with silver vs paraffin gauze with chlorhexidine vs charcoal dressing	Unclear if all patients had chronic wounds; no objective wound-healing outcomes
Nakayama, 1993 <sup>140</sup>	Mixed wounds, some chronic	Sparfloxacin 200 mg/day vs sparfloxacin 300 mg/day	No objective wound-healing outcomes; not solely chronic wounds
Nasar, 1982 <sup>75</sup>	Pressure ulcers	Debrisan vs Eusol and paraffin	Some patients were additionally given systemic antibiotics, but insufficient details were given about this. Some patients switched treatments during the trial
Norton, 1962 <sup>74</sup>	Pressure ulcers	Zinc cream vs silicone cream vs silicone and antiseptic vs PhisoHex	The unit of allocation was wards
Pardes, 1993 <sup>141</sup>	Patients with venous leg ulcers	Mupirocin (2%) ointment vs vehicle	No objective wound-healing outcomes
Parish, 1984 <sup>142</sup>	Mixed wounds, mainly leg ulcers and pressure ulcers	Ceftizoxime vs cefamandole	No objective wound-healing outcomes
Parish, 1984 <sup>143</sup>	Patients with skin infections, many arising from pressure ulcers	Ceforanide vs cefazolin	No objective wound-healing outcomes
Parish, 1986 <sup>144</sup>	Patients with skin infections; some with ulcers	Ceftazidime 1.5 g/day vs ceftazidime 3 g/day	No objective wound-healing outcomes; not solely chronic wounds
Perez-Ruvalcaba, 1987 <sup>145</sup>	Patients with skin infections, some with ulcers	Ciprofloxacin vs cefotaxime	No objective wound-healing outcomes
Peterson, 1989 <sup>146</sup>	Patients with peripheral vascular disease (some had diabetes mellitus) and lower-limb infection	Ciprofloxacin 1500 mg/day vs ciprofloxacin 2000 mg/day	No objective wound-healing outcomes
Ramirez-Ronda, 1987 <sup>147</sup>	Patients with skin infections, some with ulcers	Ciprofloxacin vs cefotaxime	No objective wound-healing outcomes
Ramirez-Ronda, 1989 <sup>148</sup>	Patients with skin infections, some with ulcers	Ciprofloxacin vs ceftazidime	No objective wound-healing outcomes
Robson, 1991 <sup>149</sup>	Patients with pressure ulcers	Study 1: growth factor vs placebo vs silver sulphadiazine Study 2: disaccharide preparation vs placebo vs silver sulphadiazine	Growth factor and disaccharide preparation evaluated within 2 double-blind placebo-controlled RCTs; for both trials, silver sulphadiazine was allocated to any additional ulcers in a non-randomised, unblinded fashion

continued

TABLE 12 contd Excluded studies

Study	Participants/wounds	Interventions	Reasons for exclusion
Seidel, 1991, <sup>106</sup> 1993, <sup>150</sup> 1994 <sup>151</sup> (duplicate publications)	Diabetic foot ulcers	Gentamicin and piperacillin given by transvenous retrograde perfusion vs same given via the usual intravenous route	Patients selected their own treatment; no objective wound-healing outcomes
Self, 1987 <sup>152</sup>	Patients with skin infections	Ciprofloxacin vs cefotaxime	Not chronic wounds; microbiological outcomes only
Slutkin, 1984 <sup>153</sup>	Patients with acute skin infections; a small number had ulcers	Cefonicid vs cefazolin	Not chronic wounds; no objective wound-healing outcomes
Smith, 1993 <sup>154</sup>	Patients with skin infections; some with ulcers	Fleroxacin vs amoxicillin plus clavulanate	No separate data for chronic wounds; no objective wound-healing outcomes
Spencer, 1967 <sup>155</sup>	Mixed wounds	Biozyme (contains neomycin) lotion vs biozyme ointment	Insufficient methodological information and authors not contactable
Subramanian, 1990 <sup>156</sup>	Patients with skin ulcers of various aetiologies (some had pressure ulcers), and various durations	Human placental dressing vs antibiotics (selected according to sensitivities)	Separate data not available for chronic wounds; unclear which are chronic wounds
Tan, 1985 <sup>157</sup>	Patients with skin and soft-tissue infections; some had chronic wounds	Timentin vs Moxalactam	Separate data not available for chronic wounds; no objective wound-healing outcomes
Tan, 1993 <sup>158</sup>	Patients with skin and soft-tissue infections; some had chronic wounds	Piperacillin-tazobactam vs ticaracillin-clavulanate	Separate data not available for chronic wounds; no objective wound-healing outcomes
Tassler, 1993 <sup>159</sup>	Patients with skin and soft-tissue infections	Fleroxacin vs amoxycillin plus clavulanate potassium	Separate data not available for chronic wounds; no objective wound-healing outcomes
Wilkinson, 1988 <sup>160</sup>	Patients with skin infections, some with ulcers	Mupirocin (2%) vs neosporin	Separate data not available for chronic wounds; no objective wound-healing outcomes
Williams, 1985 <sup>161</sup>	Patients with sclerotic ulcers of hands/fingers	Saline vs DMSO (2%) vs DMSO (70%)	Ulcers are of sclerotic origin





# **Systematic reviews of wound care management: (4) diabetic foot ulceration**

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## Contents to Part 4

<b>Glossary and list of abbreviations</b> .....	113	<b>5 Conclusions</b> .....	155
<b>Executive summary to Part 4</b> .....	119	Implications for future research .....	155
<b>1 Introduction</b> .....	123	<b>Acknowledgements</b> .....	157
Aims .....	124	<b>References</b> .....	159
<b>2 Methods</b> .....	125	<b>Appendix 1</b> Wagner's system for the classification of diabetic feet .....	165
Study inclusion criteria .....	125	<b>Appendix 2</b> Databases searched and search strategies .....	167
Search strategy .....	125	<b>Appendix 3</b> Hand-searching .....	171
Relevance and validity of primary studies .....	126	<b>Appendix 4</b> Advisory panel .....	173
Data extraction .....	126	<b>Appendix 5</b> Data extraction form .....	175
Data synthesis .....	126	<b>Appendix 6</b> Summary of included studies .....	179
<b>3 Results</b> .....	127	<b>Appendix 7</b> Quality assessment of included studies .....	213
Studies excluded from the review .....	127	<b>Appendix 8</b> Summary of excluded studies .....	223
Studies included in the review .....	127		
Prevention of diabetic foot ulceration .....	127		
Treatment of diabetic foot ulceration .....	130		
<b>4 Discussion</b> .....	151		
Prevention of diabetic foot ulceration .....	151		
Treatment of diabetic foot ulceration .....	151		
Summary .....	152		



## Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context but a glossary is provided for the non-specialist reader. In some cases usage differs in the literature but the term has a constant meaning throughout this review.

### Glossary

**Alginate dressings** Developed from seaweed derivatives, these contain calcium alginate fibres (e.g. Sorbsan<sup>®</sup>, Steriseal<sup>®</sup>), or a mixture of calcium and sodium alginates in the case of Kaltostat<sup>®</sup> (BritCair<sup>®</sup>). When the alginate material comes into contact with wound exudate or serum, sodium ions in the body fluid are exchanged with the calcium ions in the dressing, forming the more soluble sodium alginate. The highly absorbent sodium alginate forms a gel over the wound. As these dressings are non-adherent, a secondary dressing must be placed over their surface.

**Allevyn<sup>®</sup>** (Smith & Nephew Medical) A polyurethane foam, hydrophilic, absorbent, trilaminar dressing, which has a non-adherent wound contact layer provided by a polyurethane net.

**Arginine-glycine-aspartic acid (RGD) peptide matrix** (Argidene Gel<sup>®</sup>, formerly Telio-Derm Gel<sup>®</sup>, Telios Pharmaceuticals, San Diego, CA, USA) The peptide matrix contains the arginine-glycine-aspartic acid amino acid sequence, by which cells *in vivo* become attached to extracellular matrix macromolecules via surface integrin receptors. The matrix is a sterile non-preserved clear viscous gel, formulated in phosphate-buffered saline and dispensed from a single-use syringe container. The functional ingredient of RGD peptide matrix is a complex formed by the combination of a synthetic 18 amino acid peptide and sodium hyaluronate. It also contains added unconjugated sodium hyaluronate as a viscosity-increasing agent, and therefore does not require preparation from patient samples.

**Basic fibroblast growth factor (bFGF)** (Farmitalia Carlo Erba, Milan, Italy) A heparin-binding single-chain peptide of 146 amino acids, with a ubiquitous distribution in mesoderm- and neuroectoderm-derived tissues, this is a potent mitogen for all cell types involved in the healing process. It is highly angiogenic and chemotactic for fibroblasts and endothelial cells. bFGF is produced by recombinant DNA technology using *Escherichia coli* type b.

**Cadexomer iodine** (Iodosorb<sup>®</sup>, Perstorp Pharma) This consists of hydrophilic beads containing 0.9% w/w iodine. The uptake of aqueous media into the beads (1 g Iodosorb absorbs up to 7 ml fluid) results in the liberation of iodine. Iodosorb is available as beads and a paste.

**Callosity (callus)** A hard, thick area of skin occurring in parts of the body that are subjected to pressure or friction, particularly the soles of the feet and the palms of the hands.

**Charcot arthropathy** A painless swelling and disorganisation of the joints which is the result of diabetic neuropathy.

**Claudication** A cramp-like pain that occurs in the legs on walking. It may cause a limp or, if severe, prevent the sufferer from walking. The usual cause is narrowing or blockage of the arteries in the legs due to arteriosclerosis. Intermittent claudication occurs when a person has to stop every so often to let the pain, caused by the build up of waste products in the muscles, subside.

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**Collagen-alginate dressing** (e.g. Fibracol<sup>®</sup>, Johnson & Johnson Medical Inc., Arlington, TX, USA) A dressing that combines the structural support of collagen and the gel-forming properties of alginates into a sterile, soft, absorbent and comfortable topical wound dressing.

**Computerised planimetry** A wound-tracing technique where the outline of the wound is traced and the surface area computed.

**CT-102 activated platelet supernatant (APST)** (Curative Technologies, Setauket, NY, USA) (synonym: platelet-derived wound-healing formula (PDWHF)) A combination of growth factors released from  $\rho$ -granules of human platelets by thrombin.

**Cultured human dermal replacement tissue** (e.g. Dermagraft<sup>®</sup>, Advanced Tissue Sciences, CA, USA) (synonyms: skin replacement, skin equivalent) A neonatal dermal fibroblast cultured onto a bioabsorbable mesh to produce a living metabolically active tissue containing the normal dermal matrix protein and cytokines.

**Custom-made orthotic device** A device made of rigid, durable, plastic material and manufactured using a plaster cast of the patient's foot.

**Debridement** The removal of foreign material and devitalised or contaminated tissue from or adjacent to a wound until the surrounding healthy tissue is exposed.

**Diabetic education** Knowledge and/or skills assumed to be crucial for the optimal control by patients of their diabetes.

**Diabetic foot** A complex pathology of the foot associated with diabetes; secondary to neuropathy and vascular insufficiency. Bone and joint deformities may also be a feature, with neuropathy resulting in dropped metatarsal heads, and claw toes leading to abnormal loading.

**Diabetes mellitus** A heterogeneous group of diseases that have in common glucose intolerance.

**Dimethyl sulphoxide (DMSO)** A simple, highly polar chemical compound. It is thought to aid healing by increasing tissue oxygen saturation mediated by local vasodilation, decreased thrombocyte aggregation and increased oxygen diffusion to the tissue.

**Duoderm** (Granuflex<sup>®</sup>, Convatec, Uxbridge, UK, marketed as DuoDerm<sup>®</sup> in the USA) A hydrocolloid dressing containing colloids and elastomeric and adhesive components.

**Elasto-Gel<sup>®</sup>** (Southwest Technologies, Inc., Kansas City, KS, USA) A moist hydrogel dressing, consisting of 65% glycerine, 17.5% water and 17.5% hydrogel polyacrylamide.

**Epidermal growth factor (EGF)** This stimulates keratinocyte proliferation and locomotion and inhibits fibroblast proliferation. It is a chemoattractant for mesodermal and epidermal cells.

**Fibracol-collagen-alginate** (Johnson & Johnson Medical, Arlington, TX, USA) A combination of collagen and calcium alginate.

**Gangrene** The death and decay of a part of the body due to a deficiency in or the cessation of the blood supply. Causes include disease, injury, atheroma in major blood vessels, frostbite and severe burns. **Dry gangrene** is the death and withering of tissues caused simply by the cessation of the local blood circulation; **moist gangrene** is the death and putrefactive decay of tissue due to bacterial infection.

**Granulation** The newly formed vascular connective tissue normally produced in the healing of wounds of soft tissue and ultimately forming the cicatrix. It consists of small, translucent, red, nodular masses of granulation that have a velvety appearance.

**Growth factors** A group of multifunctional peptides thought to promote cellular proliferation and migration and protein synthesis. They may be derived from platelets, endothelial cells, monocytes, tissue macrophages, fibroblasts or epidermal cells.

**Hydrocolloid dressing** A mixture of adhesive, absorbent polymers and a gelling agent (sodium carboxymethyl cellulose). The dressing is opaque and gas and water impermeable. It interacts with the wound fluid to form a gel over the wound.

**Hydrogel dressing** A matrix of polymers with up to 90% water content. It is non-adherent and needs to be covered with secondary dressing. It is absorbent and semi-transparent. Hydrogels transmit moisture vapour and oxygen.

**Hyperbaric oxygen therapy (HBOT)** The administration of oxygen at greater than normal atmospheric pressure. The procedure is performed in specially designed chambers that permit the delivery of 100% oxygen at three times normal atmospheric pressure. The technique is employed to overcome the natural limit of oxygen solubility in blood. It has been used both as a single treatment and in combination with other standard treatments.

**Iamin-Gel<sup>®</sup>** (Procyte Corp., Kirkland, WA, USA) A peptide complex glycyl-L-histidyl-L-lysine : copper (GHK-Cu, a 2 : 1 molar complex of peptide and copper). Code name PC1020, Presatide copper acetate.

**Iloprost** A stable prostacyclin analogue which inhibits platelet aggregation and has vasodilatory properties.

**Insulin-dependent diabetes mellitus (IDDM)** (synonym: type 1 diabetes) A condition characterised by insulin deficiency, sudden onset, severe hyperglycaemia and rapid progression to ketoacidosis and death unless treated with insulin. Disease onset may occur at any age, but is most common in childhood or adolescence.

**Ischaemia** A deficiency of blood in a body part due to the functional constriction or actual obstruction of a blood vessel.

**Ketanserin** A quinazoline derivative; a potent 5HT<sub>2</sub> serotonergic receptor antagonist with no agonistic properties.

**Lipo-PGE<sub>1</sub>** A PGE<sub>1</sub> (a vasodilator) incorporated in lipid microspheres.

**MeZinc<sup>®</sup>** (Molnlycke, Sweden) An adhesive zinc oxide tape used as a debriding agent.

**Neuroischaemic ulcer** An ulcer associated with mixed ischaemic neuropathic disease.

**Neuropathic ulcer** An ulcer that usually occurs on the plantar surface of the foot. It is often associated with sensory neuropathy and is therefore often painless. It is typically surrounded by callus tissue, as it occurs at sites of high mechanical pressure.

**Non-insulin-dependent diabetes mellitus (NIDDM)** (synonym: type 2 diabetes) A condition characterised by the ability to survive without ketoacidosis in the absence of insulin therapy. It is usually of slow onset and patients usually exhibit a tendency to obesity.

**Occlusive hydrocolloid dressing** A dressing that prevents air from reaching the wound surface, and retains moisture, heat and body fluids.

**Orthotic device** (plural: orthoses) An externally applied device used in treating callus formation by redistributing loads on the foot. It can be worn in a standard shoe.

**Peripheral vascular disease** A general or unspecified disease of the blood vessels outside the heart.

**PGE<sub>1</sub>-CD** Contains 20 mg of PGE<sub>1</sub> as an  $\alpha$ -cyclodextrin clathrate compound

**Platelet-derived growth factor (PDGF)** A potent mitogen (i.e. it promotes cellular proliferation) for fibroblasts, endothelial cells and smooth muscle cells. It is also a potent chemoattractant for monocytes, neutrophils and fibroblasts. It is available in a human recombinant form as becaplermin.

**Platelet-derived wound-healing formula (PDWHF)** The most extensively studied growth factor in wound management. It is derived from platelets and contains many wound-healing factors (e.g. platelet factor 4, PDGF, transforming growth factor- $\beta$  and  $\beta$ -thromboglobulin related peptides). (See: CT-102 activated platelet supernatant.)

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**Podiatry** (formerly known as chiropody) The management of disorders of the feet.

**Polymeric membrane dressing**

**(POLYMEM)** A dressing composed of a combined urethane prepolymer, with water-soluble and hydrophilic components, and glycerol, which acts as a bacteriostatic agent.

**Polyurethane gel dressing** A dressing that contains a hydrophilic wound-contact surface and a hydrophilic backing to prevent leakage. It is opaque, absorbent, non-adherent, and transmits moisture vapour and oxygen.

**Prostaglandin E<sub>1</sub> (PGE<sub>1</sub>)** A potent vasodilator and antiplatelet agent that is claimed to be effective in peripheral vascular occlusive disease.

**Recombinant human form of platelet-derived growth factor (rhPDGF-BB), homodimer**

(Chiron Corp., Emeryville, CA, USA) This is produced from genetically engineered yeast cells into which the gene for the β-chain of PDGF has been inserted.

**Sorbsan®** (Maersk, Redditch, UK) A slightly coarse, sheet, net dressing that is prepared as a

textile fibre from the calcium salts of alginic acid. It is also available in the form of a rope or wool dressing. It is absorbent and non-adherent.

**Systemic hyperbaric oxygen therapy (s-HBOT)** A hyperbaric chamber that is pressurised with air.

**Total contact casting (TCC)** A plaster shell moulded around the lower leg and reinforced by splints, with a fibre glass roll applied around the plaster and a walking heel attached. It is used to promote an equal distribution of weight over the whole surface of the foot. Is extremely commonly used in many diabetic foot clinics.

**Wound healing** Wounds such as diabetic foot ulcers heal 'from the bottom up' by secondary intention or granulation. Healing begins with an inflammatory phase (characterised by vasodilation, increased capillary permeability and complement activation), followed by a proliferative phase in which new tissue is manufactured to fill the wound space. Finally, when the wound defect has been filled with new, granulation tissue, the surface of the wound covers over with epithelial cells.

**List of abbreviations**

aFGF           acidic fibroblast growth factor  
 ABPI           ankle/brachial pressure index  
 APST           activated platelet supernatant  
 ARI            absolute risk increase<sup>\*</sup>  
 bFGF           basic fibroblast growth factor  
 CI              confidence interval  
 DMSO          dimethyl sulphoxide  
 EGF            epidermal growth factor

GHK-Cu        glycyl-L-histidyl-L-lysine : copper  
 HbA<sub>1c</sub>        glycated haemoglobin A<sub>1c</sub><sup>\*</sup>  
 hPDWHF       homologous platelet-derived wound-healing formula  
 HBOT          hyperbaric oxygen therapy  
 IDDM          insulin-dependent diabetes mellitus  
 NIDDM         non-insulin-dependent diabetes mellitus  
 NNT            number needed to treat<sup>\*</sup>

*continued*

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OHG	oral hyperglycaemic *	RCT	randomised controlled trial
OR	odds ratio	RGD	arginine-glycine-aspartic acid
PDAF factor	platelet-derived angiogenesis factor	rhPDGF-BB	recombinant human form of platelet-derived growth factor, homodimer
PDGF	platelet-derived growth factor	RRI	relative risk increase*
PDWHF	platelet-derived wound-healing formula	s-HBOT	systemic hyperbaric oxygen therapy
PF-4	platelet factor-4	TCC	total contact casting
PGI <sub>2</sub>	iloprost	TGF- $\beta$	transforming growth factor- $\beta$
PGE <sub>1</sub>	prostaglandin E <sub>1</sub>	WMD	weighted mean difference
PGE <sub>1</sub> -CD	prostaglandin PGE <sub>1</sub> -cyclodextrin clathrate		
		* Used only in tables and figures	



## Executive summary to Part 4

### Objective

To estimate the clinical- and cost-effectiveness of interventions for the prevention and treatment of diabetic foot ulcers.

### Methods

#### Data sources

Nineteen electronic databases, including MEDLINE, CINAHL and the British Diabetic Association database, were searched up to the end of 1998. Specialist journals, including *Practical Diabetes* and *Diabetes Care*, were hand-searched. Conference proceedings were also hand-searched, and the reference sections of retrieved papers checked for further studies. An expert advisory panel was consulted.

#### Study selection

##### Study design

Randomised controlled trials (RCTs), whether published or unpublished, with no restriction on date or language, that evaluated an intervention for the prevention or treatment of diabetic foot ulcers were included. Trials including patients with wounds of various aetiologies were included if results for diabetic foot ulcer patients were presented separately.

In subject areas where no RCTs were available, non-RCTs that contained a contemporaneous control group were included.

##### Participants

Diabetic patients with a foot ulcer (treatment studies) or those deemed, by presence of callus for example, to be at risk of foot ulceration (prevention studies).

##### Interventions

Any intervention for the prevention and/or treatment of diabetic foot ulcers was eligible for inclusion. Studies evaluating the following preventive interventions were identified: podiatry, screening and prevention programmes, footwear, education and elastic compression stockings. Studies evaluating the following treatment interventions were identified: skin equivalents, wound

dressings, topical applications, hyperbaric oxygen therapy, ketanserin, prostaglandins, growth factors and antibiotics.

##### Outcome measures

Studies were included if they measured any of the following outcomes: the development or resolution of callus and incidence of ulceration (prevention studies); and any quantitative measure of ulcer healing (proportion of patients healed, reduction in wound size, time to healing), ulcer recurrence rates, side-effects and amputation rates (treatment studies).

### Included studies

Thirty nine trials and two UK economic evaluations were included in the review. Twenty three studies were excluded. The 39 included studies evaluated various prevention and treatment modalities for diabetic foot ulcers.

### Quality of studies

Most of the research evaluating interventions for the prevention and treatment of diabetic foot ulcers is poorly reported and/or of poor methodological quality. Shortcomings such as small sample size, poor (or unclear) baseline comparability of groups, short follow-up, inadequate reporting of randomisation, large loss to follow-up, lack of an intention-to-treat analysis, poor reporting and lack of blinding of outcome assessment pose particular problems for the interpretation of results.

### Results

#### Prevention trials

One large trial of a screening and foot protection programme reported significantly fewer major amputations in the intervention group. Two small trials of custom-made footwear have been undertaken. One demonstrated a significant benefit on callus eradication over podiatry (odds ratio (OR) = 18.84; 95% confidence interval (CI), 6.02 to 58.96), while the second reported a significant reduction in ulcer recurrence as a consequence of

wearing therapeutic shoes with custom-moulded insoles (OR = 0.29; 95% CI, 0.11 to 0.74). A trial of outpatient podiatric care reported a significantly greater reduction in callus in the patients receiving podiatric care. Clearly, further evaluation is needed of podiatric and footwear interventions for prevention of diabetic foot ulcer. One trial evaluated the effect of wearing compression hosiery on diabetic foot ulcer incidence and, while fewer ulcers developed in the hosiery group, the difference was not significant.

There have been five evaluations of different educational programmes; only one of these (of a brief, simple educational package) demonstrated a statistically significant benefit on the prevention of diabetic foot lesions (OR = 0.31; 95% CI, 0.15 to 0.63).

### Treatment trials

There has been one trial of total contact casting (TCC), a treatment designed to reduce weight-bearing. In this study significantly more ulcers healed with TCC than with standard treatment (OR = 11.59; 95% CI, 3.27 to 41.09).

There have been two trials comparing skin replacement dressings (Dermagraft<sup>®</sup>, Smith & Nephew) with standard care. Pooling of the data from these two trials showed that, although more ulcers had healed completely in the Dermagraft group at 12 weeks compared with the standard care group, the difference was not significant (OR = 1.47; 95% CI, 0.88 to 2.45).

One trial of systemic hyperbaric oxygen therapy (s-HBO) reported a significant reduction in the number of major amputations in the treatment group. A trial of topical HBO found no significant difference.

Two trials of topical ketanserin demonstrated a significantly increased rate of ulcer healing with ketanserin, whereas a trial of oral ketanserin found no effect.

Preliminary research into the effects of iloprost and prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) on diabetic foot ulcer healing suggests possible benefits. However, good quality, large-scale trials are needed to confirm this.

Five trials of topical growth factors were identified. Two trials of platelet-derived wound healing factor (PDWHF)/CT-102 were sufficiently similar to be pooled. PDWHF/CT-102 was more effective in healing diabetic foot ulcers than was saline (pooled OR = 4.47; 95% CI, 1.79 to 11.17). A multicentre

trial of human recombinant platelet-derived growth factor (PDGF) gel showed a significantly greater healing of diabetic foot ulcers in treatment group compared with the placebo group (OR = 2.67; 95% CI, 1.27 to 5.65). Finally, a trial of topical arginine-glycine-aspartic acid (RGD) peptide matrix compared with saline gauze resulted in significantly more ulcers healed in the RGD peptide matrix group (OR = 4.19; 95% CI, 1.33 to 13.25). Although these studies were of relatively good quality, the sample sizes were far too small to draw any definitive conclusions. Growth factors should be compared with current standard treatments in large, multicentre studies.

There have been only nine trials of non-drug dressings and topical applications in diabetic foot ulcer management. All these trials were small and no firm conclusions can be drawn regarding the relative effects of the interventions. In a small trial of 40 patients, significantly more ulcers healed with dimethyl sulphoxide (DMSO) than standard care (OR = 11.44; 95% CI, 3.28 to 39.92). A trial of glycyl-L-histidyl-L-lysine : copper (Iamin-Gel<sup>®</sup>) which compared two treatment regimens found a significant benefit associated with Iamin-Gel in terms of ulcer area healed. A trial of topical phenytoin in 100 patients reported a significant reduction in time to complete healing associated with phenytoin.

Neither of two trials of debriding agents (one of zinc oxide tape and one of cadexomer iodine) demonstrated an impact on ulcer healing. Only two trials of antibiotics for diabetic foot ulcers have been undertaken, and only one of these compared antibiotic with placebo; no significant difference in healing rates was found.

### Conclusions

Much uncertainty remains over the most effective and cost-effective interventions for the prevention and treatment of diabetic foot ulcers. However, certain interventions (e.g. growth factors, skin replacements) show promise but need further and more rigorous evaluation. Future studies should take account of those interventions that have shown promise in these 'pilot' studies, and build on what has been learned, by choosing appropriate comparison treatments for trials, ensuring an adequate sample size and avoiding the shortcomings of the existing studies. In addition, there is little evidence of the longer term effectiveness of these treatments, as the majority of studies did not incorporate a long follow-up. The role of weight-

bearing as part of the overall treatment needs to be clarified through further investigation. Researchers may wish to consider the development of a condition-specific outcome measure for diabetic foot care studies, and it is clear that researchers need to be more mindful of the need for unbiased,

objective assessment of ulcer healing in future trials. In the absence of any clear evidence, this review strongly suggests that more good quality RCTs, alongside economic evaluations, are needed to determine the relative clinical- and cost-effectiveness of these interventions.



# Chapter I

## Introduction

Ulceration of the foot is a common and debilitating complication of diabetes mellitus, and is estimated to affect 15% of people with diabetes at some time in their life.<sup>1-4</sup> Many factors, including peripheral neuropathy, peripheral vascular disease and repeated trauma from weight-bearing, place the diabetic patient at increased risk for the development of foot ulcers,<sup>5-8</sup> which in turn can lead to disability, diminished quality of life, limb loss and mortality.<sup>9</sup> Recurrence rates of 41% and 35% for neuropathic and neuroischaemic ulcers have been reported over a 3-year follow-up period,<sup>10</sup> rising to 70% over 5 years.<sup>11</sup>

Neuropathic ulcers usually occur on the plantar surface of the foot, are generally painless and are typically surrounded by callus tissue, which usually occurs at sites of high mechanical pressure. The abnormal distribution of load that occurs in neuropathic feet leads to local areas of high pressure on the plantar surfaces, and it has long been established that neuropathic ulceration develops on the site of highest load.<sup>12</sup>

Clinical observations show that the development of ulceration on the foot is frequently preceded by callus formation. Hyperkeratosis intensifies the forces on the subcutaneous tissues and, if left untreated, often results in ulceration,<sup>8</sup> although the natural history of progression of callus formation to ulceration is not well understood.<sup>13</sup> The neuroischaemic ulcer is described as usually occurring at the margins of the foot, frequently painful and often associated with gangrene.<sup>8</sup>

The USA National Commission on Diabetes reports that an estimated 5–15% of all diabetic patients require a lower extremity amputation at some time in their lives. Two epidemiological studies of diabetic amputees<sup>14,15</sup> which systematically assessed neuropathy, ulceration and other factors prior to amputation found that foot ulcers preceded 84–85% of the approximately 50,000 amputations performed annually in the USA.<sup>16</sup> Furthermore, up to two-thirds of all non-traumatic amputations carried out in the USA are performed on diabetic patients who present with an initial ulcer that progresses to gangrene.<sup>17-20</sup>

The St Vincent Declaration of 1989 (to which the UK is a signatory) called for a reduction by one-half of major limb amputations resulting from diabetes by the year 2000.<sup>21</sup> Programmes that encompass the provision of specific foot care education, the early detection of foot damage, aggressive ulcer treatment and the prevention of recurrence of ulcers are thought to be an important part of the overall care of the diabetic patient.<sup>22-24</sup>

Diabetic foot ulcers are a major cost to the health-care system and the most costly aspect in the treatment of people with diabetes. The number of hospital admissions has served as a proxy for estimating direct healthcare costs. According to one study involving 845 diabetic outpatients, 12% of hospital admissions and 21% of total hospital days were attributable to lower extremity ulcers,<sup>25</sup> with such care accounting for approximately 1.25 million hospital-bed-days per year at a cost of some £220 million.<sup>26</sup>

Costs in the community are, however, more difficult to estimate, but a study in Nottingham, UK, found nearly seven times as many patients with diabetic foot problems in the community as in hospital during one single week. Furthermore, the median duration of lesions found was 4 months, and nearly 10% had been present for over 1 year. In this study, district nurses made an average of three visits per week per patient.<sup>27</sup>

There is no consensus regarding the optimal local treatment of diabetic foot ulcers, due to problems of identifying infection and differentiating between patients with ischaemia and neuropathy. Numerous treatment modalities have been developed with the overall goal of preventing infection and promoting healing. Standard wound care of diabetic ulcers consists of the use of antibiotics to control infection, mechanical debridement of necrotic tissue and callus, and the application of various protective dressings.<sup>28</sup> Specially fitted footwear also forms part of the standard wound care programme, since many foot ulcers are induced by pressure from ill-fitting shoes.<sup>29</sup>

Other currently available treatments include hyperbaric oxygen treatment (HBOT),<sup>30</sup> and total



contact casting (TCC).<sup>31,32</sup> The latter is a plaster shell moulded around the lower leg and reinforced by splints, with a fibreglass roll applied around the plaster, and a walking heel attached.

Newer technologies, such as the topical application of platelet-derived growth factor (PDGF) preparations are being developed and made available for therapeutic use.<sup>33,34</sup> Several growth factors have been identified in animal models as playing a role in accelerating wound healing by stimulating cellular movement, replication and matrix synthesis.<sup>35,36</sup> These include PDGF, epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), transforming growth factor and insulin-like growth factor, CT-102 activated platelet supernatant (APST) (also known as platelet-derived wound-healing formula (PDWHF)) and a recombinant human form of PDGF (rhPDGF-BB).

However, the impact of such growth factors on the healing of diabetic foot ulcers, and their cost-effectiveness, is uncertain.

Ketanserin is another potential wound-healing treatment, which is thought to increase the formation of granulation tissue by increasing capillary perfusion.<sup>37-39</sup>

## Aims

- To assess the clinical- and cost-effectiveness of interventions to prevent and treat diabetic foot ulcers.
- To identify significant gaps in the research evidence.
- To outline the type of research needed to provide relevant information to the NHS.

## Chapter 2

### Methods

A systematic review of the research evidence was carried out following guidelines established by the NHS Centre for Reviews and Dissemination.<sup>40</sup>

#### Study inclusion criteria

##### Study design

Evaluations were included if they were randomised controlled trials (RCTs) (published or unpublished), irrespective of the date and language of the report, that evaluated the effectiveness of an intervention to prevent or treat diabetic foot ulcers. Non-RCTs that contained a contemporaneous control were eligible in the absence of RCTs for a particular intervention.

Economic evaluations, comparing at least two alternative prevention or treatment methods (i.e. cost-effectiveness, cost-benefit or cost-utility), were included, with no date, language or geographical restrictions. Studies of cost analysis on the resource inputs of at least two alternatives were included. Cost analysis studies were restricted to those with data from 1985 onwards and were limited to studies based in the UK and reported in English, so that the costings were relevant to the NHS.

##### Types of participant

This review was confined to patients with foot ulcers resulting from diabetes mellitus. Therefore, trials that included only patients with surgical wounds, burns or non-diabetic leg ulcers (e.g. venous ulcers) were excluded. Trials including patients with wounds of various aetiologies were excluded unless a subgroup of diabetic patients for which there were separate results could be identified (e.g. where stratified randomisation had been employed).

##### Outcome measures

We regarded ulcer incidence and/or callus development as valid outcomes for ulcer prevention trials. There appears to be a consensus in the literature that the presence of callus (along with the vascular and neurological status of the diabetic patient) is a valid predictor of a future site of ulceration (unless pressure is relieved), and that callus prevention can prevent subsequent ulceration.

We regarded ulcer healing as the most valid outcome measure for the treatment trials. Objective measures of ulcer healing include: the proportion of ulcers completely healed by a specific time point; the proportion of ulcers with a reduction (> 50%) in wound area; the time to complete healing; tracking of the rate of change in ulcer area by measuring ulcer size using wound-tracing techniques and computerised planimetry (this technique traces the outline of an ulcer and geometrically calculates the surface area); and Wagner's system for classifying ulceration.<sup>41</sup> The Wagner grading system is the most widely used classification scheme and classifies lesions by ulcer depth or extent of necrosis (appendix 1). Trials with outcomes such as recurrence, infection and amputation rates were only included if these accompanied the primary outcomes (as above).

#### Search strategy

##### Databases

Nineteen databases were searched up to the end of 1998 for RCTs and economic evaluations, with no restriction on the date of study or the language in which the report was written. The databases and the search strategies used for MEDLINE and CINAHL are listed in appendix 2. The National Research Register was searched to identify ongoing research in the NHS.

The NHS Economic Evaluation Database and EconLit were searched for economic evaluations. Economic analyses were sought by adding economic-related search terms to those already used in the search strategy for clinical trials. E-mail postings were sent to the Health Economics Study Group list and the International Health Economics Association to locate economic studies. Where there was no apparent economic analysis in the clinical trials located, the authors of trials published after 1985 were sent a letter asking for details of trial-based economic evaluations or cost analyses.

##### Hand-searching

Citations of all primary papers and the reference lists of review articles obtained were further

scrutinised for additional relevant studies. Relevant conference proceedings were hand-searched and the authors were contacted for the full report. A number of wound-dressing manufacturers were contacted to provide details of trials they had conducted. Five specialist wound care journals and the proceedings from 12 relevant specialist conferences were systematically hand-searched in order to locate further trials (see appendix 3).

### **Advisory panel**

Specialists in the field of wound care were invited to form an advisory panel (appendix 4) with whom we consulted to gain a wider perspective of current issues in the area of diabetic foot ulceration, and to call upon their knowledge of the relevant literature and ongoing research. Each member was asked to comment on the protocol, the list of references of trials identified and a final draft of the review.

### **Relevance and validity of primary studies**

The decision of whether a trial should be included or excluded was based on the inclusion and exclusion criteria outlined in the study protocol. The principal reviewer selected the studies to be included in the review (by type of trial, intervention, participants and outcome measures) after which a second reviewer independently cross-checked all studies included and excluded from the review. The methodological quality of the

included studies was also assessed independently by the two reviewers (see appendix 7).

### **Data extraction**

Relevant details of each included study were extracted by the primary reviewer onto a pre-prepared data extraction form (appendix 5). Where details were missing or unclear from the reports (particularly relating to the randomisation procedure) this information was sought from the author. A second reviewer independently checked the data extraction of all trial studies included in the review.

### **Data synthesis**

The results were largely considered in terms of a narrative review. Where appropriate, a quantitative pooling of Peto odds ratios (ORs) using a fixed-effects model was performed to combine the results of those trials that had sufficiently similar interventions and outcome measures. Graphs are included at the end of chapter 3, serving as a summary of the information from the included trials. Summary results of treatment effectiveness are expressed as Peto ORs with 95% confidence intervals (CI) for individual trial outcomes. Statistical heterogeneity among studies was checked using the  $\chi^2$  test and is displayed on graphs where relevant. The meta-analysis and the production of figures were done using Revman 3.0 software (Cochrane Collaboration, Oxford, UK).

## Chapter 3

### Results

#### Studies excluded from the review

Twenty three studies were excluded from the review. These are listed in appendix 8 along with the reasons for exclusion.

#### Studies included in the review

Thirty-nine studies met the inclusion criteria. The details of these studies are summarised in appendix 6 (*Tables 1–13*), and the methodological quality of the included studies is presented in appendix 7 (*Tables 14–26*). Two UK economic evaluations were identified, one of a prevention programme and another of a treatment (skin replacement).

The 39 included studies evaluated various prevention and treatment modalities for diabetic foot ulcers. There were 10 trials that evaluated prevention modalities: footwear (2), hosiery (1), education (5), screening and foot protection programme (1) and podiatry (1). There were 29 trials that evaluated treatment modalities: footwear (1), skin replacement (2), hyperbaric oxygen (2), ketanserin (3), prostaglandins (3), growth factors (5), dressings and topical applications (9), debridement (2) and antibiotics (2).

#### Prevention of diabetic foot ulceration

##### Podiatry and footwear (3 studies)

It has been postulated that the high dynamic vertical pressure at the site of callus formation may ultimately result in ulcer development,<sup>42–45</sup> and so calluses on the plantar surface of the foot in diabetic patients are usually removed. Traditional podiatric treatment of callus involves paring of the hyperkeratotic skin and the application of moisturisers and hypoallergenic padding. Some companies have marketed shoes for diabetic patients, but few comparative studies have been done.

Orthoses are externally applied devices that may be used in treating callus formation by decreasing abnormal loads on the foot.<sup>46</sup> Orthotic devices made by podiatrists can be accommodated to fit into standard shoes, although diabetic patients

often have a more substantial orthosis (e.g. cork, rubber and low-density thermoplastic). Semi-flexible and rigid orthoses are usually manufactured from thermoplastic materials of different densities, such as vitrathene.

Two RCTs have evaluated the effects of orthotic devices: one measured callus reduction as an outcome, and the other ulcer incidence. A third RCT evaluated a podiatric package of care involving patient education and podiatric treatments such as custom moulded insoles. This third trial also used resolution of callus as an outcome (*Table 1*).

##### Custom-made orthotic device versus conventional callus treatment

In one RCT<sup>13</sup> 20 diabetic patients with plantar callus were randomised to either a conventional callus treatment (application of moisturisers and hypoallergenic padding) by a podiatrist ( $n = 11$  with 32 calluses) or a custom-made orthotic device (worn for at least 7 h/day) made of a rigid durable plastic material and manufactured using a plaster cast of the patient's foot ( $n = 9$  with 22 calluses). At 12 months there were fewer calluses on feet of patients who received the device compared to those in the podiatry-only group, but the difference was not statistically significant (OR = 0.08; 95% CI, 0.00 to 1.41). At 12 months, those using the orthotic device reported significantly more lower grade calluses compared with the conventionally treated group (OR = 18.84; 95% CI, 6.02 to 58.96) (*Figures 1 and 2*, at the end of this chapter). Importantly, the rate of incidence of ulcers was not reported, and therefore whether any calluses became ulcers cannot be ascertained. Furthermore, callus grade was subjectively and crudely measured (reported as 'improved', 'no change' or 'deterioration') with no quantitation of the magnitude of change. There was no long-term follow-up evaluation, so treatment effects over time cannot be assessed. Also, multiple calluses per patient were studied, thus making it difficult to interpret the results. A larger study of orthotics, incorporating outcomes such as ulceration and amputation, and including sufficient follow-up and adequate statistical power, is needed.

##### Therapeutic shoes versus non-therapeutic shoes

Uccioli and co-workers<sup>47</sup> evaluated the efficacy of manufactured shoes (Podiabetes, Buratto, Italy)

specially designed for diabetic patients at high risk of ulceration. Sixty-nine patients with previous foot ulcers and those considered to be at high risk of foot ulceration were alternately assigned to wear either therapeutic shoes with custom-moulded insoles or their own ordinary non-therapeutic shoes. At 1 year follow-up the number of ulcer relapses (defined as the development of a new ulcer at the site of the previous one or a new ulcer at another site) was significantly lower (OR = 0.29; 95% CI, 0.11 to 0.74) and the mean ulcer-free time was significantly greater in the Podiabetes group ( $p < 0.02$ ) (Figure 3 and Table 1).

#### **Podiatry versus written foot care instructions**

One RCT from Finland compared a podiatry service *per se* with written foot care instructions alone in 530 diabetic patients aged between 10 and 79.<sup>48</sup> The podiatric care involved as many visits as deemed appropriate by the podiatrist, individualised patient education, foot treatments such as toenail cutting, callus debridement, foot exercise and the provision of bespoke footwear insoles. At 1-year follow-up, podiatric care had resulted in significantly greater reductions in the prevalence and the size of non-calcaneal callus. The incidence of ulceration was too low to detect a difference.

#### **Conclusions**

One small trial<sup>13</sup> suggests that an orthotic device has no apparent benefit over podiatry in eradicating callus from the feet of diabetic patients. A second small trial<sup>47</sup> showed a significant reduction in ulcer recurrence in patients wearing special shoes. Finally, a large trial found a significant reduction in non-calcaneal callus associated with a complex intervention of multifaceted podiatric care.

#### **Hosiery (elastic stockings) (1 study)**

Elastic stockings have been shown to improve the microcirculation and the abnormally increased capillary permeability in venous disease.<sup>49</sup> The mechanism of action in diabetic patients who may have similar microcirculatory disturbances is unclear.

#### **Elastic compression stockings versus no hosiery**

Elastic compression stockings (Sigvaris 802, Ganzoni, St Gallen, Switzerland) ( $n = 74$ , 148 limbs) were compared with no hosiery ( $n = 75$ , 150 limbs) in an RCT that measured the incidence of diabetic foot ulcers in patients with neuropathy and microangiopathy over a 4-year period.<sup>50</sup> Significantly fewer ulcers developed in the patients wearing stockings (OR = 0.31; 95% CI, 0.10 to 0.98) and there were fewer ulcerated limbs at year

4, although this did not reach significance (OR = 0.33; 95% CI, 0.11 to 1.00) (Figures 4 and 5 and Table 2). However, it is not clear from the study whether patients or their limbs (in cases of bilateral ulceration) were randomised. This may have biased the results. It is also noteworthy that diabetic patients who were likely to have advanced arterial disease were excluded from the study.

#### **Educational interventions (5 studies)**

Surveys have shown that some diabetic patients do not have the knowledge or skills assumed to be crucial for optimal control of their diabetes.<sup>51</sup> Educational programmes have therefore been traditionally viewed as an important element of good healthcare for diabetic patients. Typically, educational programmes are designed to teach patients specific skills, provide information relevant to their illness, and motivate the patients to participate in their treatment.<sup>52</sup>

Five RCTs have evaluated interventions of a multifaceted nature, all of which included educating patients about foot care, with the aim of preventing diabetic foot ulcers (Figure 6 and Table 3).

#### **Traditional education programme versus no education**

Bloomgarden and co-workers<sup>53</sup> compared a 'traditional' diabetic patient education programme with standard practice. The former comprised nine education sessions including foot care and the early detection of infection. The programme was illustrated by a film, 'Diabetic Foot Care', and card games were used to emphasise various aspects of foot care, signs of infection and nutritional information. The educational group ( $n = 127$ ) attended  $5.7 \pm 2.7$  clinic visits and the control group ( $n = 139$ ) attended  $5.2 \pm 2.7$  visits over approximately 1.5 years. The trial differentiated between those patients who attended at least seven education classes (classified as graduates,  $n = 79$ ) and those attending fewer than seven classes (classified as non-graduates,  $n = 48$ ). There was no statistically significant difference in the incidence of foot lesions between the education group and the control group (OR = 0.66; 95% CI, 0.30 to 1.49). However, there was a high attrition rate (38%) (i.e. non-graduates defined as having attended seven or less of the nine sessions) in the educational arm of the study, making the findings difficult to interpret.

#### **Structured diabetes treatment and teaching programme versus no programme**

Pieber and co-workers<sup>54</sup> found no difference in the incidence of ulcers between patients receiving a



structured diabetes treatment and teaching programme, including basic information about diabetes, foot care and glucose monitoring, and those receiving routine patient care over 6 months (OR = 0.55; 95% CI, 0.06 to 5.37). The teaching programme was supported by various teaching materials. However, the number of patients with callus formation and poor nail care nearly halved after participation in the teaching programme ( $p < 0.001$ ). The short duration of follow-up (6 months) and consequent low incidence of foot ulcers reduced the power of this study.

#### **Intensified insulin treatment versus routine diabetes care**

Reichard and co-workers<sup>55</sup> evaluated the effect of an 18-month programme of intensified insulin treatment and education on the development of foot lesions. The programme consisted of individual diabetes education, home glucose monitoring, interpretation of blood glucose tests to modify treatment, and continuous tutoring with face-to-face and telephone contact. There was no significant difference in the incidence of foot ulcers between the group receiving the intensified insulin treatment ( $n = 48$ ) and those receiving standard insulin treatment (routine diabetes care consisting of a visit by a physician every 4 months) (OR = 0.14; 95% CI, 0.01 to 1.43). However, this study has very low power as it involved only 89 patients, of whom only three developed ulcers.

#### **Risk reduction intervention (healthcare provider, healthcare systems intervention, behavioural contracts) versus no intervention**

Litzelman and co-workers<sup>56</sup> evaluated the effect of a 12-month intervention that included foot care education and the negotiation of behavioural 'contracts' with patients. The behavioural contracts concerned desirable foot care behaviours, such as washing rather than soaking feet, inspecting feet and shoes and the filing of calluses. The programme was reinforced through telephone and postcard reminders 2 weeks after the education sessions. Healthcare providers for the intervention group were given practice guidelines and information flow sheets on foot-related risk factors for amputation in diabetic patients and were prompted to examine the feet and provide foot care education. The incidence of foot ulcers was 4% in the intervention group compared with 9% in the control group, which received usual care (OR = 0.43; 95% CI, 0.19 to 1.00). Although fewer patients in the intervention group had a foot or limb amputation this difference was not statistically significant (OR = 0.32; 95% CI, 0.05 to 1.86). The intervention group was also more likely to

report appropriate self-care behaviours and to receive foot care education from healthcare providers.

#### **Brief educational intervention versus no education**

The influence of a simple education programme on the incidence of lower extremity amputations and ulceration in diabetic patients was examined in one RCT.<sup>57</sup> The educational group received a weekly or bimonthly 1-hour education class (depending on attendance rate), which included slides depicting infected diabetic feet and amputated limbs and simple instructions regarding how to care for their feet. At 1-year follow-up, ulceration and amputation were three times greater in the control group. (Ulceration: OR = 0.31; 95% CI, 0.15 to 0.63. Amputation: OR = 0.34; 95% CI, 0.16 to 0.73.)

#### **Conclusions**

Firm conclusions about the effects of teaching programmes on preventing lower extremity complications of diabetes cannot be drawn because the interventions evaluated were complex packages of care and education. It is difficult to disentangle the effects of foot care education from the other aspects of diabetes care such as glycaemic control. There has been no systematic programme of research in the area of educational interventions to reduce foot problems (and other secondary complications) in people with diabetes. Most of the studies were small and underpowered and more research is needed.

#### **Screening and foot protection programme (1 study)**

One trial of a complex intervention combining screening and a foot care programme was identified.<sup>58</sup>

#### **Foot care programme versus usual care**

Patients ( $n = 2001$ ) were randomised to usual care or to the experimental screening and foot care programme.<sup>58</sup> The experimental group received a primary foot screening examination using Semmes–Weinstein monofilaments, biothesiometry and palpation of pedal pulses. Patients found to have abnormalities in any of these areas were given a follow-up appointment where the tests were repeated and additional examinations (measurement of the ankle/brachial pressure index (ABPI), transcutaneous oxygen, foot pressures, X-rays) were also made. Patients with foot deformities, history of foot ulceration or an ABPI of  $\leq 0.75$  were deemed to be at high risk of ulceration (127 of 1001 in the experimental group) and were entered

into the foot protection programme. The foot protection programme involved a weekly foot clinic where podiatry, support hosiery, protective footwear and patient education was provided. Control-group patients were silently tagged and continued to receive usual care. An economic evaluation was undertaken as part of this study, and data relating to the cost of the screening and protection programme were calculated. At the end of the 2-year follow-up, the incidence of foot ulceration was 2.4% in the experimental group and 3.5% in the control group (difference not significant). Importantly, however, there was a significantly greater number of major amputations in the control group (12 in the control group versus one in the experimental group,  $p < 0.01$ ). The total cost of the 2-year programme was £100,372 at 1992–1993 costs, with a mean cost per patient of £100. Using £12,000 as an estimate of the cost of a major amputation, the foot clinic was cost-effective in terms of amputations prevented.

## Treatment of diabetic foot ulceration

### Total contact casting (1 study)

TCC is used to promote equal distribution of weight over the whole surface of the foot and involves the application of a plaster.<sup>59</sup> TCC is widely used in diabetic foot clinics.

### Total contact casting versus standard treatment

Mueller and co-workers<sup>60</sup> randomised 40 diabetic patients with plantar ulcers to either TCC or standard treatment (including footwear to reduce weight-bearing) until ulcer healing occurred. Significantly more ulcers healed in the TCC group (OR = 11.59; 95% CI, 3.27 to 41.09) and these healed more rapidly (weighted mean difference (WMD) 23.0 days; 95% CI, -40.9 to -5.0) (Figures 7 and 8 and Table 5). However, the follow-up period was very short.

### Cultured human dermal replacement tissue (Dermagraft) (2 studies)

Dermagraft is composed of neonatal dermal fibroblasts cultured onto a bioabsorbable mesh to produce a living, metabolically active tissue containing the normal dermal matrix proteins and cytokines. It is hypothesised that the matrix components and cytokines produced by the fibroblasts provide a basis for rapid and complete healing.<sup>61</sup> The living fibroblasts are said to have the potential for responding to the recipient's tissue and modulating the secretion of growth

factors necessary for healing. Since the ability to synthesise normal tissue matrix proteins is diminished in diabetes, it is assumed that the engrafting of normal matrix components provided by Dermagraft may contribute to the rate and quality of healing.<sup>62</sup>

One research group in the USA has studied Dermagraft in two RCTs: the first was a pilot study involving 50 patients, and the second was a 20-site multicentre study in which 281 patients were randomised (Figures 9 to 11 and Table 6).

### Dermagraft versus standard care: pilot study

Gentzkow and colleagues<sup>62</sup> randomised patients with non-insulin-dependent diabetes mellitus (NIDDM) or insulin-dependent diabetes mellitus (IDDM) to receive one of four alternative treatment regimens:

- Group A: standard care + 1 piece Dermagraft per week for 8 weeks.
- Group B: standard care + 2 pieces Dermagraft fortnightly for 8 weeks.
- Group C: standard care + 1 piece Dermagraft fortnightly for 8 weeks.
- Group D: standard care only (debridement, therapeutic shoes, instructions to avoid weight-bearing).

At 12 weeks, significantly more patients had completely healed in group A (50%) than group D (8%) (OR = 7.5; 95% CI, 1.35 to 41.55;  $p = 0.03$ ) (see Figure 9). However, the groups were not comparable at baseline, and the ulcers of patients in group D were of longer mean duration (87 weeks) than in group A (50 weeks). A regimen of one piece of Dermagraft per week for 8 weeks was deemed to be optimal, and was used in the subsequent multicentre trial.

### Dermagraft versus standard care: multicentre trial

In this 20-site multicentre trial, 281 people with NIDDM or IDDM and foot ulcers of neuropathic origin (area > 1 cm<sup>2</sup>) were randomised to receive Dermagraft (1 piece per week for 8 weeks) or no Dermagraft.<sup>63,64</sup> All patients received standard care of sharp debridement, infection control, saline gauze, therapeutic shoes and instructions to avoid weight-bearing.

The primary end-point was the number of ulcers healed at 12 weeks. At this point 22% of the Dermagraft group and 11% of the control group had been lost to follow-up. The reasons for loss were not reported by treatment group. At 12 weeks,

40 patients had completely healed in the Dermagraft group (39% of those patients remaining; 29% of those randomised) compared with 40 patients in the control group (32% of those remaining; 28% of those randomised) (OR = 1.25; 95% CI, 0.73 to 2.14) (see *Figure 10*).

At 20 weeks follow-up (i.e. 32 weeks after treatment commenced), 50 patients were completely healed in the Dermagraft group. However, 37% of this group had been lost to follow-up. Similarly, 39 patients were completely healed in the control group, but 35% were lost to follow-up (OR = 1.82; 95% CI, 1.02 to 3.27). Thus the proportions of patients healed at 32 weeks were: Dermagraft, 57% of those remaining, 36% of those randomised; control, 42% of those remaining, 28% of those randomised (see *Figure 11*).

The trialists explored further the reasons for poor healing in some of the Dermagraft patients and identified a direct relationship between the metabolic activity of the original Dermagraft given to each patient and healing. Consequently, subgroup analysis showed the best healing rates to have occurred in those patients who had received metabolically active Dermagraft at every treatment. The trialists indicate that "appropriate controls will ensure that all patients receive metabolically active Dermagraft at every implantation".<sup>63,64</sup> Pooling of data from the two studies indicated that, although more ulcers were completely healed in the Dermagraft group at 12 weeks (one piece of Dermagraft applied weekly for 8 weeks) than in the control group, this difference was not significant (OR = 1.47; 95% CI, 0.88 to 2.45) (see *Figure 12*).

### Conclusions

While the results for Dermagraft from one trial look promising, more research is needed, with longer and more complete follow-up, before it can be considered as a standard therapy. The large loss to follow-up in the multicentre study mitigates against the drawing of any useful conclusions from the study. It will be particularly important to elucidate the characteristics of patients who might stand to benefit the most from Dermagraft (patients with arterial disease were excluded from the trial), and identify what, if any, is the added benefit of Dermagraft over other techniques used to treat neuropathic ulcers; particularly those techniques that adjust weight-bearing, such as TCC.

The cost-effectiveness of Dermagraft has been modelled<sup>65</sup> using this multicentre trial data. Posnett and co-workers<sup>65</sup> reported that Dermagraft

was more cost-effective (£3475 per ulcer healed for Dermagraft) compared with standard therapy alone (£4327 per ulcer healed). However, the methodological problems of the original trial clearly reduce the reliability of these estimates.

### Hyperbaric oxygen therapy (2 studies)

HBOT has been employed as single treatment or in combination with dressings, topical agents and/or antibiotics. There are numerous theories postulating the mechanism of action of HBOT. It has been suggested that oxygen plays an important role in wound healing by increasing the rate of epithelialisation, collagen synthesis and the degree of cellular differentiation. HBOT results in an increased amount of oxygen dissolving in the plasma of the ulcer.<sup>66</sup>

Two RCTs have evaluated the effectiveness of HBOT for treating diabetic foot ulcers (*Figures 13 to 16* and *Table 7*).

### Systemic hyperbaric oxygen therapy versus standard care

Faglia and co-workers<sup>67</sup> evaluated whether systemic hyperbaric oxygen therapy (s-HBOT) plus standard care (debridement, antibiotics and provision of orthopaedic devices) decreases the number of major amputations (thigh or ankle) in diabetic patients with severe foot ulcers compared with standard care alone. Patients with sensorimotor or autonomic neuropathy were included. Patients who were randomised to s-HBOT were placed in a hyperbaric chamber pressurised with air, where they breathed oxygen for 90-minute sessions on a daily basis for an average of 38 sessions. The decision to carry out a major amputation was taken by the consultant surgeon who was blinded to the treatment groups. The rate of major amputation was lower (OR = 0.22; 95% CI, 0.07 to 0.72) and significantly more limbs were saved (OR = 4.45; 95% CI, 1.38 to 14.29) in the treated group (see *Figures 10* and *11*) with significantly more minor amputations in the s-HBOT group (OR = 2.54; 95% CI, 0.99 to 6.53). Overall, there was no statistically significant difference in the total number of amputations (OR = 0.95; 95% CI, 0.34 to 2.64) (see *Figures 14* and *15*). Unfortunately, this trial did not measure quality of life or functional status as outcomes, and therefore it is impossible to determine whether the reduced rate of major amputations was associated with better or worse functional status and quality of life. It is noteworthy that there were more patients in the control group who had claudication suggestive of severe peripheral vascular disease at baseline ( $p = 0.07$ ).



### **Topical hyperbaric oxygen therapy versus no hyperbaric oxygen therapy**

In an earlier small study, Leslie and co-workers<sup>30</sup> assessed the benefit of 2-weeks topical HBOT (Topox, Jersey City, NJ, USA) in 28 patients with diabetic foot ulcers compared to no HBOT (see *Table 7*). No significant differences were found in changes in ulcer area or depth between the HBOT group ( $n = 12$ ) (WMD 10%, 95% CI, -7.4 to 27.4) and the control group ( $n = 16$ ) (WMD 8.5%; 95% CI, -12.6 to 29.6) at day 14 (*Figures 17 and 18*). The mean baseline ulcer area and depth was found to be greater in the HBOT group. There was poor comparability of ulcer area at baseline, with larger ulcers in the control group and deeper ulcers in the treatment group.

### **Ketanserin (3 studies)**

Ketanserin, a quinazoline derivative, is a potent 5HT<sub>2</sub> receptor antagonist with no agonistic properties.<sup>68</sup> Oral and intravenous ketanserin have been extensively tested in the treatment of hypertension<sup>69</sup> and in Raynaud's syndrome.<sup>70</sup> It is proposed that ketanserin inhibits platelet aggregation and improves the flow of the blood, particularly blood filterability.<sup>69,71</sup> It is suggested that ketanserin may increase the formation of granulation tissue induced by an increased capillary perfusion.<sup>39</sup>

Three RCTs have evaluated ketanserin for the treatment of diabetic foot ulcers (see *Table 8*).

#### **Ketanserin ointment (2%) versus placebo**

Janssen and co-workers<sup>72</sup> evaluated the efficacy of a 2% ketanserin ointment compared with a vehicle placebo in a double-blind trial. Ointments were applied for a period of 2–8 weeks in 299 patients with chronic skin ulcers, including 45 diabetic patients. Ulcers were scored in terms of the formation of granulation tissue on a scale of 0–3, where a score of 0 denoted complete absence of granulation tissue in the original wound bed (i.e. 0% of the initial surface) and 3 denoted complete coverage by granulation tissue of the original wound bed (i.e. 100% of the initial surface). The intermediate scores of 1 and 2 represented approximately 33% and 66% of the initial surface covered. Analysis was performed on the change in wound area as a function of time for the different subgroups (relative area expressed as a percentage of the initial area). The initial rate of healing of the ulcers in diabetic patients was 196% greater in the group treated with 2% ketanserin ointment (Sufrexal<sup>®</sup>, Janssen Pharmaceuticals) compared with vehicle ointment ( $p < 0.001$ ). It is important to note, however, that the trial did not follow ulcers up to complete healing, and the clinical

significance of the increased initial rate of healing is unclear. The ketanserin-treated ulcers continued to heal, while all the control ulcers stopped reducing in area after 5 weeks and then worsened. Randomisation was not stratified by type of wound, and therefore analysis of a subgroup of diabetic patients may be biased.

#### **Topically applied ketanserin (2%) versus placebo (normal saline)**

A single-blind RCT evaluated the effectiveness of topically applied ketanserin (2%) (Sufrexal) on ulcer-size reduction compared with placebo (normal saline).<sup>73</sup> One-hundred and forty NIDDM patients with neuropathic foot ulcers (Wagner grades 2 and 3) of a median duration of 8 weeks were recruited. The ketanserin group showed a consistently greater percentage reduction in ulcer area from the fourth week with a sustained difference of 22–23% up to week 12, when the mean percentage reduction of ulcer area was 87% for the ketanserin group and 63% for placebo. The mean absolute difference in ulcer area was also in favour of ketanserin (WMD 13.66 cm<sup>2</sup>; 95% CI, 7.7 to 19.6;  $p < 0.001$ ) (*Figure 19*). No local or systemic adverse effects were reported. The study concluded that topical ketanserin resulted in significantly greater rates of ulcer healing when applied as part of a comprehensive programme. However, a limitation of the trial was that the outcome measurement of surface area ignored wound volume, and there was no assessment of complete healing.

#### **Oral ketanserin versus placebo**

Apelqvist and co-workers<sup>74</sup> evaluated the effectiveness of oral ketanserin on wound healing in 45 patients with diabetic foot ulcers and peripheral vascular disease. Patients were randomised to either ketanserin or placebo for a period of 3 months after an initial placebo run-in period. No statistically significant difference in wound healing was found (wound healing was defined as either intact skin for at least 3 months or a 50% wound reduction in ulcer size) (OR = 1.59; 95% CI, 0.42 to 6.05) (*Figure 20*). However, since the trial was small, a type II error cannot be discounted. The ketanserin group had a significantly lower mean baseline systolic toe pressure than did the control group ( $p < 0.05$ ), biasing the study against ketanserin. Eight patients developed gangrene (six in the placebo group and two in the ketanserin group), resulting in a total of six amputations.

#### **Prostaglandins and iloprost (3 studies)**

Iloprost is a stable prostacyclin analogue which inhibits platelet aggregation and has vasodilatory properties. It was suggested as early as 1979 that

iloprost (PGI<sub>2</sub>) may have an effect on severe peripheral vascular disease and trophic lesions.

Three RCTs have evaluated prostaglandins in the treatment of diabetic foot ulcers (Table 9).

#### **Iloprost versus placebo**

In one RCT, Brock and co-workers<sup>75</sup> (a duplicate of the study by Muller<sup>76</sup>) randomised 109 diabetic patients with ischaemic lesions to either intravenous iloprost ( $n = 56$ ) for 6 h/day at an individually tolerated dose up to 2 ng/kg per minute or to a placebo ( $n = 53$ ). In addition, all patients received intensive topical therapy (debridement, antibiotics and dressings). At the end of the 28-day study period, the iloprost-treated patients showed more partial (> 30%) or total healing of their lesion than patients in the placebo-treated group (OR = 4.75; 95% CI, 2.17 to 10.41) (Figure 21). The percentage of patients who were free from pain increased over the study period from 23% to 42% in the iloprost group and from 38% to 48% in the control group. However, the groups were not comparable for pain at baseline.

Prostaglandin E<sub>1</sub> (PGE<sub>1</sub>), a potent vasodilator and antiplatelet agent, is claimed to be effective in treating peripheral vascular occlusive disorders.<sup>77</sup> In two trials from the same group (and reported in the same paper), PGE<sub>1</sub> was incorporated in lipid microspheres (lipo-PGE<sub>1</sub>) designed to accumulate at vascular lesions, and to avoid the adverse reactions and local pain often associated with PGE<sub>1</sub> administration. Lipo-PGE<sub>1</sub> has been extensively used in Japan since 1988. PGE<sub>1</sub>-cyclodextrin clathrate (PGE<sub>1</sub>-CD) contains 20 µg PGE<sub>1</sub> as an α-cyclodextrin clathrate compound. Both trials included patients with neuropathy and ischaemia.

#### **Lipo-PGE<sub>1</sub> versus placebo**

Toyota and co-workers<sup>78</sup> compared the effect of lipo-PGE<sub>1</sub> ( $n = 90$ ) with placebo ( $n = 86$ ) in patients with diabetic leg ulcers in a double-blind trial (trial 1). Each ampoule of lipo-PGE<sub>1</sub> contained 10 µg PGE<sub>1</sub> and was administered daily for 2–4 weeks. The impact of treatment on the diabetic ulcers was graded arbitrarily as ulcers ‘markedly improved’ (80–100% decrease in ulcer size), ‘ulcers improved’ (> 50% decrease in ulcer size) or ‘no clear change including worsening’ of ulcer. More patients in the PGE<sub>1</sub> group showed a greater clinical improvement in ulcer size (markedly improved), but this difference was not statistically significant (OR = 2.45; 95% CI, 0.98 to 6.09). Significantly more ulcers in the PGE<sub>1</sub> group demonstrated an improvement (> 50% decrease in ulcer area) (OR = 2.62; 95% CI, 1.38 to 4.98) (Figures 22 and 23). Side-effects

occurred in 6.9% of patients receiving lipo-PGE<sub>1</sub> and 4.8% of control patients.

#### **Lipo-PGE<sub>1</sub> versus PGE<sub>1</sub>-CD**

Toyota and co-workers<sup>78</sup> also compared lipo-PGE<sub>1</sub> ( $n = 105$ ) with PGE<sub>1</sub>-CD ( $n = 97$ ) in an RCT (trial 2). Each ampoule of PGE<sub>1</sub>-CD contained 20 µg PGE<sub>1</sub> as an α-cyclodextrin clathrate compound. PGE<sub>1</sub>-CD was mixed with 300 ml saline and infused intravenously over approximately 1 hour, daily for 4 weeks. The percentage of patients showing a clinical improvement in ulcers (defined as an 80–100% decrease in ulcer area) was greater in the lipo-PGE<sub>1</sub> group compared to the PGE<sub>1</sub>-CD group (OR = 0.30; 95% CI, 0.13 to 0.70). There was no difference between the groups in the proportion of ulcers showing a > 50% decrease in ulcer area (OR = 0.98; 95% CI, 0.52 to 1.85). It is worth emphasising, however, that both trials utilised an outcome measure based on subjective gradings of change in area and there is potential for bias in these assessments.

#### **Growth factors (5 studies)**

Growth factors play an important role in the wound-healing process, and the advent of recombinant DNA technology has promoted investigation of their potential as topical agents to accelerate healing. Growth factors are multifunctional peptides thought to promote cellular proliferation and migration and protein synthesis.

A number of growth factors isolated from human platelets have been identified as being the most promising as potential wound-healing agents. These include EGF, bFGF, PDGF, homologous PDWHF (hPDWHF) and the arginine-glycine-aspartic acid (RGD) peptide matrix.<sup>36,79,80</sup>

rhPDGF-BB has been produced from genetically engineered yeast cells into which the gene for the β-chain of PDGF has been inserted. Animal studies have shown that rhPDGF-BB accelerates the wound-healing cascade by promoting the growth of granulation tissue.<sup>81,82</sup> rhPDGF-BB is available for clinical use in the UK as becaplermin and is licensed for use in diabetic foot ulcers. However, only one clinical trial of rhPDGF-BB has been conducted with diabetic patients with foot ulcers.

bFGF is a potent mitogen for all cell types involved in the wound-healing process and is highly angiogenic and chemotactic for fibroblasts and endothelial cells.<sup>83</sup> *In vivo* studies of animal models showed that topical bFGF accelerates healing.<sup>84,85</sup> Furthermore, the topical application of bFGF resulted in an improvement in tissue repair in diabetic mice.<sup>86</sup>

The RGD peptide matrix contains the arginine-glycine-aspartic acid amino acid sequence by which cells *in vivo* become attached to extracellular matrix macromolecules via surface integrin receptors.<sup>87,88</sup> The RGD peptide matrix is designed to provide a provisional topical synthetic extracellular matrix that acts to substitute the damaged natural matrix at the ulcer site.

A series of five RCTs<sup>4,34,89-91</sup> has evaluated various growth factors in the treatment of diabetic foot ulcers, including four by Steed and co-workers<sup>4,34,89,90</sup> at the Institute of Wound Healing, Pittsburg, USA (Figures 24 to 26 and Table 10).

CT-102 APST is a combination of growth factors released from the  $\rho$ -granules of human platelets by thrombin. Two trials have evaluated topically applied CT-102 for the treatment of diabetic ulcers.

#### **CT-102 activated platelet supernatant versus placebo**

Steed and co-workers<sup>34</sup> compared CT-102 APST ( $n = 7$ ) with placebo (normal-saline-moistened gauze dressings) ( $n = 6$ ) in 13 diabetic patients with neurotrophic foot ulcers over a 20-week period. CT-102 APST was prepared from homologous platelets and contained multiple growth factors including platelet-derived angiogenesis factor (PDAF), PDGF, EGF, platelet factor-4 (PF-4), transforming growth factor- $\beta$  (TGF- $\beta$ ), acidic fibroblast growth factor (aFGF) and bFGF. All patients were supplied with a half-shoe, and a wheelchair, crutches or a walking frame to reduce weight-bearing. These small treatment groups were not well matched for age, duration of diabetes, duration of ulceration, or the area and volume of ulcers at baseline (all favouring the control group). There was no significant difference in ulcer healing between the two groups at 20 weeks (OR = 7.64; 95% CI, 0.93 to 62.53). However, the small sample size in this trial and the imbalance of groups at baseline for key variables render this trial completely uninformative.

#### **CT-102 activated platelet supernatant versus placebo**

Holloway and co-workers<sup>90</sup> compared three different dilutions of topical CT-102 APST (1/10 ( $n = 15$ ); 33/1000 ( $n = 13$ ); 1/100 ( $n = 21$ )) with placebo (the latter consisting of normal saline solution followed by isotonic platelet buffer) ( $n = 21$ ) over a period of 20 weeks. Ulcer healing was significantly greater in treated ulcers (all dilutions combined) than in the saline-treated control group (OR = 3.94; 95% CI, 1.43 to 10.90)

(see Figure 24). The 1/100 dilution appeared to be the optimum for achieving complete wound healing (OR = 7.39; 95% CI, 2.00 to 27.29) (see Figure 25). No statistically significant differences were found in the adverse-event profiles of patients. However, the median duration of wounds was shorter in all treatment groups than the placebo group at baseline. Pooling of the data from the above two studies suggests a statistically significant increase in complete healing of ulcers in favour of CT-102 (OR = 7.46; 95% CI, 2.46 to 22.63) (see Figure 26).

#### **rhPDGF-BB gel versus placebo gel**

In a multicentre trial,<sup>89</sup> once-daily topical application of rhPDGF-BB gel was compared to a vehicle gel placebo in 118 diabetic outpatients with chronic neuropathic foot ulcers over a 20-week period. The proportion of wounds healed was significantly greater in the group treated with rhPDGF-BB (OR = 2.67; 95% CI, 1.27 to 5.65) (see Figure 24).

#### **Arginine-glycine-aspartic acid peptide matrix versus placebo**

In another multicentre trial, Steed and co-workers<sup>4</sup> evaluated topically applied RGD peptide matrix (applied twice a week) with placebo (saline-moistened gauze). Sixty-three diabetic patients with neuropathic ulcers were included who otherwise received standard care over a 10-week period. The proportion of completely healed ulcers was significantly greater in the treated group (OR = 4.19; 95% CI, 1.33 to 13.25).

#### **bFGF versus normal saline**

Richard and co-workers<sup>91</sup> compared topical bFGF with normal saline in 17 diabetic outpatients with neuropathic foot ulcers over 18 weeks. Although more ulcers healed in the placebo group the difference was not statistically significant (OR = 0.33; 95% CI, 0.05 to 2.12).

#### **Conclusions**

Three of the five trials of growth factors for the treatment of diabetic foot ulcers showed a significant benefit associated with their use (see Figure 24). However, none of these trials can be viewed as anything but preliminary pilot studies, as all were small in size. Further, larger studies are needed.

#### **Topical dressings and applications (9 studies)**

There are many different types of wound dressing on the market, although none is designed and marketed specifically for diabetic foot ulcers. Nine RCTs have evaluated various topical applications

and dressings for the treatment of diabetic foot ulcers (Figures 27 to 31 and Table 11).

### **Hydrocellular dressing versus alginate-based dressings**

In an unpublished RCT Baker<sup>92</sup> compared 10 diabetic patients with neuropathic foot lesions receiving a hydrocellular dressing (Allevyn) with nine receiving a calcium alginate dressing (Sorbsan) plus a secondary low-adherent absorbent dressing over a 12-week period. The number of ulcers healed was significantly greater in the Allevyn group (OR = 7.37; 95% CI, 1.12 to 48.58). However, the ulcers in the Sorbsan group were of longer duration at baseline, potentially biasing the trial in favour of Allevyn.

Foster and co-workers<sup>93</sup> compared the effectiveness of the Allevyn dressing with a calcium-sodium alginate dressing (Kaltostat, Britcair) on wound healing in 30 patients. No significant differences were observed between the two groups in the number of ulcers healed (OR = 1.30; 95% CI, 0.31 to 5.38).

In total the two studies described above looked at only 49 patients. In the absence of significant heterogeneity, and because both trials compared Allevyn with alginate-based dressings, the results of the studies were pooled. Overall there was no significant difference in healing rates between Allevyn and the alginate dressings (OR = 2.44; 95% CI, 0.78 to 7.57) (see Figure 28).

### **Hydrogel dressing versus Betadine<sup>®</sup> cream, dry gauze plus chlorhexidine**

Elasto-Gel, a moist hydrogel dressing, is thought to reduce the shearing forces which are thought to be implicated in diabetic foot ulcer aetiology. Vandeputte and co-workers<sup>94</sup> compared Elasto-Gel with wounds cleansed with a dermal wound cleanser (Flami-clens<sup>®</sup>, saline water buffered by 8% acetic acid) with a control group treated with a dry gauze (Betadine cream) twice daily and irrigated with 0.05% chlorhexidine solution. There was no significant difference between the groups in the rate of healing (OR = 1.55; 95% CI, 0.36 to 6.61) (see Figure 27). However, the rate of toe amputation, callus formation and infection were significantly lower in the Elasto-gel group than the control group ( $p < 0.053$ ,  $p < 0.05$  and  $p < 0.01$ , respectively).

### **Polymeric membrane dressing versus wet-to-dry saline gauze dressing**

Blackman and co-workers<sup>95</sup> compared a semi-permeable polymeric membrane dressing

(Polymem<sup>®</sup>, which is composed of a combined urethane prepolymer with water-soluble and hydrophilic components, with glycerol included as a bacteriostatic agent) ( $n = 11$ ) with wet-to-dry saline gauze dressings ( $n = 7$ ) over a 6-month period. After 2 months of treatment, there was no significant difference in ulcer healing between the groups (OR = 6.39; 95% CI, 0.54 to 75.62) (see Figure 27). Patients were followed up for 6 months; however, after 2 months five patients who were initially randomised to conventional therapy crossed over to the polymeric group due to failure to heal, and therefore only data obtained at 2 months are presented.

### **Hydroactive dressing versus hydrocellular dressing**

Clever and co-workers<sup>96</sup> compared Cutinova Hydro<sup>®</sup> (Beiersdorf), an adhesive 'hydroactive' polyurethane gel dressing, with a hydrocellular dressing (Allevyn) in the treatment of neuropathic diabetic foot ulcers in 40 patients over a 16-week period. Both dressings are said to create a moist wound-healing environment and were used in combination with standard treatment (pressure relief and infection control). No difference was found between the two groups in terms of time to healing (WMD 4.76 days; 95% CI, -7.41 to 16.93) (see Figure 29) or reduction in wound size at 4 weeks (WMD -1.1 mm<sup>2</sup>; 95% CI, -41.7 to 39.5) (see Figure 30).

### **Collagen-alginate topical dressing versus standard normal-saline-moistened gauze**

Fibracol is a combination of collagen and calcium alginate. Collagen is believed to promote healing by providing a framework for the formation of new tissue while calcium alginate is used to provide a moist wound interface.

Donaghue and co-workers<sup>97</sup> compared the efficacy and safety of Fibracol with regular saline-moistened gauze in 75 patients for a maximum period of 8 weeks. Patients were randomly assigned in a 2 : 1 ratio to the two treatment groups. No statistically significant difference was found between the groups in terms of complete healing (OR = 1.07; 95% CI, 0.35 to 3.25) (see Figure 27) or mean time to complete healing (WMD 2.80 days; 95% CI, -8.8 to 14.4) (see Figure 29).

### **Dimethyl sulphoxide solution versus conventional treatment**

Dimethyl sulphoxide (DMSO) is believed to aid healing by increasing tissue oxygen saturation mediated by local vasodilation,<sup>98</sup> decreasing thrombocyte aggregation<sup>99</sup> and increasing oxygen



diffusion to the tissue.<sup>100</sup> In experimental models, DMSO, a simple highly polar chemical compound, was found to alleviate ischaemic damage.<sup>101,102</sup>

Lishner and co-workers<sup>103</sup> compared the effect of DMSO solution with conventional treatment in 40 patients with chronic, resistant diabetic ulcers. The ulcers of 14 patients in the DMSO group completely healed by 15 weeks of daily treatment compared to two patients in the control group (OR = 11.44; 95% CI, 3.28 to 39.92) (see *Figure 27*).

#### **Topical treatment with glycyl-L-histidyl-L-lysine : copper**

The peptide complex glycyl-L-histidyl-L-lysine : copper (GHK-Cu, a 2 : 1 molar complex of peptide and copper) is thought to have biological activities and be a potential modulator of the wound-healing process. The compound has been reported to be a potent chemoattractant for cells essential in the healing process.<sup>104</sup>

A multicentre study comprising two double-blind RCTs<sup>105</sup> was conducted to evaluate the safety and effectiveness of GHK-Cu formulated in a topical gel (Iamin-Gel) for the treatment of chronic neuropathic diabetic ulcers. Iamin-Gel was compared with the corresponding vehicle. The first trial involved one group receiving 2% Iamin-Gel ( $n = 40$ ) and the other vehicle gel ( $n = 42$ ), after initial debridement, for a period of up to 8 weeks. Significantly more plantar ulcers healed with Iamin-Gel compared to the control group (defined as the median area percentage closure) (98.5% versus 60.8%;  $p < 0.05$ ), the proportion of patients healing 98% or better. Subgroup analysis showed that the Iamin-Gel was significantly more effective in healing larger ( $> 100 \text{ mm}^2$  initial ulcer area) plantar ulcers than vehicle (median 89.2% versus -10.3%;  $p < 0.01$ ). The incidence of infections was also significantly lower with Iamin-Gel (7% versus 34%;  $p < 0.05$ ).

In the second trial ulcers were treated with vehicle gel for an initial 4-week period and then either 2% Iamin-Gel ( $n = 49$ ) or 4% Iamin-Gel ( $n = 50$ ) for an additional 8 weeks. The mean percentage area healed was 40% with Iamin-Gel 2% and 68.2% with Iamin-Gel 4%. However, it is noteworthy that 20% of patients initially randomised were excluded from the analysis as the final analysis was confined to the subgroup of patients who had plantar ulcers (80% initial sample). It is impossible to tell from the data what impact this selective analysis had on the final result. Furthermore, the method of measuring ulcer healing is biased in favour of smaller wounds and dependent on an even

distribution of ulcer size between groups at baseline (data not presented).

#### **Topical phenytoin versus sterile occlusive dressing**

The effectiveness of topical phenytoin in the treatment of diabetic foot ulcers was compared with dry sterile occlusive dressing in one controlled trial.<sup>106</sup> Fifty patients were treated with topical phenytoin, and 50 control patients (matched for age, sex, and ulcer area, depth, chronicity and infection) were treated with a dry occlusive dressing. Significantly more patients receiving the phenytoin powder achieved healthy granulation at day 7 compared with controls (OR = 3.10; 95% CI, 1.32 to 7.26). The mean time to complete healing was significantly lower with phenytoin ( $p < 0.05$ ), and the mean percentage reduction in ulcer area at 35 days was significantly increased (*Figure 31*).

#### **Debridement (2 studies)**

Two trials have evaluated topical debriding agents for the treatment of diabetic foot ulcers (*Figures 32 and 33 and Table 12*).

#### **Cadexomer iodine ointment dressing versus standard treatment (various)**

Cadexomer iodine ointment (Iodosorb) comprises a modified starch matrix (cadexomer) into which iodine (0.9%) has been physically incorporated. It has been described as highly hydrophilic and antibacterial, able to dissolve debris and necrotic tissue,<sup>107,108</sup> and potentially useful in the treatment of diabetic foot ulcers with exudate.<sup>3</sup>

Apelqvist and Tennvall<sup>109</sup> compared the effectiveness and cost-effectiveness of cadexomer iodine (Iodosorb) with standard dressings in diabetic patients with cavity ulcers of the foot. Although more ulcers healed completely in the cadexomer group by 12 weeks, the difference was not significant (OR = 3.04; 95% CI, 0.59 to 15.56) (see *Figure 32*).

#### **Adhesive zinc oxide tape versus DuoDerm (hydrocolloid dressing)**

Apelqvist and co-workers<sup>110</sup> compared a zinc oxide tape (MeZinc) with an occlusive hydrocolloid dressing (DuoDerm) in diabetic patients with necrotic foot ulcers. MeZinc was more effective in completely eradicating or reducing (by  $> 50\%$ ) the necrotic area than was DuoDerm (OR = 4.44; 95% CI, 1.34 to 14.70) (see *Figure 33*). However, complete ulcer healing was not used as an outcome measure. An increase of  $> 50\%$  in necrotic area was observed in nine patients (four in the MeZinc

group and five in the the DuoDerm group). Treatment was discontinued in eight of these patients because of this increase in size of the necrotic area. Adverse events were commonly seen in both groups, including maceration of skin edges, pain and oedema.

**Antibiotics (2 studies)**

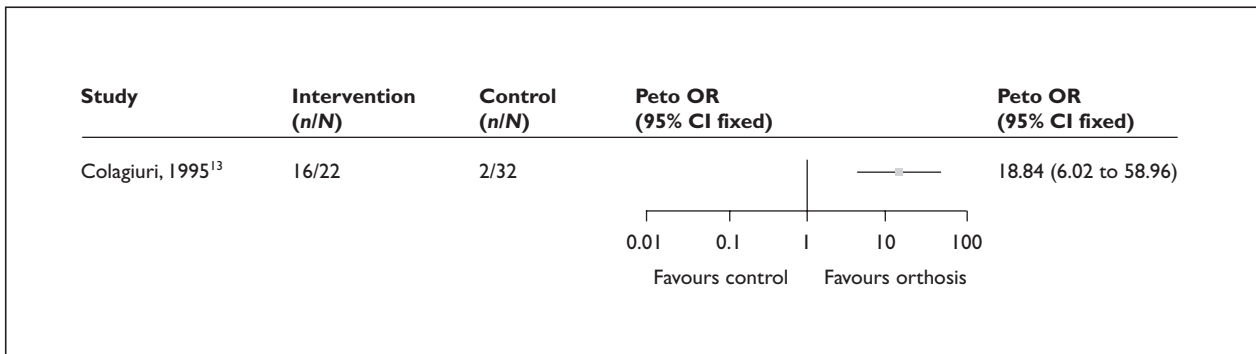
The majority of diabetic foot ulcers are infected,<sup>111,112</sup> most commonly with *Staphylococcus* and *Streptococcus* species. Only two RCTs have evaluated antibiotics for the treatment of foot ulcers in diabetic patients and measured wound healing as an outcome (Figure 34 and Table 13).

**Clindamycin hydrochloride versus cephalixin**

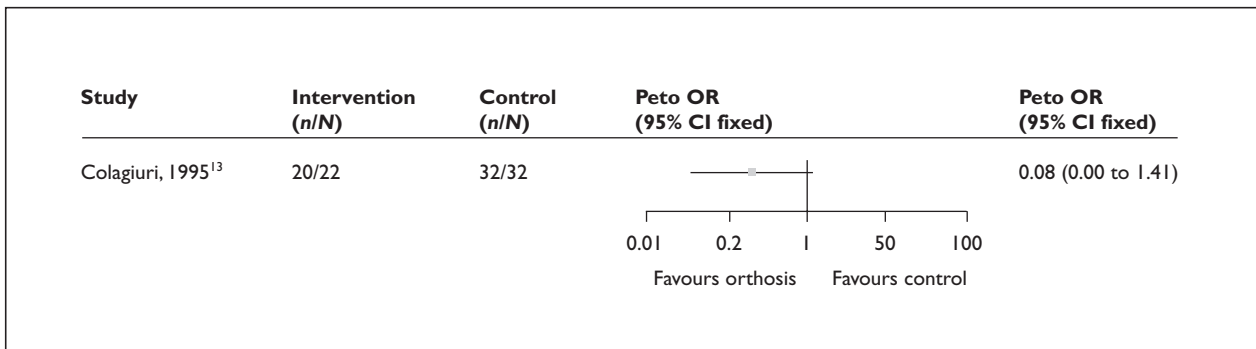
Lipsky and co-workers<sup>113</sup> found no significant difference in wound healing between patients who received 2 weeks of either oral clindamycin or oral cephalixin (OR = 1.30; 95% CI, 0.43 to 3.90) (see Figure 34).

**Amoxicillin + clavulanic acid versus standard therapy**

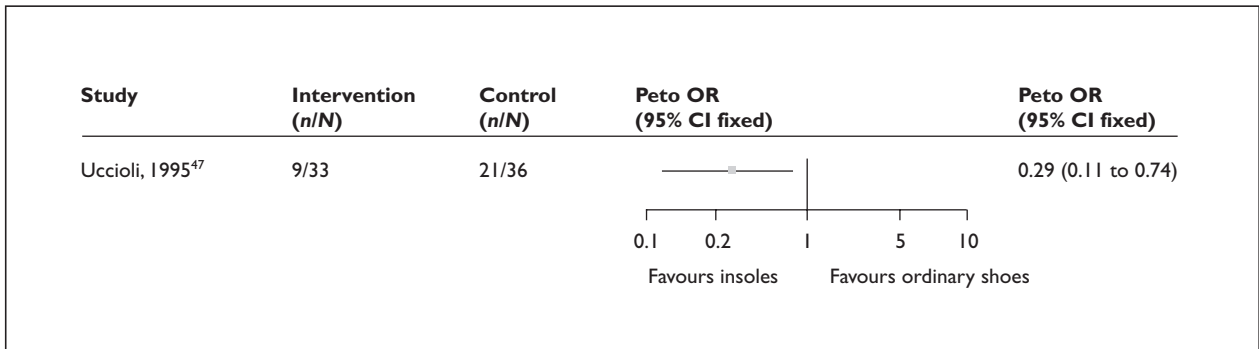
Chantelau and co-workers<sup>114</sup> compared the effect of a 28-day course of amoxicillin + clavulanic acid with placebo, and found no significant difference in ulcer healing rates (OR = 0.48; 95% CI, 0.14 to 1.68) (see Figure 34 and Table 13).



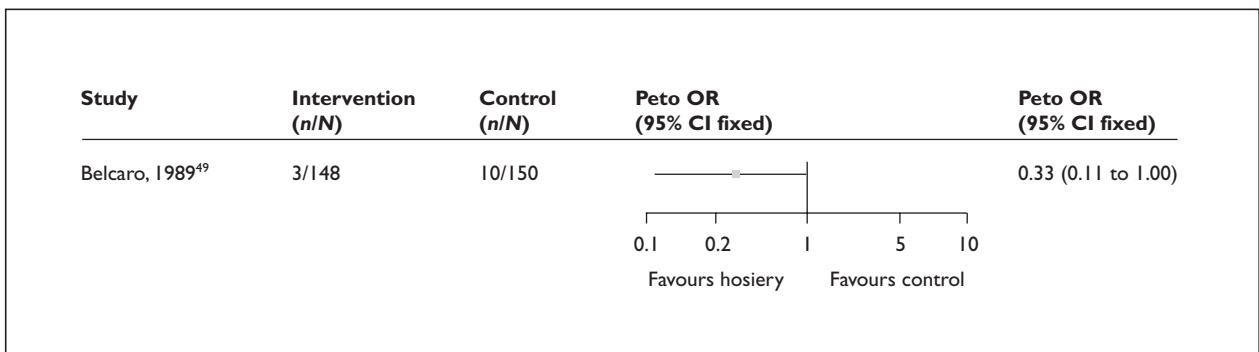
**FIGURE 1** A comparison of a custom-made rigid orthotic device with traditional podiatric callus treatment of callus for the outcome of number of calluses improved at 12 months (multiple calluses per patient)



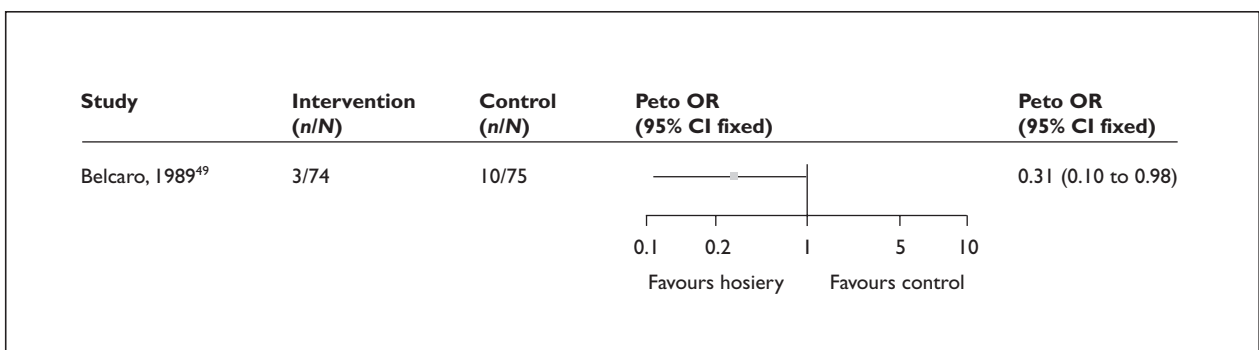
**FIGURE 2** A comparison of a custom-made rigid orthotic device with traditional podiatric callus treatment of callus for the outcome of total number of calluses at 12 months (multiple calluses per patient)



**FIGURE 3** A comparison of therapeutic shoes with custom-moulded insoles with ordinary shoes in diabetic patients for the outcome of ulcer relapses at 1 year



**FIGURE 4** A comparison of the effectiveness of elastic compression stockings with no stockings for the prevention of diabetic foot ulcers (number of ulcerated limbs at year 4)



**FIGURE 5** A comparison of the effectiveness of elastic compression stockings with no stockings for the prevention of diabetic foot ulcers (total number of ulcers at year 4)

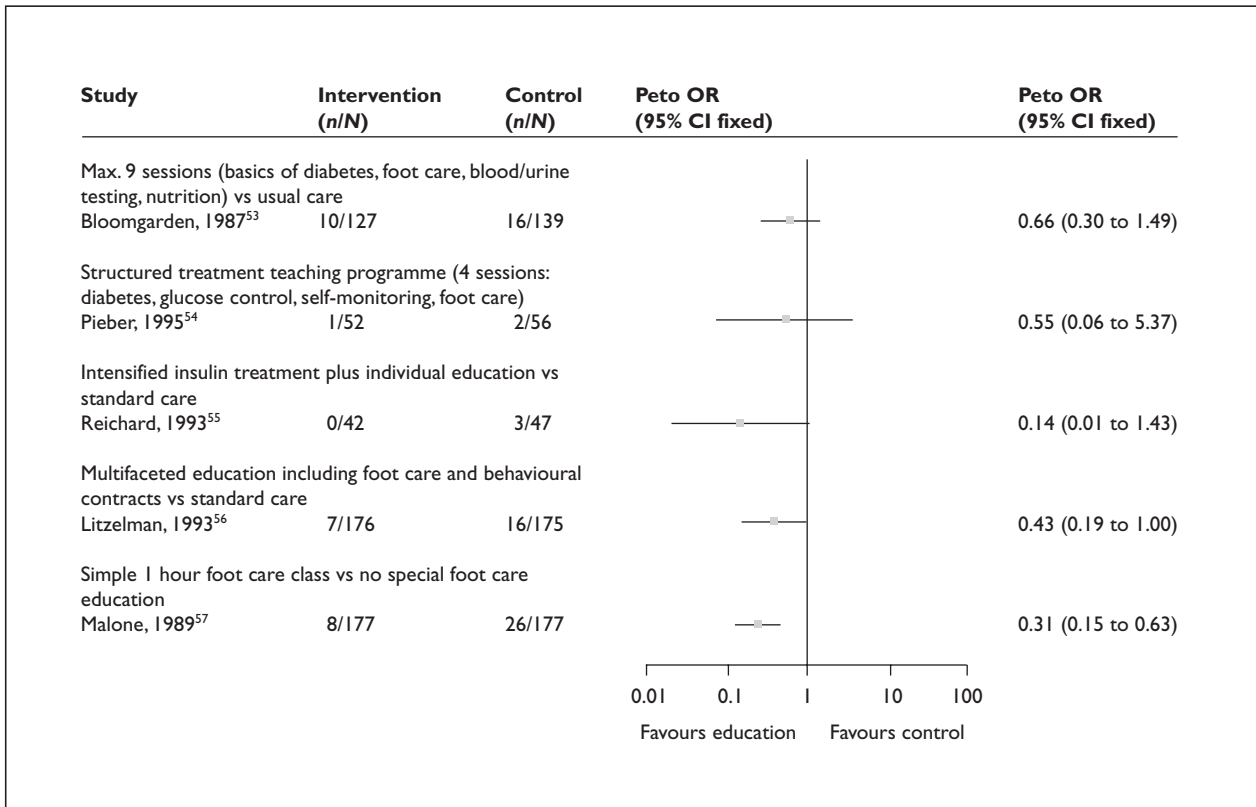


FIGURE 6 The impact of different diabetes educational programmes on the development of foot ulcers in diabetic patients

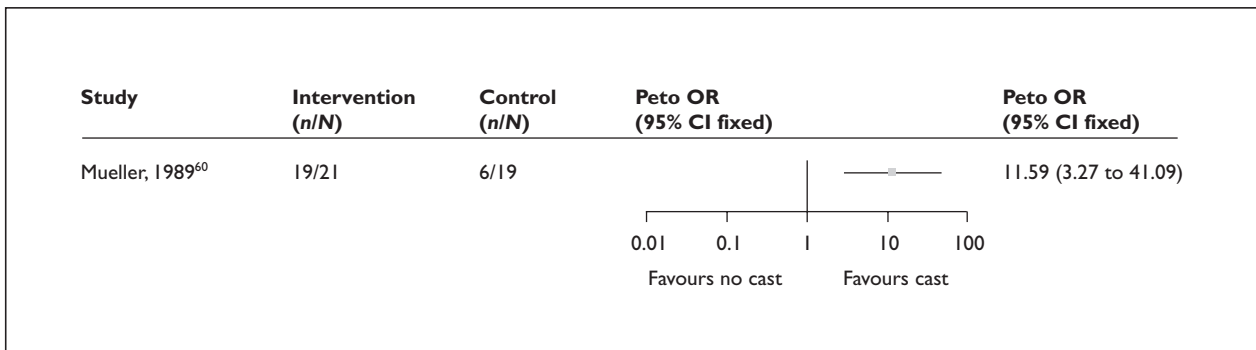


FIGURE 7 The effectiveness of TCC compared with traditional dressings on the healing of diabetic foot ulcers

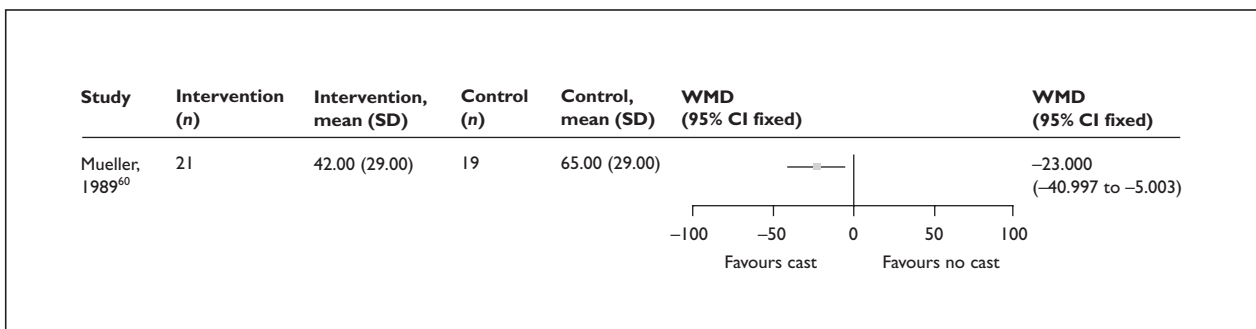
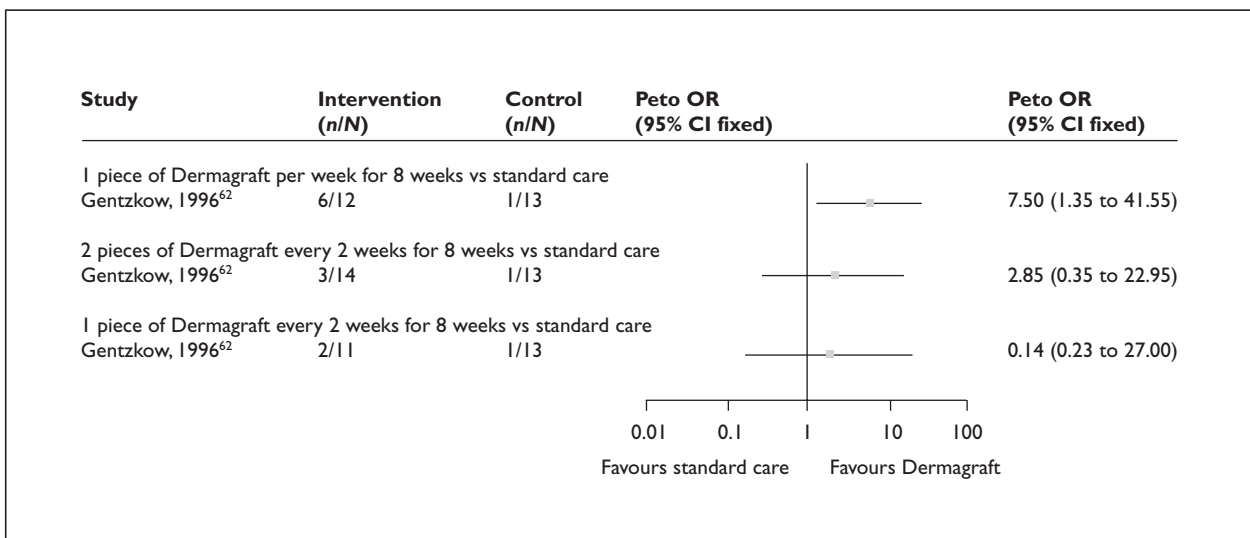
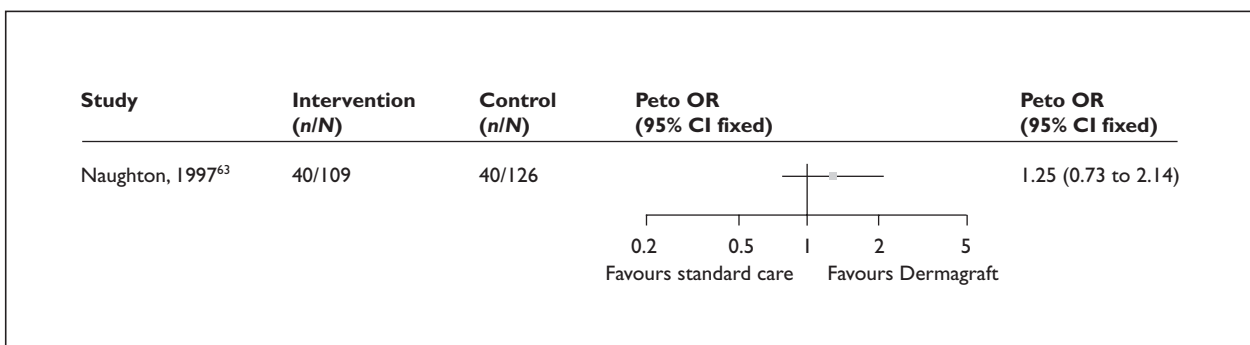


FIGURE 8 The effectiveness of TCC compared with traditional dressings on the mean time to healing of diabetic foot ulcers

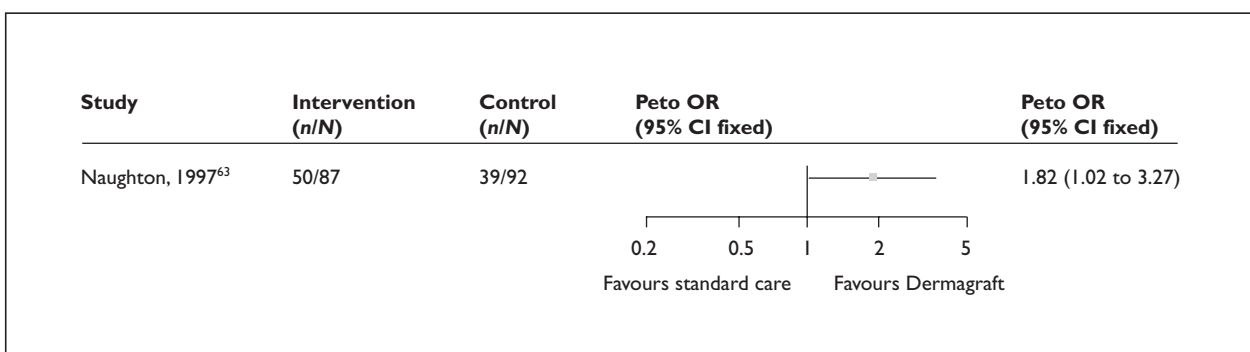




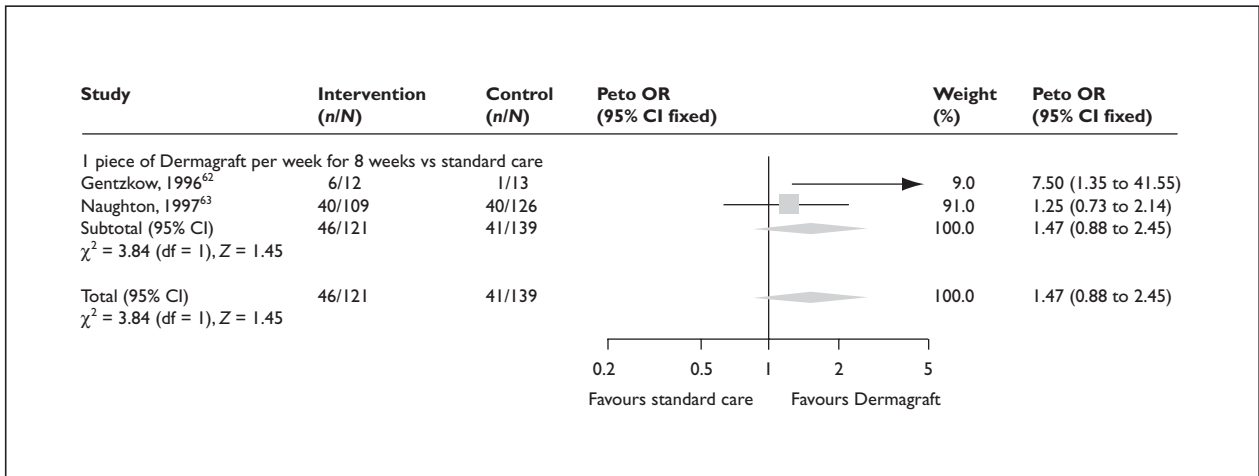
**FIGURE 9** A study comparing three dosage regimens of Dermagraft with standard care (debridement, dressings, pressure relief) on the number of diabetic foot ulcers healed by 12 weeks



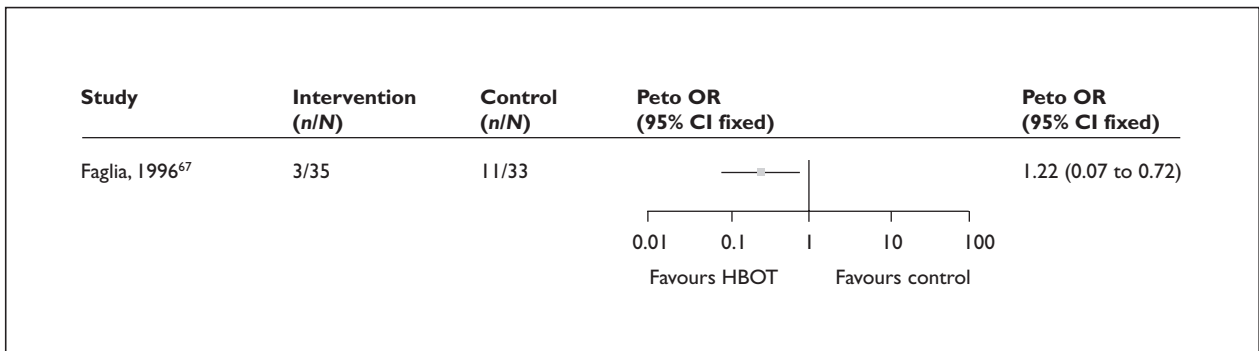
**FIGURE 10** A study comparing the impact on 12-week healing of one piece of Dermagraft applied weekly for 8 weeks versus standard care (debridement, infection control, dressings, pressure relief)



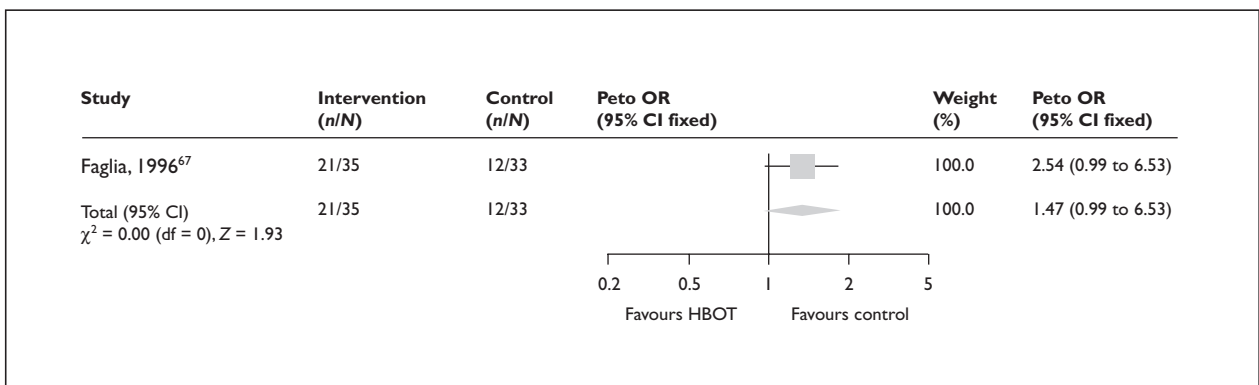
**FIGURE 11** A study comparing the impact on 20-week healing of one piece of Dermagraft applied weekly for 8 weeks versus standard care (debridement, infection control, dressings, pressure relief)



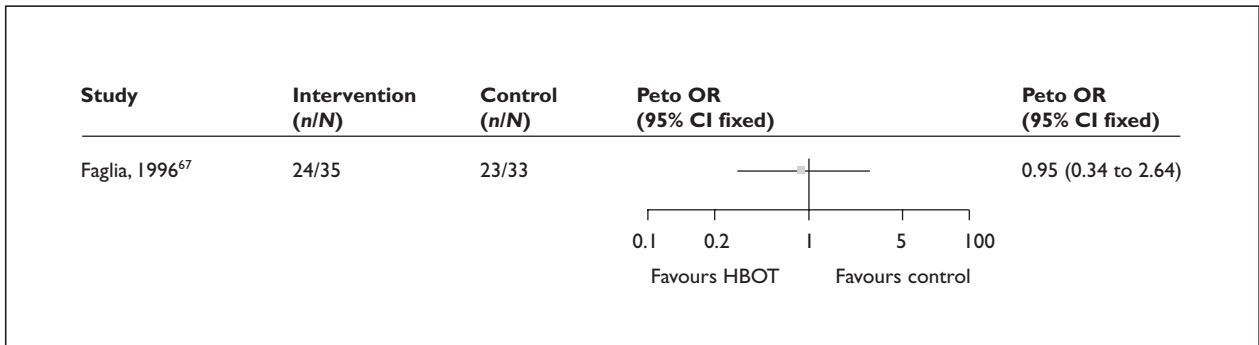
**FIGURE 12** Pooled estimate (fixed effects model) of the effect on diabetic foot ulcer healing at 12 weeks of Dermagraft (one piece applied weekly for 8 weeks) compared with standard care (debridement, infection control, dressings, pressure relief)



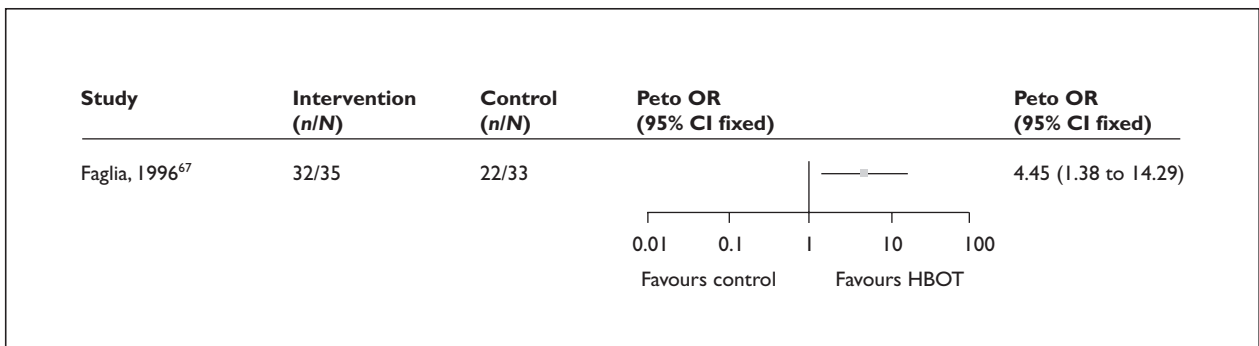
**FIGURE 13** A comparison of HBOT with no HBOT on the rate of above- or below-knee (i.e. 'major') amputation in diabetic patients



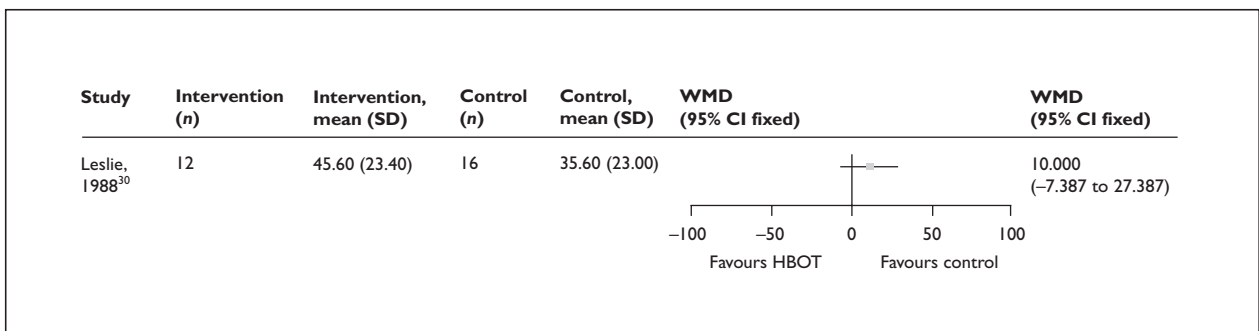
**FIGURE 14** A comparison of HBOT with no HBOT on the rate of forefoot and/or toe (i.e. 'minor') amputations in diabetic patients



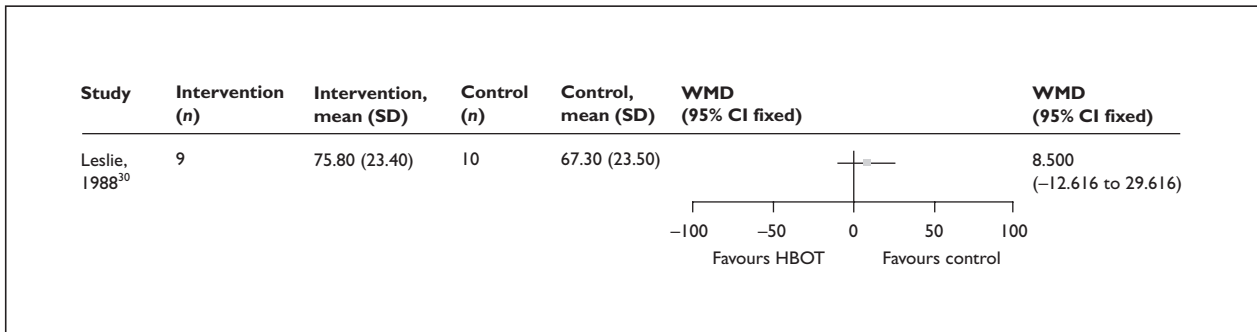
**FIGURE 15** A comparison of HBOT with no HBOT on the rate of all amputations in diabetic patients



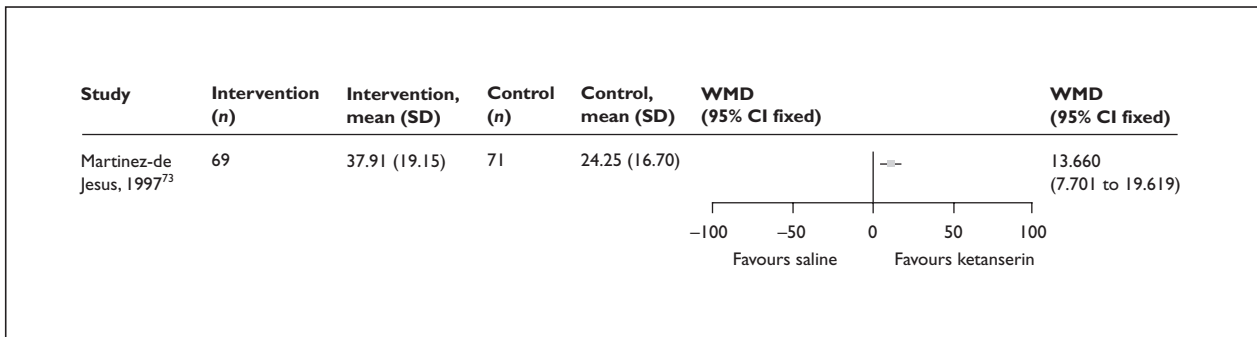
**FIGURE 16** A comparison of HBOT with no HBOT on the number of patients with salvaged limbs (preservation of plantar support and ulcer healing despite minor amputations)



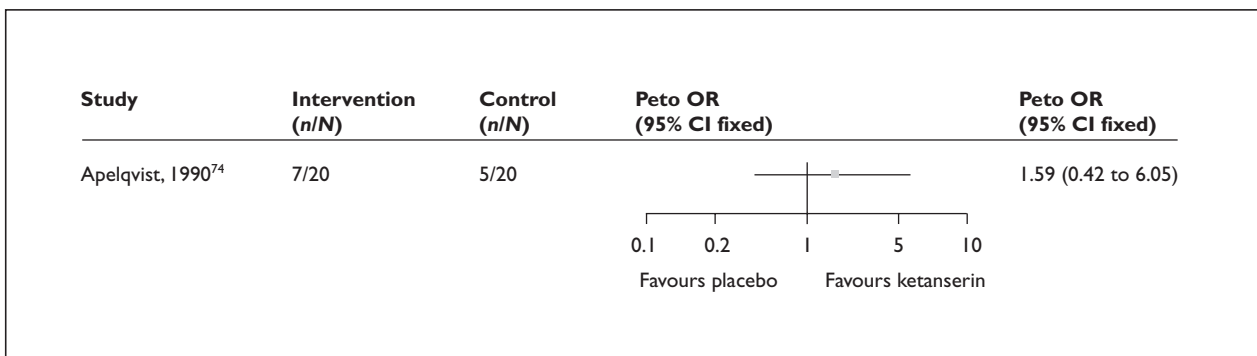
**FIGURE 17** A study comparing topical hyperbaric oxygen with no hyperbaric oxygen on the percentage of baseline ulcer area at day 14



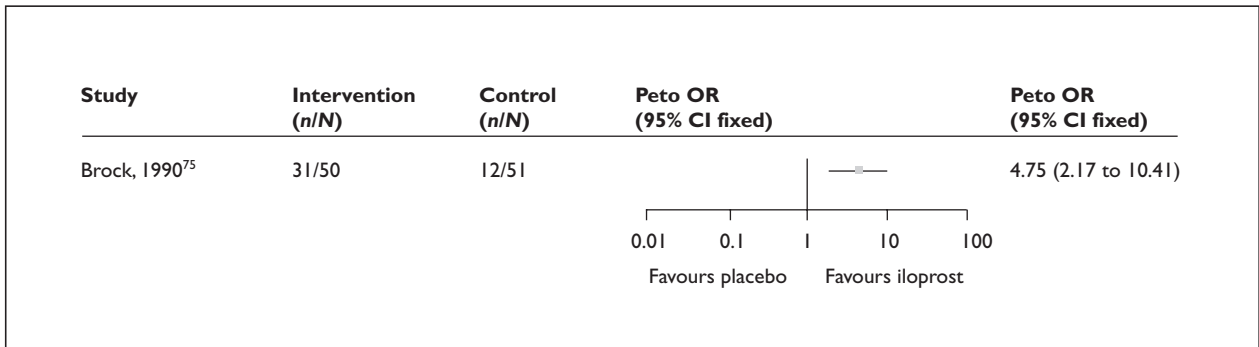
**FIGURE 18** A study comparing topical hyperbaric oxygen with no hyperbaric oxygen on the percentage of baseline ulcer depth at day 14



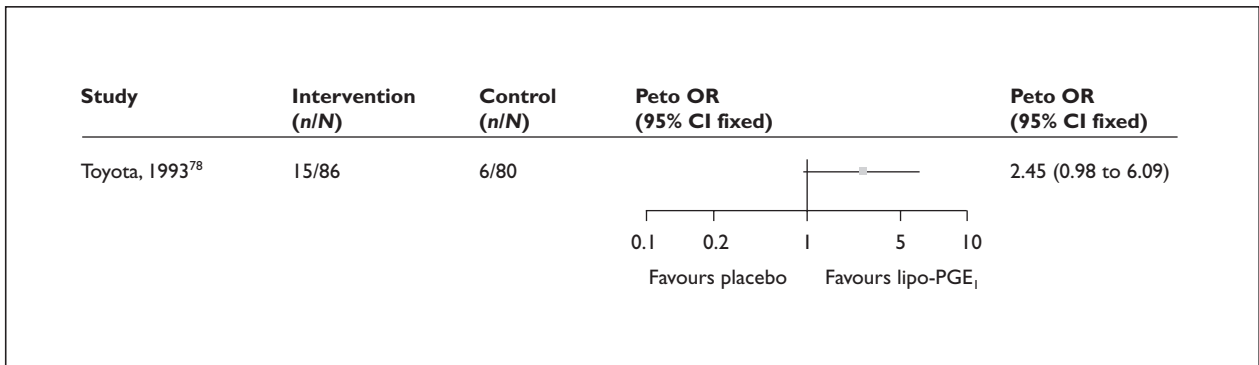
**FIGURE 19** A comparison of topical ketanserin with placebo on the percentage reduction in the area (cm<sup>2</sup>) of diabetic foot ulcers at 12 weeks (WMD with 95% CI)



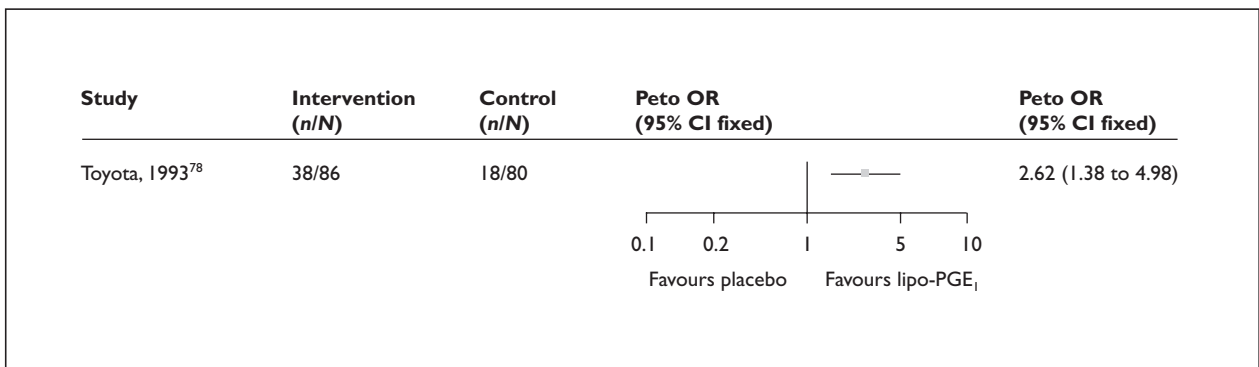
**FIGURE 20** A comparison of oral ketanserin with placebo on the number of diabetic foot ulcers completely healed



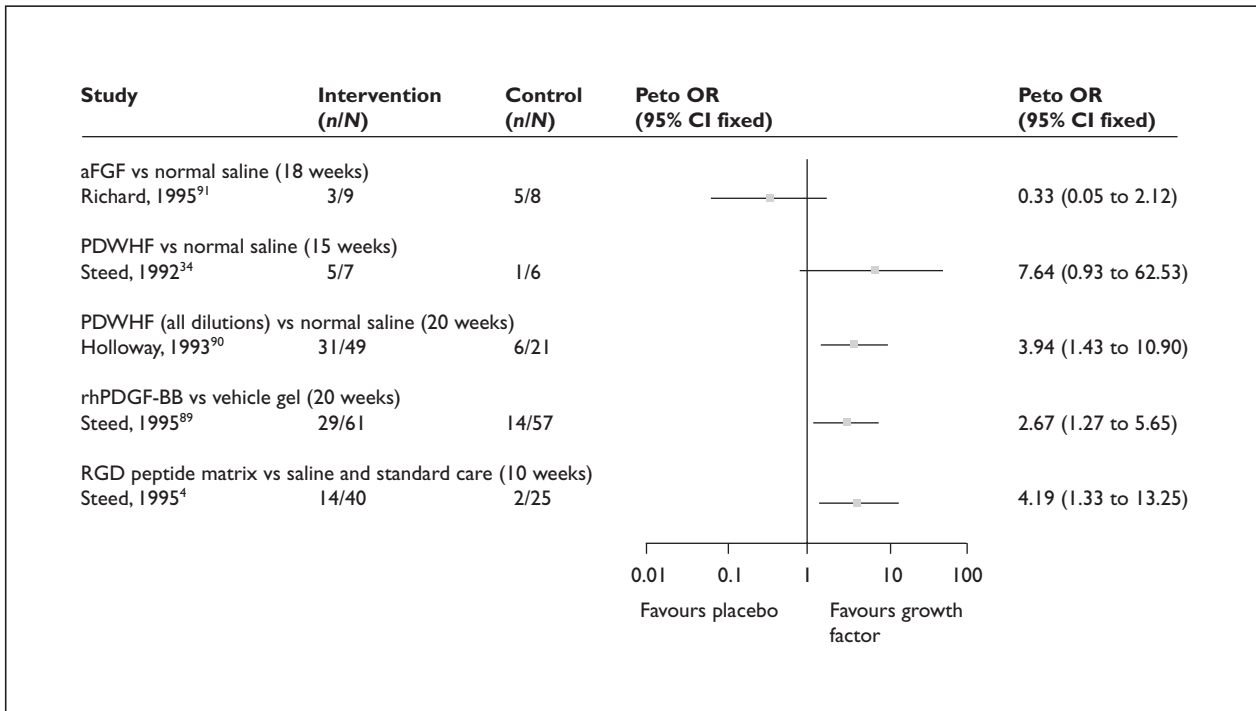
**FIGURE 21** A comparison of iloprost with placebo for the complete or partial (> 30% of wound surface) healing of diabetic foot ulcers at 4 weeks



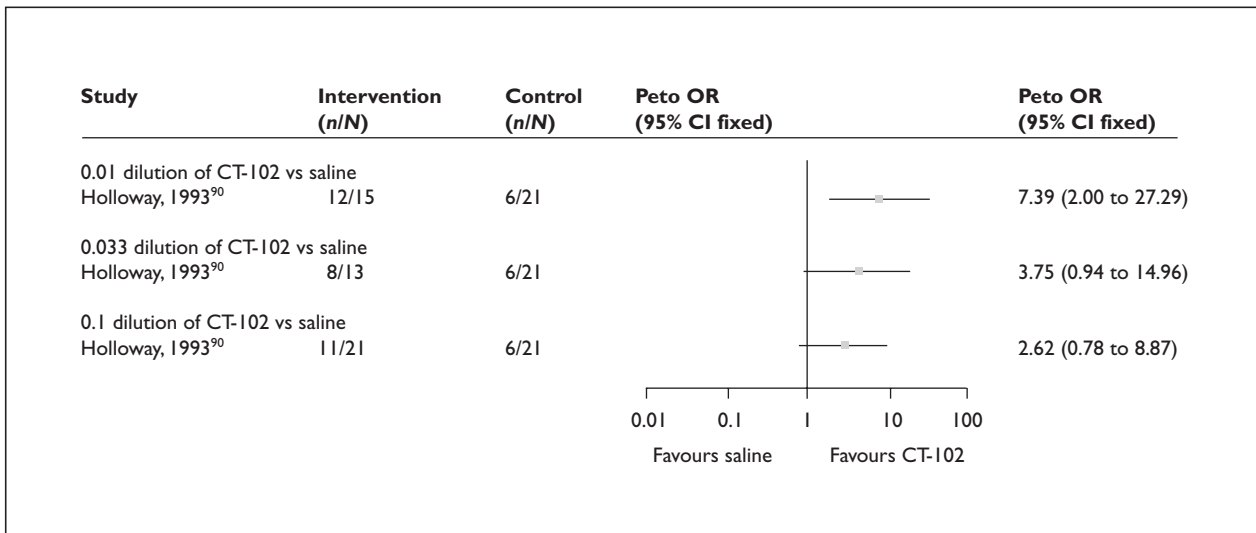
**FIGURE 22** A comparison of lipo-PGE<sub>1</sub> with placebo for the healing (80–100% reduction in size) of diabetic foot ulcers



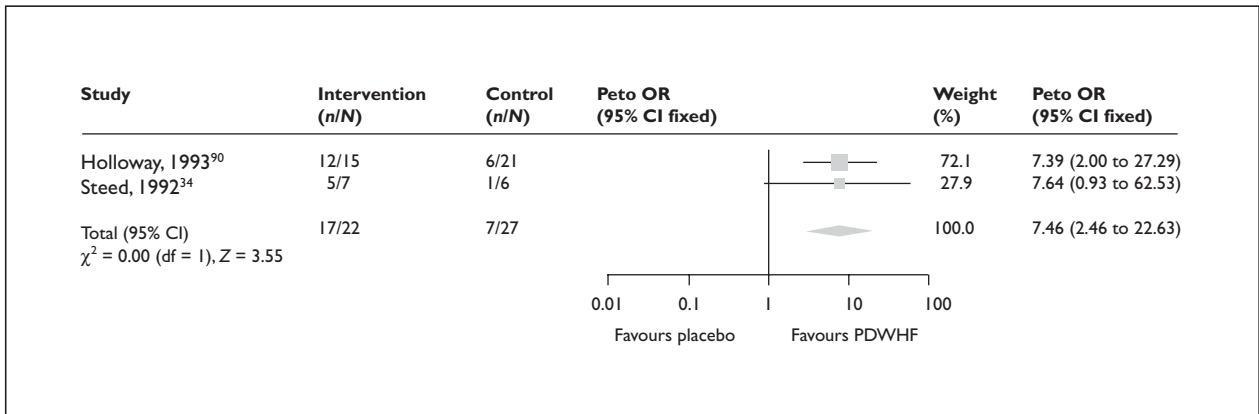
**FIGURE 23** A comparison of lipo-PGE<sub>1</sub> with placebo for the healing (> 50% reduction in size at 4 weeks) of diabetic foot ulcers



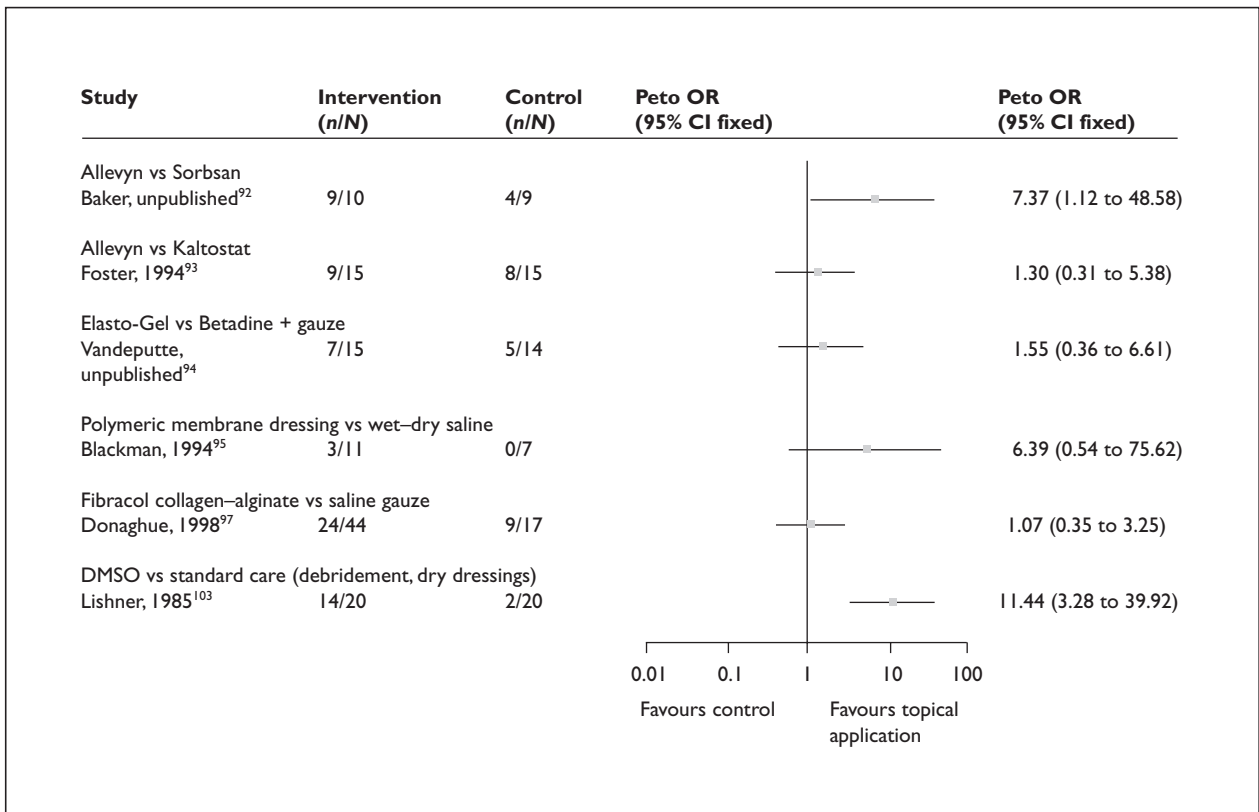
**FIGURE 24** Comparisons of various growth factors with normal saline or vehicle gel on the complete healing of diabetic foot ulcers



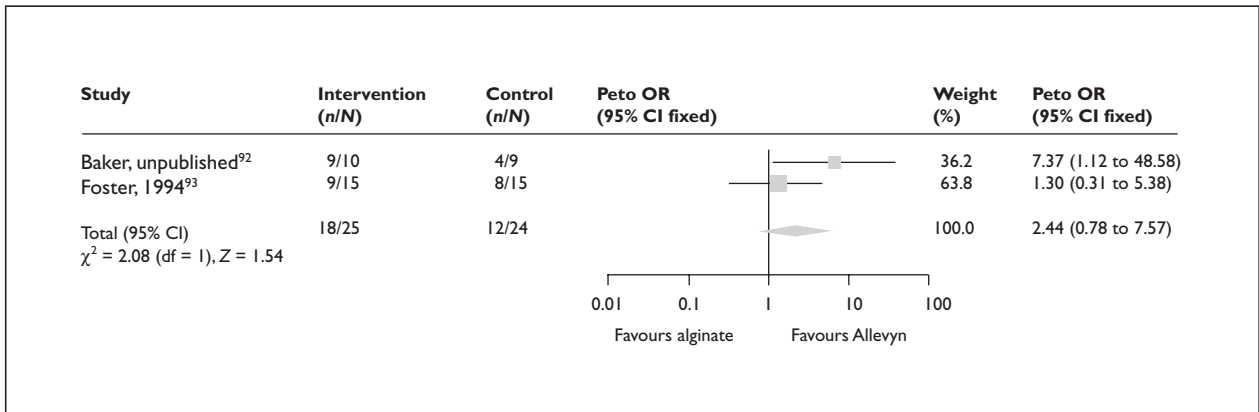
**FIGURE 25** Three different dilutions of CT-102 APST (PDWHF) compared with normal saline for the healing of diabetic foot ulcers



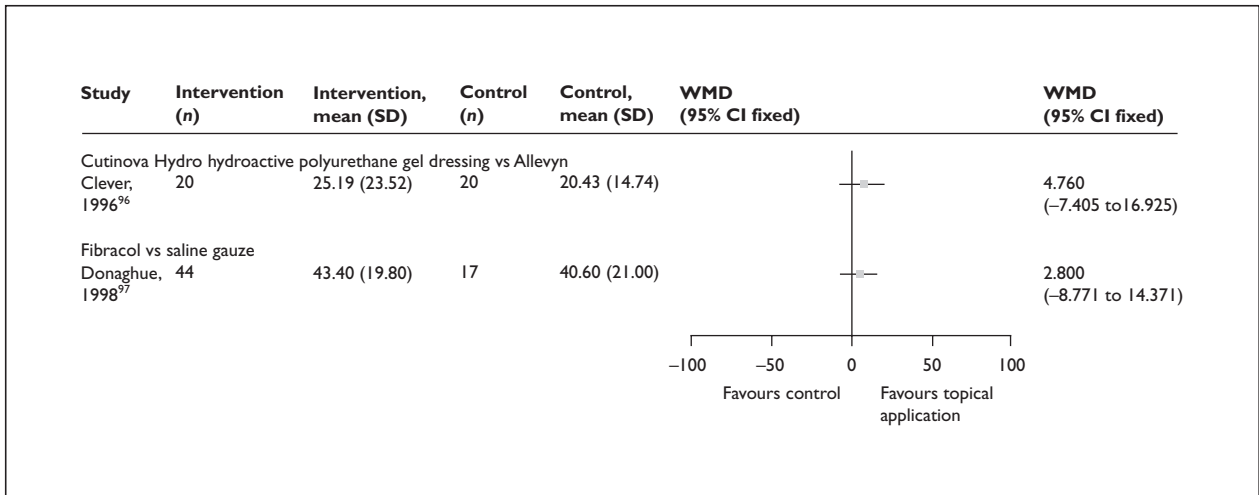
**FIGURE 26** A pooled estimate (fixed effects model) of the effect of CT-102 APST (PDWHF) compared with saline on the complete healing at 20 weeks of diabetic foot ulcers



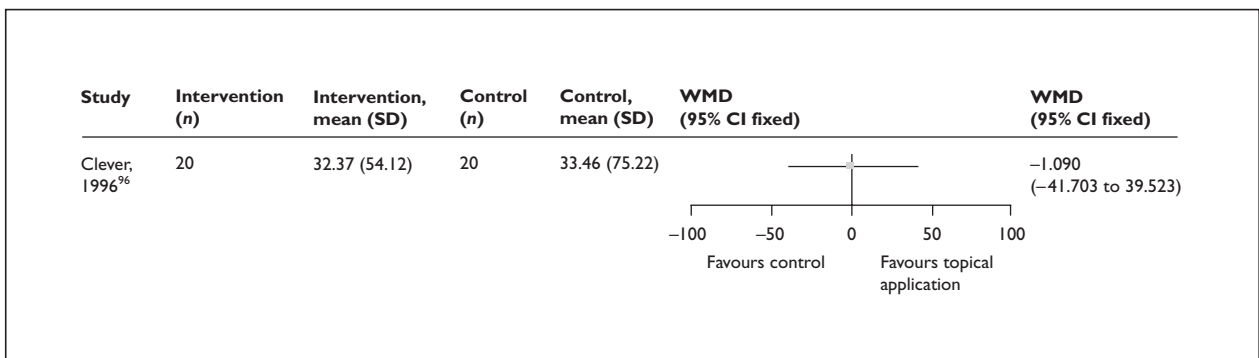
**FIGURE 27** Various dressings and topical wound applications compared with standard care for the healing of diabetic foot ulcers (different lengths of follow-up)



**FIGURE 28** A pooled estimate (fixed effects model) of the effect of a hydrocellular dressing (Allevyn) versus alginate-based dressings (Sorbsan and Kaltostat) for the complete healing of diabetic foot ulcers

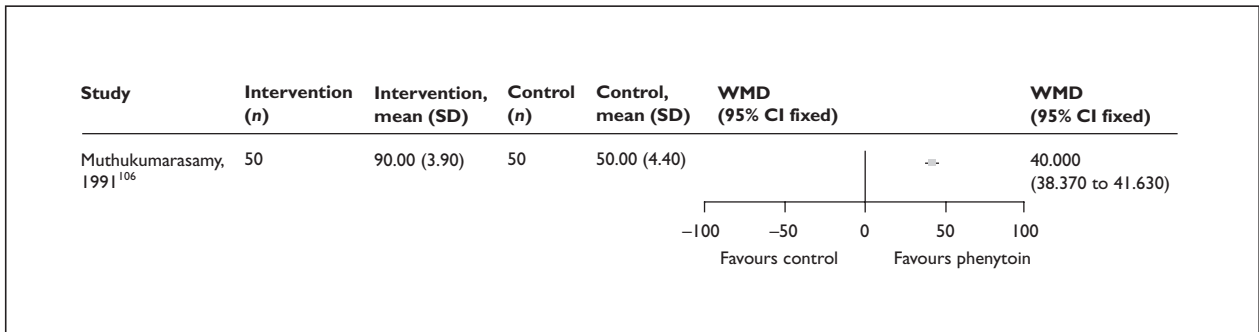


**FIGURE 29** Comparisons of various dressings and topical agents on the mean time to complete healing (days) of diabetic foot ulcers

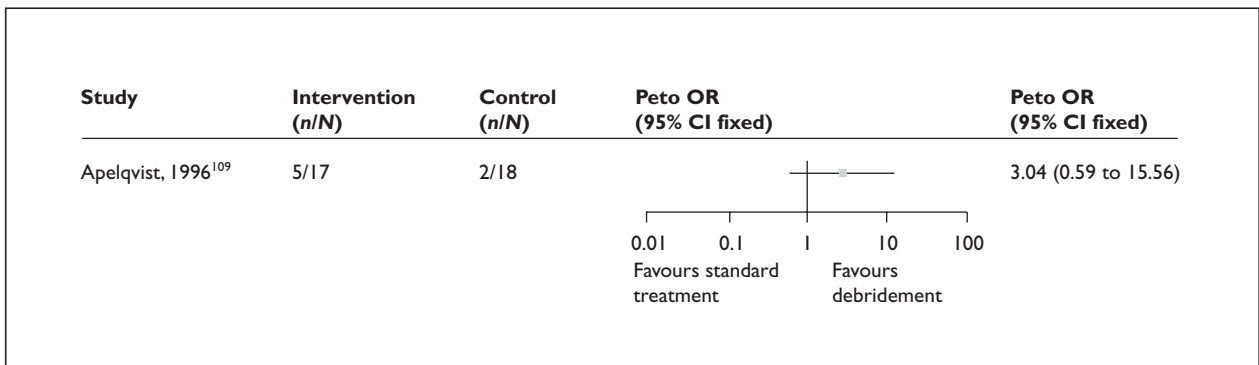


**FIGURE 30** A comparison of a hydroactive dressing (Cutinova Hydro) with a hydrocellular dressing (Allevyn) on the reduction in diabetic foot ulcer area ( $\text{mm}^2$ ) at 4 weeks

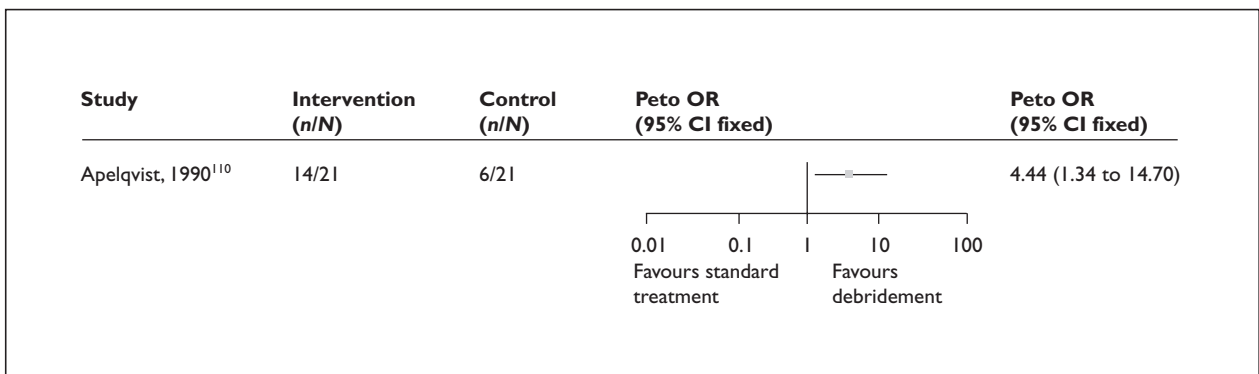




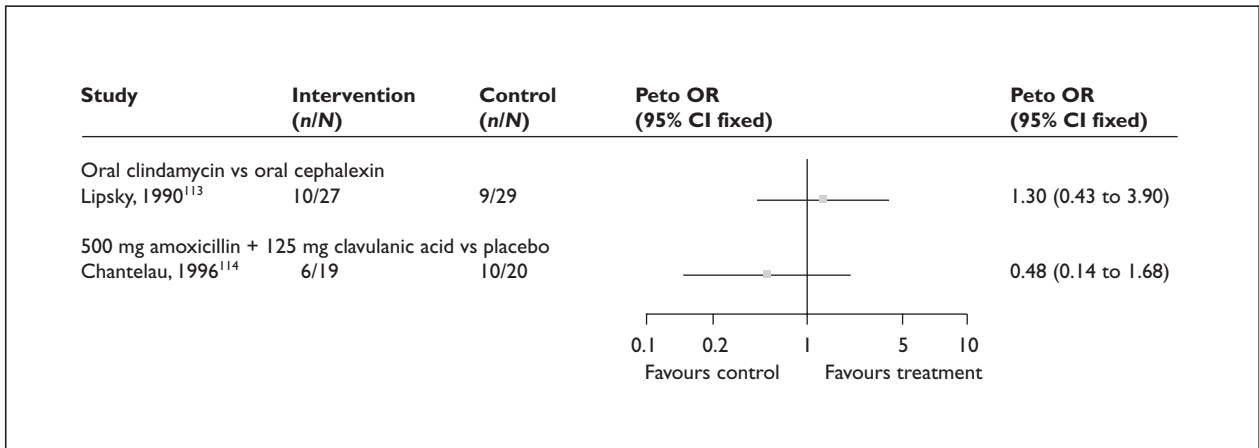
**FIGURE 31** A comparison of topical phenytoin powder with a dry occlusive dressing for the treatment of diabetic foot ulcers (mean percentage reduction in ulcer area at 35 days)



**FIGURE 32** A comparison of cadexomer iodine with standard treatment (gentamicin, saline gauze, streptokinase/streptodornase) for the healing of diabetic foot ulcers



**FIGURE 33** A comparison of adhesive zinc oxide tape (MeZinc) with hydrocolloid (DuoDerm) for the total disappearance or reduction (> 50%) of necrotic tissue in diabetic foot ulcers



**FIGURE 34** Two studies evaluating the impact of antibiotics on the healing of diabetic foot ulcers



# Chapter 4

## Discussion

### Prevention of diabetic foot ulceration

Little rigorous evaluation has been done of the prevention of diabetic foot ulcers, and only 10 RCTs were identified. These RCTs evaluated footwear, hosiery, podiatry, a screening and foot protection programme, and various educational programmes.

#### Podiatry and footwear

There is weak evidence, from one trial of 69 patients, that moulded footwear may influence ulcer recurrence at 12 months.<sup>47</sup> A second study found no difference between a custom-made orthotic device and conventional podiatry for the treatment of foot calluses in diabetic patients, but the study was underpowered and methodologically flawed.<sup>13</sup> An evaluation of podiatric (individualised patient education and foot care) reported a significantly greater reduction in non-calcaneal callus in the podiatry group compared with the control group, and the size of the calluses reduced to a significantly greater extent during the 12 months of follow-up in the podiatry group.

#### Hosiery

There is weak evidence from one small trial (75 patients) that elastic stockings may reduce the incidence of foot ulcers in diabetic patients with neuropathy and small vessel disease.<sup>50</sup>

#### Education

Although there has always been a strong interest in education as a strategy to prevent diabetic foot ulceration, surprisingly little has been done in the way of evaluating the effectiveness of diabetic patient education programmes. The American Association of Diabetes Educators lists more than 1000 hospitals that currently implement education programmes for diabetic patients.<sup>115</sup>

Only five trials of diabetic patient education programmes (with the common element of foot care) were identified which assessed ulceration as an outcome. The evidence from four of these trials found no significant effect on the prevention of foot lesions. Two of these studies also assessed amputation rates (foot or limb) at follow-up. The

fifth study reported that ulceration and amputation rates were reduced by two-thirds in patients receiving the educational programme.<sup>57</sup>

### Screening and a foot protection programme

One large trial of a combined screening and foot protection programme reported a statistically significant reduction in major amputations over a 2-year period.<sup>58</sup>

### Treatment of diabetic foot ulceration

#### Total contact casting

The evidence from one small RCT (40 patients) suggests that TCC may be a more effective treatment for diabetic foot ulcers than conventional wound dressings and accommodative footwear.<sup>60</sup>

#### Skin replacements

Skin replacements are a new group of products produced from cell culture. We have identified two trials of skin replacements, both of which evaluated Dermagraft.<sup>62,63</sup> Pooled together, the results of these studies suggest that Dermagraft may increase diabetic foot ulcer healing over 32 weeks. However, flaws in these studies (e.g. significant loss to follow-up) mean that more clinical and economic evaluation with adequate follow-up is needed before Dermagraft can be considered a standard therapy for the treatment of diabetic foot ulcers.

#### Hyperbaric oxygen therapy

One trial of systemic HBOT reported a significant increase in limb salvage.<sup>67</sup> However, without data on quality of life, limb function and cost-effectiveness, it is impossible to draw any firm conclusions for practice.

#### Ketanserin

Two small trials are suggestive of a benefit of 2% topical ketanserin on ulcer healing. However, more research is needed.<sup>72,73</sup>

#### Prostaglandins

The single trial of iloprost<sup>75,76</sup> and trials of PGE<sub>1</sub> and PGE<sub>1</sub>-CD<sup>78</sup> have shown positive results in that

intravenous infusions of iloprost resulted in greater ulcer healing than did placebo, and PGE<sub>1</sub> and PGE<sub>1</sub>-CD resulted in a significant reduction in ulcer area. However, the poor quality of these trials, namely the subjective outcome measures used, and a lack of blinded outcome assessment, precludes any definitive conclusions being drawn about the effectiveness of prostaglandins as a treatment for diabetic foot ulcers.

### Growth factors

The results from the growth factor trials are encouraging and show a consistent trend towards effectiveness. However, the extent to which debridement plays a role in influencing the rates of healing needs further elucidation. There has been no work to optimise the delivery vehicle or to identify the effect of contact with wound fluid on the activity of the growth factors. However, most of these studies involved very small sample sizes and further multicentre trials are urgently needed now that becaplermin (rhPDGF) is licensed for use in diabetic foot ulcer care in the UK. No economic analyses of growth factor use were identified, and future clinical trials should also measure cost-effectiveness.

### Dressings and topical agents

It is impossible to say at this stage whether any particular dressing is more effective for treating diabetic foot ulcers. All nine RCTs identified involved very small numbers of patients, and only one comparison (of Allevyn with alginate) has been replicated.

Two topical agents, DMSO and Iamin-Gel (2%), looked promising in small pilot studies, but clearly require evaluation in larger trials.

Generally, trials in this area were small in size and short in follow-up. In light of the lack of conclusive evidence of the most effective and cost-effective dressing, further research is needed, taking particular account of the need for larger sample sizes and the need for meaningful comparisons with widely used alternatives.

### Debridement

The effect of debridement *per se* (e.g. surgical debridement) on diabetic foot ulcer healing has not been evaluated. Two RCTs of topical debriding agents were identified. MeZinc, an adhesive zinc oxide tape, was more effective than DuoDerm, an adhesive occlusive hydrocolloid dressing, in eliminating necrotic tissue.<sup>110</sup> However, analysis was not by intention-to-treat and 20% of patients in the study withdrew due to an increase

in the area of necrosis, pain and oedema. A second debriding agent, cadexomer iodine, was compared with standard treatment and was found to be associated with significantly increased healing rates.

### Antibiotics

Two trials of antibiotics, which assessed ulcer healing as an outcome, were included in the review. The first found no significant difference in healing rate in patients receiving combined amoxicillin and clavulanic acid compared with placebo.<sup>114</sup> The second found no difference in healing rates when patients received clindamycin or cephalexin.<sup>113</sup>

### Summary

In common with many other aspects of wound care, the research in the area of the prevention and treatment of diabetic foot ulcers is extremely poor quality and relatively uninformative. Diabetic foot ulcers are multifactorial in aetiology, and the design and practice of clinically meaningful and scientifically robust trials is a challenge. Given the way in which most of the research has been designed and conducted, the review and interpretation of these trials is hampered by:

- small sample sizes with poor baseline equivalence across groups
- a lack of clarity as to the aetiology of the ulcers in each study (neuropathy, vascular disease or a combination?)
- the interacting effects of debridement and other treatment modalities within studies (the question of how much wound debridement contributes to wound healing has never been answered for any type of wound)
- the confounding effects of weight-bearing and patient compliance (with regard to relieving pressure)
- the methods of measuring outcomes being poorly developed, with little use of quality-of-life measures and widespread use of unblinded, subjective outcome measures
- a common lack of distinction between patients with IDDM and NIDDM.

Many of the studies reviewed lost large numbers of patients to follow-up, with drop-outs rarely accounted for in the final analysis. Further RCTs of sufficient size and duration of follow-up are warranted, alongside economic evaluations in order to compare the clinical- and cost-effectiveness of

different modalities in the prevention and treatment of diabetic foot ulcers.

As a consequence of the design and quality of the research in this area, there is not one element of

clinical practice that can be wholeheartedly recommended on the basis of unequivocal research findings. The small number of comparisons that yielded statistically significant findings were themselves small and unreliable.



## Chapter 5

# Conclusions

Much uncertainty remains over the most effective and cost-effective interventions for the prevention and treatment of diabetic foot ulcers. However, there are certain interventions (e.g. growth factors, skin replacements) that show promise but need further and more rigorous evaluation. There is no rapid growth in research or product availability in this area, but nevertheless treatments such as rhPDGF (becaplermin) and skin equivalents such as Dermagraft are available in the UK and licensed for use in diabetic foot ulcers. Such products are costly, and robust clinical and cost evaluations are required before their use becomes widespread. Importantly, traditional standard treatments such as antibiotics, which are prescribed routinely for diabetic foot ulceration by some clinicians in the UK, remain unevaluated.

Future studies should take account of those interventions that have shown promise in these 'pilot' studies and build on what has been learned, by choosing appropriate comparison treatments for trials, ensuring adequate sample size and avoiding the shortcomings of the existing studies. Also, there has been little evidence of the longer term effectiveness of these treatments, as the majority of studies did not incorporate a long follow-up period. The role of weight-bearing as part of the overall treatment needs to be clarified through further investigation. Researchers may wish to consider the development of a condition-specific outcome measure for diabetic foot care studies, and it is clear that researchers need to be more mindful of the need for unbiased, objective assessment of ulcer healing in future trials. In the absence of any clear evidence, this review strongly suggests that more good quality RCTs alongside economic evaluations are needed to determine the relative clinical- and cost-effectiveness of these interventions.

### Implications for future research

When well-conducted, RCTs give the most reliable estimates of effect and are least likely to be biased. Future trials evaluating any prevention or treatment intervention need to take into account the following methodological factors described below.<sup>40</sup> Assessment of such factors can be made

more systematic with the use of checklists and several are available for use with RCTs. The quality checklist used in this review is given in appendix 7.

### The method and degree of allocation concealment at randomisation

Open randomisation (i.e. the person recruiting the patients into the study knows which treatment the next patient recruited will receive) is associated with exaggerated treatment effects of the order of 30–40%. Therefore, researchers should strive to achieve concealed randomisation. Several trial reports in the review either were not clear about the randomisation procedure used or used open methods of allocation. Methods of concealing allocation include: centralized randomisation schemes; randomisation schemes controlled by a pharmacy; numbered or coded containers in which capsules from identical-looking, numbered bottles are administered sequentially; on-site computer systems, where allocations are in a locked unreadable file; and sequentially numbered opaque, sealed envelopes.

### Blinding

Blinding is the process whereby the treatment assignment is kept secret from the key stakeholders in the research. Blinding the patient from the treatment received (not always possible in wound care) contributes to the minimisation of **performance bias**, since knowing the treatment may affect a patient's response to it. Blinding the care providers and researchers in a trial helps protect against **selection bias**, **performance bias**, **attrition bias** and **detection bias**. It is particularly important that the investigator assessing the outcomes of a treatment should be unaware of which treatment the patient received (blinded outcome assessment). Although detection bias becomes less important the more objective the outcome measure (e.g. alive or dead), it is clearly important in studies of wound healing, where even the boundary between healing and healed may be quite blurred.

### Adequate sample size

A well-designed study is based on a sample size determined *a priori* to have sufficient power to detect worthwhile treatment effects. Evidence of *a priori* determination of sample size was absent from



the vast majority of studies in this review, and most were clearly vastly underpowered. Studies that lack power run a high risk of type II error (i.e. a failure to detect a true treatment effect). This problem was compounded in the studies reviewed here, where no opportunity for combining underpowered studies was offered due to the lack of replication of similar comparisons.

### **Adequate length of follow-up to enable measurement of total healing times**

It was impossible to determine the longer term benefits (including the proportion of ulcers finally healed) from the studies included in the review as follow-up times were too short. Duration of follow-up should be sufficient to capture the moment of wound closure in a high proportion of participants, as wound-healing rate is essentially a proxy outcome measure; its relation to total healing time is poorly understood.

### **Reporting of withdrawals**

Ideally, all participants randomised into a trial should be included in the final analysis. Reasons for withdrawal should be clearly documented, as it is clearly important to distinguish between patients who experienced adverse events and withdrew from a trial, patients who withdrew consent, and patients who were lost to follow-up (and perhaps died). The reasons for loss of patients should be clearly recorded along with the treatment group they were lost from and, wherever possible, they should be included in the final analysis. Doubts about the validity of trials in this review emerged when a substantial proportion of those who were randomised dropped out without any further mention, particularly in studies where more patients were lost from one group than another (**attrition bias**). Patients should be analysed in the groups to which they were randomised, irrespective of treatment received and protocol deviations (**intention-to-treat analysis**).

### **Baseline comparability of groups**

An adequately sized, RCT should ensure the even distribution of patients between treatment groups for key prognostic characteristics. Problems arise (as in most trials in this review) when studies were too small to allow an even distribution of patients for some characteristics. This was particularly the case for such important prognostic factors for wound healing as baseline ulcer size and duration. When patient characteristics differ in important

respects between treatment groups, it is impossible to confidently attribute health outcomes to the interventions under study. Trialists should not only recruit sufficient patients and ensure concealed allocation, they should also clearly report the baseline characteristics of the patients by group. Analysis should be undertaken to confirm baseline comparability, and if differences exist they should be adjusted for in the analysis.

### **Reporting of adverse events**

The beneficial effect of any healthcare intervention has to be weighed against adverse effects, and these should be clearly reported (by group) in the trial report.

### **Economic analysis**

Measures of clinical effectiveness alone are rarely sufficient to guide healthcare decision-makers, since small incremental improvements in clinical effectiveness may not be worth the costs.

### **Stratified randomisation**

A number of trials in wound care have recruited patients with wounds of different aetiologies without any stratification. It is completely plausible that diabetic ulcers may respond differently from venous leg ulcers to particular treatments, but this is impossible to detect if results are not presented separately. Furthermore, stratified randomisation of patients by their diagnosis (and other important prognostic variables such as baseline wound size) will help to ensure evenly balanced groups.

### **Choosing clinically relevant outcomes**

There is an absence of validated, condition-specific outcome measures in chronic wound research. This hampers the measurement of quality of life in wound-healing studies, since as many of these chronic wounds primarily affect the elderly, and are themselves consequences of other health conditions, generic quality of life measures are unlikely to detect changes in quality of life associated with wound healing. The objective measure of changes in wound size is also poorly undertaken in wound research, with some trialists using healing rates (i.e. rate of change of area or volume) as a proxy measure for time to healing. The problems associated with the use of these poor objective measures of healing are compounded by the small sample sizes used and the poorly balanced groups at baseline. This issue has been discussed in more detail in another review in this series.<sup>116</sup>



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## Appendix I

### Wagner's system for the classification of diabetic feet

Grade	Lesion
0	No open ulcers, but bony deformaties and/or hyperkeratoses that increase the risk of ulcer formation
1	Ulceration extending into the dermis or a superficial ulcer
2	Ulceration penetrating the dermis and extending into a tendon and/or joint capsule
3	Ulceration extending into bone with or without osteomyelitis
4	Localised gangrene (forefoot or heel)
5	Gangrene involving a major part of the foot



## Appendix 2

### Databases searched and search strategies

This search strategy was designed to serve a series of systematic reviews of chronic wound management (see, for example, Bradley and co-workers<sup>116</sup>) and was therefore not designed to search specifically for studies on diabetic foot ulcers. A database of trials in wound care was assembled for the series of reviews and has formed the basis of the Cochrane Wounds Group specialist register of trials. This 'master' database was then searched separately for each review.

The principal search strategy is outlined below.

#### Databases searched

- ISI Science Citation Index (on BIDS)
- BIOSIS (on Silver Platter)
- British Diabetic Association Database (BDAD)
- CINAHL (on OVID CD-ROM)
- CISCOM, the database of the Research Council for Complementary Medicine
- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Wounds Group register of trials
- Current Research in Britain (CRIB)
- Database of Abstract of Reviews of Effectiveness (DARE) (NHS Centre for Reviews and Dissemination)
- Dissertation Abstracts
- DHSS Data (on Knight-Ridder Datastar)
- EconLit
- EMBASE (on Knight-Ridder Datastar)
- Index to Scientific and Technical Proceedings (searched on BIDS)
- MEDLINE (on OVID and Silver Platter CD-ROM)
- National Research Register (to locate ongoing research in the NHS)
- NHS Economic Evaluation Database (NHS Centre for Reviews and Dissemination)
- Royal College of Nursing Database (CD ROM)
- System for Information on Grey Literature in Europe (SIGLE – Blaise Line)

#### MEDLINE search strategy (OVID version)

MEDLINE was searched for RCTs from 1966 to December 1998 using a mixture of free text terms and the following MeSH headings:

WOUND INFECTION  
 PILONIDAL CYST  
 WOUNDS AND INJURIES  
 WOUND HEALING  
 LEG ULCER  
 VARICOSE ULCER  
 SKIN ULCER  
 DECUBITUS

The MEDLINE search strategy used was as follows:

1. decubitus ulcer/ or foot ulcer/
2. leg ulcer/ or varicose ulcer/
3. pilonidal cyst/
4. skin ulcer/
5. diabetic foot/
6. ((plantar or diabetic or heel or venous or stasis or arterial) adj ulcer\$).tw.
7. ((decubitus or foot or diabetic or ischaemic or pressure) adj ulcer\$).tw.
8. ((pressure or bed) adj sore\$).tw.
9. ((pilonidal adj cyst) or (pilonidal adj sinus) or bedsore\$).tw.
10. ((diabetic adj foot) or (cavity adj wound)).tw.
11. ((varicose or leg or skin) adj ulcer\$).tw.
12. (decubitus or (chronic adj wound\$)).tw.
13. ((sinus adj wound\$) or (cavity adj wound\$)).tw.
14. or/1-13
15. debridement/ or biological dressings/ or bandages/
16. occlusive dressings/ or clothing/ or wound healing/
17. antibiotics/ or growth substances/ or platelet-derived growth factor/
18. fibroblast growth factor/ or electrical stimulation therapy.ti,ab,sh.
19. lasers/ or nutrition/ or surgery/ or surgery, plastic/
20. surgical flaps/ or skin transplantations/ or homeopathy/ or homeopathic/
21. acupuncture therapy/ or acupuncture/ or alternative medicine/
22. alternative medicine/ or massage/ or iloprost/ or alginates/
23. zinc/ or zinc oxide/ or ointments/ or anti-infective agents/
24. dermatologic agents/ or colloids/ or cushions/ or wheelchairs/
25. beds/ or wound dressings/

26. (debridement or dressing\$ or compress\$ or cream\$ or (growth adj factor\$)).tw.
27. (pressure-relie\$ or (recombinant adj protein\$) or bandag\$ or stocking\$).tw.
28. (antibiotic\$ or (electric adj therapy) or laser\$ or nutrition\$ or surg\$).tw.
29. (homeopath\$ or acupuncture or massage or reflexology or ultrasound).tw.
30. (iloprost or alginate\$ or zinc or paste\$ or ointment\$ or hydrocolloid\$).tw.
31. ((compression adj therapy) or (compression adj bandag\$) or wrap\$).tw.
32. (bed\$ or mattress\$ or wheelchair\$ or (wheel adj chair) or cushion\$).tw.
33. ((wound adj dressing\$) or vitamin\$ or bind\$ or gauze\$ or heals or healing).tw.
34. (diet or lotion\$ or infect\$ or reduc\$ or (wound adj healing)).tw.
35. (treat\$ or prevent\$ or epidemiol\$ or aetiol\$ or etiol\$ or therap\$ or prevalence or incidence).tw.
36. or/15–35
37. 14 and 36
38. random allocation/ or randomized controlled trials/
39. controlled clinical trials/ or clinical trials phase I/ or clinical trials phase II/
40. clinical trials phase III/ or clinical trials phase IV/ or clinical trials overviews/
41. single-blind method/ or double-blind method/
42. publication bias/ or review/ or review, academic/
43. review tutorial/ or meta-analysis/ or systematic review/
44. ((random\$ adj controlled adj trial\$) or (prospective adj random\$)).tw.
45. ((random adj allocation) or random\$ or (clinical adj trial\$) or control\$).tw.
46. ((standard adj treatment) or compar\$ or single-blind\$ or double-blind\$).tw.
47. (blind\$ or placebo\$ or systematic\$ or (systematic adj review)).tw.
48. (randomized controlled trial or clinical trial).pt. or comparative study.sh.
49. or/38–48
50. 37 and 49
51. limit 50 to human
52. burns/ or wounds, gunshot/ or corneal ulcer/ or exp dentistry/
53. peptic ulcer/ or duodenal ulcer/ or stomach ulcer/
54. ((peptic adj ulcer) or (duodenal adj ulcer) or traum\$).tw.
55. ((aortocaval adj fistula) or (arteriovenous adj fistula)).tw.
56. (bite adj wound\$).tw.

57. or/52–56
58. 51 not 57

## CINAHL search strategy (OVID version)

The CINAHL search strategy used was as follows:

1. pressure ulcer/ or foot ulcer/ or leg ulcer/ or skin ulcer/
2. diabetic foot/ or diabetic neuropathies/
3. diabetic angiopathies/ or diabetes mellitus/co
4. pilonidal cyst/ or surgical wound infection/
5. ((plantar or diabetic or heel or venous or stasis or arterial) adj ulcer\$).tw.
6. ((decubitus or foot or diabetic or ischaemic or pressure) adj ulcer\$).tw.
7. ((pressure or bed) adj sore\$).tw.
8. ((pilonidal adj cyst) or (pilonidal adj sinus) or bedsore).tw.
9. ((diabetic adj foot) or (cavity adj wound)).tw.
10. ((varicose or leg or skin) adj ulcer\$).tw.
11. (decubitus or (chronic adj wound\$)).tw.
12. ((sinus adj wound\$) or (cavity adj wound\$)).tw.
13. or/1–12
14. debridement/ or biological dressings/ or occlusive dressings/
15. (bandages.ti,sh,ab,it. and “Bandages and Dressings”/) or compression garments/ or antibiotics/
16. electric stimulation/ or Laser Surgery/ or lasers/th lasers/ or Nutrition Care (Saba HHCC)/ or diet therapy/ or Nutrition Therapy (Iowa NIC)/
17. surgery, reconstructive/ or surgery, plastic/ or surgical flaps/
18. surgical stapling/ or skin transplantation/ or alternative therapies/
19. acupuncture/ or massage/ or zinc/ or ointments/
20. antiinfective agents, local/ or antibiotics/ or dermatologic agents/
21. dermatology nursing/ or colloids/ or beds and mattresses/
22. flotation beds/ or wheelchairs/ or positioning:wheelchair/ or positioning:therapy/
23. patient positioning/ or positioning/ or wound care/ or wound healing/
24. (debridement or dressing\$ or compress\$ or cream\$).tw.
25. ((growth adj factor\$) or pressure relie\$ or (recombinant adj protein\$) or bandag\$).tw.
26. (stocking\$ or antibiotic\$ or (electric adj therapy) or laser\$ or nutrition\$ or surg\$).tw.

27. (iloprost or alginate\$ or zinc or paste\$ or ointment\$ or hydrocolloid\$).tw.
28. ((compression adj therapy) or (compression adj bandag\$) or wrap\$).tw.
29. (bed\$ or mattress\$ or wheelchair\$ or (wheel adj chair) or cushion\$).tw.
30. ((wound adj dressing\$) or vitamin\$ or bind\$ or gauze\$ or heals or healing).tw.
31. (diet or lotion\$ or infect\$ or reduc\$ or etiol\$ or (wound adj healing)).tw.
32. (treat\$ or prevent\$ or epidemiol\$ or aetiol\$ or therap\$ or prevalence or incidence).tw.
33. "Bandages and Dressings"/ or skin transplantation/ or homeopathy/
34. or ointments/ or "beds and mattresses"/
35. or/14-34
36. 13 and 35
37. clinical trials/ or single-blind studies/ or double-blind studies/
38. control group/ or placebos/ or meta analysis/
39. ((random\$ adj clinical adj trial\$) or (prospective adj random\$)).tw.
40. ((random adj allocation) or random\$ or controlled clinical trial\$ or control).tw.
41. (comparison group\$ or (standard adj treatment) or compar\$).tw.
42. (single-blind\$ or (single adj blind) or double-blind or (double adj blind)).tw.
43. (blind\$ or placebo\$ or systematic or (systematic adj review)).tw.
44. (meta analysis or meta-analysis).tw. or (trials or trial or prospective).tw.
45. (clinical trials).sh. or (comparative studies).sh.
46. or/37-45
47. 36 and 46
48. burns/ or wounds, gunshot/ or corneal ulcer/ or exp dentistry/
49. peptic ulcer/ or duodenal ulcer/
50. ((peptic adj ulcer) or (duodenal adj ulcer) or trauma).tw.
51. (burn\$ or (gunshot adj wound\$) or (corneal adj ulcer) or dentist\$ or (bite adj wound)).tw.
52. or/48-51
53. 47 not 52

### Database search terms for economic studies

Searches were based on the CRD Economic Search Strategy for MEDLINE. The search terms used were as follows:

exp Economics  
 exp costs and cost analysis  
 cost  
 costs  
 economics\*  
 pharmaco-economic\*  
 cba  
 cost benefit  
 cea  
 cost effectiveness  
 cua  
 health



## Appendix 3

### Hand-searching

Several relevant nursing journals had already been hand-searched for RCTs, including the *Journal of Advanced Nursing* and the *International Journal of Nursing Studies*. In addition, the following are already indexed on MEDLINE or CINAHL: *Professional Nurse*, *Nursing Times* and the *Nursing Standard*. In addition, the following journals were hand-searched for relevant studies:

- *CARE – Science and Practice*, 1979–1990
- *Decubitus*, 1987–present
- *Journal of Tissue Viability*, 1991–present
- *Journal of Wound Care*, 1991–present
- *Phlebology*, 1986–present.

In order to identify economic evaluations hand-searches were made of:

- *Health Economic Evaluation*, December 1992
- *Medical Care – Health Care Cost Benefit and Cost-Effectiveness Analysis*, 1979–1990

- *Spilker's International Bibliography of Health Economics*, 1986
- *Department of Health Register of Cost-effectiveness Studies*, 1994.

The following conference proceedings were also hand-searched for references to trials and authors were contacted to request a full report:

- 1st–5th European Conferences on Advances in Wound Management, 1991–1995
- 3rd–5th Annual Symposia on Advanced Wound Care, 1990–1992
- 1996 Symposium on Advanced Wound Care & Medical Research Forum on Wound Repair
- Going into the '90s: The Pharmacist and Wound Care, 1992
- Second Joint British/Swedish Angiology Meeting, 1991
- Societas Phlebologica Scandinavia Symposium on Venous Leg Ulcers, 1985.





## Appendix 4

### Advisory panel

Dr Mary Bliss, Consultant Geriatrician, Department of Medicine for the Elderly, Homerton Hospital, Homerton Row, London E9 6SR, UK.

Professor Nick Bosanquet, Imperial College School of Medicine, Department of General Practice, Norfolk Place, London W2 1PG, UK.

Professor Andrew Boulton, Department of Medicine, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK.

Dr Richard Bull, Department of Dermatology, Homerton Hospital, Homerton Row, London E9 6SR, UK.

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Dr Raj Mani, Southampton University Hospitals Trust, Medical Physics Department, Southampton SO9 4XY, UK.

Andrea Nelson, Research Fellow, Department of Health Studies, University of York, York YO10 5DD, UK.

Dr Steve Thomas, Director, Surgical Materials Testing Laboratory, Bridgend General Hospital, Bridgend, Mid Glamorgan, UK.

Dr Ewan Wilkinson, Liverpool Health Authority, Hamilton House, 24 Pall Mall, Liverpool L3 6AL, UK.



# Appendix 5

## Data extraction form

The data extraction form used for each individual study included in this review is given below.

**Data abstractor:**

**Review of:**

**Author(s)**

**Title**

**Source of reference**

**Country of study**

**Study setting**

**No. of patients**

**Type of wound**

**Treatments**

**Type of patient (age range, sex, primary, diagnosis, etc.)**

**Authors' conclusion**

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### STUDY DESIGN

RCT

Double-blind method

Single-blind method

Unblinded

Other design

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### KEY POINTS

Clear inclusion and exclusion criteria

Sample size adequate to show a significant difference, if present

- Record of withdrawal/drop-out rate, with reasons
  - All clinically relevant outcomes reported
  - Major design/implementation problems
- 

**Sample size**

Patient population? (how sampled)

No. of patients accepted into study

No. of arms arm in trial

No. in each arm

*A priori* power calculation?

If so, power =

**Inclusion criteria**

**Exclusion criteria**

**Patient characteristics**

Age

Sex

Medical condition

etc.

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**DESIGN DETAILS**

Single centre/multicentre trial

**Study type**

Randomised controlled trial/matched control/unmatched concurrent control/historic control/crossover study

**Allocation**

Was it random?

Unit of randomisation?

Method of randomisation

Was it concealed?

**Intervention details**

Care setting

Treatment group(s) and dosage

Control(s)

Co-interventions

Duration of intervention

Who delivered intervention?

Was the carer blinded ?

Was the patient blinded?

**Outcomes measures**

What were they?

How were they measured?

When were they measured?

Is this a valid assessment of the outcome measure?

Was assessment blinded?

Inter-assessor reliability measured?

Length of follow-up

**Costs**

Considered?

Cost-effectiveness details

**(If the study is an economic evaluation then a separate assessment procedure, used by the NHS Centre for Reviews and Dissemination for such economic evaluations, will be followed.)**

**Analysis**

Which analyses performed?

Were subgroups considered?

Intention-to-treat analysis?

Adjustment for confounding?

Exploration of heterogeneity?

**Results**

No. of withdrawals

Reasons for withdrawal

No. lost to follow-up

**Results of analyses (summary)**

**Authors' conclusions**

**Other comments**

Baseline comparability of groups

Comparability of interventions

---

**GENERAL QUALITY OF STUDY**

# **Appendix 6**

## Summary of included studies



TABLE 1 RCTs of footwear for the prevention of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
Colagiuri, 1995, <sup>13</sup> Australia	20 diabetic patients with plantar calluses (5 men; 15 women), aged 46–75 years (mean $\pm$ SD 66 $\pm$ 8 years)	<b>I (n = 9):</b> Custom-made rigid orthotic device (worn at least 7 h/day) <b>C (n = 11):</b> Traditional podiatrist treatment of callus (paring of hyperkeratotic skin, application of moisturisers and hypoallergenic padding) <b>Duration of treatment and follow-up:</b> 12 months	<b>Mean <math>\pm</math> SD duration of diabetes:</b> All patients: 8.4 $\pm$ 7.5 years (range 1 month to 24 years) I: 10.7 $\pm$ 7.6 years C: 7.9 $\pm$ 6.6 years <b>Mean <math>\pm</math> SD weight:</b> All patients: 75 $\pm$ 10 kg I: 74.1 $\pm$ 6.5 kg C: 76.2 $\pm$ 13.9 kg <b>Mean <math>\pm</math> SD No. of calluses:</b> I: 2.4 $\pm$ 1.0 C: 2.9 $\pm$ 1.4 <b>Evidence of neuropathy:</b> I: 3 patients C: 5 patients	<b>Total No. of calluses at 12 months:</b> I: 20/22 (91%) C: 32/32 (100%) (OR = 0.08; 95% CI, 0.00 to 1.41) <b>Mean callus grade:</b> I: 1.2 C: 1.7 <b>No. of calluses improved:</b> I: 16/22 (73%) C: 2/32 (6%) (OR = 18.84; 95% CI, 6.02 to 58.96) No side-effects or difficulties reported, except for minor adjustments required to the devices Cost of device approx. Australian \$100
Ronnemaa, 1997, <sup>48</sup> Finland	530 patients (both NIDDM and IDDM) aged 10–79 years (mean $\pm$ SD 46.9 $\pm$ 19.1 years), selected from a register as having not seen a podiatrist in the preceding 6 months and without an obvious need for foot care	<b>I (n = 267):</b> Visited podiatrist as many times in 1 year as deemed appropriate by podiatrist. Podiatric care involved personalised patient education on an individual patient basis. Education included proper footwear, hygiene, cutting of toenails and risk. Podiatric care involved treatments, such as debridement of callus, bespoke insoles, treatment of ingrown toenails and exercise <b>C (n = 263):</b> Written instructions only (no detail given) <b>Duration of treatment and follow-up:</b> 12 months	<b>Prevalence of callosities in calcaneal region:</b> I: 18.5% C: 16.8% <b>Prevalence of non-calcaneal callosities:</b> I: 54.5% C: 51.3% <b>Mean <math>\pm</math> SD initial diameter of largest calcaneal callus:</b> I: 40.5 $\pm$ 30.8 mm C: 30.6 $\pm$ 28.5 mm <b>Mean <math>\pm</math> SD initial diameter of largest non-calcaneal callus:</b> I: 16.6 $\pm$ 10.2 mm C: 15.2 $\pm$ 9.8 mm <b>Mean <math>\pm</math> SD serum fructosamine:</b> I: 3.46 $\pm$ 0.67 $\mu$ mol/l C: 3.41 $\pm$ 0.66 $\mu$ mol/l	<b>Prevalence of callosities in calcaneal region at 12 months:</b> I: 12.0% C: 15.5% No significant difference in change between groups ( $p = 0.14$ ) <b>Prevalence of non-calcaneal callosities at 12 months:</b> I: 39.5% C: 48.2% Significant difference in change between groups ( $p = 0.009$ ) <b>Mean <math>\pm</math> SD diameter of largest calcaneal callus at 12 months:</b> I: 25.5 $\pm$ 28.8 mm C: 28.3 $\pm$ 26.8 mm No significant difference in change between groups ( $p = 0.065$ )
C, control group; I, intervention group				
continued				

**TABLE 1 contd** RCTs of footwear for the prevention of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
				<p>Mean <math>\pm</math> SD diameter of largest non-calcaneal callus at 12 months:                      I: 11.4 <math>\pm</math> 10.3 mm                      C: 14.4 <math>\pm</math> 9.9 mm                      Significant difference in change between groups (<math>p &lt; 0.001</math>)</p>
Uccioli, 1995, <sup>47</sup> Italy	69 diabetic patients (43 men, 26 women) from two teaching hospitals (Rome and Milan) with an absence of ulceration, absence of previous minor or major amputations and absence of major foot deformities	<p><b>I (n = 33):</b> Therapeutic shoes with custom-moulded insoles</p> <p><b>C (n = 36):</b> Ordinary non-therapeutic shoes</p> <p><b>Duration of treatment and follow-up:</b> 12 months</p>	<p>Mean <math>\pm</math> SD age:                      I: 59.6 <math>\pm</math> 11 years                      C: 60.2 <math>\pm</math> 8.2 years</p> <p>Mean <math>\pm</math> SD duration of diabetes:                      I: 16.8 <math>\pm</math> 12.7 years                      C: 17.5 <math>\pm</math> 8 years</p> <p>Type 1/type 2 diabetes:                      I: 8/25 patients                      C: 9/27 patients</p>	<p>Ulcer relapses at 1 year:                      I: 9/33 (27%) patients                      C: 21/36 (58%) patients                      (OR = 0.29; 95% CI, 0.11 to 0.74)</p> <p>Mean <math>\pm</math> SD ulcer-free time:                      I: 9.1 <math>\pm</math> 3.7 months                      C: 3.7 <math>\pm</math> 3.1 months                      (<math>p &lt; 0.02</math>)</p>
C, control group; I, intervention group				

TABLE 2 RCTs of elastic stockings for the prevention of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
Belcaro, 1992, <sup>50</sup> Italy	160 patients with diabetic microangiopathy. Subjects with severe proteinuria and renal impairment, frequent history of ketosis, poorly controlled diabetes, heavy smokers, hypertension or cardiovascular disease and previous diabetic foot ulcers were excluded. 149 patients completed the study	<b>I (n = 74):</b> Standard below-knee elastic stockings with 25 mmHg compression at ankle for at least 6 h/day  <b>C (n = 75):</b> No stockings  <b>Duration of treatment and follow-up:</b> 4-year follow-up	<b>Gender (male/female):</b> I: 36/38 C: 39/36  <b>Mean ± SD age:</b> I: 52.8 ± 11 years (34–68 years) C: 53.2 ± 12 years (33–68 years)  <b>Mean ± SD duration diabetes:</b> I: 15.4 ± 7 years C: 15.1 ± 8 years  Groups comparable for sex, age distribution, duration of diabetes, supine resting flux, flux on dependency and venoarteriolar response	<b>No. of ulcerated limbs at year 4:</b> I: 3/148 (2%) C: 10/150 (7%) (OR = 0.33; 95% CI, 0.11 to 1.00)  <b>Total No. of ulcers at year 4:</b> I: 3/74 (4%) C: 10/75 (13%) (OR = 0.31; 95% CI, 0.10 to 0.98)  <b>Withdrawals:</b> I: 6 C: 5
C, control group; I, intervention group				

**TABLE 3** RCTs of patient education programmes for the prevention of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
Bloomgarden, 1987, <sup>53</sup> USA	749 insulin-treated diabetics (predominantly black and Hispanic and type 2 diabetic patients) identified from clinic register. 373 patients were randomised to the education group and 376 to the control group. Of the 749 randomised patients, 483 were excluded for reasons including death, moved away, unreachable, and declined to take part. Thus a total of 266 patients completed the final assessment at 1.5 ± 0.3 years	<p><b>I (n = 127):</b> Diabetic patient education programme. Patients were offered nine teaching sessions. Graduates (n = 79) defined as those attending ≥ 7 classes, and non-graduates (n = 48) as those attending ≤ 7 classes (mean ± SD attendance 5.7 ± 2.7 clinic visits). The education programme covered: understanding diabetes (basic physiology, foot and skin care, early detection of infections, urine and blood glucose testing, focus on prevention and early detection, risk factors for macrovascular disease); nutrition (individual diet instruction, basic nutrition, weight loss, the diabetic diet (behavioural techniques, food purchasing and meal planning)). All patients in the education group also received the control intervention</p> <p><b>C (n = 139):</b> Patients had contact at each visit with their physician and nurse, who reviewed medications and specific problems). (Mean ± SD attendance 5.7 ± 2.7 clinic visits for 1.5 ± 0.3 years)</p>	<p>Gender (female): I: 77% C: 67%</p> <p>Mean ± SD age: I: 56 ± 12 years C: 59 ± 13 years (p = 0.709)</p> <p>Mean ± SD duration diabetes: I: 13 ± 8 years C: 14 ± 9 years</p> <p>Education (none/not completed high school/high-school graduate): I: 10%/63%/28% C: 10%/60%/30%</p> <p>Type 2 diabetes: I: 96% C: 91%</p> <p>Foot lesions (callus, nail dystrophy, fungal infection): I: 30% C: 44%</p> <p>Ulcer or amputation: I: 6% C: 9%</p>	<p>No. of patients with foot lesions: No lesions: I, 61; C, 48</p> <p>Minor lesions (callus, nail dystrophy, fungal infection): I, 56; C, 75</p> <p>Severe lesions (ulcer or amputation): I, 10/127 (7.9%); C, 16/139 (11.5%) (OR = 0.66; 95% CI, 0.30 to 1.49)</p> <p>Lost to follow-up: I: 18 patients C: none</p>
Pieber, 1995, <sup>54</sup> Austria	108 NIDDM patients from seven general practices from a rural area in Southern Austria	<p><b>I (n = 52):</b> Structured diabetes treatment and teaching programme (DTTP) comprising a weekly session (90–120 minutes) for 4 weeks. The programme covered the basics of diabetes, self-monitoring of glycosuria, diet, weight loss, foot care, physical activity, sick-day rules and late complications, all supported by teaching materials</p>	<p>Mean ± SD duration of diabetes: I: 7.6 ± 5.6 years C: 6.9 ± 6.1 years</p> <p>Mean ± SD body weight: I: 82.1 ± 14.5 kg C: 81.8 ± 13.1 kg</p>	<p>No. of calluses at 6 months: I: 22 (49%) patients C: 40 (82%) patients (p &lt; 0.001)</p> <p>No. of ulcers at 6 months: I: 1/52 C: 2/56 (OR = 0.55; 95% CI, 0.06 to 5.37)</p>
C, control group; I, intervention group				
continued				

TABLE 3 contd RCTs of patient education programmes for the prevention of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
		<p><b>C (n = 56):</b> Routine patient care</p> <p><b>Duration of treatment:</b> 6 months</p>	<p>Mean <math>\pm</math> SD body mass index: I: 30.2 <math>\pm</math> 4.7 C: 30.2 <math>\pm</math> 4.5</p> <p>Mean <math>\pm</math> SD % HbA<sub>1c</sub> (glycated haemoglobin A<sub>1c</sub>): I: 8.6 <math>\pm</math> 1.8 C: 8.8 <math>\pm</math> 2.1</p> <p>No. of amputations: I: 1 C: 1</p> <p>No. of ulcers: I: 1 C: 2</p> <p>No. of calluses: I: 35 (78%) patients C: 40 (82%) patients</p>	<p>No. of withdrawals: I: 7 patients C: 6 patients</p> <p>Reasons for withdrawal: severe illness or hospitalisation, 8; moved away, 3; refused to participate, 2</p> <p>DTTP reduced routine healthcare costs by an average of Austrian shillings 594 (UK £33) per patient per year due to reduced prescription of oral hypoglycaemics (OHGs). In the control group, an increase of Austrian shillings 546 (UK £30) was observed mainly because of an increase in the prescription of OHGs. The costs of glycosuria self-monitoring in the DTTP was 8% and the cost of the learning material was 6% of the routine diabetes treatment costs</p>
Reichard, 1993, <sup>55</sup> Sweden	102 patients (54 men, 48 women) with IDDM, non-proliferative retinopathy, normal serum creatinine concentrations and unsatisfactory blood glucose control	<p><b>I (n = 48):</b> Intensified insulin treatment consisting of individual education (covering the action of insulin, intermediary metabolism, home glucose monitoring and the interpretation of blood glucose tests to modify treatment) followed by continuous tutoring with frequent face-to-face and telephone contact, initially every second week and then at longer intervals</p> <p><b>C (n = 54):</b> Standard insulin treatment comprising continuation of routine diabetes care, physician visit every 4 months, advised to measure blood glucose concentrations, but the results only discussed at regular visits and used to improve treatment</p>	<p>Mean <math>\pm</math> SD age: I: 30 <math>\pm</math> 8 years C: 32 <math>\pm</math> 7 years</p> <p>Mean <math>\pm</math> SD duration of diabetes: I: 18 <math>\pm</math> 6 years C: 16 <math>\pm</math> 4 years</p> <p>Symptoms of peripheral neuropathy: I: 5 (12%) patients C: 8 (17%) patients</p> <p>Mean <math>\pm</math> SD body mass index: I: 22.6 <math>\pm</math> 2.1 C: 22.8 <math>\pm</math> 2.9</p>	<p>Foot ulcers developed at 7.5-year follow-up: I: 0/42 patients C: 3/47 (6%) patients (OR = 0.14; 95% CI, 0.01 to 1.43)</p> <p>No. of withdrawals: Total: 13 Due to death: I, 4; C, 3 Moved away: I, 2; C, 4</p>
C, control group; I, intervention group				
<i>continued</i>				

**TABLE 3 contd** RCTs of patient education programmes for the prevention of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
Litzelman, 1993, <sup>56</sup> 1997, <sup>136</sup> USA	395 patients aged > 40 years with NIDDM diagnosed after age 30 years, seen at least twice in preceding year by the same provider. Diagnosis of diabetes based on the National Diabetes Data Group criteria or the presence of disease requiring medication for the control of hyperglycaemia, intention to obtain care from the GP for the next 2 years, body weight ideal or heavier than ideal	<p><b>Duration of treatment and follow-up:</b> treatment, 18 months; follow-up, 3, 5 and 7.5 years</p> <p><b>I (n = 191):</b> Multifaceted patient, healthcare provider and healthcare systems intervention consisting of foot-care education for patients and behavioural contracts regarding desired foot-care behaviours, and phone and postcard reminders sent at 1 and 3 months. Healthcare providers received specific practice guidelines for assessment, diagnostic work-up, treatment, and referral recommendations</p> <p>Also, prompts placed in patients' notes</p> <p><b>C (n = 205):</b> usual care (not described)</p> <p><b>Duration of treatment and follow-up:</b> 12 months</p>	<p><b>Mean ± SD duration of diabetes:</b> I: 9.6 ± 8.0 years C: 10.1 ± 8.1 years</p> <p><b>IDDM:</b> I: 52/191 (27%) patients C: 47/205 (23%) patients</p>	<p><b>Serious foot lesions</b> (defined as a severity grade of at least 1.3, which indicates a minor, non-ulcerated lesion with clinical evidence of healing sufficient to close previous interruption of the cutaneous barrier or a blister): I: 7/176 (4%) C: 16/175 (9%) (OR = 0.43; 95% CI, 0.19 to 1.00)</p> <p><b>Amputation rate (foot or limb):</b> I: 1/191 (0.5%) C: 4/205 (2%) (OR = 0.32; 95% CI, 0.05 to 1.86)</p> <p><b>Mean ± SD time to first clinic visit:</b> I: 3.9 ± 2.6 months C: 4.1 ± 3.0 months (p = 0.12)</p> <p><b>Total No. of visits:</b> I: 2.2 ± 1.4 C: 2.3 ± 1.5 (p = 0.7)</p> <p><b>Lost to follow-up:</b> Total: 43/395 (11%) Death: 11 Moved away: 15 Illness: 6 Transportation problems: 3 Other: 8</p>
C, control group; I, intervention group				
				<i>continued</i>

TABLE 3 contd RCTs of patient education programmes for the prevention of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
Malone, 1989, <sup>57</sup> USA	203 diabetic patients with foot infections, ulceration or prior amputation referred to either the podiatry or vascular surgery clinic between 1984 and 1985. Patients with uninfected foot ulcers or prior amputation were also included	<p><b>I (n = 103 patients, 203 limbs):</b> A simple 1-hour education class that included a review of slides depicting infected diabetic feet and amputated diabetic limbs, plus a simple set of patient instructions for the care of the diabetic foot on a weekly or bimonthly basis depending on the rate of attendance. After satisfactory completion of the education class, there were no further attempts at short-term or long-term education</p> <p><b>C (n = 100 patients, 193 limbs):</b> No special foot care education</p> <p><b>All patients:</b> Routine diabetic teaching with respect to diet, weight, exercise and medication</p> <p><b>Duration of follow-up:</b> 1–26 months, both groups I: median, 12 months; mean, 13.2 months C: median, 8 months; mean, 9.2 months</p>	No data presented. The authors reported no statistically significant differences between the groups in the incidence of foot deformities, neuropathy, gangrene, prior amputation, prior foot ulcer, hypertrophic nails, medical management of diabetes, prior diabetic foot education or level of distal pulses. The incidence of prior distal (below-knee) vascular reconstruction was higher in the control group (not significant). However, the incidence of foot callous was significantly higher in the intervention group ( $p < 0.05$ )	<p><b>Success rate</b> (defined as the continued absence of foot infections, ulceration or foot or leg amputation): I: 160/177 (90%) limbs C: 128/177 (72%) limbs (OR = 3.28; 95% CI, 1.92 to 5.60; <math>p &lt; 0.0005</math>)</p> <p><b>Incidence of foot ulceration:</b> I: 8/177 (4.5%) limbs C: 26/177 (14.6%) limbs (OR = 0.31; 95% CI, 0.15 to 0.63; <math>p &lt; 0.005</math>)</p> <p><b>Failure</b> (defined as the occurrence of foot infection, ulceration, or foot or leg amputation): Incidence of infection: I, 2/177 (1%) limbs; C, 2/177 (1%) limbs (not significant)</p> <p>Foot or limb amputation: I, 7/177 (4%) limbs; C, 21/177 (12%) limbs (OR = 0.34; 95% CI, 0.16 to 0.73; <math>p &lt; 0.025</math>)</p> <p><b>Lost to follow-up:</b> Total: 21 (all deaths) I: 13 C: 8</p>

C, control group; I, intervention group

TABLE 4 Screening and foot protection programme

Study	Sample and setting	Intervention	Baseline characteristics	Results
McCabe, 1998, <sup>38</sup> UK	2001 diabetic patients recruited from weekly diabetes outpatient clinic. All but 4 patients (who already had ulcers) were randomly allocated to intervention and control groups	<p><b>I:</b> Screening: Primary foot screening examination using Semmes-Weinstein monofilaments plus biothesiometry and palpation of foot pulses. Any abnormality reviewed at a second appointment, at which the ankle/brachial pressure index (ABPI), transcutaneous oxygen concentration and foot pressures were measured and x rays taken. Patients with foot deformities or a history of ulceration or an ABPI <math>\leq 0.75</math> were deemed high risk and entered into the prevention programme. Patients not meeting any of these criteria were deemed lower risk and received no further treatment</p> <p><b>Prevention programme:</b> Weekly attendance at diabetic foot clinic with podiatry, hygiene maintenance, support hosiery, protective shoes, and education about foot hygiene and inspection.</p> <p><b>C:</b> Usual care (patients silently tagged and continued to receive usual outpatient care)</p> <p><b>Duration of follow-up:</b> 2 years</p>	Not given	<p>Incidence of ulceration: I: 24/1001 (2.4%) C: 35/1000 (3.5%) (<math>p &gt; 0.14</math>)</p> <p>Incidence of ulcers progressing to amputation: I: 29% C: 66%</p> <p>Incidence of amputation (major/minor): I: 7 (1/6) C: 25 (12/13) (<math>p &lt; 0.04</math>)</p> <p>Difference in rate of major amputations: <math>p &lt; 0.01</math></p> <p>Difference in rate of minor amputations: <math>p &gt; 0.15</math></p> <p>Costs: Cost of primary screening: £4.23/patient Cost of secondary screening: £74.86/patient</p> <p>Total cost of screening and prevention programme for 1001 patients: £100,372 (= £100.27/patient) Mean cost of amputations prevented: £9125</p>
C, control group; I, intervention group				



TABLE 5 RCTs of footwear for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
Mueller, 1989, <sup>60</sup> USA	40 diabetic patients (27 men, 13 women) with plantar ulcers from a diabetic foot centre and physical therapy department at Washington University School of Medicine	<p><b>I (n = 21):</b> Total contact casting (TCC). The ulcer was covered with one thin layer of gauze, with cotton placed between the toes to prevent maceration, a stockinette applied to lower leg with 1/8-inch felt pads applied to the malleoli and anterior tibia and a foam pad placed around the toes. The TCC plaster shell was moulded around the lower leg and reinforced with splints and a walking heel attached to the plantar surface; fibre glass roll was applied around the plaster for extra durability</p> <p><b>C (n = 19):</b> Traditional dressing treatment (dressing changes and accommodative footwear)</p> <p><b>Length of treatment and follow-up:</b> 3 months (unclear) or until ulcers healed</p>	<p><i>Mean ± SD age:</i> I: 54 ± 10 years C: 55 ± 12 years</p> <p><i>IDDM/INIDDM:</i> I: 5/16 C: 6/13</p> <p><i>Mean ± SD ulcer area:</i> I: 1.8 ± 2.5 cm<sup>2</sup> C: 2.8 ± 3.4 cm<sup>2</sup></p> <p><i>Ulcer grade (I/2):</i> I: 15/6 C: 13/6</p> <p><i>Mean ± SD ulcer duration:</i> I: 155 ± 195 days C: 175 ± 200 days</p>	<p><i>Healing (defined as complete skin closure with no drainage):</i> I: 19/21 (90%) C: 6/19 (32%) (OR = 11.59; 95% CI, 3.27 to 41.09)</p> <p><i>Mean ± SD (range) time to healing:</i> I: 42 ± 29 days (8–91 days) C: 65 ± 29 days (12–92 days) (OR = -23.00; 95% CI, -40.997 to -5.003)</p> <p><i>Infections requiring hospitalisation:</i> I: 0/21 C: 5/19 (26%) (p &lt; 0.05)</p> <p><i>Withdrawals:</i> I: 2 (one due to acute infection and referral to vascular surgeon; one due to refusal of additional cast, reporting that it was cumbersome and interfered with daily activities)</p> <p>TCC requires careful application, close follow-up and patient compliance with scheduled appointments to minimise complications</p>

C, control group; I, intervention group

**TABLE 6** RCTs evaluating Dermagraft (a cultured human dermis) for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
Gentzkow, 1996, <sup>62</sup> USA	50 patients (enrolled at 5 institutions) with NIDDM (n = 15) or IDDM (n = 35) under reasonable control, who were hospitalised in the previous 6 months for hyperglycaemia or ketoacidosis. Patients had a full-thickness (> 1 cm <sup>2</sup> ) plantar foot ulcer, a wound bed free of necrotic debris and infection and suitable for a skin graft (no exposed tendon, bone or joint, no tunnels or sinus tracts that could not be debrided), and adequate circulation in the foot	<p><b>I1 (n = 12):</b> One piece of Dermagraft applied weekly for 8 weeks + standard care</p> <p><b>I2 (n = 14):</b> Two pieces of Dermagraft applied every 2 weeks for 8 weeks + standard care</p> <p><b>I3 (n = 11):</b> One piece of Dermagraft applied every 2 weeks for 8 weeks + standard care</p> <p><b>I4 (n = 13):</b> Standard care (sharp debridement, ulcers covered with non-adherent dressing, saline-moistened gauze added to fill remaining volume of ulcer and secured by adhesive covering and pressure-relief instructions given to avoid weight-bearing on treated foot and custom-fitted therapeutic shoes supplied (Apex Ambulator))</p> <p><b>Duration of treatment and follow-up:</b> treatment, 8 weeks; follow-up, 4 weeks</p>	<p>Gender (male/female): I1: 84 I2: 11/3 I3: 7/4 I4: 9/4</p> <p>Mean age: I1: 62.7 years I2: 66.2 years I3: 62.7 years I4: 53.8 years</p> <p>IDDM/NIDDM: I1: 7/5 I2: 9/5 I3: 9/2 I4: 10/3</p> <p>Mean ulcer duration: I1: 50.4 weeks I2: 40.7 weeks I3: 43.2 weeks I4: 47.0 weeks Overall: 55.3 weeks</p> <p>Mean ulcer area: I1: 2.2 cm<sup>2</sup> I2: 2.3 cm<sup>2</sup> I3: 3.3 cm<sup>2</sup> I4: 1.9 cm<sup>2</sup> Overall: 2.43 cm<sup>2</sup></p> <p>Mean HbA<sub>1c</sub>: I1: 8.0% I2: 8.2% I3: 8.4% I4: 9.1%</p>	<p>Complete healing (100% wound closure) at 12 weeks: I1: 6/12 (50.0%) I4: 1/13 (7.7%) (OR = 7.50; 95% CI, 1.35 to 41.55; p = 0.03)</p> <p>I2: 3/14 (21.4%) I4: 1/13 (7.7%) (OR = 2.85; 95% CI, 0.35 to 22.95)</p> <p>I3: 2/11 (18.2%) I4: 1/13 (7.7%) (OR = 2.51; 95% CI, 0.23 to 27.00) (absolute risk increase (ARI) = 42%; number needed to treat (NNT) = 2; 95% CI, 1 to 13. Relative risk increase (RRI) = 55%; 95% CI, 27.5 to 37.47)</p> <p>50% wound closure by week 12: I1: 9/12 (75%) I2: 7/14 (50.0%) I3: 2/11 (18.2%) I4: 3/13 (23.1%) (p &lt; 0.05 for I1 vs I4 and I1 vs I3) (ARI = 52%; NNT = 2; 95% CI, 1 to 8. RRI = 22.5%; 95% CI, 30 to 85)</p> <p>Follow-up (incidence of wound infection): I1: 17 I2: 29 I3: 27 I4: 23</p> <p>Lost to follow-up: Dermagraft-treated (not stated which dose): 3 I4: 1</p> <p>Side-effects: Infection occurred frequently in all groups but the difference in incidence between those receiving Dermagraft and those receiving standard therapy was not significant</p>
I, I1, I2, I3, I4, intervention groups				
<i>continued</i>				

**TABLE 6 contd** RCTs evaluating Dermagraft (a cultured human dermis) for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
Naughton, 1997, <sup>63</sup> Pollak, 1997, <sup>64</sup> Multicentre/USA	281 NIDDM or IDDM patients with foot ulcers (size > 1.0 cm <sup>2</sup> ) of neuropathic origin	<p><b>I (n = 139):</b> One piece of Dermagraft applied every week for 8 weeks + standard therapy</p> <p><b>C (n = 142):</b> Standard therapy alone (sharp debridement, infection control, saline-moistened gauze dressings, therapeutic shoes and instructions to avoid weight-bearing)</p> <p><b>Duration of treatment and follow-up:</b> treatment, 8 weeks; follow-up, 12 and 20 weeks</p>	Baseline comparability between groups not reported	<p>83.6% were analysed at 12 weeks</p> <p><i>Complete healing</i> (defined as full epithelialisation of wound with absence of drainage) <i>at 12 weeks:</i> I: 40/109 (39% of patients remaining, 29% of patients randomised) C: 40/126 (32% of patients remaining, 28% of patients randomised) (OR = 1.25; 95% CI, 0.73 to 2.14)</p> <p><i>Complete healing at 20 weeks:</i> I: 50/87 (57% of patients remaining, 36% of patients randomised) C: 39/92 (42% of patients remaining, 28% of patients randomised) (OR = 1.82; 95% CI, 1.02 to 3.27)</p> <p><i>Lost to follow-up at 12 weeks:</i> I: 22% C: 11% Reasons for losses not reported</p> <p><i>Lost to follow-up at 20 weeks:</i> I: 37% C: 35%</p> <p>No significant differences were found between Dermagraft and control patients in the occurrence of wound infections</p> <p><i>Cost-effectiveness:</i><sup>65</sup> Dermagraft: £3475 per ulcer healed Standard therapy alone: £4327 per ulcer healed</p>
C, control group; I, intervention group				

**TABLE 7** RCTs of hyperbaric oxygen therapy for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
Faglia, 1996, <sup>67</sup> Italy	70 consecutive diabetic subjects (48 men, 20 women, 2 drop-outs) with foot ulcers hospitalised in a diabetology unit. Lesions classified according to Wagner. <sup>41</sup> Full-thickness gangrene (grade IV) or abscess (grade III) included and grade II ulcers included if the ulcer was large and infected and showed a defective healing in 30 days of outpatient therapy	<b>I (n = 35):</b> Systemic hyperbaric oxygen therapy: Breathing of pure oxygen in a multiplace hyperbaric chamber, pressurised with air, with a soft helmet. First phase: 2.5 absolute atmosphere (ATA), 90 minutes per daily session. Second phase: 2.4–2.2 ATA for an average of 38 ± 8 sessions  <b>Standard therapy:</b> Aggressive multidisciplinary therapeutic protocol (radical debridement by consultant surgeon, antibiotic therapy and provision of orthopaedic devices to remove mechanical stress and pressure at site of ulcer while maintaining ambulation). The orthoses were made up of Alkaform <sup>®</sup> insole moulded in a plaster cast and an extra deep special shoe with a rigid sole  <b>C (n = 33):</b> Standard therapy alone	<b>Mean ± SD age:</b> I: 61.7 ± 10.4 years C: 65.6 ± 9.1 years (p = 0.10)  <b>Insulin therapy:</b> I: 21/35 C: 22/33 (p = 0.62)  <b>Oral therapy:</b> I: 14/35 C: 11/33  <b>Mean ± SD duration of diabetes:</b> I: 16 ± 10 years C: 19 ± 9 years  <b>Claudication:</b> I: 4/35 C: 10/33  <b>Sensorimotor neuropathy:</b> I: 35/35 C: 31/33  <b>Autonomic neuropathy:</b> I: 17/35 C: 15/33  <b>Previous ulcer:</b> I: 9/35 C: 12/33  <b>Wagner grade II:</b> I: 4/35 C: 5/33  <b>Wagner grade III:</b> I: 9/35 C: 8/33  <b>Wagner grade IV:</b> I: 22/35 C: 20/33	<b>Limbs salvaged</b> (defined as the preservation of the plantar support and the ulcer healed despite minor (toe or forefoot) amputation): I: 32/35 (91%) C: 22/33 (67%) (OR = 4.45; 95% CI, 1.38 to 14.29)  <b>Major amputations</b> (above or below the knee, decided by a consultant blind to treatment groups): I: 3/35 (9%) C: 11/33 (33%) (OR = 0.22; 95% CI, 0.07 to 0.72)  <b>Minor amputations (forefoot):</b> I: 5/35 (9%) C: 4/33 (12%) (OR = 1.20; 95% CI, 0.30 to 4.85)  <b>Amputations of the toe:</b> I: 16/35 (46%) C: 8/33 (24%) (OR = 2.53; 95% CI, 0.94 to 6.78)  <b>No amputation:</b> I: 11/35 (31%) C: 10/33 (30%) (OR = 1.05; 95% CI, 0.38 to 2.93)  <b>Total amputations:</b> I: 24/35 (69%) C: 23/33 (70%) (OR = 0.95; 95% CI, 0.34 to 2.64)  <b>Withdrawals:</b> I: 1 (refused treatment) C: 1 (died of an acute stroke 6 days after admission)
C, control group; I, intervention group				
continued				

TABLE 7 contd RCTs of hyperbaric oxygen therapy for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
Leslie, 1988, <sup>30</sup> USA	28 diabetic patients (16 men, 12 women) with well-demarcated foot ulcers (defined as: circular or elliptical in shape; at or below the level of the ankle; no visible bone exposure; no associated gangrene; not deemed to require urgent amputation; no crepitation, severe ischaemia or persistent fever > 100°F)	<p><b>I (n = 12):</b> Topical hyperbaric oxygen administered in two daily 90-minute sessions with the topical hyperbaric leg chamber, which provided humidified 100% oxygen at pressures cycling between 0 and 30 mmHg every 20 seconds, as recommended by the manufacturers</p> <p><b>C (n = 16):</b> No hyperbaric oxygen</p> <p><b>All patients:</b> Intravenous antibiotics, wet-to-dry dressings and bed rest)</p> <p><b>Duration of treatment and follow-up:</b> 14 days</p>	<p><i>Mean ± SD age:</i> I: 52.8 ± 8.6 years C: 46.2 ± 8.5 years</p> <p><i>IDDM/NIDDM:</i> I: 0/12 C: 4/12</p> <p><i>Mean ± SD duration of diabetes:</i> I: 11.4 ± 7.6 years C: 13.2 ± 8 years</p> <p><i>Mean ± SD duration of foot ulcer:</i> I: 6.4 ± 6.2 weeks C: 6.2 ± 7.8 weeks</p> <p><i>Mean ± SD ulcer area:</i> I: 551.8 ± 546.7 mm<sup>2</sup> C: 319.6 ± 255.7 mm<sup>2</sup></p> <p><i>Mean ± SD ulcer depth:</i> I: 8.1 ± 4.5 mm<sup>2</sup> C: 4.8 ± 3.3 mm<sup>2</sup></p> <p><i>Previous amputations:</i> I: 7 C: 5</p>	<p>Change in ulcer size area defined as maximum width × maximum length (mm), measured with a ruler by the same observer, and depth measured with a sterile probe, and photographed</p> <p><i>Mean % of baseline ulcer area at day 7:</i> I (n = 12): 67.1 ± 18.3 C (n = 16): 69.6 ± 34.5 (WMD -2.50; 95% CI, -22.32 to 17.32)</p> <p><i>Mean % of baseline ulcer area at day 14:</i> I (n = 12): 45.6 ± 23.4 C (n = 16): 35.6 ± 23 (WMD 10.00; 95% CI, -7.387 to 27.387)</p> <p><i>Mean ulcer depth as % of baseline ulcer depth at day 7:</i> I (n = 9): 95.9 ± 9.1 C (n = 10): 89.5 ± 29.2 (not significant)</p> <p><i>Mean ulcer depth as % of baseline ulcer depth at day 14:</i> I (n = 9): 75.8 ± 23.4 C (n = 10): 67.3 ± 23.5 (not significant)</p> <p><i>Withdrawals:</i> I: 1 (due to death)</p>

C, control group; I, intervention group

TABLE 8 RCTs of ketanserin for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
Janssen, unpublished, <sup>72</sup> Germany	299 patients with chronic skin ulcers of whom 45 were diabetic patients with foot ulcers (daily serum glucose level < 200 mg/dl). The remaining patients had pressure sores (n = 80), venous leg ulcers (n = 134), inoperable arterial insufficiency and arteriolar insufficiency (n = 40)	<b>I (n = 150):</b> Twice daily 2% ointment of ketanserin (Sufrexal)  <b>C (n = 149):</b> Polyethylene glycol vehicle alone  <b>All patients:</b> Conventional wound care, consisting of surgical or mechanical debridement or mechanical debridement  <b>Duration of treatment and follow-up:</b> 2–8 weeks	Some baseline characteristics (e.g. sex, age, baseline ulcer area, baseline extent of granulation) were not reported by wound type  <i>Gender (male/female):</i> I: 44/106 C: 45/102 (2 not mentioned)  <i>Mean age:</i> I: 70.2 years C: 69.6 years  <i>Mean duration of diabetic ulcers:</i> I: 21 days C: 24 days  <i>Granulation tissue score (0–3 scale) for all ulcers:</i> I: 0.84 C: 0.88  <i>Mean wound area for all ulcers:</i> I: 9.41 cm <sup>2</sup> C: 11.03 cm <sup>2</sup>	Subgroup analysis of patients with diabetic foot ulcers (n = 45):  <i>Increase in initial healing velocity</i> (defined as the wound area at a given time divided by initial wound area as a function of time): 2.96-fold increase (196% faster) in ketanserin-treated patients (p < 0.001)  <i>Note:</i> Randomisation was not stratified by wound type and baseline characteristics were not presented by wound type. Therefore it is impossible to judge the validity of the findings
Apelqvist, 1990, <sup>74</sup> Sweden	45 (26 men, 19 women, 5 excluded during run-in period) diabetic outpatients with deep foot ulcers (defined as a lesion extending to muscle tendon or bone) or a superficial ulcer with an area of > 1 cm <sup>2</sup> (an open lesion or necrosis through the full thickness of the dermis) and severe vascular disease, and with a systolic toe pressure below 45 mmHg	<b>I (n = 20):</b> ketanserin (20 mg, 3 times daily for 1 month, then 40 mg 3 times daily for 2 months)  <b>C (n = 20):</b> Placebo  <b>All patients:</b> 2-week run-in of placebo  <b>Other treatments used:</b> antibiotics in 26 cases of infection, dressings (I, 15; C, 11), footwear corrected (I, 17; C, 14) and surgical debridement performed when required (C, 4)  <b>Duration of treatment:</b> 3 months	<i>Mean ± SD age:</i> Overall: 70 ± 10 years I: 71 ± 10 years C: 67 ± 10 years  <i>Onset of diabetes (before age 30/after age 30):</i> 30/10  <i>Mean ± SD duration of diabetes:</i> Overall: 17 ± 12 years I: 20 ± 12 years C: 18 ± 12 years  <i>Presence of retinopathy:</i> I: 7 C: 6	<i>Ulcers healed (intact skin for at least 3 months):</i> I: 7/20 (35%) C: 5/20 (25%) (OR = 1.59; 95% CI, 0.42 to 6.05)  <i>Ulcers improved (wound area reduced by ≥ 50%):</i> I: 4/20 (20%) C: 2/20 (10%)  <i>Ulcers healed or improved:</i> I: 11/20 (55%) C: 7/20 (35%) (not significant)
C, control group; I, intervention group				
continued				

TABLE 8 contd RCTs of ketanserin for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
			<p>Mean (range) duration of ulcer: 23 weeks (2–105 weeks)</p> <p>Depth of ulcer (superficial/deep): I: 8/12 C: 7/13</p> <p>Median (range) wound area: I: 2.0 cm<sup>2</sup> (0.8–2.4 cm<sup>2</sup>) C: 1.5 cm<sup>2</sup> (1.0–160 cm<sup>2</sup>)</p>	<p>Ulcers deteriorated/no improvement (development of deep ulcer or increase of ≥ 50% of initial ulcer area): I: 6/20 (30%) C: 6/20 (30%)</p> <p>Incidence of gangrene (continuous necrosis of skin and underlying structures such as muscle, tendon joint or bone): I: 2/20 (10%) (2 amputations) C: 6/20 (30%) (4 amputations)</p> <p>Deaths: I: 1/20 (5%) C: 1/20 (5%)</p> <p>Withdrawals: Five during the run-in period (death, 3; cardiovascular accident, 1; gangrene with severe pain at rest and consequent major amputation, 1)</p> <p>No differences reported for adverse reactions; compliance good</p>
Martinez-de Jesus, 1997, <sup>73</sup> Mexico	140 local NIDDM patients with neuropathic foot ulcers of Wagner grades II and III, < 100 cm <sup>2</sup> in area with a median duration of 8 weeks	<p><b>I (n = 69):</b> Topical ketanserin (Sufrexal)</p> <p><b>C (n = 71):</b> Placebo (normal saline)</p> <p><b>All patients:</b> Treatment with systemic antibiotics, where necessary; weight avoidance; and surgical debridement of necrotic tissue and lavage with normal saline</p>	<p>Gender (male/female): I: 31/38 C: 28/93</p> <p>Mean ± SD age: I: 59.7 ± 10.7 years C: 60.7 ± 12.1 years</p> <p>Mean ± SD duration of diabetes: I: 23.3 ± 26.5 years C: 21.7 ± 9.5 years</p> <p>Grade of ulcers (Wagner III/III): I: 44/25 C: 50/21</p> <p>Mean ± SD No. of previous amputations: I: 0.5 ± 0.6 C: 0.6 ± 0.7</p>	<p>Mean ± SD reduction in ulcer area at 12 weeks: I: -37.91 ± 19.1 cm C: -24.25 ± 16.7 cm</p> <p>Mean reduction in ulcer area at 12 weeks: I: 87% C: 63% (<i>p</i> &lt; 0.001)</p> <p>Mean ± SD area at 12 weeks: I: 6.84 ± 6.50 cm<sup>2</sup> C: 15.45 ± 10.40 cm<sup>2</sup></p>
C, control group; I, intervention group				
				continued

**TABLE 8 contd** RCTs of ketanserin for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
			<p>Mean <math>\pm</math> SD No. of surgical debridements:                      I: <math>1.6 \pm 0.69</math>                      C: <math>1.5 \pm 0.75</math></p> <p>Mean <math>\pm</math> SD ulcer area:                      I: <math>44.75 \pm 20.8 \text{ cm}^2</math>                      C: <math>39.70 \pm 17.9 \text{ cm}^2</math></p>	
<p>C, control group; I, intervention group</p>				



TABLE 9 RCTs of prostaglandins for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
Brock, 1990, <sup>75</sup> Germany/ multicentre  (Duplicate of Muller, 1988 <sup>76</sup> )	109 (61 men, 48 women) diabetic patients (9 IDDM, 100 NIDDM) from 11 clinics with ischaemic and/or neuropathic foot ulcers and previously unsuccessful treatment	<b>I (n = 56):</b> Intravenous iloprost (individually tolerated dose up to 2 ng/kg per minute for 6 h/day)  <b>C (n = 53):</b> Placebo (identical solvent volumes)  <b>All patients:</b> Intensive basic therapy (not described)  <b>Duration of treatment and follow-up:</b> treatment, 28 consecutive days; follow-up, 11 months (range 4–27 months)	Age: ≤ 40 years: I, 2; C, 2 41–50 years: I, 4; C, 5 51–60 years: I, 10; C, 8 61–70 years: I, 16; C, 17 71–80 years: I, 24; C, 21  Type of diabetes (IDDM/NIDDM): I: 6 (11%)/50 (89%) C: 3 (6%)/50 (94%)  Duration of diabetes: <2 years: I, 1 (2%); C, 5 (10%) 2–3 years: I, 4 (7%); C, 8 (15%) >3 years: I, 50 (89%); C, 40 (75%)	Partial healing (> 30%) or total healing of the largest ulcer (assessed by photographs) at 4 weeks: I: 31/50 (62%) C: 12/51 (23.5%) (OR = 4.75; 95% CI, 2.17 to 10.41)  Withdrawals: I: 3, due to side-effects (foot and leg pain, raised blood pressure, angina) C: 1, due to headache, nausea and vomiting  Lost to follow-up: I: 9/31 (29%) responders C: 2/12 (17%) responders
Toyota, 1993, <sup>78</sup> Japan/multicentre/ trial I	170 diabetic inpatients (101 men, 69 women, 6 drop-outs) aged < 70 years with spontaneous pain, sensory disturbance, or ulcers of the lower limbs related to their diabetes	<b>I (n = 90):</b> One ampoule of lipo-PGE <sub>1</sub> (2 ml lipid microspheres containing 10 µg PGE <sub>1</sub> mixed with 10 ml saline and injected intravenously at the median cubital vein as a bolus once daily)  <b>C (n = 86):</b> Placebo (2 ml lipid emulsion only)  <b>Duration of treatment:</b> 2 weeks	Type of diabetes (IDDM/NIDDM): I: 7/80 C: 9/74  Median duration of diabetes: I: 12 years C: 10 years  Median duration of diabetic neuropathy: I: 1.4 years C: 2.0 years  No. of leg ulcers: I: 30 C: 26  Note: Baseline area of ulcers not reported	Patients with reduced ulcer size (defined as largest divided by smallest diameters, but graded arbitrarily):  80–100% decrease in ulcer size (all patients): I: 15/86 (17.4%) C: 6/80 (7.5%) (OR = 2.45; 95% CI, 0.98 to 6.09)  >50% decrease in ulcer size at 4 weeks (all patients): I: 38/86 (44.2%) C: 18/80 (22.5%) (OR = 2.62; 95% CI, 1.38 to 4.98)  Side-effects: I (n = 87): 6 (6.9%) C (n = 83): 4 (4.8%)  Withdrawal due to side-effects: I: 3 (3.4%) C: 3 (3.6%)
C, control group; I, intervention group				
continued				

**TABLE 9 contd** RCTs of prostaglandins for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
Toyota, 1993, <sup>78</sup> Japan/multicentre/ trial 2	202 diabetic inpatients (137 men, 57 women, 8 excluded) aged < 70 years with spontaneous pain, sensory disturbance or ulcers of the lower limbs related to diabetes. Eight patients excluded because of protocol violations (I1, 4/105; I2, 4/97)	<b>I1 (n = 105):</b> PGE <sub>1</sub> -CD 40 µg/day as PGE <sub>1</sub> (freeze-dried preparation contained 20 µg PGE <sub>1</sub> as an α-cyclodextrin clathrate compound) mixed with 300 ml saline and infused intravenously (bolus or drip infusion) over about 1 hour  <b>I2 (n = 97):</b> Lipo-PGE <sub>1</sub> (10 µg/day as PGE <sub>1</sub> )  <b>Duration of treatment:</b> 4 weeks	<i>Type of diabetes (IDDM/NIDDM):</i> I1: 17 (18.3%)/76 (81.7%) I2: 19 (18.8%)/82 (81.2%)  <i>Median duration of diabetes:</i> I1: 12 years I2: 11 years  <i>Median duration of diabetic neuropathy:</i> I1: 2.2 years I2: 2.0 years  <i>Leg ulcers present:</i> I1: 27 I2: 24  <i>Note:</i> Baseline area of ulcers not reported	Patients with reduced ulcer size (defined as largest divided by smallest diameters, but graded arbitrarily):  <i>80–100% decrease in ulcer size at 4 weeks (all patients):</i> I1: 6/84 (7%) I2: 20/89 (22%) (OR = 0.30; 95% CI, 0.13 to 0.70)  <i>&gt; 50% decrease in area at 4 weeks (all patients):</i> I1: 27/84 (32%) I2: 29/89 (32.5%) (OR = 0.98; 95% CI, 0.52 to 1.85)  <i>Side-effects:</i> I1 (n = 101): 24 (24%) I2 (n = 93): 12 (13%)  <i>Withdrawals due to side-effects:</i> I1: 11 (11%) I2: 6 (6.5%)
I1, I2, intervention groups				

TABLE 10 RCTs of growth factors for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
Steed, 1992, <sup>34</sup> USA	13 diabetic patients (9 men, 4 women) from two outpatient wound clinics, with chronic neurotrophic foot ulcers unhealed after at least 8 weeks of standard treatment, supine periwound transcutaneous oxygen tension > 30 mmHg, platelet count $\geq 100,000/\text{mm}^3$ . Patients with clinical signs of infection were excluded	<b>I (n = 7):</b> Topically applied CT-102 APST (PDVWHF) was applied to cotton gauze, placed on the ulcer in the evening, covered with petrolatum-impregnated gauze and changed every 12 hours <b>C (n = 6):</b> Normal saline gauze dressings for 24 hours <b>All patients:</b> Agreed to be totally non-weight-bearing, using half-shoes (IPOS North American, Niagara Falls, NY) or wheelchairs, crutches or walkers. Aggressive debridement performed on entry <b>Duration of treatment:</b> 20 weeks or until complete wound healing	<b>Mean <math>\pm</math> SD age:</b> I: 58.7 $\pm$ 12.4 years C: 54.2 $\pm$ 12.9 years ( $p = 0.5316$ ) <b>Mean <math>\pm</math> SD duration of diabetes:</b> I: 26 $\pm$ 6.6 years C: 10.3 $\pm$ 5.9 years <b>Mean <math>\pm</math> SD <math>T_c\text{PO}_2</math>:</b> I: 51 $\pm$ 8.4 mmHg C: 45 $\pm$ 7.4 mmHg <b>Mean <math>\pm</math> SD (range) duration of ulcer:</b> I: 17 $\pm$ 15.87 months (4–48 months) C: 13 $\pm$ 14.37 months (3–42 months) <b>Mean <math>\pm</math> SD ulcer area:</b> I: 864.3 $\pm$ 457.6 mm <sup>2</sup> C: 412.2 $\pm$ 259.5 mm <sup>2</sup> <b>Mean <math>\pm</math> SD ulcer volume:</b> I: 7385.1 $\pm$ 7184.1 mm <sup>3</sup> C: 4391.2 $\pm$ 3553.8 mm <sup>3</sup>	<b>Ulcers completely healed:</b> I: 5/7 (71%) (week 15) C: 1/6 (17%) (week 20) (OR = 7.64; 95% CI, 0.93 to 62.53) <b>Mean <math>\pm</math> SD reduction in ulcer area:</b> I: 200.3 $\pm$ 448.7 mm <sup>2</sup> C: 206.5 $\pm$ 193.6 mm <sup>2</sup> <b>Mean <math>\pm</math> SD reduction in ulcer volume:</b> I: 857.7 $\pm$ 1800.7 mm <sup>3</sup> C: 1951.2 $\pm$ 2179.6 mm <sup>3</sup> <b>Mean reduction in ulcer area at 20 weeks:</b> I: 94% C: 73% ( $p \leq 0.02$ ) <b>Mean <math>\pm</math> SD daily reduction in ulcer volume:</b> I: 73.8 $\pm$ 112.2 mm <sup>3</sup> /day C: 21.8 $\pm$ 19.9 mm <sup>3</sup> /day ( $p < 0.05$ ) <b>Mean <math>\pm</math> SD daily reduction in ulcer area:</b> I: 6.2 $\pm$ 1.8 mm <sup>2</sup> /day C: 1.8 $\pm$ 1.1 mm <sup>2</sup> /day ( $p < 0.05$ )
Holloway, 1993, <sup>90</sup> USA	97 diabetic patients with at least one chronic, non-healing ulcer of $\geq 8$ weeks duration, wounds between 500 and 50,000 mm <sup>3</sup> , a supine periwound transcutaneous oxygen tension of $\geq 30$ mmHg, no signs of systemic wound infection. 27 patients were withdrawn: 16 randomised patients did not meet the entry criteria and were removed from the study. Of the 81 patients who remained in the study, 11 were excluded from the efficacy analysis due to non-compliance, leaving 70 patients (52 men, 18 women)	Three different dilutions of CT-102: <b>I1 (n = 15):</b> 0.01 dilution <b>I2 (n = 13):</b> 0.033 <b>I3 (n = 21):</b> 0.1 <b>C (n = 21):</b> Placebo (physiologic saline solution followed by isotonic platelet buffer) <b>All patients:</b> Minor debridement on entry to remove fibrin, callous and necrotic tissue	<b>Gender (male/female):</b> I1: 11/4 I2: 10/3 I3: 17/4 C: 14/7 <b>Mean <math>\pm</math> SD age:</b> I1: 60.7 $\pm$ 13.5 years I2: 59.4 $\pm$ 13.8 years I3: 62.6 $\pm$ 8.6 years C: 60.4 $\pm$ 9.6 years	<b>Ulcers completely healed:</b> I1: 12/15 (80%) C: 6/21 (29%) (OR = 7.39; 95% CI, 2.00 to 27.29) I2: 8/13 (62%) C: 6/21 (29%) (OR = 3.75; 95% CI, 0.94 to 14.96) I3: 11/21 (52%) C: 6/21 (29%) (OR = 2.62; 95% CI, 0.78 to 8.87)
C, control group; I, I1, I2, I3, intervention groups				
continued				

**TABLE 10 contd** RCTs of growth factors for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
		<b>Duration of treatment:</b> 20 weeks or until complete healing	<p><b>Median wound duration:</b>                      I1: 15.7 months                      I2: 17.6 months                      I3: 11.7 months                      C: 25.3 months</p> <p><b>Mean ± SD wound severity score:</b>                      I1: 37.7 ± 8.7                      I2: 32.2 ± 7.3                      I3: 29.2 ± 6                      C: 35.9 ± 7.7</p> <p><b>Mean ± SD wound area:</b>                      I1: 756 ± 633 mm<sup>2</sup>                      I2: 600 ± 441 mm<sup>2</sup>                      I3: 603 ± 742 mm<sup>2</sup>                      C: 507 ± 609 mm<sup>2</sup></p> <p><b>Mean ± SD wound volume:</b>                      I1: 5460 ± 5454 mm<sup>3</sup>                      I2: 4500 ± 4800 mm<sup>3</sup>                      I3: 5788 ± 1163 mm<sup>3</sup>                      C: 3236 ± 2592 mm<sup>3</sup></p> <p><b>Mean ± SD HbA<sub>1c</sub>:</b>                      I1: 6.6 ± 1.3                      I2: 7 ± 1.2                      I3: 6.5 ± 1.3                      C: 6.7 ± 1.3</p> <p><b>T<sub>c</sub>PO<sub>2</sub>:</b>                      I1: 51 ± 8                      I2: 50 ± 8                      I3: 47 ± 17                      C: 48 ± 9</p>	<p><i>Comparison of all 3 dilutions pooled with placebo for complete healing:</i>                      I1 + I2 + I3: 31/49 (63%)                      C: 6/21 (29%)                      (OR = 3.94; 95% CI, 1.43 to 10.90)</p> <p><i>Mean decrease in volume at week 20:</i>                      I1 + I2 + I3: 94.9%                      C: 82.7%                      (p = 0.005)</p> <p><i>Mean decrease in area at week 20:</i>                      I1 + I2 + I3: 93.0%                      C: 77.1%                      (p = 0.002)</p> <p><i>Mean decrease in volume:</i>                      I1: 96.9%                      I2: 90.7%                      I3: 96.0%</p> <p><i>Mean decrease in area:</i>                      I1: 95.7%                      I2: 87.8%                      I3: 94.3%</p> <p><i>Median time to 80% healing:</i>                      I1 + I2 + I3: 46 days                      C: 92 days                      (p = 0.037)</p> <p><i>Median time to 50% healing:</i>                      I1 + I2 + I3: 21 days                      C: 26 days                      (p = 0.119)</p> <p><i>Withdrawals:</i> 16 patients did not meet the inclusion criteria and were removed from the study. An additional 11 patients were excluded from the analysis due to non-compliance with treatment, an insufficient period of treatment due to early</p>
C, control group; I, I1, I2, I3, intervention groups				
				<i>continued</i>

TABLE 10 contd RCTs of growth factors for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
				<p>amputation, occluded vascular graft, or failure to return to follow-up visits. Frequently reported adverse events were cellulitis, worsening of wound and a burning sensation, but differences were not significant between groups</p> <p>Loss to follow-up after 12 weeks: 4 patients and 5 patients missed the last or second to last visit, respectively</p>
Steed and the Diabetic Ulcer Study Group, 1995, <sup>89</sup> USA/multicentre	118 diabetic outpatients aged $\geq 19$ years with chronic neuropathic foot ulcers (present for at least 8 weeks without healing), free of infection, with adequate arterial blood supply (indicated by a transcutaneous oxygen tension of $\geq 30$ mmHg)	<p><b>I (n = 61):</b> Topically applied rhPDGF-BB gel (becaplermin) in vehicle. The drug was formulated into a gel at a concentration of 30 <math>\mu</math>g rhPDGF-BB/g and applied to the target ulcer every 24 hours</p> <p><b>C (n = 57):</b> Placebo gel (vehicle alone)</p> <p><b>All patients:</b> 'Best standard wound care' (sharp debridement of callus and necrotic tissue, systemic antibiotics for infected wounds and instructions for pressure relief)</p> <p><b>Duration of treatment:</b> 20 weeks or until complete healing</p>	<p>Mean age: I: 63.2 years C: 58.3 years</p> <p>Gender (male/female): I: 43/18 C: 46/11</p> <p>Mean (range) time since ulcer onset: I: 81.8 weeks (6.6–536.0 weeks) C: 74.5 weeks (6.7–349.6 weeks)</p> <p>Mean area of target ulcer: I: 5.5 cm<sup>2</sup> C: 9.0 cm<sup>2</sup></p> <p>Median area of target ulcer: I: 3.1 cm<sup>2</sup> C: 4.9 cm<sup>2</sup></p> <p>Mean depth of target ulcer: I: 0.64 cm C: 0.65 cm</p> <p>One patient from the placebo group was a significant outlier. Excluding this patient from the target ulcer area measurement resulted in the following changes: Mean: C, 7.2 cm<sup>2</sup> Median: C, 4.7 cm<sup>2</sup> Range: C, 0.6–35.8 cm<sup>2</sup></p>	<p>Healing (defined as 100% closure of the ulcer with epithelialisation of the target ulcer): I: 29/61 (48%) C: 14/57 (25%) (OR = 2.67; 95% CI, 1.27 to 5.65)</p> <p>Median reduction in wound area: I: 98.8% C: 82.1% (not significant, <math>p &lt; 0.09</math>)</p> <p>Rate of recurrence within 8.6 weeks: I: 26% C: 46%</p> <p>Incidence of at least one adverse event: I: 31/61 (51%) C: 34/57 (60%)</p> <p>Overall incidence of wound-related infections, including cellulitis, infection and osteomyelitis: I: 11.4% C: 26.3%</p> <p>Withdrawals: I: 14 (23%) C: 18 (31.6%)</p>
C, control group; I, intervention group				
				continued

**TABLE 10 contd** RCTs of growth factors for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
Steed, 1995, <sup>4</sup> USA	Three institutional, 3 private US clinics providing ambulatory care. 65 (49 men, 16 women) diabetic patients with chronic (of at least 1 month duration) full-thickness neurotrophic foot ulcers (which penetrated through the epidermis into the dermis without exposure of bone or tendon); ulcers measured 1–5 cm <sup>2</sup> in surface area	<b>I (n = 40):</b> RGD peptide matrix (applied topically twice weekly) <b>C (n = 25):</b> Placebo (topical saline) + standard care <b>Length of treatment and follow-up:</b> 10 weeks or day of healing	<b>Mean ± SE (range) age:</b> I: 61.8 ± 1.9 years (37–88 years) C: 61.0 ± 2.2 years (36–80 years) <b>Mean ± SE ulcer duration:</b> I: 16.5 ± 2.7 months (1–72 months) C: 19.0 ± 3.5 months (1–60 months) <b>Mean ± SE ulcer area:</b> I: 3.5 ± 0.5 cm <sup>2</sup> (1.0–13.6 cm <sup>2</sup> ) C: 3.5 ± 0.6 cm <sup>2</sup> (1.0–12.3 cm <sup>2</sup> ) No statistically significant differences between the two groups were observed with respect to age, sex, ulcer duration or size, or ulcer characteristics (e.g. granulation, eschar and necrotic tissue)	<b>Ulcers completely healed within 10 weeks:</b> I: 14/40 (35%) C: 2/25 (8%) (OR = 4.19; 95% CI, 1.33 to 13.25) <b>Mean ± SD % ulcer closure at 10 weeks:</b> I: 72.3 ± 6.8 C: 29.9 ± 26.5 (p < 0.03) <b>Ulcers &gt; 50% healed at 10 weeks:</b> I: 75% C: 48% (p = 0.03) <b>Mean closure of ulcers of baseline area ≤ 5.0 cm<sup>2</sup>:</b> I (n = 33): 79% C (n = 22): 58% <b>Withdrawals:</b> I: 8/40 (20%) C: 6/25 (24%) <b>Incidence of adverse events per patient:</b> I (n = 26): 0.65 C (n = 29): 1.16
Richard, 1995, <sup>91</sup> France	17 diabetic patients (outpatients for preceding 6 weeks; 16 men, 1 woman; 1 IDDM, 16 NIDDM) with chronic neurotrophic foot ulcer (Wagner grade I–III, wound measured > 0.5 cm in largest diameter), higher than 30 vibration perception threshold (either at great toe or medial malleolus), an absence of significant peripheral vascular disease (evidenced by Doppler waveform analysis) or wound infection	<b>I (n = 9):</b> Topical basic fibroblast growth factor (bFGF) <b>C (n = 8):</b> Placebo (normal saline). Applied daily during the first 6 weeks as inpatient treatment, then twice weekly for the last 12 weeks <b>Duration of treatment:</b> 18 weeks treatment or until complete healing. Actual treatment duration (units not stated): I, 87.7 ± 38.0; C, 64.8 ± 29.5	<b>Mean ± SD duration of diabetes:</b> I: 20.9 ± 12.3 years C: 18.8 ± 9.5 years <b>Mean ± SD largest diameter of ulcer:</b> I: 18.0 ± 12.0 mm C: 18.1 ± 6.2 mm <b>Wagner grade I:</b> I: 2 C: 1 <b>Wagner grade II:</b> I: 4 C: 1	<b>Complete healing:</b> I: 3/9 (33%) C: 5/8 (63%) (OR = 0.33; 95% CI, 0.05 to 2.12) <b>Mean ± SD % of initial ulcer perimeter:</b> I: 35.8 ± 49.6 C: 47.2 ± 36.4 (not significant) <b>Mean ± SD time to 50% healing:</b> I: 9.3 ± 2.1 weeks C: 5.8 ± 0.4 weeks (not significant)
C, control group; I, intervention group				
continued				

**TABLE 10 contd** RCTs of growth factors for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
			Wagner grade III: I: 3 C: 3  Mean $\pm$ SD ulcer duration: I: 22.4 $\pm$ 27.9 months C: 27.9 $\pm$ 42.2 months	Mean $\pm$ SD reduction in ulcer area: I: 0.23 $\pm$ 0.20 cm <sup>2</sup> C: 0.31 $\pm$ 0.24 cm <sup>2</sup> (not significant)
<i>C, control group; I, intervention group</i>				

**TABLE 11** RCTs of dressings and topical agents for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
Baker, unpublished, <sup>92</sup> UK	20 outpatients (10 men, 9 women, 1 not accounted for) attending a foot clinic with clean (slough free) neuropathic diabetic foot ulcers located on weight-bearing areas of the foot, aged > 18 years, with palpable pedal pulses, and no history of intermittent claudication or rest pain	<b>I1 (n = 10):</b> Allevyn (hydrocellular dressing) <b>I2 (n = 10):</b> Sorbsan (calcium alginate dressing) + a low-adherent, absorbent dressing <b>Duration of treatment:</b> 12 weeks or until ulcer healed	<b>Mean ± SD age:</b> I1: 58.9 ± 18.5 years I2: 54.1 ± 15.8 years <b>Mean ulcer duration:</b> I1: 19.8 ± 21.9 days I2: 26.3 ± 49.2 days <b>Mean ulcer area:</b> I1: 0.89 ± 0.62 cm <sup>2</sup> I2: 0.82 ± 0.73 cm <sup>2</sup> <b>No previous ulceration episodes:</b> I1: 3 I2: 4 <b>One previous ulceration episode:</b> I1: 2 I2: 3 <b>Two previous ulceration episodes:</b> I1: 2 I2: 0 <b>No. of previous ulceration episodes not known:</b> I1: 3 I2: 2	<b>Ulcers healed at week 12:</b> I1: 9/10 (90%) I2: 4/9 (44%) (OR = 7.37; 95% CI, 1.12 to 48.58) <b>Median time to healing:</b> I1: 28 days I2: > 84 days <b>Withdrawals:</b> I1: 1 (poor compliance) I2: 2 (1 poor compliance; 1 due to wound producing little exudate, and thus Sorbsan contra-indicated)  No adverse effects reported from either dressing. Allevyn was found to be more absorbent ( <i>p</i> < 0.001), less adherent to wounds ( <i>p</i> < 0.006) and easier to remove than Sorbsan ( <i>p</i> < 0.011). Patient comfort was good but there was no significant difference between I1 and I2
Foster, 1994, <sup>93</sup> UK	30 diabetic outpatient clinic patients (20 men, 10 women) aged > 18 years, with a clean foot ulcer and willing/able to comply with the protocol	<b>I1 (n = 15):</b> Polyurethane foam hydrophilic dressing (Allevyn) <b>I2 (n = 15):</b> Kaltostat (calcium-sodium alginate dressing) <b>Duration of treatment:</b> 8 weeks or until ulcer fully healed, whichever occurred sooner	<b>Gender (male/female):</b> I1: 12/3 I2: 8/7 <b>Mean age:</b> I1: 61 years I2: 70 years <b>IDDM/INIDDM:</b> I1: 6/9 I2: 4/11 <b>Mean ulcer area:</b> I1: 88 mm <sup>2</sup> I2: 79 mm <sup>2</sup>	<b>No. of ulcers healed at week 8:</b> I1: 9/15 (60%) I2: 8/15 (53%) (OR = 1.30; 95% CI, 0.31 to 5.38) <b>Withdrawals:</b> I1: 0 I2: 4 (severe pain, 1; dressing had plugged a plantar lesion, preventing free drainage of exudate, 3; 1 of the latter patients developed cellulitis)
I1, I2, intervention groups				
				<i>continued</i>



TABLE 11 contd RCTs of dressings and topical agents for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
			<p>Mean ulcer duration: I1: 107 days I2: 170 days</p> <p>Origin (ischaemia/neuropathy): I1: 6/9 I2: 4/11</p> <p>Ulcer depth (superficial/deep): I1: 12/3 I2: 13/2</p>	
Vandeputte, unpublished <sup>94</sup>	29 diabetic patients (13 men, 16 women) with foot ulcers (neuropathic and non-neuropathic) and patients who had already had a toe amputation	<p><b>I1 (n = 15):</b> Elasto-Gel (moist hydrogel dressing, consisting of 65% glycerine, 17.5% water and 17.5% polyacrylamide) plus cleansing with a dermal wound cleanser (Flami-clens with saline water + 0.8% vinegar acid as buffer)</p> <p><b>I2 (n = 14):</b> Betadine cream plus dry gauze (treated twice daily and irrigated with chlorhexidine 0.05% solution)</p> <p><b>Duration of treatment:</b> 3 months</p>	<p>Mean age: I1: 62.6 years I2: 65.3 years</p> <p>Neuropathy: I1: 9/15 (60%) I2: 9/14 (64%)</p> <p>Infection present before trial: I1: 1/15 (7%) I2: 1/14 (7%)</p> <p>Completely mobile: I1: 12/15 (80%) I2: 11/14 (79%)</p> <p>Less than completely mobile: I1: 3/15 (20%) I2: 3/14 (21%)</p>	<p>Complete healed at 3 months: I1: 7/15 (47%) I2: 5/14 (36%) (OR = 1.55; 95% CI, 0.36 to 6.61)</p> <p>Infection: I1: 1/15 (20%) I2: 7/14 (50%) (OR = 0.12; 95% CI, 0.02 to 0.61)</p> <p>Formation of callus: I1: 7/15 (47%) I2: 14/14 (100%) (OR = 0.08; 95% CI, 0.02 to 0.38)</p> <p>Amputation (toes): I1: 1/15 (7%) I2: 5/14 (36%) (OR = 0.18; 95% CI, 0.03 to 1.06)</p> <p>Withdrawals: I2: 2 (death)</p> <p>Patient comfort reported as better with hydrogel</p>
Blackman, 1994, <sup>95</sup> USA	18 diabetic patients (17 men, 1 woman) with a partial- or full-thickness open wound or foot ulcer free of hard eschar	<b>I1 (n = 11):</b> Polymeric membrane dressing	Gender (male/female): I1: 11/0 I2: 6/1	Only data from 2 months are presented, as the 6-months results may be biased as some patients initially randomised to I2 crossed over to I1
I1, I2, intervention groups				
continued				

**TABLE 11 contd** RCTs of dressings and topical agents for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
		<p><b>I2 (n = 7):</b> Conventional therapy (wet-to-dry saline gauze dressing)</p> <p><b>Duration of treatment:</b> 6 months or until ulcer healed</p>	<p>Mean ± SE age: I1: 59 ± 5 years I2: 51 ± 4 years</p> <p>Mean ± SE ulcer area: I1: 2.67 ± 1.20 cm<sup>2</sup> I2: 1.81 ± 0.75 cm<sup>2</sup></p> <p>Mean ± SE ulcer duration: I1: 25 ± 7 weeks I2: 28 ± 6 weeks</p> <p>HbA<sub>1c</sub>: I1: 8.4 ± 0.9% I2: 9.5 ± 1.1%</p>	<p>Ulcers completely healed at 2 months: I1: 3/11 (27%) I2: 0/7 (OR = 6.39; 95% CI, 0.54 to 75.62)</p> <p>% of baseline ulcer size at 2 months: I1: 35 ± 16 I2: 105 ± 26 (OR = -70.00; 95% CI, -91.46 to -48.54)</p> <p>Substantial improvement in ulcer size at 2 months: I1: 10/11 (91%) I2: 2/7 (29%) (OR = 14.14; 95% CI, 2.01 to 99.78)</p> <p>Withdrawals: 5 subjects randomised to I2 crossed over to I1 after 2 months of treatment (3 healed completely and 2 were lost to follow-up). A further 2 patients in each group progressed to Wagner stage III ulcers and were not included in the final analysis</p>
Clever, 1996, <sup>96</sup> Germany	40 diabetic outpatients (32 men, 8 women) aged 18–80 years with superficial neuropathic ulcers of 1–5 cm diameter and with no clinical or radiological signs of osteomyelitis	<p><b>I1 (n = 20):</b> Cutinova Hydro (hydroactive polyurethane gel dressing) + standard treatment (pressure relief, wound debridement and infection control) + wound cleansing</p> <p><b>I2 (n = 20):</b> Allevyn (hydrophilic polyurethane foam dressing) + standard treatment (pressure relief, wound debridement and infection control) + wound cleansing</p> <p><b>Duration of treatment:</b> 16 weeks or until healed</p>	<p>Gender (male/female): I1: 15/5 I2: 17/3</p> <p>Mean ± SD age: I1: 58.9 ± 11.6 years I2: 53.2 ± 14.6 years</p> <p>Mean ± SD ulcer duration: I1: 162.37 ± 325.55 days I2: 165.00 ± 318.68 days</p> <p>Mean ulcer area: I1: 205.09 mm<sup>2</sup> I2: 207.83 mm<sup>2</sup></p>	<p>Mean ± SD time to healing: I1: 25.19 ± 23.52 days (median 15.5 days) I2: 20.43 ± 14.74 days (median 16.5 days) (OR = 4.760; 95% CI, -7.405 to 16.925)</p> <p>Wound area at 4 weeks: I1: 32.37 ± 54.12 mm<sup>2</sup> I2: 33.46 ± 75.22 mm<sup>2</sup> (OR = -1.09; 95% CI, -41.7 to 39.5)</p> <p>Withdrawals: I1: 2 I2: 4</p>
I1, I2, intervention groups				
				continued

TABLE 11 contd RCTs of dressings and topical agents for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
			<p>Systemic antibiotics used/not used: I1: 14/6 I2: 15/5</p> <p>Ulcer recurrence: I1: 15/20 (75%) I2: 15/20 (75%)</p>	No differences in patient comfort based on subjective product evaluation (investigator); patients found showering slightly easier with Cutinova Hydro
Donaghue, 1998, <sup>97</sup> USA	75 diabetic patients (54 men, 21 women) with foot ulcers of at least 1 cm <sup>2</sup> in size (after initial debridement), who were aged ≥ 21 years, had an adequate nutritional intake, as indicated by serum albumin of > 2.5 g/dl, and an adequate blood flow to the lower extremities	<p><b>I (n = 50):</b> Collagen-alginate topical wound dressing (Fibracol) + dressing-change instructions and weight-bearing limitation</p> <p><b>C (n = 25):</b> Regular gauze moistened in normal saline + dressing-change instructions and weight-bearing limitations</p> <p><b>Duration of treatment and follow-up:</b> 8 weeks or until ulcer healed</p>	<p>Mean (range) age: I: 59 years (30–81 years) C: 60 years (33–79 years)</p> <p>Mean ± SE ulcer area: I: 2.2 ± 0.5 cm<sup>2</sup> C: 3.3 ± 0.8 cm<sup>2</sup></p> <p>Mean (range) duration diabetes: I: 19 years (4–47 years) C: 17 years (2–25 years)</p> <p>Mean ± SE ulcer duration: I: 153 ± 83 years C: 241 ± 131 years</p> <p>Wagner stage I ulcers: I: 8 (9%) C: 1 (6%)</p> <p>Wagner stage II ulcers: I: 31 (70%) C: 15 (88%)</p> <p>Wagner stage III ulcers: I: 5 (11%) C: 1 (6%)</p>	<p>Ulcers completely healed: I: 24/44 (54.5%) C: 9/17 (52.9%) (OR = 1.07; 95% CI, 0.35 to 3.25)</p> <p>Mean ± SD time to complete healing: I: 43.40 ± 19.80 days C: 40.60 ± 21.00 days (OR = 2.80; 95% CI, –8.771 to 14.371)</p> <p>Mean ± SD reduction in wound area: I: 80.6 ± 0.1% C: 61.1 ± 0.3%</p> <p>Results of survival analysis – 50% wound area reduction: I: 43/50 (86%) C: 15/25 (60%) (OR = 6.80; 95% CI, 2.31 to 20.00)</p> <p>Results of survival analysis – mean time required to ≥ 50% wound healing: I: 2.4 ± 0.3 weeks C: 2.5 ± 0.7 (not significant)</p> <p>Withdrawals: I: 6/50 (12%) C: 8/50 (16%)</p> <p>Patients' assessment of perceived efficacy favoured Fibracol dressing compared to their previous treatment. No difference in the number or severity of reported adverse reactions between groups</p>
C, control group; I, I1, I2, intervention groups				
				continued

**TABLE 11 contd** RCTs of dressings and topical agents for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
Lishner, 1985, <sup>103</sup> Israel	40 hospitalised diabetic patients (22 men, 18 women), aged 46–78 years (mean 65.5 years) with chronic, resistant, perforating ulcers present for 7–36 months. Hyperglycaemia controlled by insulin in 26 patients and by sulfonylurea drugs in 14 patients. All patients had diabetic nephropathy (defined by serum creatinine $\geq 2.5$ mg/100 ml) and neuropathy; 26 had 2+ proteinuria and 20 had peripheral vascular disease	<b>I (n = 20):</b> Conventional treatment (see below) + local application of dimethyl sulphoxide (DMSO) (500 ml of a 25% solution of DMSO in normal saline) for 20 minutes 3 times daily. Infected ulcers were treated with 80 mg garamycin added to the solution. If no healing occurred by the sixth week, the concentration of DMSO was increased to 50%  <b>C (n = 20):</b> Conventional treatment (debridement, dry dressings, broad spectrum of antibiotics when cellulitis present and the provision of soft shoes)  <b>Duration of treatment or follow-up:</b> 20 weeks	<b>Mean duration of diabetes:</b> I: 14 years C: 15.5 years  <b>Peripheral vascular disease:</b> I: 14/20 (70%) C: 12/20 (60%)  <b>Mean duration of ulcer:</b> I: 16 months C: 14 months	<b>Ulcers completely healed:</b> I: 14/20 (70%) C: 2/20 (10%) (OR = 11.44; 95% CI, 3.28 to 39.92)  <b>Ulcers partially healed:</b> I: 4/20 C: 5/20 (not significant)  <b>Withdrawals:</b> not stated  DMSO solution is reported to have brought prompt and lasting analgesia in patients with peripheral vascular disease with painful ulcer areas. A 25% DMSO solution was reported to be well tolerated, a 50% solution caused local irritation of skin and a burning sensation that required cessation of DMSO application for 2–4 days
Mulder, 1994, <sup>105</sup> USA/multicentre	181 diabetic outpatients with controlled diabetes, neuropathic full-thickness ulcers (e.g. below knee), a Doppler blood pressure $\geq 40$ mmHg and aged 21–90 years. Minimum ulcer size 0.5 × 0.5 cm (25 mm <sup>2</sup> ); maximum ulcer size approx. 2700 mm <sup>2</sup> . Exclusion criteria: patients with osteomyelitis or gangrene of the target limb, Wilson's disease, no conditions known to cause ulceration (e.g. venous stasis or vasculitis). Patients were stratified based on ulcer location (plantar or 'other') resulting in approx. 80% plantar ulcers and 20% 'other' locations on the lower leg. The plantar ulcer group was subdivided into two groups based on ulcer area at entry, designated as large ( $\geq 100$ mm <sup>2</sup> ) or small (< 100 mm <sup>2</sup> )	<b>Trial 1</b> Immediate treatment (after initial sharp debridement) with:  <b>I1 (n = 42, plantar = 32):</b> Vehicle gel for up to 8 weeks  <b>I2 (n = 40, plantar = 28):</b> lamin-Gel 2% for up to 8 weeks  <b>Trial 2</b> Delayed treatment for a 4 week lead-in period:  <b>I1 (n = 49, plantar = 39):</b> lamin-Gel 2% for an additional 8 weeks  <b>I2 (n = 50, plantar = 42):</b> lamin-Gel 4% for an additional 8 weeks	Mean age 60 years; mean diabetic history 15 years; 44 type 1 diabetes, 137 type 2 diabetes; 114 insulin dependent  No statistically significant differences reported in baseline characteristics, including ulcer area and ulcer duration, between groups	An intention-to-treat analysis was carried out, but only within groups (plantar, large and small ulcer groups).  <b>Trial 1</b> No. of patients with $\geq 98\%$ ulcer closure: All plantar: I1, 31%; I2, 54% Large plantar: I1, 6%; I2, 43% ( $p < 0.05$ ) Small plantar: I1, 56%; I2, 64%  % Wound closure (weekly tracings of ulcer margins): All plantar (median area): I1, 60.8%; I2, 98.5% ( $p < 0.05$ ) Mean $\pm$ SEM: I1, 10.4 $\pm$ 21.1%; I2, 70.4 $\pm$ 10.2% Small plantar (median): I1, 98.5%; I2, 98.5% Large plantar (median): I1, -10.4%; I2, 89.2% ( $p < 0.01$ )
C, control group; I, I1, I2, intervention groups				
continued				

TABLE 11 contd RCTs of dressings and topical agents for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
		<p><b>All patients:</b> A comprehensive ulcer care programme of sharp debridement, routine superficial debridement and cleansing, daily dressing changes, metered dosing of the gel, standardised pressure-relieving footwear, and patient education. Affected lesions were treated with systemic antibiotics, and patients with clinically significant limb oedema received supportive care</p>		<p><i>Infections of plantar ulcers:</i> I1: 34% I2: 7% (<math>p &lt; 0.05</math>)</p> <p><i>Withdrawals:</i> 4 (not stated in which group)</p> <p><b>Trial 2</b></p> <p><i>Median % wound closure:</i> I1: 15.6/39 (40%) I2: 28.6/42 (68%)</p> <p><i>Mean <math>\pm</math> SEM wound closure:</i> I1: 31.1 <math>\pm</math> 10.1% I2: 33.9 <math>\pm</math> 12.9%</p>
Muthukumarasamy, 1991, <sup>106</sup> India	100 NIDDM inpatients, aged 40–80 years, with foot ulcers of type I and II of Meggitt's (1976) clinical classification	<p><b>I (n = 50):</b> Daily topical phenytoin powder in a thin uniform layer with a sterile dry dressing</p> <p><b>C (n = 50):</b> Dry sterile occlusive dressing</p> <p><b>All patients:</b> On entry, ulcers were debrided of all necrotic tissue and slough and cleansed with saline. In patients with clear secondary infection, systemic antibiotics appropriate to the culture and sensitivity data were administered for up to 4 days</p> <p><b>Duration of treatment and follow-up:</b> 35 days</p>	<p>Groups reported to be matched for age, sex, ulcer area, depth, duration and chronicity, but no data presented</p> <p><i>Gender (male/female):</i> I: 27/23 C: 27/23</p>	<p><i>Mean time to complete healing:</i> I: 21 days C: 45 days (<math>p &lt; 0.05</math>)</p> <p><i>Mean <math>\pm</math> SD reduction in ulcer area at 35 days:</i> I: 90 <math>\pm</math> 3.9% C: 50 <math>\pm</math> 4.4% (<math>p &lt; 0.005</math>)</p> <p>Excess granulation tissue was observed in 18 phenytoin-treated patients</p>

C, control group; I, I1, I2, intervention groups

**TABLE 12** RCTs of debridement for the treatment of diabetic necrotic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
Apelqvist, 1996, <sup>109</sup> Sweden	41 outpatients (Caucasians aged > 40 years) with previously known diabetes mellitus and deep exudating ulcers below the ankle (Wagner ulcer grade I or II), with an ulcer area > 1 cm <sup>2</sup> and a systolic blood pressure > 30 mmHg or a systolic ankle pressure > 80 mmHg (if > 1 ulcer, the largest was chosen)	<p><b>I (n = 22):</b> Topical treatment with a cadexomer iodine ointment dressing (Iodosorb); changed once daily during the first week and daily or every second or third day during the study. Prior to inclusion in the study, footwear was provided or corrected, as necessary, and where there were signs of infection (i.e. cellulitis) oral antibiotics (ciprofloxacin, cephalosporines, metronidazole, clindamycin) were given</p> <p><b>C (n = 19):</b> Standard treatment, comprising gentamicin solution (Garamycin® 80 mg/ml injected twice daily) for ulcer, or dry saline gauze (Mesalt®, an absorptive dressing, changed once or twice daily) and streptokinase (Streptodornase®) for moist necrotic lesions</p> <p><b>All patients:</b> When ulcers had stopped exuding, petroleum gauze (Jelonet®) was used until the end of the study. All patients were treated as outpatients by a multidisciplinary foot care team</p> <p><b>Duration of treatment and follow-up:</b> 12 weeks</p>	Not stated	<p><i>Complete healing (defined as intact skin):</i> I: 5/17 (29%) C: 2/18 (11%) (OR = 3.04; 95% CI, 0.59 to 15.56)</p> <p><i>Improvement of &gt; 50% in Wagner grade:</i> I: 12/17 (71%) C: 13/18 (72%) (not significant)</p> <p><i>Total improvement at end of 12 weeks:</i> I: 12 C: 13 (not significant)</p> <p><i>Surgical revision:</i> I: 3/17 (18%) C: 5/18 (28%)</p> <p><i>Withdrawals:</i> 2 due to violation of inclusion criteria (ulcer size &gt; 25 cm<sup>2</sup> and/or Wagner grade III ulcer), 2 due to hospitalisation (myocardial infarction and heart failure) and 1 non-compliant. No adverse reactions reported</p> <p><i>Costs:</i> Direct-cost calculation made for dressing materials and drugs, staff and transportation. Cadexomer was associated with lower weekly treatment costs</p>
Apelqvist, 1990, <sup>110</sup> Sweden	44 diabetic outpatients (26 men, 18 women) with necrotic foot ulcers (superficial full-thickness skin ulcer below ankle and with systolic toe pressure > 45 mmHg or absence of cutaneous erythema; ulcers 1–25 cm <sup>2</sup> in area with > 50% of area covered with dry/wet necrotic tissue); if > 1 ulcer, the largest was chosen	<p><b>I1 (n = 22):</b> Adhesive zinc oxide tape (MeZinc)</p> <p><b>I2 (n = 22):</b> Adhesive occlusive hydrocolloid dressing (DuoDerm)</p> <p><b>Duration of treatment:</b> 5 weeks</p>	<p><i>Mean ± SD duration of diabetes:</i> Overall: 20 years (2–54 years) I1: 22 ± 15 years I2: 19 ± 12 years</p> <p><i>Gender (male/female):</i> I1: 10/12 I2: 16/8</p>	<p><i>Total disappearance or reduction of &gt; 50% in the initial necrotic area:</i> I1: 14/21 (67%) I2: 6/21 (29%) (OR = 4.44; 95% CI, 1.34 to 14.70)</p> <p><i>Reduction in necrotic area of 25–50%:</i> I1: 1/22 (5%) I2: 2/22 (9%)</p>
C, control group; I, I1, I2, intervention groups				
continued				

TABLE 12 contd RCTs of debridement for the treatment of diabetic necrotic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
			<p>Mean <math>\pm</math> SD age: Overall: 63 (23–86) years I1: 63 <math>\pm</math> 13 years I2: 62 <math>\pm</math> 18 years</p> <p>No. of patients treated with insulin: I1: 17 I2: 18</p> <p>Median duration of foot ulcers: Overall: 9 weeks (1–105 weeks)</p> <p>Median (range) ulcer area: I1: 2.2 cm<sup>2</sup> (1–10.5 cm<sup>2</sup>) cm<sup>2</sup> I2: 2.2 cm<sup>2</sup> (0.9–20.4 cm<sup>2</sup>)</p> <p>Median (range) area of necrosis: I1: 1.5 cm<sup>2</sup> (0.5–10.5 cm<sup>2</sup>) I2: 1.6 cm<sup>2</sup> (0.9–19.2 cm<sup>2</sup>)</p> <p>No. of dry necrotic ulcers: I1: 15 I2: 16</p> <p>No. of wet necrotic ulcers: I1: 7 I2: 6</p>	<p>No change in necrotic area (<math>\pm</math> 25%): I1: 1/22 (5%) I2: 3/22 (14%)</p> <p>Increase of 25–50% in necrotic area: I1: 1 I2: 5</p> <p>Failure of treatment (defined as an increase of &gt; 50% in necrotic area): I1: 4 I2: 5</p> <p>Withdrawals: Treatment was discontinued in 8 patients due to an increase in necrotic area of &gt; 100% associated with pain and oedema. One patient was treated with DuoDerm showed signs of cellulitis and treated with antibiotics</p> <p>Patients excluded: I1: 1 I2: 1</p> <p>Side-effects: A common adverse effect seen in both groups was maceration of the skin edges, possibly due to neuropathy</p>
C, control group; I, I1, I2, intervention groups				

**TABLE 13** RCTs of antibiotic therapy for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
Lipsky, 1990, <sup>113</sup> USA	60 male diabetic outpatients referred from various clinics and emergency departments, with non-limb-threatening lower-extremity infections (lesion defined as the recent development of purulence or at least two of the following: erythema, warmth, tenderness, drainage). Patients were included if they had clinically infected lesions. Infections were classified as acute infection with concomitant ulceration, acute infection of a pre-existing chronic ulcer, abscess and cellulitis	<b>I1 (n = 27):</b> Oral clindamycin (Cleocin, 300 mg) <b>I2 (n = 29):</b> Oral cephalexin (Keflex, 500 mg) four times daily <b>Duration of treatment and follow-up:</b> treatment, 2 weeks or until infection cleared. Follow-up, 15 ± 9 months	<i>Mean ± SEM age:</i> I1: 59.4 ± 2.3 years I2: 62.7 ± 2.4 years <i>IDDM/NIDDM (%):</i> I1: 70/85 I2: 62/97 <i>Infection present for &lt; 1 month:</i> I1: 96% I2: 97%	<i>Ulcers completely healed:</i> I1: 10/27 (40%) I2: 9/29 (33%) (OR = 1.30; 95% CI, 0.43 to 3.90) <i>Ulcers substantially smaller:</i> I1: 14/27 (56%) I2: 18/29 (67%) <i>Ulcers unimproved:</i> I1: 1/27 (4%) I2: 0/29 (0%) <i>Ulcers with no signs or symptoms of infection:</i> I1: 21/27 (78%) I2: 21/29 (72%) <i>Ulcers with most signs and symptoms of infection resolved:</i> I1: 5/27 (19%) I2: 4/29 (14%) <i>Withdrawals:</i> 4 due to subtle bone changes suggestive of osteomyelitis, insistent on being hospitalised for entire duration of antibiotic treatment or failure to take study antibiotic <i>Patients lost to follow-up:</i> 12 (21%) due to death
Chantelau, 1996, <sup>114</sup> Germany	44 diabetic patients (28 men, 16 women) with skin and soft tissue lesions of the forefoot, presence of polyneuropathy, foot lesion Wagner grade IA (superficial, with or without cellulitis) to Wagner IIA (deeper, reaching to joints and tendons)	<b>I1 (n = 22):</b> Oral antibiotics (500 mg amoxicillin + 125 mg clavulanic acid) three times daily <b>I2 (n = 22):</b> Placebo <b>All patients:</b> Standard treatment, comprising absolute pressure relief (half-shoes + crutches or wheelchair), daily wound cleansing (topical disinfectant (Dibromol <sup>®</sup> solution)), sterile dressings (sterile cotton gauze and paraffinated non-adhering gauze (Adaptic <sup>®</sup> )) (specialised nurse)	<i>Gender (male/female):</i> I1: 16/6 I2: 12/10 <i>Mean age:</i> I1: 58 years (95% CI, 54 to 62) I2: 59 years (95% CI, 55 to 63) <i>Mean duration of diabetes:</i> I1: 22 years (95% CI, 17 to 27) I2: 19 years (95% CI, 14 to 24) <i>Mean ulcer size:</i> I1: 214 mm <sup>2</sup> (95% CI, 154 to 274) I2: 220 mm <sup>2</sup> (95% CI, 162 to 422)	<i>Ulcers completely closed within 20 days:</i> I1: 6/19 (32%) I2: 10/20 (50%) (OR = 0.48; 95% CI, 0.14 to 1.68) <i>Mean reduction in ulcer radius:</i> I1: 0.27 mm <sup>2</sup> /day (95% CI, 0.15 to 0.39) I2: 0.41 mm <sup>2</sup> /day (95% CI, 0.21 to 0.61) <i>Withdrawals:</i> 5 (I1, 3; I2, 2) within 6 days of enrolment, due to unchanged ulcer appearance associated with non-compliance or bacteria unresponsive to the antibiotic
I1, I2, intervention groups				
<i>continued</i>				



**TABLE 13 contd** RCTs of antibiotic therapy for the treatment of diabetic foot ulcers

Study	Sample and setting	Intervention	Baseline characteristics	Results
		<b>Duration of treatment:</b> 20 days	No. of patients with HbA <sub>1c</sub> < 8%: I1: 9 I2: 10  No. of patients on insulin therapy: I1: 11 I2: 12	Optimal compliance with pressure relief (graded on clinical judgement): I1: 16/19 (84%) I2: 18/20 (90%) (not significant)
I1, I2, intervention groups				

## **Appendix 7**

### Quality assessment of included studies

TABLE 14 Studies of footwear for the prevention of diabetic foot ulcers

Study	Concealment of allocation	Sample size (No. of arms: sizes of groups)	A priori sample-size calculation described	Baseline comparability of groups reported	Inclusion/exclusion criteria stated	Adequate follow-up period	Withdrawals and No. lost to follow-up stated (with reasons)	Intention-to-treat analysis
Colagiuri, 1995 <sup>13</sup>	X	20 (2: 9/11)	X	X	Diabetes callus only weak	X	X	X
Ronnemaa, 1997 <sup>48</sup>	Unclear	530 (2: 267/263)	X	Appear broadly comparable for foot variables, but data on previous ulcer history, duration of diabetes, age, etc., not reported by group	✓	✓	✓	X
Uccioli, 1995 <sup>47</sup>	Quasi-random alternate allocation (CCT)	69 (2: 33/36)	X	✓	✓	X	X	X
✓, yes; X, no								

TABLE 15 Studies of elastic stockings for the prevention of diabetic foot ulcers

Study	Concealment of allocation	Sample size (No. of arms: sizes of groups)	A priori sample-size calculation described	Baseline comparability of groups reported	Inclusion/exclusion criteria stated	Adequate follow-up period	Withdrawals and No. lost to follow-up stated (with reasons)	Intention-to-treat analysis
Belcaro, 1992 <sup>50</sup>	X	160 (2: 74/75)	X	✓	✓	✓	✓	X
✓, yes; X, no								

TABLE 16 Studies of patient education for the prevention of diabetic foot ulcers

Study	Concealment of allocation	Sample size (No. of arms: sizes of groups)	A priori sample-size calculation described	Baseline comparability of groups reported	Inclusion/exclusion criteria stated	Adequate follow-up period	Withdrawals and No. lost to follow-up stated (with reasons)	Intention-to-treat analysis
Bloomgarden, 1987 <sup>53</sup>	X	266 (2: 127/139)	$\alpha = 0.5$ , power 0.95	Fasting blood glucose higher and a greater number of hospitalisations in the education group; foot lesions more frequent in the control group (all $p < 0.05$ )	X	No follow-up	✓	X
Pieber, 1995 <sup>54</sup>	Non-randomised study	107 (2: 52/55)	X	✓ Comparable	✓	6 months	✓	X
Reichard, 1993 <sup>55</sup>	X	102 (2: 48/54)	X	✓	Weak	✓	✓	X
Litzelman, 1993, <sup>55</sup> 1997 <sup>136</sup>	X	352 (2: 191/205)	X	Higher haemoglobin A <sub>1c</sub> in the intervention group	✓	X	✓	X
Malone, 1989 <sup>57</sup>	Allocation by odd/even numbers of social security numbers	✓	X	✓	✓	2 years	✓	X

✓, yes; X, no

TABLE 17 Studies of screening and a foot protection programme for the prevention of diabetic foot ulcers

Study	Concealment of allocation	Sample size (No. of arms: sizes of groups)	A priori sample-size calculation described	Baseline comparability of groups reported	Inclusion/exclusion criteria stated	Adequate follow-up period	Withdrawals and No. lost to follow-up stated (with reasons)	Intention-to-treat analysis
McCabe, 1998 <sup>58</sup>	X	2001 (2: 1001/1000)	X	X	✓	✓	✓	✓

✓, yes; X, no

TABLE 18 Studies of footwear for the treatment of diabetic foot ulcers

Study	Concealment of allocation	Sample size (No. of arms: sizes of groups)	A priori sample-size calculation described	Baseline comparability of groups reported	Inclusion/exclusion criteria stated	Adequate follow-up period	Withdrawals and No. lost to follow-up stated (with reasons)	Intention-to-treat analysis
Mueller, 1989 <sup>60</sup>	X	40 (2: 21/19)	X	✓	✓	X	✓	X
✓, yes; X, no								

TABLE 19 Studies of Dermagraft (cultured human dermis) for the treatment of diabetic foot ulcers

Study	Concealment of allocation	Sample size (No. of arms: sizes of groups)	A priori sample-size calculation described	Baseline comparability of groups reported	Inclusion/exclusion criteria stated	Adequate follow-up period	Withdrawals and No. lost to follow-up stated (with reasons)	Intention-to-treat analysis
Gentzkow, 1996 <sup>62</sup>	Sealed envelopes	50 (4: 12/14/11/13)	X	Age significantly lower in control group	✓	✓	Withdrawals: X Lost to follow up: ✓	✓
Naughton, 1997, <sup>63</sup> Pollak, 1997 <sup>64</sup>	X	281 (2: 139/142)	X	X	✓	✓	✓	✓
✓, yes; X, no								

TABLE 20 Studies of hyperbaric oxygen therapy for the treatment of diabetic foot ulcers

Study	Concealment of allocation	Sample size (No. of arms: sizes of groups)	A priori sample-size calculation described	Baseline comparability of groups reported	Inclusion/exclusion criteria stated	Adequate follow-up period	Withdrawals and No. lost to follow-up stated (with reasons)	Intention-to-treat analysis
Faglia, 1996 <sup>67</sup>	Random number tables	67 (2: 35/33)	✓	✓	X	X	✓	X
Leslie, 1988 <sup>30</sup>	Random number tables	28 (2: 12/16)	X	✓	✓	X	✓	X
✓, yes; X, no								

**TABLE 21** Studies of ketanserin for the treatment of diabetic foot ulcers

Study	Concealment of allocation	Sample size (No. of arms: sizes of groups)	A priori sample-size calculation described	Baseline comparability of groups reported	Inclusion/exclusion criteria stated	Adequate follow-up period	Withdrawals and No. lost to follow-up stated (with reasons)	Intention-to-treat analysis
Janssen, unpublished <sup>72</sup>	X	45 (2)	X	No subgroup baseline comparability for diabetic patients only	✓	✓	X	X
Apelqvist, 1990 <sup>74</sup>	X	44 (2: 22/22)	X	✓	✓	X	✓	Not sure
Martinez-de Jesus, 1997 <sup>73</sup>	Alternate assignment following time of presentation	140 (2: 69/71)	X	✓	✓	X	NA	✓

✓, yes; X, no, NA, not applicable

TABLE 22 Studies of prostaglandins for the treatment of diabetic foot ulcers

Study	Concealment of allocation	Sample size (No. of arms: sizes of groups)	A priori sample-size calculation described	Baseline comparability of groups reported	Inclusion/exclusion criteria stated	Adequate follow-up period	Withdrawals and No. lost to follow-up stated (with reasons)	Intention-to-treat analysis
Brock, 1990 <sup>75</sup> (Duplicate of Muller, 1988 <sup>76</sup> )	Allocation by order in which patients handed in their consent	109 (2: 56/53)	X	✓	✓	✓	✓	X
Toyota, 1993 <sup>78</sup>	X	176 (2: 90/86)	X	✓	✓	X	✓	X
Toyota, 1993 <sup>78</sup>	Envelope method	202 (2: 105/97)	Not stated	✓	✓	X	✓	X
✓, yes; X, no								

**TABLE 23** Studies of growth factors for the treatment of diabetic foot ulcers

Study	Concealment of allocation	Sample size (No. of arms: sizes of groups)	A priori sample-size calculation described	Baseline comparability of groups reported	Inclusion/exclusion criteria stated	Adequate follow-up period	Withdrawals and No. lost to follow-up stated (with reasons)	Intention-to-treat analysis
Steed, 1992 <sup>34</sup>	Not stated	13 (2: 7/6)	X	✓	✓	X	4 patients entering compassionate use study were mentioned	?
Holloway, 1993 <sup>90</sup>	Computer-generated list (provided by Curative Technologies, Inc.) of random numbers	97 (4: 15/13/21/21)	X	✓ Comparable	✓	X	✓	For some patients
Steed, 1995 <sup>89</sup>	Computer-generated randomisation schedule for each centre	118 (2: 61/57)	X	✓	✓	X	✓	X
Steed, 1995 <sup>4</sup>	2 : 1 randomisation ratio: assignment by prearranged randomisation order	65 (2: 40/25)	X	✓	✓	1 year, but no follow-up evaluation	✓	X
Richard, 1995 <sup>91</sup>	X	17 (2: 9/8)	X	✓	✓	X	✓	?

✓, yes; X, no



TABLE 24 Studies of dressings and topical agents for the treatment of diabetic foot ulcers

Study	Concealment of allocation	Sample size (No. of arms: sizes of groups)	A priori sample-size calculation described	Baseline comparability of groups reported	Inclusion/exclusion criteria stated	Adequate follow-up period	Withdrawals and No. lost to follow-up stated (with reasons)	Intention-to-treat analysis
Baker, unpublished, 1993 <sup>92</sup>	Computer-generated randomisation code	19 (2: 10/9)	X	✓	✓	X	✓	✓
Foster, 1994 <sup>93</sup>	X	30 (2: 15/15)	X	✓	✓	X	✓	X
Vandeputte, unpublished <sup>94</sup>	Pre-prepared randomisation listing	29 (2: 15/14)	X	✓	✓	X	✓	X
Blackman, 1994 <sup>95</sup>	Not stated	18 (2: 11/7)	X	✓	X	X	✓	X
Clever, 1996 <sup>96</sup>	X	40 (2: 20/20)	X	✓	✓	X	Numbers given, but no detail	X
Donaghue, 1998 <sup>97</sup>	X	75 (2: 50/25)	X	✓	✓	X	Numbers given stated that there was no significant difference between completers and withdrawals	✓
Lishner, 1985 <sup>103</sup>	Alternate allocation	40 (2: 20/20)	X	✓	X	X	X	X
Mulder, 1994 <sup>105</sup>	X	First comparison: 42/40 Second comparison: 49/50	X	X	✓	X	X	X
Muthukumarasamy, 1991 <sup>106</sup>	Matched control	100 (2: 50/50)	✓	✓	✓	X	X	X

✓, yes; X, no

**TABLE 25** Studies of debridement for the treatment of diabetic foot ulcers

Study	Concealment of allocation	Sample size (No. of arms: sizes of groups)	A priori sample-size calculation described	Baseline comparability of groups reported	Inclusion/exclusion criteria stated	Adequate follow-up period	Withdrawals and No. lost to follow-up stated (with reasons)	Intention-to-treat analysis
Apelqvist, 1990 <sup>110</sup>	X	44 (2: 22/22)	X	✓	✓	X	✓	X
Apelqvist, 1996 <sup>109</sup>	Computer-generated list of randomly permuted blocks of patients	41 (2: 22/19)	X	No details given, but it was stated that the 2 groups had similar clinical characteristics	✓	X	✓	X
✓, yes; X, no								

**TABLE 26** Studies of antibiotics for the treatment of diabetic foot ulcers

Study	Concealment of allocation	Sample size (No. of arms: sizes of groups)	A priori sample-size calculation described	Baseline comparability of groups reported	Inclusion/exclusion criteria stated	Adequate follow-up period	Withdrawals and No. lost to follow-up stated (with reasons)	Intention-to-treat analysis
Lipsky, 1990 <sup>113</sup>	Not stated	60 (2: 27/29)	X	✓	✓	✓ 15 ± 9 months	✓	X
Chantelau, 1996 <sup>114</sup>	Computer-generated randomisation code	44 (2: 22/22)	X	✓	✓	X	✓	X
✓, yes; X, no								



# **Appendix 8**

## Summary of excluded studies

TABLE 27 Studies on education

Study	Details	Reason for exclusion
Rettig, 1986, <sup>138</sup> USA	RCT comparing individualised instruction in diabetes self-care in the home from health nurses, compared with usual care ( <i>ad hoc</i> education)	Foot outcomes reported as 'foot appearance score' but the meaning of these scores is not clear
Kruger, 1992, <sup>137</sup> USA	RCT comparing interactive teaching on foot care plus lecture for diabetic adults; control group received lecture alone. Data concerning patients' knowledge about foot care, condition of feet and glycated haemoglobin collected	No data relating to the condition of the feet were presented
Barth, 1991, <sup>117</sup> Australia	RCT evaluating the effectiveness of an intensive foot care education programme (including extended time-span, greater patient contact time, practical foot care training sessions and cognitive motivational techniques based on the Heckhausen and Kuhl theory of cognitive motivation) compared with a conventional programme (current standard education practice in Australia for people with type 2 diabetes for 14 hours, held on 3 consecutive days with 8–10 participants per group)	'Foot problems' as an outcome measure was not well defined in the report, although this was specifically defined at baseline and included calluses and ulcers. Clarification of what constituted a 'foot problem' was sought from the author, but relevant information pertaining to calluses and/or foot ulcers could not be extracted from the information provided

TABLE 28 Studies on stockings

Study	Details	Reason for exclusion
Belcaro, 1989, <sup>49</sup> Italy	RCT evaluating the effects of elastic stockings used a for 24-week period in patients with diabetic microangiopathy	The study specifically measured microcirculatory parameters (i.e. no wound healing)

TABLE 29 Studies on hyperbaric oxygen therapy

Study	Details	Reason for exclusion
Baroni, 1987, <sup>118</sup> Italy	CCT evaluating the efficacy of hyperbaric oxygen in the treatment of severe diabetic ulcers and leg gangrene <b>Patient sample:</b> 28 diabetic inpatients with ulceronecrotic foot lesions	Patients were not randomised to the two groups (personal communication)
Belch, 1994–97, <sup>119</sup> UK	Single-blind RCT comparing the efficacy of hyperbaric oxygen + conventional ulcer treatment with placebo + conventional ulcer treatment in healing leg ulcers in patients with diabetes mellitus <b>Inclusion criteria:</b> Diabetic adults aged > 40 years with leg ulcers of a minimum of 1 month duration <b>Exclusion criteria:</b> Peripheral vascular disease sufficiently severe to warrant revascularisation/ radical intervention, patients in whom healing was unlikely to occur (e.g. tissue oxygen did not increase after breathing 100% oxygen), acute respiratory infection, advanced chronic obstructive airways disease, unstable angina, inability to consent	This RCT never took place due to lack of funding (personal communication)
Oriani, 1990, <sup>120</sup> Italy	CCT evaluating the efficacy of hyperbaric oxygen therapy (HBOT) and no HBOT in the treatment of diabetic gangrene	The control group comprised patients who refused to enter the HBOT chamber due to psychological factors (non-randomised trial)

TABLE 30 Studies on prostaglandins

Study	Details	Reason for exclusion
UK Severe Limb Ischaemia Study Group, 1991 <sup>121</sup>	Double-blind RCT comparing intravenous iloprost with placebo (solvent without iloprost) for 14–28 days in 151 patients with ischaemia of the lower limb presenting as ulcers or gangrene and/or rest pain	Data not presented separately for diabetic patients

TABLE 31 Studies on growth factors

Study	Details	Reason for exclusion
Knighton, 1990, <sup>33</sup> USA	<p>RCT comparing platelet-derived wound-healing formula (PDWHF) with placebo for 8 weeks was evaluated in 32 patients with chronic, non-healing, cutaneous wounds of the lower extremity</p> <p><b>Inclusion criteria:</b> The presence of a chronically non-healing, full-thickness, cutaneous ulcer of a lower extremity of at least 8 weeks duration and a normal peripheral blood platelet count</p> <p><b>Exclusion criteria:</b> Failure to follow protocol instructions on two or more clinic visits, amputation of the extremity before completion of the trial, any extensive surgical intervention (such as arterial bypass) after randomisation, or failure to return to clinic for follow-up visits</p>	Patients with wounds of mixed aetiologies, including patients diagnosed as having diabetes mellitus, but data for those with diabetes were not presented separately

TABLE 32 Studies on topical agents

Study	Details	Reason for exclusion
Altman, 1993, <sup>122</sup> USA	RCT comparing the effectiveness of a hydrogel wound-repair device (Nu-Gel <sup>®</sup> ) with standard gauze dressing moistened with normal saline in the management of full-thickness chronic wounds of the lower extremities, such as venous ulcer, arterial ulcer, diabetic ulcer and dehisced surgical incision	A study comprising mixed wounds; data for patients with diabetic foot ulcers were not presented separately
Di Mauro, 1991, <sup>123</sup> Italy	RCT comparing lyophilised collagen with hyaluronic acid medicated gauze in 20 patients with diabetic foot ulcers	Very poorly reported trial design with little information given about patient characteristics and few data reported
Foster, 1994, <sup>124</sup> UK	Study assessing the effect of OpSite <sup>®</sup> dressings, compared with no treatment, on pain experienced in the feet and legs of 33 patients with chronic diabetic neuropathy. The study design consisted of a run-in period of 2 weeks, followed by a period of 4 weeks when OpSite was applied to one of the painful legs, and then followed by a further period of 4 weeks when OpSite was switched to the opposite leg	Not a study of diabetic foot ulceration
Bradshaw, 1989, <sup>125</sup> UK	It was decided to establish an RCT at the Manchester Foot Hospital to compare the effectiveness of Kaltostat (a soft, white, non-woven dressing prepared from calcium alginate) with sterile gauze and polynoxylin gel dressings for the treatment of diabetic foot ulcers in the absence of severe vascular disease. It was intended that 50 patients would be recruited into the study, 25 in each group. The trial commenced in February 1988 with an intended completion date of December 1988	It proved impossible to recruit sufficient numbers of suitable patients to the trial and by December 1988 only six patients had been recruited. Instead, individual case studies were presented

TABLE 33 Studies on antibiotics

Study	Details	Reason for exclusion
Akova, 1996, <sup>126</sup> Turkey	RCT evaluating the efficacy and safety of parenteral sulbactam–ampicillin (1.5 g SAM (0.5 g sulbactam + 1 g ampicillin, Duocid <sup>®</sup> , Pfizer, Turkey) intravenously, four times daily) in 74 patients with severe diabetic foot infections (49 with osteomyelitis, 25 with soft tissue infections). The duration of treatment was adjusted according to the severity of infection. Follow-up was for 18 months  <b>Inclusion criteria:</b> Aged $\geq 18$ years with severe diabetic foot infections admitted to Hacettepe University Hospitals between 1989 and 1992, a foot lesion classified in either group II or III using Gibbons and Eliopoulos criteria of lower extremity infections	Although the criteria for healing were described in the methods section as the “disappearance of purulent discharge or cellulitis, development of the granulation tissue, and resolution of the fever and other systemic signs and symptoms”, no results pertained to ulcer healing. Outcomes were specifically related to antimicrobial response
Bradsher, 1984, <sup>127</sup> USA	RCT comparing the efficacy and safety of 1 g ceftriaxone daily and 3–4 g cefazolin daily in 84 hospitalised adults with skin and soft tissue infections. A variety of infections, including bacteriologically proven cellulitis, suppurative diabetic foot ulcer, soft tissue abscess and other miscellaneous infections, were treated  <b>Exclusion criteria:</b> Patients who had received antibiotics in the previous 72 hours or patients with either renal failure, pregnancy, lactation, neutropenia or significant penicillin hypersensitivity	20 of the 84 patients had diabetes mellitus, but healing data for this group were not presented separately
Peterson, 1989, <sup>128</sup> USA	RCT evaluating oral the fluoroquinolone ciprofloxacin (750 mg vs 1000 mg twice daily) for lower extremity infections in patients with diabetes, peripheral vascular disease or both	Mixed patients (diabetes mellitus, 46; osteomyelitis, 31; cellulitis, 16); healing data were not presented separately for the diabetic patients
Ramani, 1993, <sup>129</sup> India	Randomisation unclear. CCT evaluating the effectiveness of 8 weeks of oral pentoxifylline (400 mg three times daily), compared with conventional therapy (vasodilators and topical therapy), in 40 diabetic patients with ischaemic foot ulcers	Although it is clear from the paper that the clinical evaluation included ‘degree of ulcer healing’ no data were presented in the results relating to this. Results of ulcer healing at the end of treatment or follow-up were requested from the authors but none were forthcoming
Self, 1987, <sup>130</sup> USA	Double-blind RCT comparing the efficacy of ciprofloxacin with that of cefotaxime for the treatment of skin and skin structure infections in hospitalised patients  <b>Exclusion criteria:</b> Known pregnancy, hypersensitivity to either quinolones or cephalosporins, and abnormal renal function	Non-diabetic patients. Patients had wounds of various aetiologies, such as cellulitis, abscesses, wound infections and miscellaneous infections (including infected burn sites). Healing was not reported as an outcome

continued



**TABLE 33 contd** Studies on antibiotics

Study	Details	Reason for exclusion
File, 1983, <sup>131</sup> USA	Single-blind RCT evaluating cefoxitin alone (1–2 g intravenously) with a combination of cefoxitin + amdinocillin (10 mg/kg intravenously) in 45 patients with diabetes mellitus <b>Exclusion criteria:</b> Patients allergic to penicillin or cephalosporins, and patients who required other antibiotics during the study period	Healing not reported as an outcome
Hughes, 1987, <sup>132</sup> USA	RCT evaluating cefoxitin, compared with cephalosporin, for 5 days in 63 patients with diabetes or peripheral arterial insufficiency with lower extremity soft tissue infection	The primary outcome of wound measurement was not included
Grayson, 1994, <sup>133</sup> USA	RCT evaluating imipenem + cilastatin, compared with ampicillin + sulbactam, in 92 patients with diabetes and limb-threatening infection of a lower extremity	The primary outcome of wound measurement was not included
Tan, 1993, <sup>134</sup> USA	RCT evaluating piperacillin + tazobactam, compared with ticarcillin + clavulanate, in 251 patients with various bacterial skin infections, including acutely infected pressure ulcers, traumatic wound infections, diabetic or ischaemic foot infections and acute infections of decubitus ulcers	Infection eradication was a primary outcome, but wound healing was not an outcome

**TABLE 34** Studies on electrotherapy

Study	Details	Reason for exclusion
Lundeberg, 1992, <sup>135</sup> Sweden	RCT comparing electrotherapy with placebo electrotherapy	Study was of venous leg ulcers in diabetic patients



# Health Technology Assessment panel membership

This report was identified as a priority by the Pharmaceutical Panel.

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