

A systematic review of foot ulcer in patients with Type 2 diabetes mellitus. II: treatment

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Received 19 November 1998; revised 2 February 1999; accepted 7 March 1999

Abstract

Aim To assess the value of treatments for foot ulcers in patients with Type 2 diabetes mellitus.

Methods A systematic review of interventions to treat diabetic foot ulcers.

Results The evidence base for treating infections and dressing wounds is poor. A number of new and potentially promising treatments are being developed but currently available studies are often small, inadequately powered and use different methods and outcomes.

Conclusions Given the prevalence, morbidity and healthcare costs of diabetic foot disease, it is surprising that available trials provide inadequate evidence to improve upon current empirically based treatment approaches. Substantial effort and resources should be deployed in order to investigate both new and existing treatments in a co-ordinated, systematic and consistent manner, so that a proper evidence base can be established for this important disease area.

Diabet. Med. 16, 889–909 (1999)

Keywords diabetes mellitus, diabetic foot, systematic review, treatment

Abbreviations G-CSF, granulocyte colony stimulating factor; HBO, hyperbaric oxygen; rbFGF, recombinant basic fibroblast growth factor; RGDpm, arginine-glycine-aspartic acid peptide matrix; rhPDGF, recombinant platelet-derived growth factor; TCC, total contact casting

Introduction

Approximately 2% of the British population are estimated to have Type 2 diabetes mellitus, of which about 5% are estimated to have a foot ulcer of varying severity at any point in time [1]. The morbidity associated with diabetic foot ulcers is considerable. A prospective study of 314 consecutive diabetic patients with foot ulcers referred to a multidisciplinary team in a university hospital reported that healing was achieved in 62% of patients, amputation in 25%, while 13% of patients died with unhealed ulcers [2]. Foot ulcers are susceptible to infection and polymicrobial infection may spread rapidly, causing overwhelm-

ing tissue destruction [3]. This infection process is the main reason for major amputation following ulceration in patients with predominantly neuropathic ulceration. Amputations may also result from critical ischaemia resulting from non-reconstructable peripheral vascular disease.

Traditional approaches to diabetic foot ulcers include desloughing and debridement, pressure relief (e.g. rest, special footwear and shoe inserts and casting), antibiotic treatment for infection and wound dressing. New treatments under evaluation include cultured human dermis, granulocyte colony stimulating factor (G-CSF), growth factor, hyperbaric oxygen (HBO) therapy, ketanserin and developments in dressing technology.

Trials of interventions for ulcerated feet commonly stratify ulcer severity according to the Wagner system:

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grade 0, intact skin; grade I, superficial ulcer; grade II, deep ulcer; grade III, osteomyelitis and/or deep abscess; grade IV, forefoot gangrene; and grade V, hindfoot gangrene [4].

Methods

The search strategy and methods used in this review are reported in a previous publication [1]. Studies were examined if they specifically addressed an intervention for patients with diabetic foot ulcers. In each area considered, the best available evidence was used [5] and where randomized, controlled trials were available, studies of lesser design were excluded unless they added a further dimension to the understanding. This review does not address vascular surgical techniques, the appropriate method or timing of amputation or subsequent management.

Treatment of foot ulcers

Antibiotic therapy

Polymicrobial, mixed aerobic/anaerobic infections are common in diabetic foot ulcers but the degree of associated cellulitis or osteomyelitis is very variable. In general, trials have differentiated between superficial colonization (non-limb-threatening) and deep tissue infection (potentially limb-threatening). Four randomized trials were identified that assessed the efficacy of antibiotic therapy specifically in diabetic patients with infected ulcers (see Table 1). Two of these trials addressed non-limb-threatening infection, one addressed non-limb-threatening but treatment-resistant infection and one addressed invasive infection.

Chantelau *et al.* [6] randomized 44 patients to oral amoxicillin plus clavulanic acid or matched placebo. Patients had neuropathic ulcers of severity 1A (superficial with or without cellulitis) to 2A (deeper, reaching to joints and tendons) on the Wagner and Harkless classification (a modified Wagner scale). At 20 days follow-up, no significant differences were apparent between treatment and placebo in the number of ulcers healed or the mean reduction in ulcer size. Completely closed lesions occurred in 32% of patients receiving antibiotics and 50% of patients receiving placebo.

Lipsky *et al.* [7] randomized 56 patients with an infected lesion regardless of type or duration to oral clindamycin or oral cephalexin in an outpatient setting. At 2 weeks, no statistically significant differences were found between treatments, either for response to infection or wound healing, the latter occurring in 40% of patients receiving clindamycin and 33% receiving cephalexin.

Lipsky *et al.* [8] randomized 88 patients to intravenous ofloxacin followed by oral ofloxacin or intravenous ampicillin sulbactam followed by oral amoxicillin clavulanate in patients who were hospitalized for soft tissue infections that had not responded to outpatient management but which were not limb-threatening. At 28 days

there were no statistically significant differences in the efficacy of the two therapies. Cure occurred in 49% of the ofloxacin group and 56% of the amino-penicillin group.

Grayson *et al.* [9] randomized 93 patients to intravenous imipenem/cilastatin or intravenous ampicillin/sulbactam. Patients had severe infections of the lower extremities, threatening to the lower limb and identified by the presence of cellulitis, with or without ulceration or purulent discharge. Osteomyelitis was diagnosed in 59 (63%) patients. For the first 5 days, treatment followed randomization, thereafter treatment could be adaptive in the instance of inadequate response. No significant differences were found between the two treatment groups after 5 days or at the end of definitive treatment. After 5 days, cure had been effected in 60% of the ampicillin/sulbactam group and 58% of the imipenem/cilastatin group.

A number of other randomized trials of antibiotics have been conducted on groups of patients, including a proportion with diabetic foot ulcer [10–13]. These studies similarly found no statistically significant differences in clinical response.

The two outpatient trials for non-invasive infections found no difference between antibiotic regimens, and no improvement relative to placebo. It is uncertain whether all antibiotics are ineffective in this group of patients or just the particular regimen used by Chantelau and colleagues. Patients with invasive cellulitis often require supplementary surgical intervention. Despite the apparent treatment success reported by Grayson *et al.* [9], 66% of their patients had a lower limb amputation during the following year, although the operation was limb sparing in most cases.

Dressings and topical agents for foot ulcers

While simple gauze dressings are often employed by clinicians, there are newer forms of dressing available. Alginate, foam, hydrogel and hydrocolloid dressings have been designed and promoted on the basis that they absorb wound exudate and control the level of wound hydration.

Eight randomized trials (see Table 2) and two controlled trials were identified, assessing the efficacy of various dressings and topical agents in diabetic patients with ulcers. These can be broadly grouped into trials comparing newer dressings or gels with gauze dressings and trials comparing the newer dressings with one another.

Di Mauro *et al.* [14] randomized 20 patients to a lyophilized type I collagen dressing or hyaluronic acid medicated gauze. The severity of ulceration in these patients is unclear. A significant improvement in the mean time to wound healing was reported for the collagen dressing compared to the medicated gauze (mean time 32.4 days vs. 49.0 days, $P = 0.001$).

Ahroni *et al.* [15] randomized 39 patients in an American outpatient setting to a calcium alginate dressing or to dry sterile gauze. Patients had foot ulcers penetrating

the epidermis but not involving joint spaces, tendon or bone. Ulcers with severe infection, cellulitis, osteomyelitis or evidence of systemic toxicity were excluded. After 4 weeks there were no significant differences between the two groups in the number of ulcers healed (alginate 25%; gauze 37%; $P = 0.65$).

Blackman *et al.* [16] randomized 18 patients with partial or full thickness foot ulcers of Wagner stage I or II to a semi-permeable polymeric membrane dressing or a conventional wet to dry saline gauze dressing, with primary analysis after 2 months. The polymeric dressing included a bacteriostatic agent and a non-ionic surfactant as a cleansing agent. At 2 months follow up, the change from baseline of ulcer size in the polymeric dressing group was significantly smaller than with gauze dressing (35% vs. 105%) ($P < 0.03$).

Mulder *et al.* [17] evaluated the use of a topical gel: a GHK–Cu complex (glycyl-L-histidyl-L-lysine peptide, copper complex). Patients with neuropathic full thickness ulcers were randomized to four groups. Immediately after debridement, two groups were randomized to GHK–Cu gel or vehicle alone. Significantly better plantar ulcer healing was observed in the GHK–Cu gel group (median area percentage wound closure, 98.5% vs. 60.8% $P < 0.05$), although the most benefit was seen in patients with large ulcers that did not respond well to control treatment. Two further groups were randomized to different concentrations of GHK–Cu gel after a 4-week delay following debridement, and no significant differences were seen in these groups compared with each other or the control group. This led the authors to suggest that the gel interacted with the process of debridement. The dressing used in all patient groups was plain gauze.

Apelqvist and Tennvall [18] evaluated topical treatment with cadexomer iodine ointment dressing in addition to standard treatment. Forty-one patients with ulcers of Wagner stage I or II and surface area greater than 1 cm² were randomized. After 12 weeks, there were no significant clinical differences between the groups in completely healed ulcers or clinical improvement. An analysis of costs was conducted purporting to show that cadexomer iodine achieved significant cost-savings owing predominantly to a reduced frequency of dressing changes. However, substantially more patients were withdrawn from the ointment group as a result of deteriorating disease or protocol violation (thus removing high-cost patients and invalidating the analysis).

Donaghue *et al.* [19] randomized 75 patients (in a 2:1 ratio) to a combination collagen–alginate dressing or to regular gauze moistened in saline, with a follow-up period of 8 weeks. Patients were excluded if ischaemia, infection or osteomyelitis were identified. No statistically significant differences were found between the groups in any outcome reported. Significantly more patients withdrew from the

gauze dressing arm than the collagen–alginate arm (32% vs. 12%).

Lishner *et al.* [20] allocated 40 patients in a prospective, controlled study where, in addition to conventional care, the treatment group received a foot bath containing dimethylsulphoxide (DMSO) solution for 20 min, three times a day. Patients enrolled had not responded to previous treatment and had deep, or perforated, ulcers. Garamycin was added to the solution when infection occurred and the concentration of DMSO was doubled if no healing occurred by the sixth week. At 15 weeks, healing had occurred in 14 patients in the DMSO group and two in the control group ($P = 0.0001$). It is unclear to what extent improvement was a result of the active therapy or the process of regular foot bathing in the treatment group.

Muthukumarasamy *et al.* [21] conducted a prospective matched case-control study comparing daily topical phenytoin powder with a dry sterile occlusive dressing in 100 patients. Groups were matched for age, sex, ulcer area and depth and chronicity at baseline, although there was a non-significant trend to smaller ulcer size in the phenytoin group. Tropic ulcers or ulcers with gross cellulitis, deep slough or ischaemic gangrene were excluded. Ulcers were assessed using a clinical impression scale A–E, where A denotes deterioration and E denotes complete healing. At 35 days, ulcer healing was significantly better with phenytoin on the impression scale.

Although some findings appear promising, neither a positive or negative finding can be regarded as conclusive when based on one small trial. Findings need confirmation from other well-conducted studies using common methods and endpoints. The stated importance of the newer dressings and the inappropriateness of gauze (see, for example, the British National Formulary [22]) does not appear substantiated by the limited evidence from randomized, controlled trials.

Foster *et al.* [23] randomized 30 patients to a polyurethane foam dressing or a calcium–sodium alginate dressing, with treatment over an 8-week period or until the ulcer was healed. No significant differences in ulcer healing were apparent at 8 weeks (foam 60%, alginate 53%).

Clever and Dreyer [24] randomized 40 patients to one of two polyurethane gel dressings in addition to standard care. Patients had pure, superficial neuropathic ulcers, diameter 1–5 cm. There were no differences between the two groups in terms of time to healing, reduction in wound size at 4 weeks or frequency of change of dressing.

The two head-to-head trials comparing newer dressing technologies suggest broad equivalence but no firm conclusions can be drawn from these small and unrepeated studies [23,24].

Table 1 Randomized trials of antibiotic treatment

Author	Interventions	Trial detail	Results
Chantelau, 1996 [6]	<p>INT: Amoxicillin (500 mg) and clavulanic acid (125 g) CON: Placebo</p> <p>All patients had necrotic tissue debrided and lesion cleansed. Complete pressure relief was provided by half shoes and walking aid or wheelchair. Outpatients received cleansing and dressings daily in their homes from qualified nurses.</p> <p>INT: antibiotics taken three times daily. Treatment could be discontinued during the study if pathogens or lesion were unresponsive to therapy.</p>	<p>Blinding level: double blind (patient and doctor)</p> <p>Concealment of allocation: unclear (a computer-generated randomization code was used)</p> <p>Baseline comparability: yes</p> <p>Numbers randomized: INT: 22; CON: 22</p> <p>Loss to follow-up: INT: 3; CON: 2</p>	<p>Completely closed lesions (within 20 days): INT: 6/19 (32%); CON: 10/20 (50%)</p> <p>Mean reduction in ulcer radius (mm²/day): INT 0.27 (95% C.I: 0.15–0.39); CON: 0.41 (95% C.I:0.21–0.61)</p>
Lipsky <i>et al.</i> 1990 [7]	<p>T1: oral clindamycin hydrochloride (300 mg) T2: oral cephalexin (500 mg)</p> <p>Diabetic outpatients, at an acute care hospital. All patients had lesions cleansed and debrided, and were given instructions for care and dressing of lesions.</p> <p>Patients in both groups received oral therapy four times daily for 2 weeks. Patients whose infections failed to improve or worsened were withdrawn and hospitalized for parenteral therapy.</p>	<p>Blinding level: clinician blinded</p> <p>Concealment of allocation: not reported</p> <p>Baseline comparability: yes</p> <p>Numbers randomized: T1: 27; T2: 29</p> <p>Loss to follow-up: T1 + T2: 4</p>	<p><i>Wound healing (size of ulceration) at 2 weeks:</i> healed: T1: 10/25 (40%); T2 9/27 (33%) healing progress: T1: 14/25 (56%); T2 18/27 (67%) unimproved: T1: 1/25 (4%); T2 0/27 (0%) (4 patients did not have open wounds)</p> <p><i>Infection response:</i> cured: T1 21/27 (78%); T2 21/29 (72%) improved: T1 5/27 (19%); T2 4/29 (14%) failed: T1 1/27 (4%); T2 4/29 (14%)</p> <p>No differences between treatments were statistically significantly different</p>

Table 1 continued

Author	Interventions	Trial detail	Results																														
Lipsky <i>et al.</i> 1997 [8]	<p>T1: IV ofloxacin and then oral ofloxacin T2: IV ampicillin/sulbactam and then oral amoxicillin/clavulanic acid</p> <p>Both treatments were given for 14–28 days. IV therapy ran for about 1 week in both groups. Patients not improving could receive additional antibiotic therapy (metronidazole to the ofloxacin group, and gentamicin or trimethoprim-sulfamethoxazole to the amino-penicillin regimen).</p> <p>T1: Intravenous ofloxacin (400 mg) followed by oral ofloxacin (400 mg) every 12 h T2: Intravenous ampicillin (1–2g)/sulbactam (0.5–1g) followed by amoxicillin (500 mg)/clavulanic acid (125g) every 8 h.</p>	<p>Blinding level: none apparent Concealment of allocation: not reported Baseline comparability: yes Numbers randomized: T1: 55; T2: 53 Loss to follow-up: T1: 8; T2: 12</p>	<p>Cure (at 28 days): T1: 23/47 (49%); T2: 23/41 (56%) Improvement: T1: 17/47 (36%); T2: 11/41 (27%) Failure: T1: 7/47 (15%); T2: 7/41 (17%) Side-effects: T1: 17/47 (36%); T2: 9/41(22%) No side-effect was reported to be severe enough to lead to discontinuation of therapy.</p>																														
Grayson <i>et al.</i> 1994 [9]	<p>T1: Imipenem/cilastatin T2: Ampicillin/sulbactam</p> <p>T1: Intravenous, 500 mg every 6 h, mean duration of therapy was 13 days T2: Intravenous, 3g every 6 h, mean duration of therapy was 15 days.</p> <p>Sharp debridement was carried out where indicated. Treatment could be modified after 5 days for non-response, but blinding to the randomized treatment was maintained</p>	<p>Blinding level: double blind (patient and doctor) Concealment of allocation: yes Baseline comparability: yes Numbers randomized: T1: 48 episodes in 46 patients T2: 48 episodes in 47 patients Loss to follow-up: none</p>	<p><i>Clinical assessment at 5 days:</i></p> <table border="1"> <thead> <tr> <th></th> <th>T1</th> <th>T2</th> </tr> </thead> <tbody> <tr> <td>Cure</td> <td>29 (60%)</td> <td>28 (58%)</td> </tr> <tr> <td>Improvement</td> <td>18 (38%)</td> <td>17 (35%)</td> </tr> <tr> <td>Failure</td> <td>1 (2%)</td> <td>3 (6%)</td> </tr> <tr> <td>Indeterminant</td> <td>0 (0%)</td> <td>0 (0%)</td> </tr> </tbody> </table> <p><i>Clinical assessment at end of therapy:</i></p> <table border="1"> <thead> <tr> <th></th> <th>T1</th> <th>T2</th> </tr> </thead> <tbody> <tr> <td>Cure</td> <td>41 (85%)</td> <td>39 (81%)</td> </tr> <tr> <td>Improvement</td> <td>0 (0%)</td> <td>0 (0%)</td> </tr> <tr> <td>Failure</td> <td>6 (13%)</td> <td>8 (17%)</td> </tr> <tr> <td>Indeterminant</td> <td>0 (0%)</td> <td>1 (2%)</td> </tr> </tbody> </table> <p>No differences between treatments were statistically significant</p>		T1	T2	Cure	29 (60%)	28 (58%)	Improvement	18 (38%)	17 (35%)	Failure	1 (2%)	3 (6%)	Indeterminant	0 (0%)	0 (0%)		T1	T2	Cure	41 (85%)	39 (81%)	Improvement	0 (0%)	0 (0%)	Failure	6 (13%)	8 (17%)	Indeterminant	0 (0%)	1 (2%)
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Table 2 Randomized trials of dressings and topical agents

Author	Interventions	Trial detail	Results																														
Di Mauro <i>et al.</i> 1991 [14]	T1: Lyophilized type I collagen dressing T2: Gauze dressing medicated with Hyaluric acid Ulcers were debrided and repeatedly washed with saline and local antibiotic therapy. The dressing was renewed every two days T1: the dressing tablet was moistened with saline and antibiotic solution before application to surface ulcers and used dry, cut and moulded when inserted in fistulas	Blinding level: not stated Concealment of allocation: unclear, consecutive allocation Baseline comparability: patients were reported comparable although comparisons were not quantified Numbers randomized: T1: 10; T2: 10 (19 patients had foot ulcers, one had a wrist ulcer) Loss to follow-up: none	Mean days (SE) to wound healing: T1: 32.4 (8.6); T2: 49.0 (11.0); ($P=0.001$)																														
Ahroni <i>et al.</i> 1993 [15]	T1: Calcium alginate dressing changed once daily T2: Dry sterile gauze (nonadherent dressing) changed twice daily. Ulcers received thorough debridement at baseline and patients received instructions for foot care. Wounds were cleansed with half strength hydrogen peroxide and rinsed with saline. Patients attended weekly outpatient clinics. Oral antibiotics were prescribed for signs of soft tissue infection	Blinding level: none Concealment of allocation: not reported Baseline comparability: yes, except significantly more patients in T2 entered the study on antibiotics ($P=0.03$) Numbers randomized: T1: 20; T2: 19 Loss to follow-up: none	<p><i>At 4 weeks:</i></p> <table border="1"> <thead> <tr> <th></th> <th>T1</th> <th>T2</th> </tr> </thead> <tbody> <tr> <td>Healed</td> <td>5 (25%)</td> <td>7 (37%)</td> </tr> <tr> <td>Unhealed</td> <td>10 (50%)</td> <td>9 (47%)</td> </tr> <tr> <td>Withdrawn</td> <td>5 (25%)</td> <td>3 (16%)</td> </tr> </tbody> </table> <p>trend $P=0.65$</p> <p><i>Eventually (time not stated):</i></p> <table border="1"> <thead> <tr> <th></th> <th>T1</th> <th>T2</th> </tr> </thead> <tbody> <tr> <td>Healed</td> <td>12</td> <td>14</td> </tr> <tr> <td>Unhealed</td> <td>3</td> <td>2</td> </tr> <tr> <td>Surgery</td> <td>2</td> <td>0</td> </tr> <tr> <td>Amputation</td> <td>2</td> <td>2</td> </tr> <tr> <td>Expired</td> <td>1</td> <td>1</td> </tr> </tbody> </table> <p>trend $P=0.68$</p> <p><i>For patients not withdrawn:</i> Healing rate, area: (mm^2/day (SD)) T1: -2.19 (4.0); T2: -2.04 (2.61), $P>0.99$ Healing rate, linear (mm/day (SD)) T1: 0.094 (0.147); T2: 0.084 (0.100), $P=0.87$</p>		T1	T2	Healed	5 (25%)	7 (37%)	Unhealed	10 (50%)	9 (47%)	Withdrawn	5 (25%)	3 (16%)		T1	T2	Healed	12	14	Unhealed	3	2	Surgery	2	0	Amputation	2	2	Expired	1	1
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Blackman <i>et al.</i> 1994 [16]	T1: Semi-permeable polymeric membrane dressing T2: Conventional therapy (wet to dry saline gauze dressing) Wounds were surgically debrided before treatment where necessary and patients were given self-care advice and guidance on changing dressings Ulcer assessment occurred every 3 weeks, patients were allowed to cross-over from T2 to T1 after 2 months	Blinding level: not reported Concealment of allocation: not reported Baseline comparability: yes Numbers randomized: T1 + T2: 20 Loss to follow-up: 2 patients in each group progressed to Wagner stage III ulcers and were not included in the final analysis.	<p><i>Ulcer size at 2 months:</i> Initial size (cm^2 (SE)) T1: 2.67 (1.2) T2: 1.81 (0.75) Final size (cm^2 (SE)) T1: 0.84 (0.37) T2: 2.77 (1.85) % of baseline T1 35(16); T2: 105(26) ($P<0.03$) Complete healing at 2 months: T1: 3/11(27%); T2: 0/7 (0%) Substantial improvement in ulcer size at 2 months: T1: 10/11 (91%); T2: 2/7 (29%)</p>																														
Mulder <i>et al.</i> 1994 [17]	<i>Immediate treatment after debridement</i> T1: Gel (vehicle) T2: GHK–Cu gel-2% <i>Four week lead in period with vehicle only, following debridement</i> T3: GHK–Cu gel-2%	Blinding level: evaluator blinded Concealment of allocation: not reported Baseline comparability: not quantified, but stated comparable Numbers randomized: T1: 42 (32 plantar); T2: 40 (28 plantar)	<p><i>Immediate treatment groups, plantar ulcer patients:</i> Median area percentage wound closure: T1: 60.8%; T2: 98.5%; ($P<0.05$) Target ulcer infections/adverse events: T1: 34%; T2: 7%; ($P<0.05$)</p> <p><i>Delayed treatment groups plantar ulcer patients:</i></p>																														

Table 2 continued

Author	Interventions	Trial detail	Results																				
	T4: GHK–Cu gel-4% GHK–Cu: glycl-L-histidyl-L-lysine: copper in a topical gel. Gels were applied topically to the wound for 8 weeks All patients received sharp debridement at enrolment, routine superficial debridement and cleansing, daily dressing changes (gauze), metered dose of the gel, standardized pressure-relieving footwear, patient education, and affected lesions treated with systemic antibiotics, patients with clinically significant limb oedema received supportive care	T3: 49 (39 plantar); T4: 50 (42 plantar) Loss to follow-up: none	Median area percentage wound closure: T3: 40.0%; T4: 68.2%; (<i>P</i> = NS)																				
Apelqvist <i>et al.</i> (1996) [18]	T1: Cadexomer iodine ointment applied topically to the wound for 8 weeks in addition to standard care T2: Standard care Standard treatment was dry saline gauze changed once or twice daily, gentamicin solution for infection, streptodornase/streptokinase for necrotic tissue. Footwear were provided or corrected where necessary and oral antibiotics were used where there were signs of infection. When ulcers stopped exuding, petroleum gauze was then used in both groups. Patients were treated as outpatients by a multidisciplinary foot care team. All patients had signs of severe sensory neuropathy: VPT > 30 T1: Cadexomer iodine was changed once daily during first week and daily or every 2nd or 3rd day subsequently	Blinding level: evaluator blinded Concealment of allocation: unclear; computer generated list of randomly permuted blocks of patients where the size of blocks was unknown to the investigator Baseline comparability: not detailed, the authors report no major differences between groups in clinical characteristics Numbers randomized: T1: 22; T2: 19 Loss to follow-up T1: 5; T1: 1	Complete healing (defined as intact skin): T1: 5/17 (29%); T2: 2/18(11%); <i>p</i> = NS Clinically relevant improvement (area reduced by > 50% or improvement in Wagner grade): T1: 12/17(71%); T2: 13/18 (72%); <i>p</i> = NS Weekly cost <table border="1"> <thead> <tr> <th></th> <th>T1</th> <th>T2</th> <th></th> </tr> </thead> <tbody> <tr> <td>staff</td> <td>380</td> <td>884</td> <td><i>P</i> < 0.0001</td> </tr> <tr> <td>transportation</td> <td>100</td> <td>243</td> <td><i>P</i> < 0.0001</td> </tr> <tr> <td>material & drugs</td> <td>423</td> <td>294</td> <td><i>P</i> = NS</td> </tr> <tr> <td>total</td> <td>903</td> <td>1421</td> <td><i>P</i> < 0.01</td> </tr> </tbody> </table>		T1	T2		staff	380	884	<i>P</i> < 0.0001	transportation	100	243	<i>P</i> < 0.0001	material & drugs	423	294	<i>P</i> = NS	total	903	1421	<i>P</i> < 0.01
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Donaghue (1996) [19]	T1: Collagen alginate topical wound dressing T2: Gauze moistened in saline All patients received initial debridement, instructions on dressing changes (as often as required), and adhesive foam pads to limit weight bearing. Patients had weekly outpatient clinics	Blinding level: none Concealment of allocation: not reported Baseline comparability: yes Numbers randomized: T1 : 50; T2 : 25 Loss to follow-up: T1: 6; T2: 8	Complete healing: T1: 24/44 (55%); T2: 9/17 (53%) Mean time to complete healing weeks (SD): T1: 6.2 (0.4); T2: 5.8 (0.8) Mean percentage reduction in wound area (SD): T1: 80.6 (0.1)%; T2: 61.1 (0.3)% Patients achieving ≥ 50% wound area reduction: T1: 43/44 (98%); T2: 15/17 (88%) Mean time required to 50% wound healing, weeks (SD): T1: 2.4 (0.3); T2: 2.5 (0.7) No differences between dressings were statistically significant. No difference was found in the number and severity of adverse reactions between groups.																				
Lishner <i>et al.</i> (1985) [20]	T1: Topical dimethylsulfoxide solution in addition to conventional treatment T2: Conventional treatment T1: ulcer soaked in a foot bath consisted of 500 ml 25% solution of DMSO in normal saline, for 20 min	Design: Non-randomized prospective controlled study, sequential allocation Baseline comparability: inadequately reported Numbers included: T1: 20; T2: 20	Complete healing (closure of ulcer): T1: 14/20 (70%); T2: 2/20 (10%) Partial healing: T1: 4/20 (20%); T2: 5/20 (25%) No change:																				

Table 2 continued

Author	Interventions	Trial detail	Results
	<p>three times a day. When ulcers were infected, 80 mg garamycin was added to the solution. If no healing occurred by the sixth week the concentration of DMSO was raised to 50%. A fresh solution was prepared every 3 days</p> <p>All patients received debridement of ulcers, removal of slough, dry dressing, antibiotics when cellulitis present and were instructed to wear soft shoes. Patients were hospitalized for evaluation and instruction and thereafter received ambulatory care</p>	Loss to follow-up (%): None	<p>T1: 2/20 (10%); T2: 13/20 (65%)</p> <p>Test for trend, $P < 0.001$.</p> <p>DMSO solution was reported to achieve a beneficial analgesic effect in patients with peripheral vascular disease and painful ulcers</p> <p>The 25% solution was reported to be well tolerated but the 50% solution sometimes caused local irritation of skin and a burning sensation requiring cessation of DMSO solution bath for 2–4 days</p>
Muthukumarasamy <i>et al.</i> (1991) [21]	<p>T1: Topical phenytoin</p> <p>T2: Dry sterile occlusive dressing</p> <p>All patients received appropriate antibiotics. All ulcers were debrided and cleansed with saline at baseline and on a daily basis</p>	<p>Design:</p> <p>Non-randomized prospective matched case control study (patients matched by age, sex, duration of ulcer (weeks) and initial ulcer size)</p> <p>Numbers included: T1: 50; T2: 50</p> <p>Loss to follow-up: none</p>	<p>Ulcers assessed on clinical impression scale at Day 35</p> <p>T1: A-0; B-0; C-8; D-22; E-20</p> <p>T1: A-0; B-11; C-15; D-13; E-12</p> <p>A: Detioration, E: Complete healing</p> <p>Percentage wound cultures negative (Day 35):</p> <p>T1: 88%; T2: 60% ($P < 0.005$)</p> <p>Reduction in ulcer area reported significantly better in phenytoin group at day 7 ($P < 0.01$) and days 14–35 ($P < 0.005$)</p> <p>Excess granulation tissue in 18 patients treated with phenytoin was controlled by cessation of treatment.</p> <p>No other adverse reactions were reported</p>
Foster <i>et al.</i> (1994) [23]	<p>T1: Polyurethane foam hydrophilic dressing</p> <p>T2: Calcium-sodium alginate dressing</p> <p>All patients received prophylactic antibiotic treatment. Patients were seen weekly in a diabetic outpatient clinic for assessment and wound debridement</p> <p>T2: Calcium-sodium alginate dressings were moistened with saline before use</p>	<p>Blinding level: not reported</p> <p>Concealment of allocation: not reported</p> <p>Baseline comparability: inadequate detail provided</p> <p>Numbers randomized: T1: 15; T2: 15</p> <p>Loss to follow-up: none</p>	<p>Number of ulcers healed at week 8:</p> <p>T1: 9/15 (60%); T2: 8/15 (53%); $P = NS$</p>
Clever and Dreyer (1996) [24]	<p>T1: Hydroactive polyurethane gel dressing</p> <p>T2: Hydrophilic polyurethane foam dressing</p> <p>All patients received standard treatment: half shoe pressure relief, therapeutic footwear, crutches as necessary, infection control with antibiotics, wound cleansing, debridement and removal of callus as required in a diabetic foot clinic</p>	<p>Blinding level: none reported</p> <p>Concealment of allocation: not reported</p> <p>Baseline comparability: yes, except smoking</p> <p>T1: 9/20; T2: 4/20; $P < 0.01$</p> <p>Numbers randomized: T1: 20; T2: 20</p> <p>Loss to follow-up: T1: 2; T2: 4</p>	<p>Mean time to healing (SD):</p> <p>T1: 25.19 days (23.52) T2: 20.43 days (14.74)</p> <p>Median time to healing (range):</p> <p>T1: 16.5 days (4–76) T2: 15.5 days (4–52)</p> <p>Wound size at 4 weeks (SD):</p> <p>T1: 32.37 mm² (54.12) T2: 33.46 mm² (75.22)</p> <p>No differences between groups were statistically significant</p>

Cultured human dermis

Cultured human dermis (Dermagraft) consists of neonatal dermal fibroblasts cultured *in vitro* onto a bioabsorbable mesh to produce a living, metabolically active tissue, containing normal dermal matrix proteins and cytokines [25]. Two industry-sponsored randomized trials of Dermagraft for the treatment of diabetic foot ulcers were found (see Table 3).

Gentzkow *et al.* [25] randomized 50 patients with chronic ulcers to three different dose regimens of Dermagraft or standard care alone. Over 8 weeks, treatment groups received: 1 one piece of Dermagraft applied weekly; 2 two pieces applied every 2 weeks; or 3 one piece of Dermagraft applied every 2 weeks. Ulcers were full thickness with an area $>1\text{ cm}^2$ at enrolment; assessment was at 12 weeks. Only the first group (one piece of Dermagraft per week) demonstrated healing significantly better than control, although a dose-response effect was apparent. In the first treatment group, 50% of ulcers healed compared to 8% in the control group ($P=0.03$). No adverse reactions to Dermagraft were reported or differences in the rate of infection of the wound between groups.

Naughton *et al.* [26] randomized 281 patients with chronic neuropathic full-thickness foot ulcers in a multi-centre trial comparing Dermagraft and conventional care. Dermagraft was applied every week for 8 weeks in the treatment group, in addition to the conventional therapy. At 12 weeks, ulcer healing had occurred in 38.5% of patients receiving Dermagraft and 31.7% of patients receiving conventional care ($P=0.14$). Differential loss to follow-up occurred (22% from Dermagraft vs. 11% from control), making interpretation of findings problematic, for example, if loss to follow-up was a result of a deteriorating condition, this pattern would inflate the average score achieved by Dermagraft. The study suggests a dose-response effect with patients receiving all grafts doing better than those who did not. However, ability to receive more treatment may simply be correlated with less severe ulceration at baseline.

Although concerns about the trial estimates remain, a meta-analysis of trial results in terms of a risk difference was conducted. Using a random effects model, weekly Dermagraft is estimated to result in a non-significant 21% increase in ulcers healing at 12 weeks (95% CI -13% to 56%).

Casting

A number of casting techniques may be used in the care of diabetic foot ulcers, although only one comparative trial that evaluated total contact casting (TCC) was identified, involving the snug application of a plaster to promote equal distribution of weight over the plantar surface of the foot. The trial randomized 40 diabetic patients with foot ulcers

(without gross infection, osteomyelitis or gangrene) to either TCC or standard treatment (Table 4) [27]. Accommodative footwear was provided to the control group. Both groups were told to reduce weight bearing and follow-up was for 3 months or until ulcer healing occurred. Complete skin closure with no drainage occurred in 19 of 21 patients in the TCC group (90%) and six of 19 in the standard treatment group (32%). The absolute risk reduction was thus 58.9% (95% CI 30.3–78.3%). Mean time to ulcer healing and infections requiring hospitalization also significantly favoured TCC. The preliminary finding from this one small trial suggests further investigation of this intervention is appropriate.

Hyperbaric oxygen therapy

HBO treatment involves immersing the wound in a pure oxygen atmosphere, either with steady or cyclical raised pressure, in a leg chamber or by placing the whole patient in a chamber. A number of possible mechanisms form the rationale for this treatment, including improved oxygen supply promoting the proliferation of granulation tissue (although the case for this comes from studies of ischaemic leg ulcers) and an antibacterial effect on anaerobic organisms. Two randomized trials were identified that evaluated the effectiveness of HBO therapy for diabetic foot ulcers (see Table 5).

Leslie *et al.* [28] randomized 28 patients to HBO treatment (90 min, twice daily for 2 weeks) or to clinical management alone. All patients had well demarcated foot ulcers, without gangrene or other major complications. HBO was topically applied using a leg chamber and cycled pressure (up to 1.04 atmospheres every 20 s). Ulcers in both groups improved significantly, but there were no statistically significant differences between groups at 2 weeks follow-up.

Faglia *et al.* [29] randomized 70 patients to HBO or standard care alone. Patients had full thickness gangrene (Wagner grade IV), abscess (Wagner grade III), or persistent large and infected ulcer (Wagner Grade II). At baseline, the control group had more claudication ($P=0.07$). Treatment group patients sat in a hyperbaric chamber, breathing pure oxygen pressurized at 2.5–2.2 atmospheres in 90 minute daily sessions. The treatment group received an average of 38 sessions and patients were followed until discharge. Major amputation was significantly lower in the treated group (8.6%) than the control group (33.0%) ($P=0.016$). There were no significant differences in minor amputations.

These two small studies have a number of differences that may explain their conflicting results, besides chance. The study by Leslie and colleagues did not involve severe grade ulcers, used topical rather than inhaled oxygen therapy and did not use a substantially raised or sustained

Table 3 Randomized controlled trials of cultured human dermis

Author	Interventions	Trial detail	Results
Gentzkow <i>et al.</i> (1996) [25]	T1: 1 piece of Dermagraft applied weekly for 8 weeks and standard care T2: 2 pieces of Dermagraft applied every two weeks for 8 weeks and standard care T3: 1 piece of Dermagraft applied every 2 weeks for 8 weeks and standard care T4: Standard care: sharp debridement, saline gauze dressing and pressure relief (including high quality therapeutic shoes)	Blinding level: unclear Concealment of allocation: yes: sealed envelopes Baseline comparability; T4 are younger than T1/T2/T3 and have trend of longer mean ulcer duration. Numbers randomized: T1: 12; T2: 14; T3: 11; T4: 13 Loss to follow-up: none	Complete wound closure (week 12): T1: 6/12 (50%); T2: 3/14 (21.4%); T3: 2/11 (18.2%); T4: 1/13 (7.7%); T1 vs. T4: $P=0.0350$ % wound closure (week 12): T1 : 9/12 (75%); T2 : 7/14 (50%); T3: 2/11 (18.2%); T4: 1/13 (7.7%); T1 vs. T4: $P=0.017$
Naughton <i>et al.</i> (1997) [26]	T1: Cultured human dermis and dressing T2: Conventional wound dressing All patients received conventional care: debridement, infection control and special shoes and inserts. T1: Cultured human dermis (Dermagraft) application, weekly, 8 applications in total T2: Saline-moistened gauze dressings	Blinding level: unclear Concealment of allocation: not reported Baseline comparability: not reported Numbers randomized: T1: 139; T2: 142 Loss to follow-up: T1 : 30; T2 : 16	Ulcer healed: T1: 42/109 (38.5%); T2: 40/126 (31.7%); $P=0.138$ Ulcer response was correlated with the number of implants received and significant differences are seen in subgroups who received all or most of their implants compared to the control group. However patients receiving more implants may be the ones with the most favourable prognosis making such analyses unreliable. Differential loss to follow-up makes interpretation of findings problematic. No safety problems were reported and no significant differences were found between Dermagraft and control patients in the occurrence of wound infections

Table 4 Randomized controlled trial of total contact casting

Author	Interventions	Trial detail	Results
Mueller <i>et al.</i> 1989 [27]	<p>T1: Total contact casting</p> <p>T2: Normal dressing and accommodative footwear provision</p> <p>T1: The ulcer was covered with a thin layer of gauze, cotton was placed between the toes to prevent maceration, a stocking applied to lower leg with felt pads, and foam pad placed around toes. The plaster shell was moulded around the lower leg, reinforced with splints and a walking heel was attached to the plantar surface. A fibreglass roll was applied around the plaster for extra durability. Casts were removed after 5–7 days for inspection and if there were no complications the cast was reapplied and changed every 2–3 weeks.</p> <p>T2: Patients received, wet-to-dry dressing, changed 2–3 times daily, by patient, carer or visiting nurse, and were told to avoid weight bearing</p> <p>All patients received routine wound care and debridement</p>	<p>Blinding level: not reported</p> <p>Concealment of allocation: not reported</p> <p>Baseline comparability: yes</p> <p>Numbers randomized: T1: 21; T2: 19</p> <p>Loss to follow-up: none</p>	<p>Ulcer healed:</p> <p>T1: 19/21 (90%) T2: 6/19 (32%); $P < 0.05$</p> <p>Time to ulcer healed, day (SD):</p> <p>T1: 42 (29); T2: 65 (29)</p> <p>Infection requiring hospitalization:</p> <p>T1 0/21 (0%); T2: 5/19 (26%); $P < 0.05$</p> <p>Amputation:</p> <p>T1 0/21 (0%); T2: 2/19 (11%)</p>

Table 5 Randomized controlled trial of hyperbaric oxygen therapy

Author	Interventions	Trial detail	Results
Leslie <i>et al.</i> (1988) [28]	T1: Topical hyperbaric oxygen T2: No HBO T1: HBO was administered in two daily 90 min sessions with a topical hyperbaric bed chamber which provided humidified 100% oxygen at pressures cycling between 0 and 30 mmHg every 20 s	Blinding level: none apparent Concealment of allocation: yes Baseline comparability: yes Numbers randomized: T1: 12; T2: 16 Loss to follow-up: T2: 1	Ulcer area (% of baseline, \pm SD) at day 7: T1: 67.1 ± 18.3 ; T2: 69.6 ± 34.5 ; $P = \text{NS}$ Ulcer area (% of baseline, \pm SD) at day 14: T1: 45.6 ± 23.4 ; T2: 35.6 ± 23 ; $P = \text{NS}$ Changes in ulcer depth, in a subgroup of patients who could be assessed, revealed no statistically significant differences between treatment groups
Faglia <i>et al.</i> (1996) [29]	T1: Hyperbaric oxygen and usual care T2: Usual care T1: Patients sat in a hyperbaric chamber breathing pure oxygen in 90 minute sessions, daily and pressurized at 2.5 atmospheres in the acute phase, reducing to weekly and 2.2–2.4 atmospheres in the reparative phase. T2: Standard therapy: aggressive multidisciplinary therapeutic protocol. Patients received radical debridement by a consultant surgeon, antibiotic therapy and were provided with orthopaedic devices to remove mechanical stress and pressure at the site of the ulcer while maintaining ambulation. The orthosis were made up of Alkaform insole moulded in plaster cast and an extra deep special shoe with a rigid sole	Blinding level: evaluator blinded Concealment of allocation: not stated Baseline comparability: yes Numbers randomized: T1: 36; T2: 34 Loss to follow-up: T1: 1; T2: 1	Transcutaneous oxygen tension (mmHg \pm SD): T1: 14.0 ± 11.8 ; T2: 5.0 ± 5.4 ; $P = 0.0002$ Major amputation: T1: 3/35 (8.6%); T2: 11/33 (33.3%); $P = 0.016$ Minor amputation: T1: 21/35 (60%); T2: 12/33 (36%) No amputation: T1: 11/35 (31%); T2: 10/33 (30%); $P = \text{NS}$ Two patients showed symptoms of barotraumatic otitis which did not interrupt treatment

pressure. It is unclear whether any of these aspects may be important in achieving benefit from HBO therapy.

The results of Faglia *et al.* [29], achieved in severely ulcerated feet, merit further research. Such investigation should include cost-effectiveness analysis at the outset, since access to a hyperbaric chamber may be problematic and costs of developing such facilities may prove prohibitive.

Ketanserin

Ketanserin is a 5HT₂ serotonergic receptor antagonist, reported to inhibit platelet aggregation, block vasoconstriction, improve tissue perfusion and increase granulation tissue formation. It can be administered orally or topically. Two randomized trials that have evaluated ketanserin in diabetic foot ulcers were identified (see Table 6).

Apelqvist *et al.* [30] randomized 45 patients to oral ketanserin or placebo. Patients enrolled had a deep or superficial ulcer with an area of 1 cm² or more, and a systolic toe pressure below 45 mmHg. At 3 months, no statistically significant difference was found in wound healing (defined as either intact skin or 50% wound reduction in ulcer size).

Martinez-de Jesus *et al.* [31] randomized 140 diabetic patients with neuropathic foot ulcers (< 100 cm², Wagner grade II or III) to topically applied ketanserin (2%) ointment or (unmatched) normal saline. By 2 weeks, 21 patients (13%) had withdrawn and are not included in the findings: it is unclear whether dropout was equivalent between groups. At 12 weeks, the average percentage reduction in ulcer area was 87.0% for ketanserin and 62.8% for placebo ($P < 0.001$): this equated to average daily reductions in ulcer areas of 4.5 mm²/day and 2.88 mm²/day, respectively.

These trials report different endpoints, making comparison between studies problematic. The respective bioavailabilities of topical or oral ketanserin are not clear. The (relatively) large study by Martinez-de Jesus *et al.* [31] implies a clinically important benefit from topically applied ketanserin when used in addition to comprehensive care in relatively severe ulcers but requires further confirmatory evaluation.

Growth factors

Growth factors are applied directly to the wound surface with the intention of stimulating cellular movement, replication and matrix synthesis, leading to healing in chronic non-healing wounds. Six randomized controlled trials were found, in which four types of growth factor have been used in the treatment of diabetic foot ulcers (Table 7). CT-102 is derived from a thrombin-induced human platelet process; rhPDGF is a recombinant platelet derived

growth factor; rbFGF is a recombinant basic fibroblast growth factor using *Escherichia coli* type β ; and RGDpm is an arginine-glycine-aspartic acid peptide matrix. All studies, bar one, were conducted in the USA, all were conducted double-blind and all required patients to have adequate arterial blood supply (most commonly transcutaneous oxygen tension ≥ 4 kPa (30 mmHg)).

Steed *et al.* [32] randomized 13 patients to receive CT-102 (dilution 0.01, applied twice daily with dressing change) or matched placebo (normal saline). Patients had diabetic neuropathic ulcers of greater than 8 weeks duration, no wound infection and agreed to be totally non-weight-bearing. In the CT-102 group, five of seven ulcers were healed at 20 weeks compared with only one of six in the placebo group ($P < 0.05$). Average reduction in area was 94% for CT-102 compared with 73% for placebo. Adverse events were not reported.

Holloway [33] randomized 97 patients to three different dilutions of CT-102 (0.1, 0.033 and 0.01) or matched placebo (normal saline solution or isotonic platelet buffer) in a multicentre trial. Twenty-seven patients were removed from the analysis owing to protocol violation, 11 after randomization. Wounds were chronic, diabetic non-healing ulcers of at least 8 weeks duration. The best results were seen at the lowest dilution: 80% of wounds treated at a dilution of 0.01 CT-102 healed vs. 29% in the placebo group ($P = 0.01$). However, this group contributed six of the 11 randomized patients removed from the analysis. The mean volume reduction for CT-102 (all dilutions) was 94.9% vs. 82.7% in the placebo group ($P = 0.005$) and this showed no significant variation by dilution. A similar finding occurred in ulcer area reduction. No differences in adverse events were reported between groups.

In a multicentre trial, Steed *et al.* [34] randomized 65 patients, with chronic full-thickness neuropathic foot ulcers, to RGDpm (Argidene) or placebo (normal saline). RGDpm was applied topically twice weekly for up to 10 weeks in patients who otherwise received conventional care, including twice weekly clinics. At baseline, ulcers were of at least 1-month duration, penetrating the skin without exposing the bone or tendon and free of infection. At 10 weeks, the percentage of patients whose ulcers had completely healed was significantly greater in the RGDpm group, 35% vs. 8% in the control group ($P = 0.02$). A significantly greater proportion had achieved greater than 50% ulcer closure (75% RGDpm vs., 48% placebo, $P = 0.03$). No significant difference in adverse events between groups was observed.

In a French pilot study, Richard *et al.* [35] randomized 17 patients suffering from chronic neuropathic foot ulcers of Wagner grade I–III without infection to receive rbFGF or placebo (normal saline) daily for 6 weeks and then twice weekly for 12 weeks. After 18 weeks, three of nine ulcers healed with rbFGF and five of eight in the placebo group ($P = \text{NS}$). There was no significant change rate of healing of

Table 6 Randomized controlled trials of ketanserin

Author	Interventions	Trial detail	Results
Apelqvist <i>et al.</i> (1990) [30]	T1: Oral ketanserin T2: Placebo All patients received a 2-week placebo run in. Check up visits occurred at monthly intervals. Antibiotics were used in response to infection, footwear were corrected and surgical debridement provided where required T1: oral ketanserin (20 mg three times daily for 1 month then 40 mg three times daily for 2 months)	Blinding level: double blind Concealment of allocation: not reported Baseline comparability: yes, except hypertension more common in ketanserin group ($P < 0.05$) and systolic arm pressure lower in ketanserin group ($P < 0.05$) Numbers randomized: T1 = 20; T2 = 20 Loss to follow-up: none (5 lost in run in period)	Ulcer healed: T1: 7/20 (35%); T2: 5/20 (25%) Improved (wound size decreased by 50% or more): T1: 4/20 (20%); T2: 2/20 (10%) No improvement/deterioration: T1: 6/20 (30%); T2: 6/20 (30%) Gangrene (*amputated): T1: 2/20 (10%) (2*); T2: 6/20 (30%) (4*) Deceased: T1: 1/20 (5%); T2: 1/20 (5%) No comparisons were statistically significant
Martinez-De Jesus <i>et al.</i> (1997) [31]	T1: Topical ketanserin (2%) ointment T2: Placebo (unmatched, saline) All patients were hospitalized for debridement, systemic antibiotic treatment, foot rest and correction of fasting hyperglycaemia caused by sepsis. Patients received outpatient care after discharge	Blinding level: single (patient blinded) Concealment of allocation: no, sequential allocation Baseline comparability: yes, except smoking: more common in the ketanserin group ($P = 0.043$) Numbers randomized: T1 + T2: 161 Loss to follow-up: T1 + T2: 21	Mean reduction in ulcer area (%): T1: 87%; T2: 62.8%; $P < 0.001$ Average daily reductions in ulcer area (mm ² /day): T1: 4.5; T2: 2.88 No adverse effects were detected. Numbers analysed: T1: 69; T2: 71. 21 subjects had left the study by 2 weeks and are not included although it is unreported as to which treatment these were randomized

percentage of area healed at 18 weeks. No drug-related adverse events were observed.

Steed *et al.* [36] randomized 118 patients, to receive rhPDGF (Becaplermin 30 µg/g) once daily or placebo in a multicentre trial. All patients had chronic neuropathic foot ulcers free of infection, attended as outpatients and were followed for 20 weeks, or until healing. After 20 weeks, 48% of ulcers healed with rhPDGF compared with 25% in the placebo group ($P=0.01$). The treatment effect was consistent across centres. Adverse events were not reported.

Wieman *et al.* [37] randomized 382 patients to receive either 100 µg/g or 30 µg/g rhPDGF (Becaplermin) once daily, or placebo, in a multicentre trial. All patients had chronic neuropathic foot ulcers free of infection, attended as outpatients and were followed for 20 weeks, or until healing. After 20 weeks, 50% of ulcers healed with 100 µg/g rhPDGF compared with 35% in the placebo group, $P=0.007$. No differences in outcome were found between 30 µg/g rhPDGF and placebo groups. Variation of treatment effect across centres was not reported. No differences in adverse events or withdrawals were observed between groups. This study found no benefit for 30 µg/g rhPDGF, contrasting with Steed *et al.* [34]. The investigators suggest this difference may be a result of better infection control and the use of a relatively small number of experienced centres for treatment in the study reported by Steed *et al.* [36].

The available trials of growth factors suggest potentially important benefits from three applied growth factor in addition to conventional care: CT-102 (dilution 0.01), RGDpm and rhPDGF. On the basis of one small pilot study, there is no evidence for the use of rbFGF. When reported, growth factors appear well tolerated, with no drug-related side-effects. These findings need confirmation from further trials, including assessment of cost-effectiveness.

Granulocyte-colony stimulating factor

G-CSF increases both the production and release of neutrophils from the bone marrow, enhancing the ability to fight infection in the blood. Recombinant G-CSF has been shown to reduce neutropenia in vulnerable patients undergoing chemotherapy treatment for a number of cancers, thus lessening infections and their sequelae. While people with diabetes are not neutropenic, diabetes is said to represent an immunocompromised state because of neutrophil dysfunction secondary to hyperglycaemia. It is hypothesized that improved neutrophil production and function will also improve bactericidal activity in foot ulcer [38].

Gough *et al.* [38] randomized 40 diabetic patients with foot infections featuring extensive cellulitis to intravenous G-CSF (Filgrastim) or placebo for 7 days (Table 8). All

patients received antibiotic therapy until resolution. There was a statistically significant reduction in median time to hospital discharge, resolution of cellulitis, withdrawal of intravenous antibiotics and negative swab culture for patients receiving G-CSF. At day 7, cellulitis had resolved in 55% of patients on G-CSF and 20% on placebo ($P=0.05$), and healing had occurred in 21% of patients on G-CSF and 0% on placebo ($P=0.09$).

This initial result indicates that G-CSF treatment should receive more extensive evaluation. Filgrastim is expensive. Using the median reported dose, seven days of treatment in British primary care costs approximately £540 to purchase per patient (British National Formulary [22]). Nevertheless, the apparently significant reductions in the use of other health care resources mean that the cost-effectiveness of G-CSF intervention for foot infection should be explored formally.

Education of patients with foot ulcers

One American randomized trial of an educational intervention was retrieved, involving 203 diabetic patients with either uninfected ulcers or previous amputation [39]. In addition to usual care, the intervention group received a single 1-h education session on foot care which included a slide-show of infected feet and amputated limbs and a patient instruction checklist (Table 9). Follow-up was longer in the intervention than in the control group (mean follow-up 13.2 and 9.2 months, respectively).

The study showed a reduction in the combined endpoint of limbs free of infection, ulcer or amputation, favouring education (education 90%, control 72%). Although there were no significant differences in infection or mortality during follow-up, there was an excess of ulceration (education 5%, control 15%) and amputation (education 4%, control 12%) in the control group. Statistical calculations assumed 'independence' of limbs. Since the outcomes for ulcers belonging to individual patients may be correlated, this may result in over-precision.

The educational intervention contains a 'scare-tactic' component and it is unclear whether this approach is generalizable. Nonetheless, the reduction in morbidity at approximately 1-year is impressive and the method merits evaluation in other contexts.

Discussion

With a few notable exceptions, trials reported in this review are characterized by small patient numbers, inadequate reporting of methods and a lack of repetition of any one method or a common approach to measurement. To illustrate this point, suppose a 50% relative improvement in an outcome is considered worthwhile (i.e. a new treatment achieving 60% success at some endpoint instead of 40%). In order that a trial be adequately

Table 7 Randomized controlled trials of growth factors

Author	Interventions	Trial detail	Results
Steed <i>et al.</i> (1992) [32]	T1: Topical CT-102 Solution (0.1 dilution) T2: Placebo. (matched) All patients agree to be totally nonweight-bearing, were provided with a half-shoe, wheelchair crutches or walker. Patients were evaluated as outpatients weekly then fortnightly. Dressings were changed twice daily by patient or carer. CT-102, platelet derived wound healing formula, was applied twice daily with dressing change or matched placebo (normal saline) Aggressive debridement was performed at baseline. Normal saline cotton gauze dressings were used throughout the study	Blinding level: double blind Concealment of allocation: not recorded Baseline comparability: yes, except duration of diabetes greater in T1 group ($P=0.001$) Numbers randomized: T1 = 7; T2 = 6 Loss to follow-up: None	Ulcer healing: T1: 5/7 (71%); T2: 1/6 (17%) Percentage reduction in ulcer area: T1: 94%; T2: 73%; $P < 0.02$ Daily reduction in ulcer volume, mean (SE) mm ³ /day: T1: 73.8 (42.4); T2: 21.8 (8.1); $P < 0.05$ Daily reduction in ulcer area, mean (SE) mm ² /day: T1: 6.2 (1.8); T2: 1.8 (0.4); ($P < 0.05$)
Holloway <i>et al.</i> (1993) [33]	T1: Topical CT-102 Solution (0.1 dilution) T2: Topical CT-102 Solution (0.033 dilution) T3: Topical CT-102 Solution (0.01 dilution) T4: Placebo. (matched) All patients underwent debridement of necrotic, infected or bony tissue at entry, then subsequent debridement of callus and necrotic tissue as required, and were seen weekly for two weeks and then biweekly	Blinding level: double blind Concealment of allocation: not clear, a computer generated list was used Baseline comparability: yes Numbers randomized: 81 in total Loss to follow-up: T1: 1; T2: 3; T3: 6; T4: 1	Wound healing: T1: 11/21 (52%); T2: 8/13 (62%); T3: 12/15 (80%); T4: 6/21 (29%), T1 vs. T4: $P = 0.01$ Mean (SD) area reduction (at 20 weeks or last visit): T1 + T2 + T3: 93.0 (14.4)%; T4: 77.1 (25.7%); $P = 0.002$ (T1: 96.0%; T2: 90.7%; T3: 96.9%) Mean (sd) volume reduction (at 20 weeks or last visit): T1 + T2 + T3: 94.9 (12.0)%; T4: 82.7 (21.5)%; $P = 0.005$ (T1: 94.3%; T2: 87.8%; T3: 95.7%) No differences in adverse events were reported between groups.
Steed <i>et al.</i> (1995) [34]	T1: Topical RGDpm viscous solution T2: Placebo (not matched for viscosity) T1: Arginine-glycine-aspartic acid peptide matrix (RGDpm) was applied topically twice weekly, by syringe, with dressing change and debridement (if necessary) at a clinic visit for up to 10 weeks T2: Patients received matched care but without RGDpm All patients were given shoes and shoe inserts at the first visit	Blinding level: double blind Concealment of allocation: no, prearranged randomization order Baseline comparability: yes Numbers randomized: T1: 40; T2: 25 Loss to follow-up: none	Wound healing: T1: 14/40 (35%); T2: 2/25 (8%); $P = 0.02$ Ulcer: > 50% closure by 10 weeks: T1: 75%; T2: 48%; $P = 0.03$ There was no statistically significant relationship between treatment and adverse events

Table 7 continued

Author	Interventions	Trial detail	Results
Richard <i>et al.</i> (1995) [35]	T1: Topical rbFGF solution (as spray) T2: Placebo (matched) T1: Topical recombinant basic Fibroblast Growth Factor, as solution 5 µg/mL, applied once daily on an inpatient basis for 6 weeks and then twice weekly for 12 weeks (at home if appropriate) A spray device was used once or twice for each treatment, delivering 50 µl per use	Blinding level: double blind Concealment of allocation: not reported Baseline comparability: Yes Numbers randomized: T1 = 9; T2 = 8 Loss to follow-up: none	Complete healing: T1: 3/9 (33%); T2: 5/8 (63%); $P = 0.23$
Steed <i>et al.</i> (1996) [36]	T2: Topical 30 µg/g rhPDGF gel T2: Placebo (matched) All patients received sharp debridement or ulcers at baseline and subsequent debridement of callus and necrotic tissue as required. Treatment occurred at 10 centres although the five smallest are pooled together T1: patients received topical recombinant human platelet-derived growth factor (rhPDGF – becaplermin) gel. Details of frequency and duration of use are not recorded. Gel dose is not recorded in the paper but Wieman <i>et al.</i> (1998) report it as 30 µg/g	Blinding level: double blind Concealment of allocation: yes Baseline comparability: apparently, inadequate detail Numbers randomized: T1 + T2 = 118 Loss to follow-up: not reported	Ulcer healing (100% ulcer closure, with target ulcer epithelialization): T1: 48%; T2: 25%; $P = 0.01$ Data are reported as percentages and it is not possible to assess the validity of the analysis or statistic
Wiemann 1998 [37]	T1: Topical 100 µg/g or rhPDGF gel T2: Topical 30 µg/g rhPDGF gel T3: Placebo (matched) All patients received sharp debridement or ulcers at baseline and subsequent debridement of callus and necrotic tissue as required T1/T2: patients received topical recombinant human platelet-derived growth factor (rhPDGF – becaplermin) gel. Gel was applied once daily at dressing change until healing	Blinding level: double blind Concealment of allocation: yes Baseline comparability: yes Numbers randomized: T1: 124; T2: 132; T3: 127 Loss to follow-up T1; 2; T2: 1; T3: 1	Ulcer healing: T1: 61/123 (50%); T2: 48/132 (36%); T3: 44/127 (35%); T1 vs. T3: $P = 0.007$ Time to healing (35th percentile): T1: 86 days; T3: 127 days; T1 vs. T3: $P = 0.013$ No differences in outcome were found between 30 µg/g rhPDGF and placebo groups. Variations of treatment effect across centres were not reported No differences in adverse events or withdrawals were observed between groups

Table 8 Randomized controlled trial of granulocyte-colony stimulating factor

Author	Interventions	Trial detail	Results
Gough <i>et al.</i> 1988 [38]	<p>T1: intravenous granulocyte-colony stimulating factor (G-CSF, filgrastim)</p> <p>T2: Placebo</p> <p>T1: G-CSF was administered as a daily subcutaneous injection for 7 days. The initial dose was 5 µg/kg daily reducing to 2.5 µg/kg if absolute neutrophil count exceeded $2.5 \times 10^9/l$</p> <p>All patients received combination i.v. antibiotic therapy until cellulitis and discharge had resolved. Glycaemic control was optimized. Foam dressings were used throughout</p> <p>12 patients in each group had evidence of osteomyelitis at randomization</p>	<p>Blinding level: double blind</p> <p>Concealment of allocation: not reported</p> <p>Baseline comparability: yes</p> <p>Numbers randomized: T1: 20; T2: 20</p> <p>Loss to follow-up: none</p>	<p>Time to hospital discharge, median (days): T1: 10; T2: 17.5; $P=0.02$</p> <p>Time to resolution of cellulitis, median (days): T1: 7; T2: 12; $P=0.03$</p> <p>Time to cessation of i.v. antibiotics, median (days): T1: 8.5; T2: 14.5; $P=0.02$</p> <p>Time to negative swab culture, median (days): T1: 4; T2: 8; $P=0.03$</p> <p>Surgery (debridement under general anesthetic of amputation): T1: 0/20; T2: 4/20; $P=0.114$</p> <p>Cellulitis resolved at day 7</p> <p>T1: 11/20; T2: 4/20; $P=0.05$</p> <p>Ulcer healed at day 7:</p> <p>T1: 4/19; placebo 0/20; $P=0.09$</p> <p>No patients were withdrawn due to side-effects; 3 G-CSF patients experienced transient bone pain not requiring analgesia</p>

Table 9 Randomized controlled trial of education of patients with foot ulcers

Author	Interventions	Trial detail	Results
Malone <i>et al.</i> 1989 [39]	<p>INT: One education session (foot care) in addition to usual care</p> <p>CON: Usual care</p> <p>CON: hospital diabetic patients received routine diabetic teaching on diet, weight, exercise and medication</p> <p>INT: patients received a 1-h educational class which included a slide-show of infected feet and amputated limbs and patient instruction checklist</p>	<p>Blinding level: none apparent</p> <p>Concealment of allocation: yes (based on odd/even last digit of Social Security number)</p> <p>Baseline comparability: yes, except INT: foot callus more common</p> <p>Numbers randomized: INT: 103 (203 limbs); CON: 100 (193 limbs)</p> <p>Loss to follow-up: (limbs): INT: 26; CON: 16</p>	<p><i>Clinically assessed at 2 years</i></p> <p>Limbs without infection, ulcer or amputation: INT: 160/177 (90%); CON: 128/177 (72%); $P \leq 10.0005$</p> <p>Infected limbs: INT: 2/177 (1%); CON: 2/177 (1%); $P = NS$</p> <p>Ulcerated limbs: INT: 8/177 (5%); CON: 26/177 (15%); $P \leq 0.005$</p> <p>Amputated limbs: INT: 7/177 (4%); CON: 21/177 (12%); $P \leq 0.025$</p> <p>Mortality: INT: 3%; CON: 4%; $P = NS$</p> <p>Statistical calculations assume ‘independence’ of limbs</p>

powered to detect this improvement (with an 80% chance of correctly detecting a real effect and with a 5% chance of incorrectly rejecting a null hypothesis of no effect) would require randomizing approximately 100 patients to each treatment arm. Seldom do investigators give a rationale for their sample size or for the difference between treatments they expect to find. Few trials randomized 50 or more patients to each treatment arm.

Many trials have the characteristics of pilot studies and so are unsuited to inform treatment policy. They are rather a guide to an agenda for further research. Trials are generally industry funded and the motivation for their conduct cannot be ignored. Where one or two small, single centre studies exist, previous experience has indicated that the value of treatments can be substantially misrepresented as a result of publication bias, where interesting, but chance, results reach the public domain.

A further problem in interpreting trials arises from unsatisfactory classification and enrolment of patients into studies. Treatments may be expected to achieve variable effects for cellulitis of different extent and appearance, e.g. localized cellulitis around an ulcer, ulcers with relatively little cellulitis but underlying osteomyelitis, and those with considerable cellulitis. Similarly, there needs to be strict control of the severity of peripheral vascular disease. It may be valuable, when trying to understand the influence of a particular treatment on disease, to conduct studies on much better defined ulcer types. A common aspect of trials, in both treatment and control groups, is radical debridement and cleansing of wounds. This alone seems to be influential in facilitating ulcer healing and may be synergistic in effect with other treatments (see for example Steed *et al.* [36]),

Available trials of antibiotics for infected foot ulcers are uninformative. No robust evidence of the relative effectiveness or cost-effectiveness of any dressing has emerged, despite the received wisdom regarding newer dressing types. The role of cultured human dermis, G-CSF, growth factors, HBO therapy, ketanserin, and TCC can neither be ruled in nor out on the basis of available evidence, although some of these technologies show considerable promise. Caution is appropriate, since the medical literature contains many examples of auspicious early findings from trials refuted by definitive studies.

The treatment of diabetic ulcers appears to be a 'Cinderella' research area. Currently available and new treatments appear in need of a comprehensive and co-ordinated trial programme if both the morbidity arising from diabetic foot ulcers and the ambitions of the St Vincent Declaration [40] are to be tackled in earnest.

Acknowledgements

This systematic review was conducted for the purpose of developing a National Evidence-Based Clinical Guideline.

The authors are grateful to members of the foot care working group, not co-authoring this paper, who contributed to the interpretation of the evidence: Andrew Boulton, Sheila Clarkson, Alethea Foster, and Mary Pierce. Any errors remain the responsibility of the authors.

The authors are grateful for access to an early draft of a systematic review conducted jointly by NHS Centre for Reviews and Dissemination and the Department of Health Studies at the University of York, which assisted in the identification of studies.

Funding for this work was provided by the NHS Executive and the British Diabetic Association.

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