

Clinical Guidelines for  
**Type 2 Diabetes**

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(Please note these are available as two separate files: appendices 1–10 and appendices 11–26)

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## Note on nomenclature

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Throughout the guideline documents we have used the classifications recommended by the American Diabetes Association (ADA) and the World Health Organisation (WHO). This classification defines Type 2 diabetes as: disease of adult onset, which may originate from insulin resistance and relative insulin deficiency or from a secretory defect.

Where journal papers and other works are discussed, the nomenclature that they have used has been left unchanged. Therefore some papers cited in these guidelines refer to non-insulin dependent diabetes (NIDDM) and insulin dependent diabetes (IDDM).

## Neuropathic pain

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This guideline does not address the issue of neuropathic pain in people with diabetes. It is hoped that future guidelines on pain management will address this issue.

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# 1. Key messages

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## **General management approach**

- ◆ Effective care involves a partnership between patients and professionals and all decision making should be shared.
- ◆ Arrange recall and annual review as part of ongoing care.
- ◆ As part of annual review, trained personnel should examine patients' feet to detect risk factors for ulceration.
- ◆ Examination of patients' feet should include:
  - ◆ testing of foot sensation using a 10 g monofilament or vibration
  - ◆ palpation of foot pulses
  - ◆ inspection for any foot deformity and footwear
- ◆ Classify foot risk as: **at low current risk; at increased risk; at high risk; ulcerated foot**

## **Care of people at low current risk of foot ulcers** (normal sensation, palpable pulses)

- ◆ Agree a management plan including foot care education with each person.

## **Care of people at increased risk of foot ulcers** (neuropathy or absent pulses or other risk factor)

- ◆ Arrange regular review, 3–6 monthly, by foot protection team
- ◆ At each review:
  - ◆ inspect patient's feet
  - ◆ consider need for vascular assessment
  - ◆ evaluate footwear
  - ◆ enhance foot care education.

NB If patient has had previous foot ulcer or deformity or skin changes manage as *high risk* (see below)

## **Care of people at high risk of foot ulcers** (neuropathy or absent pulses + deformity or skin changes or previous ulcer)

- ◆ Arrange frequent review (1–3 monthly) by foot protection team
- ◆ At each review,
  - ◆ inspect patient's feet
  - ◆ consider need for vascular assessment
  - ◆ evaluate and ensure the appropriate provision of
    - ◆ intensified foot care education
    - ◆ specialist footwear and insoles
    - ◆ skin and nail care
- ◆ Ensure special arrangements for access to the foot protection team for those people with disabilities or immobility. (D)

## **Care of people with foot care emergencies and foot ulcers**

- ◆ Foot care emergency (new ulceration, swelling, discolouration)
  - ◆ refer to multidisciplinary foot care team within 24 hours.
- ◆ Expect that team, as a minimum, to:
  - ◆ investigate and treat vascular insufficiency
  - ◆ initiate and supervise wound management
    - ◆ use dressings and debridement as indicated;
    - ◆ use systemic antibiotic therapy for cellulitis or bone infection as indicated
  - ◆ ensure an effective means of distributing foot pressures, including specialist footwear, orthotics and casts

- ◆ try to achieve optimal glucose levels and control of risk factors for cardiovascular disease

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## 2. Guideline development

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## Introduction

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This clinical guideline is an update of the Type 2 diabetes foot care clinical guidelines published by the Royal College of General Practitioners (RCGP) in 2000 (Hutchinson et al 2000). Full details of the methods used in the development of the original guideline are found within the full guideline document ([www.sheffield.ac.uk/guidelines](http://www.sheffield.ac.uk/guidelines) and [www.rcgp.org.uk](http://www.rcgp.org.uk)).

Since publication of the original guideline, the National Institute for Clinical Excellence (NICE) has been established and the methods used in this revised guideline are those employed in NICE guideline development (see NICE guideline development manuals, available at [www.nice.org.uk](http://www.nice.org.uk)).

The aim of the guideline is to provide recommendations to help health care professionals in their management of people with Type 2 diabetes. The guideline is aimed at all health care professionals providing care to people with diagnosed Type 2 diabetes in primary and secondary care, irrespective of location. Depending on the type, stage and severity of clinical problem, the guidelines may also be valuable to those who work in the tertiary sector of diabetes care.

The guideline aims to cover the foot care and management of people with diagnosed Type 2 diabetes. It does not cover people who have not been diagnosed as having Type 2 diabetes, for example those in a pre-diabetic state or people with impaired glucose tolerance.

Key features of the guideline are that:

- it is evidence based, where evidence is available
- in areas where evidence is lacking this is made clear, and the consensus methods used are clearly described
- recommendations are explicitly linked to evidence where it is available
- the recommendations, methods and conclusions in the guideline are explicit and transparent.

## Using guidelines

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Guidelines are only one type of information that health care professionals may use when making decisions about patient care. It is assumed that this guideline, like all guidelines, will be used by health care professionals who will also bring to bear their clinical knowledge and judgement in making decisions about caring for individual patients. It may not always be appropriate to apply either specific recommendations or the general messages in this document to each individual or in every circumstance.

## Responsibility and support for the guideline

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The guideline update was commissioned by NICE. The development of the guideline was undertaken by SchARR, a provider partner in the National Collaborating Centre for Primary Care (NCC-PC). The guideline development group (GDG) was convened by the NCC-PC. The GDG

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comprised both members from the original development group and new members. Two service users were identified via Diabetes UK. The guideline development group consisted of relevant health care professionals, patient representatives and guideline developers, including a systematic reviewer. The membership of guideline development group is shown in Appendix 20.

## Scope of the foot care guideline

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The scope of this revised guideline was in essence that of the original guideline, which was the detection, management and treatment of the “at-risk foot”. It does not however cover areas such as salvage treatments (including surgery). As part of the revision process the scope was subjected to a consultation exercise as with all new NICE guidelines. The only major change was the inclusion of Charcot osteoarthropathy. The scope of this revised guideline can be found in Appendix 21.

The key clinical questions that the group considered in the revision process remained therefore those of the original guideline.

The guideline is therefore concerned with:

- **Care of the diabetic foot without complications**
  - organisation between primary and secondary care
  - the role of health care professionals
  - patient education
- **The foot at raised risk of complications**
  - definition
  - identification
  - prevention of complications
  - patient education
- **The ulcerated foot**
  - diagnosis
  - treatment
  - patient education
- **Charcot osteoarthropathy**

In the original guideline the development group derived a foot care clinical pathway to help them identify and consider the key clinical questions that needed to be addressed by the guideline. This is shown in Appendix 22.

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## Economic analysis

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### Review of existing economic studies.

Both the original guideline and this revision searched for existing papers that were economic studies. Additionally any cost, or cost-effectiveness information included in any paper was considered. The original guideline included a systematic appraisal of available evidence of effectiveness, compliance, safety and health service resource use and costs of medical care for foot complications in Type 2 diabetes. Following the review, economic analyses attempted a robust presentation showing the possible bounds of cost-effectiveness that may result. The range of values used to generate low and high cost-effectiveness estimates reflected available evidence and the concerns of the original development group. In this revision any additional economic studies were identified and included.

### Undertaking of own economic studies.

Additional economic analyses (including modelling) were not undertaken due to the lack of available, robust information about the areas of potential interest.

### Estimating the cost impact of the guide

The remit of the guidelines does not include any cost impact analyses, therefore none were undertaken.

## Evidence identification

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### **Literature searching**

Searching was undertaken to identify research evidence that had become available since the time of the original guideline. Searches were limited to 1996-2002/3 and to English language papers. No study or publication type restrictions were applied.

The following electronic databases were searched, for the period 1996 until the time of the searches (October 2002 and March 2003 [for Charcot osteoarthopathy]).

- Cochrane Collaboration Trials Register (CCTR)
- Cochrane Database of Systematic Reviews (CDSR)
- Cinahl
- DARE
- Embase
- HTA database
- Medline
- NHS EED
- PreMedline
- PsycINFO
- Science Citation Index
- Social Sciences Citation Index

The following internet resources were also searched, for the period 1996 until the time of the searches.

- Development and Evaluation Committees (e.g. Trent Working Group on Acute Purchasing)
- National Guideline Clearinghouse
- National Research Register
- NICE
- SIGN
- TRIP database

## Sifting and reviewing the evidence

Studies were considered for inclusion if they addressed some aspect of screening, management, care, prevention or education relating to the foot care of people with diabetes. In each area considered, the best evidence available was used. For interventions, we only considered systematic reviews or meta-analyses of randomised controlled trials, or randomised controlled trials.

Studies which addressed Type 1 as well as Type 2 diabetes were included since, although their aetiology is different, their management is almost identical. Most of the evidence is presented as a qualitative overview (narrative) as it was not possible (on the whole) to undertake and present a meta-analysis of studies.

## Evidence grading

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Studies retrieved were assessed for relevance in terms of helping answer the key clinical questions. Once a paper was assessed as being relevant it was then assessed for methodological quality.

For studies where our concern is that of what intervention seems to be most effective, then in our assessment of those studies our key concern was the quality of the study in terms of the various aspects of study validity. Firstly, if a study can credibly demonstrate the causal relationship between treatment and outcome then it can be said to have internal validity. Secondly, if the findings can be generalised from the specific study sample to a wider population then it is said to be generalisable or to have external validity. Thirdly, if the study actually measures what it says it measures then it is said to have construct validity.

Once individual papers had been assessed for methodological quality and relevance in terms of our key clinical questions, they were graded according to the levels of evidence. We have used the following grading which differentiates in level I between meta-analyses and RCTs and in level II different types of experimental design. These distinctions are not used by NICE (where Ia and Ib are not differentiated nor are IIa or IIb).

## Classification of Evidence

Evidence level	Description
<b>Ia:</b>	evidence from meta-analysis of randomised controlled trials
<b>Ib:</b>	evidence from at least one randomised controlled trial
<b>IIa:</b>	evidence from at least one controlled study without randomisation
<b>IIb:</b>	evidence from at least one other type of quasi-experimental study
<b>III:</b>	evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
<b>IV:</b>	evidence from expert committee reports or opinions and/or clinical experience of respected authorities

This classification is most appropriate for questions of causal relationships, and is usually used to assign studies, dealing with causal relationships, to levels of evidence. In some areas of management, studies looking at causation may not be available or may not be the appropriate study type. Therefore different types of study design will also have been assessed for quality and graded according to the classification outlined, even though the classification is most appropriate for causal relationship studies.

## Incorporation of new evidence

The newly identified and accepted research evidence was incorporated into the existing evidence review, undertaken for the development of the original guideline. This was identified as being new material for the guideline development group. The guideline development group therefore considered the entire body of evidence, that previously identified and that newly identified in their discussions.

## Derivation and grading of recommendations

The derivation of recommendations usually involves assessment of evidence, processes of interpretation and consensus to arrive at recommendations. The mix of evidence, interpretation and consensus will vary between topic areas. The grading of recommendations takes account of this and therefore variation may occur between different groups presented with the same evidence. Whilst evidence statements can be formulated without reference to the context in which clinicians practise, this is not always the case with recommendations.

Recommendations were graded A to D, as shown below.

## Grading of Recommendations

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- A** directly based on category I evidence
  - B** directly based on category II evidence, or extrapolated recommendation from category I evidence
  - C** directly based on category III evidence, or extrapolated recommendation from category I or II evidence
  - D** directly based on category IV evidence, or extrapolated recommendation from category I, II or III evidence
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## Areas without consensus

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There may be areas where the group was unable to reach consensus on an area, no matter whether evidence is available or not. Where this has happened there is scope to report that a consensual recommendation could not be reached, to present the opposing views, and leaving the final view to the user of the guidelines.

## NICE validation process

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As part of the NICE validation process, this revised guideline has been subjected to two periods of stakeholder consultation. The second consultation process was also open to non-stakeholders.

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### 3. Background to foot care for people with diabetes

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## Introduction

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Diabetes is a complex metabolic disorder, characterised by a raised blood glucose concentration. Diabetes is becoming increasingly common in the UK. It is estimated that approximately 1.3 million people have diagnosed diabetes (the age-standardised prevalence of diagnosed diabetes is estimated to be 2.23 per 100 males and 1.64 per 100 females). The incidence of diabetes has been estimated at 1.7 new diagnoses per 1000 population per year. It is also thought that many people have undiagnosed Type 2 diabetes (with estimates of between 600,000 to 800,000 people who have not been diagnosed.). By the year 2010 it is projected that the number of people in the United Kingdom with diabetes will reach 3 million, and that the majority of these new cases will be of Type 2 diabetes (Department of Health 2002). Most people who have diabetes in the UK have Type 2 diabetes (approximately 85%). Type 2 diabetes is usually diagnosed in people over the age of 40, however it is increasingly being diagnosed in younger people, including children. Type 2 diabetes is more common in certain groups, estimates are of up to six times more common in people of South Asian descent, three times more common in those of African and African-Caribbean descent, and is more common in people of Chinese descent compared with the white population. Prevalence also rises with age, with one in 20 people over the age of 65 in the UK having diabetes and one in five in people over the age of 85 years. Whilst diabetes is more common in men, women are at greater risk of dying from the disease (Department of Health 2001).

As a chronic disease, Type 2 diabetes can have a major impact on almost all aspects of life, not just health and well-being, including life expectancy, lifestyle, work and income.

Foot problems in diabetes results from complications such as peripheral vascular disease or neuropathy. Peripheral vascular disease is the damage caused to large blood vessels supplying lower limbs. This can result in poor circulation, which can result in pain, and also predispose to the development of foot ulcers and ultimately amputation. Peripheral neuropathy, degeneration of the peripheral nerves, which leads to loss of sensation and autonomic dysfunction may also lead to severe foot problems.

### The impact and cost of diabetes

The National Service Framework (Department of Health 2001) described the costs and impact associated with diabetes. This includes the significant direct personal costs, for people with diabetes, including costs associated with managing their diabetes. The average cost in 1999 was estimated to be £802 per year plus lost earnings. The presence of diabetic complications increases personal expenditure three-fold, and doubles the chance of having a carer.

The impact on the National Health Service and social care was also discussed in the National Service Framework. It was estimated that around 5% of total NHS resources and up to 10% of hospital in-patient resources are used for the care of people with diabetes. People with diabetes are twice as likely to be admitted to hospital as the general population and, once admitted, are likely to have a length of stay that is up to twice the average. It was also argued that the presence of diabetic complications increases NHS costs more than five-fold, and increases by five the chance of a person needing hospital admission. One in 20 people with diabetes incurs social services costs and, for these people, the average annual costs were £2,450 (1999). More than three-quarters of these costs were associated with residential and nursing care, while home help services accounted for a further one-fifth. The presence of complications increased social services costs four-fold.

The costs associated with foot ulcers was looked at by Ramsey et al. (1999). This was a partial US cost study. It attempts to cost the care required over a two-year period for an individual with a newly diagnosed foot ulcer compared to patients with diabetes without a foot ulcer. It is therefore a

partial cost of illness study. Reported in 1995 US dollars with a 5% discount rate applied to year two costs, the costs were derived by comparing matched pairs of patients diabetes with newly diagnosed ulcers and without foot ulcers. Few details are given as to the actual source or methods of costing, in contrast to the statistical analysis applied to the data. Costs appear to be based entirely on a database of accounting costs, although it is claimed that this is an accurate method of calculating the actual costs of services. It does include items such as overheads.

Results show that the costs of foot ulcer patients outstrip those of non foot ulcer patients by a factor of approximately 1.5-2.4 times in the year before diagnosis, 5.4 times greater in the year following diagnosis, and remain at 2.8 times greater in the second year.

### **Delivering care**

It is clear that a partnership between the person with diabetes and the health care professionals and others involved in their care, including informal carers, can improve both outcomes and quality of life for people with diabetes.

A postal survey (response rate 70%) of general practices conducted in late 1997 found that 96% of responding practices had diabetes registers (identifying 1.9% of their population as having diabetes). Seventy one per cent of responding practices held clinics run by a GP and nurse or by a nurse alone. Overall, practices provided most of the care for 73% of their patients with diabetes (Pierce et al 2000).

Inequalities exist in risk of developing diabetes, in access to health care services and health outcomes, with those less socially advantaged likely to have higher risk of development, poorer access and outcomes.

### **Prevalence of clinical diabetic polyneuropathy**

In a large retrospective cohort study of 8,905 patients with Type 1 or Type 2 diabetes, in a health maintenance organisation (USA), the cumulative incidence for foot ulcers over three years (1993-1995) was 5.8%. Of these, 77 (15%) developed osteomyelitis and 80 (15.6%) required amputation. Survival at three years was lower for foot ulcer patients than for age and sex matched patients with diabetes but without foot ulcers ( $p < 0.001$ ) (Ramsey et al 1999).

In a survey of 2633 Spanish patients with diabetes, aged 15-74 years, 22.7% had diabetic polyneuropathy, diagnosed as a neuropathy Disability Score of  $>5$  regardless of Neuropathy Symptom Score, or a Neuropathy Disability Score of 3-5 in conjunction with a Neuropathy Symptom Score of at least 5 (Young et al 1993). No differences in prevalence were seen by sex, but the prevalence in insulin-dependent patients was 12.9% and in non-insulin dependent patients 24.1% ( $p < 0.001$ ). Prevalence increased with increasing age and with increasing duration of diabetes since diagnosis ( $p < 0.001$ ). Prevalence was lower in those attending primary care centres (21.0%) compared with those being treated in hospital clinics (26.7%) ( $p < 0.05$ ). Multiple logistic regression analysis found that age and duration of diabetes were both associated with diabetic polyneuropathy in Type 2 patients ( $p < 0.001$ ) whereas the association was only seen for duration of diabetes in Type 1 patients ( $p < 0.05$ ). A second model also found an association between the origin of patients (in terms of whether they attended, and were recruited from, hospital clinics or primary health care centres) as well as the other two factors, in Type 2 patients, with those from hospitals having higher prevalence ( $p < 0.001$ ) (Cabezas-Cerrato 1998).

### **Incidence of amputation**

In a cohort study of a population-based sample of Type 1 and Type 2 people with diabetes in Wisconsin, followed up for between four and ten years, the ten year cumulative incidence of lower-

limb amputation was 5.4% in Type 1 and 7.3% in Type 2. In those with Type 2, logistic regression identified a history of ulcers (OR 3.3, 95% CI 1.6, 6.8), glycosated haemoglobin level (OR 1.3, 95% CI 1.1, 1.5), duration of diabetes (OR 1.6 for 10 years, 1.1, 2.5), sex (OR 2.6 for men, 1.3, 4.9), diastolic blood pressure (OR 0.7 for 10 mm Hg, 0.5, 1.0) and proteinuria (OR 2.4, 1.0, 5.7) as significantly associated with incidence of lower-extremity amputation (all  $p < 0.05$ ) (Moss SE et al 1996). At the 14 year follow-up in the same study, a multiple logistic regression analysis found that the same variables, with the exception of proteinuria, were associated with lower limb amputation in Type 2 patients. More severe retinopathy was also found to be a risk factor (OR for one step 1.07, 1.00, 1.13) (Moss et al 1999).

Patients with current foot ulcers rated their health-related quality of life (assessed using the EQ-5D) significantly lower than patients who had healed primarily without amputation ( $p = 0.004$ ). However quality of life is reduced after major amputations (Tennvall and Apelqvist 2000).

Morris et al (1998) reported a retrospective cohort study of all 221 first lower-limb amputations in Tayside, Scotland between January 1993 and December 1994 and on a prevalence cohort of 7,079 patients with diabetes on January 1st, 1993. Of the 221, sixty had diabetes, of which four were Type 1 and fifty six Type 2. The age and sex standardised incidence density per 100,000 person years in Type 1 was 20.10 and in Type 2, 247.91.

New et al (1998) used a population based district diabetes information system in Salford, England to determine the incidence and prevalence of lower limb amputation, 1992 to 1996, and the proportion in those recently diagnosed with diabetes. The incidence of diabetes-related lower limb amputation was 475 per 100,000 diabetic patient years (19.2 per 100,000 population per year), with 16 (20.2%) of the amputations occurring within one year of diagnosis of diabetes. The age standardised incidence rate of diabetes related to lower limb amputations was 13.1 (95% CI 9.0, 17.2) times greater than for the general population.

In Denmark the incidence rate for major amputations in patients with diabetes (both Type 1 and Type 2) fell between 1981 and 1995 (Holstein et al, 2000).

## The burden of foot problems

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Among people with diabetes, foot complications are common. Overall, 20–40% of people with diabetes are estimated to have neuropathy (depending on how it is defined and measured) and about 5% have a foot ulcer (Kumar et al, 1994; Neil et al, 1989; Walters et al, 1992).

The St Vincent declaration called for a 50% reduction in amputation from diabetic gangrene, reflecting the belief that much morbidity is preventable by better patient management (World Health Organisation, 1990). A retrospective survey of the population of people with diabetes in Newcastle-upon-Tyne (UK) undergoing non-traumatic amputation (that is planned amputations undertaken as part of treatment rather than those caused by trauma such as road traffic accident), found that of the patients receiving hospital care, only half had complete foot evaluations in the year preceding initial ulceration or gangrene (Deerochanawong et al, 1992). Another retrospective study investigated causal pathways to amputation in a series of 80 diabetic lower-extremity amputees. A causal sequence of minor trauma, cutaneous ulceration and wound-healing failure applied to 72% of amputations (Pecoraro et al, 1990). This guideline addresses the evidence that improved outcomes are achievable by appropriate monitoring and intervention.

## Natural history of foot complications in diabetes

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The diabetic foot may be defined as a group of syndromes in which neuropathy, ischaemia, and infection lead to tissue breakdown resulting in morbidity and possible amputation (World Health Organisation, 1995).

Peripheral neuropathy in feet leads to loss of sensation and autonomic dysfunction. Peripheral vascular disease in the form of atherosclerosis of the leg vessels causes loss of circulation (ischaemia which is often bilateral, multisegmental, and distal). Infection often complicates neuropathy and ischaemia and is responsible for considerable damage in diabetic feet. Two broad pathologies result from these processes.

*Neuropathic feet*, where good circulation remains, are warm, numb, dry, usually painless and pulses remain palpable. Neuropathic ulcers, found mainly on the soles of feet, and neuropathic (or Charcot) joints are the two main complications which may result.

*Neuro-ischaemic feet* are cool and pulses are absent. Pain at rest, ulceration at the edges of the foot from localised pressure damage, and gangrene may occur in addition to neuropathic complications.

Approximately 50% of people with diabetes who present at dedicated foot clinics have neuropathic feet and approximately 50% have neuro-ischaemic feet (Edmonds et al, 1986, Thomson et al, 1991). Purely ischaemic feet, where these occur, are managed identically to neuro-ischaemic feet (Edmonds et al, 1996). In a local population study of 1077 diabetic patients, 7.4% were found to have past or present foot ulceration, of which 39.4% were neuropathic, 24.2% were vascular and 36.4% mixed (Walters et al 1992). More broadly, glycaemic control, ethnic background, duration of disease and cardiovascular factors are all associated with increased risk of complications.

Foot ulcers are susceptible to infection and polymicrobial infection may spread rapidly causing overwhelming tissue destruction (Edmonds et al, 1986). This process is the main reason for major amputation in neuropathic feet. Potential strategies to minimise the sequelae of foot complications include: early recognition of the 'at risk' foot; prompt use of preventative measures; and rapid and intensive treatment of foot complications in multidisciplinary foot care services.

## 4. Foot care: general management approach

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# General management approach

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## Recommendations

Effective care involves a partnership between patients and professionals and all decision making should be shared. (D)

The role that any informal carers of the person with diabetes has in providing care and receiving information to allow them to fulfil this role should be discussed with the person with diabetes, and any decisions about this should be that of the person with diabetes. (D)

Arrange recall and annual review as part of ongoing care. (A)

Health care professionals and other personnel involved in the assessment of diabetic feet should receive adequate training. (D)

As part of annual review, trained personnel should examine patients' feet to detect risk factors for ulceration. (A)

To improve knowledge, encourage beneficial self-care and minimise inadvertent self-harm, healthcare professionals should discuss and agree with patients a management plan that includes appropriate foot care education.\* (B)

Extra vigilance should be used for people who are older (over 70 years of age), have had diabetes for a long time, have poor vision, have poor footwear, smoke, are socially deprived or live alone. (C)

Health care professionals may need to discuss, agree and make special arrangements for people who are housebound or living in care or nursing homes to ensure equality of access to foot care assessments and treatments. (D)

## Evidence statements

*Where people with diabetes and general practices are willing participants and when an organised system of recall and review is in place which specifies components of foot care, shared care arrangements between hospital and general practice provide levels of surveillance as good as hospital diabetes clinic attendance alone. (Ib)*

*An agreed plan of management between people with diabetes and health care professionals is important to achieve adequate levels of care. (Ib)*

*Prompt and appropriate information exchange between primary and secondary care, and with patients, improves communication and quality of care. (IV)*

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\* See Appendix 26 for issues and topics that might be covered in patient education.

## Introduction

Shared care has been defined as “the joint participation of hospital consultants and general practitioners in the planned delivery of care for patients with a chronic condition, informed by enhanced information exchange over and above routine discharge and referral notices” (Hickman et al, 1994). Studies of the consequences of organising care have used several models: e.g. devolving care of certain patients to primary care until a problem occurs, or retaining annual visits to a hospital clinic with interim care in general practice. Details of the workings of a number of shared care schemes in the UK have been reviewed (Greenhalgh, 1994).

## Evidence

Randomised trials comparing the effectiveness of general practice or hospital care are the subject of a Cochrane review (Griffin and Kinmonth, 1997). This review identified five trials from Australia or the British Isles evaluating Type 2 diabetes or both Type 2 and Type 1 diabetes patients (Porter, 1982; Hayes et al, 1984; Hoskins et al, 1993; Hurwitz et al, 1993; DICE, 1994).

Only one new randomised controlled study was identified as published in the past four years. Donohoe et al (2000) examined the impact of an integrated care model for use in general practices and compared against current care plus an unrelated educational intervention in five control practices. The integrated care model comprised an organisational framework centred on the primary care-based annual review and examination of the diabetic foot. It incorporated practice visits, education of the whole primary care team on the recognition, examination and management of the diabetic foot, referral criteria and responsibilities of professionals. Foot care leaflets outlining the patients’ roles and responsibilities in the integrated care arrangements were also provided for dissemination to patients by the practices and the Semmes Weinstein monofilament was introduced to practice staff. Randomisation was at practice level and the five practices in the intervention group received regular reinforcement visits over a six-month period. In addition a further separate education programme was provided for chiropodists in the intervention group. Outcomes were changes over a six-month period in patient attitude to, and knowledge of, foot care. Whilst knowledge and attitude improved in both groups, significant differences between the group only occurred in the attitude scores (change 3.18, 95% confidence interval 1.29, 5.07) in favour of the intervention group. Improvements in the intervention group were also seen in the health professionals’ knowledge ( $p < 0.001$ ), producing a change between groups of 13.46 (95% CI 8.30, 18.62), and in appropriate referrals to specialised foot clinics ( $p = 0.05$ ).

In two British studies (Hurwitz et al, 1993; DICE, 1994) which featured regular prompting of patients and/or doctors, and reviews with specified components, overall mortality and glycaemic control were at least as good in general practice as with hospital outpatient care while losses to follow-up were significantly lower. One of these studies found that primary care patients were more likely to be referred to a chiropodist than hospital attenders (DICE, 1994) whilst the other found no significant difference (Hurwitz et al, 1993). The consequent benefit, in foot-health terms, of the increased review and referral in these studies is not known.

An Australian study (Hoskins et al, 1993) demonstrated that similar levels of follow-up could be achieved either with properly structured shared care or hospital care, but loss to follow-up in both groups was considerable, limiting the usefulness of the endpoint comparisons.

The early British studies (Porter, 1982; Hayes et al, 1984) differ from the others in that no automated system of recall was provided to prompt either patients or GPs to initiate a consultation. The first study (Porter, 1982) was published as a letter and although outcomes appear equivalent, insufficient detail is presented for an adequate assessment. In the second study (Hayes et al, 1984) nearly all local GP practices agreed to participate and there was a relatively long period of follow-

up (5 years) compared to other studies. This study suggests poorer follow-up and overall mortality for patients receiving solely general practice rather than hospital care.

There are a number of potential problems in trying to interpret and generalise the findings of these trials. The two recent British studies enrolled self-selecting local practices. Patients randomised were self-selecting, stabilised, had no major medical complications, and were already attending hospital. The follow-up in these two trials was two years. The relative success of shared care in the later trials may be due to the implementation of structured recall and review but also due to the use of (enthusiastic) volunteer practices and patients, to relatively short follow-up periods and the trial context. A district-wide audit of diabetes care of patients discharged into primary care (where most practices had registers and recall systems) suggested an erratic and generally poor standard of supervision (Dunn et al, 1996). Other studies have questioned the care received by patients in the community (Day et al, 1987; Wilkes et al, 1980).

The unit of randomisation and analysis in each of the trials is the patient. However, some GPs will have provided care for more than one patient randomised to the same intervention introducing a form of clustering, potentially reducing degrees of freedom and leading to spurious accuracy. Additionally, GPs may have seen patients randomised to both shared care and hospital care introducing contamination. Given these concerns statistical pooling of data, at the level of the patient, by meta-analysis is not appropriate.

None of the trials reported components of foot surveillance or foot complications in any detail. The optimal period for routine surveillance of emergent foot problems is unclear but the trials featuring structured recall and review used periods of 3 to 6 months. Neither do the trials provide guidance on the relative merits of diabetes mini-clinics in general practice as opposed to care provided in routine GP consultations. One trial featured 2 mini-clinics and 1 routine care practice in the shared care group but did not show stratified findings (DICE, 1994).

A review (Hampson et al, 1996) suggested that at discharge to general practice the exchange of information between specialists and both GPs and patients may be unhelpfully delayed and inadequate in content. Structured notes are advocated, containing details of diagnosis, examinations and procedures, history and progress, admission and discharge treatments, a management plan and problem list. Similarly specialists require, when handling GP referrals, information including the reason for referral, past medical history, summary of the complaint and symptoms, GPs clinical findings and investigations, diagnosis, drug (and other treatment) details, allergies and patient expectations. Ultimately centralised computer databases of patient records could provide a solution, but the importance of structured communication appears an important facet of collaborative shared care.

There are a number of ways in which the care of people with diabetes overall and for their foot problems can be managed in a general practice. Smith et al (1998), in a retrospective study, examined the impact upon care of the use of an electronic management system in a sub-speciality diabetes clinic in the USA compared with providers in the same clinic using paper medical records only. The electronic system is designed to allow entry of clinical information in real time and automatic entry of laboratory data. It also provides predetermined option responses and a paper report at the end of the clinical consultation. Eighty two patients were randomly selected from a billing database of patients with diabetes, either Type 3, 39 of whom were cared for by providers using the electronic management system and 43 had paper records only. Each medical record was reviewed comprehensively by a trained nurse for data parameters documented in the previous 12 months. Baseline characteristics did not differ between the two groups of patients, but the number of foot examinations were significantly increased ( $p < 0.001$ ) in those patients whose providers used the electronic system, along with other performance indicators in the management of diabetes.

The Diabetes NSF and Diabetes Information Strategy are recent policy initiatives that may have a significant impact upon care for people with diabetes in terms of information, record and registers.

## Comment

No evidence was found to specify the precise components, or method of transmission, of information, but the guideline development group felt it was good practice when organising services to give careful consideration to communication between primary care and specialist services.

A multi-disciplinary group was set up, under the aegis of the British Diabetic Association, to report on the implementation of the St Vincent Declaration guidelines with respect to diabetic feet (Edmonds et al, 1996). Among its recommendations was specific consideration of the role of co-ordinated multi-disciplinary teams in providing care. This detailed the respective roles of the chiropodist, diabetologist, general practitioner, nurse, orthotist, radiologist and surgeon arranged variously in hospital, community care and vascular service teams. There is no formal comparative evidence to indicate if any optimal arrangement of health care professionals in the care of diabetic feet exists. However, the guideline development group felt it is good practice to ensure that a multi-disciplinary team of professionals are available and co-ordinated to promptly provide the full range of appropriate services to patients.

## General management approach references

(with evidence grades where appropriate)

- |    |                                    |    |                                    |
|----|------------------------------------|----|------------------------------------|
|    | Day JL et al (1987)                | Ib | Hayes TM et al (1984)              |
|    | DICE (1994)                        |    | Wickman M et al (1994)             |
| Ib | <a href="#">Donohoe et al 2000</a> | Ib | Hoskins PL et al (1993)            |
|    | Dunn NR et al (1996)               | Ib | Hurwitz B et al (1993)             |
|    | Edmonds M et al (1996)             | Ib | Porter AMD (1982)                  |
|    | Greenhalgh T (1994)                |    | <a href="#">Smith et al (1998)</a> |
|    | Griffin S et al (1999)             |    | Wilkes E et al (1980)              |
| Ib | Hampson JP et al (1996)            |    |                                    |

DR. RUPNATHUJI (DR. RUPAK NATHUJI)

# Patient education

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## Recommendation

**Structured patient education should be made available to all people with diabetes at the time of initial diagnosis, and then as required on an ongoing basis, based on a formal, regular assessment of need. [NICE 2003]**

**Offer patient education on an ongoing basis.\* (A)**

**Use different patient education approaches until optimal methods appear to be identified in terms of desired outcomes. (B)**

## Evidence statements

*Educational interventions can improve foot care knowledge and behaviour in the short term (up to 18 months). (Ib)*

*There is insufficient evidence currently available to recommend a specific type of education or provide guidance on the setting for, or frequency of, sessions. (NICE, Technology Appraisal 60)*

## **Introduction**

Educational strategies seek to address the perception that whilst relatively simple actions by the patient and physician may minimise foot complications, often these simple procedures are not systematically applied. This may happen because patients are unaware, are embarrassed or do not understand the importance of basic care. It may be because specialist services (in foot care: podiatry, orthotics or orthopaedics) are unavailable or have long waiting lists. Finally, the health care system may not be organised in such a way that regular examination by, and education from, health care professionals does occur (Cohen, 1983). Recent studies are a response to evidence from surveys which suggest that people with diabetes may not have sufficient skills or knowledge to properly manage the disease (Thomson et al, 1992; Masson et al, 1989; Collier, 1971). The common elements of patient education are foot hygiene, awareness of fungal infections, and actions required for cutaneous injuries.

## **Evidence**

Educational interventions varied in their form, setting, length of follow-up (range 6 months to 7 years) and size of study population (between 50 and 530 randomised). Studies consistently reported relative improvements in knowledge about foot care and behaviour in intervention groups, although the importance of these changes is hard to assess. No other consistent patterns are present in study methods or findings, and it is necessary to interpret the findings of studies individually.

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\* See Appendix 26 for issues and topics that might be covered in patient education.

A systematic review by Valk et al (2002) assessed the evidence from randomised controlled trials that used educational programmes for the prevention of foot ulcers in people with diabetes. Whilst the literature was searched up to March 2001, of the eight included studies (Barth 1991; Bloomgarden 1987; Kruger 1992; Rommemaa 1997 & Hamalainen 1998; Litzelman 1993; Malone 1989; Mazzuca 1986; Rettig 1986), all but two of these (Rommema 1997 & Hamalainen 1998, Mazzuca 1986) had been included in the first foot care guideline evidence. The publication dates of the other two fell within the time scope also of the first guideline. Following their systematic appraisal of the existing evidence, Valk et al concluded that the methodological quality of the evidence was poor and the results conflicting. The evidence suggests that patient education may have positive, but short lived effects on patient foot care knowledge and behaviour, and it may reduce foot ulceration and amputation particularly in high risk patients.

To determine if foot care education provided by a podiatrist is effective in the longer term, Hamalainen et al (1998) randomised 530 Finnish patients aged 10-80 years with diabetes and no obvious current need for podiatry into those (n=267) referred to a podiatrist for a 45 minute individual counselling session plus treatment as many times as judged appropriate over a one year period and 263 who received written instructions on foot care. Knowledge scores increased over time (measured at one and seven years of follow-up) in both groups and both sexes but differences between the intervention and control group were only significant at one year (p=0.025). For self care, scores improved significantly in time in both groups, although in men there were no differences between the intervention and control groups. However for women, scores were higher than those for the men at all time periods, they increased significantly more over time in the podiatrist group (p=0.011) and they were significantly higher in the podiatrist group compared with the control group at both one year (p<0.001) and at seven years (p<0.05). The biggest changes occurred over the first year of follow-up. Visits to a podiatrist were similar between intervention and control group at baseline but proportionately more patients in the intervention group had visited a podiatrist at the seven year follow-up (intervention 82.3% vs 49.7%) (p<0.001). In the six years preceding the seven-year follow-up, both men and women in the intervention group had visited a podiatrist more often (mean number of visits, men 5.2±SD 9.1, women 9.0±9.5) than those in the control group (men 2.6± 7.2, women 3.7± 5.8) (p<0.001), although the number of visits tailed off and was not significantly different between the two groups in the last two years (p=0.06). There were no differences in number of physician inspections of the feet, prevalence of foot or toe abnormalities or problems. The benefits of a counselling session plus one year of podiatrist support can be maintained for several years afterwards without further intervention.

Campbell and colleagues (1996) looked at a number of parameters associated with diabetes management and control over a 12 month period, including podiatrist consultations, in Type 2 patients randomised to provision of one of four education programmes. At early follow-ups (three and six months), the numbers consulting a podiatrist differed significantly between the four programmes: minimal; group education, individual education; and behavioural, being higher in the last group. However at 12 months, there were no statistical differences in numbers consulting between the four groups.

Pieber et al (1995) evaluated an education programme (general diabetes care and foot care) in general practice in 107 patients. Intervention patients (in groups of 4-8) received 4 weekly sessions (1½-2 hours each) covering a range of aspects of diabetes care. At 6 months, callus formation and other measures of skin condition were significantly improved in the education group.

Litzelman et al (1993) evaluated a foot care education programme conducted (in groups of 1-4) by nurse clinicians in a general practice setting with 396 patients. Intervention patients agreed to personalised behavioural contracts, reinforced by telephone and postcard reminders at 1 and 3 months. This study included an organisational intervention for health care providers who were given practice guidelines, informational flow sheets and prompts to perform visual examination and

provide education. At 1 year, there was a significant reduction in serious lesions for patients receiving the educational intervention. There were 4 amputations in the control group and 1 in the intervention group ( $p=0.2$ ). Considerably improved rates of visual examination and provision of education during clinician contact were reported in the intervention group. The agreement of individual management plans between health professionals and patients is a central tenet of consensus statements on care (Edmonds et al, 1996). The study by Litzelman and colleagues provides some evidence to support this view.

Kruger et al (1992) evaluated a participatory foot care education programme with 50 patients beginning hospital diabetes care. Both groups received a normal education package (a videotape and supplementary explanation from an instructor, instructions to examine feet and use a checklist daily). The intervention group additionally received participatory hands-on teaching and learning sessions (including actual foot washing, inspection, care of corns and calluses, cutting toe-nails, evaluating problems and suitable footwear) and an education kit with materials (buff pads and an inspection mirror). At 6 months no changes in knowledge or behaviour were observed.

Barth et al (1991) evaluated an intensive foot care education intervention, recruiting selectively 70 patients by radio and newspaper campaigns as well as from general practice and diabetes centres. Patients in both groups received a conventional education programme including 1 hour on foot care. The intervention group received an additional 9 hours of education over a 4-week period. These sessions used a motivational technique and were taken by a podiatrist and a psychologist. The intensive care group showed significantly greater compliance with advice to consult a podiatrist ( $p=0.008$ ) and a greater reduction in foot problems ( $p<0.006$ ) at 1 month but neither of these effects were significant at 6 months.

One study (Malone et al, 1989) enrolled only patients with infection, ulceration or prior amputation and this is discussed in a following section (see: *Education for patients with foot ulcers*).

Bloomgarden et al (1987) evaluated a diabetes clinic programme consisting of 9 education sessions – covering general areas of diabetes care as well as foot care, and using various media: films, a card game, slides and role-playing – in 202 patients. No statistically significant differences in the occurrence of foot lesions were found between groups at 18 months. Of patients enrolled to the education intervention, 56% attended 7 or more sessions. These ‘graduates’ of the programme showed better knowledge and behaviour scores than those who didn’t graduate. Approximately 90% of patients in this study were black or Hispanic.

Rettig et al (1986) evaluated a diabetes home education programme (covering general areas of diabetes care as well as foot care) in 471 patients. Intervention patients were visited and assessed by a nurse, who tailored the education programme during the home visits to suit the individual needs of the patient. The findings at 6 months post enrolment, show no difference between groups in foot appearance scores (based upon a checklist of 16 abnormal conditions observed during foot inspection) or hospitalisation.

### **NICE Technology Appraisal 60 (2003)**

NICE issued guidance about patient education models in diabetes in 2003. Although this was concerned with models for all of diabetes patient education, rather than foot care specifically, the findings and guidance are of relevance. The NICE guidance was based on eight trials (six randomised controlled trials [RCTs] and two controlled clinical trials [CCTs]) concerned with general self-management education for Type 2 diabetes. The outcomes considered were generally HbA1c, with body mass index (BMI) or weight also being reported in some studies. The guidance also reported trials considered with focused self-management, but foot care aspects of diabetes did not appear to have been addressed in the considered trials.

The following key messages are from the NICE technology appraisal.

“There is insufficient evidence currently available to recommend a specific type of education or provide guidance on the setting for, or frequency of, sessions.

However, to achieve maximum effectiveness some principles of good practice are clear:

- ♦ educational interventions should reflect established principles of adult learning
- ♦ education should be provided by an appropriately trained multidisciplinary team to groups of people with diabetes, unless group work is considered unsuitable for an individual
- ♦ sessions should be accessible to the broadest range of people, taking into account culture, ethnicity, disability and geographical issues, and could be held either in the community or at a local diabetes centre
- ♦ educational programmes should use a variety of techniques to promote active learning (engaging individuals in the process of learning and relating the content of programmes to personal experience), adapted wherever possible to meet the different needs, personal choices and learning styles of people with diabetes, and should be integrated into routine diabetes care over the longer term.

Multidisciplinary teams providing education should include, as a minimum, a diabetes specialist nurse (or a practice nurse with experience in diabetes) who has knowledge of the principles of patient education and a dietitian. Although not formally assessed in this appraisal, input from other disciplines, such as podiatry, has potential value. The composition of the team and the way that members interact may vary between programmes, but team functioning should be tailored to the needs of different groups of people with diabetes.”

## Comment

The available studies provide inconsistent messages about the value of education and interpretation is weakened by small studies, different endpoints used by different investigators, and lack of a common approach. Only two of the larger studies reported serious lesions as endpoints. One indicated that where patients agree behavioural contracts and receive periodic reminders then foot ulcers could be prevented over 1 year (Litzelman et al 1993). Another study, spacing nine educational sessions over 18 months and using a range of teaching media, found no significant change, (Bloomgarden et al, 1987). A further factor complicating interpretation is that patients enrolled in studies may be at certain phases in disease processes making their clinical values atypical. Consequently both treatment and control groups may show considerable improvement over the period of follow-up (regression to the mean) making analyses of findings more complex.

Intensive, prompted education requiring action from both patients and clinicians may reduce foot complications over relatively short-term periods of time although the evidence is inconclusive concerning the best method. Available trials of education feature inadequate follow-up to assess the potential for primary care prevention of foot complications. The value of education interventions in the longer term is unknown and it is likely that important messages and habits will need reinforcing periodically in patients and health professionals. Better foot care awareness in patients and health professionals will be worthwhile if it increases the likelihood of early detection and appropriate response to factors raising the likelihood of ulceration.

The guideline development group also considered the issues of what key points/topics should be covered in patient education, particularly from the viewpoint of what would people with diabetes need to know about in relation to foot care. Whilst recognising that that it was not possible to give definitive answers in this area, they have produced a framework of key points that might provide a useful starting point. This was developed from a consensus of the guideline development group rather than from research literature, as this is not available. This framework is presented in Appendix 26.

### **Patient education references**

(with evidence grades where appropriate)

- |     |   |     |   |
|-----|---|-----|---|
| Ib  | Barth R et al (1991)                    | Ib  | Malone JM et al (1989)                              |
| Ib  | Bloomgarden ZT et al (1987)             | III | Masson EA et al (1989)                              |
|     | <a href="#">Campbell et al (1996)</a>   |     | <a href="#">NICE Technology Appraisal 60 (2003)</a> |
|     | Cohen S (1983)                          | Ib  | Pieber TR et al (1995)                              |
| III | Collier BN (1971)                       | Ib  | Reichard P et al (1993)                             |
|     | Edmonds M et al (1996)                  | Ib  | Rettig BA et al (1986)                              |
| Ib  | Kruger S et al (1992)                   | III | Thomson FJ et al (1992)                             |
|     | <a href="#">Hamalainen et al (1998)</a> | Ia  | <a href="#">Valk et al (2002)</a>                   |
| Ib  | Litzelman DK et al (1993)               |     |   |

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## 5. Foot examination and risk classification

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# Foot examination and monitoring

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## Recommendations

**Regular (at least annual) visual inspection of patients' feet, assessment of foot sensation, and palpation of foot pulses by trained personnel is important for the detection of risk factors for ulceration. (A)**

**Examination of patients' feet should include:**

- ♦ testing of foot sensation using a 10 g monofilament or vibration (using biothesiometer or calibrated tuning fork) (A)
- ♦ palpation of foot pulses (A)
- ♦ inspection for any foot deformity
- ♦ inspection of footwear (A)

**Monofilaments should not be used to test more than ten patients in one session and should be left for at least 24 hours to 'recover' (buckling strength) between sessions. (C)**

**Classify foot risk as:**

- ♦ low current risk (normal sensation, palpable pulses)
- ♦ at increased risk (neuropathy or absent pulses or other risk factor)
- ♦ at high risk (neuropathy or absent pulses + deformity or skin changes or previous ulcer)
- ♦ ulcerated foot (C)

**Self-monitoring and inspection of feet by people with diabetes should be encouraged. (D)**

## Evidence statements

*Evaluation of skin, soft tissue, musculoskeletal, vascular, and neurological condition on an annual basis is important for the detection of feet at raised risk of ulceration. (Ib)*

*Both vibration perception threshold measurement using a biothesiometer and sensation threshold measurement using a 10 gram monofilament accurately predict neuropathic patients at raised risk of ulceration. The 10 gram monofilament is convenient and easy to use. (III)*

*Longevity and recovery testing suggests that each monofilament will survive usage on approximately 10 patients before needing a recovery time of 24 hours (to restore buckling strength) before further use. (III)*

*Identification of neuropathy based on insensitivity to a 10 gram monofilament is convenient and appears cost-effective. (III)*

*Comparisons of different methods of measuring neuropathy reveal no dominant technique. (III)*

*Self-monitoring and inspection of feet by people with diabetes, when it can be done, is a useful practice to help identify any problems as early as possible. (IV)*

## Introduction

Fundamental foot care in people with diabetes involves adequate monitoring and the opportunity to reinforce messages of self-care (Boulton et al, 1998). Many people with diabetes are unable to perform this monitoring because of poor eyesight and reduced mobility, making it difficult to inspect their feet (Thomson et al, 1992; Masson et al, 1989), thus regular contact between professionals and patients is important (Edmonds et al, 1996).

Regular foot inspection by a health care professional should include visual inspection of the legs, dorsal, plantar and posterior surfaces of the foot and between the toes. Vascular examinations involve palpation of the pulses in the lower extremities and inspection of the feet and legs for evidence of ischaemic changes. Musculoskeletal evaluation includes foot and ankle range of motion inspection for bone abnormalities and analysis of gait and stance. Neurological examinations may include tests for vibration by a biothesiometer, tuning fork (only calibrated tuning forks should be used), or cutaneous pressure sensation using a 10 gram monofilament. The ability to identify feet at risk of ulceration has been demonstrated prospectively in studies.

## Evidence

Pham et al (2000) conducted a prospective study of 248 patients from three large foot centres in the USA. As well as a complete history and physical examination patients were assessed for abnormalities associated with neuropathy, peripheral vascular disease and foot deformity. Neuropathic symptoms were assessed with a modified Neuropathy Symptom Score and its severity with the Neuropathy Disability Score. Other measurements included the vibration perception threshold, cutaneous perception using Semmes Weinstein monofilaments, plantar foot pressure, joint mobility, and peripheral vascular disease. During a 30 month follow-up, 73 patients (29%) developed foot ulcers, on 95 feet (19%). Multivariate logistic regression analysis for risk of ulceration identified high neuropathy disability scores ( $\geq 5$ ), vibration perception thresholds ( $\geq 25V$ ), Semmes-Weinstein monofilaments ( $\geq 5.07$ ) and foot pressures ( $\geq 6 \text{ kg/cm}^2$ ). Sensitivity and specificity for these factors, either singly or in pairs, ranged from 58-99% and 28-78% respectively with the usual trade-off between sensitivity and specificity. The most sensitive variable (99%) was a high neuropathy disability score and/or Semmes Weinstein monofilament, whilst the most specific variable (78%) was a high neuropathy disability score and/ or foot pressure. Sex, race, duration of diabetes, history of previous foot ulceration, and palpable pulses were not significant predictors.

Pacaud et al (1999) looked for clinical indicators of neuropathy in a prospective study of 160 Canadian outpatients, 46 with Type 1 and 113 with Type 2 diabetes, attending a diabetes clinic. Patients completed a questionnaire that asked about diabetes duration, history of foot examinations and problems, and other related conditions (retinopathy and nephropathy) and their follow-up. Patients also underwent bilateral foot examinations to measure their vibration perception threshold (Vibraton II) and any neuropathy, using Semmes-Weinstein monofilaments. Patients had a mean age of 57 years but Type 1 patients were younger on average at 43 years than Type 2 at 62 years. Duration of diabetes was 16 years on average in the total group, but 22 years in Type 1, compared with only 13 years in Type 2 patients. Moderate to severe neuropathy, as assessed by vibration perception threshold (VPT) was present in 56.4% of the patients studied, with more Type 2 (63.4%) than Type 1 (38.7%) ( $p < 0.05$ ) patients affected. For the Type 2 patients, 43% had moderate to severe neuropathy within the first five years from diagnosis, and the proportion increased with longer duration of the disease. The VPT results correlated well ( $r = 0.86$ ,  $p < 0.05$ ) with the monofilament results, and using the VPT as a standard, the monofilament technique was 97% sensitive and 89% specific for neuropathy. However presence of symptoms was a poor indicator of neuropathy, as neuropathy was present in 44% of patients who had no symptoms. Presence of

retinopathy was also neither very sensitive (45%) nor specific (61%) as a test for neuropathy. Foot examination was also not be a good identifier of neuropathy as the authors found that 40% of the patients had never had their feet examined, whilst only 43% of Type 1 and 37% of Type 2 patients had in the preceding year. There was no difference in presence of moderate or severe neuropathy between those who had been examined (53.3%) and those who had not (60.3%) ( $p>0.05$ ).

A prospective study in a Native American Indian population, categorised patients by visual deformity (hallux, varus or valgus, claw and hammer toes, bony prominence or Charcot osteoarthropathy), by using a 10g monofilament, and by patient history of ulceration or amputation (Rith-Najarian, 1992). Sensation status was determined by applying the filament to 8 points on the plantar surface of each foot of blindfolded patients. Patients who failed to sense the filament at one or more locations were retested twice before being classified as insensate. Patients were followed for 32 months or until first ulcer or amputation if sooner. Combining categories 1–3 provides a test sensitivity of 93% and specificity of 86% for predicting ulceration, with Likelihood Ratios, LR (positive test) = 5.2 (95%CI: 4.0 to 6.7); LR (negative test) = 0.12 (95%CI: 0.05 to 0.27). An ulcer was about 5 times as likely to occur in a patient with a history of disease or lack of sensation than in a patient without these factors.

Category	patients	died	ulcers	amputation*
0: Sensate, no history of disease*	266	7	4 (1.5%)	0 (0%)
1: Insensate	30	1	7 (23.3%)	0 (0%)
2: Insensate with deformity	16	3	6 (37.5%)	1 (6.3%)
3: History of disease*	46	8	24 (52.2%)	13 (28.3%)

\*In lower extremity

Paisley et al (2002) tested the Neuropen (Owen-Mumford Ltd), a device to assess both pain and pressure perception against current clinical tests, the neuropathy disability score and vibration perception threshold, to evaluate peripheral nerve function in 124 patients with Type 1 or Type 2 diabetes attending either a diabetes centre or a high risk diabetes foot clinic, in Manchester, England. The Neuropen has an interchangeable 10g monofilament for cutaneous pressure assessment and a calibrated tip for assessing pain sensation, both contained within a plastic pen-like hand held device. The sensitivity and specificity of the Neuropen to identify patients with moderate to severe neuropathy were calculated against neuropathy disability score abnormal cut-off values defined as  $\geq 6/10$ , and for a vibration perception threshold of  $>25V$ . Sensitivity ranged from 82-92% in detecting abnormal neuropathy disability scores and 82-96% in detecting abnormal vibration perception thresholds. Specificities were 31-68% and 32-71% respectively. The best sensitivities could be obtained with either the neurotip or the monofilaments but the highest specificities were obtained with a combination of both the neurotip and the monofilaments. The Neuropen therefore may provide an inexpensive alternative screening method for identifying those patients with diabetes and moderate to severe neuropathy. In this study the mean age (SD) of the patients was 55.4 (13.7), 84 were male, 40 female, 34 had Type 1 and 80 Type 2 diabetes, and duration of diabetes was, on average, 10 years (range 0.5-43 years), and 18% had a history of foot ulcers. The authors provided no details of ethnicity of the population studied.

A study, in an outpatient clinic in Liverpool, examined the reproducibility of screening using a monofilament, biothesiometer and palpitation of pedal pulses (Klenerman et al, 1996). The investigators reported that only the monofilament gave adequately reproducible results (over 85%) for measurements repeated after 2 weeks.

Booth et al (2000) investigated the accuracy of 10g monofilaments. They tested 4 types of monofilament, a total of 160, with results for 158 being reported. Each monofilament was subjected to 10 mechanical bucklings of 10 mm while the load cell detected the maximum buckling force. They also investigated longevity of the monofilaments. They found that most monofilaments produced by Owen Mumford and Bailey Instruments were buckling within 0.5 g of 10 g of buckling force, with the remaining monofilaments from these batches falling within 1.0 g of deviation (mean buckling forces were  $10.1 \pm 0.4$  g for the Owen Mumford filaments and  $9.7 \pm 0.4$  g for the Bailey Instruments monofilaments). Significantly fewer (76%) of the Semmes-Weinstein monofilaments manufactured by North Coast Medical buckled within 1.0 g of 10 g of force ( $p < 0.001$ ). These filaments generally exhibited a negative deviation with most buckling forces falling to  $< 10$  g ( $8.6 \pm 0.3$  g). A similar pattern emerged with Timesco/Sensory Testing Systems monofilaments ( $8.1 \pm 0.5$  g). In terms of longevity, performed on Bailey Instruments and Owen Mumford monofilaments, most monofilaments remained within 10% of 10 g of buckling force after 100 continuous compressions, but by 200 compressions, only 50% of monofilaments were within this range. They indicated that their findings implied that centres using North Coast Medical or Timesco/Sensory Testing Systems monofilaments may be producing far too many false-positive results (i.e., they may be categorising patients as insensate who are in fact sensate).

All monofilaments (except the Timesco/Sensory Testing Systems monofilaments) have the Conformity European (CE) mark awarded by the Medical Devices Agency. They concluded that longevity and recovery testing suggests that each monofilament will survive usage on  $\sim 10$  patients before needing a recovery time of 24 h before further use.

Kumar and colleagues (1991) commented that filaments were easy to use, light (150g) and cheap (£12/set) when compared to a biothesiometer weighing 2.5kg, requiring a power source and costing £400. Considering the findings of the available prospective studies and relative performance in head-to-head studies with surrogate endpoints it is likely that monofilaments provide a portable and cost-effective alternative in first-line monitoring for neuropathy.

A prospective study, in a diabetes centre and foot clinic in Manchester, used a biothesiometer and categorised patients, without previous ulceration or significant ischaemia, according to their vibration perception threshold (VPT) at enrolment (Young et al, 1994). The endpoint was the first ulcer regardless of cause, and results at the end of the study are tabulated below, after (up to) 4 years follow-up. Using a threshold of  $> 25$ V, these results indicate a test sensitivity of 83%, and a specificity of 62%, with Likelihood Ratios, LR (positive test) = 2.2 (95%CI: 1.8 to 2.5); LR (negative test) = 0.27 (95%CI: 0.14 to 0.48)

VPT (Voltage)	patients	ulcers	incidence
<15V	209	6	3.0%
16-24V	58	2	3.4%
>25V	202	40	19.8%*

\* $p < 0.01$ , group 3 vs. group 1

Abbott et al (1998) report the incidence of foot ulcer after 1 year in a prospective study of 1033 patients with established neuropathy (VPT  $\geq 25$  V on at least 1 foot and VPT  $\leq 30$ V on both feet). Patients were originally enrolled in a randomised control trial in which active treatment showed no benefit, and so both treatment and placebo groups are analysed together. For each 1 unit increase in VPT at study baseline, the hazard of first ulcer increased by 5.6%. Each unit increase in the muscle and reflex components of the Michigan diabetic polyneuropathy (DPN) score increased the hazard of first ulcer by 5.0%.

A number of other techniques are available for assessing neuropathic deficit: e.g. the tactile circumferential discriminator (TCD) (Vileikyte et al, 1997); the graduated tuning fork (Thivolet et al, 1990; Liniger et al, 1990b); thermal discrimination devices and others (Liniger et al, 1990a). However these have not been prospectively evaluated but (generally) compared with other techniques for their ability to detect existing ulcers. A number of such studies have directly compared biothesiometers and monofilaments but not found either to be superior (Kumar, 1991; Vileikyte et al, 1997).

### Screening to detect those at risk of amputation

Mayfield et al (2000) looked at the effectiveness of foot examinations as one method for decreasing the risk of foot amputation. Their patients were Pima Indians with diabetes enrolled in a diabetes programme or receiving care in a general medical clinic. Clinicians in all health care settings were encouraged to conduct foot examinations on all patients with diabetes and delivery of these recommendations was monitored through an annual chart audit. Two hundred and forty four patients were recruited to the study, 61 who had had a previous nontraumatic amputation of a lower extremity between 1985 and 1992, and 183 with no amputation by 1992. From medical records the pivotal event leading to the amputation was identified and records were then examined for a 36 month period retrospective to that pivotal event for: the number of clinic visits; number and type of foot examinations; number of missed appointments; management and delivery of foot care; and other health conditions and diabetes complications. Once identified, the pivotal event was assigned to three randomly selected patient controls for every patient case, and their records were examined in a similar method. Over 1100 foot examinations were performed in a 36 month period. However, when the independent effect of foot examination on the risk of amputation was examined in a logistic model, that controlled for differences in demographics, diabetes severity, and foot risk conditions, receiving one or more foot care examinations during a three year period did not provide significant benefit (odds ratio 0.55, 95% confidence interval 0.17, 1.7, p=0.31). Nonadherence with foot care recommendations was also not associated with risk of amputation (OR 1.9, 95% CI 0.88, 4.3, p=0.10).

### **Comment**

No direct evidence was found to identify the optimal content or frequency of visual inspections and examinations, but regular surveillance at a minimum frequency of once annually was held by the guideline development group to be good clinical practice where no complications have previously been found. The benefits of monitoring people with diabetes without foot complications arise from the ability to detect feet at raised risk and the reduced morbidity achieved by aggressive intervention. Hence primary and secondary care should work together to identify a package of care for patients at raised risk of ulceration.

Adequate glycaemic control has been demonstrated to reduce the incidence and progression of microvascular disease in Type 1 (insulin dependent diabetes) patients (Diabetes Control and Complications Trial Research Group, 1993; Reichard et al, 1993). Direct evidence that improved glucose control will equally benefit Type 2 diabetes patients (for whom macrovascular, rather than microvascular, complications are of greater relative importance) is inadequate. A review of available epidemiological and trial evidence suggested a trend towards greater neuropathy with poor glycaemic control but the evidence is far from conclusive (Gaster et al, 1998). The UK Prospective Diabetes Study, which reported in 1998, discussed the impact of differing levels of glycaemic and blood pressure control in terms of macro and micro vascular disease but did not report specific outcomes concerning diabetic foot ulcers.

**Examination and monitoring references** (with evidence grades where appropriate)

	Abbott CA et al (1998)	III	Paisley et al (2002)
	<a href="#">Booth &amp; Young (2000)</a>		
	Boulton AJM et al (1998)	IIb	<a href="#">Pham et al (2000)</a>
	DCCT Research Group (1993)	Ib	Reichard P et al (1993)
	Edmonds M et al (1996)	III	Rith-Najarian et al (1992)
	Gaster B et al (1998)	III	Thivolet C et al (1990)
III	Klenerman L et al (1996)	III	Thomson F et al (1992)
III	Kumar S et al (1991)	Ib	UK Prospective Diabetes Study Group (1998)
III	Liniger C et al (1990a)	III	Vileikyte L et al (1997)
III	Liniger C et al (1990b)	III	Young M et al (1994)
III	Masson EA et al (1989)		
III	<a href="#">Mayfield et al (2000)</a>		
III	<a href="#">Pacaud et al (1999)</a>		

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# Risk factors

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## *Evidence statements*

*A range of risk factors has been identified to indicate an increased risk of ulceration. (III)*

*Modifiable risk factors include peripheral vascular disease, neuropathy, foot deformities, plantar callus, smoking. (III)*

## **Introduction**

Epidemiological and clinical risk factors for ulceration have been extensively but inconclusively researched.

## **Evidence**

Reported markers of increased risk are old age, duration of diabetes, neuropathy, peripheral vascular disease, renal disease, foot deformities, plantar callus, previous ulceration or amputation, poor vision, poor footwear, cigarette smoking, social deprivation and social isolation (Pecoraro et al, 1990; Walters et al, 1992; Chaturvedi et al, 1996; Kumar et al, 1994; Caddick et al, 1994; Murray et al, 1996; de Sonnaville et al, 1997; Litzelman et al, 1997a, b; Abbott et al, 1998). Studies using different methods and patient data and including selections of risk factors come to different conclusions about their relative importance in predicting complications. Hence, deciding at what level, and in what combinations these manifestations become clinically important is hampered by the lack of availability of good intervention studies taking a range of thresholds. However, these risk factors are all easily observable by trained health professionals.

### **Risk factors for diabetic foot ulceration (see Table 1)**

Four papers were identified in which risk factors associated with development of foot ulcers were examined (Sriussadaporn et al 1997, Frykberg et al 1998, Boyko et al 1999, and Kastenbauer et al 2001). The study designs were case control (Sriussadaporn et al 1997) and cohort (Frykberg et al 1998, Boyko et al 1999, Kastenbauer et al 2001), although Frykberg et al only report baseline characteristics of subjects. Two of the populations studied had Type 2 diabetes, the other two involved both Type 1 and Type 2 (Frykberg et al 1998, Boyko 1999). In Frykberg et al, of the 251 North American patients studied, (126 men, 125 women) of either Caucasian, black or Hispanic race, 99 patients had a current or prior history of ulceration, with 33 with active ulcers. A multivariate logistic regression analysis for risk of ulceration identified three significant factors, having a vibration perception threshold  $\geq 25V$  (OR 4.4, 95% CI 2.58, 7.54), having a Semmes-Weinstein monofilament test  $\geq 5.07$  (OR 4.1, 1.89, 8.87), and a maximum peak plantar pressure  $\geq 6\text{kg/cm}^2$  (2.1, 11.32, 3.39), after controlling for age, sex, diabetes duration, and race. The case control study, which took place in Thailand, compared 55 patients with full thickness ulcers mid calf or below with 110 patients without ulcers, matched for age. All patients with a previous history of foot ulcer were excluded. In a multiple logistic regression analysis, the risk of developing a foot ulcer was associated with peripheral nerve status – absence of short-latency somatosensory evoked potentials (odds ratio 1.67, 95% CI 0.31, 8.97,  $p < 0.001$ ), visual acuity (OR=0.233 per unit decrease in decimal visual acuity, 95% CI 0.005, 0.39,  $p < 0.005$ ) and fasting plasma glucose level (OR=1.01

per mmol/l increase, 95% CI 1.00, 1.02,  $p < 0.005$ ), after controlling for HbA1c, urea, creatinine, diabetes knowledge, and foot care.

Of the two cohort studies, Kastenbauer et al followed up 187 Austrian patients (excluding 25 withdrawals from the study) without a history of foot ulceration once a year for up to 54 months (mean follow up 3.6 years). Ten patients developed 18 neuropathic foot ulcers during the study period, producing an annual incidence of first foot ulceration of 1.6% (95% CI 0.7, 2.6) and an incidence density of 21.7 per 1000 person years (95% CI 8.2, 35.1). In a multiple stepwise Cox Proportional Hazards regression analysis, the predictors of foot ulceration were having an elevated vibration perception threshold (relative risk 25.4, 95% CI 3.1, 205,  $p = 0.0024$ ), an elevated mean plantar pressure (RR 6.3, 95% CI 1.2, 32.7,  $p = 0.0291$ ), a daily intake of alcohol (RR 5.1, 95% CI 1.1, 24.0,  $p = 0.0404$ ), mediasclerosis (RR 0.07, 95% CI 0.01, 0.6,  $p = 0.0174$ ). The other non-significant covariates in the model were age, diabetes duration, weight, oral antidiabetic therapy, insulin use, history of angiography, flatfoot deformity, hallux valgus, oxford shoes, varicosis, dry skin, skeletal abnormalities, HbA1c, triglycerides, stage or peroneal nerve conduction velocity, and diastolic blood pressure. The Seattle Diabetic Foot Study provided the results for the second cohort study (Boyko et al 1999). In this large study, 749 veterans with diabetes with 1483 lower limbs and no current foot ulcer, were followed up at 12 – 18 month intervals with a foot examination, and quarterly by postal contact to check for the presence of foot ulcers. Over a mean follow up period of 3.7 years, 162 ulcers developed, 3.0/100 person years. Using a Cox proportional hazards stepwise model, nine variables were found to be risk factors for foot ulcer: sensory neuropathy by 10g monofilament (RR 2.17, 95% CI 1.52, 3.08,  $p < 0.001$ ), history of foot ulcer (1.63: 1.17, 2.26,  $p = 0.004$ ), history of amputations (2.81: 1.84, 4.29,  $p < 0.001$ ), insulin use (1.59: 1.14, 2.22,  $p = 0.006$ ), dorsal foot transcutaneous oxygen tension (mm Hg) (0.80: 0.69, 0.93,  $p = 0.004$ ), weight (1.23; 1.06, 1.43,  $p = 0.006$ ), ratio of ankle systolic pressure to brachial systolic pressure (0.83; 0.73, 0.96,  $p = 0.011$ ), Charcot deformity (3.49; 1.22, 9.92,  $p = 0.019$ ), vision  $< 20/40$  (1.93; 1.42, 2.63,  $p < 0.001$ ). Other non-significant variables excluded in the multivariate model include height, diabetes duration, Type 2 diabetes, random glucose, HbA1c, erythrocyte sedimentation rate, serum creatinine, claudication, peripheral vascular disease, history of vascular bypass surgery, changes in heart rate with timed breathing, no hallux vibration sensation, no Achilles tendon reflex, foot numbness, foot pain, special footwear, hallux limitus, hammer claw/toe ulcer history, hallux joint mobility, extensor digitorum brevis test result, chronic lower limb oedema.

In a fifth paper the authors (Margolis et al 2000) conducted a meta-analysis of (white) patient data from the standard care groups in five randomised controlled trials, not all of which had been published, to identify risk factors for delayed healing of neuropathic diabetic foot ulcers. Patients were receiving off loading, debridement, or moist wound dressing treatments. Factors significantly associated with healing within 12 weeks or 20 weeks included an ulcer duration of less than six months, an ulcer of small size, and at twelve weeks, but not 20 weeks.

### **Risk factors for lower limb complications in people with diabetes (see Table 1)**

El Shazly et al (1998) conducted a case control study of 348 people with either type 1 or Type 2 diabetes and major complications of the lower extremities, defined as having a foot ulcer, claudication, gangrene and/or ischaemic rest pain lasting 15 days or more, bypass or angioplasty for peripheral vasculopathy, or amputation within previous 12 months and 1050 controls (no complications of the lower extremities). Multivariate logistic regression analysis identified a number of significant risk factors for developing lower limb complications. These included being 50-70 years of age, male, not married, having Type 1 diabetes or being Type 2 on insulin treatment, having cardio or cerebrovascular disease, diabetic neuropathy, abnormal HbA1c, needing help to reach a health care facility, no regular follow-up visits, and no educational intervention. Non significant factors included level of education, employment status, presence of diabetic retinopathy,

nephropathy, or hypertension, co-morbid conditions, duration of diabetes, smoking and alcohol consumption.

### **Risk factors for lower limb amputations in patients with diabetes (see Table 1)**

Four papers were identified that examined the risk factors for lower limb amputation, all were cohort studies, three prospective (Lehto et al 1996, Adler et al 1999, Hamalainen et al 1999) and one retrospective (Gurlek et al 1998). In three studies the populations involved Type 1 and Type 2 patients, whilst the patients in the fourth study were Type 2 only (Lehto et al 1996). In the smallest of the four studies, medical records were retrospectively examined for 147 consecutive patients (97 men, 50 women, 11 Type 1, 136 Type 2) initially referred to a medical centre in Turkey between 1992 and 1996 (Gurlek et al 1998). Fifty four patients (36.7%) had had an amputation. A logistic regression analysis to identify significant risk factors associated with amputation identified peripheral vascular disease (odds ratio 4.0, 95% CI 1.17, 13.4,  $p=0.03$ ), presence of osteomyelitis (3.73; 1.08, 12.6,  $p=0.04$ ), and presence of grade 4 or 5 gangrenous lesions (30.8; 7.39, 121.5,  $p<0.0001$ ). Variables that were not statistically significant included age, sex, duration of diabetes, smoking history, hypertension, nephropathy, or retinopathy. The primary indication for amputation was the presence of gangrene in 66.6% of patients. Of the three prospective studies, two were based in Finland (Lehto et al 1996, Hamalainen et al 1999) and the in the third, patients were participants on the Seattle Diabetic Foot Study in the USA (Adler et al 1999). In this latter study, 776 US veterans with diabetes (98.2% male, 51 Type 1, 725 Type 2) were followed up for 0 – 5.8 years, (median 3.3 years). Thirty patients underwent amputations in this cohort and three multivariate models, incorporating different measures of peripheral vascular disease: palpation of the posterior tibialis and dorsalis pedis pulses; partial pressure of oxygen at the skin surface; and with the ankle arm index, were developed to identify risk factors associated with amputation. Former amputation, lower extremity ulcers, peripheral vascular disease, and treatment with insulin were significant factors after controlling for duration of diabetes in all three models. In addition, peripheral sensory neuropathy was also significant when the partial pressure of oxygen at the skin surface was used to measure peripheral vascular disease. The age-adjusted incidence rate for amputation in the men only, standardised to the 1991 US male diabetic population was 11.3 per 1000 patient years.

Patients in both of the Finnish studies were selected from the central register of diabetes patients receiving drug reimbursement. Hamalainen et al identified recruited their age stratified sample of 728 patients in 1987 and invited them for a follow-up examination seven years later. In Lehto et al, 1044 patients with Type 2 diabetes were selected in 1983 if they were aged between 45 and 64 years and lived in districts served by two hospitals, one in east Finland, the other in west. These patients were also followed up seven years later in 1990 with a postal questionnaire. Fifty eight of the 1044 had undergone an amputation in Lehto et al's cohort and 25 of the 728 followed up by Hamalainen et al. The incidence of amputation was similar in both sexes, 5.6% in men and 5.3% in women (Lehto et al 1996) and no differences between those treated with insulin or with diet or oral hypoglycaemic drugs, after adjustment for age, sex and severity of diabetes. Cox regression analysis (Lehto et al) and logistic regression (Hamalainen et al) were used to determine the risk factors for amputation. Considering that the patients in these two studies were identified from the same register and live in the same country, little overlap and some discrepancies were seen in the variables identified in the two studies. Significant factors identified by Lehto et al included having retinopathy (RR 3.6; 2.2, 6/1,  $p<0.001$ ), urinary protein (1.8; 1.1, 3.2,  $p=0.003$ ), total cholesterol values  $>6.2$  mmol/l (1.8; 1.1, 1.6,  $p=0.047$ ), fasting plasma glucose  $>13.4$  mmol/l (2.5; 1.5, 4.3,  $p<0.001$ ), HbA1c  $>10.7\%$  (2.4; 1.4, 4.0,  $p=0.001$ ), duration of diabetes  $>9$  years (2.2; 1.3, 3.6,  $p=0.004$ ), absence of two or more peripheral artery pulses (3.9; 2.3, 6.8,  $p<0.001$ ), femoral artery bruit on auscultation (2.1; 1.1, 4.0,  $p=0.022$ ), bilateral absence of Achilles tendon reflexes (4.3; 2.5, 7.3,  $p<0.001$ ) and bilateral absence of vibration sense (2.7; 1.6, 4.7,  $p<0.001$ ). An HbA1c  $>9.8\%$  and a duration of diabetes  $>7$  years both increased the risk for amputation independently of each other ( $p<0.01$ ). Other non-predictive variables included body mass index, previous myocardial

infarction, hypertension, smoking, triglyceride levels, and HDL cholesterol levels. Hamalainen et al found that an abnormal vibration perception threshold (odds ratio 14.5; 95% CI 3.6, 57.8,  $p=0.0001$ ), ankle/brachial pressure index (8.2; 2.8, 24.0,  $p=0.0001$ ), retinopathy (6.1; 1.9, 19.6,  $p=0.0024$ ), visual handicap (4.9; 1.4, 17.4,  $p=0.0129$ ) and being male (3.3; 1.0, 10.8,  $p=.0431$ ) were significant risk factors, whilst age at onset of diabetes, duration of diabetes, history of cardiac failure, claudication, absence of at least one peripheral pulse, and elevated serum creatinine.

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**Table 1: Risk factors**

Authors	Condition	Vibration perception threshold	Semmes-monofilament	Pulses presence	Nerve stimulation	Visual acuity/retinopathy	Fasting blood glucose levels	HbA1c/cholesterol	+ Insulin	Sex	Age	Duration of diabetes	Previous amputation/ulcer	Other factors associated	Other factors not associated
Frykberg et al 1998	Foot ulceration	Y	Y	N										plantar pressure	
Sriussad et al 1997	Foot ulceration				Y	Y	Y	N							urea, creatinine, diabetes knowledge, foot care
El Shazy et al 1998	Lower limb complication					N			Y	Y	Y	N		CHD, metabolic control, access to healthcare, poor or no FU, no health education	smoking, education
Adler et al 1999	Lower limb complication			Y					Y				Y/Y		
Kastenba et al 2001	Foot ulceration	Y			N			N			N	N		alcohol, mediasclerosis	BMI
Hamaia et al 1999	Amputation	Y		Y						Y				creatinine	
Boyko et al 1999	Foot ulcer		Y	Y	Y	Y			Y				Y/Y		
Peters et al, 2001	Foot ulcer Amputation		Y						Y				Y		
Lehto et al 1996	Amputation	Y		Y		Y	Y	Y/Y				Y			

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The one published trial of multidisciplinary intervention on the basis of risk (McCabe et al 1998, reported in the next section) took a very conservative threshold, identifying only patients with gross risk factors, and demonstrated the value of a protection programme. A number of studies have looked specifically at the role of footwear in reducing lesions in at-risk patients but require further research. No studies specifically addressing education in patients at raised risk (broadly defined) were uncovered (but see *Education for patients with foot ulcers*).

Surveys indicate sub-optimal supervision of elderly patients in hospital, residential care, and general practice (Fletcher et al, 1996; Wilkes et al, 1980; Benbow et al, 1997; Neil et al, 1989; Dornan et al, 1992). Older patients contain the greatest proportion of patients at raised risk of ulceration and other complications.

## Comment

The guideline development group felt it was important that specific consideration should be given to organising care to ensure adequate supervision of these patients with risk factors although there is no available evidence concerning the most appropriate process.

## Risk factors references

(with evidence grades where appropriate)

- |     |                                |     |                              |
|-----|--------------------------------|-----|------------------------------|
| III | Abbott CA et al (1998)         | Ib  | Kastenbauer et al (2001)     |
| Ib  | Adler et al (1999)             | III | Kumar S et al (1994)         |
| III | Benbow SJ et al (1997)         | Ib  | Lehto et al (1996)           |
| Ib  | Boyko et al (1999)             | Ib  | Litzelman DK et al (1997a,b) |
| III | Caddick SL et al (1994)        | Ib  | McCabe et al (1998)          |
| III | Chaturvedi N et al (1996)      | III | Mayfield et al (2000)        |
| III | de Sonnaville JJJ et al (1997) | III | Murray HJ et al (1996)       |
|     | Dornan TL et al (1992)         | III | Neil et al (1989)            |
| III | El Shazly et al (1998)         |     | Pecoraro RE et al (1990)     |
|     | Dunn NR et al (1996)           | III | Sriussadaporn et al (1997)   |
| III | Fletcher AK et al (1996)       | III | Walters DA et al (1992)      |
| Ib  | Frykberg et al (1998)          |     | Wilkes E et al (1980)        |
| Ib  | Gurlek et al (1998)            |     |                              |
| Ib  | Hamalainen et al (1999)        |     |                              |

## 6. Foot care management for people with diabetes

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## Recommendations

### **Care of people at low current risk of foot ulcers** (*normal sensation, palpable pulses*)

To improve knowledge, encourage beneficial self-care and minimise inadvertent self-harm, healthcare professionals should discuss and agree with patients a management plan that includes appropriate foot care education.\* (B)

### **Care of people at increased risk of foot ulcers** (*neuropathy or absent pulses or other risk factor*)

Patients with risk factors for ulceration should be referred to a foot protection team. (D)

Arrange regular review, 3-6 monthly, by a foot protection team. (D)

At each review:

- inspect patient's feet (D)
- review need for vascular assessment (D)
- evaluate footwear (D)
- enhance foot care education.\* (D)

### **Care of people at high risk of foot ulcers** (*neuropathy or absent pulses + deformity or skin changes or previous ulcer*)

Patients at high risk for ulceration should be referred to a foot protection team. (A)

Arrange frequent review, 1-3 monthly by foot protection team. (D)

At each review

- ♦ inspect patient's feet (A)
- ♦ review need for vascular assessment (D)
- ♦ evaluate provision of and provide appropriate
  - ♦ intensified foot care education (D)
  - ♦ specialist footwear and insoles (D)
  - ♦ skin and nail care (D)

Ensure special arrangements for access to the foot protection team for those people with disabilities or immobility. (D)

### Note:

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\* See Appendix 26 for issues and topics that might be covered in patient education.

All of the above recommendations are based on the evidence statements and research literature in this section (section 6) and the consensus of the guideline development group. They have been presented together to provide a structured overall approach to care for people at different levels of risk which was thought more useful to users of the guideline than presenting the recommendations by research evidence section, especially as many of the recommendations are consensus based.

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# Screening and protection programmes for patients at risk of ulceration

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## Evidence statement

***Implementing a screening and protection programme for patients with gross risk factors for ulceration reduces morbidity and is cost-effective. (Ib)***

## Evidence

Neuropathy, along with peripheral vascular disease, is a major risk factor for diabetic foot ulceration and ultimately amputation. Yet diabetic foot ulceration is preventable with careful management of those at risk.

McCabe and colleagues (1998) report a screening and protection programme conducted in an English diabetic outpatient clinic setting which randomised 2001 patients. Patients in the intervention group (n=1001) were screened and patients at raised risk (n=259) were recalled. Following a second assessment, 192 (19.2%) patients were entered into a foot protection programme. These patients had gross neuropathy indicated by foot deformities, vascular disease indicated by an ankle-brachial index  $\leq 0.75$  or a history of ulceration. Although tests with monofilaments, biothesiometer, and palpation of pedal pulses were conducted, it is unclear what role these played in patient identification. Patients in the foot protection programme were eligible for weekly clinics providing chiropody and hygiene maintenance, hosiery and protective shoes as well as education on daily hygiene, clothing and footwear. When compared to the control group, the intervention group demonstrated non-significant trends in reduced ulceration and minor amputations, and statistically significant reductions in overall and major amputation. Of those presenting with ulcers significantly fewer progressed to amputation in the intervention group (p=0.006) suggesting that ulcers were spotted sooner and treated more effectively.

When the costs of intervention are set against the costs of reduced amputation alone, the authors conclude that the intervention appears cost saving. Thus it is possible that the entrance criteria to the foot protection programme may have been too severe and a broader inclusion may be acceptably cost-effective. The study does not explore whether more patients could have received worthwhile protection if the results of the first screen had been used or if findings using thresholds from monofilament or biothesiometer measures had been adopted.

Hospital outpatient attenders enrolled in the study tended to be older patients with diabetes with a tendency for younger patients to be seen in general practice in the locality (McCabe, personal communication). This may explain a relatively high prevalence of gross risk factors. The study demonstrates the potential for screening and protection of patients at greatest risk of ulceration.

## Service configurations: National Service Framework

The National Service Framework for Diabetes (NSF-Diabetes) has described the service arrangements that should be provided for people with diabetes in respect of their foot care. In this guideline we have used these descriptions to indicate which type of foot care team should have responsibility for certain aspects of care. The actual service configurations may still vary slightly

by locality so those providing the 'Foot protection programme' we have called the 'Foot protection team' and those providing the 'Multidisciplinary foot care services' we have called 'Multidisciplinary foot care teams'.

The relevant NSF-diabetes descriptions are presented below.

### **NSF-Diabetes Service Models:**

#### **Foot Protection Programmes for people with 'at risk' feet**

##### **Objective**

To reduce the risk of lower limb complications in people with diabetes at increased risk

##### **Description**

A multidisciplinary service for people with diabetes who are at increased risk of developing lower limb complications, providing

- ◆ information and education in various media formats about foot protection, including the importance of seeking urgent advice for apparently trivial foot infections or injuries
- ◆ regular recall and review by specialist podiatrists providing callus management and, where indicated, referral to an orthotist for special footwear and other interventions aimed at minimising the risk of trauma
- ◆ early intervention for all foot lesions.

The service should be provided in settings appropriate to meet the needs of individuals, eg domiciliary services for frail older people.

##### **Benefits**

- ◆ reduced prevalence of lower limb complications in people with diabetes, including fewer amputations
- ◆ reduced need for hospital admission.

#### **Multidisciplinary foot care services for people with lower limb complications**

##### **Objective**

To provide prompt effective treatment for people who develop lower limb complications

##### **Description**

A multidisciplinary specialist foot care service providing rapid access (usually within 24 hours) for the assessment and management of people with diabetes who develop new swelling, redness, discoloration, pain or ulceration of their foot.

The core specialist foot care team should usually comprise:

- ◆ highly trained specialist podiatrists
- ◆ highly trained specialist orthotists
- ◆ nurses with training in the dressing of diabetic foot wounds
- ◆ diabetologists with expertise in diabetic lower limb complications.

The core team should have unhindered access to:

- ◆ chiropody/podiatry suites suitable for managing major wounds, extensive debridement and minor surgery

- ♦ administration of oral and parenteral antibiotics
- ♦ urgent inpatient facilities
- ♦ community nursing
- ♦ microbiology diagnostic and advisory services
- ♦ orthopaedic/podiatric surgery for management of necrotising infection and osteomyelitis
- ♦ full vascular surgery service (professional advice, physiological and radiological investigation, angioplasty and both proximal and distal revascularisation) for the management of critical ischaemia as part of the joint diabetic/vascular clinics
- ♦ in-shoe orthotic facilities, stock shoes and custom footwear
- ♦ temporary pressure relief and immobilisation devices such as walking casts.

### Benefits

- ♦ reduced pain, disability and impairment of mobility in people with diabetes who develop lower limb complications
- ♦ reduced need for amputation
- ♦ reduced need for hospital admission
- ♦ reduction in the loss of employment which often results from lower limb complications.

### Screening and protection programmes

(with evidence grades where appropriate)

Department of Health (2001b)

- Ib Litzelman DK et al (1997b)
- Ib McCabe CJ et al (1998)
- Ib Uccioli L et al (1995)

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# Footwear of patients at risk of ulceration

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## Evidence statement

*In people with diabetes with previous ulceration there is conflicting evidence about the impact of therapeutic footwear on the risk of further ulceration. (Ib)*

## Introduction

As a consequence of diabetic disease processes, notably neuropathy, changes in foot posture may lead to abnormal weight bearing. Plantar callus, a risk factor for ulceration, indicates abnormal foot pressures and occurs most frequently under the metatarsal heads. Specially designed insoles (or orthoses) as inserts to patients' shoes or in combination with specially designed shoes have been proposed as a method of reducing abnormal foot pressures and thus foot ulcers.

## Evidence

A recent randomised controlled trial by Reiber et al (2002) randomised 400 people with diabetes, with a history of foot ulcer, to either usual footwear; therapeutic shoes with cork inserts or therapeutic shoes with prefabricated inserts. The study followed patients for 2 years. In terms of reulceration, the authors say that incidence was low across the groups, with 15% in the cork insert group; 14% in the prefabricated insert group and 17% in the control (usual footwear) group. Patients assigned to therapeutic shoes did not have a significantly lower risk of reulceration compared with controls (risk ratio for the cork insert group 0.88 [95% CI 0.51-1.52] and risk ratio for the prefabricated insert group 0.85 [95% CI 0.48-1.48]). All ulcer episodes in patients assigned to therapeutic shoes and 88% of those wearing their usual shoes occurred in patients with foot insensitivity. They concluded that for people without serious foot deformities, their study did not provide evidence to support the widespread dispensing of therapeutic shoes and inserts to people with a history of foot ulcer. The importance of foot care by health care professionals was noted, they also suggested that special footwear may have a benefit for people who do not receive close attention to foot care or have severe foot deformities.

Colagiuri and colleagues (1995) randomised 20 patients to conventional podiatric care (visits every 3 months) or to the wearing of custom-made rigid plastic inserts, formed from castings of the callused feet. Enrolled patients had uncomplicated callus without history of ulceration. After 1 year, patients with inserts appeared to show improvement of grade of callus while patients receiving usual care showed little change.

Uccioli and colleagues (1995) randomised 69 patients, with previous ulceration, to therapeutic shoes including custom-made inserts or to normal footwear. At 12 month follow-up, patients with therapeutic shoes had had approximately half as many ulcer relapses or new ulcers as the normal footwear group (27.7% vs. 58.3%;  $p=0.009$ ). No details of the severity of ulceration are provided.

The study of patients with previous ulceration (Uccioli et al, 1995), featuring patients at very high risk, suggests important health benefits from appropriately designed footwear. Protective footwear was a component of the foot protection programme reported by McCabe et al (1998); however, no details are provided. An analysis of the predictive factors of ulceration suggested that the type of shoe worn may be independently important (Litzelman et al, 1997b) and raises the possibility that

people with diabetes provided with normal well-fitting shoes, that distribute abnormal pressures, may also reduce their risk of ulceration.

## Comment

This remains a research issue, where ‘optimised’ normal shoes could be usefully compared with special therapeutic shoes. Without consideration of this pragmatic alternative and confirmatory studies on larger patient numbers, the relative effectiveness and cost-effectiveness of providing therapeutic shoes remains uncertain. None the less, the guideline development group agreed that ongoing surveillance of footwear was important.

## Footwear of patients with feet at raised risk of ulceration references

(with evidence grades where appropriate)

- Ib Colagiuri S et al (1995)
- Ib Litzelman DK et al (1997b)
- Ib McCabe CJ et al (1998)
- Ib [Reiber et al \(2002\)](#)
- Ib Uccioli L et al (1995)

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## 7. Care of people with foot ulcers

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# Caring for people with foot ulcers

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## Recommendations

**For a new foot ulcer, urgent (within 24 hours) assessment by an appropriately trained health professional should be arranged. (D)**

**Ongoing care of an individual with an ulcerated foot should be undertaken without delay by a multidisciplinary foot care team. (D)**

**The multidisciplinary foot care team should comprise highly trained specialist podiatrists and orthotists, nurses with training in dressing of diabetic foot wounds and diabetologists with expertise in lower limb complications. They should have unhindered access to suites for managing major wounds, urgent inpatient facilities, antibiotic administration, community nursing, microbiology diagnostic and advisory services, orthopaedic/podiatric surgery, vascular surgery, radiology and orthotics. (D)**

**Patients who may benefit from re-vascularisation should be referred promptly. (D)**

## **Introduction**

The morbidity associated with diabetic foot ulcers is considerable. Apelqvist and Agardh (1992) report a prospective study of 314 consecutive patients with diabetes with foot ulcers referred to a multi-disciplinary foot team in a university hospital. Healing was affected in 62% of patients, amputation in 25% of patients, and 13% of patients died with unhealed ulcers. The traditional (although inadequately evaluated) approach to diabetic foot ulcers includes debridement, and antibiotic treatment. In addition, new treatments include the proposed use of hyperbaric oxygen therapy, growth factors, ketanserin, cultured human dermis and total contact casting.

Meijer et al (2001) reported significant differences in the perceived quality of life in patients with diabetes and foot ulcers and those without foot ulcers. Using the SF36 on 38 people with diabetes who had been hospitalised, 14 for diabetic foot ulcers and 24, who had no foot problems but were admitted for diabetic dysregulation. Those patients with foot ulcer problems had poorer scores for physical functioning ( $p<0.001$ ), social functioning ( $p<0.05$ ), physical roles ( $p<0.001$ ) and health experience ( $p<0.05$ ). There were no differences between the two groups in emotional role scores, mental health, vitality and pain.

Trials of ulcerated feet commonly class ulcer severity according to the Wagner system:

Grade 0	intact skin	
Grade I	superficial ulcer	
Grade II	deep ulcer	
Grade III	osteomyelitis and/or deep abscess	
Grade IV	forefoot gangrene	
Grade V	hindfoot gangrene	(Wagner 1983).

Trials reported in the following sections are characterised (with a few notable exceptions) by small patient numbers, a lack of common approach, inadequate reporting of methods and lack of repetition of any one method. To illustrate the point, suppose a 50% improvement in an outcome is considered worthwhile (i.e. a new treatment achieving 60% success at some endpoint instead of 40%). To adequately power a trial to detect this improvement (i.e. an 80% chance of correctly detecting a real effect with a 5% chance of incorrectly rejecting a null hypothesis of no effect) would require randomising approximately 100 patients to each treatment. Seldom in any of the trials reported in the following sections is a rationale given for sample size or for the difference between treatments investigators expected to find. Few of the trials randomised 50 patients to each treatment arm.

Many trials have the characteristics of pilot studies and thus were never intended to inform treatment policy but to inform areas for further research. Most trials are generally industry funded. The value of treatments can sometimes be misrepresented due to publication bias.

A further problem in interpreting these trials arises from the 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. localised cellulitis around an ulcer, ulcers with relatively little cellulitis but underlying osteomyelitis, and those with considerable cellulitis. 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.

Most aspects of the treatment of diabetic foot ulcers appear in need of a comprehensive and co-ordinated trial programme.

## Comment

The guideline development group also felt that good overall glycaemic control was likely to assist wound healing in people with diabetic foot ulcers.

## The ulcerated foot references

(with evidence grades where appropriate)

- III   Apelqvist J et al (1992)
- [Meijer et al \(2001\)](#)
- Wagner FW (1983)

# Antibiotic treatment for diabetic foot complications

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## Recommendation

**Patients with non-healing or progressive ulcers with clinical signs of active infection (redness, pain, swelling or discharge) should receive intensive, systemic antibiotic therapy. (C)**

## Evidence statements

*There is inadequate evidence to address the relative effectiveness of different antibiotic regimens for treating serious diabetic foot infections (spreading cellulitis and osteomyelitis). (Ib)*

*There is inadequate evidence to demonstrate whether antibiotics are more effective than placebo and standard wound care in healing superficial or skin deep ulcers. (Ib)*

## Introduction

Polymicrobial, mixed aerobic/anaerobic infections are common in diabetic foot wounds, suggesting the use of antibiotics with a broad spectrum of activity and low rate of toxic reactions in patients with diabetes who are often nephrologically impaired. Trials generally differentiate between infections uncomplicated by deep soft tissue involvement and ulcers which have become colonised by invasive penetrating infection (cellulitis), or where osteomyelitis is present. Only 4 randomised trials have assessed the efficacy of antibiotic therapy specifically in patients with diabetes with infected ulcers (for details see Appendix 7), although a number of other studies have addressed broader groups of patients. Two of the 4 trials addressed the treatment of non-limb threatening infection, 1 addressed non-limb-threatening but treatment-resistant infection, and 1 concerned treatment of invasive infection (cellulitis or osteomyelitis). [An ongoing trial may provide more substantive evidence about the role of antibiotic treatments in foot ulcer care.](#)

## Evidence

Chantelau et al (1996) randomised 44 patients to evaluate the efficacy of oral amoxicillin plus clavulanic acid against matched placebo. Patients had purely 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 number of ulcers healed or mean reduction in ulcer size. Completely closed lesions occurred in 32% of patients receiving antibiotics and 50% of patients receiving placebo. Mean reduction in ulcer radius was 0.27 mm<sup>2</sup>/day (95% C.I: 0.15–0.39) in the antibiotic group and 0.41 mm<sup>2</sup>/day (95% C.I: 0.21–0.61) in the placebo group.

Lipsky et al (1996) randomised 88 patients to intravenous ofloxacin (400 mg) followed by oral ofloxacin (400 mg, 12 hourly) or intravenous ampicillin (1–2 g) sulbactam (0.5–1 g) followed by amoxicillin (500 mg) clavulanate (125 g, 8 hourly). Enrolled patients were hospitalised for soft

tissue infections which had not responded to outpatient management but which were not limb threatening. Therapy lasted between 14 and 28 days according to clinical need. In the ofloxacin group, cure occurred in 49% of patients, and improvement in 36%. In the amino-penicillin group, 56% of patients were cured and 27% were improved. There were no statistical differences in the efficacy of the 2 therapies.

Grayson et al (1994) randomised 93 patients with diabetes to imipenem/cilastatin (500 mg every 6 hours) and ampicillin/sulbactam (3 g every 6 hours). Patients had severe infections of the lower extremities, threatening to the lower limbs (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 randomisation, but following this period treatment could be adaptive in the instance of inadequate response. There were no significant differences between the 2 treatment groups in terms of clinical improvement at 5 days, or cure at the end of definitive treatment. In the ampicillin/sulbactam group 81% of episodes of infection were cured (mean length of therapy 13±6.5 days), while in the imipenem/cilastatin group, 85% of episodes of infection were cured (mean length of therapy 15±8.6 days).

Lipsky et al (1990) randomised 56 patients, with an infected lesion regardless of type or duration, to oral clindamycin or oral cephalexin in an outpatient setting with assessment after 2 weeks. No statistically significant differences were found between treatments either for response to infection or for wound healing. With clindamycin 78% were cured of infection and 40% of wounds healed during follow-up, for cephalexin 72% were cured of infection and 33% of wounds healed.

A number of other randomised trials of intravenously administered antibiotics have been conducted on groups of patients, including a proportion with diabetic foot ulcer. Hughes and colleagues (1987) compared ceftizoxime and cefoxitin for lower extremity infections in 63 patients with diabetes or peripheral vascular disease. File and Tan (1983) compared amdinocillin plus cefoxitin and cefoxitin alone in 45 patients with bacterial soft tissue infections. Tan and colleagues (1993) compared piperacillin-tazobactam and ticarcillin-clavulanate in the treatment of complicated skin infections requiring hospitalisation. Bradsher and Snow (1984) compared ceftriaxone and cefazolin in 84 hospitalised patients with skin and soft tissue infections. No differences in clinical response were found in any of these studies (at  $p \leq 0.05$ ).

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. The outlook for patients with cellulitis is not encouraging. Despite the apparent treatment success reported by Grayson and colleagues (1994), 66% of patients had an amputation affecting part of the lower limb in the following year, although the operation was foot sparing in most cases.

### Cost effectiveness

McKinnon et al (1997) reports a cost-effectiveness study of ampicillin/sulbactam (A/S) versus imipenem/cilastatin (I/C) for the treatment of limb-threatening foot infections in patients with diabetes (type not stated). The study was supported by Pfizer. Analysis was based on an RCT although the economic data were collected retrospectively, see Grayson et al. (1994) for details of the trial. Ninety of 93 patients had data collected for use in the economic evaluation.

It is not clear from the paper the measure of outcome that was intended for use in cost effectiveness analysis. However, it is stated later in the paper that since “success rates were identical between each treatment group” (p.59) no cost-effectiveness ratios are required. No statistically significant difference in terms of antibiotic related length of stay and total length of stay were identified.

Resource use data were collected on drug use, treatment of adverse events and hospitalisations. These were costed in 1994 US dollars. Resource use that was not included includes items such as laboratory tests, or intensive care use. It is claimed that the average cost of a hospitalisation includes “unaccounted resources”. However, this is not an acceptable method for identifying differential resource use between intervention groups. No discounting was applied since the model is only short term.

It is also stated that the perspective of the CEA is the institution and therefore it is appropriate to exclude physician charges and outpatient visits.

Base case results indicate that A/S costs less than I/S and a limited number of one-way sensitivity analyses do not change that conclusion.

The study however, is not a cost-effectiveness study as claimed. It is a partial cost or cost-minimisation study. It is poorly conducted and is of little relevance to the UK NHS.

Eckman et al (1995) is a US cost-effectiveness study that compares a range of approaches to the diagnosis and treatment of patients with Type 2 diabetes with foot infections and suspected osteomyelitis. The options compared are

- i) treatment for presumed soft-tissue infection
- ii) culture-guided empiric treatment for presumed osteomyelitis
- iii) 71 combinations of diagnostic tests preceding antibiotic therapy for osteomyelitis
- iv) 71 combinations of tests preceding amputation
- v) immediate amputation

Analysis is based on a Markov model, run over the lifetime of patients, with data taken from existing literature. The base case analysis involves a 56 year old man who had had Type 2 diabetes. Results are presented in terms of cost per QALY with a discount rate applied to costs and benefits of both 0% and 5%.

QALYs are based on “the judgements of experienced physicians.” It is also stated that the SF-36 Physical Functioning Index is used for quality of life adjustments in the sensitivity analysis. However, insufficient details are provided of this procedure and since the SF-36 does not provide a measure of preference the validity of this method is questionable.

Inpatient cost data are derived from Medicare records for seven Boston teaching hospitals. Other relevant cost items are derived from a variety of accounting systems the validity of which is difficult to judge.

Results are not presented in an easily interpretable form, since total costs and benefits are presented separately. However, the interventions are grouped according to these costs and benefits. Those options grouped as “Tier 1” dominate those in other tiers. Within that tier the differences between strategies are very slight and, although some sensitivity analyses are performed, it is difficult to be confident that one option is preferable to another. Furthermore, given the US setting and the source of the QALY data, it is unlikely that the case for distinguishing between options within tier 1 at least could be made in the UK NHS.

## Comment

Intravenous antibiotics were agreed by the guideline development group to be appropriate care in patients with cellulitis, although adequate evidence from placebo-controlled or comparative trials is lacking.

## **Antibiotic treatment for diabetic foot complications references**

(with evidence grades where appropriate)

- |    |                          |    |                        |
|----|--------------------------|----|------------------------|
| Ib | Bradsher RW et al (1984) | Ib | Hughes CE et al (1987) |
| Ib | Chantelau E et al (1996) | Ib | Lipsky BA et al (1990) |
| Ib | File TM et al (1983)     | Ib | Lipsky BA et al (1996) |
| Ib | Grayson ML et al (1994)  | Ib | Tan JS et al (1993)    |

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# Dressings and topical agents for foot ulcers

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## Recommendations

**In the absence of strong evidence of clinical or cost effectiveness, health care professionals should use wound dressings that best match clinical experience, patient preference, and the site of the wound and consider the cost of dressings. (D)**

**Wounds should be closely monitored and dressings changed regularly. (D)**

## Evidence statement

*There is insufficient evidence to support the effectiveness of any type of protective dressing, or topical application, over any other for treating diabetic foot ulcers. (Ib)*

## **Introduction**

In many cases, foot ulcers in people with diabetes are not infected and protective bandaging is appropriate. A number of characteristics for a good dressing have been proposed (Foster et al, 1994). It should perform well in the closed environment of the shoe; not take up too much space; be capable of absorbing large quantities of exudate without plugging the wound and preventing drainage; withstand the pressures and shear forces of walking without failing; not cause side effects; and be easily lifted or removed for regular inspection without adversely affecting the wound. Whilst simple gauze dressings are often employed by clinicians, there are newer forms of dressing available. Alginate, foam, hydrogel and hydrocolloid dressings have been designed to absorb wound exudate and control the level of wound hydration.

An ongoing HTA multicentre trial which is due to report in about 3 years time, may provide more information about the role that different dressings have in the care of foot ulcers. NICE guidelines on wound care management are also being developed and may be of use in this area of care (see Appendix 23).

## **Evidence**

The trials identified can broadly be grouped into trials comparing newer dressings or gels with gauze dressings and trials comparing the newer dressings with one another. From a meta-analysis of control groups (six used saline gauze, two used gel, and one used both), in nine studies that looked at healing of diabetic foot ulcers, Margolis et al (1999), concluded that after 20 weeks of good wound care 31% of diabetic neuropathic ulcers heal. After 12 weeks of good care, 24% of neuropathic ulcers have attained complete healing.

## Dressings

Jensen et al (1998) compared two moist wound healing protocols for patients with non-infected foot ulcers  $\geq 1$  cm in diameter. All patients in a Diabetic Foot and Wound Centre, Denver, USA were treated initially with debridement to remove nonviable tissue in and around the ulcer and were also

given custom-made sandals to redistribute plantar pressures, reduce trauma, and prevent weight-bearing over the ulcer. Patients were then randomised to sixteen weeks with a 1/8 to 1/4-inch layer Carrasyn® Hydrogel Wound Dressing containing Acemannan hydrogel (n=14) or a standard wet-to-moist saline dressing (control group, n=17). Other care and bandaging was identical in the two groups. Dressings were changed daily. Outcomes were time to ulcer closure and wound area. Wound closure rate was greater (84.6%) in the treatment group than in the control group (46.1%,  $p<0.05$ ) and quicker, 10.3 weeks in the treatment group compared with 11.69 weeks in the control group (not significant). Patients in the control group also had more adverse events (4 vs 2) and patients dropping out of the study (4 vs 1).

Blackman et al (1994) randomised 18 people with diabetes, with partial or full thickness foot ulcers of Wagner stage I or II, to a semipermeable polymeric membrane dressing or a conventional wet-to-dry saline gauze dressing with primary analysis after 2 months. The polymeric dressing combined a urethane prepolymer with water soluble and hydrophilic components and additionally glycerol as a bacteriostatic agent and a non-ionic surfactant as a cleansing agent. At 2 months follow-up the polymeric dressing group ulcer size compared to baseline was significantly smaller than with gauze dressing ( $35\pm 16\%$  vs.  $105\pm 26\%$ ) ( $p<0.03$ ). Complete healing occurred in 3 ulcers (27%) in the polymeric dressing group and none in the gauze.

Ahroni et al (1993) randomised 39 people with diabetes with superficial foot ulcers, in an American outpatient setting, to a calcium alginate dressing or to dry sterile gauze. After 4 weeks, there were no significant differences between the 2 groups in number of ulcers healed (alginate: 25%; gauze 37%  $p=0.65$ ). There was also no significant difference between the rate of healing per day of the area of ulcer ( $p>0.99$ ) or by linear measurement ( $p=0.87$ ).

Two new studies evaluated the impact of a collagen wound dressing on the healing or reduction in wound area of foot ulcers in people with diabetes (Donaghue et al 1998, Veves et al 2002). Collagen is a structural protein component of connective tissue and may serve as a mechanical support and this lattice may be a stimulus to the migration of fibroblasts and to promote metabolic activity of granulation material and fibronectin. Donaghue et al's study was in a single centre in Boston, USA. Seventy-five patients with foot ulcers  $\geq 1$  cm<sup>2</sup> were assigned randomly, in a 2:1 ratio to have a collagen-alginate wound dressing (FIBRACOL, Johnson and Johnson) (n=50) or conventional treatment with saline moistened gauze (n=25) and followed up for eight weeks. No statistically significant differences were found in wound area reduction or in complete healing although multivariate analysis indicated that the overall treatment effect on ulcer areas was significantly in favour of the collagen-alginate dressing compared with the gauze dressing, when ulcer duration was included in the analysis ( $p=0.0401$ ). More study dropouts occurred in the control group compared with the treatment group (8 vs 6) although the analysis was on the basis of intention to treat. Limited power could explain some of the non-significant differences in this study but similar findings were reported in the larger study by Veves et al which took place in 11 centres and involved 276 subjects with diabetes and similar ulcer characteristics, foot ulcers  $\geq 1$  cm<sup>2</sup>. Treatment was a primary dressing of Promogran (collagen: oxidised regenerated collagen, 55:45) (Johnson and Johnson) or an isotonic sodium chloride solution-moistened gauze in the control group, with additional bandaging similar in the two groups. Dressings were changed when clinically necessary, off-loading was used with all subjects, and patients were followed up weekly for 12 weeks. No significant differences were seen between the two groups for complete wound closure, percentage reduction in ulcer size, or time to complete healing. There were also no differences in adverse events or dropouts between the two groups. Thus collagen dressings do not appear to promote better ulcer healing than saline-moistened dressings.

Donaghue et al (1996) randomised 75 patients (in a 2:1 ratio) to a combination collagen-alginate dressing or regular gauze moistened in saline with a follow up period of 8 weeks. No statistically significant differences were found between the groups in any outcome: complete healing,

percentage with 50% or greater reduction in wound size, mean time to 50% healing, mean reduction in wound size. Analysis is based on patients completing treatment; significantly more patients withdrew from the gauze dressing arm than the collagen-alginate arm (32% vs. 12%).

Di Mauro et al (1991) randomised 20 NIDDM patients to a lyophilised type I collagen dressing or hyaluric acid medicated gauze. Patients had glycaemia ( $>250$  mg%; also  $HbA_{1c}>10\%$ ) and were subject to strict alimentary regimen and insulin therapy. There was a significant difference in the mean time to wound healing with the collagen dressing compared to the medicated gauze (mean time 32.4 days vs. 49.0 days,  $p=0.001$ ).

Foster et al (1994) randomised 30 patients with foot ulcers to a polyurethane foam dressing or a calcium-sodium alginate dressing, with treatment over an 8-week period or until the ulcer was healed. Patients were over 18 years of age, had uninfected, non-sloughy or non-necrotic foot ulcers, were prescribed preventative antibiotics, and were seen weekly at a clinic where ulcers were debrided and progress monitored. No significant differences in ulcer healing were apparent at 8 weeks (foam 60%; alginate 53%).

Baker et al (unpublished) randomised 20 patients to a polyurethane foam dressing or a calcium alginate dressing with treatment and follow-up over a 12-week period. Patients had palpable pedal pulses with no history of intermittent claudication or pain at rest. Ulcer healing at 10 weeks was significantly better with the foam dressing group (90% vs. 44%). Similarly, median time to healing was 28 days with the foam dressing and 84 days with the alginate dressing.

Clever and Dreyer (1996) randomised 40 patients to 1 of 2 polyurethane gel dressings in addition to standard care. Patients had pure, superficial neuropathic ulcers, size 1–5 cm in diameter. There were no differences between the 2 groups in terms of time to healing, reduction in wound size at 4 weeks, or frequency of change of dressing.

The effectiveness of a hydrophilic dressing made of carboxyl-methyl-cellulose (Aquacel®, Convatec) for foot ulcers was investigated by Piaggese et al (2001). However this was another small study with only ten patients in each of two groups. In the control group, ulcers were treated with a saline-moistened gauze, renewed twice a day with saline to prevent dehydration. Patients were followed up weekly for eight weeks in the clinic and then to complete re-epithelialisation. Dressings were changed at home every second or third day for the treatment group and every one to two days in the control group. Healing time in the treatment group was shorter than that in the control group ( $127\pm 46$  vs  $234\pm 61$  days,  $p<0.001$ ). Other variables chosen to monitor the development of the lesion healing process also scored significantly better in the treatment group. There were no differences in adverse events or dropouts between the two groups.

Finally, in an interim analysis of 20 patients, Alvarez et al (2003) report the outcome of a randomised open label trial examining the efficacy of a non-contact normothermic wound therapy for healing diabetic neuropathic foot ulcers. The non-contact thermal wound care system maintains the wound environment at a skin surface temperature of  $37^{\circ}\text{C}$  using a double layer polyurethane film and a heating element. Warming treatments were performed three times daily, for one hour each time, with a minimum of one hour between treatments until the wound healed or for a maximum of 12 weeks. The placebo group received standard wound care of weekly debridement, moist saline gauze dressings changed daily and elastic stockinet. Both groups received initial debridement, were fitted with therapeutic healing sandals and told to avoid weight-bearing activity. Differences in healing rates between the treatment and placebo groups were not significant ( $p>0.05$  at weeks 2,4,6,8,10 and 12) although the mean percent wound closure was higher in the treatment group at each follow-up point. There was also no difference in the numbers of ulcers healed at six ( $p=0.11$ ) or 12 weeks ( $p=0.069$ ). This is an interim analysis of an ongoing trial, but it is not clear whether the authors intend to recruit more participants or to follow-up those already recruited for a longer period.

### Cost effectiveness

Ghatenakar et al. (2002) undertook a cost-effectiveness study. It compares Promogran®, a dressing (collagen and oxidised regenerated cellulose matrix), plus “good wound care” (GWC), defined as sharp debridement (if necessary) and wound cleansing, against GWC alone for patients with non-superficial diabetic foot ulcers in four countries: France, Germany, Switzerland and the UK. The basis of the cost-effectiveness analysis is a trial which showed non statistically significant benefits in terms of 12 week healing rates.

A Markov model based on different Wagner grades of ulcer severity plus death was developed and run over a one year period with monthly transitions. Extrapolating still further than the original trial was not considered feasible. Transition probabilities were derived from a prospective study of US patients (Amato et al. 1999) and healing rates from the RCT applied to the uninfected health state. Costs were derived from existing literature and from physician interviews combined with country specific unit costs. No further details of the costing methodology are supplied but readers are referred to Ghatenakar et al. (2001). Results are presented in 2000 Euros. A 5% discount factor is claimed to be applied but this was only a one year model.

It is unclear why the frequency of changes of Promogran® was below that suggested by the manufacturers.

Base case results show that Promogran® dominates GWC in all four countries, generating savings of between €169 and €1079 per patient. A small number of sensitivity analyses are performed, the majority of which result in even greater cost savings.

The whole difference between the intervention and standard care is generated by non statistically significant differences in healing rates from one RCT and are therefore highly uncertain.

### Ointments and gels

Apelqvist and Tennvall (1996) evaluated topical treatment with cadexomer iodine ointment dressing in addition to standard treatment. Forty-one patients were randomised with ulcers of Wagner stage I or II and surface area greater than 1 cm<sup>2</sup>. 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 including materials and drugs, staff and transportation (of patients and health professionals) which purported to show significant cost savings due to reduced staff costs and transportation. The cost savings arise predominantly because of the more frequent need for dressing changes in the standard care group. However, substantially more patients were withdrawn from the ointment group due to deteriorating disease or protocol violation (removing high cost patients) making it uncertain that patients evaluated are comparable. It is unclear whether dressing changes occurred on the basis of the protocol or of need, or how need was assessed.

Mulder et al (1994) 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 randomised into 4 groups. Following immediately after debridement, 2 groups were randomised to GHK-Cu gel or vehicle. 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 most benefit was seen in patients with large ulcers who did not respond well to the control treatment. Two further groups were randomised to different concentrations of GHK-Cu gel after a 4-week delay after debridement and no significant differences were seen in these groups compared with each other or the control group. This leads the authors to suggest that the gel interacts with the process of debridement. The dressing used in all patient groups was plain gauze.

Muthukumarasamy et al (1991) conducted a prospective matched case-control study, with 100 patients comparing daily topical phenytoin powder with a dry sterile occlusive dressing, in a total of 100 patients (50 in each group). Patients' ulcers were debrided at baseline, and antibiotics were provided as necessary. Groups were matched for age, sex, ulcer area and depth and chronicity at baseline, although there is a non-significant trend to small ulcer size in the phenytoin group. Ulcers with gross cellulitis, deep slough, ischaemic gangrene or tropic ulcers were excluded. Ulcers were assessed using an 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. The mean time to complete healing in the phenytoin powder group was 21 days compared to 45 days in the occlusive dressing arm ( $p < 0.05$ ). The overall percentage reduction in ulcer area was also greater in the phenytoin group ( $p < 0.005$ ).

Lishner et al (1985) allocated 40 patients in a prospective controlled study where, in addition to conventional care, the treatment group received a foot bath containing dimethylsulfoxide (DMSO) solution for 20 minutes, 3 times a day. Patients enrolled had not responded to previous treatment and had deep, or perforated, ulcers. Gentamicin was added to the solution when infection occurred and the concentration of DMSO was doubled and if no healing occurred by the sixth week. The ulcers of 14 patients in the DMSO group healed by 15 weeks compared to 2 patients in the control group. Overall improvement was significantly better in the treatment group ( $p < 0.001$ ). It is unclear to what extent improvement was due to the active therapy or to the process of regular foot bathing in the treatment group.

### Comment

Trials comparing newer dressing or gels with gauze dressing cannot provide clear messages because of their small size and lack of common method. Polymeric membrane dressing, GHK-Cu complex dressing, lyophilised collagen dressing, and proprietary moist dressing suggests improved performance over gauze, but, in each case, one small trial does not provide an adequate evidence base. The findings of dimethylsulfoxide foot-bathing and topical phenytoin powder are similarly problematic and these were not randomised. The lack of efficacy of cadexomer iodine ointment, calcium alginate dressing, and collagen-alginate dressing is inconclusive. The stated importance of the newer dressings and the inappropriateness of gauze (see for example Appendix 8 and the British National Formulary) does not appear substantiated by the available evidence from randomised controlled trials.

Although the available evidence from trials is inadequate, the guideline development group felt it was good practice to ensure that appropriate wound monitoring practices were observed, including close monitoring and regular dressing changes.

### Dressings and topical agents for foot ulcers references

(with evidence grades where appropriate)

- |    |  |     |   |
|----|--|-----|---|
| Ib | <a href="#">Alvarez et al (2003)</a>     | Ib  | Lishner M et al (1985)                          |
| Ib | <a href="#">Ahroni JH et al (1993)</a>   | 1a  | <a href="#">Margolis et al (1999)</a>           |
| Ib | <a href="#">Apelqvist J et al (1996)</a> | Ib  | <a href="#">Mulder GD et al (1994)</a>          |
| Ib | <a href="#">Blackman JD et al (1994)</a> | IIa | <a href="#">Muthukumarasamy MG et al (1991)</a> |
| Ib | <a href="#">Clever HU et al (1996)</a>   | Ib  | <a href="#">Piagessi et al (2001)</a>           |
| Ib | <a href="#">Di Mauro C et al (1991)</a>  |     | <a href="#">Jensen et al (1998)</a>             |
|    | <a href="#">Donaghue et al (1998)</a>    | Ib  | <a href="#">Veves et al (2002)</a>              |
| Ib | <a href="#">Donaghue VM et al (1996)</a> |     |   |
| Ib | <a href="#">Foster AVM et al (1994)</a>  |     |   |

# Debridement

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## Recommendation

**Dead tissue should be carefully removed from foot ulcers to facilitate healing, unless revascularisation is required. (B)**

## Evidence statement

*Limited clinical trial data suggest that healing is improved by the use of hydrogel to debride diabetic foot ulcers. (1b)*

## Introduction

Debridement is the removal of necrotic (dead) tissue by either surgical, chemical or other (eg larval therapy) means. Types of debridement include:

- autolytic debridement: this occurs naturally in healthy, moist wounds when arterial perfusion and venous drainage are maintained
- enzymatic debridement: using topical, proteolytic enzymes
- mechanical debridement: includes, wet to dry dressings and high pressure irrigation
- sharp (surgical) debridement: usually using a scalpel but may also involve tissue nippers, and/or curettes

Saap and Falanga (2002) developed a Debridement Performance Index to assess the adequacy and performance of any surgical debridement undertaken. The Index was shown to be an independent predictor of wound closure (odds ratio 2.4, 95% confidence interval 1.0-5.6) making it potentially a useful predictive tool for determining ulcer healing outcome following debridement.

## Evidence

A recent systematic review (Smith 2002) looked at the effectiveness of debridement as a treatment for diabetic foot ulcers in Type 1 or Type 2 patients. Of the five randomised controlled trials included in this review, all published between 1997 and 2000, none of the earlier ones had been included in the original foot care guideline evidence (Hutchinson et al 2000). Three of the studies assessed the effectiveness of a hydrogel as a debridement agent, one considered surgical debridement and the final one evaluated larval therapy. Sample sizes were predominantly small (<22 per group in three studies, approximately 70 per group in the other two studies) with a full description of age, sex and type of diabetes provided by a single study only. From a meta-analysis of the three hydrogel studies, the absolute risk difference was 0.23, 95% CI 0.10, 0.36) with hydrogel being more effective than gauze or standard care in healing diabetic foot ulcers. Surgical debridement and larval therapy showed no significant benefit, but both trials were small.

## Debridement references

(with evidence grades where appropriate)

Ia Smith et al (2002)

# Off-loading

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## Recommendation

**Total contact casting may be considered for people with foot ulcers unless there is severe ischaemia. (B)**

## Evidence statement

***Evidence from several small trials suggests that total contact casting may substantially improve ulcer healing in diabetic foot ulcers with Wagner grades I and II. (Ib)***

***Total contact casting is associated with unacceptable risk of inducing ulcers in people with severe ischaemia. (IV)***

## **Introduction**

Pressure is a causal factor for neuropathic foot ulcers. Therefore removal or relief from pressure should facilitate healing of foot ulcers. The removal of pressure on affected feet or joints can be achieved by avoidance of weight bearing, known as off-loading. However, achieving effective off-loading of pressure on the foot while the patient remains ambulant remains a challenge. One way of addressing the problem is the use of therapeutic shoes.

## **Evidence**

### **Footwear and total contact casting**

Armstrong et al (2001) looked at the effects on wound healing of patients with diabetes and neuropathic foot ulcers randomised to three different off-loading systems: total contact casts, a half shoe (Darco) and a diabetic walker (Aircast). Sample sizes (n=19, 24 and 20 respectively) were small but the proportion of healing was significantly higher in the total cast group (89.5%) compared with the two other groups combined (61.54%) (p=0.026, odds ratio 5.4, 95% CI 1.1, 26.1) at 12 weeks. Mean time to healing was also shorter in the total cast group (33.5±5.9 days) compared with the half shoe group (61.0±6.5) (p=0.005) but similar to that for the walker (50.4±7.2) (p=0.07). There were also some differences in daily activity with those with the total cast taking significantly less steps daily than the half shoe group (p=0.04), but a similar number to the walker group (p=0.67) which also did not differ from the half shoe group (p=0.15).

Caravaggi et al (2000) compared a non-removable total off-loading cast made with fibre glass bandages against cloth therapeutic shoes with rigid rocker-bottom soles and unloading insoles in a randomised trial of 50 patients with diabetes and neuropathic foot ulcers. There were no differences in baseline characteristics between the 26 cast and 24 shoe patients but at 30 days follow-up, ulcers had healed in 13 of the cast patients compared with 5 shoe patients (p=0.032). Similarly, the reduction in ulcer size was faster in the cast group compared with the shoe group (p=0.0004). There were no adverse effects in either group. There were no differences in patient acceptance of the two treatments.

Mueller et al (1989) randomised 40 people with diabetes with foot ulcers (without gross infection, osteomyelitis or gangrene) to either total contact casting (TCC) or standard treatment. Accommodative footwear was provided to the control group. Both groups were told to reduce weight bearing; 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 6 from 19 in the standard treatment group (32%). The proportion difference was thus 58.9% (95%CI: 30.3% to 78.3%). Mean time to ulcer healing and infections requiring hospitalisation also significantly favoured TCC. The results of this trial need confirmation.

Oedema can be reduced with the application of compression. Armstrong et al (2000) randomised 115 patients with diabetes and foot infections requiring incision and debridement to treatment with a pulsatile pneumatic foot compression system (n=52) or a placebo device, which was similar with the exception that it did not inflate and provide compression (n=45). Eighteen patients did not complete the study. Patients received treatment for eight hours per day and were followed up weekly for 12 weeks. All patients also received an off-load walker. A higher proportion of healing occurred in the active treatment group (75%, 39) compared with the placebo group (51%, 23) ( $p<0.02$ , OD 2.9, 95% CI 1.2, 6.8) and time to healing was shorter ( $p=0.04$ ). Following treatment, oedema reduction, as measured by foot circumference, was greater in the treatment group ( $p<0.001$ ). Compliance (treatment for  $>50$  hours/week) with active treatment resulted in more patients healed than non-compliance ( $p=0.03$ ).

## Silicone

Reduced plantar thickness is associated with high plantar foot pressure and risk of foot ulceration. Increasing local plantar thickness by injecting silicone may reduce plantar pressure and result in reduced callus formation, another risk factor for foot ulceration. Van Schie and colleagues (2000) enrolled 28 patients with diabetes attending a Diabetic Foot Clinic (Manchester, UK) who had established neuropathy and a callus under at least one metatarsal head, in a randomised controlled trial. In the treatment group, 14 patients received six silicone injections per site (1-5 sites) at two-weekly intervals, whilst the 14 placebo subjects received saline injections in a similar manner. Patients were all treated similarly in skin preparation and bandaging and were followed up at 3, 6 and 12 months after baseline. Outcomes included dynamic plantar pressures, plantar tissue thickness at each injected site, and callus formation as assessed by scored photographs. No statistical differences were present between the two groups at baseline. The median plantar thickness increased in the silicone-treated group from baseline to follow-up but no change was seen in the placebo group ( $p<0.005$ ). Similarly decreases in plantar pressure from baseline to follow-up were seen in the silicone group but no change or a slight increase was seen in the placebo group ( $p<0.05$ ). An intention to treat analysis found a similar relationship in tissue thickness changes at 3, 6 and 12 months ( $p<0.008$ ) and in peak plantar pressure changes, significant at 12 months ( $p<0.02$ ) although not at 3 ( $p=0.06$ ) or 6 months ( $p=0.09$ ). Trends were seen in reduction of callus formation in the silicone group compared with the placebo group but these were not significant ( $p=0.3$ ). Adverse events were similar in the two groups, with three patients developing foot ulcers in the silicone group and four in the placebo group and no significant side effects were reported.

## Comment

Although there is reasonable data about the effectiveness of total contact casting, for individuals with severe ischaemia the friction that may be caused by the wearing of a cast may in itself cause injury in terms of skin breaks and thus this must also be considered when decisions are being taken about total contact cast use.

## Offloading references

(with evidence grades where appropriate)

Ib Armstrong et al (2001)

Ib Armstrong et al (2000)

Ib Caravaggi et al (2001)

Ib Mueller M J et al (1989)

Ib Van Schie et al (2000)

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# Other treatments for foot ulcers

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## Recommendation

**Currently, there is a lack of trial evidence on the use of the following interventions in the treatment of foot ulcers and they are not recommended: cultured human dermis (or equivalent), hyperbaric oxygen therapy, topical ketanserin, or growth factors. (D)**

## Evidence statements

*The value of cultured human dermis, and equivalents, is not clear from the evidence of available trials. (Ib)*

*The value of hyperbaric oxygen therapy is not clear from the evidence of 2 available trials. (Ib)*

*Evidence from 2 trials suggests that topical ketanserin (2%) in addition to conventional care may improve the rate of healing of diabetic foot ulcers, of Wagner grades II and III. (Ib)*

*Available trials indicate that growth factors CT-102 (dilution 0.01), RGDpm and rhPDGF in addition to conventional care may improve healing in diabetic foot ulcers with Wagner grades I and II with transcutaneous oxygen tension  $TcPO_2 \geq 30$  mmHg. (Ib)*

## Cultured human dermis and cultivated equivalents

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Cultured human dermis 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 (Gentzkow et al, 1996). [Human skin and cultured equivalents have been used to treat venous ulcers](#). The effectiveness of these as a treatment for diabetic foot ulcers is also being examined.

### **Cultured human dermis**

**Note:** Dermagraft® is currently not commercially available in the UK.

Naughton et al (1997) randomised 281 patients with neuropathic full-thickness foot ulcers in a multi-centre trial comparing cultured human dermis and conventional care. Conventional care included debridement, infection control, saline-moistened gauze dressings and special shoes and inserts. Cultured human dermis 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 cultured human dermis and 31.7% of patients receiving conventional care ( $p=0.14$ ). Differential loss to follow-up occurred (22% from cultured human dermis vs. 11% from control) making interpretation of findings problematic. The study suggests a dose-response effect with patients receiving all grafts doing better than those who did not; however, ability to receive full treatment may be confounded with underlying disease.

Gentzkow et al (1996) randomised 50 patients to 3 different dose regimens of cultured human dermis or standard care alone. Treatment groups received for 8 weeks: 1 piece of cultured human dermis applied weekly, 2 pieces applied every 2 weeks or 1 piece of cultured human dermis applied every 2 weeks. Ulcers were full thickness with area  $>1 \text{ cm}^2$  at enrolment; assessment was at 12 weeks. Only the first, maximally treated, group (1 piece of cultured human dermis 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 ( $p=0.03$ ). The mean ulcer duration before enrolment was 50 weeks in the first group and 87 weeks in the control group raising a question mark about comparability at baseline. No adverse reactions to cultured human dermis were reported or differences in the rate of infection of the wound between groups.

### Cost effectiveness

A cost effectiveness study by Allenet et al (2000) assessed Dermagraft® vs. standard treatment in the treatment of foot ulcers. A Markov model is developed and transition probabilities extrapolated from a clinical trial conducted in the USA (Naughton et al. 1997) although it is doubtful that the trial was powered to detect differences across the range of health states used in the model. No indication of the uncertainty around these values is provided. No description of standard treatment is given.

Costs are presented in “current” French francs (2000) and are based on expert opinion. The assessment was over a 52 week period and no discounting was therefore applied. Cost effectiveness is presented in terms of cost per ulcer healed. Dermagraft® generates additional benefits by reducing the average time to heal and, additionally, ulcers that recur heal faster if they were originally treated with Dermagraft®. The additional cost of dermagraft is not recouped by lower ulcer treatment costs. The incremental cost per additional ulcer healed is 38,784 ff. A small number of one-way sensitivity analyses are performed which vary the ICER between 34,000 and 53,000ff. No indication of the likelihood of these ranges is given.

### Cultured skin equivalents

**Note:** Apligraf® is currently not commercially available in the UK.

Veves et al (2001) used Graftskin (Apligraf®), an allogenic bilayered cultured skin equivalent, in a multicentre randomised trial. Participants had diabetes, either Type 1 or Type 2, were aged 18-80 years and had full thickness neuropathic ulcers of  $\geq 2$  weeks duration and  $1 - 16 \text{ cm}^2$  post debridement, which had not responded (any reduction in size was  $<30\%$ ) to a screening 7 day treatment with saline-moistened gauze. One hundred and twelve people were randomised to the Graftskin treatment and 96 to a control treatment of saline-moistened gauze. Patients were followed up for twelve weeks, with dressing changes made routinely in each of the first four weeks in both groups plus other changes as necessary. All patients were fitted with customised sandals and instructed to avoid bearing weight on the affected foot. Unhealed ulcers at week five, in both groups were subsequently treated with saline-moistened gauze. Withdrawals and adverse events were similar in the two groups, but analysis was on intention to treat. Complete wound healing occurred in 56% (63) of the treatment group and 38% (36) of the control group ( $p=0.0042$ ) (OR 2.14, 95% CI 1.23, 3.74). Time to complete healing was also shorter in the treatment group, with a median time of 65 days compared with 90 days in the control group ( $p=0.0026$ ). Significant differences in time to closure were maintained in a regression analysis model ( $p=0.0001$ ) and the estimated hazard ratio indicated that an average patient treated with Graftskin had a 1.59-fold better chance for closure per unit time that a patient in the control group (95% CI 1.26, 2.00).

## Hyperbaric oxygen therapy

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Hyperbaric oxygen (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 antibacterial effect on anaerobic organisms.

One new randomised controlled study has been published since the original guideline literature survey was conducted. Heing et al (2000) carried out a trial of topical hyperbaric oxygen at 1.004 to 1.013 atmospheres on newly admitted non-ambulatory residents with life-threatening gangrene, uncontrolled diabetes and untreated sepsis in a long-term care facility in Los Angeles, USA. Patients were randomly assigned, by drawing lots, to receive oxygen for four hours/day, four days/week for four weeks (n=13 with 29 ulcers of which 21 were diabetic) or standard wound care for four weeks (n=27 with 50 ulcers of which 16 were diabetic). Numbers between the groups were unbalanced, because only two patients could be treated with oxygen therapy at any one time and any 'over-flow' new patients were included in the standard care group. Oxygen was administered topically via a 84 x 48 inch pleated polythene bag taped at chest level. Patients were similar at baseline in all parameters tested and the study was powered (89%) to treat at least 10 patients (20 wounds) with either treatment. In the oxygen therapy group, 26 (90%) of the 29 ulcers healed within 2 to 16 weeks, whereas in the standard care group, 8 had healed by 7 months, a further 3 by 15 months (22% in total). Ulcer size was significantly smaller after four weeks with the oxygen therapy, down from  $11.9 \pm 7.8 \text{ cm}^2$  to  $3.0 \pm 11.8 \text{ cm}^2$  compared with  $7.8 \pm 8.8 \text{ cm}^2$  increased to  $11.8 \pm 11.9 \text{ cm}^2$  in the standard care group ( $p < 0.001$ ). Subgroup analysis of diabetic ulcers only, found no difference between diabetic and nondiabetic necrotic ulcers in improvement per day ( $p = 0.203$ ). For diabetic ulcers classified by stage of ulceration, changes in size over four weeks between the two treatment groups, mirrored those for the total patient groups and showed that, in the oxygen therapy group, ulcer mean size reduced, whatever the stage, whilst in the standard wound care group, ulcer mean size increased, in all stages, although no statistical tests were reported.

Faglia et al (1996) randomised 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). Standard treatment included radical debridement, antibiotic therapy and provision of orthopaedic devices. Patient groups appear comparable at baseline, except that the control group had more claudication ( $p = 0.07$ ). Treatment group patients sat in a hyperbaric chamber breathing pure oxygen pressurised at 2.5–2.2 atmospheres in 90-minute daily sessions. The study was powered to detect a reduction of  $\frac{1}{3}$  in major amputation rate. 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.

Leslie et al (1988) randomised 28 patients to HBO treatment (90 minutes, twice daily for 2 weeks) or to clinical management alone. All patients had well demarcated foot ulcers without gangrene or other major complications and received debridement, intravenous antibiotics, wet-to-dry dressings and bed rest. HBO was topically applied using a leg chamber and cycled pressure (up to 1.04 atmospheres every 20 seconds). Ulcers in both groups improved significantly; however, there were no statistically significant differences between groups at 2 weeks follow-up. No significant differences were found in ulcer area or depth (as a percentage of baseline) between the HBO group and the control group at 2 weeks.

The study by Leslie and colleagues did not involve severe grade ulcers, did not use breathed but topical oxygen therapy, and did not use substantially raised or sustained pressure. It is unclear which of these effects may be important in achieving benefit from HBO therapy. Further evaluation of effectiveness, and consideration of cost-effectiveness is required.

## Ketanserin

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**Note:** this is not listed in BNF, included for completeness of review only.

Ketanserin is a 5HT<sub>2</sub> 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.

Martinez-de Jesus et al (1997) randomised 140 people with diabetes with neuropathic foot ulcers (<100 cm<sup>2</sup>, Wagner grade II or III) to topically applied ketanserin (2%) or (unmatched) normal saline. A sample size calculation of 65 per arm is presented, assuming an improvement in healing from 50% to 75%, when conventionally powered. All patients enrolled were hospitalised for debridement, parenteral antimicrobial treatment, foot rest and correction of fasting hyperglycaemia caused by sepsis. Patients received outpatient care after discharge. Groups were comparable in all important characteristics except smoking, which was more common in the ketanserin group (p=0.043). By 2 weeks, 21 patients (13%) had withdrawn and are not included in the numbers presented: it is not reported whether dropout was equivalent between groups. At 12 weeks, the average percentage reduction in ulcer area was 87.5% for intervention and 62.8% for placebo (p<0.001): this equated to average daily reductions in ulcer areas of 4.5 mm<sup>2</sup>/day and 2.88 mm<sup>2</sup>/day respectively.

Apelqvist et al (1990) randomised 40 patients to ketanserin (oral, 20 mg tid for 1 month, then 40 mg tid for 2 months) or placebo. Otherwise, all patients were offered the same treatment for their ulcers. Patients enrolled had a deep or superficial ulcer, with an area of 1 cm<sup>2</sup> 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).

Janssen et al (unpublished) randomised 299 patients, including 45 people with diabetes with chronic ulcers, to ketanserin (2% ointment) or vehicle placebo. Both groups otherwise received conventional care, and follow-up was for 8 weeks. The study reports the initial velocity of healing to be 3-fold faster with ketanserin ointment than placebo (p<0.001), in the sub group of people with diabetes. No detailed presentation of results is given for the diabetic foot ulcer sub group. Patients were not randomised into strata by wound type and baseline comparability of the people with diabetes unknown.

These trials report different endpoints making comparison between studies problematic. It is unclear what the respective bioavailabilities are of topical or oral ketanserin. The (relatively) large study by Martinez-de Jesus and colleagues indicates a clinically important benefit from topically applied ketanserin when applied in addition to comprehensive care in relatively severe ulcers, but requires further confirmatory evaluation.

## Growth factors

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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. We identified 6 randomised controlled trials, in which 4 types of growth factor have been used in the treatment of people with diabetes with foot ulcers (see Appendix 11 for details). 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  $\beta$ ; and RGDpm is an arginine-glycine-aspartic acid peptide matrix.

Wieman et al (1998) randomised 382 patients to receive either 100  $\mu\text{g/g}$  or 30  $\mu\text{g/g}$  rhPDGF once daily or placebo (vehicle gel) in a multi-centre trial. All patients had chronic neuropathic foot ulcers free of infection, received sharp debridement of ulcers at baseline and subsequent debridement of callus and necrotic tissue as required. Patients attended as outpatients and were followed for 20 weeks or until healing. After 20 weeks, 50% of ulcers healed with 100  $\mu\text{g/g}$  rhPDGF compared with 35% in the placebo group,  $p=0.007$ . No differences in outcome were found between 30  $\mu\text{g/g}$  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  $\mu\text{g/g}$  rhPDGF, contrasting with Steed et al (1995b) which found significant benefits. The investigators suggest this may be due to better infection control, and the use of a relatively small number of experienced centres for treatment, in the latter study.

Steed et al (1995a) randomised 65 patients, with chronic full-thickness neurotrophic foot ulcers, to RGDpm or placebo (normal saline) in a multi-centre trial. RGDpm was applied topically twice weekly for up to 10 weeks in patients who otherwise received conventional care, including twice-weekly clinics. Ulcers were 1–15  $\text{cm}^2$  in area, 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 completely healed was significantly greater in the RGDpm group, 35% (14/40) vs. 8% (2/25) in the control group,  $p=0.02$ . A significantly greater proportion had achieved >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 (1995) randomised 17 patients, suffering from chronic neuropathic foot ulcers of Wagner grade I to III without infection, to receive rbFGF or placebo (normal saline) daily for 6 weeks and then twice weekly for 12 weeks. After 18 weeks, 3 of 9 ulcers healed with rbFGF and 5 of 8 in the placebo group,  $p=\text{NS}$ . There was no significant change in rate of healing or percentage of area healed at 18 weeks. No drug-related adverse events were observed.

Steed et al (1995b) randomised 118 patients to receive rhPDGF (30  $\mu\text{g/g}$ ) once daily or placebo (vehicle gel) in a multi-centre trial. All patients had chronic neuropathic foot ulcers free of infection, received sharp debridement of ulcers at baseline and subsequent debridement of callus and necrotic tissue as required. Patients 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.

Holloway (1993) randomised 97 patients to 3 different dilutions of CT-102, (CT-102: 0.1, 0.033 and 0.01) or matched placebo (normal saline solution or isotonic platelet buffer) in a multi-centre trial. Some 27 patients were removed from the analysis due to protocol violation, 11 after randomisation. Wounds were chronic, diabetic non-healing ulcers of at least 8 weeks' duration and volume 500  $\text{mm}^3$  to 50,000  $\text{mm}^3$ . All patients received debridement of ulcers at baseline, subsequent debridement of callus and necrotic tissue as required, and were seen weekly for 2 weeks

and then bi-weekly. The best results were seen in the lowest dilution: 80% of wounds with CT-102–0.01 healed versus 29% in the placebo group ( $p=0.01$ ). However, this group contained 6 of the 11 patients removed from the analysis. The mean volume reduction for CT-102 (all dilutions) was 94.9% versus 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.

Steed et al (1992) randomised 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 >8 weeks duration and no wound infection. Wounds were debrided at baseline, had volumes 700 mm<sup>3</sup> to 50,000 mm<sup>3</sup>, had areas <100 cm<sup>2</sup> and involved subcutaneous tissue. Patients agreed to be totally non-weight-bearing and were evaluated as outpatients weekly then fortnightly. In the CT-102 group, 5 of 7 ulcers were healed at 20 weeks compared with only 1 of 6 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.

The available trials of growth factors indicate clinically important benefits from 3 growth factors applied in addition to conventional care: CT-102 (dilution 0.01), RSDpm and rhPDGF. On the basis of 1 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. All findings need confirmation from further trials and assessment of cost-effectiveness.

## Granulocyte-colony stimulating factor

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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, and thus reduce infections and their sequelae. While people with diabetes are not neutropenic, diabetes represents an immunocompromised state secondary to neutrophil dysfunction. It is hypothesised that improved neutrophil production and function will improve bactericidal activity in foot ulcers (Gough et al, 1998).

A small study by de Lalla et al (2001) found no differences in reduction in foot infection between 40 Italian adults with diabetes and severe limb-threatening foot infection randomised to receive G-CSF with local treatment and systemic antibiotic therapy ( $n=20$ ) or local treatment and systemic antibiotic therapy only ( $n=20$ ). G-CSF was given subcutaneously at a dosage of 263 µg daily for 21 days and reduced or discontinued if the neutrophil count exceeded certain defined values. All patients required insulin. There were no differences between the two groups of patients upon recruitment and no patient's infection was cured during the three weeks of treatment although improvement was seen in 60% (12/20) of the G-CSF group and 45% (9/20) of the standard treatment group ( $p>0.05$ ). After three weeks of treatment, one amputation was required (5%) in the G-CSF group and 5 (25%) in the conventional treatment group ( $P=0.08$ ). In further follow-up six months after recruitment there were no differences in infection, cure, or deterioration between the two groups.

In a randomised controlled study of 30 Turkish hospital patients with diabetes and infection of the skin and subcutaneous tissue (pedal cellulitis) or a foot lesion, patients either received 0.5–0.2.5µg/kg recombinant human G-SFF (filgrastim) subcutaneously once daily or every two days dependent upon neutrophil count plus local wound care and parenteral antibiotherapy, or local wound care and parenteral antibiotherapy only (Yonem et al 2001). All patients were on daily

multiple-dose injections of short-acting insulin and the study interventions were given for ten days. Outcomes were time to resolution of infection and time to hospital discharge and neither of these differed statistically between the two groups. Duration of hospitalisation was  $26.9 \pm 2.0$  versus  $28.3 \pm 2.2$  days and time to resolution of infection was  $23.6 \pm 1.8$  versus  $22.3 \pm 1.7$  days in the G-CSF and standard groups respectively.

One trial randomised 40 people with diabetes, with foot infections featuring extensive cellulitis, to intravenous G-CSF (filgrastim) or placebo for 7 days (Gough et al 1997). All patients received antibiotic therapy until resolution. A further 17 patients were excluded at the screening stage due to critical leg ischaemia, immediate surgery, renal impairment or psychiatric illness. Median time to hospital discharge, resolution of cellulitis, withdrawal of intravenous antibiotics and negative swab culture were all statistically significantly reduced. 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, 7 days of treatment costs approximately £540 per patient. However apparently significant reductions in other resources mean that the cost-effectiveness of G-CSF intervention for foot infection should be formally explored.

### Cost effectiveness

Edmonds et al (1999) describes a cost-minimisation study conducted retrospectively around an RCT of the use of filgrastim vs placebo for diabetic patients with extensive foot cellulitis. The clinical study was reported in Gough et al. (1997).

The trial was conducted in the UK but consisted of just 40 patients (20 in each arm). Given such small numbers, it is unlikely that the RCT was sufficiently powered to detect differences and a cost minimisation study may not be appropriate. Furthermore, the source of cost differences in the absence of any difference in clinical outcome requires clarification. The paper states that patients received a combination of four antibiotics in addition to either filgrastim or placebo until cellulitis and ulcer discharge was resolved. More expensive drugs would be used when penicillin hypersensitivity or drug resistance was reported.

Direct medical resource use consumed during hospital stay were calculated by reference to clinical report files and patient hospital records on a subset of 28 patients. Unit costs were calculated using “B-plan software” where possible, which is claimed to be a system which helps to calculate unit costs. Costs are presented in 1996 £’s and covered length of hospital stay, laboratory tests, diagnostic procedures, drugs and surgical interventions.

The median length of hospital stay was 10 days (filgrastim) vs. 17.5 days (placebo) ( $p=0.02$ ), time to resolution of cellulitis was 7 days (filgrastim) and 12 days (placebo), ( $p=0.03$ ), time to stopping intravenous antibiotics was 8.5 days (filgrastim) and 14.5 days (placebo), ( $p=0.02$ ), the proportion of patients where cellulitis had resolved at day 7 was 55% (11) (filgrastim) and 20% (4) (placebo), ( $p<0.05$ ), the proportion of patients in whom angiography was necessary was 20% (4) (filgrastim) and 35% (7) (placebo), ( $p=0.6$ ), the proportion of patients in whom surgery was required was 0% (filgrastim) and 20% (4) (placebo), ( $p=0.34$ ).

Costs were modelled over different treatment stages. During the “well” stage no difference was observed. Large differences were observed between the “no intervention” stage with a mean cost of £9536 (filgrastim) vs. £28,968 (placebo) but this is explained by a single outlier that was hospitalised for 100 days. In general, results show that filgrastim is cost saving and this saving is greater in patients with no tissue necrosis ( $n=20$ ).

## Electrical stimulation

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Electric current has been shown to facilitate wound healing in animal models and improve blood flow to the foot in vascular studies in diabetes patients. Peters et al (2001) conducted a randomised controlled trial to evaluate the effectiveness of electrical stimulation as a facilitator of healing of diabetic foot ulcers. Patients with diabetes and foot ulcers were randomly allocated to receive a current delivered to a Dacron-mesh silver nylon stocking (n=21) or no current but using the same electric stimulation units (n=20). The treatment comprised a dose of 50V with 80 twin peak monophasic pulses per second delivered for 10 minutes followed by 10 minutes of 8 pulses per second of current. Following electric stimulation the device went onto standby for 40 minutes, and then nightly for an 8 hour period each night, for twelve weeks or until the ulcer healed, whichever happened first. All patients also received traditional wound care of debridement, collagen wound gel, and pressure reduction at the site of ulceration. Ulcers healed in 13 (65%) of the patients who received electrical stimulation but only in 7 (35%) of the placebo group (p=0.058). When stratified by compliance (use of the device for 20 hours of more per week), in compliant patients in the treatment group 71% (10/14) healed compared with 50% (3/6) non-compliant treatment patients, 39% (5/13) compliant placebo patients and 29% (2/7) noncompliant placebo patients (p=0.037). There were no significant differences in rate of healing and average time to healing between the treatment and placebo groups. Dropouts were similar in number in the two study groups. High voltage pulsed galvanic electric stimulation may enhance wound healing when used for more than 20 hours per week but further larger studies are needed to confirm the findings of this pilot study.

## Sulodexide

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**Note:** this is not listed in BNF, included for completeness of review only.

Various medications have been considered as potential promoters of foot ulcer healing. Koblik et al (2001) conducted a pilot study to assess the impact of sulodexide, an antithrombotic drug used successfully for peripheral occlusive arterial disease, on foot ulcer healing rates. Eighteen patients with persisting diabetic foot syndrome and monolateral foot ulcers were randomised on a 2:1 ratio to treatment with insulin plus sulodexide (1 vial – 600LRV daily for 15 days, then 1 cap –250LSU for 2 months) or a similar insulin plus placebo treatment. Diet control was similar in both groups and all had a 5 day run-in phase for insulin dose adjustment.. There were no statistically significant differences in ulcer healing rates between the two groups. In the sulodexide group, 92% of foot ulcers healed in a mean time of 46.4±5.2 days compared with the placebo group, with 83% healing in 63±8.5 days (p=0.09).

## Other treatments for foot ulcers references

(with evidence grades where appropriate)

### Cultured human dermis

- Ib Gentzkow G et al (1996)
- Ib Naughton G et al (1997)
- Ib [Veves et al \(2001\)](#)

### Hyperbaric oxygen

- Ib Faglia E et al (1996)
- Ib Leslie C et al (1988)
- [Heing et al \(2000\)](#)

### Ketanserin

- Ib Apelqvist J et al (1990)
- Ib Martinez-de Jesus FR et al (1997)
- Ib Janssen et al (unpublished)

### Growth factors

- |                            |                           |
|----------------------------|---------------------------|
| Ib Holloway G et al (1993) | Ib Steed D et al (1995a)  |
| Ib Richard J et al (1995)  | Ib Steed D et al (1995b)  |
| Ib Steed D et al (1992)    | Ib Wieman TJ et al (1998) |

### Granulocyte-colony stimulating factor

- Ib Gough A et al (1997)
- Ib [Yonem et al \(2001\)](#)
- Ib [de Lalla et al \(2001\)](#)

### Electrical stimulation

- Ib [Peters et al \(2001\)](#)

### Sulodexide

- Ib [Koblik et al \(2001\)](#)

DR.RUPNATHJI ( DR.RUPNATH )

# Education for patients with foot ulcers

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## Recommendation

**For patients with foot ulcers or previous amputation, health care professionals could consider offering graphic visualisations of the sequelae of disease and providing clear, repeated reminders about foot care. (B)**

## Evidence statement

*In patients with foot ulcers or previous amputation, 1 trial indicates that education including frank presentation of the consequences of disease and a simple patient instruction checklist reduces morbidity. (Ib)*

## **Evidence**

One American randomised trial of an educational intervention was retrieved involving 203 people with diabetes with either uninfected ulcers or previous amputation (Malone et al, 1989). In addition to usual care, the intervention group received 1 (1 hour) education session on foot care which included a slide-show of infected feet and amputated limbs, and a patient instruction checklist. Follow-up was longer in the intervention than control group (mean follow-up 13.2 and 9.2 months respectively).

The study showed a significant 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 a significant excess of ulceration (education 5%, control 15%) and amputation (education 4%, control 12%) in the control group. Statistical calculations assume 'independence' of limbs which may not be valid.

Undoubtedly the educational component contains a 'scare-tactic' component and it is unclear whether this approach is generalisable. None the less the reduction in morbidity at approximately 1 year is impressive and the method merits evaluation in the British context.

## **Education for patients with foot ulcers references**

(with evidence grades where appropriate)

Ib Malone JM et al (1989)

## 8. Care of people with Charcot osteoarthropathy

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# Caring for people with Charcot osteoarthropathy

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## Recommendation

**People with suspected or diagnosed Charcot osteoarthropathy should be referred immediately to a multidisciplinary foot care team for immobilisation of the affected joint(s) and for long term management of off-loading to prevent ulceration. (D)**

## Evidence statements

*Mobilising in the active disease state leads to further joint damage. (IV)*

*The resulting deformity with neuropathy increase the risk of ulceration and protective footwear needs to be provided. (IV)*

## **Introduction**

Charcot osteoarthropathy is a progressive condition. It is characterised by dislocation of joints, fractures and destruction of the bony architecture. It is associated with severe peripheral neuropathy. In people with severe diabetic neuropathy the osseous breakdown, in most cases, is localised to the midfoot, with risk of collapse of the pedal arch. The acute swelling and the later deformity associated with this are major risk factors for ulceration and subsequently amputation. Such patients also have decreased bone mineral density compared with those without diabetes of a similar age and sex (Childs et al 1998). It is thought that bony trauma in a severely neuropathic limb may be a trigger for the development of Charcot osteoarthropathy. Continued walking promotes progression of the osteoarthropathy and worsening of the deformity.

## **Incidence and prevalence of Charcot's osteoarthropathy**

The incidence of Charcot deformity was found to be 0.3%/year in a study of people with diabetes attending a specialist hospital for diabetes (Fabrin et al 2000). Armstrong et al (1997) reported a prevalence of acute-onset Charcot's osteoarthropathy among all patients reporting to their Diabetic Foot Centre in Texas of 12.9% or 3.8%/year (55 in 426 patients, between February 1991 – June 1994 inclusive).

## **Incidence of ulceration in patients with Charcot's osteoarthropathy**

In a study of 140 feet with Charcot's osteoarthropathy in 115 patients with diabetes followed up for median time of 48 months (range 6-114 months), 43 patients developed 68 ulcers on 53 feet. The incidence rate of ulceration was 17% per year (Larsen et al 2001).

## **Screening for Charcot's osteoarthropathy**

Isotope and MR bone scans can be used as an imaging modality to help distinguish osteoarthropathy from osteomyelitis, often a difficult differential diagnosis. The Tc-99m HMPAO Labeled Leukocytes Scan may also help to distinguish those with osteomyelitis. None of these tests has 100% sensitivity and specificity. People with a Charcot deformity of the foot have serious ambulatory disabilities. Using the Sickness Impact Profile questionnaire, Dahmen et al (1995)

found reduced scores for physical, social, psychological, communicative and activities of daily life categories in 12 patients with diabetes and osteoarthopathy lesions of the foot, compared with scores expected from people without disability.

Various treatment options are available, the aim being to maintain skin integrity and avoid infection and amputation.

## Evidence

From the literature three studies only were identified that described interventions for the treatment or management of Charcot's neuroarthopathy. Two of these three were randomised double blind trials (Chantelau and Schnabel 1997, Jude et al 2001) and both were concerned with healing of the condition using outcomes such as loss of swelling and redness (Chantelau and Schnabel 1997) or reduction in foot temperature or foot pain (Jude et al 2001). The treatment approaches in the two groups differed totally. Chantelau and Schnabel administered radiotherapy whilst Jude et al delivered a single infusion of pamidronate, a biophosphate. Given the incidence of this condition, Chantelau and Schnabel took three years to recruit their 12 patients, whilst Jude et al used four centres in the UK to recruit 39 patients. The impact of both of these treatments on defined outcome compared with their placebo alternative was not significant with one exception. Symptom scores, based on an aggregation of patient assessed pain, discomfort and swelling fell in both the treatment and placebo groups within the first three months, but then continued to fall in the treatment group over the next nine months ( $p < 0.01$ ) giving a significant area under the symptom score curve difference (treatment group  $14.3 \pm 8.7$ , placebo group  $23.8 \pm 8.4$ ,  $p = 0.01$ ) (Jude et al 2001).

The other paper was a retrospective review of treatment for a cohort of patients with Charcot's neuroarthopathy. Armsrong et al (1997) treated their 55 patients with total contact casting, the frequency of changing being based upon ulcer status. Casting was replaced by removable cast walkers and ultimately by prescription footwear on the basis of clinical, radiographic and dermal thermometric signs of quiescence of the condition, with none of these terms being clearly defined. All patients were casted for  $18.5 \pm 10.6$  weeks (range 4-56 weeks) and progression to prescription footwear took  $28.3 \pm 14.5$  weeks.

## References for Charcot osteoarthopathy

(with evidence grades where appropriate)

- III Armstrong et al (1997)
- Ib Chantelau and Schnabel (1997)
- Ib Jude et al (2001)

# 9. Indications for referral

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These indications for referral are related to the recommendations for care presented in Sections 4 – 8.

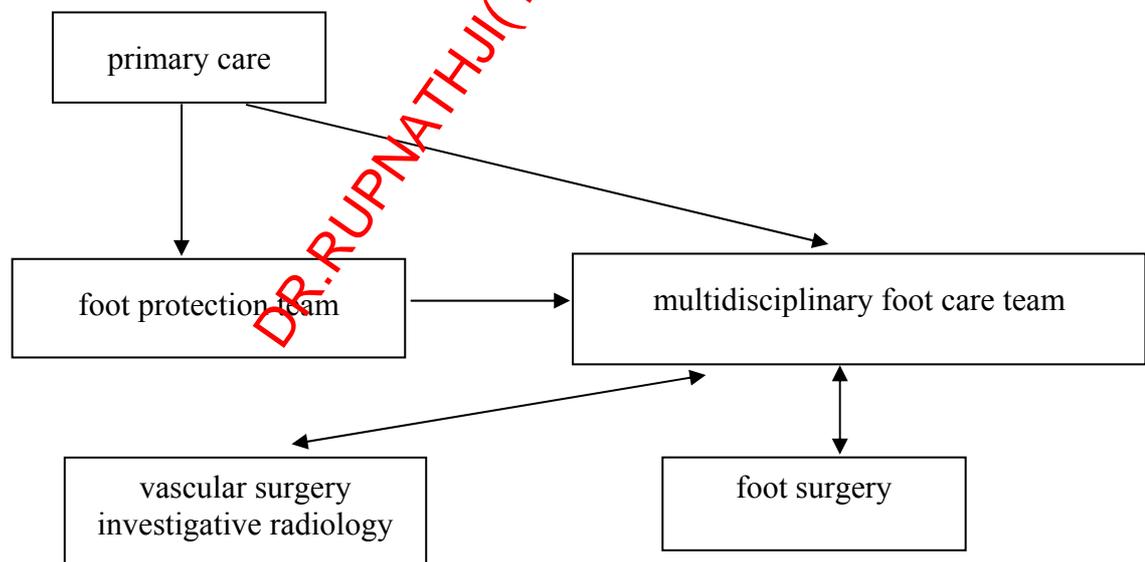
## Emergency referral

Refer patients to a multidisciplinary foot care team within 24 hours if any of the following occur:

- new ulceration (wound)
- new swelling
- new discolouration (redder, bluer, paler, blacker, over part or all of foot) (D)

## Other referrals

The model of an integrated service for people with at risk feet, using a pyramidal approach is preferred (horizontal referrals may also of course take place).



**Indications for specialist referral to:**

- specialist foot teams
  - covered by recommendations
- footwear
  - addressed in offloading section
- podiatry and orthotics
  - in primary care find those at risk, from annual examination, who have not previously identified as having at risk feet, refer on to an at-risk clinic (using existing risk classification in guideline)
- surgery – all patients should have a non-invasive vascular assessment before surgery to ensure appropriate referral to either vascular surgery or orthopaedic surgery
  - vascular surgery
    - people with critical ischaemia and people with peripheral vascular disease with a non-healing ulcer (not healing within 4 weeks) (ischaemic ulcer – ankle pressure (*ankle-brachial index*) < 0.5 or calcified arteries, monophasic), foot appearance – pink atrophic ulcer, lateral aspect
  - orthopaedic surgery
    - bad infection of neuropathic foot
    - procedure to heal rocker bottom feet
    - people without peripheral vascular disease

**Mobility assessment:**

- should form part of integrated care

**Pain management:**

- one role of the multidisciplinary foot care team is the responsibility for ensuring pain is managed in accordance with best practice

# 10. Audit criteria

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- ◆ The percentage of patients with recorded diabetes who have had a foot examination for neuropathy, peripheral pulses and deformity in the previous 15 months.
- ◆ The percentage of patients with recorded diabetes who have had their foot risk classified.
- ◆ The percentage of patients with recorded diabetes with feet at high risk of ulceration who attend a podiatry service.
- ◆ The percentage of patients with recorded diabetes with a new ulcer in the previous 12 months.
- ◆ The percentage of patients with recorded diabetes with a new below ankle amputation in the previous 12 months.
- ◆ The percentage of patients with recorded diabetes with a new above ankle amputation in the previous 12 months.
- ◆ The percentage of patients who have a record of an agreed management plan (including patient education) in the previous 15 months.

These audit criteria are consistent with those addressed by the new GP contract and the National Audit of Diabetes.

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# 11. Research issues

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The guideline development group identified the following areas which they felt were inadequately addressed by the available literature.

- ◆ Therapeutic footwear should be evaluated for effectiveness and cost-effectiveness in patients at higher risk of ulceration.
- ◆ A co-ordinated and comprehensive trial programme is required for all aspects of foot ulcer treatment and care: notably the effectiveness and cost-effectiveness of different antibiotic regimens, wound dressings and other treatments for diabetic ulcer.
- ◆ Further research is required to identify the appropriate level and combination of risk factors at which patients should be categorised as at high risk for ulceration and be offered attendance on a protection programme.
- ◆ Research is required to identify strategies for ensuring ongoing care and evaluation for people with diabetes who are elderly or have mobility problems.
- ◆ The use of standardised measures, including ulcer classification and outcome measures, in research studies would greatly enhance the ability of reviewers to undertake better analysis, including comparison of outcomes of interventions.
- ◆ The effectiveness of patient education, including patient education that uses graphic visualisations of the sequelae of disease in relation to foot ulcers, should be investigated.
- ◆ Different models, approaches and means of delivery of patient education should be investigated.
- ◆ The use of pressure relieving devices, including pressure relieving shoes, should be evaluated.
- ◆ The effectiveness of patient self-monitoring of foot problems should be evaluated.

# 12. References

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The Roman numerals indicate the evidence grading given to that particular paper.

If no grading is shown, it means that the paper was not of a type that could be graded according to the system used.

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- Young MJ, Boulton AJM, MacLeod AF et al (1993) A multicenter study of the prevalence of diabetic peripheral neuropathy in the United kingdom hospital clinic population *Diabetologia* **36**: 150-54

Excluded studies

<b>Authors, year of publication</b>	<b>Reason for rejection</b>
Ahroni JH et al, 1999	Screening for in-shoe plantar pressure
Ahroni JH, et al	Paper on reliability of Fscan inshoe system
Akova M et al, 1996	Intervention – sulbactam ampicillin, not RCT
Albert SF & Chan WY, 1996	Intervention – foot orthoses, not RCT
American Diabetes Association	Summary paper of Technical Report, 1998
Amos AF et al, 1997	Projections, data in first guideline review, no new information
Apelqvist et al, 2000	Guideline, no references
Armstrong DG et al, 1996	Surgical procedure - prophylactic surgery, not in scope
Armstrong DG, Lavery LA 1998	Non-systematic review
Armstrong, DG et al 1998	Intervention – total contact casts, not RCT
Ashry HR et al, 1997	Intervention – insoles, not RCT
Association of Physicians in India	Guideline, no references for foot care
Baker LL et al 1997	Intervention – electrical stimulation, not a RCT
Bakker , 1999	Consensus, no references
Bale S, et al, 2001	Intervention – alginate dressing, not RCT
Banks AS & McGlamry ED, 1989	Information too old
Bennett SP et al 2003	Non-systematic review of growth factor treatments
Bentomane A et al, 2000	Epidemiology, France, retrospective
Boulton AJM et al, 1998	Guideline no references
Boulton AJM, 1998	Guideline – no references
Bowering CK, 1998	Intervention – compression bandaging, not a RCT
Bradley M, et al, 1999	Systematic review but latest search date, 1997
Brem H et al, 2000	Intervention – human skin equivalent, not RCT
Bruckner et al, 1999	Intervention - education for health professionals, not in scope
Brunner U & Eberlein T, 2000	Intervention – hydrofibres, not RCT
Campbell L, et al 2000	Review, not systematic, references checked
Caputo GM et al 1998	General information on Charcot foot
Colberg SR & Swain DP, 2000	Review – exercise, no foot specific, not systematic
Connolly JF & Csencsitz TA 1998	Case studies of complications
Cooper PS 2002	Review, not systematic
Conti SF 1999	Non-systematic review
Curran MP & Plosker GL. 2002	Non-systematic review of use of skin substitute
Dargis V et al, 1999	Intervention – multidisciplinary approach, not RCT
Dimitrakoudis D & Bril V, 2002	Screening, but no gold/ideal standard
Donaghue VM et al, 1996	Intervention – in-shoe pressure relief footwear, not RCT
Ebskov LB et al, 1998	Amputation and survival, not in scope
Elliott J et al 2002	Assessment tool for diabetic foot, information piece
Faglia E et al 1996	Intervention – peripheral percutaneous transluminal balloon angioplasty, not a RCT
Farber et al 2002	Surgical technique
Foster AVM 2002	review, not systematic, references checked
Gill D , 1999	Review – hydrocolloids, not systematic
Giurini JM & Rosenblum BI. 1995	Surgery
Grady et al 2000	Non-systematic review plus case studies
Guse ST 1997	Information piece
Guzman-Gardeazabal E. et al, 2000	Intervention – becaplermin gel, not RCT

Hanna GP et al 1997	Intervention – transcatheter for limb salvage, not RCT
Harvima IT et al, 1999	Intervention – allogenic skin cell, not RCT
Hogge et al, 2000	Review, not systematic, references checked
Holstein P et al, 2000	Amputations, incidence
Jiang YD et al, 1999	Intervention – education programmes, not RCT
Kastenbauer T et al, 1998	Intervention – running shoes, not RCT
Keith S et al, 2000	Intervention – vacuum-assisted closure, not true randomisation
Kiegler D & Gries A, 1997	Review of $\alpha$ -lipoic acid, not systematic
Klenerman L et al	Screening – in first guideline review
Lavery L et al, 1995	Amputation, not in scope
Lavery LA et al, 1996	Intervention – reduce foot pressures, not RCT
Ledda MA et al, 1997	Intervention – foot self-care programme, not RCT
Lobmann R et al, 2001	Intervention – footwear, not RCT
Miller MS, 1999	Intervention – topical recombinant human platelet derived growth factor (Becaplermin), not RCT
Mumcuglu KY et al 1998	Intervention – maggot therapy, not RCT
O’Meara S et al, 2000	Systematic review, latest search date, December 1998
Pataky Z et al, 2000	Intervention – foot pressure device, not RCT
Pham DT et al, 1996	Post amputation, not in scope
Pham HT et al, 1999	Intervention – human skin equivalent, subgroup of study by Veves et al, used Veves et al
Piaggese A et al, 1998	Intervention – surgery, not in scope
Pinzur MS et al, 1999	Guideline – latest references 1997, so all in first foot care guideline
Premalatha G et al 2002	Screening sensitivity of instruments for peripheral vascular disease
Rajbhandari SM et al, 1999	Screening, transcutaneous oxygen pressure, no sensitivity or specificity information
Rollins G et al, 2000	Guideline, no references
Sams HH et al, 2002	Intervention – graftskin, report from one centre in multicentre trial, used paper of full trial
Sauseng S et al, 1999	Examination of plantar pressures in patients with and without plantar ulceration as potential explanatory factor for development of foot ulcers.
Schindl A et al, 1998	Intervention – laser irradiation RCT, outcome changes in local skin temperature, lab-based study
Smiel JM et al, 1999	Review – becaplermin gel, 4 unpublished RCTs, not systematic
Smiell JM,	Review, becaplermin gel, 6 unpublished clinical trials, not systematic
Spencer S, 2000	Systematic review, all references in first guideline review, except 1, from unpublished data, still unpublished.
Sriussadaporn S et al, 1998	Self-care observational study, reject
Steed DL et al, 1996	In first guideline review
Suico JG et al, 1998	Same study as Litzelman et al 1993 in first guideline review, paper reports on
Van Gils CC et al, 1999	Surgical procedure – vascular surgery, not in scope
Weiman TJ,	Review, becaplermin gel, 4 unpublished RCTs, not systematic
Wong MWN et al 2001	Intervention – debridement and herbal drinks, not RCT
Zimny S et al, 2001	Screening for blood flow – transcutaneous oxygen pressure, early evidence, n=21

## Excluded Studies - references

- Ahroni J H, Boyko E J, Forsberg C, (1999) Clinical correlates of plantar pressure among diabetic veterans. *Diabetes Care* **22**: 965-972.
- Ahroni J H, Boyko E J, Forsberg R, (1998) Reliability of F-Scan in-shoe measurements of plantar pressure. *Foot and Ankle International* **19**: 668-673.
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FINAL DRAFT

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