Appendix K: Deleted text from NICE guideline CG119

Retained recommendations summary table

The only recommendations from NICE clinical guideline 119 (CG119) which have not been directly updated by an evidence review are being retained and are listed in the table below. All other recommendations except for recommendations 1.2.37 – 1.2.40 from CG119 have been updated by an evidence review. Recommendations 1.2.37 – 1.2.40 are being stood down because they are replaced by guidance in lower limb peripheral arterial disease [NICE clinical guideline 147].

Rec. no.	Recommendation
1.2.1	Each hospital should have a care pathway for patients with diabetic foot problems who require inpatient care .
1.2.8	A named consultant should be accountable for the overall care of the patient and for ensuring that healthcare professionals provide timely care.
1.2.9	Refer the patient to the multidisciplinary foot care team within 24 hours of the initial examination of the patient's feet. Transfer the responsibility of care to a consultant member of the multidisciplinary foot care team if a diabetic foot problem is the dominant clinical factor for inpatient care.
1.2.10	The named consultant and the healthcare professionals from the existing team remain accountable for the care of the patient unless their care is transferred to the multidisciplinary foot care team.

Diabetic foot problems: inpatient management of diabetic foot problems

NICE clinical guideline

November 2011

This guideline was developed following the NICE short clinical guideline process. This document includes all the recommendations, details of how they were developed and summaries of the evidence they were based on.

January 2012
The section of the care pathway 'Within 24 hours of the patient being admitted or a foot problem being detected (if the patient is already in hospital)' has been amended to reflect recommendation 1.2.9 more accurately.

NICE clinical guideline 119
Inpatient management of diabetic foot problems

Ordering information
You can download the following documents from
www.nice.org.uk/guidance/CG119
- A quick reference guide – a summary of the recommendations for healthcare professionals.
- 'Understanding NICE guidance' – a summary for patients and carers.
- The full guideline – all the recommendations, details of how they were developed, and reviews of the evidence they were based on.

For printed copies of the quick reference guide or 'Understanding NICE guidance', phone NICE publications on 0845 003 7783 or email publications@nice.org.uk and quote:
- N2467 (quick reference guide)
- N2468 ('Understanding NICE guidance').

NICE clinical guidelines are recommendations about the treatment and care of people with specific diseases and conditions in the NHS in England and Wales.

This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summary of product characteristics of any drugs they are considering.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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Contents

Introduction

Topic

Diabetes is one of the biggest health challenges facing the UK today. In 2010, 2.3 million people in the UK were registered as having diabetes, while the number of people estimated as having either type 1 or type 2 diabetes was 3.1 million. By 2030 it is estimated that more than 4.6 million people will have diabetes (Diabetes UK, 2010).

As the longevity of the population increases, the incidence of diabetes-related complications also increases (Anderson and Roukis, 2007). Among the complications of diabetes are foot problems, the most common cause of non-traumatic limb amputation (Boulton et al, 2005). The feet of people with diabetes can be affected by neuropathy, peripheral arterial disease, foot deformity, infections, ulcers and gangrene.

Diabetic foot problems have a significant financial impact on the NHS through outpatient costs, increased bed occupancy and prolonged stays in hospital. In addition, diabetic foot problems have a significant impact on patients' quality of life; for example, reduced mobility that may lead to loss of employment, depression and damage to or loss of limbs. Diabetic foot problems require urgent attention. A delay in diagnosis and management increases morbidity and mortality and contributes to a higher amputation rate (Reiber et al, 1999).

The common clinical features of diabetic foot problems include infection, osteomyelitis, neuropathy, peripheral arterial disease and Charcot arthropathy.

Laboratory evaluations include blood tests, different imaging techniques, microbiological and histological investigations, but currently there is no guidance on which tests are the most accurate and cost effective.

The primary objective in managing diabetic foot problems is to promote mobilisation. This involves managing both medical and surgical problems and involving a range of medical experts in related fields (Bridges et al, 1994).

Despite the publication of strategies on commissioning specialist services for the management and prevention of diabetic foot problems in hospital ('Putting feet first', Diabetes UK 2009; 'Improving emergency and inpatient care for people with diabetes', Department of Health 2008), there is variation in practice in the inpatient management of diabetic foot problems. This variation is due to a range of factors, including differences in the organisation of care between patients' admission to an acute care setting and discharge. This variability depends on geography, individual trusts, individual specialties (such as whether the service is managed by vascular surgery, general surgery, orthopaedics, diabetologists or general physicians) and the availability of podiatrists with expertise in diabetic foot disease.

This short clinical guideline aims to provide guidance on the key components of inpatient care of people with diabetic foot problems from hospital admission onwards.

Who this guideline is for

This document is intended to be relevant to hospital staff who care for patients with diabetic foot problems.

Patient-centred care

This guideline offers best practice advice on the hospital-based care of people with diabetic foot problems.

Treatment and care should take into account patients' needs and preferences. People with diabetic foot problems should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent (available from www.dh.gov.uk/consent) and the code of practice that accompanies the Mental Capacity Act (summary available from www.publicguardian.gov.uk). In Wales, healthcare professionals should follow advice on consent from the Welsh Assembly Government (available from www.wales.nhs.uk/consent).

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

Families and carers should also be given the information and support they need.

1 Recommendations

1.1 Key priorities for implementation

The following recommendations have been identified as key priorities for implementation.

Multidisciplinary foot care team

- Each hospital should have a care pathway for patients with diabetic foot problems who require inpatient care[1].
- The multidisciplinary foot care team should consist of healthcare professionals with the specialist skills and competencies necessary to deliver inpatient care for patients with diabetic foot problems.
- The multidisciplinary foot care team should normally include a diabetologist, a surgeon with the relevant expertise in managing diabetic foot problems, a diabetes nurse specialist, a podiatrist and a tissue viability nurse, and the team should have access to other specialist services required to deliver the care outlined in this guideline.
- The multidisciplinary foot care team should:
  - assess and treat the patient's diabetes, which should include interventions to minimise the patient's risk of cardiovascular events, and any interventions for pre-existing chronic kidney disease or anaemia (please refer to 'Chronic kidney disease' [NICE clinical guideline 73] and 'Anaemia management in people with chronic kidney disease' [NICE clinical guideline 114])
  - assess, review and evaluate the patient's response to initial medical, surgical and diabetes management
  - assess the foot, and determine the need for specialist wound care, debridement, pressure off-loading and/or other surgical interventions
  - assess the patient's pain and determine the need for treatment and

[1] The term 'diabetic foot problems requiring inpatient care' refers to people with diabetes who have i) an ulcer, blister or break in the skin of the foot; ii) inflammation or swelling of any part of the foot, or any sign of infection; iii) unexplained pain in the foot; iv) fracture or dislocation in the foot with no preceding history of significant trauma; v) gangrene of all or part of the foot. Diabetes UK (2009): 'Putting feet first: commissioning specialist services for the management and prevention of diabetic foot disease in hospitals'.

access to specialist pain services
- perform a vascular assessment to determine the need for further interventions
- review the treatment of any infection
- determine the need for interventions to prevent the deterioration and development of Achilles tendon contractures and other foot deformities
- perform an orthotic assessment and treat to prevent recurrent disease of the foot
- have access to physiotherapy
- arrange discharge planning, which should include making arrangements for the patient to be assessed and their care managed in primary and/or community care, and followed up by specialist teams. Please refer to 'Type 2 diabetes: prevention and management of foot problems' (NICE clinical guideline 10).

Patient information and support

- The patient should have a named contact[2] to follow the inpatient care pathway and be responsible for:
  - offering patients information about their diagnosis and treatment, and the care and support that they can expect
  - communicating relevant clinical information, including documentation prior to discharge, within and between hospitals and to primary and/or community care.

Initial examination and assessment

- Remove the patient's shoes, socks, bandages and dressings and examine their feet for evidence of:
  - neuropathy
  - ischaemia
  - ulceration
  - inflammation and/or infection

[2] This may be a member of the multidisciplinary foot care team or someone with a specific role as an inpatient pathway coordinator.

  - deformity
  - Charcot arthropathy.

  Document any identified new and/or existing diabetic foot problems.
- Obtain urgent advice from an appropriate specialist if any of the following are present:
  - Fever or any other signs or symptoms of systemic sepsis.
  - Clinical concern that there is a deep-seated infection (for example palpable gas).
  - Limb ischaemia.

Care: within 24 hours of a patient with diabetic foot problems being admitted to hospital, or the detection of diabetic foot problems (if the patient is already in hospital)

- Refer the patient to the multidisciplinary foot care team within 24 hours of the initial examination of the patient's feet. Transfer the responsibility of care to a consultant member of the multidisciplinary foot care team if a diabetic foot problem is the dominant clinical factor for inpatient care.

Investigation of suspected diabetic foot infection

- If osteomyelitis is suspected and initial X-ray does not confirm the presence of osteomyelitis, use magnetic resonance imaging (MRI). If MRI is contraindicated, white blood cell (WBC) scanning may be performed instead.

Management of diabetic foot infection

- Each hospital should have antibiotic guidelines for the management of diabetic foot infections.

Management of diabetic foot ulcers

- When choosing wound dressings, healthcare professionals from the multidisciplinary foot care team should take into account their clinical assessment of the wound, patient preference and the clinical circumstances, and should use wound dressings with the lowest acquisition cost.

1.2 List of all recommendations

Multidisciplinary foot care team

1.2.1 Each hospital should have a care pathway for patients with diabetic foot problems who require inpatient care[3].

1.2.2 A multidisciplinary foot care team should manage the care pathway of patients with diabetic foot problems who require inpatient care.

1.2.3 The multidisciplinary foot care team should consist of healthcare professionals with the specialist skills and competencies necessary to deliver inpatient care for patients with diabetic foot problems.

1.2.4 The multidisciplinary foot care team should normally include a diabetologist, a surgeon with the relevant expertise in managing diabetic foot problems, a diabetes nurse specialist, a podiatrist and a tissue viability nurse, and the team should have access to other specialist services required to deliver the care outlined in this guideline.

1.2.5 The multidisciplinary foot care team should:

- assess and treat the patient's diabetes, which should include interventions to minimise the patient's risk of cardiovascular events, and any interventions for pre-existing chronic kidney disease or anaemia (please refer to 'Chronic kidney disease' [NICE clinical guideline 73] and 'Anaemia management in people with chronic kidney disease' [NICE clinical guideline 114]
- assess, review and evaluate the patient's response to initial medical, surgical and diabetes management

[3] The term 'diabetic foot problems requiring inpatient care' refers to people with diabetes who have i) an ulcer, blister or break in the skin of the foot; ii) inflammation or swelling of any part of the foot, or any sign of infection; iii) unexplained pain in the foot; iv) fracture or dislocation in the foot with no preceding history of significant trauma; v) gangrene of all or part of the foot. Diabetes UK (2009): 'Putting feet first: commissioning specialist services for the management and prevention of diabetic foot disease in hospitals'.

- assess the foot, and determine the need for specialist wound care, debridement, pressure off-loading and/or other surgical interventions
- assess the patient's pain and determine the need for treatment and access to specialist pain services
- perform a vascular assessment to determine the need for further interventions
- review the treatment of any infection
- determine the need for interventions to prevent the deterioration and development of Achilles tendon contractures and other foot deformities
- perform an orthotic assessment and treat to prevent recurrent disease of the foot
- have access to physiotherapy
- arrange discharge planning, which should include making arrangements for the patient to be assessed and their care managed in primary and/or community care, and followed up by specialist teams. Please refer to 'Type 2 diabetes: prevention and management of foot problems' (NICE clinical guideline 10).

Patient information and support

1.2.6 Offer patients consistent, relevant information and clear explanations that support informed decision making, and provide opportunities for them to discuss issues and ask questions.

1.2.7 The patient should have a named contact[4] to follow the inpatient care pathway and be responsible for:

- offering patients information about their diagnosis and treatment, and the care and support that they can expect

[4] This may be a member of the multidisciplinary foot care team or someone with a specific role as an inpatient pathway coordinator.

- communicating relevant clinical information, including documentation prior to discharge, within and between hospitals and to primary and/or community care.

Care: within 24 hours of a patient with diabetic foot problems being admitted to hospital, or the detection of diabetic foot problems (if the patient is already in hospital)

1.2.8 A named consultant should be accountable for the overall care of the patient and for ensuring that healthcare professionals provide timely care.

1.2.9 Refer the patient to the multidisciplinary foot care team within 24 hours of the initial examination of the patient's feet. Transfer the responsibility of care to a consultant member of the multidisciplinary foot care team if a diabetic foot problem is the dominant clinical factor for inpatient care.

1.2.10 The named consultant and the healthcare professionals from the existing team remain accountable for the care of the patient unless their care is transferred to the multidisciplinary foot care team.

Initial examination and assessment

1.2.11 Remove the patient's shoes, socks, bandages and dressings and examine their feet for evidence of:

- neuropathy
- ischaemia
- ulceration
- inflammation and/or infection
- deformity
- Charcot arthropathy.

Document any identified new and/or existing diabetic foot problems.

1.2.12 Consider a diagnosis of Charcot arthropathy if there is deformity, redness or warmth. Refer to an appropriate specialist to confirm the diagnosis.

1.2.13 Examine the patient for signs and symptoms of systemic sepsis (such as fever, tachycardia, hypotension, reduced consciousness or altered cognitive state).

1.2.14 X-ray the patient's affected foot (or feet) to determine the extent of the foot problem.

1.2.15 If the patient has a diabetic foot ulcer, assess and document:

- deformity
- gangrene
- ischaemia
- neuropathy
- signs of infection
- the size and depth of the ulcer.

1.2.16 Obtain urgent advice from an appropriate specialist if any of the following are present:

- Fever or any other signs or symptoms of systemic sepsis.
- Clinical concern that there is a deep-seated infection (for example palpable gas).
- Limb ischaemia.

1.2.17 Use pressure-relieving support surfaces and strategies in line with 'Pressure ulcers' (NICE clinical guideline 29) to minimise the risk of pressure ulcers developing.

Investigation of suspected diabetic foot infection

1.2.18 If a moderate to severe soft tissue infection is suspected and a wound is present, send a soft tissue sample from the base of the debrided wound for microbiological examination. If this cannot be

obtained, a superficial swab may provide useful information on the choice of antibiotic therapy.

1.2.19 If osteomyelitis is suspected and initial X-ray does not confirm the presence of osteomyelitis, use magnetic resonance imaging (MRI). If MRI is contraindicated, white blood cell (WBC) scanning may be performed instead.

1.2.20 Do not exclude osteomyelitis on the basis of X-rays alone. X-rays should be used for alternative diagnoses, such as Charcot arthropathy.

1.2.21 Do not exclude osteomyelitis on the basis of probe-to-bone testing.

1.2.22 Do not use the following bone scans to diagnose osteomyelitis: 99mTc-MDP-labelled scintigraphy, 99mTc-HMPAO-labelled scintigraphy, antigranulocyte Fab' fragment antibody scintigraphy or 99mTc-labelled monoclonal antigranulocyte antibody scintigraphy.

Management of diabetic foot infection

1.2.23 Each hospital should have antibiotic guidelines for the management of diabetic foot infections.

1.2.24 Do not delay starting antibiotic therapy for suspected osteomyelitis pending the results of the MRI scan.

1.2.25 Start empirical antibiotic therapy based on the severity of the infection, using the antibiotic appropriate for the clinical situation and the severity of the infection, and with the lowest acquisition cost.

1.2.26 For mild infections, offer oral antibiotics with activity against Gram-positive organisms.

1.2.27 For moderate and severe infections, offer antibiotics with activity against Gram-positive and Gram-negative organisms, including anaerobic bacteria. The route of administration is as follows:

- Moderate infection: oral or intravenous antibiotics, based on the clinical situation and the choice of antibiotic (see recommendation 1.2.23).
- Severe infection: start with intravenous antibiotics then reassess, based on the clinical situation (see recommendation 1.2.23)

1.2.28 The definitive antibiotic regimen and the duration of treatment should be informed by both the results of the microbiological examination and the clinical response to empiric antibiotic therapy.

1.2.29 Do not use prolonged antibiotic therapy for mild soft tissue infections.

1.2.30 Treat infections with MRSA in line with local and national guidance.

Management of diabetic foot ulcers

Debridement, dressings and off-loading

1.2.31 Debridement should only be done by healthcare professionals from the multidisciplinary foot care team, using the technique that best matches their specialist expertise, clinical experience, patient preference, and the site of the ulcer.

1.2.32 When choosing wound dressings, healthcare professionals from the multidisciplinary foot care team should take into account their clinical assessment of the wound, patient preference and the clinical circumstances, and should use wound dressings with the lowest acquisition cost.

1.2.33 Offer off-loading for patients with diabetic foot ulcers. Healthcare professionals from the multidisciplinary foot care team should take into account their clinical assessment of the wound, patient preference and the clinical circumstances, and should use the technique with the lowest acquisition cost.

1.2.34 Use pressure-relieving support surfaces and strategies in line with ‘Pressure ulcers’ (NICE clinical guideline 29) to minimise the risk of pressure ulcers developing.

Adjunctive treatments

1.2.35 Negative pressure wound therapy should not be routinely used to treat diabetic foot problems, but may be considered in the context of a clinical trial or as rescue therapy (when the only other option is amputation).

1.2.36 Do not offer the following treatments for the inpatient management of diabetic foot problems, unless as part of a clinical trial:

- Dermal or skin substitutes.
- Electrical stimulation therapy, autologous platelet-rich plasma gel, regenerative wound matrices and deltaparin.
- Growth factors (granulocyte colony-stimulating factor [G-CSF], platelet-derived growth factor [PDGF], epidermal growth factor [EGF] and transforming growth factor beta [TGF-β]).
- Hyperbaric oxygen therapy.

Assessment of suspected limb ischaemia

Limb ischaemia with redness and pain can be misdiagnosed as soft tissue infection. The new onset of gangrene of a digit or of the forefoot is often precipitated by soft tissue infection, even though the signs of inflammation may be attenuated by coincidental peripheral arterial disease.

1.2.37 If limb ischaemia is suspected, obtain a history of any previous cardiovascular events and symptoms, including previous treatments and/or procedures.

1.2.38 Inspect the limb for the following:

- Colour and temperature.
- Presence of gangrene or tissue loss.
- Presence or absence of a peripheral pulse.

1.2.39 Measure and document the ankle–brachial pressure where clinically possible, ensuring careful interpretation of the results.

1.2.40 Arrange prompt specialist assessment of patients with risk factors, symptoms and signs of limb ischaemia.

Care pathway

Multidisciplinary foot care team:

- Each hospital should have an inpatient care pathway, managed by a multidisciplinary foot care team.
- The team should consist of healthcare professionals with the specialist skills to deliver inpatient care, including a diabetologist, a surgeon with the relevant expertise in managing diabetic foot problems, a diabetes nurse specialist, a podiatrist and a tissue viability nurse, and the team should have access to other specialist services needed to deliver the care outlined in the guideline.
- The multidisciplinary foot care team should:
  - assess and treat the patient's diabetes, which includes minimising the risk of cardiovascular events, and interventions for pre-existing chronic kidney disease or anaemia
  - assess, review and evaluate the patient's response to initial medical, surgical and diabetes management
  - assess the foot, and determine the need for specialist wound care, debridement, pressure off-loading and/or other surgical interventions
  - assess the patient's pain and determine the need for treatment and access to specialist pain services
  - perform a vascular assessment to determine the need for further interventions
  - review the treatment of any infection
  - assess the need for interventions to prevent the deterioration and development of foot deformities
  - perform an orthotic assessment and treat to prevent recurrent disease of the foot
  - have access to physiotherapy
  - arrange discharge planning.

Patient information and support:

- Offer patients consistent, relevant information and clear explanations that support informed decision making, and provide opportunities for them to discuss issues and ask questions.
- Patients should have a named contact to provide information and to liaise between secondary and primary and/or community care.

Within 24 hours of the patient being admitted or a foot problem being detected (if the patient is already in hospital)

- A named consultant should be accountable for the care of the patient and for ensuring that healthcare professionals provide timely care.
- Refer the patient to the multidisciplinary foot care team within 24 hours of the initial examination of the patient's feet. Transfer the responsibility of care to a consultant member of the multidisciplinary foot care team if a diabetic foot problem is the dominant clinical factor for inpatient care.

Initial examination and assessment

- Examine the feet and record details of new and/or existing foot problems.
- Examine the patient for signs and symptoms of systemic sepsis.
- X-ray the affected foot (or feet).
- Use pressure-relieving support surfaces and strategies in line with 'Pressure ulcers' (NICE clinical guideline 29).

If you suspect the following, obtain advice from an appropriate specialist:

- Charcot arthropathy
- a deep-seated infection
- systemic sepsis
- limb ischaemia.

Diabetic foot ulcers

Investigation

Record the size and depth of the ulcer. Assess and record any signs of infection, ischaemia, neuropathy, gangrene or deformity.

Management

Debridement should only be done by healthcare professionals from the multidisciplinary foot care team using the technique that best matches their expertise, clinical experience, patient preference and site of the ulcer.

When choosing wound dressings, healthcare professionals from the multidisciplinary foot care team should take into account the wound, patient preference and the clinical circumstances, and should use wound dressings with the lowest acquisition cost.

Offer off-loading. Healthcare professionals from the multidisciplinary foot care team should take into account the wound, patient preference and the clinical circumstances, and should use the technique with the lowest acquisition cost.

Use pressure-relieving support surfaces and strategies in line with NICE clinical guideline 29.

Interventions not recommended

Negative pressure wound therapy, unless in the context of a clinical trial or as rescue therapy (when the only other option is amputation).

Dermal or skin substitutes, electrical stimulation therapy, autologous platelet-rich plasma gel, regenerative wound matrices, deltaparin, growth factors, hyperbaric oxygen therapy, unless in the context of a clinical trial.

Diabetic foot infection

Investigation

Send a deep soft tissue sample (or a superficial swab) for microbiological examination.

If you suspect osteomyelitis but the initial X-ray was not diagnostic, carry out magnetic resonance imaging (MRI) or white blood cell scanning if MRI is contraindicated.

Management

Start antibiotic therapy based on infection severity, using the antibiotic with the lowest acquisition cost appropriate for the clinical situation. Take into account local antibiotic guidelines as well as the microbiology results.

Do not delay starting therapy for suspected osteomyelitis pending MRI results.

For mild infections, offer oral antibiotics with activity against Gram-positive organisms.

For moderate and severe infections, offer antibiotics with activity against Gram-positive and Gram-negative organisms, including anaerobic bacteria. For moderate infections use oral or intravenous; for severe infections start with intravenous and then reassess.

Interventions not recommended

- ***Investigation***
  X-rays or probe-to-bone testing to exclude osteomyelitis.
  Bone scans to diagnose osteomyelitis.
- ***Management***
  Prolonged antibiotic therapy for mild soft tissue infections.

Suspected limb ischaemia

Obtain a history of any previous cardiovascular events and symptoms, including treatments and/or procedures.

Inspect the limb for colour and temperature, gangrene or tissue loss and presence or absence of a peripheral pulse.

Measure and document the ankle–brachial pressure where clinically possible and interpret the results carefully.

Arrange prompt specialist assessment.

3 Evidence review and recommendations

'Inpatient management of diabetic foot problems' (NICE clinical guideline 119) is a NICE short clinical guideline. For details of how this guideline was developed see appendix B.

Introduction

The guideline is structured into six sections based on the review questions. Evidence in each section is presented in the summary of GRADE (Grading of Recommendations Assessment, Development and Evaluation) profiles and relevant evidence statements (which are cross-referred to individual summaries of GRADE profiles). Additional information, such as the full GRADE evidence profiles and outputs of different analyses, such as meta-analyses, summaries of receiver–operator–characteristics (ROC) and others, are available in the appendices. References of all included studies are also available in appendix C.

Section	Guideline section number	Number of studies included
Key components and organisations of hospital care	3.1	5
Assessment, investigation and diagnosis of diabetic foot problems	3.2	35
Debridement, wound dressings and off-loading	3.3	14
Antibiotics for diabetic foot infections	3.4	13
Adjunctive treatments for diabetic foot problems	3.5	37
Timing for surgical management to prevent amputation	3.6	0
Total		104

Health economic modelling

Examination of the existing literature and the quality of the evidence available suggested that an economic analysis would not be possible for the majority of this guideline. However, the Guideline Development Group (GDG) considered that analyses would be required in two areas to help inform decision making. Firstly, does magnetic resonance imaging (MRI) for the diagnosis of osteomyelitis represent a cost-effective use of resources? Secondly, are hyperbaric oxygen therapy (HBOT) and negative pressure wound therapy

cost-effective treatments for diabetic foot problems? These areas are considered in sections 3.2.4 and 3.5.4. Given the low quality of the evidence these analyses should be considered as exploratory. No other areas were considered for health economic modelling.

3.1 Assessment, investigation and diagnosis of diabetic foot problems

3.1.1 Review question

What are the clinical utilities of different assessment, investigative or diagnostic tools in examining and diagnosing diabetic foot problems in hospital?

3.1.2 Evidence review

The systematic search retrieved 9817 studies. Of these, 35 studies were included for this review question (for the review protocol and inclusion/exclusion criteria, please see appendix B). All the evidence was grouped and synthesised by individual tests and/or assessments rather than individual studies. Where possible, if information was available in the studies, evidence was presented in:

- Characteristics of included studies.
- Summary of GRADE profiles with Youden index, where appropriate (with common cut-off > 0.5 as a 'good test').
- Results of individual studies (see appendix E).
- Full GRADE evidence profiles (see appendix D).
- Forest plots (where appropriate) (see appendix F).
- Summary of ROC (where appropriate) (see appendix F).
- Van der Bruel plots (where appropriate) (see appendix G).
- Evidence statements.

The decision not to conduct a meta-analysis for this review question (that is, to not produce a ‘point summary’ across the studies) was made because of the following methodological reasons.

- Not all studies used the same single definitive reference standard (please see table 2).
- Variability of pre-test probabilities among studies (please see the ranges in the full GRADE evidence profiles, appendix D).
- Variability in the quality of the included studies (please see QUADAS [Quality Assessment of Studies of Diagnostic Accuracy included in Systematic Reviews] methodological quality graph, appendix E).
- High risk of heterogeneity (please see confidence intervals of the forest plots, and the summary ROC, appendix F).

Although a ‘point summary’ (or pooled estimate) was not produced for this review question, a summary of ROC (without pooled estimates) was provided where appropriate as a visual guide to aid discussion, but not as a sole decision tool for recommendations. Other factors were discussed in order to draw conclusions for recommendations, such as:

- assessing the ‘width’ of the range of results in GRADE profiles
- assessing the confidence intervals in a forest plot
- assessing the clinical utility (Smart 2006) of individual tests, for example:
  - appropriateness: effectiveness and accuracies, relevance to practice
  - accessibility: resource implications and procurement
  - practicality: functionality, suitability, training and knowledge
  - acceptability: whether acceptable to healthcare professionals, patients and carers, society (public or stakeholder groups)
- health economic evaluation.

Table 2: Characteristics of included studies

Study	Index test	Reference standard
Al-Khawari et al. (2005)	• MRI	Culture growth or characteristic histological findings in diagnosing osteomyelitis
Beckert et al. (2006)	• DUSS	Wound-based clinical scoring system
Beltran et al. (1990)	• MRI	Aspiration, pathological examination, and plain radiographs in detecting osteomyelitis
Boyko et al. (1997)	• Medical history information • Physical examination findings • Clinical tests	AAI ≤0.5 in diagnosing severe peripheral vascular disease
Croll et al. (1996)	• MRI • 99mTc bone scan • In-WBC • Plain radiographs	Pathological specimen, or bone culture in diagnosing osteomyelitis
Devillers et al. (1998)	• 3 -phase 99mTc-MDP-labelled bone scintigraphy • 99mTc-HMPAO-labelled leukocyte scintigraphy	Radiographic and/or bacteriological or histological results or clinical follow up in diagnosis of diabetic foot infection
Ertugrul et al. (2009)	• ESR • Wound sizes	Histopathology, microbiology and MRI with conventional spin echo in diagnosing osteomyelitis
Ertugrul et al. (2006)	• Microbiological processing • MRI • 99mTc-MDP-labelled leukocyte scan	Histopathological findings in diagnosing osteomyelitis
Gardner et al. (2009)	• Classical signs: – Increasing pain – Erythema – Oedema – Heat – Purulent exudate	High microbial load in detecting infections

	• Signs specific to secondary wounds: – Serous exudate – Sanguineous exudate – Delayed healing – Discoloured granulation – Friable granulation – Pocketing – Foul odour – Wound breakdown	
Grayson et al. (1995)	• Probe-to-bone	Histological tests in detecting osteomyelitis
Harvey et al. (1997)	• 99mTc-HMPAO-labelled leukocyte scintigraphy • 99mTc-MDP-labelled bone scintigraphy	Histology, bone cultures and radiographic results in diagnosing osteomyelitis
Harwood et al. (1999)	• Sulesomab • In-WBC and 99m-Tc bone scan	Histology and/or microbiological cultures in detecting osteomyelitis
Kaleta et al. (2001)	• ESR	Histological examination (pathological reports) in diagnosing osteomyelitis
Keenan et al. (1989)	• 3-phase 99mTc-MDP bone scintigraphy • In-WBC	Culture and/or histological examination in diagnosing osteomyelitis
Kreitner et al. (2000)	• Three-dimensional contrast-enhanced MRA	DSA evaluating arteries of the distal calf and foot
Lapeyre et al. (2005)	• MRA	DSA detecting critical limb ischaemia
Larcos et al. (1991)	• 111-In-WBC • 99mTc-MDP-labelled bone scintigraphy • Radiographs	Surgery (bone culture or biopsy) and clinical follow-up in diagnosing osteomyelitis
Levine et al.	• MRI	Pathological and histological determination, surgical observation and clinical

(1994)	• Plain-film roentgenography • 111-In-WBC scintigraphy • 99mTc bone scan	resolution in diagnosing osteomyelitis
Malabu et al. (2007)	• ESR • Haematocrit • Haemoglobin • Platelet count • Red cell distribution width • White cell count	Bone scan, MRI, radiographs or the ability to probe an open wound to bone in detecting osteomyelitis
Morrison et al. (1995)	• MRI	Histological analysis of biopsy specimens OR Clinical and radiographic demonstration of progression in detecting osteomyelitis
Newman et al. (1991)	• Roentgenography • 111-In-WBC (4 h and 24 h) • Bone scans	Bone biopsy and culture in diagnosing osteomyelitis
Newman et al. (1992)	• MRI • Leukocyte scanning	Bone specimens for histology and culture in diagnosing osteomyelitis
Oyibo et al. (2001)	• Wagner wound classification system • University of Texas diabetic wound classification system	Comparing the utility of two wound scores
Palestro et al. (2003)	• 99mTc-labelled monoclonal antibody • In-WBC • 3-phase (99mTc-MDP-labelled bone scintigraphy)	Bone biopsy examination and culture in diagnosing osteomyelitis
Poirier et al. (2002)	• 99mTc-MDP bone scintigraphy • 99mTc-HMPAO-labelled leukocyte scan	Radiological examination, bacteriological and histological studies in diagnosing osteomyelitis
Remedios et al. (1998)	• 99m-Tc nanocolloid • MRI	Histological and microbiology tests in detecting osteomyelitis
Rozzanigo et al. (2009)	• MRI	Bacteriological and/or histological tests in detecting osteomyelitis
Rubello et al.	• LeukoScan (4 h and 18–24 h)	Microbiological findings or other laboratory and imaging techniques in detecting

(2004)		bone infection
Shaw et al. (2007)	• The Visitrak system • A digital photography and image processing system • An elliptical measurement method using the standard formula	Wound measurement in diabetic foot wounds
Shone et al. (2006)	• Probe-to-bone	Clinical signs of osteomyelitis, supported by MRI and microbiological analysis of deep tissue samples
Slater et al. (2004)	• Swab cultures	Deep tissue biopsy to accurately identify bacterial pathogens in diabetic foot wounds
Strauss et al. (2005)	• Wagner (1979), US • Forrest and Gamborg-Neilsen (1984), Sweden • Knighton et al. (1986), US • Pecoraro and Reiber (1990), US • Lavery et al. (1996), US • MacFarlane and Jeffcoate (1999), UK • Foster and Edmunds (2000), UK	The new wound score (clinical utility)
Wang et al. (1990)	• MRI • Plain radiographs	Histological examination in detecting osteomyelitis
Weinstein et al. (1993)	• MRI • Plain radiographs • 99mTc/Ga scan	Histological examination in diagnosing osteomyelitis
Yuh et al. (1989)	• MRI • Bone scans • Plain radiographs	Pathological tests detecting osteomyelitis

99m-Tc = technetium-99m; AAI = ankle–arm index; DSA = digital subtraction angiography; DUSS = diabetic ulcer severity score; ESR = erythrocyte sedimentation rate; Ga = gallium; HMPAO = hexamethylpropylamine oxine; In-WBC = indium leukocyte scanning; MDP = methylene diphosphonate; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging.

The clinical utility of different diabetic ulcer/wound scores

There are numerous wound scores available that are used by healthcare professionals in the field. However, most scores have not been validated in different data sets or study populations. There is a lack of evidence that assesses the clinical utility of these wound scores. From the systematic searches, only three studies were identified that met the inclusion/exclusion criteria (Beckert et al. 2006; Strauss et al. 2005; Oyibo et al. 2001). These three studies were of low quality and therefore needed cautious interpretation. The evidence was presented in the summary of GRADE profiles and evidence statements (which were cross-referred to the relevant summary of GRADE profiles) (also see results of individual studies in appendix E; full GRADE evidence profiles in appendix D).

Summary of GRADE profile 2:
Clinical utility of different diabetic ulcer/ wound scores

<table>
<tr><th colspan="3">Study characteristics</th><th colspan="2">Summary of findings</th></tr>
<tr><td>No. of studies</td><td>No. of patients</td><td>Clinical parameters/evaluation criteria</td><td>Summary of findings</td><td>GRADE quality</td></tr>
<tr><td colspan="5">DUSS</td></tr>
<tr><td>1
[B]</td><td>1000</td><td>Palpable pedal pulses
Probing to bone
Ulcer location
Multiple ulcerations</td><td>Multivariate analysis: an increase of 1 point reduced the chance for healing by 35% (at the end of follow-up).</td><td>Low</td></tr>
<tr><td>1
[B]</td><td>1000</td><td>Palpable pedal pulses
Probing to bone
Ulcer location
Multiple ulcerations</td><td>
<table>
<tr><th>Score</th><th>Wound duration (days) (median range)</th><th>Surgery (%)</th></tr>
<tr><td>0</td><td>29 (2 to 597)</td><td>9</td></tr>
<tr><td>1</td><td>26.5 (1 to 2922)</td><td>17</td></tr>
<tr><td>2</td><td>31 (1 to 4018)</td><td>27</td></tr>
<tr><td>3</td><td>42 (1 to 18708)</td><td>37</td></tr>
<tr><td>4</td><td>61 (3 to 1516)</td><td>50</td></tr>
</table>
</td><td>Low</td></tr>
<tr><td colspan="5">Comparison of Wagner wound score and UT wound scores</td></tr>
<tr><td>1
[O]</td><td>194</td><td>Wagner wound classification system (grade 0 to 5)
UT diabetic wound classification system (stage A to D, each stage has grade 1 to 3)</td><td>Positive trend with increased number of amputations
Wagner grade: χ^2 trend = 21.0, $p < 0.0001$
UT grade and stage: χ^2 trend = 23.7, $p < 0.0001$ and χ^2 trend = 15.1, $p = 0.0001$

Cox regression analysis
Only the UT stage had a predictive effect on healing time ($\chi^2 = 10.3$, df = 3, $p < 0.05$). The higher the stage at presentation, the less likely it was for that ulcer to heal within the study period (hazard ratio = 0.8, 95% CI: 0.67 to 0.98, $p < 0.05$).</td><td>Low</td></tr>
<tr><td colspan="5">Evaluation of diabetic foot wound scores</td></tr>
<tr><td>1
[S]</td><td>N/A
Qualitative evaluation</td><td>Number of criteria
Objectivity of findings to evaluate each criterion
Scoring permutations
Versatility
Guide to seriousness
Integration with wound information
Integration with patient information
Documentation of progress
Validity
Reliability</td><td>Assessment scores:
<table>
<tr><th>Test</th><th>Total</th></tr>
<tr><td>WAG[1]</td><td>7</td></tr>
<tr><td>FOR[2]</td><td>4</td></tr>
<tr><td>KNI[3]</td><td>4</td></tr>
<tr><td>PEC[4]</td><td>3</td></tr>
<tr><td>LAV[5]</td><td>10</td></tr>
<tr><td>JEF[6]</td><td>11</td></tr>
<tr><td>FOS[7]</td><td>8</td></tr>
</table>
</td><td></td></tr>
</table>

[B] = Beckert et al. (2006)

[S] = Strauss et al. (2005)

[O] = Oyibo et al. (2001)

[1] Wagner (1979), US

[2] Forrest and Gamborg-Neilsen (1984), Sweden

[3] Knighton et al. (1986), US
[4] Pecoraro and Reiber (1990), US
[5] Lavery et al. (1996), US
[6] MacFarlane and Jeffcoate (1999), UK
[7] Foster and Edmunds (2000), UK
CI = confidence interval; df = degrees of freedom, DUSS = diabetes ulcer severity score, UT = University of Texas

The clinical utility of assessment, investigative or diagnostic tools for diabetic foot infections

From the systematic searches, only two studies were identified that met the inclusion/exclusion criteria. Both studies needed cautious interpretation as both were subjected to a high risk of bias. The evidence was presented in the summary of GRADE profiles and evidence statements (which were cross-referred to the relevant summary of GRADE profiles) (also see results of individual studies in appendix E; full GRADE evidence profiles in appendix D).

Summary of GRADE profile 3: Clinical signs of diabetic foot infections

Study characteristics			Summary of findings					
No. of studies	No. of patients	Clinical signs	Pre-test probability	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Post-test probability (+ve)	Post-test probability (despite [-ve])	GRADE quality
Clinical signs of diabetic foot infection (reference standard: high microbial loads > 1 million organisms per gram of tissue)								
1 [G]	64	Increasing pain	0.39	12 (26 to 32)	100 (90 to 100)	1.00	0.37	Very low
1 [G]	64	Erythema	0.39	32 (15 to 53)	77 (60 to 89)	0.47	0.53	Very low
1 [G]	64	Oedema	0.39	20 (6 to 41)	77 (60 to 89)	0.36	0.40	Very low
1 [G]	64	Heat	0.39	12 (2 to 31)	84 (69 to 94)	0.33	0.40	Very low
1 [G]	64	Purulent exudate	0.39	28 (12 to 49)	64 (47 to 79)	0.33	0.42	Very low
1 [G]	64	Serous exudate	0.39	88 (69 to 97)	73 (64 to 81)	0.42	0.04	Very low
1 [G]	64	Sanguineous exudate	0.39	84 (64 to 95)	90 (76 to 97)	0.84	0.11	Very low
1 [G]	64	Delayed healing	0.39	48 (23 to 69	54 (37 to 70)	0.40	0.39	Very low
1 [G]	64	Discoloured granulation	0.39	28 (12 to 49)	85 (69 to 94)	0.54	0.36	Very low
1 [G]	64	Friable granulation	0.39	0 (0 to 14)	77 (61 to 89)	0.00	0.46	Very low
1 [G]	64	Pocketing	0.39	40 (21 to 61	59 (42 to 74)	0.38	0.40	Very low
1 [G]	64	Foul odour	0.39	20 (6 to 41)	87 (73 to 96)	0.50	0.32	Very low
1 [G]	64	Wound breakdown	0.39	0 (0 to 14)	95 (83 to 99)	0.00	0.41	Very low

[G] = Gardner et al. (2009)

CI = confidence interval

Summary of GRADE profile 4: Swab cultures

Study characteristics			Summary of findings	
No. of studies	No. of patients (wounds)	Outcomes	Association between swabs and deep tissue cultures	GRADE quality
Swab cultures in diabetic wounds not involving bone (reference standard: deep tissue biopsy)				
1 [S]	56 (60)	Swabs contained all organisms found in deep tissue biopsy	49/60 (82%)	Low
1 [S]	56 (60)	Swabs and deep tissue cultures identical	37/60 (62%)	Low
1 [S]	56 (60)	Swabs contained all organisms found in deep tissue biopsy plus additional organisms	12/60 (20%)	Low
1 [S]	56 (60)	Swabs lacked organism(s) found in deep tissue biopsy	11/60 (18%)	Low

[S] = Slater et al. (1997)

The diagnostic accuracy of different tests in diagnosing osteomyelitis

From the systematic searches, 26 studies were identified that met the inclusion/exclusion criteria. Most of these studies investigated the diagnostic accuracy of different imaging tests in diagnosing osteomyelitis. Only five studies investigated the diagnostic accuracy of blood tests and the use of clinical signs and symptoms. The quality of the evidence was of moderate/low quality, and was presented in the summary of GRADE profiles and evidence statements (which were cross-referred to the relevant summary of GRADE profiles) (also see results of individual studies in appendix E; full GRADE evidence profiles in appendix D; forest plots [where appropriate] in appendix F; summary of ROC [where appropriate] in appendix F; Van der Bruel plots [where appropriate] in appendix G).

Summary of GRADE profile 5: Imaging (single testing)

Study characteristics			Summary of findings					
No. of studies	No. of patients	Pre-test probability	Sensitivity (%)	Specificity (%)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	GRADE quality
See appendix C: Full GRADE evidence profile 6 – MRI								
10 [A, B, C, E, L, M, R, W, We, Y]	Range: 14 to 62	Range: 0.33 to 0.86	Range: 77 to 100	Range: 60 to 100	Range: 0.75 to 100	Range: 0 to 0.62	Range: 0.38 to 1.0	Low
See appendix C: Full GRADE evidence profile 7 – 99mTc-MDP-labelled scintigraphy								
11 [C, D, E, Hd, Hy, K, L, N, Pa, Po, Y]	Range: 22 to 94	Range: 0.29 to 0.88	Range: 50 to 100	Range: 0 to 67	Range: 0.36 to 0.95	Range: 0.0 to 1.0	Range: -0.06 to 0.58	Low
See appendix C: Full GRADE evidence profile 8 – 99mTc-HMPAO-labelled scintigraphy								
3 [D, Hd, Hy]	Range: 52 to 122	Range: 0.40 to 0.66	Range: 86 to 91	Range: 56 to 97	Range: 0.8 to 0.94	Range: 0.09 to 0.23	Range: 0.47 to 0.85	Moderate
See appendix C: Full GRADE evidence profile 9: In-WBC								
8 [C, Hd, K, La, L, N1, N2, Pa]	Range: 12 to 111	Range: 0.27 to 0.68	Range: 33 to 100	Range: 22 to 78	Range: 0.28 to 0.85	Range: 0.0 to 0.40	Range: 0.01 to 0.78	Low
See appendix C: Full GRADE evidence profile 10: anti-granulocyte Fab' fragment antibody scintigraphy								
1 [Ru] 4 hours	78	0.79	92 (82 to 97)	75 (48 to 93)	0.93	0.29	0.67	Moderate
1 [Ru] 24 hours	78	0.79	92 (82 to 97)	88 (62 to 98)	0.97	0.26	0.80	Moderate
See appendix C: Full GRADE evidence profile 11: plain radiographs								
8 [C, D, La, L, N, W, We, Y]	Range: 26 to 62	Range: 0.29 to 0.86	Range: 22 to 75	Range: 17 to 94	Range: 0.17 to 0.89	Range: 0.24 to 0.67	Range: -0.40 to 0.50	Low
See appendix C: Full GRADE evidence profile 12: 99mTc-labelled monoclonal antigranulocyte antibody								
1 [Pa]	25	0.40	90	67	0.64	0.09	0.57	Low
See appendix C: Full GRADE evidence profile 13: probe-to-bone								
2 [G, S]	Range: 76 to 104	Range: 0.20 to 0.66	Range: 0.38 to 0.66	Range: 0.85 to 0.92	Range: 0.38 to 0.66	Range: 0.08 to 0.15	Range: 0.30 to 0.51	Low

[A] = Al-Khawari (2007): reference standard = histological analysis

[B] = Beltran (1990): reference standard = aspiration/pathological examination/plain films

[C] = Croll (1996): reference standard = pathological specimen or bone culture

[D] = Devillers (1998): reference standard = radiographic/bacteriological/histological results/clinical follow-up

[E] = Ertugrul (2006): reference standard = histopathological analysis

[G] = Grayson (1995): reference standard = histological and microbiology tests in detecting osteomyelitis

[Hd] = Harwood (1999): reference standard = histological and/or microbiological cultures

[Hy] = Harvey (1997): reference standard = histology, bone cultures and radiographic results

[K] = Keenan (1989): reference standard = culture and/or histological examination

[La] = Larcos (1991): reference standard = bone culture/biopsy/clinical follow-up

[L] = Levine (1994): reference standard = pathological/histological/surgical examination/clinical follow-up

[M] = Morrison (1995): reference standard = histological analysis or clinical and radiographic demonstration despite conservative antibiotic therapy

[N] = Newman (1991): reference standard = bone biopsy and culture

[N1] = Newman (1991) (4 hours): reference standard = bone biopsy and culture

[N2] = Newman (1991) (24 hours): reference standard = bone biopsy and culture

[Pa] = Palestro (2003): reference standard = bone biopsy and culture/clinical follow-up

[Po] = Poirier (2002): reference standard = radiological examination or histopathological analysis

[R] = Rozzanigo (2009): reference standard = bacteriological and/or histological tests

[RU] = Rubello (2004): reference standard = microbiological findings/CT scan/MRI/clinical follow-up

[S] = Shone (2006): reference standard = clinical signs of osteomyelitis, supported by MRI and microbiological analysis of deep tissue samples.

[W] = Wang (1990): reference standard = histological examination

[We] = Weinstein (1993): reference standard = histological examination

[Y] = Yuh (1989): reference standard = pathological tests

99mTc = technetium-99m; MRI = magnetic resonance imaging.

Summary of GRADE profile 6: Imaging (combination tests): other imaging tests (combination)

Study characteristics			Summary of findings					
No. of studies	No. of patients	Pre-test probability	Sensitivity (%)	Specificity (%)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	GRADE quality
99mTc-MDP-labelled scintigraphy + In-WBC								
2 [K, Pa]	25 & 39	0.40 & 0.38	Range: 80 to 100	Range: 79 to 80	Range: 0.73 to 0.75	Range: 0.0 to 0.14	Range: 0.60 to 0.79	Low
99mTc-labelled monoclonal antigranulocyte antibody + 99mTc-MDP-labelled scintigraphy								
1 [Pa]	25	0.40	90 (55 to 100)	67 (38 to 88)	0.64	0.09	0.50	Low
99mTc-MDP-labelled scintigraphy + 99mTc-HMPAO-labelled scintigraphy								
1 [Po]	83	0.49	93 (80 to 96)	98 (87 to 100)	0.97	0.07	0.91	Low
99mTc-MDP-labelled scintigraphy + Gallium 67 citrate								
1 [We]	22	0.73	69 (41 to 89)	83 (36 to 100)	0.92	0.50	0.52	Low

[K] = Keenan (1989): reference standard = culture and/or histological examination

[Pa] = Palestro (2003): reference standard = bone biopsy and culture or clinical follow-up

[Po] = Poirer (2002): reference standard = radiological examination or histopathological analysis

[We] = Weinstein (1993): reference standard = histological examination

99mTc = technetium-99m.

Summary of GRADE profile 7: Blood tests (single test): Erythrocyte sedimentation rate and other tests (single study)

Study characteristics			Summary of findings					
No. of studies	No. of patients	Pre-test probability	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	GRADE quality
ESR ≥ 60 mm/h								
2 [E, K]	29 & 46	0.52 & 0.66	89 to 92	68 to 90	Range: 0.76 to 0.94	Range: 0.12 to 0.18	Range: 0.60 to 0.79	Low
ESR ≥ 65 mm/h								
2 [E, K]	29 & 46	0.52 & 0.66	88 to 89	73 to 90	Range: 0.78 to 0.94	Range: 0.16 to 0.18	Range: 0.61 to 0.79	Low
ESR ≥ 70 mm/h								
2 [E, K]	29 & 46	0.52 & 0.66	83 to 89	77 to 100	Range: 0.80 to 1.00	Range: 0.17 to 0.19	Range: 0.60 to 0.89	Low
ESR > 70 mm/h								
2 [M, N]	28 & 43	0.51 & 0.64	28 to 91	95 to 100	Range: 0.95 to 1.00	Range: 0.09 to 0.57	Range: 0.28 to 0.86	Low
ESR ≥ 75 mm/h								
2 [E, K]	29 & 46	0.52 & 0.66	79 to 84	82 to 100	Range: 0.83 to 1.00	Range: 0.22 to 0.23	Range: 0.61 to 0.84	Low
ESR ≥ 80 mm/h								
2 [E, K]	29 & 46	0.52 & 0.66	71 to 79	91 to 90	Range: 0.89 to 1.00	Range: 0.26 to 0.29	Range: 0.62 to 0.79	Low
ESR > 100 mm/h								
1 [N]	39	0.67	23	100	1.00	0.61	0.23	Moderate
Haematocrit > 36%								
1 [M]	43	0.51	95 (77 to 100)	86 (64 to 97)	0.88	0.05	0.81	Low
Haemoglobin < 12 g/dL								
1 [M]	43	0.51	82 (60 to 95)	90 (70 to 99)	0.90	0.17	0.72	Low
Platelet count > $400x10^9$/L								
1 [M]	43	0.51	45 (24 to 68)	95 (76 to 100)	0.91	0.37	0.40	Low
Red cell distribution width > 14.5								
1 [M]	43	0.51	68 (45 to 86)	62 (38 to 82)	0.65	0.35	0.30	Low
White cell count > $400x10^9$/L								
1 [M]	43	0.51	50 (28 to 72)	81 (58 to 95)	0.73	0.39	0.31	Low

[E] = Ertugrul (2009): reference standard = histopathology/bone tissue culture/MRI conventional spin echo

[K] = Kaleta (2001): reference standard = histological examination

[M] = Malabu (2001): reference standard = bone scan/MRI/radiographs

[N] = Newman (1991): reference standard = bone biopsy and culture

CI = confidence interval; ESR = erythrocyte sedimentation rate.

Summary of GRADE profile 8: Other tests (single tests)

Study characteristics			Summary of findings					
No. of studies	No. of patients	Pre-test probability	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	GRADE quality
Microbiological processing								
1 [E]	31	0.84	92 (75 to 99)	60 (15 to 95)	0.92	0.40	0.52	Low
Ulcer inflammation								
1 [N]	41	0.68	36 (19 to 56)	81 (54 to 96)	0.77	0.58	0.17	Moderate
Clinical judgement								
1 [N]	41	0.68	32 (16 to 52)	100 (75 to 100)	1.00	0.59	0.32	Moderate
Bone exposure								
1 [N]	41	0.68	32 (16 to 52)	100 (75 to 100)	1.00	0.59	0.32	Moderate

[E] = Ertugrul (2006): reference standard = histopathological analysis

[N] = Newman (1991): reference standard = bone biopsy and culture

CI = confidence interval

Summary of GRADE profile 9: Other tests (combination tests): wound sizes (and erythrocyte sedimentation rate)

Study characteristics			Summary of findings					
No. of studies	No. of patients	Pre-test probability	Sensitivity (%)	Specificity (%)	Post-test probability (+ve)	Post-test probability (despite [-ve])	Youden index	GRADE quality
Wound size ≥ 2cm^2								
2 [E, N]	40 & 46	Range: 0.52 to 0.66	Range: 56 to 88	Range: 77 to 93	Range: 0.81 to 0.94	Range: 0.15 to 0.48	Range: 0.49 to 0.65	Low
Wound size ≥ 3 cm^2								
1 [E]	46	0.52	79	77	0.79	0.23	0.56	Low
Wound size ≥ 4 cm^2								
1 [E]	46	0.52	67	91	0.89	0.29	0.58	Low
Wound size ≥ 5 cm^2								
1 [E]	46	0.52	50	95	0.92	0.36	0.45	Low
ESR rate ≥ 65 mm/h + wound size ≥ 2 cm²								
1 [E]	46	0.52	83	77	0.80	0.19	0.60	Low
ESR rate ≥ 70 mm/h + wound size ≥ 2cm²								
1 [E]	46	0.52	79	82	0.83	0.22	0.61	Low

[E] = Ertugrul (2006): reference standard = histopathological analysis

[N] = Newman (1991): reference standard = bone biopsy and culture

ESR = erythrocyte sedimentation rate.

The clinical utility of assessment, investigative or diagnostic tools for examining peripheral arterial disease in people with diabetic foot problems

From the systematic searches, only three studies were identified that met the inclusion/exclusion criteria. These three studies were of low quality and therefore needed cautious interpretation. The evidence was presented in the summary of GRADE profiles evidence statements (which were cross-referred to relevant summary of GRADE profiles) (also see results from individual studies in appendix E; full GRADE evidence profiles in appendix D).

Summary of GRADE profile 10: peripheral arterial disease

No. of studies	No. of patients	Predictor(s)	Side of the leg	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	GRADE quality
Clinical examination of PAD (reference standard: AAI ≤ 0.5)						
1 [B]	605	Abnormal pulses and history of PAD	Right	53 (39 to 68)	91 (88 to 93)	Low
1 [B]	587	Abnormal pulses and history of PAD	Left	50 (35 to 65)	91 (89 to 93)	Low
1 [B]	605	Abnormal pulses or history of PAD	Right	93 (86 to 100)	58 (50 to 62)	Low
1 [B]	587	Abnormal pulses or history of PAD	Left	100 (93 to 100)	58 (54 to 62)	Low
1 [B]	605	Abnormal pulses and claudication <1 block	Right	33 (19 to 46)	95 (93 to 97)	Low
1 [B]	587	Abnormal pulses and claudication <1 block	Left	36 (22 to 51)	94 (92 to 96)	Low
1 [B]	605	Abnormal pulses or claudication <1 block	Right	83 (72 to 94)	71 (67 to 75)	Low
1 [B]	587	Abnormal pulses or claudication <1 block	Left	86 (76 to 97)	71 (67 to 75)	Low
No. of studies	No. of patients	Outcome	2 reviewers	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	GRADE Quality
Diagnostic accuracy of hybrid MRA for critical limb ischaemia (reference standard: DSA)						
1 [L]	31	Stenoses ≥ 50%	1	95 (86 to 98)	98 (95 to 99)	Low
1 [L]	31	Stenoses ≥ 50%	2	96 (88 to 99)	98 (95 to 99)	Low
1 [L]	31	Arterial occlusions	1	95 (88 to 97)	98 (96 to 99)	Low
1 [L]	31	Arterial occlusions	2	90 (83 to 94)	99 (97 to 100)	Low
No. of studies	No. of patients	Visualisation of arterial segments	Sensitivity and specificity	Other analysis		GRADE Quality
Comparison of contrast-enhanced MRA with DSA and change of treatment plans						
1 [K]	24	Anterior tibial; posterior tibial; peroneal; dorsal pedal; medial plantar; lateral plantar; pedal arch	N/A (no reference standard)	MRA was significantly better than DSA for dorsal pedal artery, lateral plantar arteries, and pedal arch, with $p < 0.05$ MRA revealed a patent vessel that was not seen on DSA (suitable for distal bypass grafting) in 9/24 (38%) patients, which led to a change of treatment plans for 7 patients.		Low

[B] = Boyko et al. (1997)

[L] = Lapeyre et al. (2005)

[K] = Kreitner et al. (2006)

AAI = ankle–arm index; CI = confidence interval; DSA = digital subtraction angiography; MRA = magnetic resonance angiography; PAD = peripheral arterial disease.

The clinical utility of assessment, investigative or diagnostic tools for examining Charcot arthropathy in people with diabetic foot problems

No studies were identified that met the inclusion/exclusion criteria.

3.1.3 Evidence statements

The clinical utility of different diabetic ulcer/wound scores (see Summary of GRADE profile 2)

3.1.3.1 Overall there was no strong evidence to suggest which diabetic/wound scores were better than others.

- *One observational study with 194 participants suggested that both the grades of the Wagner wound score and the grades and stages of the University of Texas diabetic wound score were positively associated with an increased number of amputations. However, only the stages of the University of Texas diabetic wound score had a predictive effect on healing time. (Low quality)*
- *One observational study with 1000 participants suggested that the scores of the Diabetic ulcer severity score (DUSS) were correlated to the chance of wound healing. (Low quality)*
- *One subjective qualitative evaluation of 7 wound scores suggested that the MacFarlane and Jeffcoate Nottingham wound score had the highest clinical utility, followed by the Lavery et al. wound score (1996); the Foster and Edmunds wound score (2000); and the Wagner wound score. (Very low quality)*

The clinical utility of assessment and diagnostic tools for diabetic foot infections (see Summary of GRADE profile 3 and 4)

Clinical signs (reference standard: high microbial loads > 1 million organisms per gram of tissue)

3.1.3.2 One observational study with 64 participants suggested that serous exudate and sanguineous exudate were significantly associated with diabetic foot infection. (Very low quality)

Swab cultures (reference standard: deep tissue biopsy)

3.1.3.3 One observational study with 56 participants suggested that swab cultures were associated with deep tissue biopsy in diagnosing diabetic foot infections. However, the study did not provide significant accuracy analysis for the association between swab cultures and deep tissue biopsy. (Low quality)

The diagnostic accuracy of different tests in diagnosing osteomyelitis
Imaging (single testing) (see Summary of GRADE profile 5)

3.1.3.4 Eleven observational studies with a range of participants (22 to 94) suggested that 99mTc-MDP-labelled scintigraphy had a sensitivities range from 50% to 100%, and a specificities range from 0% to 67% in diagnosing osteomyelitis in people with diabetic foot problems, with a Youden index range from -0.06 to 0.58. (Low quality)

3.1.3.5 Ten observational studies with a range of participants (14 to 62) suggested that MRI had a sensitivities range from 77% to 100%, and a specificities range from 60% to 100%, with a Youden index range from 0.38 to 1.00. (Low quality)

3.1.3.6 Eight observational studies with a range of participants (12 to 111) suggested that In-WBC scans had a sensitivities range from 33% to 100%, and a specificities range from 22% to 78%, with a Youden index range from 0.01 to 0.78. (Low quality)

3.1.3.7 Eight observational studies with a range of participants (26 to 62) suggested that plain radiographs had a sensitivities range from 22% to 75%, and a specificities range from 17% to 94%, with a Youden index range from -0.40 to 0.50. (Low quality)

3.1.3.8 Three observational studies with a range of participants (52 to 122) suggested that 99mTc-HMPAO-labelled scintigraphy had a sensitivities range from 86% to 91%, and a specificities range from

56% to 97%, with a Youden index range from 0.47 to 0.85. (Low quality)

3.1.3.9 One observational study with 78 participants suggested that anti-granulocyte Fab' fragment antibody scintigraphy had sensitivity of 92% (both 4 hours and 24 hours), and specificities of 75% (4 hours) and 88% (24 hours), with a Youden index of 0.67 and 0.80. (Moderate quality)

3.1.3.10 One observational study with 25 participants suggested that 99mTc-labelled monoclonal antigranulocyte antibody (Moab) had sensitivity of 90%, and specificity of 67%, with a Youden index of 0.57. (Low quality)

3.1.3.11 Two observational studies with 76 and 104 participants suggested that probe-to-bone testing had sensitivities of 38% and 66%, and specificities of 85% and 92% respectively, with a Youden index range from 0.30 to 0.51. (Low quality)

Imaging (combination testing) (see Summary of GRADE profile 6)

3.1.3.12 Two observational studies with 25 and 39 participants suggested that In-WBC plus 99mTc-MDP-labelled scintigraphy had sensitivities of 80% and 100%, and specificities of 80% and 79% respectively, with a Youden index range from 0.60 to 0.79. (Low quality)

3.1.3.13 One observational study with 25 participants suggested that Moab plus 99mTc-MDP-labelled scintigraphy had sensitivity of 90% and specificity of 67%, with a Youden index of 0.50. (Low quality)

3.1.3.14 One observational study with 83 participants suggested that 99m-HMPAO plus 99mTc-MDP-labelled scintigraphy had sensitivity of 93% and specificity of 98%, with a Youden index of 0.91. (Low quality)

3.1.3.15 One observational study with 22 participants suggested that 99mTc-MDP-labelled scintigraphy plus gallium-67 citrate scans had sensitivity of 69% and specificity of 83%, with a Youden index of 0.52. (Low quality)

Erythrocyte sedimentation rate and wound sizes (see Summary of GRADE profile 7 and 9)

3.1.3.16 Two observational studies with 29 and 46 participants suggested that ESR ≥ 60 mm/h had sensitivities of 89% and 92% and specificities of 68% and 90% respectively, with a Youden index range from 0.60 to 0.79. (Low quality)

3.1.3.17 Two observational studies with 29 and 46 participants suggested that ESR ≥ 65 mm/h had sensitivities of 88% and 89% and specificities of 73% and 90% respectively, with a Youden index range from 0.61 to 0.79. (Low quality)

3.1.3.18 Two observational studies with 29 and 46 participants suggested that ESR ≥ 70 mm/h had sensitivities of 83% and 89% and specificities of 77% and 100% respectively, with a Youden index range from 0.60 to 0.89. (Low quality)

3.1.3.19 Two observational studies with 28 and 43 participants suggested that ESR > 70 mm/h had sensitivities of 28% and 91% and specificities of 95% and 100% respectively, with a Youden index range from 0.28 to 0.86. (Low quality)

3.1.3.20 Two observational studies with 29 and 46 participants suggested that ESR ≥ 75 mm/h had sensitivities of 79% and 84% and specificities of 82% and 100% respectively, with a Youden index range from 0.61 to 0.84. (Low quality)

3.1.3.21 Two observational studies with 29 and 46 participants suggested that ESR ≥ 80 mm/h had sensitivities of 71% and 79% and specificities of 91% and 90% respectively, with a Youden index range from 0.62 to 0.79. (Low quality)

3.1.3.22 One observational study with 39 participants suggested that ESR > 100 mm/h had sensitivity of 23% and specificity of 100%, with a Youden index of 0.23. (Moderate quality)

3.1.3.23 Two observational studies with 40 and 46 participants suggested that wound size ≥ 2 cm^2 had sensitivities of 56% and 88% and specificities of 77% and 93% respectively, with a Youden index range from 0.49 to 0.65. (Low quality)

3.1.3.24 One observational study with 46 participants suggested that wound size ≥ 3 cm^2 had sensitivity of 79% and specificity of 77%, with a Youden index of 0.56. (Low quality)

3.1.3.25 One observational study with 46 participants suggested that wound size ≥ 4 cm^2 had sensitivity of 67% and specificity of 91%, with a Youden index of 0.58. (Low quality)

3.1.3.26 One observational study with 46 participants suggested that wound size ≥ 5 cm^2 had sensitivity of 50% and specificity of 95%, with a Youden index of 0.45. (Low quality)

Combination of erythrocyte sedimentation rate and wound sizes (see Summary of GRADE profile 9)

3.1.3.27 One observational study with 46 participants suggested that ESR rate ≥ 65 mm/h plus wound size ≥ 2 cm^2 had sensitivity of 83% and specificity of 77%, with a Youden index of 0.60. (Low quality)

3.1.3.28 One observational study with 46 participants suggested that ESR rate ≥ 70 mm/h plus wound size ≥ 2 cm^2 had sensitivity of 79% and specificity of 82%, with a Youden index of 0.61. (Low quality)

Other tests or examinations for diagnosing osteomyelitis (see Summary of GRADE profile 7)

3.1.3.29 There was limited moderate or low-quality evidence (single study with less than 50 participants) that suggested haematocrit >36%; haemoglobin <12 g/dL; platelet count >400x10^9/L; red cell

distribution width >14.5; white cell count >400x10 ^{9}/L; microbiological processing; clinical judgement; ulcer inflammation; and bone exposure had some accuracy in diagnosing osteomyelitis in people with diabetic foot problems.

The clinical utility of assessment, investigative or diagnostic tools for examining peripheral arterial disease (PAD) in people with diabetic foot problems (see Summary of GRADE profile 10)

Clinical examination with ankle–arm index (AAI) ≤ 0.5 as reference standard:

3.1.3.30 One observational study with 605 participants (with 605 right legs and 587 left legs examined) suggested that abnormal pulses and history of PAD had sensitivities of 53% (right leg) and 50% (left leg), and specificity of 91% (both legs) in diagnosing PAD in people with diabetic foot problems. (Low quality)

3.1.3.31 One observational study with 605 participants (with 605 right legs and 587 left legs examined) suggested that abnormal pulses or history of PAD had sensitivities of 93% (right leg) and 100% (left leg), and specificity of 58% (both legs). (Low quality)

3.1.3.32 One observational study with 605 participants (with 605 right legs and 587 left legs examined) suggested that abnormal pulses and claudication <1 block had sensitivities of 33% (right leg) and 36% (left leg), and specificities of 95% (right leg) and 94% (left leg). (Low quality)

3.1.3.33 One observational study with 605 participants (with 605 right legs and 587 left legs examined) suggested that abnormal pulses or claudication <1 block had sensitivities of 83% (right leg) and 86% (left leg), and specificity of 71% (both legs). (Low quality)

Hybrid magnetic resonance angiography (MRA) for critical limb ischaemia with digital subtraction angiography (DSA) as reference standard:

3.1.3.34 One observational study with 31 participants suggested that stenoses ≥ 50% had sensitivities of 95% (rater one) and 96% (rater

two), and specificity of 98% (both raters) in diagnosing critical limb ischaemia in people with diabetic foot problems. (Low quality)

3.1.3.35 One observational study with 31 participants suggested that arterial occlusions had sensitivities of 95% (rater one) and 90% (rater two), and specificities of 98% (rater one) and 99% (rater two). (Low quality)

Comparison of contrast-enhanced MRA with DSA and change of treatment plans:

3.1.3.36 One observational study with 24 participants suggested that MRA was significantly better than DSA for investigating dorsal pedal artery, lateral plantar arteries and pedal arch, which led to a change of treatment plans for 7 patients.

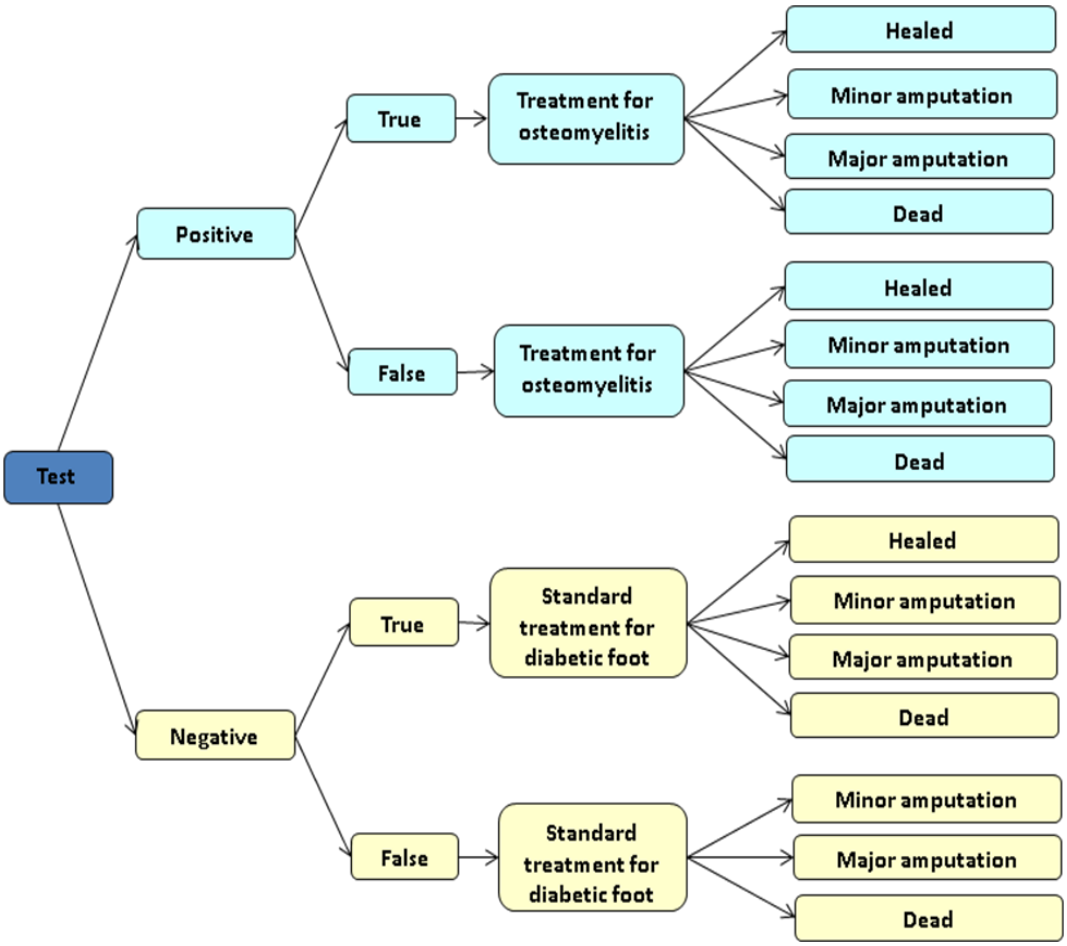
The clinical utility of assessment, investigative or diagnostic tools for examining Charcot arthropathy in people with diabetic foot problems

No studies were identified that met the inclusion/exclusion criteria.

3.1.4 Health economic modelling

A search of the literature did not identify any suitable published cost-effectiveness papers. Therefore, a de novo model was constructed. The model was a decision tree constructed in TreeAGE, with standard outcomes for a diagnostic technology (true positive, false positive, true negative and false negative). The structure is outlined in figure 1HE. The final outcomes of healed, amputation and dead are based on previous assessments of preventative treatments for diabetic foot problems and the outcomes in the clinical review.

Figure 1HE: Osteomyelitis model structure



In current practice, all patients receive an X-ray on admission, and if osteomyelitis is suspected an MRI is performed. Therefore, the true comparison is X-ray compared with X-ray plus MRI. However, the outcome of the X-ray does not lead to decisions on whether to conduct a MRI. To accurately represent the opportunity cost, no resource use was applied to performing an X-ray.

The sensitivity and specificity of MRI and X-ray were derived from the clinical review, and by choosing the mid-points from the ranges quoted. These studies were also the reference for the prevalence of osteomyelitis in this population.

The model assumed that all people who test positive for osteomyelitis get appropriate treatment and those who test negative get standard treatment.

Two simplifying assumptions were incorporated into the model: firstly, that people without osteomyelitis but incorrectly diagnosed (false positives) have the same outcomes as those without osteomyelitis correctly diagnosed (true negatives), and secondly, that people with osteomyelitis not receiving appropriate treatment (false negatives) have worse outcomes than those diagnosed correctly who receive appropriate treatment. For the base case, it was assumed that the outcomes in the false-negative arm were amputation or death. This represents a very extreme situation and was examined in the sensitivity analysis.

No long-term outcomes were considered in this analysis because there was no evidence on the long-term progression of people with osteomyelitis, or on the costs for management and readmissions. This is a potentially severe limitation of the analysis.

Outcomes are required for all these treatment arms. No suitable data were reported in the clinical studies identified by the review. Therefore, two approaches were adopted to inform the outcomes of treatment. Firstly, cost-effectiveness studies (hereafter referred to as the cost-effectiveness analysis) examining prevention of diabetic foot problems, which included the outcomes treatment of different severities for a year. The outcomes from these studies were healed, minor and major amputations, and death.

Secondly, the GDG were asked for any clinical papers that could be used to inform the model structure (hereafter referred to as the clinical study analysis). Three papers were identified to inform the arms of the model. The false-negative arm was assumed to be represented by a study that examined people not responding to treatment. These studies did not distinguish between minor and major amputations and therefore these states were merged into one state.

Utilities data were obtained from cost-effectiveness studies and several sets were used in sensitivity analyses. Costs were obtained from published studies and compared to NHS reference costs for validation. The cost of osteomyelitis treatment was assumed to be mainly made up of the cost of antibiotics. This is

because they are given for a longer duration compared with standard care (6 weeks versus 14 days) and are often given intravenously instead of orally.

The cost-effectiveness results for the two analyses are presented in table 1HE and 2HE.

Table 1HE: Deterministic and probabilistic cost-effectiveness results (per person) for the cost-effectiveness analysis

	QALY	Cost (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
Deterministic					
X-ray	0.4274	10083	-	-	-
MRI	0.4420	9923	0.0145	-160	Dominates
Probabilistic					
X-ray	0.4279	9886	-	-	-
MRI	0.4422	9728	0.0143	-158	Dominates

ICER = incremental cost-effectiveness ratio; MRI = magnetic resonance imaging; QALY = quality-adjusted life year.

Table 2HE: Deterministic and probabilistic cost-effectiveness results (per person) for the clinical study analysis

	QALY	Cost (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
Deterministic					
X-ray	0.4151	7901	-	-	-
MRI	0.4611	6868	0.0460	-1033	Dominates
Probabilistic					
X-ray	0.4135	7896	-	-	-
MRI	0.4590	6842	0.0455	-1027	Dominates

ICER = incremental cost-effectiveness ratio; MRI = magnetic resonance imaging; QALY = quality-adjusted life year.

These results indicate that using MRI is a cost-saving intervention. This is attributable to the cost of amputations (in excess of £10,000). If prompt treatment of osteomyelitis is associated with improved outcomes and reduced amputation rates, then resources could be saved and improvements made in QALYs.

The sensitivity analysis that examined the outcomes for a false negative indicated that the amputation rate would need to be 16% to 30% higher compared with the true-positive arm. In other words, inappropriate treatment results in an increase in amputation rates of 16% to 30%. In addition, there appears to be limited benefit in combining an X-ray with an MRI because MRI is more sensitive and more specific than an X-ray.

The probabilistic sensitivity analyses indicated that the conclusions of the base-case analysis are associated with high probability of being cost effective. No other sensitivity analysis materially affected the conclusion that MRI was a cost-saving diagnostic tool.

The results for £20,000 and £30,000 per QALY thresholds are presented in table 3HE for both analyses.

Table 3HE: Probability of magnetic resonance imaging being cost effective

Cost-effectiveness threshold (£ per QALY)	Probability of being cost effective	
	Cost-effectiveness analysis	Clinical study analysis
£20,000	0.91	1
£30,000	0.94	1

QALY = quality-adjusted life year.

These analyses indicate that MRIs are likely to be cost effective if delayed treatment for osteomyelitis is associated with worse outcomes and increased amputation rates. The GDG considered that, while no high-quality evidence was available to demonstrate this, it was a reasonable assumption given current clinical knowledge. Therefore, MRI appears to be a cost-effective use of resources. Please see appendix D for more details.

3.1.5 Evidence to recommendations

The clinical utility of different diabetic ulcer/wound scores

Quality of the evidence

The GDG agreed that there was limited evidence on the clinical utility of different diabetic ulcer/wound scores, and that there was no strong evidence to suggest which scores were better than others. Therefore, the GDG felt that it was not appropriate to recommend a particular score.

Other considerations

Although no particular score was recommended, the GDG felt that key characteristics of the foot (which were in most wound scores) should be documented after the initial assessment to monitor treatment progress. These key characteristics are size and depth of the ulcer; signs of infection (for

example, abscess and/or pus); ischaemia; neuropathy; gangrene; and deformity.

The clinical utility of assessment, investigative or diagnostic tools for diabetic foot infections

Quality of the evidence

The GDG agreed that there was limited evidence of low or very low quality.

Trade-off between clinical benefits and harms

Although there was a lack of evidence, the GDG considered that the accurate diagnosis of diabetic foot infections is important and has clinical benefits in term of choosing the appropriate antibiotic treatment, and that delayed appropriate treatment may incur further harm to patients. Therefore, the GDG came to the consensus that deep tissue biopsy (the gold standard commonly used in clinical practice) should be recommended to confirm suspected diabetic foot infections without osteomyelitis.

Other considerations

Although there was a lack of evidence, the GDG came to the consensus that swab cultures could be an alternative to deep tissue biopsy, if deep tissue samples were not possible to obtain due to the nature and/or severity of the wound.

The diagnostic accuracy of different tests in diagnosing osteomyelitis

Quality of the evidence

Most of the evidence was of low quality and there was only limited evidence on combination testing. Therefore, the GDG agreed that the discussion should focus on single imaging tests that have high volume of evidence, which were MRI (10 studies), 99mTc-MDP scintigraphy (11 studies), In-WBC (8 studies) and plain radiographs (8 studies).

Trade-off between clinical benefits and harms

The GDG further discussed the clinical benefits and harms of accurate diagnosis of osteomyelitis. They agreed that it is important to diagnose osteomyelitis to prevent delayed treatment, which potentially could lead to amputation. The GDG also agreed that MRI should be considered as a

diagnostic tool for suspected osteomyelitis after further discussion of the evidence and clinical utility based on the following:

- The sensitivity and specificity of MRI compared with 99mTc-MDP-labelled scintigraphy, In-WBC and plain radiographs (see Summary of GRADE profile 5)
- The summary of ROC curve and Youden index of MRI compared with 99mTc-MDP-labelled scintigraphy, In-WBC and plain radiographs (see appendix F)
- The Van der Bruel plots of MRI compared with 99mTc-MDP-labelled scintigraphy, In-WBC and plain radiographs (see appendix G).

Although the scans appear to be more accurate in the diagnosis of osteomyelitis, such scans are invasive and have an increased risk of potential adverse events. The GDG therefore considered that the accuracy of In-WBC is adequate for the diagnosis of osteomyelitis in patients in whom MRI is contraindicated.

Trade-off between net health benefits and resource use
As the GDG agreed that MRI should be considered as a diagnostic tool for suspected osteomyelitis, further health economic evaluation was conducted to assess its cost effectiveness. The economic analysis indicated that MRI would be a cost-saving intervention. More accurate diagnosis is associated with fewer amputations, therefore leading to improved health outcomes and cost savings. However, the GDG acknowledged that the model was based on poor data and was very simplistic in structure. They also noted that no long-term outcomes were included in the model, and considered that if such outcomes were included then the results would improve further.

Other considerations
Based on the GDG's knowledge, experience and expertise, a consensus was reached that if MRI is contraindicated, In-WBC may be performed as an alternative to MRI to investigate osteomyelitis.

Although X-ray and probe-to-bone are widely used in current practice, the GDG agreed that they should not be used to exclude osteomyelitis due to a

lack of strong evidence. The GDG also came to the agreement that 99mTc-MDP-labelled scintigraphy, 99mTc-HMPAO-labelled scintigraphy, antigranulocyte Fab' fragment antibody scintigraphy and 99mTc-labelled monoclonal antigranulocyte antibody scintigraphy should not be used to diagnose osteomyelitis, due to a lack of robust evidence.

The clinical utility of assessment, investigative or diagnostic tools for examining peripheral arterial disease in people with diabetic foot problems

Quality of the evidence

The GDG agreed that there was insufficient evidence (only three low-quality studies) to warrant specific recommendation on the diagnosis of PAD in people with diabetic foot problems.

Other considerations

Although there was insufficient evidence to warrant specific recommendations on the diagnosis of PAD, the GDG agreed that early identification of suspected limb ischaemia and referral to a specialist are important to ensure patients receive appropriate care in hospital. Based on the GDG's knowledge, expertise and experience, a consensus was reached to recommend the following:

- Obtain a history of any previous cardiovascular events and symptoms, including previous treatments and/or procedures.
- Inspect the limb for gangrene, tissue loss and absence or presence of a peripheral pulse, as well as the colour and temperature of the limb.
- Document the ankle–brachial pressure of the limb where clinically possible.
- Arrange prompt specialist assessment of patients with risk factors, symptoms and signs of limb ischaemia.

The clinical utility of assessment, investigative or diagnostic tools for examining Charcot arthropathy in people with diabetic foot problems

Quality of the evidence

No studies were identified that met the inclusion/exclusion criteria. In the absence of evidence, the GDG came to the consensus that X-ray may be used to investigate suspected Charcot arthropathy.

Further discussion on initial examination and key principles of care

The GDG came to the consensus that early examination of the patient's feet is important and should include:

- removing the patient's shoes, socks, bandages and dressings
- examining the feet and documenting any evidence of neuropathy, ischaemia, ulceration, inflammation or infection, deformity, or Charcot arthropathy, and also X-raying the affected foot (or feet).

The GDG also came to the consensus that assessing the signs and symptoms of systemic sepsis, deep-seated infection, Charcot arthropathy and acute limb ischaemia is important. The GDG further agreed that specialist initial assessments (cardiovascular risk; vascular and orthotic assessment; need for physiotherapy and pain management; infections; glycaemia control) should be carried out by the multidisciplinary foot care team.

3.1.6 Recommendations and research recommendations for the assessment, investigation and diagnosis of diabetic foot problems

Recommendations for the assessment, investigation and diagnosis of diabetic foot problems

Initial examination and assessment

Recommendation 1.2.11

Remove the patient's shoes, socks, bandages and dressings and examine their feet for evidence of:

- neuropathy
- ischaemia
- ulceration
- inflammation and/or infection
- deformity
- Charcot arthropathy.

Document any identified new and/or existing diabetic foot problems.

Recommendation 1.2.12

Consider a diagnosis of Charcot arthropathy if there is deformity, redness or warmth. Refer to an appropriate specialist to confirm the diagnosis.

Recommendation 1.2.13

Examine the patient for signs and symptoms of systemic sepsis (such as fever, tachycardia, hypotension, reduced consciousness or altered cognitive state).

Recommendation 1.2.14

X-ray the patient's affected foot (or feet) to determine the extent of the foot problem.

Recommendation 1.2.15

If the patient has a diabetic foot ulcer, assess and document:

- deformity
- gangrene

- ischaemia
- neuropathy
- signs of infection
- the size and depth of the ulcer.

Recommendation 1.2.16

Obtain urgent advice from an appropriate specialist if any of the following are present:

- Fever or any other signs or symptoms of systemic sepsis.
- Clinical concern that there is a deep-seated infection (for example palpable gas).
- Limb ischaemia.

Multidisciplinary foot care team

Recommendation 1.2.5

The multidisciplinary foot care team should:

- assess and treat the patient's diabetes, which should include interventions to minimise the patient's risk of cardiovascular events, and any interventions for pre-existing chronic kidney disease or anaemia (please refer to 'Chronic kidney disease' [NICE clinical guideline 73] and 'Anaemia management in people with chronic kidney disease' [NICE clinical guideline 114])
- assess, review and evaluate the patient's response to initial medical, surgical and diabetes management
- assess the foot, and determine the need for specialist wound care, debridement, pressure off-loading and/or other surgical interventions
- assess the patient's pain and determine the need for treatment and access to specialist pain services
- perform a vascular assessment to determine the need for further interventions
- review the treatment of any infection
- determine the need for interventions to prevent the deterioration and

development of Achilles tendon contractures and other foot deformities

- perform an orthotic assessment and treat to prevent recurrent disease of the foot
- have access to physiotherapy
- arrange discharge planning, which should include making arrangements for the patient to be assessed and their care managed in primary and/or community care, and followed up by specialist teams. Please refer to ‘Type 2 diabetes: prevention and management of foot problems’ (NICE clinical guideline 10).

Investigation of suspected diabetic foot infection

Recommendation 1.2.18

If a moderate to severe soft tissue infection is suspected and a wound is present, send a soft tissue sample from the base of the debrided wound for microbiological examination. If this cannot be obtained, a superficial swab may provide useful information on the choice of antibiotic therapy.

Recommendation 1.2.19

If osteomyelitis is suspected and initial X-ray does not confirm the presence of osteomyelitis, use magnetic resonance imaging (MRI). If MRI is contraindicated, white blood cell (WBC) scanning may be performed instead.

Recommendation 1.2.20

Do not exclude osteomyelitis on the basis of X-rays alone. X-rays should be used for alternative diagnoses, such as Charcot arthropathy.

Recommendation 1.2.21

Do not exclude osteomyelitis on the basis of probe-to-bone testing

Recommendation 1.2.22

Do not use the following bone scans to diagnose osteomyelitis: 99mTc-MDP-labelled scintigraphy, 99mTc-HMPAO-labelled scintigraphy, antigranulocyte Fab' fragment antibody scintigraphy or 99mTc-labelled monoclonal antigranulocyte antibody scintigraphy.

Assessment of suspected limb ischaemia

Recommendation 1.2.37

If limb ischaemia is suspected, obtain a history of any previous cardiovascular events and symptoms, including previous treatments and/or procedures.

Recommendation 1.2.38

Inspect the limb for the following:

- Colour and temperature.
- Presence of gangrene or tissue loss.
- Presence or absence of a peripheral pulse.

Recommendation 1.2.39

Measure and document the ankle–brachial pressure where clinically possible, ensuring careful interpretation of the results.

Recommendation 1.2.40

Arrange prompt specialist assessment of patients with risk factors, symptoms and signs of limb ischaemia to ensure an accurate diagnosis.

Research recommendations for the assessment, investigation and diagnosis of diabetic foot problems

See appendix A for a list of all research recommendations.

No research recommendations have been made for this section.

3.2 Debridement, wound dressings and off-loading

3.2.1 Review question

What is the clinical effectiveness of surgical or non-surgical debridement, wound dressings and off-loading in treating diabetic foot problems?

3.2.2 Evidence review

This particular review question was split into three sub-sections: i) surgical or non-surgical debridement; ii) wound dressings; and iii) off-loading. The systematic search retrieved 9817 studies. Of these, 14 studies were included for this review question (for the review protocol and inclusion/exclusion criteria, please see appendix B). One Cochrane review was identified for surgical or non-surgical debridement (which included five studies); six studies were identified for wound dressings; and seven studies were identified for off-loading. Where possible, if information was available in the studies, evidence was presented in:

- Characteristics of included studies.
- Summary of GRADE profiles.
- Full GRADE evidence profiles (see appendix D).
- Forest plots from meta-analysis (where appropriate) (see appendix H).
- Evidence statements.

Table 3: Characteristics of included studies

Author	Total no. of patients	Interventions	Follow-up period	Primary outcomes
Debridement				
Edwards et al. (2009)	46 198 140	Surgical debridement vs. non-surgical management Hydrogel vs. good wound care Hydrogel vs. larvae therapy	6 months 12–20 weeks Not reported	• Complete wound healing • Ulcer recurrence • > 50% wound reduction • Complications • Adverse events
Off-loading				
Van de Weg et al. (2008)	43	TCC + standard care vs. custom-made footwear + standard care Standard care = standard wound care + debridement	16 weeks	• Complete wound healing • Wound surface reduction
Katz et al. (2005)	41	TCC + standard care vs. RCW (iTCC) + standard care. Standard care = standard wound care + debridement	12 weeks	• Complete wound healing • Treatment-related AEs
Ganguly et al. (2008)	55	TCC + standard care vs. simple dressing (mupirocin ointment and sterile gauze) + standard care Standard care = debridement	Until complete epithelialisation and 6 months after healing.	• Complete wound healing
Armstrong et al. (2001)	63	TCC + standard care vs. RCW + standard care vs. half shoes + standard care Standard care = standard wound care + debridement	12 weeks	• Complete wound healing • Mean healing time
Mueller et al. (1989)	40	TCC + standard care vs. traditional dressing treatment (wet-to-dry saline dressing) + standard care Standard care = standard protocol	6 weeks	• Complete wound healing
Nube et al. (2006)	32	Felt deflective padding to the skin + standard care vs. felt deflective padding within the shoe + standard care (control) Standard care = standard wound care + debridement	4 weeks or until healing	• Wound size reduction at week 4
Piagessi et al. (2007)	40	TCC + standard care vs. instant casting (Optima Diab device) + standard care Standard care = standard wound care + debridement	12 weeks and up to complete re-epithelialisation	• Complete wound healing • Mean healing time • Treatment-related AEs

Dressings				
Piagessi et al. (2001)	20	Aquacel (carboxyl methyl-cellulose dressing) + debridement vs. saline-moistened gauze + debridement	8 weeks or until complete re-epithelisation	• Achieved granulation tissue • Mean healing time • Complication (infection)
Veves et al. (2002)	276	Promogan (collagen/oxidised regenerated cellulose dressing) +debridement vs. saline-moistened gauze + debridement	12 weeks	• Complete wound healing • Wound surface reduction • Wound-related AEs
Jude et al. (2007)	134	Hydrofiber (ionic silver dressing) + debridement vs. calcium alginate dressing + debridement	8 weeks	• Complete wound healing • Wound surface reduction • Withdrawal due to AEs • Mean healing time • Wound-related complications • Treatment-related AEs
Foster et al. (1994)	30	Polyurethane foam dressing + debridement and antibiotics vs. alginate dressing + debridement and antibiotics	8 weeks	• Complete wound healing
Shukrimi et al. (2008)	30	Honey dressing + debridement and antibiotics vs. standard dressing (normal saline cleansing and povidone-soaked gauze) + debridement and antibiotics	Wound ready for surgical closure or needed further debridement	• Mean time for wound to be ready for surgical closure
Jeffcoate et al. (2009)	317	Non-adherent gauze + standard care vs. Inadine (iodine impregnated dressing) + standard care vs. Aquacel (carboxyl methyl-cellulose dressing) + standard care Standard care = debridement and off-loading with standard wound care	24 weeks	• Complete wound healing • Mean healing time • Major and minor amputation • Withdrawal due to AEs • Complication (infection)

AEs = adverse events; RCW (iTCC) = removable cast walker (rendered irremovable by single roll of fibreglass casting); TCC = total contact casting.

Clinical effectiveness of surgical and non-surgical debridement in treating diabetic foot problems

One Cochrane review (which included five studies) on the clinical effectiveness of surgical and non-surgical debridement in treating diabetic foot problems was identified and included. The evidence was synthesised and presented in the following summary of GRADE profiles (for full GRADE evidence profiles, see appendix D).

Summary of GRADE profile 11: Surgical debridement vs. conventional non-surgical debridement for diabetic foot ulcers

No of studies	Design	Surgical debridement	Conventional non-surgical management	RR/NNTB (95% CI)	Absolute	GRADE quality
Number of ulcers completely healed (6-month follow-up)						
1 [E]	RCT	21/22 (95.5%)	19/24 (79.2%)	RR 1.21 (0.96 to 1.51) NNTB = N/A	166 more per 1000 (from 32 fewer to 404 more)	Low
Ulcer recurrence rates (6-month follow-up)						
1 [E]	RCT	3/22 (13.6%)	8/24 (33.3%)	RR 0.41 (0.12 to 1.35) NNTB = N/A	196 fewer per 1000 (from 293 fewer to 117 more)	Low
Number of adverse events (complications) (6-month follow-up)						
1 [E]	RCT	1/22 (4.5%)	3/24 (12.5%)	RR 0.36 (0.03 to 2.65) NNTB = N/A	80 fewer per 1000 (from 121 fewer to 206 more)	Low

[E] = Edwards and Stapley (2009): Cochrane review, included study = Piaggessi el al. (1998)

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk.

Summary of GRADE profile 12: Hydrogel vs. gauze or good wound care (control) for diabetic foot ulcers

No of studies	Design	Hydrogel	Gauze or good wound care	RR/NNTB (95% CI)	Absolute	GRADE quality
Number of ulcers completely healed (follow-up ranged from 12–20 weeks)						
3 [E]	RCT	51/99 (51.5%)	28/99 (28.3%)	RR 1.84 (1.3 to 2.61) NNTB = 4 (3 to 10)	238 more per 1000 (from 85 more to 456 more)	Low
Number of adverse events (complications) (follow-up ranged from 12–20 weeks)						
3 [E]	RCT	22/99 (22.2%)	36/99 (36.4%)	RR 0.60 (0.38 to 0.95) NNTB = 7 (4 to 69)	146 fewer per 1000 (from 18 fewer to -226 fewer)	Low

[E] = Edwards and Stapley (2009): Cochrane review, included studies = D'Hemecourt el al. (1998) (20 weeks); Jensen el al. (1998) (16 weeks); Vandeputte et al. (1997) (12 weeks).

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk.

Summary of GRADE profile 13: Hydrogel vs. larvae therapy for diabetic foot ulcers

No of studies	Design	Larvae	Hydrogel	RR/NNTB (95% CI)	Absolute	GRADE quality
Wound area reduction > 50% (follow-up not reported)						
1 [E]	RCT	36/70 (51.4%)	19/70 (27.1%)	RR 1.89 (1.21 to 2.96) NNTB = 4 (3 to 12)	241 more per 1000 (from 57 more to 531 more)	Low
Number of ulcers completely healed (follow-up not reported)						
1 [E]	RCT	5/70 (7.1%)	2/70 (2.9%)	RR 2.50 (0.5 to 12.46) NNTB = N/A	44 more per 1000 (from 15 fewer to 332 more)	Low

[E] = Edwards and Stapley (2009): Cochrane review, included study = Markevich el al. (2000)

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk.

Clinical effectiveness of off-loading in treating diabetic foot problems

Seven studies on the clinical effectiveness of off-loading in treating diabetic foot problems were identified and included. The evidence was synthesised and presented in the following summary of GRADE profiles (for full GRADE evidence profiles, see appendix D). Most studies included were head-to-head trials (comparing different types of off-loading technologies), with total contact casting (TCC) as a commonly used standard comparator.

Summary of GRADE profile 14: Total contact casting vs. custom-made temporary footwear

No of studies	Design	TCC	CTF	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (16 weeks)						
1 [V]	RCT	6/23 (26.1%)	6/20 (30%)	RR 0.87 (0.33 to 2.27) NNTB = N/A	4 fewer per 100 (from 20 fewer to 38 more)	Moderate
Wound surface reduction (cm^2) (16 weeks)						
1 [V]	RCT	23	20	Mean reduction (cm^2) (SD): TCC = -2.88 (2.5); CTF = -2.16 (3.4) Adjusted mean difference: 0.10 (95% CI: -0.92 to 0.72), p = 0.81		Moderate

[v] = Van de Weg et al. (2008)

CI = confidence interval; CTF = custom-made temporary footwear; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk; SD = standard deviation; TCC = total contact casting.

Summary of GRADE profile 15: Total contact casting vs. removable cast walker (rendered unremovable by single roll of fibreglass casting)

No of studies	Design	TCC	RCW (iTCC)	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (12 weeks)						
1 [K]	RCT	15/20 (75%)	17/21 (81%)	RR 0.93 (0.67 to 1.29) NNTB = N/A	6 fewer per 100 (from 27 fewer to 23 more)	Low
Treatment-related AEs (12 weeks)						
1 [K]	RCT	13/20 (65%)	8/21 (38.1%)	RR 1.71 (0.91 to 3.21) NNTH = N/A	27 more per 100 (from 3 fewer to 84 more)	Low

[K] = Katz et al. (2005)

CI = confidence interval; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised controlled trial; RCW (iTCC) = removable cast walker (rendered unremovable by single roll of fibreglass casting); RR = relative risk; TCC = total contact casting.

Summary of GRADE profile 16: Total contact casting vs. dressing (mupirocin ointment and sterile gauze)

No of studies	Design	TCC	Dressing	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (6 months)						
1 [G]	RCT	36/39 (92.3%)	25/33 (75.8%)	RR 1.22 (0.98 to 1.51) NNTB = N/A	17 more per 100 (from 2 fewer to 39 more)	Low

[G] = Ganguly et al. (2008)

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk; TCC = total contact casting.

Summary of GRADE profile 17: Total contact casting vs. removable cast walker

No of studies	Design	TCC	RCW	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (12 weeks)						
1 [A]	RCT	17/19 (89.5%)	13/20 (65%)	RR 1.38 (0.96 to 1.97) NNTB = N/A	25 more per 100 (from 3 fewer to 63 more)	Low
Mean healing time (days)						
1 [A]	RCT	19	20	Mean healing time (days) (SD): TCC = 33.5 (5.9); RCW = 50.4 (7.2), p = 0.07		Low

[A] = Armstrong et al. (2001)

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RCW = removable cast walker; RR = relative risk; SD = standard deviation; TCC = total contact casting.

Summary of GRADE profile 18: Total contact casting vs. half-shoes

No of studies	Design	TCC	Half-shoes	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (12 weeks)						
1 [A]	RCT	17/19 (89.5%)	14/24 (58.3%)	RR 1.53 (1.06 to 2.22) NNTB = N/A	31 more per 100 (from 3 more to 71 more)	Low
Mean healing time (days)						
1 [A]	RCT	19	24	Mean healing time (days) (SD): TCC = 33.5 (5.9); Half-shoes = 61.0 (6.5), p = 0.005		Low

[A] = Armstrong et al. (2001)

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk; TCC = total contact casting.

Summary of GRADE profile 19: Removable cast walker vs. half-shoes

No of studies	Design	RCW	Half-shoes	R/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (12 weeks)						
1 [A]	RCT	13/20 (65%)	14/24 (58.3%)	RR 1.11 (0.70 to 1.78) NNTB = N/A	6 more per 100 (from 17 fewer to 45 more)	Low

[A] = Armstrong et al. (2001)

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RCW = removable cast walker; RR = relative risk.

Summary of GRADE profile 20: Total contact casting vs. dressing (wet-to-dry dressing)

No of studies	Design	TCC	Dressing	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (6 weeks)						
1 [M]	RCT	19/21 (90.5%)	6/19 (31.6%)	RR 2.87 (1.46 to 5.63) NNTB = N/A	59 more per 100 (from 15 more to 100 more)	Low

[M] = Mueller et al. (1989)

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk; TCC = total contact casting.

Summary of GRADE profile 21: Total contact casting vs. instant casting (Optima Diab device)

No of studies	Design	TCC	Instant casting	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (12 weeks)						
1 [P]	RCT	19/20 (95%)	17/20 (85%)	RR 1.12 (0.91 to 1.38) NNTB = N/A	10 more per 100 (from 8 fewer to 32 more)	Low
Mean healing time (weeks)						
1 [P]	RCT	20	20	Mean healing time (weeks) (standard deviation): TCC = 6.5 (4.4); instant casting = 6.7 (3.4), p = 0.874		Low
Treatment-related adverse events (12-week follow-up)						
1 [P]	RCT	4/20 (20%)	5/20 (25%)	RR 0.80 (0.25 to 2.55) NNTH = N/A	5 fewer per 100 (from 19 fewer to 39 more)	Low

[P] = Piaggesi et al. (2007)

CI = confidence interval; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised controlled trial; RR = relative risk; TCC = total contact casting.

Summary of GRADE profile 22: Felt deflective padding (to the skin) vs. felt deflective padding (within the shoe)

No of studies	Design	To the skin	Within the shoe	Outcomes	Absolute	GRADE quality
Wound surface reduction (%)						
1 [N]	RCT	15	17	Wound surface reduction (%): Skin = 73%; Shoe = 74%, z = 0.02, p = 0.9		Low

[N] = Nube et al. (2006)

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk.

Clinical effectiveness of different wound dressings in treating diabetic foot problems

Six studies on the clinical effectiveness of wound dressings in treating diabetic foot problems were identified and included. The evidence was synthesised and presented in the following summary of GRADE profiles (for full GRADE evidence profiles, see appendix D). Most studies included were head-to-head trials comparing different types of dressings.

Summary of GRADE profile 23: Aquacel vs. saline-moistened gauze

No of studies	Design	Aquacel	SMG	RR/NNTB (95% CI)	Absolute	GRADE quality
Achieved granulation tissue (8 weeks)						
1 [P]	RCT	4/10 (40%)	1/10 (10%)	RR 4.00 (0.54 to 29.81) NNTB = N/A	30 more per 100 (from 5 fewer to 100 more)	Low
Mean healing time (days)						
1 [P]	RCT	10	10	Mean healing time (days) (standard deviation): Aquacel = 127 (46); SMG = 234 (61), p < 0.001		Low
Complication (infection) (8 weeks)						
1 [P]	RCT	1/10 (10%)	3/10 (30%)	RR 0.33 (0.04 to 2.69) NNTH = N/A	20 fewer per 100 (from 29 fewer to 51 more)	Low

[P] = Piagessi et al. (2001)

Aquacel = sodium carboxyl-methyl-cellulose dressing; CI = confidence interval; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised controlled trial; RR = relative risk; SMG = saline-moistened gauze.

Summary of GRADE profile 24: Promogran vs. saline-moistened gauze

No of studies	Design	Promogran	SMG	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (12 weeks)						
1 [V]	RCT	51/104 (49.5%)	39/84 (46.4%)	RR 1.06 (0.78 to 1.43) NNTB = N/A	3 more per 100 (from 10 fewer to 20 more)	Low
Wound surface reduction (%) (12 weeks)						
1 [V]	RCT	104	84	Mean wound surface reduction (%): Promogran = 64.5%; SMG = 63.8%, p > 0.05		Low
Wound-related serious adverse events (12 weeks)						
1 [V]	RCT	25/104 (24%)	35/84 (41.7%)	RR 0.58 (0.38 to 0.88) NNTH = N/A	18 fewer per 100 (from 5 fewer to 26 fewer)	Low

[V] = Veves et al. (2002)

CI = confidence interval; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; Promogran = collagen/oxidised regenerated cellulose dressing; RCT = randomised controlled trial; RR = relative risk; SMG = saline-moistened gauze.

Summary of GRADE profile 25: Hydrofiber dressing vs. calcium alginate

No of studies	Design	AQAg	CA	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (8 weeks)						
1 [J]	RCT	21/67 (31.3%)	15/67 (22.4%)	RR 1.40 (0.79 to 2.47) NNTB = N/A	9 more per 100 (from 5 fewer to 33 more)	Low
Wound surface reduction (%) (8 weeks)						
1 [J]	RCT	67	67	Mean wound surface reduction (%) (SD): AQAg = 58.1 (53.1); CA = 60.5 (42.7), p = 0.948		Low
Mean healing time (days)						
1 [J]	RCT	67	67	Mean healing time (days) (SD): AQAg = 52.6 (1.8); CA = 57.7 (1.7), p = 0.340		Low
Withdrawal due to adverse events (unspecified) (8 weeks)						
1 [J]	RCT	8/67 (11.9%)	13/67 (19.4%)	RR 0.61 (0.27 to 1.39) NNTH = N/A	8 fewer per 100 (from 14 fewer to 8 more)	Low
Wound-related complications (8 weeks)						
1 [J]	RCT	23/67 (34.3%)	26/67 (38.8%)	RR 0.88 (0.57 to 1.38) NNTH = N/A	5 fewer per 100 (from 17 fewer to 15 more)	Low
Treatment-related adverse events (8 weeks)						
1 [J]	RCT	11/67 (16.4%)	9/67 (13.4%)	RR 1.22 (0.54 to 2.76) NNTH = N/A	3 more per 100 (from 6 fewer to 24 more)	Low

[J] = Jude et al. (2007)

AQAg = Hydrofiber dressing; CA = calcium alginate; CI = confidence interval; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised controlled trial; RR = relative risk; SD = standard deviation.

Summary of GRADE profile 26: Polyurethane foam vs. alginate

No of studies	Design	Polyurethane	Alginate	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (8 weeks)						
1 [F]	RCT	9/15 (60%)	8/15 (53.3%)	RR 1.13 (0.60 to 2.11) NNTB = N/A	7 more per 100 (from 21 fewer to 59 more)	Low

[F] = Foster et al. (1994)

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk.

Summary of GRADE profile 27: Honey dressing vs. povidone-soaked gauze

No of studies	Design	Honey	Povidone	RR/NNTB (95% CI)	Absolute	GRADE quality
Mean time for wound to be ready for surgical closure (days)						
1 [S]	RCT	15	15	Mean time for wound to be ready for surgical closure (days) (range): Honey = 14.4 (7–26); povidone = 15.4 (9–36), p > 0.05.		Low

[S] = Shukrime et al. (2008)

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk.

Summary of GRADE profile 28: Aquacel vs. non-adherent gauze (1)

No of studies	Design	Aquacel	N-A	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (24 weeks)						
1 [J]	RCT	46/103 (44.7%)	41/106 (38.7%)	RR 1.15 (0.84 to 1.59) NNTB = N/A	6 more per 100 (from 6 fewer to 23 more)	Moderate
Mean healing time (days)						
1 [J]	RCT	103	106	Mean healing time (days) (SD): Aquacel = 130.7 (52.4); N-A = 125.8 (55.9), p > 0.05		Moderate
Major and minor amputation						
1 [J]	RCT	4/103 (3.9%)	2/106 (1.9%)	RR 2.06 (0.39 to 10.99) NNTB = N/A	2 more per 100 (from 1 fewer to 19 more)	Moderate
Withdrawal due to adverse events (24 weeks)						
1 [J]	RCT	11/103 (10.7%)	15/106 (14.2%)	RR 0.75 (0.36 to 1.56) NNTH = N/A	4 fewer per 100 (from 9 fewer to 8 more)	Moderate
Complication (infection)						
1 [J]	RCT	9/103 (8.7%)	7/106 (6.6%)	RR 1.32 (0.51 to 3.42) NNTH = N/A	2 more per 100 (from 3 fewer to 16 more)	Moderate

[J] = Jeffcoate et al. (2009)

Aquacel = sodium carboxyl-methyl-cellulose dressing; CI = confidence interval; N-A = non-adherent, knitted, viscose filament gauze; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised controlled trial; RR = relative risk; SD = standard deviation.

Summary of GRADE profile 29: Aquacel vs. Inadine (2)

No of studies	Design	Aquacel	Inadine	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (24 weeks)						
1 [J]	RCT	46/103 (44.7%)	48/108 (44.4%)	RR 1.00 (0.74 to 1.36) NNTB = N/A	0 fewer per 100 (from 12 fewer to 16 more)	Moderate
Mean healing time (days)						
1 [J]	RCT	103	108	Mean healing time (days) (standard deviation): Aquacel = 130.7 (52.4); Inadine = 127.8 (54.2), p > 0.05		Moderate
Major and minor amputation						
1 [J]	RCT	4/103 (3.9%)	1/108 (0.9%)	RR 4.19 (0.48 to 36.91) NNTB = N/A	3 more per 100 (from 0 fewer to 32 more)	Moderate
Withdrawal due to adverse events (24 weeks)						
1 [J]	RCT	11/103 (10.7%)	9/108 (8.3%)	RR 1.28 (0.55 to 2.96) NNTH = N/A	2 more per 100 (from 4 fewer to 16 more)	Moderate
Complication (infection)						
1 [J]	RCT	9/103 (8.7%)	12/108 (11.1%)	RR 0.79 (0.36 to 1.79) NNTH = N/A	2 fewer per 100 (from 7 fewer to 9 more)	Moderate

[J] = Jeffcoate et al. (2009)

Aquacel = sodium carboxyl-methyl-cellulose dressing; CI = confidence interval; inadine = iodine impregnated dressing; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised controlled trial; RR = relative risk.

Summary of GRADE profile 30: Non-adherent gauze vs. Inadine (3)

No of studies	Design	N-A	Inadine	RR/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (24 weeks)						
1 [J]	RCT	41/106 (38.7%)	48/108 (44.4%)	RR 0.87 (0.63 to 1.20) NNTB = N/A	6 fewer per 100 (from 16 fewer to 9 more)	Moderate
Mean healing time (days)						
1 [J]	RCT	106	108	Mean healing time (days) (standard deviation): N-A = 125.8 (55.9); inadine = 127.8 (54.2), p > 0.05		Moderate
Major and minor amputation						
1 [J]	RCT	2/106 (1.9%)	1/108 (0.9%)	RR 2.04 (0.19 to 22.14) NNTB = N/A	1 more per 100 (from 1 fewer to 19 more)	Moderate
Withdrawal due to adverse events (24 weeks)						
1 [J]	RCT	15/106 (14.2%)	9/108 (8.3%)	RR 1.70 (0.78 to 3.71) NNTH = N/A	6 more per 100 (from 2 fewer to 22 more)	Moderate
Complication (infection)						
1 [J]	RCT	7/106 (6.6%)	12/108 (11.1%)	RR 0.59 (0.24 to 1.45) NNTH = N/A	5 fewer per 100 (from 8 fewer to 5 more)	Moderate

[J] = Jeffcoate et al. (2009)

CI = confidence interval; inadine = iodine impregnated dressing; N-A = non-adherent, knitted, viscose filament gauze; NNTB = number needed to treat to benefit; RCT = randomised controlled trial; RR = relative risk.

3.2.3 Evidence statements

Clinical effectiveness of surgical and non-surgical debridement in treating diabetic foot problems

Surgical debridement vs. conventional non-surgical management (see Summary of GRADE profile 11)

3.2.3.1 One RCT with 46 participants showed that when surgical debridement was compared with conventional non-surgical management, there was no significant difference in the number of ulcers completely healed; ulcer recurrence rates; or the number of adverse events. (Low quality)

Hydrogel vs. gauze or good wound care (see Summary of GRADE profile 12)

3.2.3.2 Three RCTs with a total number of 198 participants showed that participants who received hydrogel were significantly more likely to have their ulcers completely healed, and significantly less likely to have adverse events compared with participants who received gauze or good wound care. (Low quality)

Hydrogel vs larvae therapy (see Summary of GRADE profile 13)

3.2.3.3 One RCT with 140 participants showed that participants who received larvae therapy were significantly more likely to have more than 50% wound reduction compared with participants who received hydrogel. However, in the 2 groups there was no significant difference in the number of ulcers completely healed. (Low quality)

Clinical effectiveness of off-loading in treating diabetic foot problems

Total contact casting vs. custom-made temporary footwear (see Summary of GRADE profile 14)

3.2.3.4 One RCT with 43 participants showed that there was no significant difference in complete wound healing or mean wound surface reduction between participants who received total contact casting (TCC) and custom-made temporary footwear. (Moderate quality)

Total contact casting vs. mupirocin ointment and sterile gauze (see Summary of GRADE profile 16)

3.2.3.5 One RCT with 72 participants showed that there was no significant difference in complete wound healing between participants who received TCC and simple dressing (mupirocin ointment and sterile gauze). (Low-quality)

Total contact casting vs. removable cast walker (rendered irremovable) (see Summary of GRADE profile 15)

3.2.3.6 One RCT with 41 participants showed no significant differences in complete wound healing and treatment-related adverse events between participants who received TCC or a removable cast walker (rendered irremovable by a single roll of fibreglass casting). (Low-quality)

Total contact casting vs. removable cast walker vs half-shoes (see Summary of GRADE profile 17, 18 and 19)

3.2.3.7 One RCT with 63 participants showed that there was no significant difference in complete wound healing among participants who received TCC, removable cast walkers or half-shoes. (Low quality)

3.2.3.8 One RCT with 43 participants showed that the mean wound healing time of participants who received TCC was significantly shorter compared with participants who received half-shoes. (Low quality)

Total contact casting vs. wet-to-dry dressing (see Summary of GRADE profile 20)

3.2.3.9 One RCT with 40 participants showed that participants who received TCC were significantly more likely to have complete wound healing compared with participants who received traditional dressings (wet-to-dry dressings). (Low quality)

Total contact casting vs. instant casting (Optima Diab device) (see Summary of GRADE profile 21)

3.2.3.10 One RCT with 40 participants showed no significant differences in complete wound healing, mean wound healing time and treatment-related adverse events between participants who received TCC and instant casting (Optima Diab device). (Low quality)

Felt deflective padding (to the skin) vs. felt deflective padding (within the shoe) (see Summary of GRADE profile 22)

3.2.3.11 One RCT with 32 participants showed no significant difference in mean wound surface reduction between participants who received felt deflective padding (to the skin) and felt deflective padding (within the shoe). (Low quality)

Clinical effectiveness of different wound dressings in treating diabetic foot problems

Aquacel vs. saline-moistened gauze (see Summary of GRADE profile 23)

3.2.3.12 One RCT with 20 participants showed no significant differences in the number of participants who achieved granulation tissue and number of complications (infections) between participants who received Aquacel and saline-moistened gauze. (Low quality)

3.2.3.13 The RCT with 20 participants showed that the mean wound healing time of participants who received Aquacel was significantly shorter compared with participants who received saline-moistened gauze. (Low quality)

Promogran vs. saline-moistened gauze (see Summary of GRADE profile 24)

3.2.3.14 One RCT with 188 participants showed no significant differences in complete wound healing and mean wound surface reduction between participants who received Promogran and saline-moistened gauze. (Low quality)

3.2.3.15 The RCT with 188 participants showed that participants who received Promogran had significantly fewer wound-related adverse events compared with participants who received saline-moistened gauze. (Low quality)

Hydrofiber dressing vs. calcium alginate dressing (see Summary of GRADE profile 25)

3.2.3.16 One RCT with 134 participants showed no significant differences in the following outcomes between participants who received Hydrofiber dressing and calcium alginate dressing. (Low quality):

- *Complete wound healing.*
- *Mean wound surface reduction.*

- *Mean healing time.*
- *Withdrawal due to adverse events.*
- *Wound-related complications.*
- *Treatment-related adverse events.*

Polyurethane foam dressing vs. alginate dressing (see Summary of GRADE profile 26)

3.2.3.17 One RCT with 30 participants showed no significant difference in complete wound healing between participants who received polyurethane foam dressing and alginate dressing. (Low quality)

Honey dressing vs. povidone-soaked gauze (see Summary of GRADE profile 27)

3.2.3.18 The same RCT with 30 participants showed no significant difference in the mean time for wounds to be ready for surgical closure between participants who received honey dressing and povidone-soaked gauze. (Low quality)

Aquacel vs. Inadine vs. non-adherent, knitted, viscose filament gauze (see Summary of GRADE profile 28, 29 and 30)

3.2.3.19 One RCT with 317 participants showed no significant differences in the following outcomes among participants who received Aquacel or Inadine dressing or non-adherent knitted viscose filament gauze. (Moderate quality):

- *Complete wound healing.*
- *Mean healing time.*
- *Major and minor amputation.*
- *Withdrawal due to adverse events.*
- *Complications (infection).*

3.2.4 Health economic modelling

No health economic modelling was conducted for this question.

3.2.5 Evidence to recommendations

Clinical effectiveness of surgical and non-surgical debridement in treating diabetic foot problems

Quality of the evidence

The GDG agreed that because the evidence was limited and of low quality, it was not appropriate to recommend specific techniques for debridement.

Other considerations

Although there was insufficient evidence to recommend specific techniques, the GDG agreed that debridement is important to promote wound healing, particularly for wounds with extensive necrotic tissue. The GDG discussed factors that should be considered before carrying out debridement. Based on the GDG's experience, knowledge and expertise, consensus was reached that debridement should only be carried out by members of the multidisciplinary foot care team with specialist skills, and that the technique chosen should best match their specialist expertise, clinical experience, patient preference and the site of the ulcer.

Clinical effectiveness of off-loading in treating diabetic foot problems

Quality of the evidence

The GDG agreed that because the evidence was inconclusive (most head-to-head comparisons showed no significant difference between the two comparators) and was of low quality, it was not appropriate to recommend specific techniques for off-loading.

Other considerations

Although there was insufficient evidence to recommend specific techniques, the GDG agreed that off-loading is important to promote wound healing by relieving pressure on the wound. The GDG reached consensus that off-loading should be a standard part of wound management.

The GDG further discussed the NICE guideline on pressure ulcers (NICE clinical guideline 29), and agreed that patients should have access to appropriate pressure-relieving support surfaces and strategies in line with CG29 to minimise the risk of pressure ulcer development on the affected and unaffected limb during their hospital stay.

Clinical effectiveness of wound dressings in treating diabetic foot problems

Quality of the evidence

The GDG agreed that because the evidence was inconclusive (most head-to-head comparisons showed no significant difference between the two comparators) and was of moderate/low quality, it was not appropriate to recommend specific wound dressings.

Other considerations

The GDG agreed that the use of dressings should be a standard part of wound management to prevent infections of the wound. In the absence of strong evidence on particular wound dressings, the GDG came to the consensus that the multidisciplinary foot care team should use the wound dressings with the lowest acquisition cost, taking into account their clinical assessment of the wound, the experience and preferences of the patient, and the clinical circumstances.

3.2.6 Recommendations and research recommendations for debridement, wound dressings and off-loading

Recommendations for debridement, wound dressings and off-loading

Management of diabetic foot ulcers

Debridement, dressings and off-loading

Recommendation 1.2.31

Debridement should only be done by healthcare professionals from the multidisciplinary foot care team, using the technique that best matches their specialist expertise, clinical experience, patient preference, and the site of the ulcer.

Recommendation 1.2.32

When choosing wound dressings, healthcare professionals from the multidisciplinary foot care team should take into account their clinical assessment of the wound, patient preference and the clinical circumstances, and should use wound dressings with the lowest acquisition cost.

Recommendation 1.2.33

Offer off-loading for patients with diabetic foot ulcers. Healthcare professionals from the multidisciplinary foot care team should take into account their clinical assessment of the wound, patient preference and the clinical circumstances, and should use the technique with the lowest acquisition cost.

Recommendation 1.2.34

Use pressure-relieving support surfaces and strategies in line with ‘Pressure ulcers’ (NICE clinical guideline 29) to minimise the risk of pressure ulcers developing.

Research recommendations for debridement, wound dressings and off-loading

See appendix A for a list of all research recommendations.

What is the optimum wound-healing environment and what is the optimum dressing to treat diabetic foot ulcers Further research should be undertaken to determine whether total contact foot casting is clinically effective and cost effective compared with other forms of off-loading in patients with neuropathic ulcers

3.3 Antibiotics for diabetic foot infections

3.3.1 Review question

What is the clinical effectiveness of different antibiotic regimens and antimicrobial therapies for diabetic foot infections (with or without osteomyelitis)?

3.3.2 Evidence review

The systematic search retrieved 9817 studies. Of these, 13 studies were included for this review question (for the review protocol and inclusion/exclusion criteria, please see appendix B). All 13 studies were head-to-head trials of different antibiotics, and there were no 2 studies with the same pair-wise comparisons. Where possible, if information was available in the studies, evidence was presented in:

- Characteristics of included studies.
- Summary of GRADE profiles.
- Full GRADE evidence profiles (see appendix D).
- Evidence statements.

Table 4: Characteristics of included studies

ANTIBIOTICS		
Study	Clinical variables	Outcome of interest
Lipsky et al. (1997)	IV ofloxacin changed when appropriate to 400 mg orally every 12 h. IV ampicillin/sulbactam every 6 h changed when appropriate to 500 mg of amoxicillin/125 mg of clavulanic acid orally every 8 h.	Cured or improved condition of ulcers Eradication of original pathogens or not Adverse events
Grayson et al. (1994)	Imipenem/cilastatin (I/C; 500 mg IV every 6 h). Ampicillin/sulbactam (A/S; 3 g IV every 6 h).	Cured or improved condition of ulcers Eradication of original pathogens or not Recurrence of infection after average 1-year follow-up Adverse events
Erstad et al. (1997)	Cefoxitin 2 g every 6 h. Ampicillin/sulbactam 3 g every 6 h.	Cured or improved condition of ulcers Eradication of original pathogens or not Duration of hospitalisation Adverse events
Harkless et al. (2005)	IV piperacillin/tazobactam (P/T) (4 g/0.5 g every 8 h). IV ampicillin/sulbactam (A/S 2 g/1 g every 6 h).	Cured or improved condition of ulcers Adverse events
Tan et al. (1993)	Piperacillin-tazobactam (P/T), 3 g and 375 mg respectively for 5 days and at least 48 h after resolution of signs and symptoms. Ticarcillin-clavulanate (T/C), 3 g and 100 mg respectively for 5 days and at least 48 h after resolution of signs and symptoms.	Cured or improved condition of ulcers Adverse events
Bouter et al. (1996)	Piperacillin 3000 mg QID in combination with clindamycin 600 mg (P/CL) 2 times daily Imipenem/cilastatin (I/C) 500 mg 4 times daily	Cured or improved condition of ulcers Eradication of original pathogens or not Adverse events
Lipsky et al. (2007)	IV therapy for at least 3 days with moxifloxacin (400 mg/day). Then switched to oral therapy with moxifloxacin 400 mg/day Piperacillin-tazobactam (P/T) (3.0 g/0.375 g every 6 h) for at least 3 days then switched to amoxicillin-clavulanate (A/C) suspension 800 mg every 12 h	Clinical cure rates at the TOC (test-of cure) visit (10–42 days post-therapy) Eradication of original pathogens or not Adverse events
Lipsky et al. (2008)	Pexiganan cream twice daily Or placebo cream twice daily Ofloxacin tablets 200 mg orally twice daily or placebo tablets orally twice daily	Cured or improved condition of ulcers Eradication of original pathogens or not Wound assessments

		Adverse events
Lipsky et al. (2004)	Linezolid (600 mg every l2 h either IV or orally) Ampicillin-sulbaclam (A/S, 1.5-3 g every 6 h IV), or amoxicillin-clavulanate (A/C, 500-875 mg every 8–12 h orally).	Cured or improved condition of ulcers Adverse events
Lipsky et al. (2005)	Daptomycin (4 mg/kg every 24 h IV over 30 min) Vancomycin 1 g every 12 h IV over 60 min or a semi-synthetic penicillin (nafcillin, oxacillin, cloxacillin or flucloxacillin, per the investigator's choice) given in equally divided doses totalling 4–12 g/day IV].	Clinical success rates Adverse events
Lipsky et al. (2005)	IV ertapenem (1 g bolus, followed by a saline placebo every 6 h for 3 additional doses). IV piperacillin/tazobactam (P/T 3-375 g every 6 h).	Favourable clinical response Eradication of original pathogens or not Adverse events
Hughes et al. (1987)	Ceftizoxime, up to 4 g IV every 8 h. Cefoxitin, up to 2 g IV every 4 h.	Clinical responses at 3, 6, 9, and 12 months Adverse events
HTA report Lipsky et al. (1990)	Clindamycin 300 mg orally, 4 times daily for 2 weeks. Cephalexin 500 mg orally, 4 times daily for 2 weeks	Complete healing at 2 weeks Improved lesions Adverse effects

IV = intravenously.

Summary of GRADE profile 31: Quinolones vs. broad-spectrum penicillins

Ofloxacin (IV to oral) vs. ampicillin/sulbactam (IV) amoxicillin/clavulanic acid (oral) (Lipsky et al. 1997)

No of studies	Design	Ofloxacin (IV to oral)	Ampicillin/ sulbactam (IV) to amoxicillin/ clavulanic acid (oral)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured[a] (follow-up 7 days)						
1	RCT	40/47 (85.1%)	34/41 (82.9%)	RR 1.03 (0.85 to 1.23) NNTB = N/A	2 more per 100 (from 12 fewer to 19 more)	Low
Microbiological outcome: patients achieved eradication of pathogen(s) (follow-up 7 days)						
1	RCT	39/47 (83%)	36/41 (87.8%)	RR 0.95 (0.79 to 1.12) NNTB = N/A	4 fewer per 100 (from 18 fewer to 11 more)	Low
Pathogen outcome: eradication of Gram+ aerobes (unit: pathogen) (follow-up 7 days)						
1	RCT	33/47 (70.2%)	38/43 (88.4%)	RR 0.79 (0.64 to 0.99) NNTB = 6 (3 to 79)	19 fewer per 100 (from 1 fewer to 32 fewer)	Low
Pathogen outcome: eradication of Gram- aerobes (unit: pathogen) (follow-up 7 days)						
1	RCT	18/19 (94.7%)	15/18 (83.3%)	RR 1.14 (0.90 to 1.43) NNTB = N/A	12 more per 100 (from 8 fewer to 36 more)	Low
No. of patients experienced treatment-related AEs (follow-up 7 days)						
1	RCT	17/47 (36.2%)	9/41 (22%)	RR 1.65 (0.83 to 3.29) NNTH = N/A	14 more per 100 (from 4 fewer to 50 more)	Low

Dosage: Ofloxacin 400 mg (IV and oral) every 12 hours. AmpiciIlin (1 to 2 g)/sulbactam (0.5 to 1 g) (IV) every 6 hours; then 500 mg of amoxicillin/125 mg of clavulanic acid orally every 8 hours.

[a] Cured = disappearance of all signs and symptoms associated with active infection.

AE = adverse event; CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 32: Broad-spectrum beta-lactam carbapenems vs. broad-spectrum penicillins

Imipenem/cilastatin (IV) vs. ampicillin/sulbactam (IV) (Grayson et al. 1994)

No of studies	Design	Imipenem /cilastatin (IV)	Ampicillin /sulbactam (IV)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured[a] (unit: no. of infections) (follow-up 6 days[1])						
1	RCT	39/48 (81.3%)	41/48 (85.4%)	RR 0.95 (0.80 to 1.14) NNTB = N/A	4 fewer per 100 (from 17 fewer to 12 more)	Low
Microbiological outcome: infections achieved eradiction of pathogen(s) (follow-up 6 days[1])						
1	RCT	32/48 (66.7%)	36/48 (75%)	RR 0.89 (0.69 to 1.15) NNTB = N/A	8 fewer per 100 (from 23 fewer to 11 more)	Low
No. of patients experienced significant[b] AEs (follow-up 6 days[1])						
1	RCT	7/46 (15.2%)	9/47 (19.1%)	RR 0.79 (0.32 to 1.96) NNTH = N/A	4 fewer per 100 (from 13 fewer to 18 more)	Low

Dosage: Imipenem/cilastatin (500 mg) every 6 hours. Ampicillin/sulbactam (3 g) every 6 hours.

[a] Cured = resolution of soft tissue infection.

[b] Significant = a severe reaction necessitating withdrawal of the study treatment.

[1] 6 days or until therapy was completed.

AE = adverse event; CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 33: Cephalosporins vs broad-spectrum penicillins

Cefoxitin (IV) vs ampicillin/sulbactam (IV) (Erstad et al. 1997)

No of studies	Design	Cefoxitin (IV)	Ampicillin/ sulbactam (IV)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured[a] (follow-up 5 days[1])						
1	RCT	7/18 (38.9%)	1/18 (5.6%)	RR 7.00 (0.95 to 51.25) NNTB = N/A	33 more per 100 (from 0 fewer to 279 more)	Low
Clinical outcome: length of hospital stay (days)						
1	RCT	18	18	Mean length of hospital stay (days) (range): Cefoxitin = 12.1 (4 to 39) Ampicillin/sulbactam = 21.1 (6 to 58), p = 0.06		Low
No. of patients experienced treatment- related AEs (follow-up 5 days[1])						
1	RCT	6/18 (33.3%)	7/18 (38.9%)	RR 0.86 (0.36 to 2.05) NNTH = N/A	5 fewer per 100 (from 25 fewer to 41 more)	Low

Dosage: Cefoxitin 2 g every 6 hours; Ampicillin/sulbactam 3 g every 6 hours, for at least 5 days.

[a] Cured = disappearance of all signs and symptoms associated with active infection.

[1] 5 days but could be more to the discretion of the attending surgeon.

AE = adverse event; CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 34: Antipseudomonal penicillins vs. broad-spectrum penicillins

Piperacillin/tazobactam (IV) vs. ampicillin/sulbactam (IV) (Harkless et al. 2005)

No of studies	Design	Piperacillin/ tazobactam (IV)	Ampicillin/ sulbactam (IV)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured or improvement[a] (follow-up 14–21 days)						
1	RCT	99/139 (71.2%)	100/150 (66.7%)	RR 1.07 (0.92 to 1.25) NNTB = N/A	5 more per 100 (from 5 fewer to 17 more)	Low
Pathogen outcome: eradication of Gram+ aerobes (unit: patient) (follow-up 14–21 days)						
1	RCT	51/65 (78.5%)	46/64 (71.9%)	RR 1.09 (0.89 to 1.33) NNTB = N/A	6 more per 100 (from 8 fewer to 24 more)	Low
No. of patients experienced at least 1 treatment-related AE (follow-up 14–21 days)						
1	RCT	29/155 (18.7%)	21/159 (13.2%)	RR 1.42 (0.85 to 2.37) NNTH = N/A	6 more per 100 (from 2 fewer to 18 more)	Low
Withdrawals due to treatment-related AEs (follow-up 14–21 days)						
1	RCT	18/155 (11.6%)	13/159 (8.2%)	RR 1.42 (0.72 to 2.80) NNTH = N/A	3 more per 100 (from 2 fewer to 15 more)	Low

Dosage: Piperacillin/tazobactam (4 g/0.5 g every 8 h); Ampicillin/sulbactam (2 g/1 g every 6 h), for 4 to 14 days.

[a] Cured or improvement = resolution of signs and symptoms or sufficient clinical improvement that the majority of symptoms of infection had abated.

AE = adverse event; CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 35: Antipseudomonal penicillins vs. Antipseudomonal penicillins

Piperacillin/tazobactam (IV) vs. ticarcillin/clavulanate (IV) (Tan et al. 1993)

No of studies	Design	Piperacillin/ tazobactam (IV)	Ticarcillin/ calvulanate (IV)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured[a] (follow-up 10–14 days)						
1	RCT	7/18 (38.9%)	6/17 (35.3%)	RR 1.10 (0.46 to 2.62) NNTB = N/A	4 more per 100 (from 19 fewer to 57 more)	Low

Dosage: Piperacillin/tazobactam (3 g/375 mg) every 6 hours; Ticarcillin/clavulanate (3 g/100 mg) every 6 hours, for at least 5 days.

[a] Cured = resolution of signs and symptoms.

CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 36: Beta-lactam carbapenems vs. antipseudomonal penicillins + clindamycin

Imipenem/cilastatin (IV) vs. piperacillin/clindamycin (IV) (Bouter et al. 1996)

No of studies	Design	Imipenem/ cilastatin (IV)	Piperacillin/ clindamycin (IV)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured[a] (follow-up 10 days)						
1	RCT	4/21 (19%)	6/24 (25%)	RR 0.76 (0.25 to 2.34) NNTB = N/A	6 fewer per 100 (from 19 fewer to 33 more)	Low
Microbiological outcome: patients achieved eradication of pathogen(s) (follow-up 10 days)						
1	RCT	9/20 (45%)	16/23 (69.6%)	RR 0.65 (0.37 to 1.13) NNTB = N/A	24 fewer per 100 (from 44 fewer to 9 more)	Low
No. of patients experienced treatment-related AEs (follow-up 10 days)						
1	RCT	18/21 (85.7%)	12/24 (50%)	RR 1.71 (1.11 to 2.65) NNTH = 3 (2 to 12)	36 more per 100 (from 6 more to 83 more)	Low

Dosage: Piperacillin (3000 mg QID) + clindamycin (600 mg TID); Imipenem/cilastatin (500 mg QID), for at least 10 days.

[a] Cured = resolution of signs and symptoms.

AE = adverse event; CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 37: Quinolones vs. antipseudomonal penicillins + broad-spectrum penicillins

Moxifloxacin (IV to oral) vs. piperacillin/tazobactam (IV) to amoxillin/clavulanate (oral) (Lipsky et al. 2007)

No of studies	Design	Moxifloxacin (IV to oral)	Piperacillin/ tazobactam (IV) to moxifloxin vs amoxillin/ clavulanate (oral)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured[a] (follow-up 10–42 days)						
1	RCT	28/63 (44.4%)	25/64 (39.1%)	RR 1.14 (0.75 to 1.72) NNTB = N/A	5 more per 100 (from 10 fewer to 28 more)	Low
Pathogen outcome: eradication of Gram+ aerobes (unit: pathogen) (follow-up 10–42 days)						
1	RCT	24/37 (64.9%)	27/42 (64.3%)	RR 1.01 (0.73 to 1.40) NNTB = N/A	1 more per 100 (from 17 fewer to 26 more)	Low
Pathogen outcome: eradication of Gram- aerobes (unit: pathogen) (follow-up 10–42 days)						
1	RCT	2/6 (33.3%)	7/12 (58.3%)	RR 0.57 (0.17 to 1.95) NNTB = N/A	25 fewer per 100 (from 48 fewer to 55 more)	Low
No. of patients experienced treatment-related AEs (follow-up 10–42 days)						
1	RCT	20/63 (31.7%)	8/64 (12.5%)	RR 2.54 (1.21 to 5.34) NNTH = 5 (3 to 20)	19 more per 100 (from 3 more to 54 more)	Low
Withdrawals due to treatment-related AEs (follow-up 10–42 days)						
1	RCT	15/63 (23.8%)	15/64 (23.4%)	RR 1.02 (0.54 to 1.90) NNTH = N/A	0 more per 100 (from 11 fewer to 21 more)	Low

Dosage: Moxifloxacin (400 mg/day) (IV for at least 3 days), then 400 mg orally; Piperacillin/tazobactam (3.0 g/0.375 g every 6 hours) for at least 3 days, then amoxicillin/clavulanate (800 mg every 12 hours orally), for total duration of 7 to 14 days.

[a] Cured = resolution of all signs and symptoms or sufficient improvement such that additional antimicrobial therapy was not required.

AE = adverse event; CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 38: Pexiganan cream (topical) vs. ofloxacin (oral) (quinolones) (Lipsky et al. 2008)

No of studies	Design	Pexiganan cream	Ofloxacin (oral)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured or improvement[a] (follow-up 21 days)						
1	RCT	363/418 (86.8%)	377/417 (90.4%)	RR 0.96 (0.91 to 1.01) NNTB = N/A	4 fewer per 100 (from 8 fewer to 1 more)	High
Microbiological outcome: patients achieved eradication of pathogen(s) (follow-up 21 days)						
1	RCT	154/327 (47.1%)	160/338 (47.3%)	RR 0.99 (0.85 to 1.17) NNTB = N/A	0 fewer per 100 (from 7 fewer to 8 more)	High
Pathogen outcome: eradication of Gram+ aerobes (unit: patient) (follow-up 21 days)						
1	RCT	203/370 (54.9%)	233/379 (61.5%)	RR 0.89 (0.79 to 1.01) NNTB = N/A	7 fewer per 100 (from 13 fewer to 1 more)	High
Pathogen outcome: eradication of Gram- aerobes (unit: patient) (follow-up 21 days)						
1	RCT	75/111 (67.6%)	72/103 (69.9%)	RR 0.97 (0.81 to 1.16) NNTB = N/A	2 fewer per 100 (from 13 fewer to 11 more)	High

Dosage: Pexiganan cream (twice daily); ofloxacin tablets (200 mg orally twice daily), for at least 14 days.

[a] Cured or improvement = resolution of all signs and symptoms or sufficient improvement such that additional antimicrobial therapy was not required.

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 39: Oxazolidinone vs. broad-spectrum penicillins

Linezolid (IV or oral) vs. ampicillin/sulbactam (IV) or amoxicillin/clavulanate (oral) (Lipsky et al. 2004)

No of studies	Design	Linezolid (IV)	Ampicillin/ sulbactam (IV) or amoxicillin /clavulanate (oral)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured[a] (follow-up 15–21 days)						
1	RCT	165/203 (81.3%)	77/108 (71.3%)	RR 1.14 (0.99 to 1.31) NNTB = N/A	10 more per 100 (from 1 fewer to 22 more)	Low
Pathogen outcome: eradication of Gram+ aerobes (unit: patient) (follow-up 15–21 days)						
1	RCT	143/185 (77.3%)	71/100 (71%)	RR 1.09 (0.94 to 1.26) NNTB = N/A	6 more per 100 (from 4 fewer to 18 more)	Low
Pathogen outcome: eradication of Gram- aerobes (unit: patient) (follow-up 15–21 days)						
1	RCT	65/81 (80.2%)	23/34 (67.6%)	RR 1.19 (0.92 to 1.53) NNTB = N/A	13 more per 100 (from 5 fewer to 36 more)	Low
No. of patients experienced treat-related AEs (follow-up 15–21 days)						
1	RCT	64/241 (26.6%)	12/120 (10%)	RR 2.66 (1.49 to 4.73) NNTH = 6 (4 to 12)	17 more per 100 (from 5 more to 37 more)	Low
Withdrawals due to treatment-related AEs (follow-up 15–21 days)						
1	RCT	18/241 (7.5%)	4/120 (3.3%)	RR 2.24 (0.78 to 6.47) NNTH = N/A	4 more per 100 (from 1 fewer to 18 more)	Low

Dosage: Linezolid (600 mg every 12 h either IV or per oral); ampicillin/sulbaclam (1.5 to 3 g every 6 h IV), or amoxicillin/clavulanate (500-875 mg every 8–12 hours orally), for 7 to 28 days.

[a] Cured = resolution of all signs and symptoms.

AE = adverse event; CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 40: Lipopeptide antibiotics vs. glycopeptide antibiotics

Daptomycin (IV) vs. vancomycin (IV) (Lipsky et al. 2005)

No of studies	Design	Daptomycin (IV)	Vancomycin (IV)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured[a] (follow-up 6–-20 days)						
1	RCT	10/14 (71.4%)	20/29 (69%)	RR 1.04 (0.69 to 1.56) NNTB = N/A	3 more per 100 (from 21 fewer to 39 more)	Low

Dosage: Daptomycin (4 mg/kg every 24 hours IV over 30 mins); vancomycin (1 g every 12 hours IV over 60 mins), for 7 to 14 days.

[a] Cured = resolution of all signs and symptoms.

CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 41: Lipopeptide antibiotics vs. narrow-spectrum penicillins

Daptomycin (IV) vs. nafcillin or oxacillin or cloxacillin or flucloxacillin (IV) (Lipsky et al. 2005)

No of studies	Design	Daptomycin (IV)	Nafcillin or cloxacillin or flucloxacillin (IV)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured[a] (follow-up 6–20 days)						
1	RCT	16/25 (64%)	19/27 (70.4%)	RR 0.91 (0.62 to 1.33) NNTB = N/A	6 fewer per 100 (from 27 fewer to 23 more)	Low

Dosage: Daptomycin (4 mg/kg every 24 hours IV over 30 mins) for 7 to 14 days; or a narrow-spectrum penicillin (nafcillin, oxacillin, cloxacillin or flucloxacillin, depending on the investigator's choice, given in equally divided doses totalling 4 to 12 g/day IV).

[a] Cured = resolution of all signs and symptoms.

CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 42: Antipseudomonal penicillins vs. broad-spectrum beta-lactam carbapenems

Piperacillin/tazobactam (IV) vs. ertapenem (IV) (Lipsky et al. 2005)

No of studies	Design	Piperacillin/ tazobactam (IV)	Ertapenem (IV)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured[a] (follow-up 5 days)						
1	RCT	202/219 (92.2%)	213/226 (94.2%)	RR 0.98 (0.93 to 1.03) NNTB = N/A	2 fewer per 100 (from 7 fewer to 3 more)	Low
Pathogen outcome: eradication of Gram+ aerobes (unit: pathogen) (follow-up 5 days)						
1	RCT	122/146 (83.6%)	135/151 (89.4%)	RR 0.93 (0.85 to 1.02) NNTB = N/A	6 fewer per 100 (from 13 fewer to 2 more)	Low
Pathogen outcome: eradication of Gram- aerobes (unit: pathogen) (follow-up 5 days)						
1	RCT	40/51 (78.4%)	62/67 (92.5%)	RR 0.85 (0.72 to 0.99) NNTB = 7 (4 to 62)	14 fewer per 100 (from 1 fewer to 26 fewer)	Low
No. of patients experienced treatment-related AEs (follow-up 5 days)						
1	RCT	57/291 (19.6%)	44/295 (14.9%)	RR 1.31 (0.92 to 1.88) NNTH = N/A	5 more per 100 (from 1 fewer to 13 more)	Low
Withdrawals due to treatment-related AEs (follow-up 5 days)						
1	RCT	6/291 (2.1%)	3/295 (1%)	RR 2.03 (0.51 to 8.03) NNTH = N/A	1 more per 100 (from 0 fewer to 7 more)	Low

Dosage: Ertapenem (1 g bolus, followed by a saline placebo every 6 hours for 3 additional doses, IV); piperacillin/tazobactam (3 to 375 g every 6 hours, IV), for 5 days.

[a] Cured = resolution of all signs and symptoms.

AE = adverse event; CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 43: Cephalosporins vs. cephalosporins

Ceftizoxime (IV) vs. cefoxitin (IV) (Hughes et al. 1987)

No of studies	Design	Ceftizoxime (IV)	Cefoxitin (IV)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured or improvement[a] (follow-up varied)						
1	RCT	23/28 (82.1%)	17/26 (65.4%)	RR 1.21 (0.88 to 1.66) NNTB = N/A	14 more per 100 (from 8 fewer to 43 more)	Low
No. of patients experienced treatment-related AEs (follow-up varied)						
1	RCT	16/33 (48.5%)	19/30 (63.3%)	RR 0.77 (0.49 to 1.19) NNTH = N/A	15 fewer per 100 (from 32 fewer to 12 more)	Low

Dosage: Ceftizoxime, up to 4 g IV every 8 hours. Cefoxitin, up to 2 g IV every 4 hours.

[a] Cured or improvement = resolution of all signs and symptoms or sufficient improvement such that additional antimicrobial therapy was not required.

AE = adverse event; CI = confidence interval; IV = intravenously; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 44: Lincosamide antibiotics vs. cephalosporins

Clindamycin (oral) vs. cephalexin (oral) (Lipsky et al. 1990)

No of studies	Design	Clindamycin (oral)	Cephalexin (oral)	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Clinical outcome: cured or improvement[a] (follow-up varied)						
1	RCT	10/25 (40%)	9/27 (33.3%)	RR 1.20 (0.59 to 2.46) NNTB = N/A	7 more per 100 (from 14 fewer to 49 more)	Low

Dosage: Clindamycin (300 mg orally), 4 times daily for 2 weeks. Cephalexin (500 mg orally), 4 times daily for 2 weeks.

[a] Cured or improvement = resolution of all signs and symptoms or sufficient improvement such that additional antimicrobial therapy was not required.

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

3.3.3 Evidence statements

Ofloxacin (IV to oral) vs. ampicillin/sulbactam (IV) to amoxicillin/clavulanic acid (oral) (see Summary of GRADE profile 31)

3.3.3.1 One RCT with 88 participants showed no significant difference in the number of clinical cures, eradication of pathogen(s) overall, eradication of Gram-negative aerobes and the number of treatment-related adverse events between participants who received ofloxacin (IV to oral) and participants who received ampicillin/sulbactam (IV) to amoxicillin/clavulanic acid (oral). (Low quality)

However,

3.3.3.2 The same RCT with 88 participants showed that the eradication of Gram-positive aerobes in patients who received ampicillin/sulbactam (IV) to amoxicillin/clavulanic acid (oral) was significantly higher compared with patients who received ofloxacin (IV to oral). (Low quality)

Imipenem/cilastatin (IV) vs. ampicillin/sulbactam (IV) (see Summary of GRADE profile 32)

3.3.3.3 One RCT with 96 participants showed no significant differences in the number of clinical cures, eradication of pathogen(s) overall and the number of treatment-related adverse events between participants who received imipenem/cilastatin (IV) and participants who received ampicillin/sulbactam (IV). (Low quality)

Cefoxitin (IV) vs. ampicillin/sulbactam (IV) (see Summary of GRADE profile 33)

3.3.3.4 One RCT with 36 participants showed no significant differences in the number of clinical cures, length of hospital stay and treatment-related adverse events between participants who received cefoxitin (IV) and participants who received ampicillin/sulbactam (IV). (Low quality)

Piperacillin/tazobactam (IV) vs. ampicillin/sulbactam (IV) (see Summary of GRADE profile 34)

3.3.3.5 One RCT with 314 participants showed no significant differences in the number of clinical cures or improvements, eradication of Gram-positive aerobes, treatment-related adverse events, and withdrawals due to treatment-related adverse events between participants who received piperacillin/tazobactam (IV) and participants who received ampicillin/sulbactam (IV). (Low quality)

Piperacillin/tazobactam (IV) vs. ticarcillin/clavulanate (IV) (see Summary of GRADE profile 35)

3.3.3.6 One RCT with 35 participants showed no significant differences in the number of clinical cures between participants who received piperacillin/tazobactam (IV) and participants who received ticarcillin/clavulanate (IV). (Low quality)

Imipenem/cilastatin (IV) vs. piperacillin/clindamycin (IV) (see Summary of GRADE profile 36)

3.3.3.7 One RCT with 45 participants showed no significant differences in the number of clinical cures and eradication of pathogen(s) overall between participants who received imipenem/cilastatin (IV) and participants who received piperacillin/clindamycin (IV). (Low quality)

However,

3.3.3.8 The same RCT with 45 participants showed that the number of treatment-related adverse events in patients who received imipenem/cilastatin (IV) was significantly higher compared with participants who received piperacillin/clindamycin (IV). (Low quality)

Moxifloxacin (IV to oral) vs. piperacillin/tazobactam (IV) to amoxillin/clavulanate (oral) (see Summary of GRADE profile 37)

3.3.3.9 One RCT with 127 participants showed no significant differences in the number of clinical cures, eradication of pathogens (both Gram-positive and Gram-negative aerobes), and withdrawals due to treatment-related adverse events between participants who received moxifloxacin (IV to oral) and participants who received piperacillin/tazobactam (IV) to amoxillin/clavulanate (oral). (Moderate quality)

However,

3.3.3.10 The same RCT with 127 participants showed that the number of participants who experienced treatment-related adverse events was significantly higher in those receiving moxifloxacin (IV to oral) compared with those receiving piperacillin/tazobactam (IV) to amoxillin/clavulanate (oral). (Moderate quality)

Pexiganan cream (topical) vs. ofloxacin (oral) (see Summary of GRADE profile 38)

3.3.3.11 One RCT with 835 participants showed no significant differences in the number of clinical cures and eradication of pathogen(s) (including both Gram-positive and Gram-negative aerobes) between participants who received Pexiganan cream (topical) and participants who received ofloxacin (oral). (High quality)

Linezolid (IV or oral) vs. ampicillin/sulbactam (IV) or amoxicillin/clavulanate (oral) (see Summary of GRADE profile 39)

3.3.3.12 One RCT with 361 participants showed no significant differences in the number of clinical cures, eradication of both Gram-positive and Gram-negative aerobes, and withdrawals due to treatment-related adverse events between participants who received linezolid (IV or oral) and participants who received ampicillin/sulbactam (IV) or amoxicillin/clavulanate (oral). (Low quality)

However,

3.3.3.13 The same RCT with 361 participants showed that the number of participants who experienced treatment-related adverse events was significantly higher in those who received linezolid (IV or oral) compared with those who received ampicillin/sulbactam (IV) or amoxicillin/clavulanate (oral). (Low quality)

Daptomycin (IV) vs. vancomycin (IV) (see Summary of GRADE profile 40)

3.3.3.14 One RCT with 43 participants showed no significant difference in the number of clinical cures between participants who received Daptomycin (IV) and participants who received vancomycin (IV). (Low quality)

Daptomycin vs. nafcillin or cloxacillin or flucloxacillin (IV) (see Summary of GRADE profile 41)

3.3.3.15 One RCT with 52 participants showed no significant difference in the number of clinical cures between participants who received Daptomycin (IV) and participants who received nafcillin or cloxacillin or flucloxacillin (IV). (Low quality)

Piperacillin/tazobactam (IV) vs. ertapenem (IV) (see Summary of GRADE profile 42)

3.3.3.16 One RCT with 586 participants showed no significant difference in the number of clinical cures between participants who received piperacillin/tazobactam (IV) and participants who received ertapenem (IV). (Moderate quality)

3.3.3.17 The same RCT with 586 participants showed no significant differences in the eradication of Gram-positive aerobes, the number of participants experiencing adverse events, and withdrawals due to treatment-related adverse events between participants who received piperacillin/tazobactam (IV) and participants who received ertapenem (IV). (Low quality)

However,

3.3.3.18 The same RCT with 586 participants showed that the eradication of Gram-negative aerobes was significantly higher in participants receiving ertapenem (IV) compared with those receiving piperacillin/tazobactam (IV). (Low quality)

Ceftizoxime (IV) vs. cefoxitin (IV) (see Summary of GRADE profile 43)

3.3.3.19 One RCT with 63 participants showed no significant differences in the number of clinical cures and treatment-related adverse events between participants who received ceftizoxime (IV) and participants who received cefoxitin (IV). (Low quality)

Clindamycin (oral) vs. cephalexin (oral) (see Summary of GRADE profile 44)

3.3.3.20 One RCT with 52 participants showed no significant difference in complete healing between participants who received clindamycin (oral) and participants who received cephalexin (oral). (Low quality)

3.3.4 Health economic modelling

No health economic modelling was conducted for this question.

3.3.5 Evidence to recommendations

The clinical effectiveness of different antibiotic regimens and antimicrobial therapies for diabetic foot infections (with or without osteomyelitis)

Quality of the evidence

The GDG agreed that the evidence was inconclusive (almost all head-to-head comparisons of different antibiotics showed no significant differences and there were no two studies with the same pair-wise comparisons) and was of low quality. Due to insufficient evidence, the GDG felt that it was not possible to make recommendations on individual antibiotics.

Other considerations

Although there was insufficient evidence to recommend individual antibiotics, the GDG agreed that antibiotic treatment is crucial to treat diabetic foot infections. With reference to the GDG's experience, knowledge and skills, the GDG reached consensus on the following:

- Each hospital should have antibiotic guidelines for treating diabetic foot infections; and MRSA should be treated based on local and national guidance.
- Antibiotic therapy for suspected osteomyelitis should not be delayed pending MRI results.
- Empirical antibiotic therapy should be started based on severity, followed by a definitive antibiotic regimen that is informed by microbiology results.
- Antibiotics with the lowest acquisition cost appropriate for the clinical situation and severity should be used. Antibiotics with activity against Gram-positive organisms should be used for mild infections and antibiotics

with activity against both Gram-positive and Gram-negative organisms (including anaerobic bacteria) should be used for moderate and severe infections.

- The route of administration should be:
  - mild infections: oral
  - moderate infections: oral or intravenous (based on the clinical situation and choice of antibiotics)
  - severe infections: intravenous initially then reassessed, based on the clinical situation.
- Prolonged antibiotic therapy for mild soft tissue infections should not be offered.

3.3.6 Recommendations and research recommendations for antibiotics for diabetic foot infections

Recommendations for antibiotics for diabetic foot infections

Management of diabetic foot infection

Recommendation 1.2.23

Each hospital should have antibiotic guidelines for the management of diabetic foot infections.

Recommendation 1.2.24

Do not delay starting antibiotic therapy for suspected osteomyelitis pending the results of the MRI scan

Recommendation 1.2.25

Start empirical antibiotic therapy based on the severity of the infection, using the antibiotic appropriate for the clinical situation and the severity of the infection, and with the lowest acquisition cost.

Recommendation 1.2.26

For mild infections, offer oral antibiotics with activity against Gram-positive organisms.

Recommendation 1.2.27

For moderate and severe infections, offer antibiotics with activity against Gram-positive and Gram-negative organisms, including anaerobic bacteria. The route of administration is as follows:

- Moderate infection: oral or intravenous antibiotics, based on the clinical situation and the choice of antibiotic (see recommendation 1.2.23).
- Severe infection: start with intravenous antibiotics then reassess, based on the clinical situation (see recommendation 1.2.23)

Recommendation 1.2.28

The definitive antibiotic regimen and the duration of treatment should be informed by both the results of the microbiological examination and the clinical response to empiric antibiotic therapy.

Recommendation 1.2.29

Do not use prolonged antibiotic therapy for mild soft tissue infections.

Recommendation 1.2.30

Treat infections with MRSA in line with local and national guidance.

Research recommendations for antibiotics for diabetic foot infections

See appendix A for a list of all research recommendations.

No research recommendations have been made for this topic

3.4 Adjunctive treatments for diabetic foot problems

3.4.1 Review question

What is the clinical and cost effectiveness of adjunctive treatments in treating diabetic foot problems, for example, dermal or skin substitutes, growth factors, hyperbaric oxygen therapy, bio-debridement, topical negative pressure therapy and electrical stimulation?

3.4.2 Evidence review

The systematic search retrieved 9817 studies. Of these, 37 studies were included for this review question (for the review protocol and inclusion/exclusion criteria, please see appendix B). From these 37 studies, 14 studies were on growth factors (G-CSF = 5; PDGF = 4; EGF = 4; TGF-β = 1); six studies were on hyperbaric oxygen therapy; seven studies were on dermal or skin substitutes; three studies were on negative pressure wound therapy; and seven studies were on other adjunctive treatments (electrical stimulation therapy, plasma gel, regenerative tissue matrix, dalteparin). Where possible, if information was available in the studies, evidence was presented in:

- Characteristics of included studies.
- Summary of GRADE profiles.
- Full GRADE evidence profiles (see appendix D).
- Forest plots from meta-analysis (see appendix H).
- Evidence statements.

Table 5: Characteristics of included studies

Author	Total no. of patients	Interventions	Dosage	Follow-up period	Primary outcomes
Growth factors					
Granulocyte colony-stimulating factor (G-CSF)					
de Lalla et al. (2001)	40	G-CSF + standard care vs. standard care only (control). Standard care = standard wound care + antibiotics.	263 micrograms subcutaneously daily for 21 days.	9 weeks, then 6 months	Amputation; overall need for surgical interventions; improvement on infection status; treatment-related AEs
Gough et al. (1997)	40	G-CSF + standard care vs. placebo + standard care only (control). Standard care = standard wound care + antibiotics.	5 micrograms/kg daily for 7 days.	7 days treatment, follow-up unclear.	Amputation; complete wound healing; overall need for surgical interventions; resolution of infection; improvement on infection status; treatment-related AEs
Kastenbauer et al. (2003)	40	G-CSF + standard care vs. placebo + standard care only (control). Standard care = standard wound care + antibiotics.	5 micrograms/kg daily for 10 days.	10 days treatment, follow-up unclear.	Amputation; complete wound healing; overall need for surgical interventions; improvement on infection status; treatment-related AEs
Viswanathan et al. (2003)	20	G-CSF + standard care vs. placebo + standard care only (control). Standard care = standard wound care + antibiotics.	5 micrograms/kg daily for 7 days.	7 days treatment, follow-up unclear.	Amputation; overall need for surgical interventions; length of hospital stay (days); improvement on infection status
Yonem et al. (2001)	30	G-CSF + standard care vs. standard care only (control). Standard care = standard wound care + antibiotics.	5 micrograms/kg daily for 3 or more days.	Unclear.	Amputation; overall need for surgical interventions; length of hospital stay (days)
Platelet-derived growth factor (PDGF)					
D'Hemecourt et al. (2005)	112	PDGF + standard care vs. standard care only (control). Standard care = debridement, dressing, off-loading.	100 micrograms/g becaplermin gel, change daily.	20 weeks	Complete wound healing; withdrawal due to treatment-related AEs; at least 1 treatment-related AEs
Hardikar et al. (2005)	110	PDGF + standard care vs. standard care only (control). Standard care = debridement, dressing, off-loading.	0.01% gel with 100 micrograms of rhPDGF-BB/g.	10 weeks, then 20 weeks follow-up	Complete wound healing; mean healing time
Robson et al. (2005)	146	PDGF + standard care vs. standard care only (control). Standard care = debridement, adaptic dressing, off-	0.01% becaplermin gel, change daily, over 20 weeks.	20 weeks	Complete wound healing

		loading.			
Wieman et al. (1998)	383	PDGF + standard care vs. placebo + standard care (control). Standard care = debridement, dressing, off-loading.	0.01% Becaplermin gel 30 micrograms or 100 micrograms daily, over 20 weeks.	20 weeks than 3 months	Complete wound healing; withdrawal due to treatment-related AEs
Epidermal growth factor (EGF)					
Afshari et al. (2005)	50	EGF + standard care vs. placebo + standard care only (control). Standard care = debridement, dressing.	1 mg of EGF/1000 mg of 1% silver sulfadiazine, once a day for 28 days.	4 weeks	Length of hospital stay (days); complete wound healing
Fernandez-Montequinn et al. (2009)	149	EGF + standard care vs. standard care only (control). Standard care = debridement, dressing, off-loading.	25 or 75 micrograms rhEGF in 5ml water for injection, daily for 2 weeks.	2 weeks	At least 50% wound reduction; treatment-related AEs - burning sensation; treatment-related AEs - shivering
Tsang et al. (2003)	59	EGF + standard care vs. standard care only (control). Standard care = Actovegin cream, debridement, dressing.	0.02% or 0.04% [wt/wt] hEGF cream + 5% Actovegin cream, daily for 12 weeks.	12 weeks then 24 weeks	Amputation; complete wound healing
Viswanathan et al. (2006)	57	EGF vs. placebo (no mention of standard wound care).	150 micrograms rhEGF cream, twice daily, for 15 weeks.	15 weeks	Complete wound healing.
Transforming growth factor beta (TGF-β)					
Robson et al. (2000)	155	TGF-β + standard care vs. standard care only (control). Standard care = debridement, dressing, off-loading.	Topical collagen sponges contained TGF-β 0.05 micrograms/cm^2, 0.5 micrograms/cm^2, or 5.0 micrograms/cm^2, twice weekly, for 21 weeks.	21 weeks	Complete wound closure.
Hyperbaric oxygen therapy (HBOT)					
Abidia et al. (2003)	18	HBOT vs. specialised wound management alone.	At 2.4 ATA for 90 mins on 30 occasions over 6 weeks.	6 weeks	Major amputation; minor amputation; complete wound healing
Doctor et al. (1992)	30	HBOT + standard care vs. standard care only (control). Standard care = dressing and debridement.	At 3.0 ATA on 4 occasions over 6 weeks.	4 weeks	Major amputation; minor amputation
Duzgun et al.	100	HBOT + standard care vs. standard care only	At 2.0 to 3.0 ATA for 90	20 to 30 days	Major amputation; minor amputation;

(2008)		(control). Standard care = dressing and debridement.	mins, twice a day, followed by once a day (alternating) for a period of 20 to 30 days.		complete wound healing; required surgical interventions
Faglia et al. (1996)	70	HBOT vs. specialised wound management alone.	At 2.2 to 2.5 ATA for 90 mins on 39 occasions over 6 weeks.	6 weeks	Major amputation
Kessler et al. (2003)	27	HBOT + standard care vs. standard care only (control). Standard care = off-loading.	At 2.5 ATA for 90 mins, twice a day, 5 days per week for 2 weeks.	2 weeks, than 1 month follow-up	Complete wound healing; mean reduction of ulcer surface area
Londahl et al. (2010)	90	HBOT + standard care vs. sham HBOT + standard care Standard care = antibiotic treatment, revascularisation, debridement, off-loading, and metabolic control.	At 2.5 ATA for 90 mins, 5 days per weeks for 8 to 10 weeks, no more than 40 sessions.	1 year	Major amputation; complete wound healing
Dermal or skin substitutes (DSS)					
Caravaggi et al. (1996)	79	DSS + standard care vs. non-adherent paraffin gauze + standard care. Standard care = debridement and off-loading.	1 or 2 applications for 7 to 10 days.	11 weeks	Complete wound healing; withdrawal due to ulcer-related AEs; overall ulcer-related AEs
Gentzknow et al. (1996)	25	DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.	1 application weekly for a total of 8 applications.	12 weeks	Complete wound healing; at least 50% wound closure; overall ulcer-related AEs
Marston et al. (2003)	245	DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.	Up to 7 applications weekly.	12 weeks	Complete wound healing; required surgical interventions; overall ulcer-related AEs
Naughton et al. (1997)	281	DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.	8 applications weekly.	12 weeks	Complete wound healing
Pham et al. (1999)	33	DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.	Maximum 5 applications from week to week 4.	12 weeks	Complete wound healing
Veves et al. (2001)	208	DSS + standard care vs. moistened gauze + standard care.	Maximum 5 applications from week to week 4.	12 weeks	Complete wound healing; median time to complete closure; withdrawal due to

		Standard care = debridement and off-loading.			ulcer-related AEs; overall ulcer-related AEs
Puttirutvong et al. (2004)	80	Meshed skin graft + standard care vs. split thickness skin graft + standard care Standard care = daily dressing	Unclear	6 months	Mean healing time.
Negative pressure wound therapy (NPWT)					
Blume et al. (2008)	335	NPWT + standard care vs. moist wound therapy + standard care (control). Standard care = off-loading.	Change every 48 to 72 hours.	16 weeks	Amputation; complete wound closure; median time to 75% wound closure; overall ulcer-related AEs.
Etoz et al. (2004)	24	NPWT vs. saline moistened gauze (control)	Change every 48 hours.	12 to 20 days	Mean reduction wound surface area (cm^2).
Armstrong & Lavery (2005)	162	NPWT + standard care vs. moist wound therapy + standard care (control). Standard care = off-loading.	Change every 48 hours.	16 weeks	Amputation; complete wound closure; median time to achieve 75–100% granulation; overall treatment-related AEs.
Other adjunctive treatments					
Electrical stimulation therapy					
Moretti et al. (2009)	30	External shock wave therapy + standard care vs. standard care only (control). Standard care = debridement, off-loading, antibiotics if needed.	3 sessions (1 or 2 mins) per day, with 0.03 mJ/mm^2 using electromagnetic lithotripter.	20 weeks	Complete wound healing, mean healing time (days)
Peters et al. (2001)	40	Electrical stimulation vs. placebo stimulation with no current (control).	50V with 80 twin peaks per second, every night for 8 hours.	12 weeks	Complete wound healing.
Autologous platelet-rich plasma gel					
Driver et al. (2006)	72	Autologous platelet-rich plasma gel + standard care vs. saline gel + standard care only (control). Standard care = dressing, off-loading.	Unclear.	12 weeks	Complete wound healing, median time to complete wound closure.
Acellular dermal regenerative tissue matrix					
Reyzelman et al. (2009)	85	Acellular dermal matrix + standard care vs. standard care only (control). Standard care = debridement, dressing, off-loading.	Single application.	12 weeks	Complete wound healing, healing rate (adjusted hazard ratio).

RGD peptide matrix					
Steed et al. (1995)	65	RGD peptide matrix + standard care vs. saline gauze + standard care only (control). Standard care = debridement, dressing.	Twice per week	10 weeks	Complete wound healing
OASIS wound matrix vs. PDGF					
Niezgoda et al. (2005)	73	OASIS wound matrix + standard care vs. PDGF + standard care. Standard care = debridement, off-loading.	OASIS = clinician to decide on weekly basis to change or not. PDGF = applied weekly for 12 hours.	12 weeks	Complete wound healing, ulcer recurrence.
Dalteparin (injection) (for diabetic patients with peripheral arterial occlusive disease)					
Kalani et al. (2003).	85	Dalteparin (injection) + standard care vs. placebo saline + standard care. Standard care = dressing, debridement, off-loading, antibiotic if required.	0.2 ml (Fragmin, 25000 units/ml) for maximum of 6 months.	6 months	Amputation, complete wound healing, at least 50% wound reduction.

AE = adverse events; ATA = absolute atmospheres; RGD = arginine-glycine-aspartic acid; rhEGF = recombinant human epidermal growth factor.

Growth factors

Summary of GRADE profile 45: Adjunctive treatment: Growth factors: Granulocyte colony-stimulating factor (G-CSF)

No of studies	Design	G-CSF	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Amputation (follow-up 10 days to 6 months)						
5 [de, G, K, V, Y]	RCT	6/85 (7.1%)	15/83 (18.1%)	RR 0.41 (0.18 to 0.95) NNTB = 9 (5 to 96)	11 fewer per 100 (from 1 fewer to 15 fewer)	Low
Complete wound healing (follow-up: unclear)						
2 [G, K]	RCT	4/39 (10.3%)	0/40 (0%)	RR 9.45 (0.54 to 164.49) NNTB = N/A	0 more per 100 (from 0 fewer to 0 more)	Low
Overall need for surgical interventions (follow-up: varied)						
5 [de, G, K, V, Y]	RCT	11/85 (12.9%)	29/79 (36.7%)	RR 0.37 (0.2 to 0.68) NNTB = 4 (3 to 9)	23 fewer per 100 (from 12 fewer to 29 fewer)	Low
Length of hospital stay (days) (follow-up: varied)						
2 [V, Y]	RCT	25	25	Mean (days) (SD): Mean difference = -1.40 (95%CI: -2.27 to -0.53)		Low
Resolution of infection (follow-up: varied)						
1 [G]	RCT	11/20 (55%)	4/20 (20%)	RR 2.75 (1.05 to 7.2) NNTB = 3 (2 to 21)	35 more per 100 (from 1 more to 100 more)	Moderate
Improvement on infection status (follow-up: varied)						
4 [de, G, K, V]	RCT	49/70 (70%)	35/70 (50%)	RR 1.40 (1.06 to 1.85) NNTB = 5 (3 to 27)	20 more per 100 (from 3 more to 42 more)	Low
Treatment-related AEs (follow-up: varied)						
3 [de, G, K]	RCT	5/60 (8.3%)	0/57 (0%)	RR 5.59 (0.71 to 44.05) NNTH = N/A	0 more per 100 (from 0 fewer to 0 more)	Low

[de] = de Lalla et al. (2001). G-CSF + standard care vs. standard care only (control). Standard care = standard wound care + antibiotics.

[G] = Gough et al. (1997). G-CSF + standard care vs. placebo + standard care only (control). Standard care = standard wound care + antibiotics.

[K] = Kastenbauer et al. (2003). G-CSF + standard care vs. placebo + standard care only (control). Standard care = standard wound care + antibiotics.

[V] = Viswanathan et al. (2003). G-CSF + standard care vs. placebo + standard care only (control). Standard care = standard wound care + antibiotics.

[Y] = Yonem et al. (2001). G-CSF + standard care vs. standard care only (control). Standard care = standard wound care + antibiotics.

AE = adverse event; CI = confidence interval; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk; SD = standard deviation.

Summary of GRADE profile 46: Adjunctive treatment: Growth factors: Platelet-derived growth factor (PDGF)

No of studies	Design	PDGF	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (follow-up mean 20 weeks)						
4 [D, H, R, W]	RCT	202/419 (48.2%)	115/325 (35.4%)	RR 1.38 (1.16 to 1.64) NNTB = 8 (5 to 18)	13 more per 100 (from 6 more to 23 more)	Moderate
Withdrawal due to treatment-related adverse events (follow-up 20 weeks)						
2 [D, W]	RCT	29/290 (10%)	26/195 (13.3%)	RR 0.94 (0.54 to 1.63) NNTH = N/A	1 fewer per 100 (from 6 fewer to 8 more)	Low
At least 1 treatment-related adverse event (follow-up 20 weeks)						
1 [D]	RCT	22/34 (64.7%)	48/68 (70.6%)	RR 0.92 (0.68 to 1.23) NNTH = N/A	6 fewer per 100 (from 23 fewer to 16 more)	Low
Mean healing time (days)						
1 [H]	RCT	58	55	Mean (days): PDGF = 46; control = 61, p = < 0.001		Low

[D] = D'Hemecourt et al. (2005). PDGF + standard care vs. standard care only (control). Standard care = debridement, dressing, off-loading.

[H] = Hardikar et al. (2005). PDGF + standard care vs. standard care only (control). Standard care = debridement, dressing, off-loading.

[R] = Robson et al. (2005). PDGF + standard care vs. standard care only (control). Standard care = debridement, adaptic dressing, off-loading.

[W] = Wieman et al. (1998). PDGF + standard care vs. placebo + standard care (control). Standard care = debridement, dressing, off-loading.

NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 47: Adjunctive treatment: Growth factors: Epidermal growth factor (EGF)

No of studies	Design	EGF	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Amputation (follow-up mean 24 weeks)						
1 [T]	RCT	2/40 (5%)	2/19 (10.5%)	RR 0.47 (0.07 to 3.12) NNTB = N/A	6 fewer per 100 (from 10 fewer to 22 more)	Low
Length of hospital stay (days) (follow-up 4 weeks)						
1 [A]	RCT	30	20	Mean (days) (SD): EGF = 29.6 (20.95); control = 28.9 (15.1) Mean difference = 0.70 (95%CI: -9.3 to 10.7)		Low
Complete wound healing (follow-up 4 to 24 weeks)						
3 [A, T, V]	RCT	69/99 (69.7%)	33/67 (49.3%)	RR 1.41 (0.76 to 2.63) NNTB = N/A	20 more per 100 (from -12 fewer to 80 more)	Low
At least 50% wound reduction (follow-up 2 weeks)						
1 [F]	RCT	78/101 (77.2%)	19/48 (39.6%)	RR 1.95 (1.35 to 2.81) NNTB = 3 (2 to 5)	38 more per 100 (from 14 more to 72 more)	Low
Treatment-related AEs - burning sensation (follow-up 2 weeks)						
1 [F]	RCT	22/101 (21.8%)	14/48 (29.2%)	RR 0.75 (0.42 to 1.33) NNTB = N/A	7 fewer per 100 (from 17 fewer to 10 more)	Low
Treatment-related AEs - shivering (follow-up 2 weeks)						
1 [F]	RCT	25/101 (24.8%)	2/48 (4.2%)	RR 5.94 (1.47 to 24.06) NNTH = 5 (3 to 11)	21 more per 100 (from 2 more to 97 more)	Low

[A] = Afshari et al. (2005). EGF + standard care vs placebo + standard care only (control). Standard care = debridement, dressing.

[F] = Fernandez-Montequinn et al. (2009). EGF + standard care vs standard care only (control). Standard care = debridement, dressing, off-loading.

[T] = Tsang et al. (2003). EGF + standard care vs standard care only (control). Standard care = Actovegin cream, debridement, dressing.

[V] = Viswanathan et al. (2006). EGF vs placebo (no mention of standard wound care).

AE = adverse event; CI = confidence interval; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk; SD = standard deviation.

Summary of GRADE profile 48: Adjunctive treatment: Growth factors: Transforming growth factor beta (TGF-β)

No of studies	Design	TGF-β	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (week 21) (follow-up 21 weeks)						
1 [R]	RCT	77/131 (58.8%)	17/24 (70.8%)	RR 0.83 (0.62 to 1.11) NNTB = N/A	12 fewer per 100 (from 27 fewer to 8 more)	Moderate

[R] = Robson et al. (2000). TGF-β + standard care vs standard care only (control). Standard care = debridement, dressing, off-loading.

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

Hyperbaric oxygen therapy

Summary of GRADE profile 49: Adjunctive treatment: Hyperbaric oxygen therapy (HBOT)

No of studies	Design	HBOT	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Major amputation (follow-up varied)						
5 [A, D, Du, F, L]	RCT	11/158 (6.9%)	37/150 (24.7%)	RR 0.30 (0.16 to 0.55) NNTB = 6 (4 to 10)	17 fewer per 100 (from 11 fewer to 21 fewer)	Low
Minor amputation (follow-up varied)						
3 [A, D, Du]	RCT	10/74 (13.5%)	26/74 (35.1%)	RR 0.92 (0.11 to 7.9) NNTB = N/A	3 fewer per 100 (from 31 fewer to 100 more)	Moderate
Complete wound healing (week 4–6) (follow-up 4 to 6 weeks)						
3 [A, Du, K, L]	RCT	67/121 (55.4%)	16/114 (14.0%)	RR 3.46 (0.91 to 13.12) NNTB = N/A	34 more per 100 (from 1 fewer to 100 more)	Moderate
Required surgical interventions (follow-up 1 months)						
1 [Du]	RCT	8/50 (16%)	50/50 (100%)	RR 0.17 (0.09 to 0.31) NNTB = 1 (1 to 2)	83 fewer per 100 (from 69 fewer to -91 fewer)	Moderate
Mean reduction of ulcer surface area (week 4)						
1 [K]	RCT	14	13	Mean (%) (SD): HBOT = 61.9 (23.3); control = 55.1 (21.5), p > 0.05		Low

[A] = Abidia et al. (2003). HBOT vs. specialised wound management alone.

[D] = Doctor et al. (1992). HBOT + standard care vs. standard care only (control). Standard care = dressing and debridement.

[Du] = Duzgun et al. (2008). HBOT + standard care vs. standard care only (control). Standard care = dressing and debridement.

[F] = Faglia et al. (1996). HBOT vs. specialised wound management alone.

[K] = Kessler et al. (2003). HBOT + standard care vs. standard care only (control). Standard care = off-loading.

[L] = Londahl et al. (2010). HBOT + standard care vs. sham HBOT + standard care. Standard care = antibiotics treatment, revascularisation, debridement, off-loading, and metabolic control.

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk; SD = standard deviation.

Dermal or skin substitutes

Summary of GRADE profile 50: Adjunctive treatment: Dermal or skin substitutes (DSS)

No of studies	Design	Dermal or skin grafts	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (week 12) - ALL (follow-up 12 weeks)						
6 [C, G, M, N, P, V]	RCT	202/452 (44.7%)	128/419 (30.5%)	RR 1.46 (1.22 to 1.73) NNTB = 7 (5 to 13)	14 more per 100 (from 7 more to 22 more)	Moderate
SUBGROUP: Complete wound healing (week 12) - Dermagraft (follow-up 12 weeks)						
3 [G, M, N]	RCT	99/281 (35.2%)	67/270 (24.8%)	RR 1.44 (1.11 to 1.87) NNTB = 10 (6 to 36)	11 more per 100 (from 3 more to 22 more)	Low
SUBGROUP: Complete wound healing (week 12) - Graftskin (follow-up 12 weeks)						
1 [V]	RCT	63/112 (56.3%)	36/96 (37.5%)	RR 1.50 (1.11 to 2.04) NNTB = 5 (3 to 20)	19 more per 100 (from 4 more to 39 more)	Low
SUBGROUP: Complete wound healing (week 12) - Hyalograft (follow-up 12 weeks)						
1 [C]	RCT	28/43 (65.1%)	18/36 (50%)	RR 1.30 (0.88 to 1.93) NNTB = N/A	15 more per 100 (from -6 fewer to 46 more)	Low
SUBGROUP: Complete wound healing (week 12) - Human skin equivalent (follow-up 12 weeks)						
1 [P]	RCT	12/16 (75%)	7/17 (41.2%)	RR 1.82 (0.97 to 3.44) NNTB = N/A	34 more per 100 (from -1 fewer to 100 more)	Low
At least 50% wound closure (week 12) - Dermagraft (follow-up 12 weeks)						
1 [G]	RCT	9/12 (75%)	3/13 (23.1%)	RR 3.25 (1.14 to 9.24) NNTB = 2 (1 to 8)	52 more per 100 (from 3 more to 100 more)	Low
Required surgical interventions (unit: ulcers) - Dermagraft						
1 [M]	RCT	13/163 (8%)	22/151 (14.6%)	RR 0.55 (0.29 to 1.05) NNTB = N/A	7 fewer per 100 (from 10 fewer to 1 more)	Low
Median time to complete closure (days) - Graftskin						
1 [V]	RCT	112	96	Median (days) (K-M): Graftskin = 65; control 90, p = 0.0026		Low
Withdrawal due to ulcer-related AEs - Graftskin/Hyalograft						
2 [C, V]	RCT	9/155 (5.8%)	15/132 (11.4%)	RR 0.51 (0.23 to 1.13) NNTH = N/A	6 fewer per 100 (from 9 fewer to 1 more)	Low
Overall ulcer-related AEs – Dermagraft/Graftskin						
4 [C, G, M, V]	RCT	72/297 (24.2%)	108/260 (41.5%)	RR 0.58 (0.46 to 0.74) NNTH = 6 (4 to 11)	17 fewer per 100 (from 11 fewer to -22 fewer)	Low

[C] = Caravaggi et al. (1996). DSS + standard care vs. non-adherent paraffin gauze + standard care. Standard care = debridement and off-loading.
[G] = Gentzknow et al. (1996). DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.
[M] = Marston et al. (2003). DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.
[N] = Naughton et al. (1997). DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.
[P] = Pham et al. (1999). DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.
[V] = Veves et al. (2001). DSS + standard care vs. moistened gauze + standard care. Standard care = debridement and off-loading.

AE = adverse event; CI = confidence interval; K-M = Kaplan-Meier; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk; SD = standard deviation.

Summary of GRADE profile 51: Adjunctive treatment: Dermal or skin substitutes (DSS)

No of studies	Design	Meshed skin graft	Split thickness skin graft	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (week 12) - ALL (follow-up 12 weeks)						
1 [P]	RCT	36	44	Meshed skin graft = 19.84 (7.37) Split thickness skin graft = 20.36 (7.21), p > 0.05		Low

[P] = Puttirutvong et al. (2004). Meshed skin graft + standard care vs. split thickness skin graft + standard care. Standard care = daily dressing

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised clinical trial.

Negative pressure wound therapy

Summary of GRADE profile 52: Adjunctive treatment: Negative pressure wound therapy (NPWT)

No of studies	Design	NPWT	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Amputation						
2 [B, A]	RCT	9/246 (3.7%)	26/251 (10.4%)	RR 0.35 (0.17 to 0.74) NNTB = 15 (9 to 43)	7 fewer per 100 (from 3 fewer to -9 fewer)	Low
Complete wound closure (week 16) (follow-up 16 weeks)						
2 [B, A]	RCT	116/246 (47.2%)	81/251 (32.3%)	RR 1.47 (1.18 to 1.84) NNTB = 7 (4 to 16)	15 more per 100 (from 6 more to 27 more)	Low
Mean reduction wound surface area (cm^2)						
1 [E]	RCT	12	12	Mean reduction (cm^2) (SD): NPWT = 20.4 (11.7); control = 9.5 (4.11) Mean difference = 10.9 (95%CI: 3.88 to 17.92)		Low
Median time to 75% wound closure (days)						
1 [B]	RCT	169	166	Median time (K-M) (days): NPWT = 58 (95%CI: 53 to 78) Control = 84 (95%CI: 58 to 89), p = 0.014		Low
Median time to achieve 75%-100% granulation (days) (baseline 0%-25% granulation)						
1 [A]	RCT	77	85	Median time (K-M) (days): NPWT = 42 (95%CI: 14 to 56) Control = 82 (95%CI: 28 to 112), p = 0.01		Low
Overall ulcer-related AEs						
1 [B]	RCT	15/169 (8.9%)	11/166 (6.6%)	RR 1.34 (0.63 to 2.83) NNTH = N/A	2 more per 100 (from -2 fewer to 12 more)	Low
Overall treatment-related AEs						
1 [A]	RCT	9/77 (11.7%)	11/85 (12.9%)	RR 0.90 (0.40 to 2.06) NNTH = N/A	1 fewer per 100 (from 8 fewer to 14 more)	Low

[B] = Blume et al. (2008): NPWT + standard care vs. control (moist wound therapy) + standard care. Standard care = off-loading.

[E] = Etoz et al. (2004): NPWT vs. control (saline moistened gauze)

[A] = Armstrong & Lavery. (2005): NPWT + standard care vs. control (moist wound therapy) + standard care. Standard care = off-loading.

AE = adverse event; CI = confidence interval; K-M = Kaplan-Meier; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk; SD = standard deviation.

Other adjunctive treatments

Summary of GRADE profile 53: Other adjunctive treatments: Electrical stimulation therapy (EST)

No of studies	Design	EST	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (12 weeks) (follow-up 12 weeks): electrical stimulation						
1 [P]	RCT	13/20 (65%)	7/20 (35%)	RR 1.86 (0.94 to 3.70) NNTB = N/A	30 more per 100 (from - 2 fewer to 94 more)	Low
Complete wound healing (20 weeks) (follow-up 20 weeks): ESWT						
1 [M]	RCT	8/15 (53.3%)	5/15 (33.3%)	RR 1.6 (0.68 to 3.77) NNTB = N/A	20 more per 100 (from - 11 fewer to 92 more)	Low
Mean healing time (days): ESWT						
1 [M]	RCT	15	15	Mean (days) (SD): ESWT = 60.8 (4.7); control = 82.2 (4.7) p < 0.001		Low

[M] = Moretti et al. (2009). ESWT + standard care vs. standard care only (control). Standard care = debridement, off-loading, antibiotics if needed.

[P] = Peters et al. (2001). EST vs. placebo stimulation with no current (control).

AE = adverse event; CI = confidence interval; ESWT = electrical shock wave therapy; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomised clinical trial; RR = relative risk; SD = standard deviation.

Summary of GRADE profile 54: Other adjunctive treatments: Autologous platelet-rich plasma gel

No of studies	Design	Autologous platelet-rich plasma gel	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (12 weeks)						
1 [D]	RCT	13/40 (32.5%)	9/32 (28.1%)	RR 1.16 (0.57 to 2.35) NNTB = N/A	4 more per 100 (from 12 fewer to 38 more)	Low
Median time to complete wound closure (days)						
1 [D]	RCT	40	32	Median time (days) Treatment = 45; control = 85, Log-rank p = 0.126.		Low

[D] = Driver et al. (2006). Autologous platelet-rich plasma gel + standard care vs saline gel + standard care only (control). Standard care = dressing, off-loading.

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 55: Other adjunctive treatments: Acellular dermal regenerative tissue matrix

No of studies	Design	Acellular dermal matrix	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (follow-up 12 weeks)						
1 [R]	RCT	32/46 (69.6%)	18/39 (46.2%)	RR 1.50 (1.02 to 2.22) NNTB = 4 (2 to 44)	23 more per 100 (from 1 more to 56 more)	Low
Healing rate (adjusted HR)						
1 [R]	RCT	46	39	Healing rate: Adjusted HR = 2.0 (95%CI: 1.0 to 3.5)		Low

[R] = Reyzelman et al. (2009). Acellular dermal matrix + standard care vs standard care only (control). Standard care = debridement, dressing, off-loading.

CI = confidence interval; HR = hazard ratio; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 56: Other adjunctive treatments: OASIS wound matrix vs. platelet derived growth factor (PDGF)

No of studies	Design	OASIS	PDGF	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (12 weeks) (follow-up 12 weeks)						
1 [N]	RCT	18/37 (48.6%)	10/36 (27.8%)	RR 1.75 (0.94 to 3.26) NNTB = N/A	21 more per 100 (from 2 fewer to 63 more)	Low
Ulcer recurrence (6 months) (follow-up 6 months)						
1 [N]	RCT	5/19 (26.3%)	6/18 (33.3%)	RR 0.79 (0.29 to 2.12) NNTB = N/A	7 fewer per 100 (from 24 fewer to 37 more)	Low

[N] = Niezgoda et al. (2005). Oasis wound matrix + standard care vs PDGF + standard care. Standard care = debridement, off-loading.

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 57: Other adjunctive treatments: Arginine-glycine-aspartic acid (RGD) peptide matrix

No of studies	Design	RGD peptide matrix	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (10 weeks) (follow-up 10 weeks)						
1 [S]	RCT	14/40 (35.0%)	2/25 (8.0%)	RR 4.36 (1.08 to 17.65) NNTB = 4 (2 to 16)	27 more per 100 (from 1 fewer to 100 more)	Low

[S] = Steed el al. (1995). RGD peptide matrix + standard care vs saline gauze + standard care only (control). Standard care = debridement, dressing.

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

Summary of GRADE profile 58: Other adjunctive treatments: Dalteparin (for diabetic patients with peripheral arterial occlusive disease [PAOD])

No of studies	Design	Dalteparin (injection)	Control	Relative risk/NNTB (95% CI)	Absolute	GRADE quality
Complete wound healing (6 months) (follow-up 6 months)						
1 [K]	RCT	14/43 (32.6%)	9/42 (21.4%)	RR 1.52 (0.74 to 3.13) NNTB = N/A	11 more per 100 (from 6 fewer to 46 more)	Low
At least 50% wound reduction (follow-up 6 months)						
1 [K]	RCT	15/43 (34.9%)	10/42 (23.8%)	RR 1.33 (0.69 to 2.56) NNTB = N/A	8 more per 100 (from 7 fewer to 37 more)	Low
Amputation (follow-up 6 months)						
1 [K]	RCT	2/43 (4.7%)	8/42 (19%)	RR 0.24 (0.06 to 1.08) NNTB = N/A	14 fewer per 100 (from 18 fewer to 2 more)	Low

[K] = Kalani et al. (2003). Dalteparin (injection) + standard care vs. placebo saline + standard care. Standard care = dressing, debridement, off-loading, antibiotic if required.

CI = confidence interval; NNTB = number needed to treat to benefit; RCT = randomised clinical trial; RR = relative risk.

3.4.3 Evidence statements

Growth factor (G-CSF) as an adjunctive treatment to standard wound care (see Summary of GRADE profile 45)

Diabetic foot-related outcomes:

3.4.3.1 Five RCTs with a total number of 168 participants showed that participants who received G-CSF with standard wound care were significantly less likely to have an amputation or other surgical interventions when compared with participants who received standard wound care alone. (Low quality)

3.4.3.2 Two RCTs with a total number of 50 participants showed that participants who received G-CSF with standard wound care had a significantly shorter length of hospital stay, when compared with participants who received standard wound care alone. (Low quality)

3.4.3.3 One RCT with 40 participants showed that participants who received G-CSF with standard wound care were significantly more likely to have resolution of infection (moderate quality) when compared with participants who received standard wound care alone.

3.4.3.4 Four RCTs with a total number of 140 participants showed that participants who received G-CSF with standard wound care were significantly more likely to have an improvement on infection status (low quality) when compared with participants who received standard wound care alone.

However,

3.4.3.5 Two RCTs with a total number of 79 participants showed no significant difference in complete wound healing between participants who received G-CSF with standard wound care and participants who received standard wound care alone. (Low quality)

Adverse events:

3.4.3.6 Three RCTs with a total number of 117 participants showed no significant difference in the number of treatment-related adverse events between participants who received G-CSF with standard wound care and participants who received standard wound care alone. (Low quality)

Growth factors (PDGF) as an adjunctive treatment to standard wound care (see Summary of GRADE profile 46)

Diabetic foot-related outcomes:

3.4.3.7 Four RCTs with a total number of 744 participants showed that participants who received PDGF with standard wound care were significantly more likely to have complete wound healing when compared with participants who received standard wound care alone. (Moderate quality)

3.4.3.8 One RCT with 113 participants showed that participants who received PDGF with standard wound care had a significantly shorter wound healing time compared with participants who received standard wound care alone. (Low quality)

Adverse events:

3.4.3.9 Two RCTs with a total number of 485 participants showed no significant differences in the number of withdrawals due to treatment-related adverse events between participants who received PDGF with standard wound care and participants who received standard wound care alone. (Low quality)

3.4.3.10 One RCT with 102 participants showed no significant differences in the number of at least one treatment-related adverse event between participants who received PDGF with standard wound care and participants who received standard wound care alone. (Low quality).

Growth factors (EGF) as an adjunctive treatment to standard wound care (see Summary of GRADE profile 47)

Diabetic foot-related outcomes:

3.4.3.11 One RCT with 59 participants showed no significant differences in the number of amputations between participants who received EGF with standard wound care and participants who received standard wound care alone. (Low quality)

3.4.3.12 One RCT with 50 participants showed no significant differences in the length of hospital stay between participants who received EGF with standard wound care and participants who received standard wound care alone. (Low quality)

3.4.3.13 Three RCTs with a total number of 166 participants showed no significant difference in complete wound healing between participants who received EGF with standard wound care and participants who received standard wound care alone. (Low quality)

However,

3.4.3.14 One RCT with 149 participants showed that participants who received EGF with standard wound care were significantly more

likely to achieve at least 50% wound reduction when compared with participants who received standard wound care alone. (Low quality)

Adverse events:

3.4.3.15 One RCT with 149 participants showed that participants who received EGF with standard wound care were significantly more likely to have shivering (treatment-related) when compared with participants who received standard wound care alone. However, there was no significant difference in those who experienced a burning sensation (treatment-related). (Low quality)

Growth factors (TGF-β) as an adjunctive treatment to standard wound care (see Summary of GRADE profile 48)

Diabetic foot-related outcomes:

3.4.3.16 One RCT with 155 participants showed no significant difference in complete wound healing between participants who received TGF-β with standard wound care and participants who received standard wound care alone. (Moderate quality)

Hyperbaric oxygen therapy (HBOT) as an adjunctive treatment to standard wound care (see Summary of GRADE profile 49)

Diabetic foot-related outcomes:

3.4.3.17 Five RCTs with a total number of 308 participants showed that participants who received HBOT with standard wound care were significantly less likely to have a major amputation (low quality) when compared with participants who received standard wound care alone.

3.4.3.18 One RCT with 100 participants showed that participants who received HBOT with standard wound care were significantly less likely to have other surgical interventions (moderate quality) when compared with participants who received standard wound care alone.

However,

3.4.3.19 Three RCTs with a total number of 148 participants showed no significant differences in the number of minor amputations between participants who received HBOT with standard wound care and participants who received standard wound care alone. (Moderate quality).

3.4.3.20 Three RCTs with a total number of 235 participants showed no significant differences in complete wound healing between participants who received HBOT with standard wound care and participants who received standard wound care alone. (Moderate quality).

3.4.3.21 One RCT with 27 participants showed no significant difference in the reduction of ulcer surface area between participants who received HBOT with standard wound care and participants who received standard wound care alone. (Low quality)

Dermal or skin substitutes as an adjunctive treatment to standard wound care (see Summary of GRADE profile 50 and 51)

Diabetic foot-related outcomes:

3.4.3.22 Six RCTs with a total number of 871 participants showed that participants who received dermal or skin substitutes (overall) with standard wound care were significantly more likely to have complete wound healing when compared with participants who received standard wound care alone. (Moderate quality). However, when subgroup analysis was carried out on the types of dermal or skin substitutes, only Dermagraft and Graftskin achieved the above effect, not Hyalograft or human skin equivalent. (Low quality)

3.4.3.23 One RCT with 25 participants showed that participants who received Dermagraft with standard wound care were significantly more likely to achieve at least 50% wound closure when compared

with participants who received standard wound care alone. (Low quality)

However,

3.4.3.24 One RCT with 314 participants showed no significant difference in the number of surgical interventions between participants who received Dermagraft with standard wound care and participants who received standard wound care alone. (Low quality)

Adverse events:

3.4.3.25 Two RCTs with a total number of 287 participants showed no significant difference in the number of withdrawals due to ulcer-related adverse events between participants who received Graftskin/Hyalograft with standard wound care and participants who received standard wound care alone. (Low quality)

3.4.3.26 Four RCTs with a total number of 557 participants showed that participants who received Dermagraft/Graftskin with standard wound care were significantly less likely to have ulcer-related adverse events, when compared with participants who received standard wound care alone. (Low quality)

Negative pressure wound therapy (NPWT) as an adjunctive treatment to standard wound care (see Summary of GRADE profile 52)

Diabetic foot-related outcomes:

3.4.3.27 Two RCTs with a total number of 497 participants showed that participants who received NPWT with standard wound care were significantly less likely to have an amputation, and significantly more likely to have complete wound closure, when compared with participants who received standard wound care alone . (Low quality)

3.4.3.28 One RCT with 24 participants showed that participants who received NPWT with standard wound care had a significantly

higher reduction in wound surface area, when compared with participants who received standard wound care alone. (Low quality)

3.4.3.29 One RCT with 335 participants showed that participants who received NPWT with standard wound care had a significantly shorter time to achieve wound closure when compared with participants who received standard wound care alone. (Low quality)

3.4.3.30 One RCT with 162 participants showed that participants who received NPWT with standard wound care had a significantly shorter time to achieve granulation when compared with participants who received standard wound care alone. (Low quality)

Adverse events:

3.4.3.31 One RCT with 335 participants showed no significant differences in the number of ulcer-related adverse events between participants who received NPWT with standard wound care and participants who received standard wound care alone. (Low quality)

3.4.3.32 One RCT with 162 participants showed no significant differences in the number of treatment-related adverse events between participants who received NPWT with standard wound care and participants who received standard wound care alone. (Low quality)

Electrical stimulation therapy as an adjunctive treatment to standard wound care (see Summary of GRADE profile 53)

Diabetic foot-related outcomes:

3.4.3.33 One RCT with 40 participants (electrical stimulation) and one RCT with 30 participants (electrical shock wave therapy) showed there was no significant difference in complete wound healing between participants who received electrical stimulation therapy with standard wound care and participants who received standard wound care. (Low quality)

3.4.3.34 The RCT with 30 participants showed that participants who received electrical shock wave therapy with standard wound care had significantly shorter healing time, when compared with participants who received standard wound care alone. (Low quality)

Autologous platelet-rich plasma gel as an adjunctive treatment to standard wound care (see Summary of GRADE profile 54)

Diabetic foot-related outcomes:

3.4.3.35 One RCT with 72 participants showed no significant differences in complete wound healing or median time to complete wound healing between participants who received autologous platelet-rich plasma gel with standard wound care and participants who received standard wound care alone. (Low quality)

Acellular dermal regenerative tissue matrix as an adjunctive treatment to standard wound care (see Summary of GRADE profile 55)

Diabetic foot-related outcomes:

3.4.3.36 One RCT with 85 participants showed that participants who received acellular dermal regenerative tissue matrix with standard wound care were significantly more likely to have complete wound healing and a faster healing rate, when compared with participants who received standard wound care alone. (Low quality)

OASIS wound matrix vs growth factor (PDGF) as an adjunctive treatment to standard wound care (see Summary of GRADE profile 56)

Diabetic foot-related outcomes:

3.4.3.37 One RCT with 73 participants showed no significant differences in complete wound healing or ulcer recurrence between participants who received OASIS wound matrix with standard wound care and participants who received PDGF with standard wound care alone. (Low quality)

RGD peptide matrix as an adjunctive treatment to standard wound care (see Summary of GRADE profile 57)

Diabetic foot-related outcomes:

3.4.3.38 One RCT with 65 participants showed that complete wound healing in participants who received RGD peptide matrix with standard wound care was significantly higher than participants who received saline gauze with standard wound care alone. (Low quality)

Dalteparin as an adjunctive treatment to standard wound care for diabetic patients with peripheral arterial occlusive disease (PAOD) (see Summary of GRADE profile 58)

Diabetic foot-related outcomes:

3.4.3.39 One RCT with 85 participants showed there were no significant differences in complete wound healing, at least 50% reduction in wound size, and amputation, between participants who received dalteparin with standard wound care, and participants who received standard wound care alone. (Low quality)

3.4.4 Health economic modelling

Negative pressure wound therapy and hyperbaric oxygen therapy.

The analysis of adjunctive therapies borrows several elements from the osteomyelitis analysis. The model structure is outlined below in figure 2HE.

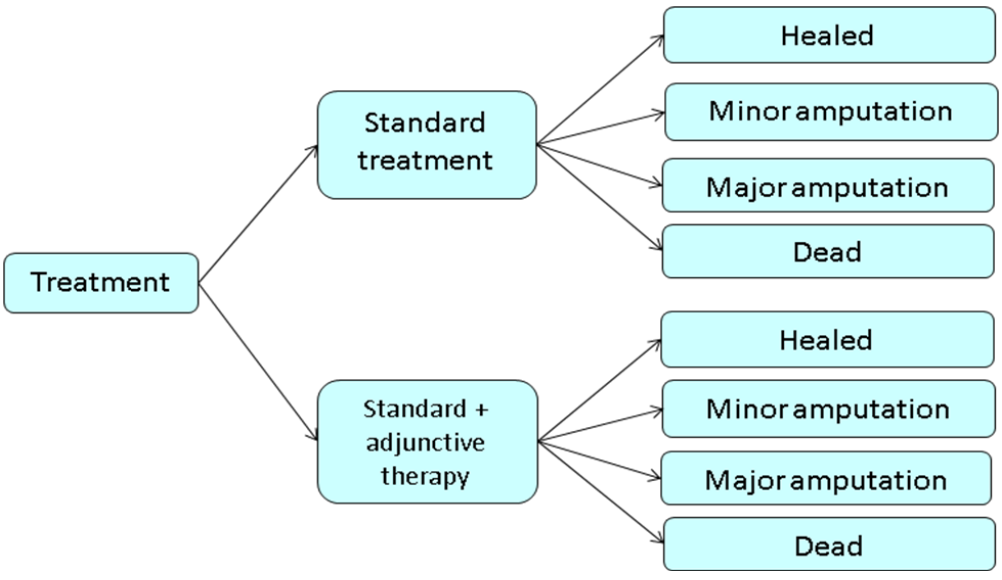


Figure 2HE: Adjunctive therapies model structure

The evidence review was once again the source of the clinical outcome data. These are reproduced in table 4HE.

Table 4HE. Clinical outcomes for adjunctive therapies

Outcome	Standard therapy	HBOT + standard therapy	NPWT + standard therapy
Healed (%)	15.6	63.2	80.34
Minor amputation (%)	35.1	13.5	3.66
Major amputation (%)	33.3	7.3	
Dead (%)	16	16	16

HBOT = hyperbaric oxygen therapy; NPWT = negative pressure wound therapy.

There was no evidence that the treatments had any effect on mortality, and there was no record of how many people actually died in the studies. Therefore, the mortality estimates were extrapolated from the cost-effectiveness study analysis (16%) and applied to the analysis. All these estimates were for 12 months.

The results for the treatments are presented below in table 5HE for negative pressure wound therapy and table 6HE for hyperbaric oxygen therapy.

Table 5HE: Cost-effectiveness results for negative pressure wound therapy (NPWT)

	QALY	Cost (£)	Incremental QALYs	Incremental costs (£)	ICER (£)
Deterministic					
Standard	0.4740	4542	-	-	-
NPWT	0.4935	5512	0.0195	970	49691
Probabilistic					
Standard	0.4728	4550	-	-	-
NPWT	0.4923	5541	0.0195	991	50821

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

Table 6HE: Cost-effectiveness results for hyperbaric oxygen therapy (HBOT)

	Cost (£)	QALY	Incremental costs (£)	Incremental QALYs	ICER (£)
Deterministic					
Standard	9599.6	0.4094	-	-	-
HBOT	11250	0.4773	1650.4	0.0674	24,486
Probabilistic					
Standard	9621	0.4091	-	-	-
HBOT	11318	0.4764	1697	0.0673	25,215

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

The results of the cost-effectiveness acceptability curves are presented in table 7HE.

Table 7HE: Probability of adjunctive treatments being cost effective.

Threshold	Hyperbaric oxygen therapy	Negative pressure wound therapy
£20,000	0.44	0.152
£30,000	0.54	0.264

These results indicate that NPWT is associated with ICERs above what is normally considered cost effective, and are unlikely to be cost effective. HBOT is associated with ICER between £20,000 per QALY and £30,000 per QALY and therefore, consideration must be given to issues of the uncertainty in the analysis. The probabilistic analysis indicates that HBOT has just over 50% probability of being cost effective at £30,000 per QALY threshold.

Sensitivity analysis indicated that it would be possible for the treatments to be considered cost effective if the difference in utility between healed and amputation was increased, the cost of amputations was higher and the costs of the interventions were reduced. The GDG noted the absence of long-term benefits in the analysis and considered that their inclusion would reduce the ICERs. However, the GDG considered that, given the uncertainty around the clinical estimates, the cost effectiveness of these therapies had not been demonstrated. Please see appendix I.

3.4.5 Evidence to recommendations

The clinical and cost effectiveness of adjunctive treatments in treating diabetic foot problems

Growth factors

Relative value placed on the outcomes considered

As adjunctive treatments were not considered as part of standard care and can be very costly, the GDG agreed that evidence on these adjunctive treatments needed to demonstrate positive effects on critical outcomes, such as preventing amputation or other surgical interventions, in order to warrant further discussion on recommendations.

Quality of the evidence

The GDG agreed that almost all the evidence was of low quality. From the evidence, only G-CSF demonstrated positive effects in 5 outcomes (including critical outcomes). There was no strong evidence on the clinical effectiveness of PDGF, EGF and TGF-β.

Other considerations

The GDG further discussed the applicability of G-CSF. The GDG agreed that G-CSF may not be applicable to the acute setting and care pathway of this particular guideline. G-CSF should only be applied to wounds that are stabilised and without moderate or severe infections, but by this point patients would have already been discharged back to primary or community settings. Given this lack of applicability to the acute hospital setting and the low-quality evidence, the GDG came to the consensus that G-CSF should not be offered as an adjunctive treatment for in-hospital patients, unless as part of a clinical trial. The same consensus was reached for PDGF, EGF and TGF-β.

Hyperbaric oxygen therapy (HBOT)

Relative value placed on the outcomes considered

(See the same section under Growth factors).

Quality of the evidence

The GDG agreed that the evidence was of low to moderate quality, and two out of the five outcomes demonstrated statistically significant positive effects. As HBOT has some low- to moderate-quality evidence on positive effects on

critical outcomes (reducing major amputation and other surgical interventions), a health economic evaluation should be carried out to further assess its cost effectiveness as an adjunctive treatment for diabetic foot problems.

Trade-off between net health benefits and resource use
The GDG noted that the cost-effectiveness results were between £20,000 and £30,000 per QALY gained and, therefore, required consideration of the uncertainty in the analysis. They noted the absence of long-term outcomes and the low quality of the clinical data that was used to populate the model, therefore giving highly uncertain results.

Dermal or skin substitutes
Relative value placed on the outcomes considered
(See the same section under Growth factors).

Quality of the evidence
The GDG agreed that the evidence was of low quality. When the GDG further examined the evidence, only low-quality evidence on Dermagraft and Graftskin demonstrated positive effects on complete wound healing; at least 50% wound closure; and median time to complete closure. However, no positive effect was demonstrated on the critical outcome (reduction in amputation).

Other considerations
The GDG further discussed the applicability of Dermagraft and Graftskin. The GDG agreed that Dermagraft or Graftskin should not be offered as an adjunctive treatment for in-hospital patients, unless as part of a clinical trial because of the following reasons:

- Low-quality evidence.
- Lack of evidence on critical outcomes (prevent amputation or other surgical interventions).
- High cost implications.
- Currently not widely used in the UK.

Negative pressure wound therapy (NPWT)

Relative value placed on the outcomes considered

(See the same section under Growth factors).

Quality of the evidence

The GDG agreed that the evidence was of low quality, and five out of the seven outcomes demonstrated positive effects. As NPWT has some evidence on positive effects on critical outcome (reducing amputation), a health economic evaluation should be carried out to further assess its cost effectiveness as an adjunctive treatment for diabetic foot problems.

Trade-off between net health benefits and resource use

The GDG noted the cost effectiveness results were higher than what is normally considered cost effective and considered to be highly uncertain given the absence of long-term outcomes and the low quality of the clinical data. However, the GDG considered that there was evidence of positive effects on a critical outcome, reducing amputation. There was also a recognition that this intervention is widely used and available in clinical practice, with clinical expertise supporting its success in the inpatient management of diabetic foot problems despite the limited clinical evidence available. The GDG therefore recommended the use of the intervention in the context of a clinical trial or as a rescue therapy to prevent amputation.

Other adjunctive treatments

Relative value placed on the outcomes considered

(See the same section under Growth factors).

Quality of the evidence

The GDG agreed that the evidence was very limited (very small number of studies) and was of low quality. Due to a lack of evidence, the GDG came to the consensus that electrical stimulation therapy, autologous platelet-rich plasma gel, regenerative wound matrices and deltaparin should not be offered as adjunctive treatments for in-hospital patients, unless as part of a clinical trial.

3.4.6 Recommendations and research recommendations for adjunctive treatments for diabetic foot problems

Recommendations for adjunctive treatments for diabetic foot problems

Adjunctive treatments

Recommendation 1.2.35

Negative pressure wound therapy should not be routinely used to treat diabetic foot problems, but may be considered in the context of a clinical trial or as rescue therapy (when the only other option is amputation).

Recommendation 1.2.36

Do not offer the following treatments for the inpatient management of diabetic foot problems, unless as part of a clinical trial:

- Dermal or skin substitutes.
- Electrical stimulation therapy, autologous platelet-rich plasma gel, regenerative wound matrices and deltaparin.
- Growth factors (granulocyte colony-stimulating factor [G-CSF], platelet-derived growth factor [PDGF], epidermal growth factor [EGF] and transforming growth factor beta [TGF-β]).
- Hyperbaric oxygen therapy.

Research recommendations for adjunctive treatments for diabetic foot problems

See appendix A for a list of all research recommendations.

Further research should be undertaken to determine the clinical and cost effectiveness of negative pressure wound therapy for diabetic foot problems.

Further research should be undertaken to determine the clinical and cost effectiveness of hyperbaric oxygen therapy for diabetic foot problems.

3.5 Timing for surgical management to prevent amputation

3.5.1 Review question

When is the optimal time for surgical management (including revascularisation and orthopaedic interventions) to prevent amputation for diabetic foot problems?

3.5.2 Evidence review

The systematic search retrieved 9817 studies. No studies were identified that met the inclusion/exclusion (for the review protocol and inclusion/exclusion criteria, please see appendix B), therefore no studies were included.

3.5.3 Evidence statements

No studies were identified that met the inclusion/exclusion criteria; therefore no evidence statement was generated.

3.5.4 Health economic modelling

No health economic modelling was conducted for this question.

3.5.5 Evidence to recommendations

As no evidence was identified, the GDG felt that they could not make any recommendation on the optimal time for surgical management (including revascularisation and orthopaedic interventions) to prevent amputation for diabetic foot problems. The GDG agreed that the current recommendation on obtaining urgent advice from an appropriate specialist experienced in managing diabetic foot problems (recommendation 1.2.16) was appropriate and sufficient in the absence of evidence.

3.5.6 Recommendations and research recommendations for timing for surgical management to prevent amputation

No recommendations have been made for this review question (see evidence to recommendations)

Research recommendations for timing for surgical management to prevent amputation

See appendix A for a list of all research recommendations.

Does early revascularisation improve outcomes in patients with diabetes and a foot ulcer?

What are the best indicators of the need to revascularise the leg in patients with diabetes and a foot ulcer?

4 Notes on the scope of the guideline

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover. The scope of this guideline is available from www.nice.org.uk/guidance/CG119 – click on 'How this guidance was produced'.

5 Implementation

NICE has developed tools to help organisations implement this guidance (see www.nice.org.uk/guidance/CG119).

6 Other versions of this guideline

6.1 Quick reference guide

A quick reference guide for healthcare professionals is available from www.nice.org.uk/guidance/CG119/QuickRefGuide

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N2467).

6.2 'Understanding NICE guidance'

A summary for patients and carers ('Understanding NICE guidance') is available from www.nice.org.uk/guidance/CG119/PublicInfo

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N2468).

We encourage NHS and voluntary sector organisations to use text from this booklet in their own information about diabetic foot problems.

7 Related NICE guidance

Published

- Anaemia management in people with chronic kidney disease. NICE clinical guideline 114 (2011). Available from www.nice.org.uk/guidance/CG114
- Venous thromboembolism: reducing the risk. NICE clinical guideline 92 (2010). Available from www.nice.org.uk/guidance/CG92
- Type 2 diabetes: newer agents. NICE clinical guideline 87 (2009). Available from www.nice.org.uk/guidance/CG87
- Surgical site infection. NICE clinical guideline 74 (2008). Available from www.nice.org.uk/guidance/CG74
- Chronic kidney disease. NICE clinical guideline 73 (2008). Available from www.nice.org.uk/guidance/CG73
- Lipid modification. NICE clinical guideline 67 (2008). Available from www.nice.org.uk/guidance/CG67
- Type 2 diabetes (update). NICE clinical guideline 66 (2008). Available from www.nice.org.uk/guidance/CG66
- Acutely ill patients in hospital. NICE clinical guideline 50 (2007). Available from www.nice.org.uk/guidance/CG50
- Pressure ulcers. NICE clinical guideline 29 (2005). Available from www.nice.org.uk/guidance/CG29
- Type 1 diabetes. NICE clinical guideline 15 (2004). Available from www.nice.org.uk/guidance/CG15
- Type 2 diabetes: prevention and management of foot problems. NICE clinical guideline 10 (2004). Available from www.nice.org.uk/guidance/CG10
- Preoperative tests. NICE clinical guideline 3 (2003). Available from www.nice.org.uk/guidance/CG3

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Type 2 diabetes: preventing pre-diabetes in adults. NICE public health guidance. Publication expected June 2011.

- Type 2 diabetes: preventing the progression from pre-diabetes. NICE public health guidance. Publication expected May 2012.
- Lower limb peripheral arterial disease. NICE clinical guideline. Publication expected October 2012.

8 Updating the guideline

NICE clinical guidelines are updated so that recommendations take into account important new information. New evidence is checked 3 years after publication, and healthcare professionals and patients are asked for their views; we use this information to decide whether all or part of a guideline needs updating. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations. Please see our website for information about updating the guideline.

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The Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring adherence to NICE guideline development processes. In particular, the panel ensures that stakeholder comments have been adequately considered and responded to. The panel includes members from the following perspectives: primary care, secondary care, lay, public health and industry.

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Declarations of interests

For the declarations of interests of all the contributors to this guideline, see www.nice.org.uk/guidance/CG119