Diabetic foot problems: 
Evidence Update March 2013

A summary of selected new evidence relevant to NICE clinical guideline 119 ‘Inpatient management of diabetic foot problems’ (2011)
Evidence Updates provide a summary of selected new evidence published since the literature search was last conducted for the accredited guidance they relate to. They reduce the need for individuals, managers and commissioners to search for new evidence. Evidence Updates highlight key points from the new evidence and provide a commentary describing its strengths and weaknesses. They also indicate whether the new evidence may have a potential impact on current guidance. For contextual information, this Evidence Update should be read in conjunction with the relevant clinical guideline available from the NHS Evidence topic page for diabetes.

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

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Contents

Introduction .................................................................................................................................. 4
Key points ...................................................................................................................................... 5

1 Commentary on new evidence ............................................................................................... 7
   Introduction ................................................................................................................................ 7
   1.1 Multidisciplinary foot care team ......................................................................................... 7
   1.2 Patient information and support ............................................................................................ 8
   1.3 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) .................................................................................. 8
   1.4 Initial examination and assessment ...................................................................................... 9
   1.5 Investigation of suspected diabetic foot infection .............................................................. 9
   1.6 Management of diabetic foot infection ................................................................................ 10
   1.7 Management of diabetic foot ulcers ..................................................................................... 11
   1.8 Assessment of suspected limb ischaemia ............................................................................. 17
   Areas not currently covered by NICE guidance ......................................................................... 18

2 New evidence uncertainties ................................................................................................…… 21

Appendix A: Methodology ........................................................................................................ 22
Appendix B: The Evidence Update Advisory Group and Evidence Update project team ....... 24
Introduction

This Evidence Update identifies new evidence that is relevant to, and may have a potential impact on, the following reference guidance:


A search was conducted for new evidence from 24 February 2010 to 1 October 2012. A total of 3361 pieces of evidence were initially identified. Following removal of duplicates and a series of automated and manual sifts, 24 items were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An Evidence Update Advisory Group, comprising topic experts, reviewed the prioritised evidence and provided a commentary.

Although the process of updating NICE guidance is distinct from the process of an Evidence Update, the relevant NICE guidance development centres have been made aware of the new evidence, which will be considered when guidance is reviewed.

Other relevant NICE guidance

The focus of the Evidence Update is on the guidance stated above. However, overlap with other NICE guidance has been outlined as part of the Evidence Update process. Where relevant, this Evidence Update therefore makes reference to the following guidance:

1. Type 2 diabetes. NICE clinical guideline 87 (2009).


Quality standards


Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk
Key points

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key points for this Evidence Update. It also indicates the EUAG’s opinion on whether the new evidence may have a potential impact on the current guidance listed in the introduction. For further details of the evidence behind these key points, please see the full commentaries.

The section headings used in the table below are taken from the guidance.

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

<table>
<thead>
<tr>
<th>Key point</th>
<th>Potential impact on guidance</th>
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<tr>
<td><strong>Introduction</strong></td>
<td></td>
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<tr>
<td>• Across England, there is an 8-fold variation in lower limb amputation rate in patients with diabetes, which may potentially reflect variation in the quality of local diabetes care delivery.</td>
<td>Yes</td>
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<tr>
<td><strong>Patient information and support</strong></td>
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<tr>
<td>• There is insufficient robust evidence on the value of patient education on inpatient management of diabetic foot problems.</td>
<td>Yes</td>
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<td><strong>Initial examination and assessment</strong></td>
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<td>• No one method for scoring diabetic foot problems appears to be consistently better than any other.</td>
<td>Yes</td>
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<td><strong>Investigation of suspected diabetic foot infection</strong></td>
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<tr>
<td>• Further research is needed on the clinical utility of DNA array technology to differentiate diabetic foot infections and to predict outcomes.</td>
<td>Yes</td>
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<td><strong>Management of diabetic foot infection</strong></td>
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<tr>
<td>• Moxifloxacin monotherapy appears to be non-inferior to standard antibiotic therapy for inpatient management of severe foot infections.</td>
<td>Yes</td>
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<tr>
<td><strong>Management of diabetic foot ulcers</strong></td>
<td></td>
</tr>
<tr>
<td>• No one method of debridement or wound dressing emerges as superior to others, and further research is needed.</td>
<td>Yes</td>
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<tr>
<td>• Shortcomings in the available evidence preclude definitive conclusions about negative pressure wound therapy and further research is needed.</td>
<td>Yes</td>
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<tr>
<td>• Topical platelet-rich plasma may be an adjunctive treatment of potential value for the healing of diabetic ulcers, although it is currently at an early stage of assessment.</td>
<td>Yes</td>
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<tr>
<td>• Adjunctive treatments with growth factors and hyperbaric oxygen are of uncertain benefit for the healing of diabetic foot ulcers.</td>
<td>Yes</td>
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</table>
### Key point

<table>
<thead>
<tr>
<th>Evidence provides useful information about the potential of revascularisation and free tissue transfer in avoiding limb amputation, but the impact of early revascularisation on outcomes remains uncertain.</th>
<th>Yes</th>
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#### Assessment of suspected limb ischaemia

- Limited evidence suggests that the ankle–brachial pressure index may not be measurable in approximately a third of patients, and may underestimate atherosclerotic disease, particularly in patients with calcification present.

#### Areas not currently covered by NICE guidance

- There may be an association between glycaemic control and risk of amputation in people with diabetes without acute foot ulceration or a history of previous amputation.
- Shortcomings in the available evidence preclude definitive assessment of complex interventions to prevent diabetic foot problems.
- No one measure has been identified as the ‘gold standard’ for assessing health-related quality of life in people with diabetic foot problems.
1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update. The commentaries focus on the ‘key references’ (those identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update), which are identified in bold text. Supporting references provide context or additional information to the commentary. Section headings are taken from the guidance.

Introduction

Variation in incidence of lower limb amputation

The introduction to NICE clinical guideline 119 (CG119) notes that diabetic foot problems may lead to loss of mobility and limb amputation, with consequent adverse impact on patients’ quality of life and significant financial impact on the NHS. It also states that there is variation in the inpatient management of diabetic foot problems, 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 and the availability of podiatrists with expertise in diabetic foot disease.

A study by Holman et al. (2012) examined the variation in recorded incidence of lower limb amputation in England, based on a review of Hospital Episode Statistics for all 151 Primary Care Trusts in England for the 3 years to 31 March 2010. Of the total 34,109 amputations during this period, 16,693 (48.9%) occurred in people with diabetes. The incidence was 2.51 per 1000 person-years in people with diabetes compared with 0.11 per 1000 person-years in people without diabetes (relative risk [RR] in diabetes=23.3). There was an 8-fold variation in incidence across all Primary Care Trusts in England in both people with diabetes (range 0.64–5.25 per 1000 person-years) and people without diabetes (range 0.03–0.24 per 1000 person-years). In people with diabetes, there was a 10-fold variation in both major amputations (range 0.22–2.20 per 1000 person-years) and minor amputations (range 0.30–3.25 per 1000 person-years).

Although amputation incidence alone may not accurately reflect the quality of local healthcare delivery, the authors concluded that regional differences in healthcare may be a potential factor in the considerable variation in amputation rate across England (although it should be noted that this can only be inferred from these data). This evidence is broadly consistent with the acknowledgement in NICE CG119 that there is regional variation in practice, and reinforces the need for more consistent delivery of diabetes care as set out in the guidance. It should be noted that the number of amputations derived from Hospital Episode Statistics differs from such information obtained from the National Diabetes Audit (as discussed in the testing report for the NICE Clinical Commissioning Group Outcomes Indicator for ‘Lower limb amputation in people with diabetes’).

Key reference

1.1 Multidisciplinary foot care team

No new key evidence was found for this section.
1.2 Patient information and support

**Patient education for preventing diabetic foot ulcers**

*NICE CG119* recommends that patients are offered consistent, relevant and clear explanations to support informed decision-making. Patients should have a named contact to follow the inpatient care pathway and be responsible for offering information about diagnosis and treatment, and the care and support that they can expect. Formal patient education is not, however, currently discussed by the guideline.

A Cochrane review by *Dorresteijn et al. (2012)* evaluated patient educational programmes for preventing foot ulcers. Prospective randomised controlled trials (RCTs), in patients with type 1 or 2 diabetes in any setting and with an explicit focus on foot care were included, and studies where the only aim was optimising blood glucose level were excluded. A total of 12 RCTs (n=2763) were included, 4 of which were performed in a secondary care setting (including 1 study conducted in the UK) and 1 in a hospital emergency department; the remainder were in community-based or primary care settings. Heterogeneity of the studies precluded pooled analysis.

The effect of patient education on ulceration and amputation was reported in only 5 of the 12 studies, one of which (n=354 limbs) reported reduced incidence of foot ulceration (RR=0.31, 95% CI 0.14 to 0.66) and amputation (RR=0.33, 95% CI 0.15 to 0.76), 1 year after a 1-hour group education session, although a similar study (n=172 patients) did not confirm these findings for either ulceration or amputation (RR=1.00, 95% CI 0.70 to 1.44; and RR=0.98, 95% CI 0.41 to 2.34 respectively). Educational interventions were shown to improve patients’ foot care knowledge in the short-term in 5 of 8 studies, and patients’ self-reported self-care behaviour was also improved in the short-term in 7 of 9 RCTs (although the authors noted that these outcomes were measured subjectively and may be prone to bias). One out of 5 RCTs found that an educational intervention was associated with improvements in callus, nail problems and fungal infections, although as podiatry was also part of the intervention, the patients saw a podiatrist more frequently. Three studies that were considered by the authors to be underpowered did not show any benefit of education.

The authors noted several limitations of the review, including that the studies varied markedly in terms of participants, control groups, outcome measures, follow up, and the methods and intensity of the educational programmes, and that most included studies were at a high or unclear risk of bias from insufficient reporting.

The authors concluded that there was insufficient robust evidence to demonstrate that limited patient education alone is effective in achieving clinically relevant reductions in the incidence of ulcers and amputations. The shortcomings of the studies included in the review preclude clear interpretation and consequently, this evidence is unlikely to have an impact on *NICE CG119*. Further research is needed on education, particularly when combined with other interventions, for preventing diabetic foot ulcers.

**Key reference**

*Dorresteijn JAN, Kriegsman DMW, Assendelft WJJ et al. (2012) Patient education for preventing diabetic foot ulceration. Cochrane Database of Systematic Reviews issue 10: CD001488*

1.3 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)

No new key evidence was found for this section.
1.4 Initial examination and assessment

Clinical utility of different diabetic ulcer/wound scores

During the development of NICE CG119 limited evidence was found on the clinical utility of different diabetic ulcer/wound scores, and therefore no particular scoring system was recommended.

*Karthikesalingam et al. (2010)* conducted a systematic review that evaluated 11 scoring systems for diabetic foot ulcers, and 6 validation or comparative studies. The heterogeneous study designs, methodologies and patient populations precluded quantitative meta-analysis. The review discussed strengths and weaknesses of the individual scoring systems (although no formal quality assessment of the scoring systems was performed). It was also noted that although many scoring systems exist for the classification of the diabetic foot, few have been validated.

The authors considered that a major problem with existing scoring systems is the inability to adjust for the presence of multiple ulcers in different positions on the diabetic foot. Standardised definitions and quantitative assessment of ischaemia and infection also present challenges. Furthermore, current scoring systems do not include systemic determinants of outcomes (for example, concomitant systemic disease or persistent hyperglycaemia).

The authors concluded that detailed scoring systems offer a valuable method for the comparison of data from different diabetic foot centres, and simplistic scoring systems may be used in clinical practice with the choice of system determined by the population under study.

The findings from this review are consistent with the view expressed in NICE CG119, with no particular scoring system emerging as better than other systems.

**Key reference**


1.5 Investigation of suspected diabetic foot infection

DNA arrays to determine infection of diabetic foot ulcers

During the development of NICE CG119, limited evidence of low or very low quality was found on the clinical utility of assessment, investigative or diagnostic tools for diabetic foot infections. Evidence relating to the use of DNA array technology was not specifically considered. No recommendations relating to diagnostic tools, including emerging technologies, were made.

A study of DNA array technology to distinguish between uninfected and infected diabetic foot ulcers was reported by *Sotto et al. (2012)*. The study evaluated 195 patients admitted to participating French centres with diabetic foot ulcers during the period April 2008 to June 2010. At admission, ulcers were clinically examined by physicians and classified on the Infectious Diseases Society of America scale as uninfected (grade 1) or infected (grade 2–4). After wound debridement, samples for bacterial culture were obtained by either swabbing the wound base, or by needle aspiration or tissue biopsy. Only patients with monomicrobial culture for *Staphylococcus aureus* were included in the study. A second wound bacterial specimen was obtained from patients with an uninfected ulcer 1 month after the first sample was taken. Oligonucleotide arrays were used to determine *S. aureus* resistance and virulence genes, and each isolate was then designated as either a colonising clonal complex (CC) or an infecting CC (colonising CCs being those of the type normally found in non-infected ulcers).

Among the 195 patients, 75 wounds were initially classified as uninfected and 120 as infected. Colonising CCs were found in 44 (59%) isolates from uninfected ulcers but in only...
Evidence Update 33 – Diabetic foot problems (March 2013)

6 (5%) isolates from infected ulcers (p<0.001). In follow-up samples, in ulcers deemed to be infected or worsening, colonising strains were found in only 6 (4%) ulcers, but infecting strains were found in 132 (96%). Conversely in ulcers deemed to have healed or have a favourable outcome, colonising strains were found in 49 (86%) ulcers, but infecting strains were found in only 8 (14%). The results may indicate the potential of DNA arrays to differentiate infected ulcers and to predict outcomes.

The major limitation of the study noted by the authors was the inclusion of diabetic foot ulcers with *S. aureus* as the only pathogen, whereas in practice ulcers are often polymicrobial. Additionally, the initial clinical diagnosis of ulcer infection may have differed between physicians, and methods used to obtain culture specimens were not the same in all patients. Finally, the study used the outcome of ulcer healing as a measure of infection rather than a more standardised and robust definition.

The limitations of this study make it unlikely to have an impact on NICE CG119, and the results and conclusions need corroboration from additional studies including cost-effectiveness evaluation. Furthermore, the test used in this study is not, at present, widely available in the UK.

**Key reference**


1.6 Management of diabetic foot infection

**Moxifloxacin monotherapy versus intravenous piperacillin/tazobactam followed by oral amoxicillin/clavulanate**

NICE CG119 recommends starting 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. For mild infections, oral antibiotics with activity against Gram-positive organisms should be offered. For moderate and severe infections, antibiotics with activity against Gram-positive and Gram-negative organisms, including anaerobic bacteria, should be offered (oral or intravenous for moderate infection, based on the clinical situation and the choice of antibiotic, and for severe infection, intravenous antibiotics should be started based on the clinical situation). It is recommended that 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. No specific antibiotics are recommended by the guideline.

Gyssens et al. (2011) conducted a double-blind, double-dummy RCT to determine if intravenous moxifloxacin 400 mg once daily followed by oral moxifloxacin 400 mg once daily (n=426) was non-inferior to intravenous piperacillin 4 g/tazobactam 0.5 g 3 times daily followed by oral amoxicillin 875 mg/clavulanate 125 mg twice daily (n=377) for the treatment of complicated skin and skin structure infections (cSSSI). Adults with a cSSSI of more than 21 days’ duration were included if they also had at least 3 of the following: purulent drainage or discharge; erythema extending from the wound edge; fluctuance, pain or tenderness to palpation; swelling or induration; fever; or elevated white blood cell count or C-reactive protein level. The study excluded patients with methicillin-resistant *S. aureus* or *S. epidermidis* or vancomycin-resistant enterococci. Patients who had taken antibiotics in the 7 days preceding study entry were also excluded, unless no response was observed despite treatment for 3 or more days and a culture showed a pathogen susceptible to the study drugs. A total of 316 (39.4%) of the 803 patients included in the study had diabetes mellitus, and 233 patients were diagnosed with diabetic foot infection. Intravenous treatment was administered for at least 3 days and until the patient was afebrile for at least 24 hours. The total duration of
treatment was 7–21 days. Analysis of results was adjusted for cSSSI subtype, severity of illness, and requirement for baseline surgery (defined as surgery within 48 hours of initiating study drugs), and the primary outcome was clinical response for the per-protocol population.

The independent data review committee considered that clinical cure in patients with diabetic foot infection in the intention to treat population was achieved in 86/123 (69.9%) of patients treated with moxifloxacin (76.4% in the per protocol population) and in 76/110 (69.1%) of patients treated with the comparator regimen (78.1% in the per protocol population). In the total population, moxifloxacin was shown to be non-inferior to the comparator regimen in both the per-protocol population and intention-to-treat population, with a clinical success rate of 88.6% versus 89.6% (p=0.758) and 82.2% versus 80.9% (p=0.632) respectively.

The authors recognised some limitations of the study, including a limited analysis of microorganisms (potentially underestimating the spectrum of infection), the unknown effect of surgery on outcomes with antibiotics, and that although the study included patients from the UK most were from Eastern Europe. Additionally, the recruitment of patients already taking antibiotics following a positive test for pathogens sensitive to study drugs may differ from recommended UK practice for initial empirical antibiotic prescribing for diabetic foot infection.

This study adds to the body of evidence on antibiotics for the treatment of diabetic foot infection, and suggests that moxifloxacin monotherapy once a day may be equivalent to other current multi-antibiotic treatments involving multiple daily doses. In the absence of cost effectiveness data, the evidence is consistent with the recommendation of NICE CG119 that selection should be based on clinical situation and lowest acquisition cost.

Key reference

1.7 Management of diabetic foot ulcers

Debridement, dressings and off-loading

NICE CG119 recommends that the approach to debridement, wound dressings and off-loading should take into account specialist expertise, clinical experience, clinical assessment of the wound, clinical circumstances, site of the ulcer, and patient preference, and should use the approach with the lowest acquisition cost.

Seven Cochrane reviews recently considered different aspects of debridement and wound dressing, of which 4 reviews were from the same group. Of the 29 RCTs on the management of diabetic foot ulcers included in these reviews, 9 were assessed in 2 or more reviews.

A Cochrane review by Edwards and Stapley (2012) assessed the effectiveness of debridement interventions on the healing of diabetic foot ulcers. Six RCTs (n=488) were included, with all studies also included in 1 or more of the other Cochrane reviews discussed in this section. Surgical debridement showed no significant difference in the proportion of ulcers completely healed within 6 months compared with non-surgical management (RR=1.21, 95% CI 0.96 to 1.51, p=0.1; 1 RCT, n=42). There was also no significant difference in the proportion of patients achieving complete ulcer healing with larvae compared with hydrogel (RR=2.5, 95% CI 0.5 to 12.5; 1 RCT, n=140). In a pooled analysis, hydrogels were however found to be significantly more effective in healing ulcers compared with gauze or standard care (RR=1.84, 95% CI 1.3 to 2.61; 3 RCTS, n=232).

A Cochrane review of 5 RCTs (n=446) by Dumville et al. (2011a) specifically examining hydrogel dressings (and including the 3 studies of hydrogels identified in the review by
Edwards and Stapley 2012), also found (from a pooled analysis of the same 3 trials, except with the exclusion of 1 treatment arm from 1 study) a significantly greater healing with hydrogel dressings compared with basic wound contact dressings (RR=1.80, 95% CI 1.27 to 2.56; 3 RCTs, n=198). The authors of both reviews discussed concerns with risk of bias in the 3 trials of hydrogels, along with differences in the length of follow-up and in the ulcer grades of included patients across the studies, indicating that this may limit any conclusions from the data.

Two Cochrane reviews assessed the use of silver-based wound dressings. A review by Bergin and Wraight (2011) focused specifically on studies conducted in patients with diabetic foot ulcers but no trials were identified that met the inclusion criteria. A review by Storm-Versloot et al. (2010) included all types of wounds and considered prevention of infection and wound healing. The review included 26 RCTs (n=2066), but the most commonly studied wounds were burns (20 studies). For the 2 studies focused on patients with diabetic foot ulcers, there were no statistically significant differences observed in wound healing with silver-containing wound dressings compared with control, in either an RCT of 40 participants (risk difference for healing within 6 weeks=−0.10, 95% CI −0.39 to 0.19), or in a second RCT of 434 participants (risk difference for healing within 8 weeks=0.09, 95% CI −0.06 to 0.24).

A Cochrane review by Dumville et al. (2011b) including 6 RCTs (n=157) assessed the effects of foam wound dressings on healing. No significant difference was seen in a pooled analysis of the number of ulcers healed with foam dressings compared with basic wound contact (RR=2.03, 95% CI 0.91 to 4.55; 2 RCTs, n=49). Nor was a significant difference seen in the number of ulcers healed with foam dressings versus either alginate dressings (RR=1.50, 95% CI 0.92 to 2.44; 2 RCTs, n=50), or hydrocolloid dressings (RR=0.88, 95% CI 0.61 to 1.26; 1 RCT, n=40).

A Cochrane review by Dumville et al. (2012a) of effects of hydrocolloid dressings on healing included 4 RCTs (n=511). Of the studies identified, 1 RCT (n=40) with a foam dressing comparator was included in the review by Dumville et al. (2011b) and 1 RCT (n=434) with a silver fibrous-hydrocolloid dressing comparator was included in the review by Storm-Versloot et al. (2010). Findings from these studies have been presented above. Additionally, from a pooled analysis the review found no significant difference in the number of ulcers healed with fibrous-hydrocolloid versus basic wound contact dressings (RR=1.01, 95% CI 0.74 to 1.38; 2 RCTs, n=229), although 1 of these trials suggested that basic wound contact dressing was more cost-effective.

A Cochrane review by Dumville et al. (2012b) of 6 RCTs (n=375) examined the effects of alginate dressings on healing. Of the studies identified, 2 RCTs (n=50) were included in the review on foam dressings by Dumville et al. (2011b) and 1 RCT (n=434) was included in both Dumville et al. (2012a) and Storm-Versloot et al. (2010). Findings from these studies have been presented above. Additionally, from a pooled analysis comparing alginate dressings to basic wound contact dressing, the review found no significant difference in the number of ulcers healed (RR=1.09, 95% CI 0.66 to 1.80; 3 RCTs, n=191).

The limitations of the trials analysed mean that there is unlikely to be any impact on NICE CG119. Overall, the evidence from all reviews discussed above is consistent with the recommendations of NICE CG119, with no one method of debridement or wound dressing emerging as superior to others.

Key references
Dumville JC, O’Meara S, Deshpande S et al. (2011a) Hydrogel dressings for healing diabetic foot ulcers. Cochrane Database of Systematic Reviews issue 9: CD009101
Adjunctive treatments

**NICE CG119** recommends that 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. **NICE CG119** also recommends that other adjunctive treatments (dermal or skin substitutes; electrical stimulation therapy, autologous platelet-rich plasma gel, regenerative wound matrices and dalteparin; growth factors; and hyperbaric oxygen therapy) are not offered for the inpatient management of diabetic foot problems, unless part of a clinical trial.

**Negative pressure wound therapy**

*Armstrong et al. (2012)* conducted a multicentre, prospective RCT to determine if mechanically powered negative pressure wound therapy was non-inferior to electrically powered negative pressure wound therapy in 132 people with non-infected, non-ischaemic, non-plantar lower extremity diabetic and venous wounds. Patients were randomly allocated to the negative pressure wound therapy device, although blinding was not possible due to the differences between interventions. Patients also received appropriate off-loading and compression therapy. Treatment continued for up to 16 weeks or complete wound closure (defined as complete re-epithelialisation without drainage). The primary outcome measure was wound size reduction, as measured from Visitrak wound measurement tracings.

The median percentage decrease in wound size with mechanically powered negative pressure wound therapy was shown to be non-inferior to the electrically powered approach after treatment for 4 weeks (−44.7% vs −28.6%, p=0.0030), 8 weeks (−73.8% vs −75.0%, p=0.0130), 12 weeks (−85.7% vs −82.1%, p=0.0051) and 16 weeks (−85.7% vs −94.0%, p=0.0044).

The study does not provide evidence of the clinical value of negative pressure wound therapy itself, however in circumstances where it may be used, these data suggest the equivalence of mechanical and electrical methods to generate negative pressure.

A systematic review by *Game et al. (2012)* examining various interventions to enhance ulcer healing identified 43 studies, of which 3 focused on negative pressure wound therapy. The review found few controlled studies, with the majority of poor methodological quality. Heterogeneity of studies prevented pooled analysis of the results.

One RCT (n=342) among the 3 studies concluded that the intervention was associated with reduced time to wound closure (96 days versus unquantifiable, p=0.001), reduced wound size after 28 days (−4.32 cm² versus −2.53 cm², p=0.021) and reduced incidence of minor amputation (7 patients versus 17 patients, p=0.035). A second, smaller RCT (n=22) reported reduced time to 90% granulation with negative pressure wound therapy (18.8 days versus 32.3 days, p=0.007). An additional study that attempted to show the benefits of negative pressure wound therapy by analysis of reimbursement claims was considered to have results...
that would be potentially explained, at least in part, by confounding factors. The authors considered that there may, possibly, be some justification for use of negative pressure wound therapy.

The data suggest the potential equivalence of mechanical and electrical methods of negative pressure generation, but shortcomings in the studies preclude definitive conclusions about the effect on healing with negative pressure wound therapy. These results are unlikely to have an impact on the recommendation in NICE CG119 to use negative pressure wound therapy only in clinical trials or as rescue therapy.

**Key references**


**Platelet-rich plasma**

Villela and Santos (2010) conducted a systematic review assessing topical platelet-rich plasma to promote healing of ulcers. The analysis of 18 studies (involving more than 30,400 participants) included 7 RCTs, 3 cross-sectional clinical studies, a multicentre retrospective cohort study (n=26,599), a multicentre case-control study (n=3830) and 4 studies with no control group. Five of the RCTs treated diabetic ulcers, of which 4 (n=123) could be meta-analysed. Among the wounds treated with platelet-rich plasma, 47 of 62 (75.8%) healed faster than those not treated in this way. In the control group, 43 of the 61 wounds (70.5%) did not heal. Two of the 4 studies showed a significant difference in healing between intervention and control. Overall, treatment with platelet-rich plasma showed a significant effect in favour of healing (odds ratio [point estimate displayed graphically] 95% CI 2.94 to 20.31). The studies included in the analysis were all small, included other interventions and had methodological differences in the preparation of platelet-rich plasma, precluding definitive interpretation.

The review by Game et al. (2012) (see ‘Negative pressure wound therapy’ in this section for details), additionally identified a single-blind RCT (n=100), considered to be of high quality, assessing the use of topical platelet-rich plasma from blood bank samples, thereby avoiding the cost associated with harvesting autologous platelets (which may be a current limitation on adoption of this therapy). After 12 weeks, significant improvement in healing was noted in the intervention group compared with the control group (79% vs 46%, p<0.05). The review authors noted that 38 of the 52 patients receiving the intervention had exposed bone at baseline and therefore considered the healing rate in this group to be higher than expected.

Taken together, this evidence suggests that the use of topical platelet-rich plasma may be a potentially valuable adjunctive treatment for diabetic ulcers, although it is currently at an early stage of assessment and trials have so far involved limited numbers of patients. The evidence is therefore unlikely to have an impact on NICE CG119.

Additional information about the study by Villela and Santos (2010) is also available in an independent critical appraisal report produced for the Centre for Reviews and Dissemination’s Database of Abstracts of Reviews of Effects.

**Key reference**


**Supporting reference**

**Growth factors**
A systematic review by Buchberger et al. (2010) for the German Agency for Health Technology Assessment examined the benefit of therapy with growth factors, alone or in combination with other technologies, in the treatment of diabetic foot ulcers. A total of 25 studies were included (14 RCTs, 9 cost-effectiveness analyses and 2 meta-analyses), with study populations ranging in size from 17 to 382 patients and study duration ranging from 12 to 20 weeks.

The authors noted that differences in standard wound care complicated the comparison of study results. They stated that the small sample sizes, methodological flaws with high potential for bias, and short duration of treatment and follow-up meant that the validity of results with regard to effectiveness and cost-effectiveness should be considered limited. The evidence is therefore unlikely to have an impact on NICE CG119.

**Key reference**

**Hyperbaric oxygen therapy**
A Cochrane review by Kranke et al. (2012) assessed the use of hyperbaric oxygen therapy for chronic wounds with similar treatment without hyperbaric oxygen. A total of 9 RCTs were included (n=471), of which 8 (n=455) involved diabetic foot ulcers and 1 involved venous ulcers.

Pooled data showed an increase in the rate of ulcer healing after 6 weeks of hyperbaric oxygen therapy compared with control treatment (RR=5.20, 95% CI 1.25 to 21.66, p=0.02; 3 RCTs, n=140 [38% of the total people with diabetes in the review]). However, there was no benefit evident on longer term follow up. For ulcers healed after 6 months, no difference from control was found (RR=1.70, 95% CI 0.90 to 3.20, p=0.10; 2 RCTs, n=112 [30% of the total people with diabetes in the review]). For healing of ulcers after 1 year, no significant difference was found between groups (RR=0.93, 95% CI 0.44 to 207.76, p=0.15; 3 RCTs, n=212 [58% of the total people with diabetes in the review]) although analysis was complicated by the reporting of results as failure to heal (rather than ulcers healed) and by no healed ulcers in the control arms in two of the studies. There was also no significant difference found in major amputation rate (RR=0.36, 95% CI 0.11 to 1.18; 5 RCTs, n=312).

Although the authors noted methodological shortcomings in the trials, they concluded that there may be evidence for a significant improvement in short-term ulcer healing with hyperbaric oxygen therapy, but not in the longer term. The authors suggested that adequately powered and designed trials are required to evaluate the appropriate use of hyperbaric oxygen.

The systematic review by Game et al. (2012) (see ‘Negative pressure wound therapy’ in this section for details), identified 3 studies on the use of hyperbaric oxygen therapy, including 1 RCT considered high quality that demonstrated significantly improved outcomes following the intervention, with healing within 12 months significantly more likely than in the control group (52% vs 27%, p=0.03). The intervention group included patients with either no evidence of peripheral arterial disease or who were deemed unsuitable for vascular reconstruction. The authors concluded that there is some evidence that may justify the use of hyperbaric oxygen therapy, although further work is required to define the population most likely to benefit from the approach.

Taken together, although suggesting potential benefits of hyperbaric oxygen, the limited nature of this evidence means it is unlikely to have an impact on NICE CG119. Further work, in line with the NICE research recommendation to determine the clinical and cost effectiveness of hyperbaric oxygen therapy, is still needed.
Key reference

Other adjunctive treatments
The systematic review by Game et al. (2012) (see ‘Negative pressure wound therapy’ in this section for details), found no new studies in the categories of sharp debridement and wound bed preparation with larvae and hydrotherapy, and resection of the chronic wound. Additional studies did not provide evidence to justify the use of treatment in the following categories: wound bed preparation using antisepsics, applications and dressing products; products designed to correct aspects of wound biochemistry and cell biology associated with impaired wound healing; application of cells, including platelets and stem cells; bioengineered skin and skin grafts; electrical, electromagnetic, lasers, shockwaves and ultrasound; and other systemic therapies.

For all these other adjunctive treatments, the evidence appears consistent with the recommendation of NICE CG119 to restrict current use to clinical trials.

Surgical management to prevent amputation
During the development of NICE CG119, evidence was reviewed on the optimal time for surgical management (including revascularisation and orthopaedic interventions) to prevent amputation for diabetic foot problems. However, no appropriate studies were identified so no recommendations on this issue were made. Two reviews recently considered surgical management to salvage limbs that may otherwise require amputation, although neither addressed the specific issue of optimal time for the intervention.

Hinchcliffe et al. (2012) performed a systematic review of the effectiveness of revascularisation of the ulcerated foot in patients with diabetes and peripheral arterial disease. A total of 49 studies (n=8290) were identified, comprising 3 non-randomised studies with an intervention and a control group (all considered of low quality and potentially subject to significant bias) and 46 case series.

Although limb salvage data was reported in the majority of studies included in the review, it was not always clearly defined. Following open surgery, the median limb salvage rate was 85% after 1 year (interquartile range [IQR] 80% to 90%; n=19 studies), 82% after 3 years (IQR 79.5% to 90%, n not reported), and 78% after 5 years (IQR 74% to 78%, n not reported). Following endovascular revascularisation, the median limb salvage rate was 78% after 1 year (IQR 70.5% to 85.5%, n not reported) and 76% after 3 years (IQR 72% to 78.5%, n=4 studies); after 5 years, 2 studies reported limb salvage rates of 56% and 77% respectively.

The authors noted that interpretation of studies demonstrating the effectiveness of revascularisation was hampered by the lack of matched control groups that did not receive the intervention, poor description of the severity of peripheral arterial disease and wound characteristics, lack of information on the indications and timing of interventions, and the poorly defined natural history of patients with peripheral arterial disease and foot ulcers. The authors concluded that there was insufficient evidence to recommend one method of revascularisation over another. They noted the need for properly controlled studies with a well-described population and outcomes that are relevant to patients with diabetes.

A systematic review by Fitzgerald O’Connor et al. (2011) examined use of free tissue transfer techniques to reduce the requirement for amputation in patients with diabetes. A total of 18 studies (n=528, of which 449 had diabetes) were included, comprising 4 prospective and 14 retrospective case series involving 543 free tissue transfers for lower limb wounds. Study sizes ranged from 9 to 79 cases, with the largest study accounting for 14.5% of the patients. Participants in all studies had undergone debridement of devitalised soft tissue and
infected bone prior to free tissue transfer. Of the flap types used across the studies, 63% were muscle-based, 35% were fasciocutaneous and 1.7% were omental. Lower leg revascularisation was carried out alongside free tissue transfer in 66% of patients (17 studies).

Pooled in-hospital mortality (reported in all 18 studies) was 4.4%. Pooled 30-day mortality was 3.9% (95% CI 1.5 to 6.2%). Pooled minor complication rate (wound infection, minor flap edge necrosis, haematoma) was 34% (95% CI 20.8 to 48.5%) and pooled major complication rate (flap loss, amputation, myocardial infarction, death) was 16% (95% CI 10.2 to 21%). The combined average flap survival rate was 91.9% (95% CI 87.5 to 96.1%). All 18 studies also reported limb salvage rate (average 83.4%, 95% CI 77.1 to 89.7) for a pooled average follow up time of 28 months (range 1 to 68 months).

No formal quality assessment of studies was conducted, and the authors noted that standard reporting criteria and validated diabetic ulcer scoring systems were not used, making it difficult to compare studies directly. Only 1 study described the total number of patients assessed for free tissue reconstruction and deemed unsalvageable, and there was little information about selection criteria for patients considered suitable for the intervention. Nevertheless, the authors concluded that free tissue transfer achieves successful wound healing in selected patients with wounds that would have required amputation. They suggested that pre-operative optimisation of vascular supply and eradication of infection are important contributors to success of the procedure. Free tissue transfer is not specifically discussed in NICE CG119 and may only be offered in specialist centres with both plastic and vascular surgeons.

Overall, the evidence from both reviews is unlikely to impact NICE CG119, but provides useful information about emerging therapeutic approaches to limb salvage. The absence of clear evidence about timing of interventions also reinforces the NICE research recommendation about impact of early revascularisation on outcomes.

**Key references**


### 1.8 Assessment of suspected limb ischaemia

**Ankle–brachial pressure index**

NICE CG119 recommends the measurement and documentation of the ankle-brachial pressure where clinically possible, ensuring careful interpretation of the results.

A study by Aerden et al. (2011) evaluated the diagnostic value of the ankle–brachial pressure index (ABPI), the contribution of arterial calcifications to any unreliability of the ABPI, and the role of the distribution of atherosclerotic lesions. A total of 187 lower extremities were assessed, in patients from a single site in Belgium with diabetic foot problems and a high suspicion of peripheral arterial disease.

The authors postulated that an ABPI that incorporated information about below-the-knee arteries was more likely to correlate with atherosclerotic disease. Therefore the standard ABPI (calculated by dividing the highest pressure of the 2 below-the-knee arteries by the highest pressure of both brachial arteries) was compared with lowest pressure ABPI (calculated by using the lowest pressure as numerator) and with average pressure ABPI
(calculated by using the average of both pressures while assuming a pressure of zero for arteries that were not found by Doppler). The Pearson coefficient, r, was used to assess correlation (r≥−0.5 defined as weak and r<−0.8 defined as strong).

The ABPI could not be determined in 64 of the 187 patients (34.2%). Two below-the-knee arterial measurements were obtained in 106 patients, with a difference of more than 20 mmHg in 40 (37.7%) of these cases. Mean ABPI was 0.91 using the standard method, 0.82 using lowest pressure and 0.83 using the average pressure. Calcifications were moderate or heavy in 57.7% of patients.

The correlation between standard ABPI and angiographic atherosclerosis was weak (r=−0.487), increased with lowest pressure ABPI (r=−0.554) and was highest using the average pressure ABPI (r=−0.534) that used all the available information about below-the-knee arteries. For all methods of ABPI calculation, correlation was consistently better for patients with no or light calcification (r=−0.540, −0.572 and −0.605, for standard, lowest pressure and average pressure ABPI respectively) than for those with moderate or heavy calcification (r=−0.397, −0.446 and −0.461 respectively). The results may be limited by the retrospective nature of the study, and the number of patients and sites involved. Furthermore, this was a high risk population, so the results need to be interpreted with caution.

This study provides limited evidence that ABPI may not be measurable in approximately a third of patients, and may underestimate atherosclerotic disease, particularly in patients with calcification present. It also indicates that average pressure ABPI may be more useful than highest or lowest pressure measurements. The evidence is consistent with the recommendation in NICE CG119 that ABPI results should be interpreted carefully.

**Key reference**

**Areas not currently covered by NICE guidance**

**Prevention of diabetic foot problems**

NICE CG119 focuses on the management of inpatients with diabetic foot problems, but does not address the primary or secondary prevention of these diabetic complications.

**Improved glycaemic control**

A meta-analysis by Adler et al. (2010) examined the association between risk of lower extremity amputation and glycaemic control, as measured by level of glycated haemoglobin (HbA1c) assessed at least an average of 6 months before an amputation. A total of 14 prospective epidemiological studies were included involving 1227 lower extremity amputations in 94,640 people with diabetes without acute foot ulceration, previous history of amputation or end stage renal disease.

The risk of lower extremity amputation increased as glycaemic control deteriorated. For each percentage point increase in HbA1c, the overall relative risk of a lower extremity amputation was 1.26 (95% CI 1.16 to 1.36). No statistically significant difference (p=0.09) in risk was observed between patients with type 1 (RR=1.18, 95% CI 1.02 to 1.38) and type 2 diabetes (RR=1.44, 95% CI 1.25 to 1.65).

The analysis has some limitations. Some of the included studies were initiated in the 1970s or early 1980s, and therefore the levels of HbA1c may not reflect those obtained in modern practice. Furthermore, the measurement of HbA1c at a single point in time may have limited significance, and may be expected to change with subsequent management. The authors also acknowledged potential bias from inadequate adjustment for confounding,
misclassification of diabetes type, and inaccurate estimates of risk. Additionally, outcomes other than amputation may be negatively affected by tight glycaemic control.

In the absence of conclusive data from clinical trials, the evidence suggests that improved glycaemic control may be associated with reduced risk of amputation, however firm conclusions about a causal link cannot be made from these results and there is unlikely to be an impact on NICE CG119. NICE clinical guidelines on type 1 (NICE CG15) and type 2 diabetes (NICE CG87) should be referred to for recommendations about glycaemic control.

Key reference

Complex interventions for preventing diabetic foot ulcers
A Cochrane review by Dorresteijn et al. (2011) assessed the effectiveness of complex interventions in the prevention of foot ulcers in people with diabetes compared with single interventions, usual care or alternative complex interventions. Complex interventions were defined as an integrated care approach combining 2 or more prevention strategies on at least 2 levels of care: the patient (such as patient education), the healthcare provider (such as patient risk assessment and referral), and/or the structure of healthcare (such as a multidisciplinary team). RCTs and cluster RCTs, in patients with type 1 or 2 diabetes in any setting and with an explicit focus on foot ulceration, were included. Studies where the only aim was optimising blood glucose level were excluded. Five RCTs were identified by the analysis (n=4949), including 2 studies conducted in the UK. The heterogeneity of the studies precluded pooled analysis.

One study (n=2001) conducted in a UK secondary care setting reported a significant and cost-effective reduction in lower extremity amputations with an intensive and comprehensive complex intervention compared with usual care (RR=0.30, 95% confidence interval [CI] 0.13 to 0.71), although there was no difference in incidence of foot ulceration (RR=0.69, 95% CI 0.41 to 1.14). Other studies showed little evidence of benefit of an education-centred or other more complex interventions.

Limitations of the evidence noted by the authors included that all studies in the review were considered at high risk of bias, meeting few predefined measures of quality. The authors also discussed the considerable differences between the studies in terms of healthcare setting, type of intervention and reported outcomes, and therefore indicated that results should be interpreted with caution. Additionally, none of the included studies were in an inpatient setting.

The authors concluded that there is no high-quality research evaluating complex interventions for preventing diabetic foot problems, and there is insufficient evidence of benefit. Limitations with currently available evidence (including the absence of studies specifically on inpatients with diabetic foot problems) prevent firm conclusions so there is unlikely to be any impact on NICE CG119. Better quality research, in relevant settings, is needed to investigate the efficacy of complex interventions for prevention of diabetic foot problems.

Key reference

Other preventative interventions
Arad et al. (2011) reported a systematic review of RCTs to assess prevention of diabetic foot ulcers in patients with a neuropathic or insensate foot at high risk of ulcer development. A total of 12 RCTs examining both primary and secondary prevention were included in the review (total number of participants not stated). There were 4 studies on patient education and intensive monitoring, 3 studies on use of therapeutic footwear or insoles, 3 studies on
temperature-guided avoidance therapy, and individual studies on surgical bone debridement and on Achilles tendon lengthening.

Of all the preventive methods, only foot-temperature guided avoidance therapy was found to be beneficial, although meta-analysis was not carried out. In all 3 studies (n=483) examining this approach, patients were instructed to contact their healthcare professional and decrease activity if self-monitored temperature showed a difference of more than 4°F compared with the same site on the other foot. Each of the studies reported a positive impact of the intervention, although a statistical analysis was presented for only 1 of these studies (odds ratio for new complications=10.3, 95% CI 1.2 to 85.3, p=0.01; n=85).

The authors considered that most studies were of low quality, particularly those reporting positive findings. The limited nature of the evidence base for interventions to prevent ulceration, above and beyond assessment and management of neuropathy, means there is unlikely to be an impact on NICE CG119.

**Key reference**

Arad Y, Fonseca V, Peters A et al. (2011) *Beyond the monofilament for the insensate diabetic foot*. Diabetes Care 34: 1041–6

**Assessment of health-related quality of life**

Although NICE CG119 notes the significant impact that diabetic foot problems may have on patients’ quality of life, recommendations about its measurement were not made. The ‘Guide to the methods of technology appraisal’ (NICE 2008) states that the EuroQoL 5D Health Utility Index (EQ-5D) is the preferred measure of health-related quality of life in adults.

Hogg et al. (2012) reported a systematic review of 53 papers (number of participants not stated) to evaluate tools used to assess health-related quality of life in patients with diabetes-related foot disease, and to identify the impact of each foot problem on quality of life. The 36-item generic tool, Short-Form Health Survey (SF-36) was the most commonly used measure, reported in 27 studies. The measure showed efficacy in assessing health-related quality of life in diabetes-related foot disease, and sensitivity when correlating scores with severity of diabetic foot ulcers and neuropathy. Although the measure was also able to show changes over time, the review indicated that it lacked specificity and may be confounded by other (non-foot) complications of diabetes. The utility form of SF-36 (SF-6D) lacks NICE approval. Only 4 studies were identified using the NICE-preferred measure of utility, EQ-5D. The disease-specific and wound-specific tools showed limitations and fail to encompass the full spectrum of diabetes-related foot disease.

The authors concluded that no one measure was identified as the ‘gold standard’ for assessing health-related quality of life in people with diabetic foot problems, and each tool has limitations. Although this evidence is unlikely to have an impact on NICE CG119, it may provide useful information for clinicians and researchers. Areas identified for further development included the most valid disease-specific instrument, measures of health-related quality of life relating to minor and major amputations, and the role of tools to measure health-related quality of life in routine clinical care.

**Key reference**


**Supporting reference**

2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified for the NHS Evidence UK Database of Uncertainties about the Effects of Treatments (UK DUETs).

Patient information and support
- Patient education for preventing diabetic foot ulceration

Management of diabetic foot ulcers

**Debridement, dressings and off-loading**
- Effectiveness of debridement of diabetic foot ulcers
- Hydrogel dressings for healing diabetic foot ulcers
- Is there any evidence to support the use of silver dressing products?
- Foam dressings for healing diabetic foot ulcers
- Hydrocolloid dressings for healing diabetic foot ulcers
- Alginate dressings for healing foot ulcers

**Adjunctive treatments**
- Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus
- Hyperbaric oxygen therapy for chronic wounds

**Surgical management to prevent amputation**
- Optimal method of revascularisation of the ulcerated foot in patients with diabetes and peripheral arterial disease

**Assessment of suspected limb ischaemia**
- Optimal method of diagnosis of peripheral arterial disease in patients with diabetes related foot disease

**Areas not currently covered by NICE guidance**

**Prevention of diabetic foot problems**
- Complex interventions for preventing diabetic foot ulceration
- What is the benefit of temperature measurements in patients with or at risk of diabetic foot who have not yet lost the sensation to SWM (Semmes-Weinstein monofilament) sensation?

**Assessment of health-related quality of life**
- Optimal patient reported outcome measurement of health related quality of life in diabetic foot patients

Further evidence uncertainties for inpatient management of diabetic foot problems can be found in the UK DUETs database and in the NICE research recommendations database.

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.
Appendix A: Methodology

Scope
The scope of this Evidence Update is taken from the scope of the reference guidance:


Searches
The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 24 February 2010 (the end of the search period for NICE clinical guideline 119) to 1 October 2012:

- AMED (Allied and Complementary Medicine Database)
- BNI (British Nursing Index)
- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- DARE (Database of Abstracts of Reviews of Effects)
- EMBASE (Excerpta Medica database)
- HMIC (Health Management Information Consortium) database
- HTA (Health Technology Assessment) database
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- NHS EED (Economic Evaluation Database)
- PreMEDLINE
- PsycINFO

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for RCTs and systematic reviews. Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from contactus@evidence.nhs.uk

There is more information about how NICE Evidence Updates are developed on the NHS Evidence website.

Table 1 MEDLINE search strategy (adapted for individual databases)

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Figure 1 Flow chart of the evidence selection process

EUAG – Evidence Update Advisory Group
Appendix B: The Evidence Update Advisory Group and Evidence Update project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

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