NICE National Institute for Health and Care Excellence

Appendix A4: Summary of evidence from surveillance

2019 surveillance of diabetic foot problems: prevention and management (2015) NICE guideline NG19

Contents:

Evidence considered in surveillance

Search and selection strategy

We searched for new evidence related to specific parts of the guideline. A focused search was undertaken for diabetic foot problems.

We found 46 studies in a search for RCTs and systematic reviews published between 01 August 2014 and 21 February 2019.

We also included:

- 2 relevant studies from a total of 7 identified by topic experts, these were also identified in our search.

From all sources, we considered 46 studies to be relevant to the guideline.

See summary of evidence from surveillance below for details of all evidence considered, and references.

Selecting relevant studies

Due to the large number of studies identified in the initial search, the following strategies were taken to ensure only relevant studies were selected:

- Studies with a sample size lower than 50 were excluded.
- Pilot studies were excluded

- Systematic reviews (with the exception of Cochrane reviews) were excluded

Ongoing research

We checked for relevant ongoing research; of the ongoing studies identified, 1 study was assessed as having the potential to change recommendations; therefore, we plan to check the publication status regularly, and evaluate the impact of the results on current recommendations as quickly as possible. This study is:

- Comparing treatments for diabetic foot ulcers

Intelligence gathered during surveillance

Views of topic experts

We sent questionnaires to 20 topic experts and received 7 responses. The topic experts were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty.

All 7 topic experts agreed that no update to the guideline is needed at this time. Topic experts highlighted that there have been no substantial changes in this area for any age group and commented that the guideline remains current and relevant in clinical practice.

Other sources of information

We considered all other correspondence received since the guideline was published. Several studies were highlighted on the guideline issue log, and also identified in our search for new evidence. This included topical antimicrobial use and wound healing trials, which were included in the evidence summary, and Granexin gel, for which no new evidence was found.

Summary of evidence from surveillance

Studies identified in searches are summarised from the information presented in their abstracts.

Feedback from topic experts who advised us on the approach to this surveillance review, was considered alongside the evidence to reach a view on the need to update each section of the guideline.

A full list of guideline recommendations can be found on the website at the following link: https://www.nice.org.uk/guidance/ng19

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

Surveillance proposal

No new information was identified.

This section of the guideline should not be updated.

1.2 Care across all settings

Surveillance proposal

No new information was identified.

This section of the guideline should not be updated.

1.3 Assessing the risk of developing a diabetic foot problem

Surveillance proposal

No new information was identified.

This section of the guideline should not be updated.

1.4 Diabetic foot problems

Surveillance proposal

No new information was identified.

This section of the guideline should not be updated.

1.5 Diabetic foot ulcer

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

Casts and offloading devices

We identified 4 RCTs(1–4) evaluating casts and/or offloading devices for the treatment of diabetic foot ulcers (see table 1).

The interventions evaluated in the evidence included:

- Total contact casts
- Lightweight fibreglass casts
- Custom-made knee-high casts
- Removable walking casts

Overall improvements were seen with total contact casts for the outcomes of time to ulcer healing and proportion of ulcers healed, and with removable walking casts for the outcomes of non-severe adverse events and patient acceptance. No improvements were seen with total contact casts for mean healing time or non-severe adverse events, or with fibreglass casts/custom casts for the outcome of proportion of ulcers healed.

Grafting

We identified 2 RCTs(5,6) and 1 Cochrane(7) review assessing grafting for the treatment of diabetic foot ulcers (see table 2).

Improvements were seen with the human acellular dermal matrix, DermACELL for proportion of completely healed wounds compared to usual care, but not when compared to a second acellular dermal matrix called Graftjacket.

Recurrence rate and appearance of the wound improved at 12 months when split thickness skin grafting (STSG) plus acellular dermal matrix was compared to STSG alone. However, no improvements were seen for rate of complete wound closure or complications at 4 weeks post graft.

Improvements were seen in healing rate and incidence of lower limb amputation when skin grafts or tissue replacements were compared to usual care, with no difference in adverse events seen.

Oxygen therapy and negative pressure

We identified 5 RCTs(8–12) and 3 Cochrane reviews(13–15) assessing casts and/or offloading devices for the treatment of diabetic foot ulcers (see table 3).

Overall, the evidence indicated that:

- Improvements were seen in wound healing using active continuous oxygen diffusion therapy compared to moist wound therapy (2 studies).
- Negative pressure wound therapy improved the number of wounds healed compared to wound dressings alone.
- Hyperbaric therapy improved the rate of ulcer healing but not health related quality of life (HRQoL).
- Ozone therapy improved ulcer surface area compared to antibiotic treatment, however no improvements were seen when compared to usual care for ulcer surface area, or for either comparator for number of ulcers healed.
- Transdermal continuous oxygen therapy or daily breathing of oxygen at 244 kPa for 90 minutes did not improve wound healing compared with control.

Additional therapies

We identified 2 RCTs(16,17) and 1 Cochrane review(18) assessing additional therapy interventions for the treatment of diabetic foot ulcers (see table 4).

Shockwave therapy

Focused extracorporeal shockwave therapy (ESWT) plus standard care improved the number of ulcers healed compared to sham therapy plus standard care.

Phototherapy

A Cochrane review found that phototherapy improved complete wound healing compared to no phototherapy or usual care.

Helium-neon laser therapy plus usual care did not improve ulcer surface area compared to infrared laser therapy plus usual care in one small RCT.

Prevention

We identified 1 Cochrane review(19) assessing the prevention of diabetic foot ulcers (see table 5).

Intensive complex interventions (no further information stated) were found to have improvements over usual care for the outcomes of cost-effectiveness (1 study), amputations (2 studies) and foot ulcers (1 study).

Supplements

We identified 7 RCTs(20–26) assessing the use of supplements for the treatment of diabetic foot ulcers (see table 6).

Improvements in ulcer size and depth were observed in studies examining vitamin D, omega-3 fatty acids from flaxseed oil, probiotics, magnesium oxide, magnesium oxide plus vitamin E and zinc sulphate compared to a placebo.

No improvements were seen for arginine, glutamine and beta-hydroxy-beta-methylbutyrate supplementation for either total wound closure or time to wound healing.

Telemedicine

We identified 2 RCTs(27,28) assessing telemedicine monitoring and follow up care for people with diabetic foot ulcers (see table 7).

The evidence found for telemedicine was mixed for the outcome of amputations, however no benefits of telemedicine were seen for any other outcome.

Topical treatments

We identified 9 RCTs(29–38) and 3 Cochrane reviews(39–41) assessing topical treatments for diabetic foot ulcers (see table 8).

The following interventions improved ulcer healing and ulcer size when compared to a placebo or usual care alone:

- Single application acellular dermal matrix (D-ADM),
- Tri-layer porcine small intestine submucosa,
- Autologous platelet-rich plasma (PRP), dehydrated human amnion/chorion membrane allograft,
- LeucoPatch device plus usual care, recombinant human epidermal growth factor (rhEGF)
- 11 different growth factors (from a Cochrane review).

Improvements in complete ulcer closure were seen when the integra dermal regeneration template was compared to sodium chloride gel.

Viable cryopreserved placental membrane improved the number of ulcers healed and average cost per patient when compared to a human fibroblast-derived dermal substitute.

Number of wounds completely healed at 12 weeks was improved with the use of EpiCord (dehydrated human umbilical cord allograft) compared to alginate wound dressings.

The following interventions did not improve outcomes when compared with usual care:

- Clostridial collagenase ointment
- Honey.

Wound dressings

We identified 4 RCTs(42–45) and 1 Cochrane review(46) assessing the use of wound dressings for diabetic foot ulcers (see table 9).

Improvements in time to wound closure, proportion of ulcers healed and time to ulcer healing was seen for graffix (a human viable wound matrix), Epifix and wound dressing with sucrose octasulfate compared to usual care, a control dressing or Apligraf (Epifix only).

No clear differences were seen when various wound dressings were compared to each other in the Cochrane review.

Intelligence gathering

Initial intelligence gathering highlighted MTG17 The Debrisoft monofilament debridement pad for use in acute or chronic wounds which recommends the use of the Debrisoft monofilament debridement pad for both acute and chronic wounds, this is linked in the diabetic foot pathway.

MTG42 UrgoStart for treating leg ulcers and diabetic foot ulcers supports the use of the UrgoStart dressing for diabetic foot ulcer treatment. NG19 does not currently specify what type of wound dressing should be used, however MTG42 is linked within the diabetic foot pathway.

An NIHR study is being tracked which aims to compare treatments for diabetic foot ulcers. This trial aims to compare 4 different interventions over 5 comparison groups, including usual care, hydrosurgical debridement, decellularized dermal allograft and negative pressure wound therapy.

The 2018 National Diabetic Foot Audit was highlighted during stakeholder consultation, this has now been replaced by the 2019 edition. The conclusions of the audit broadly support the recommendations in NG19, particularly in areas such as referral time and involvement of multidisciplinary foot care service. The audit highlighted that around 50% of people could not access an 'urgent' referral as there was no pathway in place to support this, however over 80% of people accessed a next working day service.

Impact statement

Casts and offloading devices

Recommendation 1.5.5 currently suggests a non-removable cast should be offered to people with non-ischaemic, uninfected fore or mid foot ulcers, with offloading also being an option for general treatment of diabetic foot ulcers in recommendation 1.5.4. The evidence found at this review suggests patients' acceptability was improved with a removeable device, however this did not correlate with improved ulcer healing. As removable devices did not show an improvement in ulcer healing, the guideline will not be updated in this area until evidence of benefits from this intervention is shown.

Grafting

Recommendation 1.5.11 states to consider the use of dermal or skin substitutes in addition to standard care when healing has not progressed with standard care alone. The evidence found at this review suggests that an acellular dermal matrix offers improvements in wound healing over usual care or a placebo. Different dermal matrix products were used in the 3 studies and all had significant improvements in either wound healing rate or 12-month ulcer recurrence or both. As no specific product was superior in these comparisons, the current recommendation stating to consider dermal substitutes is sufficient.

Oxygen therapy and negative pressure

Recommendation 1.5.9 states to consider negative pressure wound therapy under the advice of a multidisciplinary foot care team. One study found that number of wounds healed was significantly increased with negative pressure therapy compared to wound dressings alone. This supports recommendation 1.5.9, no further evidence was found to suggest any changes are required to the recommendation at this time.

Recommendation 1.5.12 states that hyperbaric oxygen therapy should not be used outside the context of a clinical trial. The evidence found at this review found both advantages and disadvantages with each oxygen-based therapy. Hyperbaric therapy improved ulcer healing rate but not HRQoL, ozone therapy improved ulcer surface area but not when compared to usual care. No improvements were seen for breathing concentrated oxygen, however wound directed active continuous oxygen diffusion improved number of wounds healed and rate of ulcer closing. The results found at this review span a number of different interventions, with no clear evidence of superiority. This supports the current recommendations and does not suggest any changes are needed at this time.

Additional therapies

Focused shockwave therapy plus usual care improved the number of ulcers healed compared to a sham device plus usual care. There are currently no recommendations on shockwave therapy in NG19. A comparison between shockwave therapy and other treatment options would be required before an impact on the recommendations could be assessed, as this trial compared to a placebo only.

Phototherapy was found to improve complete wound healing in a Cochrane review, with helium-neon laser therapy showing no improvement over usual care. There are currently no recommendations covering either of these additional therapies. As the evidence is inconclusive no impact is anticipated at this time. In addition, the Cochrane review had a small number of participants included in its meta-analysis and as such further evidence would be required to confirm the results.

Prevention

A Cochrane review found that intensive complex interventions to prevent diabetic foot ulcers led to improvements in cost-effectiveness, amputation rates and foot ulcers. As the abstract did not disclose the nature of these interventions, they may or may not already be included in the guideline recommendations. No impact is anticipated at this time.

Supplements

Six supplements were found to improve ulcer size and depth, with one showing no difference over standard care for total wound closure or healing time. There are no recommendations for supplements as a treatment strategy, however recommendation 1.2.4 states that nutritional services should be included in the multidisciplinary foot care team. Further studies are required with comparisons between supplements, as the evidence found at this review involved placebo comparison only. No impact is anticipated at this time.

Telemedicine

The use of telemedicine for monitoring showed no advantage over standard outpatient care, with only amputation rate having an improvement when telemedicine follow up in primary care was used. Telemedicine is not currently included in the recommendations. The evidence found at this review supports this and no impact is anticipated.

Topical treatments

The evidence found at this review suggests that the majority of topical treatments result in a significant improvement in one or more of: ulcer healing, ulcer size, ulcer depth, complete ulcer closure and number of ulcers healed. This included autologous PRP (1 Cochrane review) and growth factors (1 RCT, 1 Cochrane review) and the LeucoPatch device (highlighted by a topic expert). Recommendation 1.5.12 currently states that autologous PRP and growth factors should not be used outside the context of a clinical trial. The review for autologous PRP was a small part of a full Cochrane review, the majority of studies in the review were on other factors, and as such further studies are required where this is the primary intervention method. The studies on growth factors were primarily using platelet derived products, with improvements seen for all of the products used. The authors of the Cochrane review noted a high risk of systemic bias and as such further evidence would be required in this area before a change to the recommendations would be considered.

Wound dressings

A number of wound dressings showed improvements in proportion of ulcers healed, time to wound healing, complete wound closure at 12 weeks and adverse events when compared to usual care or a placebo dressing, however little evidence was found comparing these dressings to each other. Wound dressings are included in recommendations 1.5.4 and 1.5.10, however no specific type of dressing is suggested. The evidence found at this review supports the use of wound dressings as an intervention rather than a specific product. No impact is anticipated at this time.

Overall conclusions

Overall, the evidence found at this surveillance review showed a number of positive improvements with the variety of interventions studied. A large number of these support existing recommendations. Where new treatment options were found, the evidence was thinly spread across multiple products, with no evidence of product superiority found. This is in line with topic expert feedback which suggested the new trials available would be unlikely to impact the current recommendations. An NIHR study is being tracked which aims to compare treatments for diabetic foot ulcers. This will be evaluated for impact on the guideline once results are available.

New evidence is unlikely to change guideline recommendations.

1.6 Diabetic foot infection

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

None found.

Intelligence gathering

An antimicrobial prescribing guideline (APG) for diabetic foot infection is currently in development which will impact the recommendations in this section. Systemic antibiotics have not been included in this surveillance review due to this in development guideline. For details on the proposed changes to recommendations 1.6.6 to 1.6.15 please see the evidence tab where all relevant documents will be stored for the diabetic foot infection APG.

An ongoing NIHR funded trial was highlighted by a topic expert comparing wound swab sampling with tissue sampling. This may impact on the APG recommendations which currently state to reassess antibiotic treatment according to antimicrobial susceptibility results. Several stakeholders during the consultation on the draft APG recommendations suggested that wound swabs do not necessarily give accurate results, as the causative organisms may be deeper within the wound rather than on the surface. The results for this trial will be assessed once available for any impact on the guideline recommendations.

Impact statement

Systemic antibiotics have not been included in this surveillance review due to the development antimicrobial prescribing guideline (APG) for diabetic foot infection.

New evidence is unlikely to change guideline recommendations.

1.7 Charcot arthropathy

Surveillance proposal

No new information was identified.

This section of the guideline should not be updated.

Research recommendations

Research recommendation	Summary of findings
Does intensive monitoring of people at risk of diabetic foot disease reduce the morbidity associated with developing the disease and is such monitoring cost effective?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
When and with what criteria should people with diabetes be referred to the foot protection service or the multidisciplinary foot care service?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
What is the role of educational models and psycho-behavioural interventions in prevention of diabetic foot complications?	A Cochrane review was found that included educational components as part of multi-component interventions, however it was difficult to draw conclusions specific to patient education.
What strategies may be useful in the prevention of Charcot arthropathy?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
What is the clinical effectiveness of different dressing types in treating diabetic foot problems?	Evidence was found relating to a number of different wound dressings however no evidence of product superiority was found, evidence was thinly spread across multiple dressings, with many trials comparing dressings to a placebo rather than current practice.
What is the effectiveness of different footwear, insoles and orthoses in the prevention of foot problems?	Evidence was found relating to casts and offloading, however benefits were not seen for ulcer healing for removable devices.
How often should people with diabetic foot problems (foot ulcers, soft tissue infections, osteomyelitis or gangrene) be reviewed?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
What is the clinical effectiveness of negative pressure wound therapy in the treatment of diabetic foot ulcers?	Evidence from 1 study was found relating to negative pressure therapy which supports the current recommendation. Further studies are required in this area to confirm the results.

Research recommendation	Summary of findings
What is the clinical effectiveness of maggot debridement therapy in the debridement of diabetic foot ulcers?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
Which risk stratification tools can be used to predict the likelihood of Charcot arthropathy?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
When is it safe to stop contact casting in the treatment of acute Charcot arthropathy?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
Within the hospital based MDT, when is it appropriate and effective to refer people with diabetes who have foot problems to specialist services such as investigative or interventional radiology, orthopaedic or vascular services, specialist pain management and specialist orthotics?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Data summary tables

Key to the tables

Type of study: CR = Cochrane review; RCT = randomised controlled trial

n = number of participants. The number of participants was not always reported in the abstract. For Cochrane reviews the number of studies is entered.

Table 1 – Casts and offloading

Study	Type	n	Intervention	Comparator	Outcome	Result
Lavery, L. A et al (2015)(1)	RCT	73	Total contact casts	Healing sandals	Proportion of ulcers healed	No improvement with intervention
					Time to ulcer healing	Improvement with intervention

Study	Type	n	Intervention	Comparator	Outcome	Result
			Total contact casts	Shear-reducing footbed boot	Proportion of ulcers healed	Improvement with intervention
					Time to ulcer healing	No improvement with intervention
Jeffcoate, W.; et al. (2017)(2)	RCT	425	Lightweight fibreglass cast plus usual care	Usual care alone	Percentage of ulcers healed in 24 weeks	No improvement with intervention
Bus, S. A.; et al. (2018)(3)	RCT	60	Custom-made knee-high cast [BTCC]	Prefabricated ankle high forefoot-offloading shoe	Proportion of ulcers healed	No improvement with intervention
Piaggesi, A.; et al (2016)(4)	RCT	60	Total contact cast	Irremovable walking boot	Mean healing time	No improvement with intervention
					Non-severe adverse events	No improvement with intervention
				Removable walking cast	Mean healing time	No improvement with intervention
			Removable walking cast	Total contact cast	Non-severe adverse events	Improvement with intervention
					Patient acceptance	Improvement with intervention

Table 2- Grafting.

Study	Type	n	Intervention	Comparator	Outcome	Result
Walters, Jodi; et al. (2016)(5)	RCT	168	Human acellular dermal matrix DermACELL	Conventional care	Proportion of completely healed ulcers	Improvement with intervention
				Second acellular dermal matrix, Graftjacket	Proportion of completely healed ulcers	No improvement with intervention
Hu, Z.; et al. (2016)(6)	RCT	52	Split thickness skin grafting	STSG only	Recurrence at 12 months	Improvement with intervention

			(STSG) over acellular dermal matrix		Appearance and lower Manchester Scar Scale score	Improvement with intervention
					Rate of complete wound closure	No improvement with intervention
					Complications at 4 weeks post grafting	No improvement with intervention
Santema, T. B.; et al. (2016)(7)	CR	17 studies (n=1655)	Skin grafts or tissue replacement	Usual care	Healing rate	Improvement with intervention
					Adverse events	No improvement with intervention
		2 studies	Skin grafts or tissue replacement	Usual care	Incidence of lower limb amputation	Improvement with intervention

Table 3 -Oxygen therapies and negative pressure.

Study	Type	n	Intervention	Comparator	Outcome	Result
Driver, V. R.; et al. (2017)(8)	RCT	122	Transdermal continuous oxygen therapy (TCOT) + moist wound therapy	Sham device + moist wound therapy	Proportion of ulcers healed	No effect with intervention
Fedorko, L.; et al. (2016)(9)	RCT	103	Daily, 90 minutes of breathing oxygen at 244 kPa for 30 days (HBOT)	Placebo - daily breathing air at 125 kPa	Criteria for amputation met	No improvement with intervention
					Wounds healed	No improvement with intervention
Niederauer, M. Q.; et al. (2017)(10)	RCT	100	Active continuous oxygen diffusion therapy active CDO device	Placebo device providing moist wound therapy only	Wounds healed	Improvement with intervention
					Ulcer rate of closure	Improvement with intervention

Kranke, P.; et al. (2015)(13)	CR	12 studies, (n=577)	Hyperbaric oxygen therapy	Studies excluding HBOT (with or without sham therapy)	Rate of ulcer healing	Improvement with intervention
Li, G.; et al. (2017)(11)	RCT	103	Hyperbaric oxygen therapy	Sham	Health related quality of life	No improvement with intervention
Liu, J.; et al. (2015)(14)	CR	3 studies, (n=212)	Ozone therapy	Antibiotic treatment	Number of ulcers healed	No improvement with intervention
					Ulcer surface area	Improvement with intervention
				Usual care	Number of ulcers healed	No improvement with intervention
					Ulcer surface area	No improvement with intervention
Niederauer, Mark Q.; et al. (2018)(12)	RCT	100	Active continuous oxygen diffusion therapy active CDO device	Placebo device providing moist wound therapy only	Time to 50% ulcer closure	Improvement with intervention
					Proportion of ulcers healed	Improvement with intervention
Liu, Z.; et al. (2018)(15)	CR	5 studies, (n=486)	Negative pressure wound therapy	Wound dressings	Number of wounds healed	Improvement with intervention

Table 4 – additional therapies.

Study	Type	n	Intervention	Comparator	Outcome	Result
Snyder, Robert; et al. (2018)(16)	RCT	336	Focused extracorporeal shockwave therapy (ESWT) and standard care	Sham therapy and standard care	Proportion of ulcers healed	Improvement with intervention

Wang, H. T.; et al. (2017)(18)	CR	8 studies, (n=316)	Phototherapy	No phototherapy/usual care	Meta-analysis of 4 studies (n=116): Complete wound healing	Improvement with intervention
Tantawy, S. A.; et al. (2018)(17)	RCT	65	Helium-neon laser therapy + conventional therapy	Infrared laser therapy + conventional therapy	Ulcer surface area	No improvement with intervention

Table 5 – Prevention.

Study	Type	n	Intervention	Comparator	Outcome	Result
Hoogeveen, R. C.; et al. (2015)(19)	CR	6 studies, (n=5011)	Intensive complex interventions	Usual care	Cost-effectiveness	Improvement with intervention
					Amputations	Improvement with intervention
					Amputations and foot ulcers	Improvement with intervention

Table 6 – Supplements.

Study	Type	n	Intervention	Comparator	Outcome	Result
Armstrong, D. G.; et al. (2014)(20)	RCT	270	Arginine, glutamine and beta-hydroxy-beta-methylbutyrate drink for 16 weeks	Control drink	Total wound closure	No improvement with intervention
					Time to wound healing	No improvement with intervention
Razzaghi, R.; et al. (2017)(21)	RCT	60	50,000 IU vitamin D supplements every 2 weeks for 12 weeks	Placebo	Ulcer size and depth	Improvement with intervention

Soleimani, Z.; et al. (2017)(22)	RCT	60	1000 mg omega-3 fatty acids from flaxseed oil BD for 12 weeks	Placebo	Wound size and depth	Improvement with intervention
Mohseni, S.; et al. (2018)(23)	RCT	60	Probiotic	Placebo	Ulcer size and depth	Improvement with intervention
Razzaghi, R.; et al. (2018)(24)	RCT	70	250mg magnesium oxide tablet daily for 12 weeks	Placebo	Ulcer size and depth	Improvement with intervention
Afzali, Hassan; et al. (2019)(25)	RCT	57	250 mg magnesium oxide + 400 IU vitamin E daily for 12 weeks	Placebo	Ulcer size and depth	Improvement with intervention
Momen-Heravi, M.; et al. (2017)(26)	RCT	60	220mg zinc sulphate tablet daily for 12 weeks	Placebo	Ulcer size	Improvement with intervention

Table 7 - Telemedicine.

Study	Type	n	Intervention	Comparator	Outcome	Result
Rasmussen, B. S.; et al. (2015)(27)	RCT	374	Telemedical monitoring	Standard outpatient monitoring	Complete ulcer healing	No improvement with intervention
					Amputation	No improvement with intervention
					Death	No improvement with intervention
Smith-Strøm, H.; et al. (2018)(28)	RCT	182	Telemedicine follow up in primary care in collaboration with specialist health care	Standard outpatient care	Time to ulcer healing	No improvement with intervention
					Proportion of amputations	Improvement with intervention

Table 8 – Topical treatments.

Study	Type	n	Intervention	Comparator	Outcome	Result
Tettelbach, William; et al. (2019)(29)	RCT	155	EpiCord - dehydrated human umbilical cord allograft	Alginate wound dressings	number of wounds healed completely in 12 weeks	Improvement with intervention
Cazzell, S.; et al. (2017)(30)	RCT	168	Single application D-ADM (acellular dermal matrix)	Standard care	Proportion of closed ulcers remaining closed at 4 weeks post-termination	Improvement with intervention
Jimenez, Juan Carlos; et al. (2017)(31)	RCT	215	Clostridial collagenase ointment, 2 mm daily for 12 weeks	Usual care	Ulcer size	No improvement with intervention
Cazzell, Shawn M.; et al. (2015)(32)	RCT	82	Tri-layer procine small intestine submucosa	Standard care	Proportion of ulcers closed at 12 weeks	Improvement with intervention
Martinez-Zapata, M. J.; et al. (2016)(39)	CR	2 studies, (n=189)	Autologous platelet-rich plasma (PRP)	Usual care	Foot ulcer healing	Improvement with intervention
Ananian, Charles E.; et al. (2018)(33)	RCT	62	Viable cryopreserved placental membrane	Human fibroblast-derived dermal substitute	Proportion of ulcers healed	Improvement with intervention
					Average per patient costs	Improvement with intervention
Tettelbach, William; et al. (2019)(34)	RCT	110	Dehydrated human amnion/chorion membrane allograft	Standard care with alginate dressings	Percentage of ulcers completely healed	Improvement with intervention
					Time to healing	Improvement with intervention
Game, Frances; et al. (2018)(35)	RCT	269	LeucoPatch device + care	Standard care	Proportion of ulcers healed	Improvement with intervention
					Time to ulcer healing	Improvement with intervention

Park, K. H.; et al. (2018)(36)	RCT	167	0.005% recombinant human eidermal growth factor (rhEGF) spray, twice daily until ulcer healing or 12 weeks	Equivalent volume of saline spray	Complete wound healing	Improvement with intervention
					Wound healing speed	Improvement with intervention
					Median time to 50% wound closure	Improvement with intervention
Marti-Carvajal, A. J.; et al. (2015)(40)	CR	28 studies, (n=2365)	11 different growth factors plus standard care	placebo/ no growth factor plus standard care	Increased wound healing with any growth factor	Improvement with intervention
Jull, A. B.; et al. (2015)(41)	CR	2 studies, (n=93)	topical honey	not stated	Healing rate	No improvement with intervention
Driver, V. R.; et al. (2015)(37)	RCT	307	Integra Dermal Regeneration Template (IDRT)	0.9% sodium chloride gel	Complete ulcer closure	Improvement with intervention
Dumville, J. C.; et al. (2017)(38)	CR	945	antimicrobial dressings	non-antimicrobial dressings	number of ulcers healed	Improvement with intervention

Table 9 - Wound dressings.

Study	Type	n	Intervention	Comparator	Outcome	Result
Edmonds, M.; et al. (2018)(42)	RCT	240	Wound dressing with sucrose octasulfate	Wound dressing alone (same dressing)	Proportion of ulcers healed at 20 weeks	Improvement with intervention
Lavery, L. A.; et al. (2014)(43)	RCT	97	Grafix, human viable wound matrix	Usual care	Complete wound closure at 12 weeks	Improvement with intervention
					Time to wound closure	Improvement with intervention
					Adverse events	Improvement with intervention

					Wound related infections	Improvement with intervention
Zelen, C. M.; et al. (2015)(44)	RCT	60	Epifix	Apligraf	Proportion of ulcers healed	Improvement with intervention
					Time to ulcer healing	Improvement with intervention
				Standard care	Proportion of ulcers healed	Improvement with intervention
					Time to ulcer healing	Improvement with intervention
Edmonds, Michael E.; et al. (2018)(45)	RCT	240)	Sucrose octasulfate dressing + standard care	Control dressing (same dressing without sucrose octasulfate) + standard care	Proportion of ulcers healed	Improvement with intervention
Wu, L.; et al. (2015)(46)	CR	30 studies	various wound dressings	alternate dressings	difference in wound healing	Unclear

References

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