Appendix 3A – Characteristics of included studies/Risk of bias table summaries

1. Ali 2013 [1]	**Methods**	Randomized Clinical Trial Texas classification used.
	Participants	A) 35 (25M10F, age <50 yrs. = 10, age > 50 yrs. = 25, 7 smoking, 10 Hgba1c </= 7) B) 35 (23M/12F, age < 50yrs = 12, age > 50 yrs. = 23, 8 smoking, 9 Hgba1c </= 7) No statistical difference in demographics between both groups nor in initial glycemic or cholesterol control.
	Interventions	A) Cutimed Sorbact B) Standard Dressing (Saline cleansed povidone-soaked gauze dressing)
	Outcomes	No outcomes were reported that were targeted in this review.
	Notes	Outcomes reported in this study include comparison of foot inspection pre- and post-intervention (i.e. edema, pulse, temperature, skin color). Other outcomes included comparison of wound granulation and grade pre- and post-intervention, and wound changes and pain pre- and post-intervention (i.e. wound size, wound depth, and exudates). Reported that edema, impaired pulse, cold extremities, and abnormal skin color demonstrated better improvements in the study group. Improvements in granulation tissue and wound grade were reported in

		the study group. Reported that the study group patients had higher wound grades than control at study onset. These findings were found to be statistically significant differences. Wound size but not depth improved in the study group and was found to be statistically significant.
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Study Reports randomization of subjects but does not specifically identify the method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not Reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Low risk	The study reports blind assessment of the outcomes was done by trained nurses not involved in the study.
Incomplete outcome data (attrition bias)	Unclear risk	Not reported
Selective outcome reporting (reporting bias)	Low risk	Unclear if a protocol was prepared for this study. The outcomes discussed in the methods section were reported in the results. The point estimates reported in this study included dichotomous nominal cutoff values in lieu of mean point estimates it is unclear if the cutoffs assigned were arbitrary.
Other Bias	Unclear risk	The study text reports that 60 patients were enrolled in the study however the tables suggest that 70 were enrolled in the study.

2. Amini 2013[2]	**Methods**	Randomized Clinical Trial 6 months' duration or until complete wound healing Weekly wound evaluations (photo documentation) Plain x-rays and bone scan to exclude osteomyelitis
	Participants	40 patients from a diabetic foot ulcer clinic Hgba1c = 8.9 +/- 2.3 #patients, gender, mean age +/-SD, diabetes duration, smoker, BMI, PVD A) 20, 14M/6F, 55.3 +/- 9.5 yrs., 14.4 +/- 8.2 yrs., 0.05, 27.9, 0.60 B) 20, 10M/10F, 55 +/- 9.6 yrs., 15.2 +/- 6.2 yrs., 0.10, 28.7, 0.40 Reported that the only statistically significant difference was more heart disease in the ultrasound group.
	Interventions	A) Low frequency (20-60kHz) ultrasound assisted wound therapy + standard wound care B) Standard wound care alone (All wounds reported to be initially surgically debrided and thereafter as needed. Daily dressing changes All patients received offloading and antibiotics.
	Outcomes	1) Proportion Healed

		A) 0.60 B) 0.55 Not statistically significant difference 2) Complete healing Time A) 61.6 +/- 84 days B) 81.2 +/- 78.4 days
	Notes	Other outcomes reported included: Mean wound size reduction at 6 months A) 0.879 +/- 0.338 B) 0.824 +/- 0.33 No statistically significant difference
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	RCT reported. Specific method of sequence generation reported as simple randomization.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not Reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	Not reported
Selective outcome reporting (reporting bias)	Low risk	Preselected outcomes in the methods section were reported in the results section. No pre-specified protocol was reported.
Other Bias	Unclear risk	Sharp debridement reportedly performed initially and as needed.

3. **Apelqvist 1990**[3]	**Methods**	-Open randomized controlled study 5-week study Blinded evaluation Weekly evaluation included color photos and evaluation by combined foot care team (diabetologist, orthopedist, orthotist, podiatrist, and a nurse) Study reports footwear corrected when necessary. Intervention stopped for surgical debridement, hospitalization, noncompliance, increase in size or necrosis of the ulcer by 50%, and reaction to dressing.
	Participants	44 outpatients 26M/18F, mean age 63 yrs. (23-86), Hgba1c = 8.2 mean duration of diabetes = 20 yrs. (2 - 54), A) 22, 8.4 +/- 1.4, 22 +/- 15, B) 22, 8.0 +/- 2.1, 19 +/- 12,
	Interventions	A) Hydrocolloid B) Adhesive Zinc Oxide tape Ulcers cleaned with sterile saline. Dressing changes daily for 1st week then every 3 days afterwards where wound and surrounding area inspected and assessed.
	Outcomes	1) Proportion healed

		A) 5/22 = 0.227 B) 9/22 = 0.409 2) Proportion of Infections A) 1/22 = 0.045 B) 0/22 = 0 Not statistically significant difference 2) Complete healing Time A) 61.6 +/- 84 days B) 81.2 +/- 78.4 days
	Notes	Changes in necrotic ulcer area were also reported.
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomized study reported. Method of sequence generation not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not Reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Low risk	Blinded evaluation was reported.
Incomplete outcome data (attrition bias)	Unclear risk	Not reported
Selective outcome reporting (reporting bias)	Low risk	Prespecified protocol not reported. Prespecified outcomes in the methods section reported in the results.
Other Bias	Unclear risk	Study financially supported by industry.

4. Baker 1993[4]	**Methods**	RCT - Pilot Study Duration - 12 weeks Limited - Abstract available only
	Participants	19 with neuropathic foot ulcers, number of participants in each intervention group not reported. Age, sex, grade or duration of wounds, severity of peripheral arterial disease, presence of infection and diabetes disease severity not reported.
	Interventions	A) Allevyn Hydrocellular dressing B) Sorbsan Calcium-Alginate dressings
	Outcomes	1) Proportion of ulcers healed 90% vs 44% at 12 weeks 2) Median time to healing 28 days vs. 84 days
	Notes	Allevyn Hydrocellular reported as significantly more absorbent (p= 0.001) and less adherent or easier to remove (p=0.011) than the alginate dressing.
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomization was reported. Specific method of sequence generation was unspecified.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not Reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	Unclear risk	Not reported

Selective outcome reporting (reporting bias)	Unclear risk	No protocol reported or clearly pre-specified outcomes in methodology. Only abstract available.
Other Bias	High risk	Other significant covariates and differences between intervention groups not reported.
5. **Belcaro 2010**[5]	**Methods**	Open-label registry randomized pilot study. 4 weeks Categorized: venous ulcers and diabetic ulcers
	Participants	148 patients A) 34 patients, 16M/18F, Mean Age 56.5 +/- 4.4 years B) 32 patients, 13M/19F Mean Age 55.3 +/- 3.2 years
	Interventions	A) Multivalent silver oxide Ag4O4 ointment + elastic compression B) Control group (standard cleaning and elastic compression management methods without silver ointment)
	Outcomes	Complete closure of the ulceration A) 39% b) 16% (p </=0.05).
	Notes	Notes The study also reported the following outcomes of noninvasive vascular investigations to exclude major vascular problems that could result in decreased perfusion. These include Skin PO2 and Skin flux.

		perimalleolar Skin (P02) (Oxygenation in the skin of the affected limb) Baseline at 4 weeks A) 43 mmHg 53 mmHg (increase of 23.3%) B) 44 mmHg 48mmHg (increase of 9.1 %) (p </= 0.05) Laser Doppler flowmetry perimalleolar Skin flux (RF) Baseline at 4 weeks A) 3.22 flux units 2.36 flux units (decrease of -26.7%) B) 3.21 flux units 3.01 flux units (decrease of -6.2%) (p </= 0.05) Total surface area reduction of the ulcer A) -89.0% B) -23.9% (p </= 0.05)
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The study reports that the patients were randomly assigned however method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported

Blinding (performance bias and detection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not Reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	Low risk	The study reported no dropouts.
Selective outcome reporting (reporting bias)	High risk	No protocol was available for this study and the outcomes were not all clearly pre-specified in the methods section of the study.
Other Bias	Unclear risk	The study does not compare the intervention groups on other risk factors that could influence outcomes. No further detail was provided on how balanced both intervention groups were.

6. **Blackman 1994**[6]	**Methods**	RCT Surface area tracings of wound margins. Foot ulcer measurements every 3 weeks for a follow up period of 24 weeks. Cross-over design after two months to group A Subjects encouraged to obtain orthotic footwear Subjects followed until ulcer healed, or until 6 months had elapsed.
	Participants	18 subjects Type 1 and 2 DM #, gender, mean age, Hgba1c, A) 11, 11M/0F, 59 +/- 5yrs, 8.4 +/- 0.9 B) 7, 6M/1F, 51 +/- 4yrs, 9.5 +/- 1.1 No statistically significant difference
	Interventions	A) Polymeric dressing B) Wet to dry saline dressing Dressing changes at minimum once daily or when saturated. 4 wounds surgically debrided in group A and 3 in group B prior to start.
	Outcomes	1) Proportion healed A) 0.73 OR 0.27

		B) 0 (p </=0.05).
	Notes	Other outcomes reported included: Ulcer size reduction A) 35 +/- 16% B) 105 +/- 28% -> 35 +/- 11% (post-crossover, p < 0.02, 5 subjects were crossed over from conventional treatment to polymeric membrane after two months of treatment) Statistically significant difference (p < 0.03)
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Reported that subjects were randomly assigned. Method of sequence generation not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not Reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	High risk	2 patients from each group progressed to Wagner grade 3 and were not included in the study.
Selective outcome reporting (reporting bias)	Low risk	Prespecified protocol not reported. Prespecified outcomes in the methods section were reported in the results.
Other Bias	High risk	2 patients in underwent debridement in their referring physician's office during the study. No patient obtained new orthotic footwear. The study was industry

		supported.

7. **Bowling 2011**[7]	**Methods**	Prospective randomized, controlled, double blind, pilot study. Weekly treatments for 4 weeks. Semi-quantitative wound tissue cultures post-debridement at baseline and week 4. Maximum wound size Length X Width
	Participants	20 patients #, Gender M/F, Type 1/2, Duration of diabetes, Hgba1c % A) 10, 6/4, 3/7, 21.2 +/- 9.0 yrs., 9.3 +/- 1.7, B) 10, 6/4, 2/8, 17.5 +/- 7.2 yrs., 8.1 +/- 1.9,
	Interventions	A) Jet lavage debridement with superoxide aqueous solution + hydrogel B) Jet lavage debridement with saline solution + hydrogel All dressing changes every 3-4 days, specified treating physician Superoxide solution or saline applied at every dressing change.
	Outcomes	The study qualitatively reports no adverse effects were recorded. The study did not report that 15% of the study ulcers were healed. The study reported no statistically significant results between the two treatments ($p>0.05$).

		No further information was specified on the outcomes of interest for this review.
	Notes	Wound bioburden (bacterial load) was reported on an ordinal scale as scatted (0/+), light (+), medium (++), heavy (+++) Reduction in bacterial load at week 4 A) 1.6 +/- 1.3 -> 1.1 +/- 1.2 B) 1.7 +/- 1.4 -> 1.2 +/- 1.2 No statistically significant difference (p = 0.9) The study reports trend toward a 75% reduction in necrotic tissue in the study group (p>0.05)
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomized controlled pilot study. Method of sequence generation reported as computer-generated block randomization scheme.
Allocation concealment (selection bias)	Low risk	Reported that medical centers were provided with sealed randomization envelopes for conducting the treatment assignment.
Blinding participants	Unclear risk	The authors report that this was a double-blind study, however it is not specified which combination of participants, personnel delivering the intervention, or outcome assessors was blinded.
Blinding personnel delivering intervention	Unclear risk	The authors report that this was a double-blind study, however it is not specified which combination of participants, personnel delivering the intervention, or outcome

		assessors was blinded.
Blinding outcome assessors	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	Unclear risk	Not reported
Selective outcome reporting (reporting bias)	High risk	No pre-specified protocol was reported. The outcomes pre-specified in the methods section were reported in the outcomes. However full numeration for both groups was not reported in the results.
Other Bias	Unclear risk	Offloading status was not reported.
Notes		

8. **Clever 1995**[8]	**Methods**	Open, randomized, controlled study comparing two polyurethane dressings 40 patients Objective clinical evaluation: ulcer tracings, photographs, and date of healing. At end of treatment, both the investigator and patient evaluated the wound care product subjectively.
	Participants	A) 20 patients, 15M/5F, age 58.85 +/- 11.64 years B) 20 patients, 17M/3F, age 53.15 +/- 14.62 years No statistically significant difference was reported in gender or age. Sample age range 18 - 80 Pure neuropathic superficial diabetic ulcer of 1-5 cm in diameter. No clinical or radiological signs of osteomyelitis or tendon involvement. Study reports no statistically significant differences between intervention groups in terms of ankle-brachial pressure index, threshold of vibration, average duration of ulcer before entering study, and number of recent recurrences. Number of Smokers (9 vs 4, $p < 0.01$) was statistically significant.

	Interventions	A) Hydroactive polyurethane gel dressing Cutinova Hydro + standard therapy* B) Hydrophilic polyurethane foam dressing Allevyn + standard therapy* "Dressing changes reportedly performed as often as required, but at least once a week." *Standard therapy included: (i) pressure relief comprising a half-shoe or so-called "heel sandal" therapeutic footwear with cushioned insoles and crutches as required to meet individual needs. (ii) infection control with systemic antibiotics if required, (iii) wound cleansing with Ringer's solution, and (iv) debridement with removal of callus if needed
	Outcomes	Time to Healing A) 25.19 ± 23.52 days B) 20.43 ± 14.74 days ($p > 0.2$) Proportion healed A) 14/20 = 0.70 B) 16/20 = 0.80 Excluding dropouts, 88% of the patients were healed in an average of 23 days, 50% within 16 days.

	Notes	Dressing changes by patient's in-between the weekly assessments: A) 2.23 ± 2.19 times B) 2.37 ± 2.18 times, No statistically significant difference (p > 0.2) The study reported "subjective product evaluation" including ease of showering with dressing (p > 0.1), absorption capacity (p > 0.1), handling and suitability (lack of side-effects or skin problems) (p > 0.2), and all were found to not be statistically significant. No details on the subjective evaluation were specified.
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomization reported but method of sequence generation not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	High risk	2 patients in group A and 4 patients in group B were reported to not have completed the study. It is unclear how the missing data were addressed.
Selective outcome reporting (reporting bias)	High risk	The study broadly reported outcomes in the methods section but did not specify all outcomes that were reported in the results. No protocol specified.
Other Bias	High risk	Unclear if both groups were

		adequately balanced for confounders or other risk factors including disease severity. Prospective wound healing study was possible due to financial support from manufacturer.
Notes		

9. D'Hemecourt 1998[9]	**Methods**	RCT Multi-centered (10 sites); Evaluator-blind Study period was not reported. Follow up period was 140 days.
	Participants	172 patients A) 68 B) 70 C) 34 45 women/127 men; 19 years or older; Type 1 / Type 2 diabetes. At least one full thickness Stage 3 or Stage 4 chronic diabetic ulcer of the lower extremity. Wound size (area and depth) measured at baseline.
	Interventions	A) Good wound care* B) Good wound care & NaCMC hydrogel C) Good wound care & Becaplermin Off-loading of pressure and systemic control of infection for all wounds. *'Good wound care' was defined by the study authors as follows: "this regimen consisted of daily dressing changes, sharp debridement of the ulcer when deemed necessary by the investigator, systemic control of infection if present, and off-loading of pressure".
	Outcomes	1. Proportion with complete wound healing at 20 weeks

		A) 15 / 68 (22%) B) 25 / 70 (36%) 2. Time to complete healing A) 141 days * B) 98 days * 3. Proportion with Infection A) 0.28 B) 0.30
	Notes	Largest trial with regard to patient numbers * It is unclear if these are mean or median times to healing. Two other indicators reported in the study included: Pain reported as adverse event A) 10 / 68 (15%) B) 11 / 70 (16%) Wound related adverse events A) 25 / 68 (37%) B) 19 / 70 (27%)
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The method of sequence generation procedure was not specified: "patients were randomly assigned in a 2:2:1 ratio to one of three

		treatment groups".
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding participants	Unclear risk	Statement by authors from published study: "both the NaCMC gel and Becaplermin gel treatment groups were conducted in double-blind fashion; the group receiving good wound care alone was blinded to the investigator by a third party".
Blinding personnel delivering intervention	Unclear risk	Blinding of personnel delivering the intervention: yes - control group; unclear - intervention groups (see statement from authors above).
Blinding outcome assessors	Low risk	Blinding of outcomes assessor: yes. Study described as "evaluator-blind".
Incomplete outcome data (attrition bias)	Low risk	Intention-to-treat analysis was conducted. However, the specific Intention to treat analytic method was not reported.
Selective outcome reporting (reporting bias)	Low risk	Four parameters pre-specified as outcomes, all of which were reported
Other Bias	High risk	Baseline differences in group size and ulcer characteristics (mean area, depth, and duration): Good wound care (n=68): n=65 at stage III; 3.5 cm2; 67cm; 24 weeks. NaCMC gel (n=70): n=70 at stage III; 3.2 cm2; 69 cm; 24 weeks. Becaplermin gel (n=34): n=32 at stage III; 2.4 cm2; 33cm; 11 weeks. The group receiving Becaplermin gel were not comparable with the two other groups. 'Good wound care' included "sharp debridement of the ulcer when deemed necessary by the investigator". No other data reported on diabetes disease severity or other risk factors.
Notes		

10. Donaghue 1998[10]	**Methods**	75 patients enrolled in an

		open-label design with random assignment to two groups in 2:1 ratio. Wagner classification used. Offloading prescribed to all patients with self-adhesive felted foam and window at wound site and use of healing sandals. Seen weekly until target ulcer healed or maximum of 8 weeks. Exit interview to determine satisfaction level.
	Participants	# Gender Age (range) Duration of DM(range) Weight Creatinine Albumin Proportion M/F yrs. (yrs.) (lbs.) (mg/dl) (gms/dl) Retinopathy A) 50, 33/17, 59 (30-81), 19 (4-47), 195 +/- 45, 1.2 +/- 0.6, 3.72 +/- 0.07 0.56 B) 25, 21/4, 60 (33-79), 17 (2-25), 214 +/- 49, 1.14 +/- 0.06, 3.79 +/- 0.11 0.76 No statistically significant difference in any of these baseline participant characteristics was reported in the study.
	Interventions	A) Collagen Alginate B) Saline gauze Patients or caregivers given instructions to change as often as required.

	Outcomes	1) Proportion healed A) 24/50 = 0.48 B) 9/25 = 0.36 No statistically significant difference (p=0.3933) 2) Mean time to complete healing A) 43.4 +/- 2.8 days B) 40.6 +/- 2.8 days The study authors reported that there were no differences in the number or severity of adverse effects (p=0.453) No other information was provided.
	Notes	The study also reported: Baseline values: Additional outcome included: Mean percent reduction of the wound area at the end of the study was reported as: A) 80.6 +/- 6% B) 61.1 +/- 26% No statistically significant difference (p=0.4692) The study reported wound size reduction rate in a multivariate analysis to be

		statistically significant in favor of Collagen alginate over saline gauze (p=0.049). No other information was provided. Subgroup analysis was reported for wounds of less than 6 month's duration and the authors report a faster healing rate for Collagen alginate over saline gauze, but the result was not statistically significant.
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Random assignment to treatment groups was reported but method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported.
Blinding outcome assessors	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	Unclear risk	75 patients enrolled, 61 completed study, 14 withdrawals (6 patients in group A and 8 in group B did not complete the study, 5 withdrew no reason reported, 3 patients missed > 2 visits, and 6 patients experienced adverse events). The authors report that all 75 patients enrolled were included in the intention to treat analysis. The method used in the intention to treat analysis to address the 14 withdrawals was unspecified.
Selective outcome reporting (reporting bias)	High risk	No protocol was specified in the report. The outcomes reported in the results section were not explicitly prespecified outcomes in the methods section.
Other Bias	Unclear risk	The study reported adverse effects

		were not statistically significant between both groups. Specific information on adverse effects was not reported.
Notes		

11. EhsanUrRehman 2013[11]	**Methods**	60 subjects randomly assigned to two groups. non-probability purposive sampling Wound measurements were done on day 15. Wagner grade I & II ulcers. Length, width, and maximum perpendicular depth of ulcer were measured and multiplied post-surgical debridement
	Participants	Not reported.
	Interventions	A) Honey soaked dressing B) Povidone-iodine/normal saline dressing Daily dressing changes All wounds washed with saline prior to Surgical debridement at the time of presentation.
	Outcomes	1) Proportion healed A) 24/50 = 0.48 B) 9/25 = 0.36 No statistically significant difference (p=0.3933) 2) Mean time to complete healing A) 43.4 +/- 2.8 days

		B) 40.6 +/- 2.8 days The study authors reported that there were no differences in the number or severity of adverse effects (p=0.453) No other information was provided, Proportion healed A) 0.867 B) 0.733
	Notes	Other outcomes reported include: % decrease in wound size A) 80.81 +/- 17.27% B) 54.63 +/- 3.42%
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Subjects reported randomly assorted into two groups. Method of sequence generation not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported.
Blinding outcome assessors	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	Unclear risk	Not reported
Selective outcome reporting (reporting bias)	High risk	The study reports swab and culture would be carried out in the methods section, but infection not reported in the results. Other outcomes reported in the results section were not pre-specified in the methods section.
Other Bias	High risk	Prespecified outcomes not reported in methods section. Comorbidities used as exclusion criteria reported in methods section but not specified. No patient baseline

		characteristics reported unclear whether both groups balanced for confounding. Non-probability purposive sampling which could produce sampling bias.
Notes		

12. Foster 1994[12]	**Methods**	RCT, Stratified according to neuropathic or ischemic diabetic foot ulcers Study length 8 weeks or until the ulcer. Weekly clinic assessments of wounds and dressings, and where ulcers were debrided.
	Participants	30 Patients A) 15 patients, 12M/3F, mean age 61, DMT1 = 6 B) 15 patients 8M/7F, mean age 70, DMT1 = 4
	Interventions	A) Hydrocellular polyurethane foam dressing Allevyn B) Calcium sodium alginate dressing changes All wounds washed with saline prior to Surgical debridement at the time of presentation.
	Outcomes	Proportion Healed A) 9/15 = 0.60 B) 8/15 = 0.533 No statistically significant difference in time to healing between both intervention groups.
	Notes	Study reported that some evidence ulcer more likely to heal if IDDM as opposed to NIDDM (p=0.07). Also, smaller ulcers or ulcers

		of neuropathic origin more likely to heal. A statistically significant difference was reported favoring Polyurethane foam dressings over Calcium alginate dressings in 1) time taken for application (2.1 +/- 0.6 minutes vs 3.2 +/- 1.0 minutes), and in subjective ordinal scales including ease of application ($p<0.001$), absorbency ($p<0.01$), patient comfort ($p<0.01$), non-adherence ($p<0.01$), and ease of removal (0.001). % decrease in wound size A) 80.81 +/- 17.27% B) 54.63 +/- 3.42%
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Study reports randomization but method of sequence generation is unspecified.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported.
Blinding outcome assessors	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	High risk	4 patients from the alginate group withdrew due to: severe pain (1); plugged lesion prevented free drainage of exudate (3) with one becoming infected. Unclear how incomplete outcome data were addressed.
Selective outcome reporting (reporting bias)	High risk	Study pre-specified a number of "ideal" parameters in the introduction including infection

		however all were not reported in the results section. No parameters were pre-specified in the methods section.
Other Bias	High risk	The study reported stratification was conducted to ensure that a more equitable number of individuals with neuropathic, ischemic ulcers, traumatic wounds in each intervention group. However, no mention was made on whether other risk factors such as diabetes disease severity was balanced in both intervention groups. Duration of ulcer was longer in the calcium alginate group (170 days vs 107 days).
Notes		

13. Goretti 2008[13]	**Methods**	RCT; Randomized into two groups.

	Participants	A) 20 B) 20 Wounds > 5 cm2, ABI >/= 0.9 and two arteries in the ankle palpable by pulse or Doppler. Age, gender, diabetes type, duration of diabetes, proportion of wounds infected, or other data not provided.
	Interventions	A) Super-oxidized solution (SOS) treatment B) Standard local treatment with povidone iodine Frequency or number of times intervention used was not reported. The study abstract mentions that the patients received metabolic control, systemic antibiotics, and offloading as necessary, but no further detail was provided.
	Outcomes	1. Proportion Healed A) 0.85 B) 0.53 (p<0.01, statistically significant difference) 2. Healing Time A) 10.5 +/- 1.3 weeks B) 16.5 +/- 1.7 weeks (p<0.01, statistically significant difference) The study reports weekly visits to record lesions

		clinical signs of infection, microbiological sampling, eventual new debridement procedures, and adverse events. No further detail is available.
	Notes	Other outcomes that were reported include: Sterilization of lesions (ST) A) 5.5 +/- 2.1 weeks B) 16.2 +/- 6.6 weeks (p<0.01, statistically significant difference) Number of Debridement procedures (ND) A) 3/20 B) 9/20 (p<0.01, statistically significant difference) Adverse Events (NA) A) 4 B) 9 No other information provided other than a statement that no differences were observed in (NA)
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Published abstract only. Randomization reported but the

		method of sequence generation used was not specified
Allocation concealment (selection bias)	Unclear risk	Published abstract only. Not reported.
Blinding participants	Unclear risk	Published abstract only. Not reported.
Blinding personnel delivering intervention	Unclear risk	Published abstract only. Not reported.
Blinding outcome assessors	Unclear risk	Published abstract only. The study reports weekly visits to "blindly" record lesions clinical signs of infection, microbiological sampling, eventual new debridement procedures, and adverse events. Unclear if other outcomes were blinded.
Incomplete outcome data (attrition bias)	Unclear risk	Published abstract only. Not reported.
Selective outcome reporting (reporting bias)	Low risk	Published abstract only. Results were available for all outcomes reported in the methods section however unclear if protocol was written ahead of the study.
Other Bias	Unclear risk	Published abstract only. Other sources of bias not discernible.
Notes		

14. Hammouri 2004[14]	**Methods**	203 patients allocated randomly to two groups, 3 excluded.
	Participants	200 patients, 112M/88F, Mean age = 58 A) 100 58M/42F, (24-100), B) 100 54M/46F, (22-100)
	Interventions	A) Honey/Normal Saline, washed with normal saline post-debridement B) Povidone Iodine/H2O2 (3:1) washed with same solution post-debridement All dressings applied 3 times daily then declined as treatment progresses in both groups.
	Outcomes	1) Time to healing A) Median 21 days, (7-70 days), SD = 15.97 B) Median 32 days, (7-90 days), SD = 20.89 Statistically significant difference (p<0.001) 2) Treatment Cost A) 282 +/- 66.33 Jordan Dinar, B) 616 +/- 192.97 Jordan Dinar, Statistically significant difference (p<0.001) 3) Proportion amputations

		A) 0.10 B) 0.20 Statistically significant difference (p<0.05)
	Notes	Other outcomes reported: Hospital stay A) Median 23 days (7-42 days), SD = 8.26 B) Median 13 days (7-56 days), SD = 14.54 Statistically significant difference (p<0.001)
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The authors report random allocation. Method of sequence generation is not specified in the report.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	The authors report that 3 patients were excluded from the analysis that died from other medical illness.
Selective outcome reporting (reporting bias)	High risk	No protocol is reported. The study authors report healing, hospital stay, and cost as the respective outcomes of interest in the methods section. These were reported in the results section. The study reported amputation proportion, bioburden reduction which were not explicitly pre-specified in the methods section.
Other Bias	High risk	The study authors did not report exclusion criteria and reported only

		diabetic foot ulcers as inclusion criteria. Baseline characteristics of the ulcers in each group were not reported. Disease severity indicators including Hgba1c, duration of diabetes was not reported. Grade of diabetic foot ulcers not reported. Debridement under anesthesia is reported but study authors do not specify whether this was an initial debridement only or if debridement were conducted throughout the course of the study.
Notes		

15. Jeffcoate 2009[15]	**Methods**	A multicenter, prospective, observer-blinded, parallel group randomized controlled trial. Research nurse monitored every two weeks. Primary endpoint number of ulcers healing in each group within 24 weeks. Ulcers monitored by nurses every two weeks. Blinded wound assessments made at baseline, 12 weeks, 24 weeks, 4 weeks after healing, and 12 weeks after the 24-week assessment. Healing defined as complete epithelialization with no drainage for 4 weeks and confirmed by a blinded assessor. If an ulcer was assessed as healed at any point the authors stated that ulcer was reassessed at 2 and 4 weeks after healing. If the ulcer recurred within 4 weeks or at any point up to 24 weeks, the patient was re-entered into the study using the allocated dressing. The study reported on ulcer-related endpoints, patient-related endpoints, and process related endpoints. A health economics

		evaluation which included the direct costs associated with dressings used and patient travel costs was reported. The quality-of-life assessment included SF-36 questionnaire, a visual analogue scale for pain, and the CWIS (Cardiff wound impact schedule).
	Participants	# Gender M/F Age (yrs.) DM Type 1/2 DM duration (yrs.) Total 317, 240/76, 59.6 +/- 12.6, 240/76, 15.7 +/- 10.8 A) 103, 81/22, 59.5 +/- 11.5, 22/81, 16.0 +/- 11.4 B) 108, 81/27, 58.8 +/- 13.2, 25/83, 15.3 +/- 9.8 C) 106, 78/27, 61.9 +/- 12.8, 78/27, 15.8 +/- 11.4
	Interventions	A) Hydrofiber dressing Aquacel B) Iodine impregnated gauze C) Non-adherent viscous filament gauze Other care reported to include regular use of debridement, offloading, The study reports dressings were changed daily, on alternate days, and 3X/week depending on the need by the patient or caregiver who received training, or by the nurse. If patient changed the dressing, then nursing oversight was conducted every two weeks. The study reported that off-loading was variable, and 42% of participants were issued the

		preferred casting device, two centers issued no casting devices, one center issued 1.
	Outcomes	1) Proportion of ulcers healed A) 46/103 = 0.447 B) 48/108 = 0.444 C) 41/106 = 0.387 No statistically significant difference (p=0.38) 2) Proportion of ulcers recurring A) 3/103 = 0.029 B) 7/108 = 0.065 C) 3/106 = 0.028 3) Time to healing A) 125.8 +/- 55.9 days B) 127.8 +/- 54.2 days C) 130.7 +/- 52.4 days No statistically significant difference (p=0.80) 4) Proportion amputated A) 4/103 = 0.039 B) 1/108 = 0.009 C) 2/106 = 0.019 Statistical significance not

		reported. 5) Proportion infected A) 54/103 = 0.524 B) 71/108 = 0.657 C) 48/106 = 0.453 Statistical significance not reported 6) Treatment cost A) 194.03 B) 184.17 C) 141.1 Statistical significance not reported 7) Quality of life index A) 0.382 B) 0.384 C) 0.394 No statistically significant difference (p=NS)
	Notes	Other outcomes reported: Hospital stay A) Median 23 days (7-42 days), SD = 8.26 B) Median 13 days (7-56

		days), SD = 14.54 Statistically significant difference (p<0.001)
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomization was reported to be stratified by center, size, using block size of nine design. Randomization was also stratified across the whole population by ulcer area in three groups. The study reports that randomization lists were created using statistical software.
Allocation concealment (selection bias)	Low risk	The randomization lists and records of the allocation details were reported to be held at a central location and each recruiting center telephoned.
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Low risk	The study reports that the clinician in charge of care and assessing for healing was blinded to the randomization group.
Incomplete outcome data (attrition bias)	Low risk	The authors reported that 88 participants (27.8%) out of the 317 enrolled were withdrawn. The reasons for withdrawal were reported as: Adverse event = 35 Protocol violation = 24 Loss to follow up = 7 Consent withdrawal = 16 Death = 5 Other = 1 Intention to treat analysis was carried out using last observation

		carried forward.
Selective outcome reporting (reporting bias)	Low risk	No protocol was available or referred to in the study. The outcomes reported in the results were pre-specified in the methods section.
Other Bias	High risk	The study reported 88 withdrawals out of 317 participants, last observation carried forward was utilized as intention to treat. This may have biased the results in either direction.
Notes		

16. Jensen 1998[16]	**Methods**	RCT; Randomized into 2 groups.

		Study period was not reported. Follow up period was 20 weeks.
	Participants	31 patients A) 14 B) 17 No description of age, sex, type of diabetes, or disease severity was reported. Wound area measured at baseline. Average duration of ulceration A) 8.9 months B) 3 months
	Interventions	A) Carrasyn hydrogel wound dressing (CHWD) cleansed with ULTRAKLENZ wound cleanser. B) Wet-to-moist saline gauze cleansed with ULTRAKLENZ wound cleanser. Adjunctive wound care included all patients who initially received sharp debridement to remove all non-viable (dead) tissue and all patients received custom made healing sandals for pressure redistribution. Dressings changes were conducted daily. Saline moist gauze remoistened as needed. Patients evaluated weekly using wound tracings and computer planimetry.
	Outcomes	1. Proportion with complete wound healing at 16 weeks (Defined as 100% wound re-epithelialization) A) 11/13 84.6%

		B) 6/13 46.1% P=0.05 2. Time to complete healing A) 10.3 weeks * B) 11.69 weeks * 3. Proportion with amputation A) 0/14 = 0 B) 1/17 = 0.059 4. Proportion with Infection A) 2/14 = 0.143 B) 1/17 = 0.059 5. Cost A) 7.01 - ($/day) B) 12.28 - ($/day)
	Notes	* It is unclear if these are mean or median times to healing. 13/14 patients completed the study in the Hydrogel group whereas 13/17 completed the study in the control group. Other outcomes that were reported in this study included: Complications

		A) 2/14 (14%) B) 4/17 (24%)
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomization was reported but method of sequence generation not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	High risk	5 patients dropped out (n=1 in Group A; n=4 in Group B): no intention-to-treat analysis or other method of handling missing data were specified.
Selective outcome reporting (reporting bias)	Unclear risk	No protocol available. No parameters clearly pre-specified as outcomes in the methods section.
Other Bias	High risk	No Group A and Group B data reported on ulcer size, depth, on entry to trial other than ulcer with minimum of 1cm diameter; and Wagner grade II thickness. However, the trial report suggests that Group A had average ulcer duration of 8.9 months compared with 3 months for group B. Study supported by an educational grant from Carrington Laboratories, Inc. (the manufacturers of Carrasyn).
Notes		

17. Lalau 2002[17]	**Methods**	Open - label multicenter randomized controlled trial. Study reported 13 centers throughout France

		participated. Number of wound dressings and adverse events recorded weekly. Follow up visits scheduled at weeks 1, 2, 4, 6 to monitor healing efficacy and safety. Planimetric evaluation used for surface area. The study reported a 6-week treatment period, though efficacy analysis was reduced to 4 weeks due to premature cessation of treatment in 13 patients. Reported that there was no revision to efficacy criteria. The study reported that conservative management was carried out using pressure relieving methods.
	Participants	77 patients enrolled, 13 withdrawn #, Gender, Age, BMI, DM type, Diabetes duration, Hgba1c, # revascularizations, TcPO2, A) 39, 22M/17F, 60.8 +/- 10.7 yrs., 27.6 +/- 5.11, 15/24, 19.2 +/- 11.8 yrs., 7.6 +/- 2.0, 13, 44.6 +/- 12.3 B) 38, 23M/25F, 63.5 +/- 12.8 yrs., 27.3 +/- 5.52, 16/22, 16.9 +/- 8.9 yrs., 7.9 +/- 1.5, 4, 42.6 +/- 10.3 No statistically significant difference in participants except for # revascularizations.
	Interventions	A) Calcium Alginate

		B) Vaseline Gauze The study reported daily dressing changes initially until thoroughly debrided, then once granulation occurred, every 2 - 3 days depending on exudate amount as determined by nurses. The authors reported no other local treatments except unrestricted saline. The study reported that mechanical debridement was authorized, as necessary.
	Outcomes	Proportion of infections A) 1/39 = 0.026 B) 3/38 = 0.079
	Notes	Proportion of patients with granulation tissue > 75% of wound area, and a 40% decrease in wound surface area. Secondary outcomes included: pain on dressing changes, cumulative number of dressing changes, and number of adverse events. All were reported not to be statistically significant except for pain and cumulative number of dressing changes in favor of calcium alginate.
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomization of participants was reported. The method of random sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported

Blinding outcome assessors	Low risk	The study reported that an independent investigator, blind to the allocated treatment, was assigned to analyze wound surface areas. Analysis reportedly performed two times for each patient, and a third as warranted.
Incomplete outcome data (attrition bias)	Unclear risk	77 patients enrolled, and 64 completed the study for the full 6 weeks. 13 withdrawals - 1 consent withdrawal, and 4 adverse events in the Calcium Alginate group, 1 ineffective treatment, 1 aggravation, and 6 adverse events in the Vaseline group. The study reports that due to the loss of data because of the 13 withdrawals the study was shortened to efficacy analysis at 4 weeks.
Selective outcome reporting (reporting bias)	Low risk	No protocol was reported in the study. Outcomes pre-specified in the methods section were reported in the results section.
Other Bias	High risk	The revascularizations were reportedly higher in the Calcium Alginate group. Subgroup analysis on acute versus chronic lesions was also reported but demonstrated no statistically significant difference. Most of the lesions were chronic and reportedly may have been more refractory to treatment.
Notes		

18. Markevich 2000[18]	**Methods**	RCT; Multi-centered; Double-blind Study period not reported, follow up period was 10 days
	Participants	140 patients,

		A) 70 B) 70 Average Age: 53.6 +/- 15.4 years. Average duration of Diabetes: 15.8 +/- 10.7 years No description of sex, type of diabetes, disease severity, infection status, offloading status, or wound grade, other than qualitative statement that depth and volume were comparable at baseline between both groups.
	Interventions	A) Larval therapy (green bottle fly - Lucilia sericata 6-10 larva per 1 cm2 of wound surface area) removed after 72 hours B) Hydrogel (no data on frequency of dressing change)
	Outcomes	Complete healing (no data as to time this took) A) 5/70 (7.1%) B) 2/70 (2.8%) (no report of whether this was a statistically significant difference was mentioned)
	Notes	A) Average Surface area of wound 14.9 cm2 B) Average Surface area of wound 15.14 cm2 (no statistically significant difference) Qualitatively reported in abstract that surface area,

		depth, and volume, surrounding skin, tissue quality, exudate, odor, and glucose levels were comparable at baseline, but no numerical data were provided. Assessments reported every 3 days during first 10 days. At 10 days granulation tissue covering 50% of wound was higher in larval therapy (60% vs 34.3%; p<0.001 statistically significant difference) Proportion of patients with greater than 50% reduction in wound area was higher in the larval group than in the hydrogel group (51.1% vs 27.1% p<0.05, statistically significant difference)
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Published abstract only - Randomization reported but method of sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Published abstract only - allocation concealment not reported.
Blinding participants	Unclear risk	N.B. RCT described as "double-blind" by study authors, but no further detail given. Blinding of participants - not reported (published abstract only): This may be difficult due to nature of treatments - larval therapy vs. hydrogel.
Blinding personnel delivering intervention	Unclear risk	Blinding of personnel - not reported (published abstract only): This may

		be difficult due to nature of treatments - larval therapy vs. hydrogel.
Blinding outcome assessors	Unclear	Blinding of outcome assessors: not reported (published abstract only).
Incomplete outcome data (attrition bias)	Unclear risk	Published abstract only - incomplete outcome data were not reported, if incomplete outcome data were present then assessment and how outcome data were addressed is not discernible.
Selective outcome reporting (reporting bias)	Unclear risk	Published abstract only - selective reporting not discernible.
Other Bias	Unclear risk	Published abstract only - other bias not discernible.
Notes		

19. Mazzone 1993[19]	**Methods**	RCT, Method of random sequence generation was not reported.
	Participants	19 A) 11 B) 8

		No data on age, sex, or other patient specific demographics or characteristics were reported.
	Interventions	A) Polymeric membrane foam dressing B) Wet to Dry saline gauze mesh dressing
	Outcomes	Complete healing (no data on the time to this endpoint reported) A) 5/70 (7.1%) B) 2/70 (2.8%) (no report of whether this was a statistically significant difference was mentioned)
	Notes	Wound size reduction was reported as well. No other information on other risk factors such as diabetes type, duration, or disease severity was reported. No data reported on wound size or grade between treatment groups.
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The study reports randomization however method of random sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	Not reported
Selective outcome reporting (reporting bias)	Unclear risk	Not discernible; abstract only available.

Other Bias	High risk	No data were reported on study participant characteristics between treatment groups, nor on other risk factors such as diabetes type, duration, or disease severity. No data reported on wound size or grade between treatment groups.
Notes		

20. Munter 2006[20]	**Methods**	Randomized controlled trial Duration = 4 weeks Reported that patients were assessed weekly at wound clinic as judged necessary. Study reports that

		participating clinics used same clinical guidelines and data-collection forms.
	Participants	619 patients, Multi-etiology ulcers Mean age = 55.2 +/- 9.4 yrs., Duration of diabetes = 14.8 yrs. # Age Gender M/F (%), A) 326, 69.8 +/- 13.7 yrs., 38/62 B) 293, 68.8 +/- 14.1 yrs., 39/61
	Interventions	A) Silver releasing hydrophilic polyurethane foam dressing Mean dressing changes = 3.1 days B) Local Best Practice (Study reports that this ranged from gauze, moist wound healing, wound healing products, to antimicrobial treatments) Mean dressing changes = 2.1 days Wound management included compression therapy. DFU's comprised 8% of Silver and 8% Local best practice group
	Outcomes	The study conducted a subgroup analysis for diabetic foot ulcers. The study reported one of the outcomes of interest for this review, quality of life. The authors did not specify the results of this outcome for the subgroup of diabetic foot ulcers instead it was reported that the results were comparable for all parameters between the two treatment groups, except for

		wound progress, exudate, and odor.
	Notes	The study reported other outcomes such as ulcer area reduction, slough, wound progress, maceration, exudate, leakage, ease of dressing use and time spent, malodor, pain, and cost effectiveness.
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The study reports open prospective parallel, block randomized evaluation. Specific method of sequence generation was a computer-generated list.
Allocation concealment (selection bias)	Unclear risk	The study reports that the computer-generated sequence list was in sealed envelopes.
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	The study reports that to include patients in the analysis all missing data were addressed with last observation carried forward and obtained data were analyzed as intention to treat.
Selective outcome reporting (reporting bias)	Low risk	There was no protocol available or reported in the study. The outcomes reported in the outcomes section were pre-specified in the methods section.
Other Bias	High risk	The study reports private financial support.
Notes		

21. Ogce 2007[21]	**Methods**	Randomly assigned 30 days' study duration Weekly follow up with 4 follow ups. Study reports that participating clinics used same clinical guidelines and data-collection forms.

	Participants	60 patients, Gender = 36M/24F, mean age = 59.85, Hgba1c = 7.73, BMI = 25.06 24.47 #, DM Type (1/2) Mean Age Hgba1c A) 30, 0.867/0.133 59.47 yrs., 7.60%, B) 30, 0.733/0.267 60.23 yrs., 7.86%
	Interventions	A) Hydrocolloid dressing (combined with paste for wound cavities, and powder for infection) B) Classic wound dressing Daily dressing changes
	Outcomes	The study reported that healing was much better and faster in the experimental group.
	Notes	The article was only available in Turkish and was translated using Google translate as were all non-English language publications that were retrieved through our search and accepted in this review. The translation was of higher quality for some languages and difficult in others. This study was among those that was difficult to translate. This posed a limitation in data extraction.
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Random assignment reported but method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported

Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	Not reported
Selective outcome reporting (reporting bias)	High risk	No protocol was available or reported in the study. The outcomes reported in the results were not explicitly pre-specified in the methods section.
Other Bias	Unclear risk	Limited reporting.
Notes		

22. Piaggesi 2001[22]	**Methods**	Study duration = 8 weeks All subject's initial surgical debridement + postoperative pressure relieving shoes + crutches Weekly assessments: Photographed lesions traced

		on acetate film to measure maximal dimensions. Wound depth measured by probe and volume by gel.
	Participants	24 identified, 20 enrolled, 4 withdrawn A) 10, 61.3 +/- 7.5 years Duration of diabetes = 16.1 +/- 8.9 years Hgba1c = 8.9 +/- 3.1% ABPI = 1.0 +/- 0.2 B) 10, 63.1 +/- 4.6 years, Duration of diabetes = 14.8 +/- 6.2 years Hgba1c = 8.1 +/- 2.7% ABPI = 1.1 +/- 0.3
	Interventions	A) Saline moistened gauze (renewed twice daily with saline to prevent drying) B) Sodium Carboxy-Methyl Cellulose Hydrofiber (Aquacel) changed every 2nd or 3rd day depending on extent of exudate produced by wound. Dressing changes by trained relative or visiting nurse.
	Outcomes	1) Proportion healed A) 10/10 = 1 B) 9/10 = 0.90 2) Healing Time

		A) 234 +/- 61 days B) 127 +/- 46 days Statistically significant difference 3) Proportion with Infection A) 1/10 = 0.30 B) 3/10 = 0.10 4) Proportion amputations a) 1/10 b) 0/10 No statistically significant difference
	Notes	
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Study reports random assignment, but specific method of sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Low risk	Reported that blindly evaluated by one of the authors.
Incomplete outcome data (attrition bias)	High risk	24 eligible patients, 20 enrolled and randomized. 2 refused consent, 1 due to missed visits, 1 due to neuro-osteoarthropathy.
Selective outcome reporting (reporting bias)	Low risk	The study states a protocol was written and submitted to an ethics committee however this was unavailable, however the methods section reported the outcomes to be studied including: 1) rate of reduction in lesion volume, 2) rate

		of granulation tissue, 3) infective complications, and 4) healing time. These outcomes are reported in the results section. Proportion requiring amputation was also reported that was not in methods section.
Other Bias	Unclear risk	Reported that manufacturers not involved in any part of experiment. Amputations reported but difficult to determine if in same individuals or different individuals based on the report. Unclear if groups were balanced for other risk factors.
Notes		

23. Piaggesi 1998[23]	**Methods**	Randomized into 2 treatment groups Study period 1995. Follow up period was 24 weeks. Patients were followed twice a week.
	Participants	42 patients with 46 ulcers A) 22 patients, (17 NIDDM / 3

		IDDM), 24 ulcers Mean age = 63.24 +/- 13.46 years Duration of diabetes = 18.2 +/- 8.41 years Hgba1c = 9.5 +/- 3.8% B) 24 patients, (19 NIDDM / 2 IDDM), 22 ulcers Mean age = 65.53 +/- 9.87 Duration of diabetes = 16.84 +/- 10.61 years Hgba1c = 8.9 +/- 2.2% No description of sex Baseline wound area measurement not reported.
	Interventions	A) Control - Non-surgical conventional treatment including pressure relief and regular dressing (type of dressing not reported. B) Treatment - Surgical debridement, removal of bone segments
	Outcomes	1. Complete healing at 6 months: Group A = complete re-epithelialization of lesions; Group B = formation of continuous scar A) 19/24 (79%) B) 21/22 (95%) 2. Healing time A) 48.7 +/- 36.99 days

		B) 130.38 +/- 90.49 days 4. Recurrence rate A) 8/24 (33%) B) 3/22 (14%) 5. Infective complications A) 3/24 (13%) B) 1/22 (5%) 6) Amputations A) 1/24 = 0.04 B) 0/22 = 0
	Notes	
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Exact sequence generation not reported: "a table of randomization".
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Non-surgical debridement and pressure relief vs. surgical debridement. Blinding of participants difficult due to nature of treatments – nonsurgical control vs. surgical intervention.
Blinding personnel delivering intervention	Unclear risk	Blinding of personnel: difficult due to nature of treatments - non-surgical control vs. surgical intervention. Yes - Group A. Physicians and nurses treating Group A (control) patients were unaware of their patients' involvement in the trial: "the whole treatment course of

		group A patients from initial debridement to follow-up visit was performed by physicians and nurses unaware of the participation of patients in the study and did not differ from the standard protocol of treatment of non-complicated neuropathic ulcerations in our foot clinic". Unclear - Group B. It was not reported if personnel for the Group B (intervention) were aware of their patients' participation in the trial.
Blinding outcome assessors	Unclear risk	Blinding of outcome assessors: unclear who conducted outcome assessment for both Groups (A and B).
Incomplete outcome data (attrition bias)	Unclear risk	Patient numbers at follow-up were not reported.
Selective outcome reporting (reporting bias)	Low risk	Four parameters were pre-specified as outcomes, all of which were reported.
Other Bias	High risk	Group B given antibiotics 5 days after surgery: "general therapy for group B patients differed from group A in that systemic parenteral therapy with wide-spectrum antibiotics was given 5 days after surgery, according to the protocols of our hospital for the prophylaxis of nosocomial infection".
Notes		

24. Rhaiem 1998[24]	**Methods**	Randomization of subjects into 3 groups Study period was 1992 - 1995, Follow-up period was 40 +/- 13 days
	Participants	80 patients, Gender 59M/21F, DM type 1/2 = 61/19, mean age = 56 +/-

		32 yrs. (26 - 89), diabetes duration = 13 +/-10.6 yrs. (1 - 26) yrs., peripheral neuropathy 74.6%, smokers 55%, Alcohol users 21%, infected wounds at baseline = 51.7% G1: 16 patients G2: 24 patients G3: 40 patients
	Interventions	3 treatment groups: A) G2: cleaning ulcers with hydrogen peroxide 3% + antibiotic-therapy + local applied Jam sugar B) G3: cleaning ulcers with hydrogen peroxide 3% + antibiotic-therapy (40 patients) C) G1: cleaning ulcers with hydrogen peroxide 3% + local applied Jam sugar
	Outcomes	ln groups 1 and 2 (using sugar): 47.5% of ulcers healed, compared with group 3 in which 40% of ulcers healed with a mean delay respectively of 6 and 9 weeks. Proportion healed A) G1 and G2 = 0.475 B) G1 = 0.40 Not a statistically significant difference.
	Notes	This study was translated using Google translate from French into English.
Risk of bias table		

Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The study reports randomization but does not specify the method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	Not reported.
Selective outcome reporting (reporting bias)	High risk	The study does not report whether a protocol was pre-established. The methods section of the study does not pre-specify the outcomes reported in the results section.
Other Bias	High risk	The study does not explicitly report whether the subjects received off-loading. It is not mentioned in the study how the determination of ischemic wounds was established. The study does not clarify. The study reports the combined healing proportion for the G1 and G2 groups, it does not report the proportion separately. The study reports that 51.7% of wounds were infected, no information was provided on whether infected or ischemic wounds were balanced between the 3 treatment groups.
Notes		

25. Roberts 2001[25]	**Methods**	RCT Dressing changed and wound assessment with tracings were reported to occur weekly. Study duration was 13 weeks

	Participants	30 patients 23M/7F Type 1 DM Median Age = 59.5 years Range (37-77) Neuropathic ulcers of the plantar surfaces. Median wound size for sample was 123 mm2, range (21 - 350 mm2) Median wound size for Hydrocellular foam was 114.5 mm2 and 144.5 mm2 for saline soaked low adherent dressing. Median Wound duration 15.2 weeks, range (1 week - 6 years) ABPI < 0.8 A) 14 B) 16
	Interventions	A) Allevyn hydrocellular foam dressing B) Saline soaked (low adherent) dressing and standard podiatric care
	Outcomes	1) Proportion healed over 13 weeks A) 6/14 = 43% B) 4/16 = 25% 2) Time to healing - Not significantly different between both groups p = 0.325
	Notes	The study also reported the proportion of patients in each group that demonstrated a

		50% area reduction over 13 weeks: A) 13/14 = 93% B) 12/16 = 75% The study reports that after adjusting for covariate risk factors: age, sex, ulcer size and duration, the hydrocellular dressing was associated with a significantly faster response (p=0.013), than saline soaked (low adherent) dressing.
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Randomization was reported however method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	Published abstract only - allocation concealment not reported.
Blinding participants	Unclear risk	Published abstract only - blinding not reported.
Blinding personnel delivering intervention	Unclear risk	Published abstract only - blinding not reported.
Blinding outcome assessors	Unclear risk	Published abstract only - blinding not reported.
Incomplete outcome data (attrition bias)	Unclear risk	Published abstract only - incomplete outcome data not reported.
Selective outcome reporting (reporting bias)	High risk	Not clear that a protocol was available, and methods did not pre-specify outcomes reported.
Other Bias	High risk	Published abstract only - other bias not discernible. Unclear if risk factors such as diabetes disease severity or others were balanced between the two intervention groups. Depth of wound between intervention groups was not reported. Study supported by an educational grant from

		manufacturer Smith & Nephew - Group Research Centre).
Notes		

26. Shukrimi 2008[26]	**Methods**	Wagner grade II diabetic foot ulcers Wound assessments every other day by a surgeon blinded to the material of the dressing.
	Participants	30 patients (31-51 yrs.), 15M/15F, mean age = 52.1 yrs. (31-65 yrs.), TcPO2 mean = 39 mmHg (36 - 42 mmHg)

	Interventions	A) Honey dressing B) Standard dressing (Povidone Iodine/Normal saline, 1:10) All patients received antibiotics and ulcers debrided initially surgically (debridement specimens were sent for culture) Wound dressing started on first postoperative day by nurses and reported as daily dressing changes.
	Outcomes	The outcomes of interest for this review were not reported in this study. The study reported the cost to buy a bottle of commercial honey. The study reported that a bottle of honey could be used for the entire period of study. No other information on cost was provided on the standard dressing.
	Notes	Other outcomes reported include: Time to healing for surgical closure A) 14.4 days (7-26 days) B) 15.4 days (9-36 days) Statistically significant difference ($p<0.005$) The study reported all patients had less pain in the honey group.
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The authors report randomization. Method of sequence generation not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding participants	Unclear risk	Not reported.
Blinding personnel delivering intervention	Unclear risk	Not reported.
Blinding outcome assessors	Low risk	The study authors reported blinding

		of outcome assessor.
Incomplete outcome data (attrition bias)	Unclear risk	Not reported.
Selective outcome reporting (reporting bias)	High risk	No protocol was reported in the study. The outcomes reported in the results section including wound culture results and time to healing for surgical wound closure was reported in the methods section. Cost was reported in the results section but was not pre-specified in the methods section.
Other Bias	Unclear risk	No information on diabetes disease severity such as Hgba1c or duration of diabetes was reported.
Notes		

27. Singh 2006[27]	**Methods**	Randomized clinical trial Ulcers x-ray to exclude Osteomyelitis Duration: two weeks First assessment at first day

		of debridement and again at day fourteen.
	Participants	59 patients - 60 ulcers, 33M/27F, DM type 1/2 = 5/55, mean age = 56.87 +/- 11.06 yrs. A) 33, 5/28 B) 27 0/27
	Interventions	A) Non-contact Ultrasonic debridement (24 KHz) performed every other day B) Sharp/surgical debridement conducted every other day
	Outcomes	None of the outcomes of interest for this systematic review were reported in the study.
	Notes	
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The study reports the subjects were randomized into the two treatment groups. The specific method of sequence generation was not specified.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Low risk	The study reports that assessment was done by two independent observers who were blinded.
Incomplete outcome data (attrition bias)	Unclear risk	Not reported.
Selective outcome reporting (reporting bias)	Low risk	No protocol was available or reported in the study. The outcomes reported in the results section were pre-specified in the methods section.
Other Bias	Unclear risk	The authors did not report other important risk factors for wound healing including disease severity

		and off-loading status.
Notes		

28. Tallis 2013[28]	**Methods**	Randomized controlled parallel group multicenter open label study Duration 12 weeks, patients seen weekly. Wounds are measured with

		length of long axis times greatest width perpendicular to long axis.
	Participants	48 patients, 32M/16F, 61 +/- 11.8 yrs., 45 Caucasian 3 AA A) 24, 16M/8F, 58.5 +/- 13.3 yrs., 22 Caucasian 2 AA B) 24 16M/8F, 63.5 +/- 9.8 yrs., 23 Caucasian 1 AA No statistically significant difference in demographics, including race.
	Interventions	A) Clostridial Collagenase Ointment (CCO) B) Saline Moistened Gauze (SMG) + Selective Sharp Debridement Randomized to both groups after baseline surgical debridement and 6.9 mean debridement in total for the SMG group.
	Outcomes	1) Direct mean costs per responder Physician office Wound clinic facility A) $832 $1607 B) $1042 $1980 Cost effectiveness analysis was used.
	Notes	.
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The study reports a computer-generated randomization sequence.
Allocation concealment (selection bias)	Low risk	The study reports randomization was centralized and for or each qualified patient investigative sites

		contacted the central call center for the next sequential pre-determined treatment assignment.
Blinding participants	Unclear risk	Not reported
Blinding personnel delivering intervention	Unclear risk	Not reported
Blinding outcome assessors	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	The study reports that 8 patients discontinued the study. The authors reported that an Intention to treat analysis was used. Specifically, last observation carried forward was utilized for missing wound area measurements at any of the weeks resulting from wound healing, early discontinuations, or for any other reasons.
Selective outcome reporting (reporting bias)	Low risk	No protocol was available for review or was reported in the study. The outcomes reported in the results section were pre-specified in the methods section.
Other Bias	High risk	The study reports that a total of 23 patients (28 in the CCO group, and 33 in the SMG group) in the study experienced 61 treatment-emergent adverse events. The specific nature of the events was not specified other than the adverse events were reported to be similar in the treatment groups and unrelated to the treatment.
Notes		

29. Vandeputte 1997[29]	**Methods**	Pre-prepared randomization listing Study period was not reported. Follow up period was 12 weeks. Patients were followed up every 4 weeks.
	Participants	29 patients with 30 wounds A) 15 patients (15 wounds)

		B) 14 patients (15 wounds) No description of age, sex, or type of diabetes. Baseline wound area measurement not reported.
	Interventions	A) Hydrogel B) Dry gauze (control) includes moistened gauze with antiseptic. Other ancillary wound care measures not reported.
	Outcomes	Complete Healing at 3 months A) 14/15 (93%) B) 7/14 (50%) Infective complications A) 1/15 (7%) B) 7/14 (50%) Amputations A) 1/15 B) 5/14
	Notes	 Other outcomes reported included: Peri-ulcer maceration A) 11.6% B 22.1% Low grade skin reactions/allergies reported qualitatively in both groups, no numerical data provided.
Risk of bias table		
Bias	Authors' judgment	Support for judgment

Random sequence generation (selection bias)	Low risk	Specific sequence generation procedure was not reported: "patients were allocated to treatment groups according to a pre-prepared randomization listing".
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding participants	Unclear risk	Blinding of participants was unclear in the report.
Blinding personnel delivering intervention	Unclear risk	Blinding of personnel delivering intervention was unclear.
Blinding outcome assessors	High risk	Blinding of outcome assessors: no - same nurses as personnel and outcome assessors.
Incomplete outcome (attrition bias)	Unclear risk	Lack of clarity concerning patient deaths in control group. Methods and Results sections report control group as n=14. Results section states: "one patient of the control group died. One patient had a wound on both legs. The number of legs treated was 30 (15 in each group)". Two deaths in the control group are reported in the 'Overall healing time' Table 5 in the Results section: '2 - died during trial' in the control group, although the total participants remain stated as n=14.
Selective outcome reporting (reporting bias)	Low risk	Nine parameters were pre-specified as outcomes, all of which were reported.
Other Bias	High risk	Author had an affiliation with wound product manufacturer.
Notes		

30. Whalley 2001[30]	**Methods**	RCT Randomized into 2 comparison groups Study period not reported, follow up period was 10 weeks.
	Participants	74 patients; (66 patients evaluated) no further data were available including how many patients allocated to each group. Age 55.2 +/- 9.4

	Interventions	A) Purilon Hydrogel B) Intrasite Hydrogel using Biatain Non-adhesive dressing (Coloplast A/S) as a secondary dressing Dressings changed at least every second day
	Outcomes	1. Complete healing at 10 weeks A) 35% healed B) 19% healed No report of whether this was a statistically significant difference. 2. Change in mean wound area A) 2.5 cm2 (SD 3.2) to 0.6 cm2 (SD 1.1) B) 2.4 cm2 (SD 2.9) to 1.0 cm2 (SD 1.8)
	Notes	Offloading reported in both groups. Abstract only, limited data Other outcomes reported included: Peri-ulcer maceration A) 11.6% B 22.1% Low grade skin reactions/allergies reported

		qualitatively in both groups, no numerical data provided.
Risk of bias table		
Bias	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Published abstract only - Randomization reported but method of sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Published abstract only - allocation concealment not reported.
Blinding participants	Unclear risk	Published abstract only - allocation concealment not reported.
Blinding personnel delivering intervention	Unclear risk	Published abstract only - allocation concealment not reported.
Blinding outcome assessors	Unclear risk	Published abstract only - allocation concealment not reported.
Incomplete outcome data (attrition bias)	Unclear risk	Published abstract only - incomplete outcome data were reported but assessment and how outcome data were addressed is not discernible. "66 patients were evaluable" from the 74 patients recruited.
Selective outcome reporting (reporting bias)	Unclear risk	Published abstract only - selective reporting not discernible.
Other Bias	Unclear risk	Published abstract only - other bias not discernible.
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