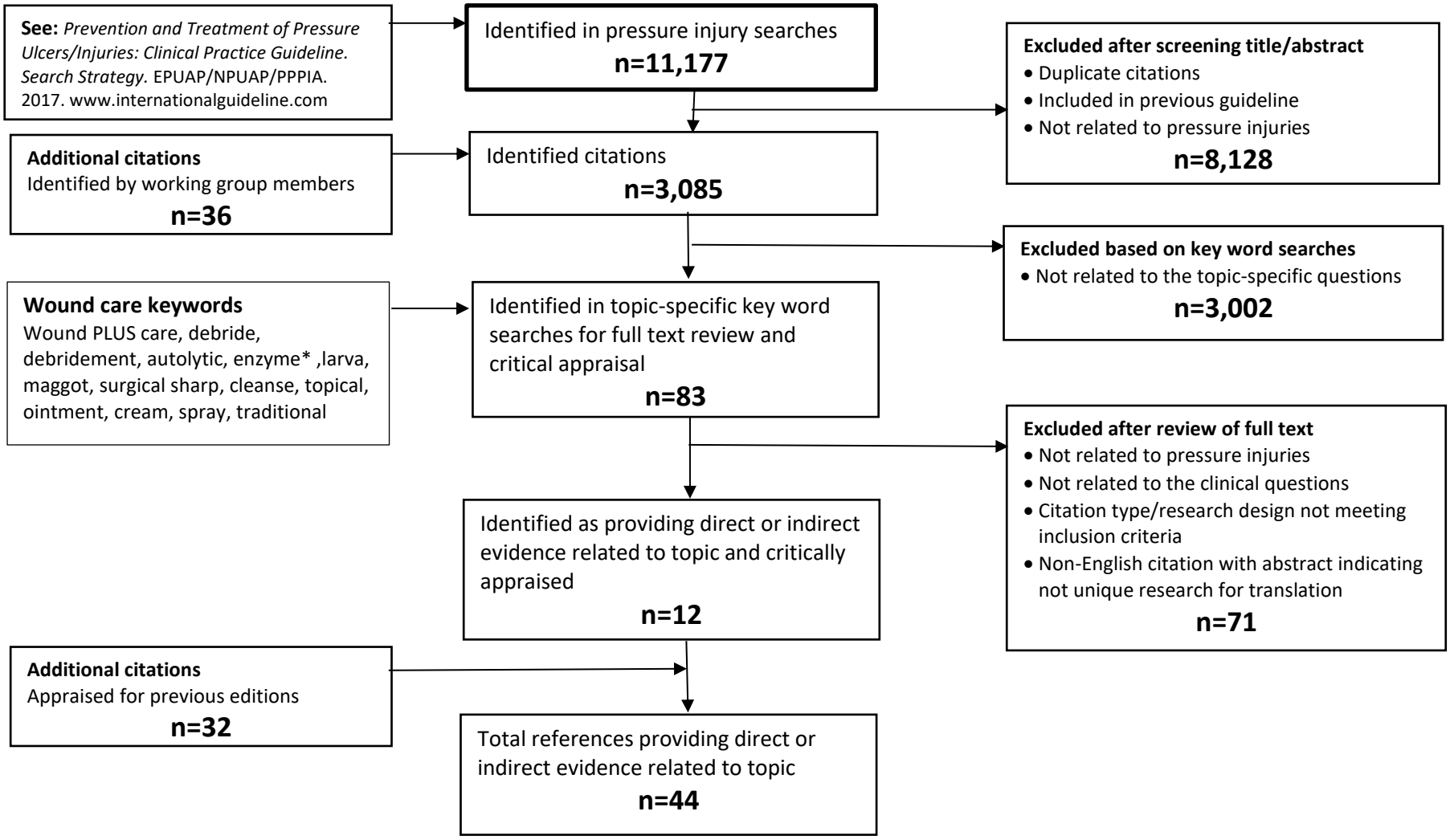
Search results for 2019 International Pressure Injury Guideline: Wound care



European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel and Pan Pacific Pressure Injury Alliance. Prevention and Treatment of Pressure Ulcers/Injuries: Clinical Practice Guideline. The International Guideline. Emily Haesler (Ed.). EPUAP/NPIAP/PPPIA; 2019

Articles Reviewed for International Pressure Injury Guideline

The research has been reviewed across three editions of the guideline. The terms pressure ulcer and pressure injury are used interchangeably in this document and abbreviated to PU/PI. Tables have not been professionally edited. Tables include papers with relevant direct and indirect evidence that were considered for inclusion in the guideline. The tables are provided as a background resources and are not for reproduction.

European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel and Pan Pacific Pressure Injury Alliance. Prevention and Treatment of Pressure Ulcers/Injuries: Clinical Practice Guideline. The International Guideline. Emily Haesler (Ed.). EPUAP/NPIAP/PPPIA; 2019

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
Wound cleansing							
Hiebert & Robson, 2016	RCT comparing HCOl to saline for use with ultrasonic debridement healing pressure injuries	Participants were recruited by unknown means (n=17, n=12 with PUs) No inclusion/exclusions criteria No patient characteristics	Randomly assigned by unknown methods to: HCOL or saline All received ultrasonic debridement plus silver dressings for 7 days	• wound complications	• Fewer wound complications were observed in the HOCl group (35% versus 80%).	• Very small study • No statistical analysis • Methods of randomization and allocation concealment not reported • No blinding	**Level of Evidence: 1** **Quality: low**
Luan, Li, & Lou, 2016	RCT comparing humanized nursing and wet therapy to regular treatment for healing pressure injuries	Individuals were recruited in one hospital in China (n=50) Inclusion criteria: Category/Stage II and III pressure injuries Participant characteristics: Average age 63±2.5years 29/50 were Category/Stage III, 21/50 Category/Stage II Primarily sacroiliac	Randomly assigned by unknown methods to: • Intervention: Treatment with humanized nursing in combination with wet healing therapy that involved cleansing with saline (n=25) • Control: disinfection with 0.5% iodophor, air exposure until scabbing. If blistering present, liquid extracted and sterile gauze applied (n=25) • 28 day study	• Criteria for outcome: ○ Healing: epithelium regenerated and PUSH score 0 ○ Effectiveness: When skin appearance was not abnormal, total score of PUSH decreased ○ Ineffectiveness: When no amelioration in the wound's condition and PUSH remained the same ○ Deterioration: when surrounding skin festered, color deepened, any secondary infection occurred and total PUSH score increased	• The experimental group noted improvement rate that was deemed statistically significant: ○ Overall: 92% experimental group vs 60% control group, p<0.001 ○ Category/Stage III pressure injuries improvement rate 92.31% versus 71.43%, p<0.001 ○ Category/Stage III pressure injuries improvement rate 91.67% versus 45.45%, p<0.001 • Pressure injury area decreased from baseline significantly in both groups, but significantly greater in experimental group (p<0.05)	• Refers to "Branden scoring" throughout • "Humanized nursing" not defined • Wet healing therapy not defined • Debridement therapy differed between groups • Cleansing solutions differed between groups • Offloading interventions only for experimental group • Questionable ethical approach • Lacking objective assessment parameters	**Level of Evidence: 1** **Quality: low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
A. Bellingeri et al., 2016	RCT exploring the **efficacy of a propylbetaine-polihexanide solution for wound cleansing**	Participants were recruited in six clinical centers in Italy (n=289) Inclusion criteria: • Aged ≥ 18 years • PU Category II or III or a vascular wound • Braden score ≥ 10 • Wound area <80cm^2 Exclusion criteria: • Terminally ill • Antibiotic/antiseptic within 10 days • Braden score < 10 • Corticosteroids, immunosuppressants, radiotherapy • Difficult to reposition • Unable to use pressure redistribution mattress • DFU • Necrotic dry eschar Participant characteristics: • Mean age 77-79 years • Approximately 35% PU, 50% VLU, 18% mixed etiology	• All wounds irrigated with syringe with 20-30mls and needle 19-20G • Application of wound irrigation pack for at least 10 minutes • Participants were randomized to receive pack of: ○ propylbetaine 0.1% and polihexanide 0.1% (PP) (n=143 randomized and analyzed, n=141 completed), or ○ normal saline (n= 146 randomized and analyzed, n=139 completed)	• Wounds assessed at every dressing change • Assessment formally at baseline, day 1, day 14, day 21 and day 28 using Bates-Jensen Wound • Assessment Tool (BWAT) (lowest score = healthier) • Wound inflammation assessment was based on five BWAT items (exudate type, exudate amount, surrounding skin color, peripheral tissue edema, peripheral tissue induration). • Pain assessment on a 11-point VAS	**Wound improvement on BWAT** • For overall BWAT score, the PP group showed significantly better improvement than the normal saline group at day 28 (p=0.028) • For wound inflammation assessment, the PP group showed significantly better improvement than the normal saline group at day 28 (p=0.03) **Pain** • There was no significant between group differences in pain scores **Adverse events** There were no adverse events during the study **Author conclusion: PP solution is superior to normal saline for reducing inflammation of the wound bed and accelerating healing in chronic wounds**	• Small attrition with no difference between groups and reason was loss to follow up or death unrelated to treatment • Approximately 25% of wounds were PUs • Does not report randomization or allocation methods	**Indirect evidence: (wounds primarily of different origin, only 25% pressure injuries, results not reported by etiology)** **Quality: Moderate**
Ho, Bensitel, Wang, & Bogie, 2012	Double blind prospective RCT **investigating pulsatile lavage for PU cleansing**	Participants recruited from an inpatient facility (n=28) Inclusion: • aged > 18 yrs with SCI • stage III and IV pelvic PUs, presenting as clean with no odor,	All participants received standard care according to clinical guidelines. Participants were randomised to receive either:	• Length, width and depth of PU obtained weekly for 3 weeks • PU depth using saline injection method • PU healing rate over the 3-week study period	Wound healing • Both linear and volume measurements showed improvements over time for both groups • Time trend analysis revealed greater improvements for	• Small number of participants and underpowered • Strict exclusion criteria excluded 221 participants	**Level of Evidence: 1** **Quality: moderate**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
		necrosis, minimal exudate, no tunnelling or fistula, no cellulitis, no erythema of surrounding tissue • PU maximum diameter of 3 to 15cm at baseline • No antibiotics within preceding 7 days • no malignancy or vascular disease associated with PU • no diabetes, heart disease or renal failure Characteristics: • Primarily ischial PUs • No significant demographic differences • Mean age 55 to 57 years	• Daily low pressure pulsatile lavage treatment with 1 litre of normal saline at 11 psi applied over 10 to 20 mins using a device designed for the procedure (n=14) or • Sham treatment in which no lavage was administered directly to the PU but participants were given the impression it had been (n=14) Dressings were removed before the commencement of treatment and replaced at the completion of treatment	• Random-coefficient models	the treatment group with the following mean between group differences: ○ Depth: -0.24 (0.09 to -0.58) cm/wk (p<0.001) ○ Width: -0.16 (0.06 to -0.39) cm/wk (p<0.001) ○ Length:- -0.47 (0.18 to -1.12) cm/wk (p<0.0001) ○ Volume: -0.33 (0.13 to -0.80) cm^3/wk (p<0.001)	• All 95% CIs span the null value, decreasing confidence in the significance of the results.	
R. Bellingeri et al., 2004	RCT exploring saline solution cleansing vs cleansing with a aloe vera/silver spray for healing pressure injuries	Participants were older adults (n=82) Inclusion criteria: • Pressure injury Category/Stage I or greater within 10 cm x 10 cm, • Admitted > 24 hours. Participant characteristics: age range 56 to 84 years	• Randomized to receive: ○ Intervention: cleansing with a saline spray with Aloe Vera, silver chloride and decylglucoside (Vulnopur®). (n=36) ○ Control: cleansing with isotonic saline solution (n=46) • 14 day study	• Pressure Sore Status Tool (PSST)	**Change in PSST at day 14** Intervention group has significantly greater reduction in PSST than isotonic saline control group (-22.7±31.3 versus -11.7±24.1, p=0.02)	• Methods of randomization and allocation concealment not reported • Unclear if blinded • No ITT analysis • Short follow up • Mechanisms of product not explained	**Level of Evidence: 1** **Quality: low**
Konya, Sanada, Sugama,	Historical control quasi-experiment **comparing**	Participants were older adults recruited in a long term care hospital (n=189)	• Participants received either:	• Rate of ulcer healing and the time it took to heal	• Healing time shorter with a pH-balanced skin cleanser and water	• Anatomical location of pressure injuries was not reported	**Level of Evidence: 2**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
Okuwa, & Kitagawa, 2005	**cleansing of the peri-wound skin with saline versus skin cleanser**	Inclusion criteria: At least 65 years of age pressure injuries Category/Stage II or greater Characteristics: Primarily Category/Stage II pressure injuries	○ cleansing of the peri-wound skin with normal saline (n = 95) or ○ cleansing with a pH-balanced skin cleanser (n = 90).	• Not reported how this was measured	• Decreased healing time only statistically significant for Category/Stage II pressure injuries (median healing 15 days versus 20 days, p=0.002), amounting to 1.79-fold faster healing •		**Quality: low**
Chizuko Konya et al., 2005	Observation study of microbial numbers on peri wound skin	Participants were recruited in a long term care facility (n=17) characteristics: 7 trochanter, 3 ischial and 7 sacral.	• Collected skin debris with a cotton ball • Periwound cleansing with normal saline in 5 participants with samples collected immediately after cleansing, 6 hours after cleansing and 24 hours after cleansing • Three participants had the same procedure above but with povidone iodine skin cleanse	• Analysis of squalene and cholesterol, proteins	• Significant decrease ($p<0.05$) in periwound microbial counts immediately after cleansing, but returned to baseline by 24 hours	• Minimal patient details • Location of pressure injury may influence findings (e.g. high contamination of sacral regions) • Legitimacy of microbial analysis is unclear • 17 recruited, only 5 used in the analysis	**Level of Evidence: 4** **Quality: low**
Topical agents for promoting wound healing							
Topical sildenafil (increases blood flow)							
Farsaei, Khalili, Farboud, & Khazaeipour, 2015	Non-blinded RCT investigating **the effect of topical sildenafil in healing PUs**	Participants screened from an ICU department in Iran (n=122 met inclusion criteria) Inclusion criteria: • Aged 18 years or over and consenting • PU grade I or II on two-digit Stirling scale (equivalent to Category/Stage I and II)	• All participants received standard care as appropriate including preparation of wound bed, pressure reduction, medical comorbidity management and nutritional support.	Daily wound inspection for 2 weeks Visual inspection Digital photography Outcome measures: change in two-digit Stirling scale score change in wound surface area (WSA)	**Completion of trial/ withdrawals** • Withdrawals excluded from analysis: 8 from treatment group, 9 from control group (death, exacerbation of wounds requiring debridement, transfer)	• Randomization and concealment methods not reported • No ITT analysis • Unclear how wound measurement made or by whom (no interrater reliability reported) • Outcome measure assumes	**Level of evidence: 1** **Quality: Low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
		• Only one PU with highest score included per participant Exclusion: • PU stage III or IV • Any sign of clinical infection (e.g. erythema, purulent exudate, increased pain or friability, bright red granulation tissue, wound surface breakdown, foul odor) • Hypersensitive to product (nb. Product contained beeswax) Characteristics: • Mean age 62 years • No significant difference in comorbidities including CV disease, diabetes, malignancy • No sig difference in wound locations • Silendafil group had significantly lower mean Stirling score at baseline (1.5 vs 1.74, p=0.001)	• Participants were randomized to receive: ○ Daily application sildenafil 10% ointment (n=60, 52 completed) ○ Daily application placebo ointment (n=62, 53 completed)		• No significant difference between groups in excluded subjects (p=0.12) **Change in two-digit Stirling scale score** Silendafil group significantly more likely to have decrease in Stirling score at day 7 (1.1 vs 1.74, p<0.001) and day 7 (0.90 vs 1.71, p<0.001). **change in WSA** Silendafil group significantly more likely to have decrease in WSA at day 14 (p=0.007) but not at day 7 (p=0.242). **Adverse events associated with treatment** • None reported • N.b. beeswax is used in product preparation.	Category/Stage regression • Participants with worsening wound condition were excluded from analysis • Wound severity was not equivalent at baseline • Silendafil is an oil-based, water resistant ointment.	
Topical atorvastatin (statin)							
Farsaei, Khalili, Farboud, Karimzadeh, & Beigmohammadi, 2014	To evaluate the effects of **topical atorvastatin on the healing process of pressure ulcers in critically ill patients**	Participants recruited in an ICU of a university-affiliated teaching hospital in Tehran, Iran (n=104) Inclusion criteria: • Category/stage I or II pressure injuries (Stirling Pressure Sore Severity Scale)	• Patients were randomized to receive: ○ topical atorvastatin 1% ointment [atorvastatin group]) (n=51) or ○ placebo ointment (n=53)	• The efficacy of each treatment was assessed on days 7 and 14. • Efficacy was determined based on the degree of healing of the existing pressure injury by using the 2-digit Stirling scale	**The mean +-SD stage of pressure ulcers** significantly decreased in the atorvastatin group compared with the control group on day 7 (0.97±0.76 vs 1.74±0.75, p<0.01) and day 14 (0.42 ±0.67 vs 1.71±0.78, p<0.01) of treatment	• Small study in single location	**Level of evidence: 1** **Quality: High**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
			• Cream applied once/day to pressure injuries for 14 days in addition to standard care		**Wound surface area** In addition, the mean±SD surface areas of ulcers in the atorvastatin group were significantly declined compared with the control group after 7 days (5.55±4.55 vs 9.41±5.03 cm2 , p<0.01) and 14 days (3.72± 4.45 vs 10.41±6.41 cm2 , p<0.01) of treatment .		
Topical insulin							
Stephen, Agnihotri, & Kaur, 2016	Non blinded RCT investigating effect of topical application of insulin versus normal saline in healing PU	Participants recruited from neurosurgical ICU and neurology wards at a trauma center in India (n=70) Inclusion criteria: Category/Stage II or III pressure injuries Exclusion criteria: • Immunodeficiency • Diabetes • Pregnancy • Osteomyelitis • peripheral vascular disease Characteristics: • Mean age control 41.46 years • Mean age intervention 43.36 years • No sig diff in LOS, wound duration, frequency of position change, baseline wound area, Pressure Ulcer Scale for Healing Length and width calculated using (PUSH) score.	Participants randomized to: • Control group: Application of sterile saline soaked gauze (normal saline 0.9%) twice daily. (n=35) • Intervention: Application of Actrapid (human insulin) sprayed using insulin syringe allowed to dry for 15 minutes then covered with sterile gauze. Applied twice daily. (n=35)	• Change in ulcer size at day 4 and day 7 • Change in PUSH score at day 4 and day 7 • Ulcer size calculated using transparent sterile paper over wound to mark borders. Two largest perpendicular diameters were measured in cm using ruler. These two measurements were multiplied to obtain total cm^2	**Change in ulcer size day 4** Sig diff in ulcer size at day 4 with intervention group demonstrating greatest reduction (p=0.043) **Change in ulcer size at day 7** Sig diff in ulcer size at day 7 wit intervention demonstrating greatest reduction (p=0.013) **Change in PUSH scores at day 4** was significant with intervention showing greater decrease (p=0.141) **Change in PUSH scores at day 7** was significant with intervention showing greater decrease (p=0.003) No adverse events reported	• Not blinded • No adjunct wound care described • Small sample size • Short follow up period • Ulcer location not described • Method for wound measurement has questionable reliability • Wound depth not part of measurement • Withdrawals excluded from analysis: 5 from intervention and 5 from control	**Level of Evidence: 1** **Quality: Low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
Topical nitric oxide cream							
Saidkhani, Asadizaker, Khodayar, & Latifi, 2016	Controlled trial exploring the effect of topical nitric oxide cream for healing PUs	Participants were recruited in ICUs in university hospitals in Iran (n=58 enrolled Inclusion criteria: • Aged ≥ 18 years • Category/Stage II PU or greater • Non-smokers Exclusion criteria: • Cancer, vascular disease, lupus, rheumatoid arthritis or renal failure • Drug use that increases levels of nitric oxide Participant characteristics: (not significantly different between groups) • Mean age 55 years • Mean BMI 32kg/m^2 • Primarily sacral ulcers • Primarily Category/Stage II PU • Most patients had complete immobility • Participants were receiving feeding tube or TPN • Baseline ulcer size approx. 9.5 on 11 point scale, tissue type 2.6 on 5 point scale, exudate 2.4 on 4 point scale.	• Participants received repositioning, ulcer cleansing and Comfeel dressing • Participants received either: ○ nitric oxide cream (sodium nitrite 6% cream followed by p citric acid 9% mixed in the wound bed) (n=29) or ○ placebo cream (n=29) • 30 mins after cream application the PU was re-irrigated and new dressing applied • Dressings changed second daily for 3 weeks	PUSH tool used to measure ulcer size (ruler; scored on a 0 to 10 scale) exudate volume (scored as 0-3 based on absorption into sterile gauze) and tissue type (scored on 0 to 4 scale with 0 being healed and 4 being necrotic) PUSH scored at baseline then weekly or 3 weeks	**Change in ulcer size** • Nitric oxide group: not significant in week 1 but significant improvement from week 2 (p=0.008) and week 3 (p=0.000). Baseline size mean size score 9.64 ± 2.49 to week 3 mean size score 8.83 ± 2.64. • Control group not significant in week 1 or 2 but was significant in week 3 (p=0.01). Baseline size mean size score 9.56± 2.59 to week 3 mean size score 9.20± 2.62. • No significant difference between groups. **Change in exudate volume** Nitric oxide group had significant decrease in exudate volume in second (p=0.01) and third weeks (p=0.005) Control group had significant decrease in exudate in week 3 (p=0.02) **Change in tissue type** Nitric oxide group had significant improvement in third week (p=0.01) Control group had significant improvement in third week (p=0.04) **Author conclusion: Nitric oxide can be used as a complementary topical**	• By acidification of nitrite (NO2), nitric oxide is released from dinitrogen • trioxide interface (N2O3) • Semi-randomized group assignment • Research attending wound and completing PUSH scores was not blinded • No statistical comparison between groups • Healing by size was not directly reported but was transferred to a 11 point scale. • Three weeks was insufficient followup to determine any difference in complete healing	**Level of evidence: 2** **Quality: Low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
					treatment to improve PU healing		
Topical phenytoin							
Inchingolo et al., 2017	RCT to demonstrate the validity of phenytoin as a topical treatment	Participants were recruited in unknown method (n=19) Inclusion criteria: Older age patients undergoing bone marrow transplant for Hodgkin's or kidney disease and maintained on bed rest Pressure injury Exclusion criteria: Serious disease	Participants received either: • Sodium phenytoin powder dissolved in saline and applied with gauze to pressure injury, with gauze remaining on pressure injury for 3 hours and replaced every 3 hours (n=11), or • Comparator: gauze soaked in saline only applied to pressure injury (n=8)	• Healing (not defined and measurement method not reported)	Pressure injuries treated with phenytoin powder healed significantly faster (19.36±3 days versus 28.75±2.43 days, p<0.001)	• Method of randomization and allocation concealment not reported • Very small sample size • Comparability of groups was not established (e.g. pressure injuries might have been different severity) • Comparability of treatment beside wound care not reported • Unknown if any withdrawals or if ITT analysis	**Level of Evidence: 1** **Quality: low**
Topical hemoglobin spray							
Tickle, 2015	Case series exploring **efficacy of hemoglobin spray for healing PUs**	Participants were recruited at multiple centers in UK by unknown methods (n=19 commenced, n=18 completed) Inclusion criteria: • Aged ≥ 18 years • PU grade 2,3 or 4 Exclusion criteria: • PU category/stage 1 • Pregnant or lactating • Unable to tolerate topical agent	• Participants were treated with hemoglobin spray • Standard wound dressing regimens were used including foams, hydrofibers, and hydorgels • Pressure redistribution and offloading	PU grading tool by EPUAP Wound size and depth Wound bed characteristics (percent of slough, granulation tissue and/or epithelial tissue) Exudate (none, mild, mod or severe) Pain on a 11 point scale from 0 to 10	**Healing** • 17/18 PUs showed reduction in size after 4 weeks • Average PU depth decreased from 0.97cm to 0.37cm • 100% PUs showed reduction in slough • Average granulation tissue increased **Author conclusions: Topical hemoglobin spray can promote healing in PUs**	• Participant recruitment not reported • Small sample size • No control group • No blinded outcome measurement • No statistical analysis • Minimal participant characteristics	**Level of evidence: 4** **Quality: Low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
		• Clinical signs of infection Participant characteristics: • Mean age 65 years (range 34 to 91) • 9 sacral PUs, 7 heel PU and elbow and hip PU) • Average wound duration was 11 weeks • Mean size 11.23cm2 (range 0.25cm2 to 52cm2)					
Topical hyaluronate cream							
Felzani et al., 2011	Double-blind RCT **comparing lysine hyaluronate cream to sodium hyaluronate cream for managing PUs**	Participants recruited from a hospital in Italy (n=50) Inclusion: • >18yrs of age • Stage I to III PU using EPUAP staging system • Mean age approx. 65 years • 18% of participants had diabetes	• All PUs were initially cleaned with saline and debrided as required. • Participants were stratified by PU stage. Randomized to receive either: o lysine hyaluronate cream (Lys-HA, n=25) or o sodium hyaluronate (SH, n=25) • For all PUs, the topical hyaluronate was applied as a thin layer across the ulcer surface and overed with fat gauze then sterile gauze. • Dressing changes were daily during the first week and every other day the second week. • Duration of active treatment of 15 days	• Wound size • Time to reach 50% reduction in wound size • Photographs and planometry were taken before the treatment and then every 3 days and at the end of the study	• PU reduction was greater and faster in the Lys-HA groups than SH groups. **Stage I PU results** (n=20, 10 each group) • The Lys-HA had significantly greater total PU healing over 15 days (90% versus 70%, p< 0.05) • Time to reach 50% reduction in wound size was faster in Lys-HA group (9 versus 15 days, p<0.05) **Stage II PUs** (n=20, 10 each group) • The Lys-HA group had significantly greater total PU healing over 15 days (70% versus 40%, p< 0.02) • Time to reach 50% reduction in wound size was faster in Lys-HA group (9.5 versus 15 days, p<0.05) **Stage III PU** (n=10 participants with 14 PUs, 7 PUs in each group) • Time to reach 50% reduction in wound size was faster in Lys-HA group (12.9 versus 19.2 days, p<0.05) • **Study conclusions: This small, underpowered study without a placebo control found lysine hyaluronate cream was**	• Small study and overall results are not reported (only stratified by PU severity) therefore unclear if adequately powered • Lack of inclusion of patients with stage IV PU • Wound size and condition and co-morbidity at commencement not reported • No reporting of effect overall (i.e. not by stratified groups) • Participants who dropped out (approx. 18%) not included in analysis • Wound size not reported • No placebo control • No definition of standard care and how this relates to intervention tested.	**Level of evidence: 1** **Quality: low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
					associated with faster healing over 15 days compared with sodium hyaluronate for stage I to III PUs. The study is of a weak quality and provides insufficient support for use of this product.		
Topical herbal preparations and Chinese medicine							
Niu, Han, & Gong, 2016	Non blinded RCT investigating effect of topical application of Ligustrazine (a plant extract) on pressure injuries	Participants were recruited in hospital in China (n=32) Inclusion criteria: • Category/Stage II or III pressure injuries Exclusion criteria: Not stated Participant characteristics: • Mean age intervention group 63.33 years • Mean age control 64.21. • No sig difference in wound duration at baseline	• intervention (n=16): Ligutrazine transdermal patch applied weekly to the wound bed for 4 weeks. Ligustrazine (an alkaloid extracted from the plant Ligusticum chuanxiong Hort) is a Chinese medicinal herb thought to have antioxidant, neuron-protection, antifibrosis, anti-nociception, vasorelaxation, anti-inflammation, and anti-proliferation properties. • control (n=16): Compound Clotrimozole cream covered with wet dressing changed 1-2 times daily.	Therapeutic effect on PUs assessed using a traditional Chinese Medicine scale. Scale applied after 4 weeks of continuous treatment. By whom pressure injuries/other outcomes were measured – not stated.	**Wound condition** Therapeutic effect on PU Intervention group: 11 healing, 9 markedly effective, 2 effective, 4 ineffective versus control Group outcomes:8 healing cases, 8 markedly effective, 2 effective, 4 ineffective No OR or CI reported, p<0.05 **Healing time** intervention 9.33 days versus 24.26 days	• In Vitro aspects of studied not included here Unblinded • Randomization method not stated. • Insufficient info on participant selection • Insufficient information on baseline wound characteristics • Unvalidated scale used to determine therapeutic effect • Unclear how 'time to healing' was calculated	**Level of Evidence: 1** **Quality: low**
Buzzi, Freitas, & Winter, 2016	Observational study evaluating the therapeutic benefits of	Participants assessed and followed up in dermatology outpatient clinic in hospital in Brazil (n=41)	Plenusdermax® (Phytoplenus Bioativos S.A., Pinhais, PR, Brazil) topical spray applied to	• Wound area calculated from photographs using planimetry	**Wound Area** All small wounds completely healed at 30 weeks and 58% of larger wounds. (No significant	Uneven group sizes during trial and in subsequent analysis.	**Level of evidence: 4**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
	Plenusdermax® , Calendula extract on the healing of pressure injuries	Inclusion criteria: • Aged 18 – 90 • No allergy to any products used. • Category/Stage II or III pressure injury, present for at least 5 weeks between 1-30 cm^2 in sacral or trochanteric region. • Non-diabetic. Exclusion criteria: • Category/Stage IV pressure injuries • Necrotic tissue unable to be debrided by nursing staff. • Infected pressure injuries • Significant co-morbidities impairing healing (renal / liver failure, anemia, malnutrition, immunocompromised). • Pregnancy, childbearing age not using contraception • Corticosteroids, Immunosupressants, radiotherapy, chemotherapy	target pressure injury twice a day after wound cleaning with sterile saline, by participants / caregivers. Product allowed to dry for 5 minutes and wound occluded with sterile gauze. (Calendula officinalis flower extracts claimed to have antinflammatory properties	• Degree of wound contraction per week (mm^2/week) . • Wound healing rate per week (WHR%). • Total follow up – 30 weeks • Sample split into two groups for analysis and presentation of results. Small pressure ulcers (1.0 – 3.9 cm^2) and large ulcers (4.0 – 11.0 cm^2). .	difference between small and large wounds p = 0.857) **Wound contraction rate** wound contraction rate was 52% higher in large wounds (No significant difference between small and large wounds (p = 0.465). **Wound healing rate** Smaller wounds healed twice as fast as large wounds (p = 0.027). **Authors conclude that Plenusdermax® , Calendula extract is a safe and promising therapy for treating pressure injuries**	Potential variability in product application by patients / carers during trial period.	**Quality: Low**
Liu, Meng, Song, & Zhao, 2013	RCT exploring a **novel Chinese herbal formula, cure rot and flat sore ointment (CRFSO) in the management of Category/Stage IV pressure injuries**	• Participants were recruited in inpatient rehabilitation in China from January 2004 to September 2010 (n=35) • Inclusion criteria: • Paraplegic patients • Category/Stage IV pressure injuries that underwent reconstruction Participant characteristics:	Participants were randomized to receive either: • Arnebia root oil (ARO) plus gentamicin wet gauze (16 patients with 11 PIs) • used (cure rot and flat sore ointment) CRFSO that contains gypsum fibrosum and three herbal	After 28 days of treatment, the wound healing results, in particular, the healing rate, effectiveness rate, improvement rate and no response rate were evaluated.	All outcome variables demonstrated significant improvement in the CRFSO group compared with the ARO group after 28 days of treatment, with a higher healing rate (85% in the CRFSO group and 45.45% in the ARO group) and lower no response rate (5% in the CRFSO group and 18.18% in the ARO group).	limited by sample size, the results 17% withdrawal rate due to poor efficacy (all in ARO group) Selection of participants and assignment to groups is very unclear Subjective outcome evaluation	**Level of Evidence: 3** **Quality: low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
		• No difference at baseline in pressure injury area	medicines applied after a saline cleanse, phototherapy, debridement of necrotic skin(19 patients with 20 PIs)		No ointment related adverse events		

Li, Ma, Yang, Pan, & Meng, 2017	To evaluate the efficacy and safety **of moist exposed burn ointment (MEBO) in the treatment of pressure ulcers in Chinese patients.**	Participants were recruited in a hospital in China (n=72)
		• Inclusion criteria:
		  • 18-75 years old
		  • Pressure injury Category/Stage III to IV
		• Exclusion criteria:
		  • Therapies that could affect healing e.g. corticosteroids, radiation therapy or chemotherapy
		  • complications of PVD
		  • malignant tumors
		  • Diabetes mellitus,
		  • Infections
		  • Severe liver, cardiac, and kidney diseases
		• Participant characteristics:
		• Age simular , sex MEBO group male 22 placebo 16, female 14 MEBO group, 20 placebo
		• Weight similar, height similar, BMI similar,
		• Hospital stay similar
		• 4 more stage III PU in MEBO group, 4 more stage IV in placebo group.
		• WSA, PUSH score, VAS all simular
		• Main diagnosis similar
			• All participants: positional change every 2 hours, mattress that helped vulnerable skin, pain control Ibuprofen 200mg evey 6 hours as needed.
			• All wounds received:
			• Betadine to clean, saline to cleanse
			• Participants randomized to receive:
			○ intervention: moist exposed burn ointment (MEBO) smeared onto wound to 1mm thickness twice daily. MEBO not removed in first 4 days of treatment, fifth day MEBO removed the MEBO applied twice a day.
			○ placebo applied to same regimen as the MEBO intervention
				• Unclear who evaluated wounds
				• Measurement at baseline, at one month, then at two months
				• Method for determining wound surface area not stated.
				• Staging system used EPUAP/NPUAP
				• Participants were in the study for two months, no follow up after this time frame.
				• States adverse events where recorded,
					Wound Surface Area cm²
					• Month one: Intervention: -8.3 (95% CI -11.7 to -6.5) versus control -3.4 (95% CI -7.5 to -2.1), mean difference -4.9 (95% CI -6.9 to -3.4, p <0.1)
					• Month two: Intervention: -14.6 (95% CI -17.1 to -7.3) control -8.7 (95% CI -12.3 to-4.6), mean difference -6.0 (95% CI -8.8 to -3.3, p <0.1)
					
					PUSH Tool
					• Month one: Intervention -4.8 (95% CI -6.1 to -3.6) versus control -3.1 (95% CI -5.7 to -2.0), mean difference -1.8 (95% CI -2.5, -1.3, p<0.1)
					• Month two: Intervention -7.3 (95% CI -9.8 to -4.1) versus control -4.7 (95% CI -6.1 to -2.9), mean difference -2.6 (95% CI -4.7, -1.5, to p<0.1)
					
					• P**ain on Visual Analogue Scale**
					• Month one: intervention -2.8 (95% CI -3.3 to -2.3) versus Control -1.6 (95% CI -
						• Any limitations: no long term follow up. Individual's medications differed.
						• No indication of where funding came from.
						• No indication of who created MEBO and its link to the organizations involved.
						• No mention of the issue of conflict of interest
							Level of Evidence: 1
							
							Quality: High

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
		• Location 4 more in MEBO group sacrum, 4 more in placebo heel, trochanter similar, buttock similar.			2.3 to -1.0), mean difference -1.4 (95% CI -1.9 to -0.9, p<0.1) • Month two : intervention -4.5 (95% CI -5.1 to -3.9) versus control -2.6 (95% CI 3.3,-2.1); mean difference -2.9 (95% CI -4.4 to -1.7, p <0.1) **Adverse events** • no major adverse effects reported, does not mention adverse effects of a lesser nature. • **Author conclusion: MEBO is a safe and effective for treating pressure ulcer**		
Zerón, Gómez, & Muñoz, 2007	RCT comparing collagen – polyvinylpyrrolidone (clg-pvp) application to saline solution for	Participants were recruited in one center I nMexico (n=24) Inclusion Aged > 65 years Category /stage II or II pressure injury Exclusion: Prior surgery Septic, ventilated, coma Taking steroids Characteristics Mean age 75-79 years	Participants were randomized to receive: local cleaning with soap, application of zinc oxide paste and clg-pvp (n=12), or local cleaning with soap, application of zinc oxide paste and placebo (n=12) Clg-pvp or placebo was applied to each pressure injury intradermically (1.5 ml at 4 equi-spaced points around the ulcer)	• Reduction in fibrous tissue • Reduction in pressure injury size • 3 weeks follow up	• The pressure injuries treated with clg-pvp experienced no significant difference in change in ulcer size (from a diameter of mean 3.4 to 1.41 cm vs mean diameter from 2.9 to 1.58 cm) (58,52% reduction versus 45.51% reduction, p>0.05)	• Tudy may be too short to detect significant difference • Small sample size • Poorly described treatment • Only measured diameter	**Level of evidence: 1 Quality: low**
Sipponen et al., 2008	Prospective, multicentre RCT investigating	Participants recruited from 11 primary care hospitals in Finland	Details of concurrent management strategies were limited.	• Primary outcome measure was complete	• The resin salve group achieved a higher rate of complete healing at 6	• No blinding or intention to treat analysis	**Level of evidence: 1 Quality: low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
	effectiveness of resin salves (*Picea abies*) in PU care	between 2005 and 2007 (n=37, n=22 completed and analysed) Inclusion: • grade II to IV PU • not requiring surgical management of PU • with or without clinical wound infection Exclusion: • Life expectancy < 6 months • Advanced malignant disease Characteristics: • No significant between group difference on baseline demographics or wound characteristics • Mean age approximately 74 to 80 years • Mean BMI 21.8, mean P-albumin 28.3 to 31.4 gL^{-1} • Primarily bedridden participants • Primarily non-smokers • Primarily stage II and III PUs	Approximately 22% of control group and 8% of treatment group were managed on a pressure mattress. Participants were randomly assigned to either: • resin salve applied at 1mm thickness between gauze layers with dressing changed third daily or daily for heavily exudating PUs (n=13 with 18 PUs) • sodium caboxymethylcellulose hydrocolloid polymer dressing (Aquacel®) or for clinically infected PUs, hydrocolloid dressing with ionic silver (Aquacel Ag®). Dressing changed third daily, or daily for heavily exudating PU. (n=9 with 11 PUs) • Some participants in both groups received concurrent antibiotics	healing of the ulcer within 6 months • Secondary outcome measures included eradication of bacterial strains cultured from ulcers at the study entry • Bacterial cultures were obtained from all PUs at baseline and 1 month, but thereafter only as clinically indicated. • PU size measured by digital photography and planimetry	months (92% versus 44%, p=0.003) • The speed of PU healing was significantly faster in the resin than in the control group (p=0.013) • Bacterial cultures from the PU area more often became negative within 1 month in the resin group • 100% of PUs in treatment group were rated fully healed or significantly improved versus 91% in the control group (p=0.003) • Drop outs in intervention included participants who required surgical intervention (n=2) and allergic reaction to the product (n=1). Drop outs were not significantly different between groups.	• Over 40% drop out of study. Although there was no significant difference in baseline characteristics between drop outs in each group, more treatment participants dropped out due to deteriorating PUs and had these cases been included in analysis there may not have been statistically significant effect. • Study failed to recruit and maintain sufficient numbers to reach a-priori sample size calculations. • Bacterial eradication analysis is complicated by the concurrent use of antibiotics for some participants	
Model of care							
Furuta, Mizokami, Sasaki, &	Cohort study **comparing outcomes for**	Consecutive patients receiving care for PU in Japan over a 4 year period (n=888 identified, n=868 recruited)	• "Furuta method" is poorly reported but appears to be a	• Patients were analyzed according to DESIGN-R severity of PU	**Duration of healing** For each DESIGN-R category of patients, compliance group had	• In most DESIGN-R groups, the baseline scores were	**Level of evidence: 3**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
Yasuhara, 2015	**patients who are treated by pharmacists who use versus do not use Furuta method**	Inclusion criteria: Assessed using DESIGN-R as being ≥D2 (equivalent to Category 2) Received care for ≥ 7 days Exclusion criteria: Missing demographic information Characteristics: • Mean age 80±11.3 years • At baseline there was some significant difference between the compliance and non-compliance groups in each analysis, primarily the DESIGN-R score had significant differences for those with D2, D4,5 and DU	guideline for pharmacists on managing pressure injuries with topical agents. • Components of the "Furuta method" include • Accurate assessment of the wound bed • Potential use of wound fixation by traction as appropriate • Selection of specific topical treatment (e.g. cadexomar iodine, povidone iodine etc) based on clinical characteristics of the PU	• Analysis compared compliance versus non-compliance where compliance was defined as the pharmacist using the "Futura method" to select topical treatment • Compliance was assessed using a pharmacist survey • Follow-up periods varied from 23 days to 70 days depending upon wound severity but were not significantly different between compliance versus non-compliance cohorts	faster healing than non-compliance group • D2 23.6 ± 36.8 days vs. 32.2 ± 16.6 days, p<0.001 • D3: 46.8 ± 245.5 days vs. 137.3 ± 52.7 days;, p<0.001 • D4, 5: 122.5 ± 225.7 days vs. 258.2 ± 92.7 days, p<0.001 • DU: 78.1 ± 298.9 days vs. 142.5 ± 79.4 days, p<0.001 **Author conclusions: using the "Futura method" of assessing the PU and selecting a topical agent based on PU characteristics is associated with faster PU healing**	significantly different suggesting different PU severities/characteristics between compliant versus non-compliant groups • "Futura" method had a very broad range of treatments, many of which may also have been selected for the non-compliant group using different assessment strategies • It is hard to determine if assessment or any specific topical treatment was associated with greater healing	**Quality: Low**
Debridement							
Wilcox, Carter, & Covington, 2013	Retrospective cohort study Investigating association between healing and debridement frequency	• Data base study using data from 525 wound clinic in US (n=364,534 wounds, 312,744 analyzed) • Inclusion: • Aged < 18 years • received at least one debridement for a wound • discharged from the system • Exclusion criteria: • Any advanced therapeutic treatment above what was considered standard care	• N/A	• Healing	**Rate of complete healing** • Overall 70.8% of wounds completely healed • 56.6%, lowest rate of all wound types in the database **Debridement** • Median number debridements was 2 (range 1 to 138) • A significantly higher proportion of wounds that received weekly or more frequent debridement	• Concurrent treatments differed • Confounding heal factors not addressed directly • Does not report type of debridement performed	**Indirect evidence (Mixed etiology)** **Quality: High**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
		Participant characteristics: • 16% of wounds were pressure injuries (VLUs was highest at 26%)			(healed in a shorter time p<0.001) • After adjusting for all other significant factors, higher debridement frequencies resulted in increased HRs for healing when compared with an interval between debridements of less than 2 weeks. (e.g. higher weekly debridement rates HR = 4.26 (95% CI 4.20 to 4.31).		
Shannon, 2013	Retrospective record review exploring outcomes of heel pressure injuries with an without debridement	Records in 15 nursing homes in the US were reviewed to identify patients who had heel PU (n=179) Inclusion: heel wound entirely covered with eschar or a blister Exclusion: Heel not totally covered with eschar or blister Heel PUs were defined as: • having entire eschar coverage (67.8% of sample)or having blister coverage (31.8% of sample)	Heel eschar managed with standard procedure to leave the eschar intact, but if eschar loosened it was removed with sharp debridement Heel blisters kept dry, intact, and offloaded unless ruptured and then managed according to wound policy.	155 PUs were followed to completion	**Heel pressure injury outcomes** • 154 of the wounds (99.3%) healed • 100% of eschar wounds healed with an average healing time of 11 weeks (range 2 to 50 weeks) • Complications included one patient who developed osteomyelitis (with eventual healing) and two cases of cellulitis and one eventual amputation in a patient with blister coverage of the ulcer	• Unclear how assessments were performed • Patient characteristics not reported • Other care not reported • No control group • 17.5% lost to follow up due to discharge or death	**Level of evidence: 3** **Quality: low**
Golinko, Clark, Rennert, A., & Boulton, 2009	Retrospective survey **of pathology reports for debrided PUs**	Participants were consecutive patients undergoing wound debridement in a tertiary hospital (n=98 patients, 139 debrided PUs) Inclusion: • Undergoing PU debridement Characteristics: • Participant and PU characteristics are not reported	Chronic wound biopsies of the skin edge, wound bed and bone were obtained.	Participant data for each debrided wound was recorded, with pathological findings reported at the level: • epidermis • dermis • subcutaneous • fascia • tendon • muscle	**Epidermal pathology reports (n=107**) 31% showed hyperkeratosis; 9% showed parakeratosis; 6% showed acanthosis; 4% showed gangrene **Dermal pathology reports (n=105)** 60% showed granulation tissue; 66% showed inflammation; 30% showed fibrosis; 24% showed necrosis; 4% showed gangrene	• No standardisation regarding PU duration or previous management • Debridement was not necessarily first debridement • Findings are based on researcher opinion rather than directly associated with the survey findings	**Level of evidence: 4** **Quality: low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
				• bone	**Subcutaneous tissue pathology reports (n=87)** 38% showed granulation tissue, 51% showed inflammation, 32% showed fibrosis, 55% showed necrosis, 11% showed gangrene **Fascial pathology reports (n=14)** 57% showed granulation tissue, 71% showed inflammation, 21% showed fibrosis, 29% showed gangrene **Bone pathology reports (n=70)** 20% showed granulation tissue, 33% showed acute osteomyelitis, 20% showed chronic osteomyelitis, 21% showed reactive bone **Study conclusions: Surgeons should debride a wound until there is an absence of hyperkeratosis in the epidermis and an absence of fibrosis in the dermis. Deep debridement of infected bone in the case of osteomyelitis is rarely associated with inhibition of soft tissue growth**	• Retrospective design • Indirect evidence: no relationship between debridement width or depth and wound healing outcomes was presented	
Enzymatic debridement							
McCallon & Frilot, 2015	Retrospective cohort study **exploring NPWT with and without clostridial collagenase ointment (CCO) for healing pressure injuries**	Participants recruited from two long term acute care hospitals in USA (n=114) Inclusion criteria: • Category/Stage III or IV pressure injury • Negative Pressure wound therapy (NPWT). • Clostridial Collagenase ointment (CCO) on the wound bed with or	• Regimen for intervention group: NPWT as therapeutic modality, some with and some without sharp debridement (n=67) • Regimen for control/comparison group: NPWT with CCO applied to the	• As per the long-term care facility documentation system on each dressing change. • One of four certified nurses consistently did the dressing changes • Pre-determined documentation protocol followed. • NPUAP staging system	**Change in BWAT over time** • The NPWT plus CCO group had significantly greater reduction in BWAT scores (-5.388±4.214 vs -3.404±4.642, p=0.022) • The NPWT plus CCO group had significantly greater change in necrotic tissue score on BWAT (-1.766 ±	• Any limitations: Retrospective design • Any comments on results, design, funding, conflict of interest, power: None	**Level of Evidence: 3** **Quality: high**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
		without topical negative pressure therapy. • Exclusion criteria None • Participant characteristics and any baseline differences: • On the cohort distribution the two groups were well matched apart	wound bed on each dressing change of NPWT. Some with and some without sharp debridement (n=47)	• All charts falling in the period October 2007 to April 2013 of patients that met the inclusion criteria. • Wounds assessed with Bates-Jensen Wound Assessment Tool (BWAT)	2.116 vs -0.021 ± 1.635, p=0.0001) Change in wound area (cm^2) No significant difference between groups (p=0.322) **Author conclusions: CCO can be used to remove necrotic tissue that persists after sharp debridement when using NPWT**		
Gilligan et al., 2017	Retrospective case-control study **to compare enzymatic debridement using clostridial collagenase ointment (CCO) with autolytic debridement using medicinal honey for treating pressure injuries**	Data taken from US Wound Registry for outpatient wound centers in USA and Puerto Rico between January 1st 2007 and December 31st 2012 (n=557) • Inclusion criteria: • Aged over 18 • At least one record with a pressure injury diagnosis code and one subsequent recorded encounter, treated with either CCO or hone Exclusion criteria: • Aged less than 18 • Pressure injury healed within 2 weeks • Treatment with both CCO and honey Participant characteristics:	Intervention group – matched cases treated with CCO. (n=446) Control/comparison group – matched patients treated with honey.(n=341)	Primary outcome measure – complete granulation tissue formation for 100% of wound bed. Achievement of 100% granulation (binary yes/no measure) and time to achieve 100% granulation. Explanatory variables – wound and patient demographics and clinical characteristics. PU grade (NPUAP staging).	**Number of treatments** Significantly fewer mean (± SD) treatment visits required by CCO group compared to honey 9.1±9.9 vs 12.6 ±16.6, p<0.001. **Granulation results at 1 year** Significantly greater percentage of CCO treated PUs achieved 100% granulation at 1 year compared to honey treated (CCO 42.0%, honey 35.2%, p=0.025). Pressure injuries treated with CCO 38% more likely to achieve 100% granulation at one year compared to honey based on logistic regression modelling (OR 1.384, 95% CI 1.057-1.812, p = 0.018) **Epithelialization results at 1 year**	• Relies on secondary data not collected specifically for research purposes. May be subject to coding errors and missing data. No control over variations in clinical practice between wound clinics.	**Level of Evidence: 3** **Quality: moderate**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
		• No significant differences between treatment groups in terms of explanatory variables (demographics, clinical characteristics).			Significantly higher proportion of CCO treated pressure injuires achieved epithelialization at 1 year (28.2% vs 21.3%, p = 0.009). CCO treated pressure injuries were 47% more likely to epithelialize compared to honey treated (OR 1.467, 95% CI 1.051 – 2.047, p = 0.024). Lower mean (± SD) number of days to achieve epithelialization in CCO treated PUs at 1 year, 288.6 ±128.9 vs 308.1±116.6, p=0.011). **Authors conclude CCO treated PUs significantly more likely to achieve 100% granulation and epithelialization at 1 year.**		
M.J. Carter, Gilligan, Waycaster, & Fife, 2016	Retrospective cohort study assessing effect of clostridial collagenase ointment(CCO) in conjunction with debridement in healing Category/Stage IV pressure injuries	Participant data extracted from National Wound Registry in the United States for people receiving treatment in hospital outpatient setting (n=434) Inclusion criteria: • Category/Stage IV pressure injury treated with CCO and debridement • > 18 yo • > 1 visit recorded in the registry Exclusion: • Only single visit recorded • < 18 yo • Category/Stage I, II, III and unstageable pressure injuries	• CCO Group – received application of CCO in conjunction with debridement (n=202) • Non CCO group– selective debridement only (n=232) • Number of selective debridements similar between groups • Frequency of debridement less in CCO group (p=0.003)	• Proportion of pressure injuries healed at 1 year • Proportion of pressure injuries healed at 2 years • Mean time to wound closure within 2 years • Database interrogated for period Jan 2007 to January 2013 • Utilized propensity scoring and Wound Healing Index	**Proportion pressure injuries closed at 1 year** CCO group 22% Non CCO group 11% **Proportion of pressure injuries closed at 2 years** CCO group 26.7% Non CCO group 13.7% **Mean time to wound closure within 2 years** CCO group 456 days (415.9-496.0) Vs non CCO group 589 days (553.4-624.5) (p<0.0001) **Hazard ratio**	• Data extracted relies on accuracy of reporting from participating hospitals. • Adjunct treatment aside from wound care not reported. • Design does not control for study bias despite inclusion of propensity score calculations. • Calculation using the wound healing index compromised by wound location.	**Level of Evidence: 3** **Quality: low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
		Characteristics: • Mean age: 63.6 to 66 years • No sig diff in age, gender, ambulatory status, co-morbidities (incl paralysis, pal care, CVD, diabetes, HPT). • Sig diff in recorded race with > number Caucasians (p=0.039) Sig diff in wound depth > 3cm at baseline: CCO group 61.7% vs no CCO group 45.9% (p< 0.0001) CCO group sig > "heavy exudate" and sig lower number of heel PUs. No sig diff in adjunct therapy in terms of wound care.			• Non CCO treated PU as ref: 1.85 (95% CI 1.28 to 2.68, p=0.001) • Hazard ratio statistically sig for the following wound locations: ○ Leg (HR: 0.41, 95% CI 0.17 to 0.98, p=0.044) ○ Sacrum/buttocks (HR: 0.27, 95% CI 0.17 to 0.43, p=0.0001) ○ Back (HR: 0.43, 95% CI 0.21 to 0.88, p=0.021 ○ Hips (HR: 0.35, 0.17-0.71, p=0.004)		
C. Waycaster & C. T. Milne, 2013	Two phase RCT	Participants were recruited in one long term care facility (n=27) Inclusion: Stage III and IV PUs ≥ 85% necrotic tissue	• Participants were randomized to receive either: ○ Hydrogel dressing (n=13) ○ Collagenase with semi-occlusive dressing (n=14) • No sharp debridement performed • All PUs irrigated, cleaned and dressed daily or more frequently	• Complete debridement within 42 days (Phase I) • Complete wound healing by 84 days (Phase II)	• Significantly more PUs managed with collagenase achieved complete debridement by 42 days compared with hydrogel (approx. 85% vs 29%, p<0.03) • Significantly more PUs managed with collagenase achieved complete wound healing by 84 days compared with hydrogel(69% vs 21%, p=0.02)	• Randomization, allocation concealment not reported • Participant characteristics not reported • No blinding	**Level of evidence: 1** **Quality: low**
Alvarez et al., 2002	RCT comparing papain-urea to collagenase for debriding	Participants were recruited in (n = 28 enrolled, 26 completed) Inclusion criteria:	• papain-urea (n=14) • collagenase (n=12) • Non adherent dressing and moist-	• Outcomes measured at 2,3 and 4 weeks • Percent devitalized tissue rated on a score of	• Significantly greater reduction in devitalized tissue for papain-urea (p < 0.0167)	• Non blinded outcome measurement	**Level of Evidence: 1** **Quality: moderate**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
	Category/Stage II to IV pressure ulcers	• Category/Stage II to IV pressure injuries • Aged > 18 years	moist saline gauze during screening period • 1-2 weeks screening before commencement then 4 week trial	1-6 indicating amount of wound covered	• Significantly greater amount of granulation ($p < 0.0167$) for papain-urea • healing rates were not different ($p > 0.05$) between groups	• Estimation of areas rather than measurement	
Pullen, Popp, Volkers, & Füsgen, 2002	double-blind RCT comparing collagenase to fibrinolysin/deoxyribonuclease for debriding	Participants had Category/Stage II to IV pressure injuries (n = 135 included, n = 78 results analyzed)	• Participants received either : ○ collagenase or ○ fibrinolysin/deoxyribonuclease	•	• No significant difference ($p = 0.164$) was found between the two groups for the reduction of devitalized tissue	• Double blind	**Level of Evidence: 1** **Quality: moderate**
Biological debridement							
Wilasrusmee et al., 2014	To conduct a cohort study and a meta-analysis to assess Maggot wound therapy (MWT) effects in mixed etiology wounds (primarily diabetic foot ulcers)	For the retrospective cohort study: 111 diabetic DFU patients, who were treated at Bang Yai Hospital, Thailand from Jan. 2008 to Dec. 2009, with 1116 person-week of follow up were included in the study. Inclusion criteria: • Presence of a single wound of the foot • Ability to walk without the use of a wheelchair or other assistive device • Data were available for at least 6 months of follow-up • No gangrenous wounds, necrotizing fasciitis, abscess, or osteomyelitis present. Observed difference between groups: patients with lower ABI, smaller wound size and shorter	Patients were assigned by physicians who were well trained in chronic wound care, to receive Maggot Wound Therapy (MWT) or Conventional Wound Therapy (CWT) at the out-patient clinic or in-patient wards, based on physician judgment. For the CWT group, the wound was dressed with normal saline or hydrogel and debridement was performed as judged by the treating physician.	• The wound was evaluated once/week by nurse practitioners and evaluated using digital photographic images. • Patients were followed up from treatment initiation until the end of December 2009. • The Kaplan-Meier Curve was applied to estimate the healing probability at 7 weeks, 14 weeks, 21 weeks and 28 weeks after receiving treatment. • All analysis were performed using STATA version 12.0. A p value < 0.05 was considered statistically significant, except for the	The estimated incidence of wound healing was 5.7/100 (95% CI; 4.49, 7.32) patient week, and the median time to healing was 14 weeks. The hazard ratio (HR) of wound healing was 7.87 time significantly higher in the MWT than the CWT ($p<0.001$) after adjusting for duration and size of ulcers, ankle brachial index (ABI), and glycated hemoglobin (HbA1c). MWT is significantly better for wound healing and more cost-effective than CWT.	This analysis was based on the retrospective cohort study of patient in Thailand, which has different cost structure than Western countries. It should also be kept in mind that patients with less severe ulcers were more likely to assign to MWT than CWT. As a result, cost analysis might be bias.	**Indirect evidence (Mixed etiology)**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
		duration of ulcers in MWT group than CWT group		heterogeneity test, for which p<0.1 was used.			
Surgical sharp debridement							
Anvar & Okonkwo, 2017	Retrospective cohort study exploring surgical sharp debridement for healing pressure injuries	Participants in nursing homes receiving skilled wound care clinic in USA (n=227, n=190 debrided) Inclusion criteria: • sacrum, sacrococcyx, coccyx, ischium, and trochanter region pressure injuries • Received at least 8 visits from skilled wound care team	• Indication for debridement was presence of necrosis, slough, or necrotic bioburden • Before debridement, oral narcotics and 20% benzocaine anesthetic • Bedside debridement performed by surgeons and surgical physician assistants • Antiseptics used at physician's discretion	Evaluation methods not reported	**Debridement** Sharp debridement performed on 59.5% of pressure injuries Mean surface area of debrided wounds was 20.76cm^2 **Wound surface area** • 73% of debrided wounds had reduction in surface area by 12 weeks and 27% had no improvement • Average wound surface area reduction at 12 weeks was 40% • 23% of wounds completely healed at 12 weeks (mean healing time 137 days)	• No blinded outcome measures • Unclear how wounds were evaluation • Selection process reported with minimal details • No confounders collected or analyzed • Biofilm was identified "visually" which is not possible • Participant details not presented (e.g. severity of wounds)	**Level of Evidence: 3** **Quality: low**
Ferrer-Sola, 2017	Observational study exploring efficacy of hydrosurgery debridement for reducing debridement time	• Participants were recruited (n=39) • Inclusion criteria: • Slow healing wound needing rapid debridement Exclusion criteria: • Dry eschar • Taking systemic anticoagulants Characteristics: • 39.7% wound from arterial insufficiency, 22.6% pressure injuries, 15.1% DFUs, 9.4% VLUs, 13.2% other etiologies	• Wounds cleansed with saline before treatment • Hydrosurgery using a pressurized saline with a vacuum around the stream that removes devitalized tissue (Versajet®) • Commenced on lowest intensity and increased as required • Delivered by nurse specialist at bedside	• Pain • Number of debridement sessions required • Wound size	**Pain** Mild-moderate pain (VAS < 5) generally reported Topical lidocaine used for 74% of participants, block anesthetic (9.3%), systemic analgesia (16.7%) **Debridement sessions** 73.6% required only one session, 18.9% two sessions, 7.5% three sessions Number sessions correlated with baseline size (r=3.07)	• Different hand pieces are used depending on wound depth • Risks from treatment include splash, inhalation of contaminated particles	**Indirect evidence (Mixed etiology)**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
		• 32.1% were <10cm^2 and 9.4% were ≥100cm^2					
Wolcott et al., 2010	Laboratory based study on animal models and application in three patients of **sharp debridement for addressing biofilm**	Participants in clinical arm were three patients with VLUs Baseline characteristics: *P. aeruginosa* infected (average 5.2 x 108 CFU/5mg bioburden)	One week after debridement bioburden was removed via sharp debridement sample was evaluated for ability of gentamicin to kill biofilm bacteria	Laboratory study	**24 hours post-debridement** Significant difference was observed between the susceptibility of day 0 pre debridement and day 1 (24 hours) ($p<0.05$) with all biofilms were more susceptible to antibiotic treatment **48 hours post-debridement** 2/3 debridements still showed higher sensitivity to antibiotics, while one of the bioburden samples had regained resistance ($p>0.05$) **72 hours post-debridement** same susceptibility levels as original mature biofilm **Author conclusions: Clinical results for chronic wounds suggest a 24–48 hour window following debridement of increased antibiotic sensitivity for wound biofilm**	• Small sample • Not pressure injuries	**Indirect Evidence (laboratory study and clinical trial with < 10 participants , not pressure injuries)** **Quality: Moderate**
Mechanical debridement							
Dowsett, Swan, & Orig, 2013	Observational case series study investigating use of a using a **monofilament fiber pad** to aide accurate	• Participants recruited (n=13) Inclusion and exclusion criteria: Not reported • Participant characteristics:	• Mechanical debridement with monofilament fiber pad • Pressure ulcer at various location were debrided with the monofilament	• Data on anatomical location, estimated Category/Stage prior to debridement • Actual Category/Stage following debridement • Time to debride the wound	**Classification** (8/13) or 61.5% of cases were re-categorized as grade 2 after debridement **Time to use device** No more than 4 minutes of debridement with	• A one-off debridement with monofilament fibre pad on wound containing thick, tenacious slough is unlikely to completely remove.	**Level of Evidence: 4** **Quality: low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
	categorization of pressure injuries	• Various pressure injury location (e.g. Chest, Hip and Penis etc) were identified	fiber pad (Debrisoft, Activa Health Care)	• Digital camera image or the Eykona Wound Measurement System 3D imaging system	monofilament fibre pad were required to reveal the wound bed The use of the monofilament fiber pad in the debridement of pressure injuries allow clinician to clearly view the wound bed (correct categorization) and therefore appropriate treatment can be provided.	• A number of consecutive treatments with the monofilament fibre pad may be necessary. • Very small study • Inter rater reliability not established	
		•	•	•		•	
Autolytic debridement							
Bale, Banks, Haglestein, & Harding, 1998	RCT comparing two amorphous hydrogels for debridement	• Participants were recruited in hospital and community settings (n=50 screened, n=38 included) Inclusion criteria: • Necrotic pressure injury • Wound not > 8cms in diameter Exclusion criteria: • Immunosuppression • Pregnancy or breast feeding Participant characteristics: • No significant between group difference	• Participants received either: ○ Group A: Amorphous hydrogel (Sterigel®) (n=21) or ○ Group B: amorphous hydrogel, type not specified (n=17) • All gel replaced daily • All wounds received a low adherent dressing and semipermeable film to cover the hydrogel	• Type of necrosis present (black, green, yellow or red) • Effect on surrounding skin measured as five descriptive categories • Pain measured on removal of dressing use three descriptors • Maximum 4 weeks or until wound debrided in full	**Debridement** Group A achieved larger size following debridement than group B (p=0.08 reported as statistically significant) **Pain** No difference between groups **Skin maceration** 8/21 in Group A and 9/17 in Group B were not macerated	• Methods of randomization and allocation concealment not reported • No blinding • Non-validated subjective outcome measurement • Participant characteristics poorly reported and unclear pressure injury severity	**Level of Evidence: 1** **Quality: low**
Colin, Kurring, Quinlan , & Yvon, 1996	RCT comparing hydrogel to dextranomer paste for debridement of pressure injuries	• Participants were recruited (n=135) • Inclusion criteria: • Exclusion criteria: • Participant characteristics: • Primarily Category/Stage III pressure injuries	• Participants received either: ○ hydrogel (n=67) or • dextranomer paste (n=68) • semipermeable film to cover the hydrogel	• Formal wound assessment and photography at baseline and every 7 days • 21 days maximum, or until pressure injury completely cleansed	**Percent reduction in area of non-viable tissue at day 21** Ranged from deterioration to 100% improvement in both groups, no between group differences (p=0.20)	• Methods of randomization and allocation concealment not reported • No blinding	**Level of Evidence: 1** **Quality: low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
				• Percent reduction in area of non-viable tissue at day 21			
Burgos et al., 2000	RCT comparing autolytic debridement to collagenase enzymatic debridement	Participants were recruited from seven hospitals in Spain (n=37) Inclusion criteria: • Category/Stage IV pressure injuries	• Participants randomized to receive: collagenase containing ointment (n=18) • hydrocolloid dressing (n=19)	• Reduction of ulcer area assessed at 1-week intervals • Pain, • granulation tissue, • exudate • odor	• After 12 weeks, 83 collagenase patients and 73.7% hydrocolloid patients had wound area reduction but no difference between groups (p=0.754) • No statistically significant differences in cost, efficacy or efficiency were detected between collagenase ointment and hydrocolloid dressing	• Greater than 30% drop out • Methods of randomization and allocation concealment not reported • No blinding • Non-validated subjective outcome measurement •	**Level of Evidence: 1** **Quality: low**
Muller, van Leen, & Bergemann, 2001	RCT comparing autolytic debridement to collagenase enzymatic debridement	Participants were recruited from a hospital in Netherlands (n=24) Inclusion criteria: • Category/Stage III pressure injuries of at least 12 months duration • Aged over 55 years	• Participants randomized to receive: collagenase containing ointment (Novuxol®) o(n=12) r • hydrocolloid dressing (Duoderm®) (n=12)	• Healing • Cost	**Healing** Wound healing was shorter with the collagenase treatment compared with the hydrocolloid treatment (mean 10 weeks vs 14 weeks, p<0.005)	• Methods of randomization and allocation concealment not reported • No blinding • Non-validated subjective outcome measurement • Participant characteristics poorly reported and unclear pressure injury severity • Costs also reported (see below)	**Level of Evidence: 1** **Quality: low**
Economics							
Chacon, Blanes, Borba, Rocha, &	Observational study exploring costs of wound care	Participants recruited in an ICU in Brazil (n=40) Inclusion criteria: • Aged over 18,	Not reported	• Mean cost per patient calculated by adding material and labor costs	**Costs** • Mean topical treatment costs for Category/Stage III and IV PIs were significantly	Minimal information on intervention	**Moderate quality economic analysis**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
Ferreira, 2017		• Category/Stage III and IV pressure injuries in the sacral, ischial and trochanteric regions. Exclusion criteria: • Category/Stage I and II PI, • PIs in other areas than listed above • PIs that were hemodynamically instable. • Participant characteristics: • No significant differences in wound size between Category/Stage III and IV pressure injuries		• Daily cost taken as total cost/number hospital days • Brazilian currency (reals R$) and then converted to US dollars in 2015 value	different (US $854.82 versus US$1785.35; p=0.004) • Mean daily topical treatment cost for Category/Stage III and IV PIs per hospitalized patient was US$ 40.83 (CI 95% US$ 28.49 to 53.17) • Costs of topical care correlated with days in hospital (r>0.4, p<0.05)		
Mearns et al., 2017	Cost effectiveness of clostridial collagenase ointment (CCO) versus honey	Data taken from US Wound Registry for outpatient wound centers in USA and Puerto Rico between January 1st 2007 and December 31st 2012 (n=557) • Inclusion criteria: • Aged over 18 • At least one record with a pressure injury diagnosis code and one subsequent recorded encounter, treated with either CCO or hone Exclusion criteria: • Aged less than 18 • Pressure injury healed within 2 weeks • Treatment with both CCO and honey	Intervention group – matched cases treated with CCO. (n=446) Control/comparison group – matched patients treated with honey.(n=341)	• Primary outcome measure – complete granulation tissue formation for 100% of wound bed. Achievement of 100% granulation (binary yes/no measure) and time to achieve 100% granulation. • Explanatory variables – wound and patient demographics and clinical characteristics. PU grade (NPUAP staging). • Markov model was constructed to assess the incremental cost-effectiveness ratios (ICERs).	One-year costs (2016 US dollars): CCO $US 6,161 versus honey $US7,149 mean difference -$US988 QALWs: CCO 22.73 versus honey 21.89 mean difference 0.84	*Study clinical efficacy reported in Gilligan et al. (2017)*	**High quality economic analysis**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
		Participant characteristics: • No significant differences between treatment groups in terms of explanatory variables (demographics, clinical characteristics).		• quality-adjusted life weeks (QALWs)			
M. J. Carter, Gilligan, Waycaster, Schaum, & Fife, 2017	Cost effectiveness (from a payer's perspective) of adding clostridial collagenase ointment (CCO) to selective debridement compared with selective debridement alone (non-CCO)	Participant data extracted from National Wound Registry in the United States for people receiving treatment in hospital outpatient setting (n= 434) Inclusion criteria: • Category/Stage IV pressure injury treated with CCO and debridement • > 18 yo • > 1 visit recorded in the registry Exclusion: • Only single visit recorded in registry • < 18 yo • Category/Stage I, II, III and unstageable pressure injuries Characteristics: • Mean age: 63.6 to 66 years • No sig diff in age, gender, ambulatory status, co-morbidities (incl paralysis, pal care, CVD, diabetes, HPT). • Sig diff in recorded race with > number Caucasians (p=0.039)	• CCO Group – received application of CCO in conjunction with debridement (n=202) • Non CCO group– debridement only (n=232) • Number of debridements similar between groups • Frequency of debridement less in CCO group (p=0.003)	• Proportion of pressure injuries healed at 1 year • Proportion of pressure injuries healed at 2 years • Mean time to wound closure within 2 years • Database interrogated for period Jan 2007 to January 2013 • Utilized propensity scoring and Wound Healing Index • A 3-state Markov model was developed to determine costs	additional 17.2 ulcer-free weeks can be gained with concurrent cost savings of $6,445 for each patient. CCO had fewer costs ($11,151 vs $17,596) and greater ulcer-free time (33.9 vs 16.8 ulcer-free weeks) Each ulcer-free week, there is a concurrent cost saving of $375 for CCO treatment	*Study clinical efficacy reported in Carter et al. (2016)*	**(Intervention): Level of Evidence: 3** **Quality: Low** **Moderate quality economic analysis**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
C. Waycaster & C. Milne, 2013	Two phase RCT	Participants were recruited in one long term care facility (n=27) Inclusion: Stage III and IV PUs ≥ 85% necrotic tissue	• Participants were randomized to receive either: ○ Hydrogel dressing (n=13) ○ Collagenase with semi-occlusive dressing (n=14) • No sharp debridement performed • All PUs irrigated, cleaned and dressed daily or more frequently	• Complete debridement within 42 days (Phase I) • Complete wound healing by 84 days (Phase II) • A Markov model was developed to determine costs	• Average cost/patient for 42 days of care was $1,817 in 2012 for the collagenase group and $1,611 for the hydrogel group. • Days spent with a granulated wound were 3.6 times higher for collagenase (23.4 vs 6.5) than with the hydrogel. • The estimated cost per granulation day was approx. 3.2 times higher for hydrogel ($249) vs collagenase ($78)	*Study clinical efficacy reported in Waycaster and Milne (2013)*	**Moderate quality economic analysis**
Muller et al., 2001	RCT comparing autolytic debridement to collagenase enzymatic debridement	Participants were recruited from a hospital in Netherlands (n=24) Inclusion criteria: • Category/Stage IV pressure injuries	• Participants randomized to receive: collagenase containing ointment (Novuxol®) o(n=12) r • hydrocolloid dressing (Duoderm®) (n=12)	• Costs • Healing time • 14 week study	**Costs** • Average costs per patient were about 5% higher with hydrocolloid than with the collagenase-containing ointment • Total costs 19,389.20 Dutch gilders vs 18 619.40 Dutch gilders	• Methods of randomization and allocation concealment not reported • No blinding • Non-validated subjective outcome measurement • Participant characteristics poorly reported and unclear pressure injury severity • Efficacy also reported (see above)	**Level of Evidence: 1** **Quality: low**

Systematic reviews for supporting discussion

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
Hao et al., 2017	Systematic review on efficacy of phenytoin for topical wound care	3 RCTs Low or unclear risk of bias	○ phenytoin may stimulate fibroblast proliferation , collagen deposition , vessel ingrowth, and enhance macrophage activity as well as reduce inflammation ○	•	Proportion of ulcers healed within trial period (eight weeks) RR 1.33 (95% CI 0.63 to 2.78, 1 study)	• Very small studies included (ranged from 26 to 83) • Indirect evidence	**Moderate quality review**
Moore & Cowman, 2013	Systematic review **investigating cleansing pressure injuries**	3 RCTs of moderate or low risk of bias	One study compares pulsatile lavage to no lavage One study compares saline to other cleanser One small study compares water to no cleansing	• Outcomes varied but included wound size and Pressure Sore Status Tool	No met-analysis **Concludes that there is some evidence for pulsatile lavage over no lavage but no particularly strong evidence for any particular technique or cleansing solution**	• Very small studies, reported above (except the tap water RCT which had only 8 participants with pressure injuries)	**High quality review**
Fernandez & Griffiths, 2012	Systematic review with meta-analysis **investigating the effectiveness of potable tap water for cleansing acute wounds (primarily lacerations)**	11 RCTs and quasi-RCTs were included Participants in the trials ranged from 2 years to 95 years. Two trials were on paediatric samples. In no trials were the wounds PU. In 5 trials the wounds were lacerations, one trial was in open fractures, one in chronic wounds and 4 in surgical wounds. The majority of trials were set in emergency wards.	The trials investigated: Tap water (8 trials) Cooled boiled water (1 trial) Distilled water (1 trial) Normal saline (1 trial)	• The primary outcome of interest was wound infection measured • objectively by bacterial counts, wound cultures, wound biopsy and/or by subjective indicators of wound infection. • Other outcomes were: proportion of wounds that healed; the rate of wound healing expressed as percentage or absolute change in wound area; costs; pain and discomfort; patient satisfaction; staff satisfaction.	• Meta-analysis results : **Tap water versus no cleansing** ○ No difference in infection rate (3 RCTs, RR 1.06, 95% CI 0.07 to 16.50) ○ No difference in wound healing (2 RCTs, RR 1.26, 95% CI 0.18 to 8.66) **Review conclusions: There is no evidence that using tap water to cleanse acute wounds in adults increases infection. However, there is not strong evidence that cleansing wounds per se increases healing or reduces infection. In the absence of potable tap water, boiled and cooled water as well as distilled water can be used as wound cleansing agents.**	• Primarily lacerations were treated, only one trial included chronic wounds • Individual trials generally low quality or had inadequate reporting	**High quality review**

Table 1: Level of Evidence for Intervention Studies

Level 1	**Experimental Designs** • Randomized trial
Level 2	**Quasi-experimental design** • Prospectively controlled study design • Pre-test post-test or historic/retrospective control group study
Level 3	**Observational-analytical designs** • Cohort study with or without control group • Case-controlled study
Level 4	**Observational-descriptive studies (no control)** • Observational study with no control group • Cross-sectional study • Case series (n=10+)
Level 5	**Indirect evidence**: studies in normal human subjects, human subjects with other types of chronic wounds, laboratory studies using animals, or computational models

Table 2: Levels of evidence for diagnostic studies in the EPUAP-NPUAP-PPPIA guideline update

Level 1	Individual high quality (cross sectional) studies according to the quality assessment tools with consistently applied reference standard and blinding among consecutive persons.
Level 2	Non-consecutive studies or studies without consistently applied reference standards.
Level 3	Case-control studies or poor or non-independent reference standard.
Level 4	Mechanism-based reasoning, study of diagnostic yield (no reference standard). Low and moderate quality cross sectional studies.

Table 3: Levels of evidence for prognostic studies in the EPUAP-NPUAP-PPPIA guideline update

Level 1	A prospective cohort study.
Level 2	Analysis of prognostic factors amongst persons in a single arm of a randomized controlled trial.
Level 3	Case-series or case-control studies, or low quality prognostic cohort study, or retrospective cohort study.

APPRAISAL FOR STUDIES PROVIDING DIRECT EVIDENCE (i.e. ELIGIBLE FOR SUPPORTING AN EVIDENCE-BASED RECOMMENDATIONS

Each criteria on the critical appraisal forms was assessed as being fully met (Y), partially met or uncertain (U), not met/not reported/unclear (N), or not applicable (NA). Studies were generally described as high, moderate, or low quality using the following criteria:

- High quality studies: fully met at least 80% of applicable criteria
- Moderate quality studies: fully met at least 70% of applicable criteria
- Low quality studies: did not fully meet at least 70% of applicable criteria

RCTS

Endnote ID	Author/year	Focussed question	Assignment randomised	Adequate concealment method	Subjects and investigators blinded	Groups comparable at commencement	Only difference btw groups was treatment	Valid, reliable outcome measure	% drop out in study arms is reported and acceptable	Intention to treat analysis	Comparable results for multiple sites	Minimal bias	Reliable conclusions	Level of evidence	Quality
5520	Farsaei et al., 2015	Y	N	N	Y	U	N	N	Y	N	N/A	U	U	1	low
16697	Luan et al., 2016	N	U	U	N	U	U	N	N	U	NA	N	N	1	Low
13977	Inchingolo et al., 2017	Y	U	U	U	U	U	U	N	U	NA	N	N	1	Low
14807	Li et al., 2017	Y	Y	U	Y	Y	Y	Y	Y	Y	U	Y	Y	1	High
16319	Niu et al., 2016	N	Y	U	U	Y	N	N	U	Y	U	Y	N	1	Low
16422	Stephen et al., 2016	Y	Y	N	N	Y	U	Y	N	Y	NA	Y	N	1	Low
7861	Farsaei et al., 2014	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	Y	Y	1	High

CROSS SECTIONAL/SURVEY/PREVALENCE STUDIES/OBSERVATIONAL

Endnote ID	Author/year	Focussed question	Sampling method	Representative sample	States number invited participants	Clear outcome measures	Valid reliable outcome measurement	Comparable results for multiple sites	Confounders identified and accounted for	Minimal bias	Reliable conclusions	Level of evidence	Quality
16538	Buzzi et al., 2016	N	N	N	N	Y	N	NA	N	U	N	4	Low
1886	Dowsett et al., 2013	N	U	N	U	U	Y	N	N	N	N	4	Low

CASE SERIES

	Author/year	Focussed question	Participant characteristics reported	Inclusion criteria defined	Consecutive recruitment	Participants entered at same disease stage	Intervention clearly reported	Outcomes relevant and defined apriori	Valid, reliable outcome measurement	Per cent drop out reported and acceptable	Estimates of random variability	Comparable results for multiple sites	Minimal bias	Reliable conclusions	Level of evidence	Quality
8096	Tickle, 2015	Y	Y	Y	N	N	Y	U	U	Y	N	N	N	N	4	low

COHORT STUDIES

	Author/year	Focussed question	Comparable source populations	States number invited	Likelihood of outcome at enrolment	Per cent drop out in study arms is reported	Comparison btw drop outs and participants	Clear outcome measures	Assessment blinded, or discuss potential bias	Valid, reliable assessment with supporting reference	More than one measure of exposure	Confounders identified and accounted for	Provides confidence intervals	Minimal bias	Reliable conclusions	Level of evidence	Quality
9751	Furuta et al., 2015	N	Y	Y	N	Y	Y	N	N	N	N	N	Y	N	N	3	low
9135	McCallon & Frilot, 2015	Y	Y	Y	U	NA	NA	Y	N	Y	Y	Y	Y	Y	Y	3	High
16988	Anvar & Okonkwo, 2017	Y	NA	N	N	NA	NA	N	N	N	N	N	N	N	U	3	Low
16304	M.J. Carter et al., 2016	Y	U	NA	NA	NA	NA	Y	U	U	Y	Y	Y	N	N	3	Low
7924	Liu et al., 2013	N	Y	N	NA	Y	N	N	U	U	U	N	N	N	N	3	Low

CASE CONTROL STUDIES

	Author/year	Focussed question	Comparable source populations	Same exclusion cases and controls	Per cent drop out in study arms is reported	Comparison btw participants and non-participants	Cases clearly defined	Established that controls are non-cases	Knowledge of primary exposure not influence case	Valid, reliable assessment of exposure	Confounders identified and accounted for	Provides confidence intervals	Minimal bias	Reliable conclusions	Level of evidence	Quality
14204	Gilligan et al., 2017	Y	Y	Y	NA	NA	Y	Y	Y	Y	Y	N	Y	U	3	Moderate

QUASI EXPERIMENTAL STUDIES

	Author/year	Focussed question	Subjects and investigators blinded	Groups comparable at commenceme	Only difference btw groups was treatment	Valid, reliable outcome measurement	Per cent drop out in study arms is reported and acceptable	Intention to treat analysis	Comparable results for multiple sites	Minimal bias	Reliable conclusions	Level of evidence	Quality
10877	Saidkhani et al., 2016	Y	N	Y	Y	N	N	N	U	N	N	2	low

ECONOMIC EVALUATIONS

	Author/year	Focussed question	Economic importance of question is clear	Choice of study design is justified	All costs are included and measured and valued appropriately	Outcome measures to answer study question are relevant and measured and valued appropriately	Discounting of future costs and outcome measures is performed correctly when appropriate	Assumptions explicit and a sensitivity analysis conducted	Results provide information relevant for policy providers	Minimal bias	Reliable conclusions	Level of evidence	Quality
14310	M. J. Carter et al., 2017	Y	U	Y	Y	Y	NA	Y	Y	Y	U	NA	Moderate
14132	Chacon et al., 2017	Y	N	N	Y	Y	NA	N	Y	N	U	NA	Low
14816	Mearns et al., 2017	Y	N	Y	Y	Y	NA	Y	Y	Y	Y	NA	High
1635	C. Waycaster & C. Milne, 2013	Y	N	Y	Y	Y	NA	N	N	N	U	NA	Moderate

SYSTEMATIC REVIEWS FOR DISCUSSION

RATING CRITERIA:
1 Partial yes: states review question, search strategy, in/exclusion criteria and risk of bias were a-priori; full yes: meta-analysis/synthesis plan, investigation of heterogeneity and justification for protocol deviation
2 Partial yes: At least 2 databases, provides keywords and search, justifies publication restrictions; full yes: searched reference lists of included studies, searched trial registries, consulted experts in field, searched grey literature, search within 24 months of review completion
3 At least two reviewers independently agreed on selection of studies to include or reviewers achieved 80% agreement on a sample of studies
4 Either two reviewers did data extraction and had >80% agreement, or two reviewers reached consensus on data to extract
5 Partial yes: list of all relevant studies that were read and excluded; full yes: every study that was excluded is independently justified
6 Partial yes: described populations, interventions, comparators, outcomes and research design; full yes: detailed descriptions of same plus study setting and timeframe for follow-up
7 FOR RCTS Partial yes: appraised risk of bias from unconcealed allocation and lack of blinding; full yes: appraised risk of bias on true randomisation, selection of reported result from multiple measurements/analyses
FOR non randomised studies: Partial yes: appraised confounding and selection bias; full yes: appraised methods to ascertain exposures and outcomes, selection of reported result from multiple measurements/analyses
8 Must include reporting of the source of funding of individual studies, or reports that the reviewers considered this even if individual funding sources aren't listed in review

Endnote ID	Author/year	PICO research question and inclusion criteria	Explicitly states a-priori protocol[1]	Rationale for selection of study designs	Comprehensive search[2]	Duplicate study selection[3]	Duplicate data extraction[4]	Excluded studies listed[5]	Adequate description of included studies[6]	Risk of bias assessed[7]	Source of funding reported[8]	Appropriate meta-analysis including weighting and adjustment for heterogeneity	Meta-analysis considers risk of bias of studies	Discussion consider risk of bias of studies	Assessment of publication bias if quantitative analysis is done	Potential conflicts of interest of authors reported and managed	Review Quality
7689	Firmino et al., 2014	N	N	N	PY	U	U	N		N	N	NA	NA	Y	N	N	Exclude
8333	Xu, Xiong, Yang, Li, & Mao, 2015				N			N		N		N		Y	N		Exclude
79339	Zhang et al., 2013				Y			N		Y		N		N	Y		Exclude
14168	Patry & Blanchette, 2017				Y			N		Y		N		N	Y		Exclude

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