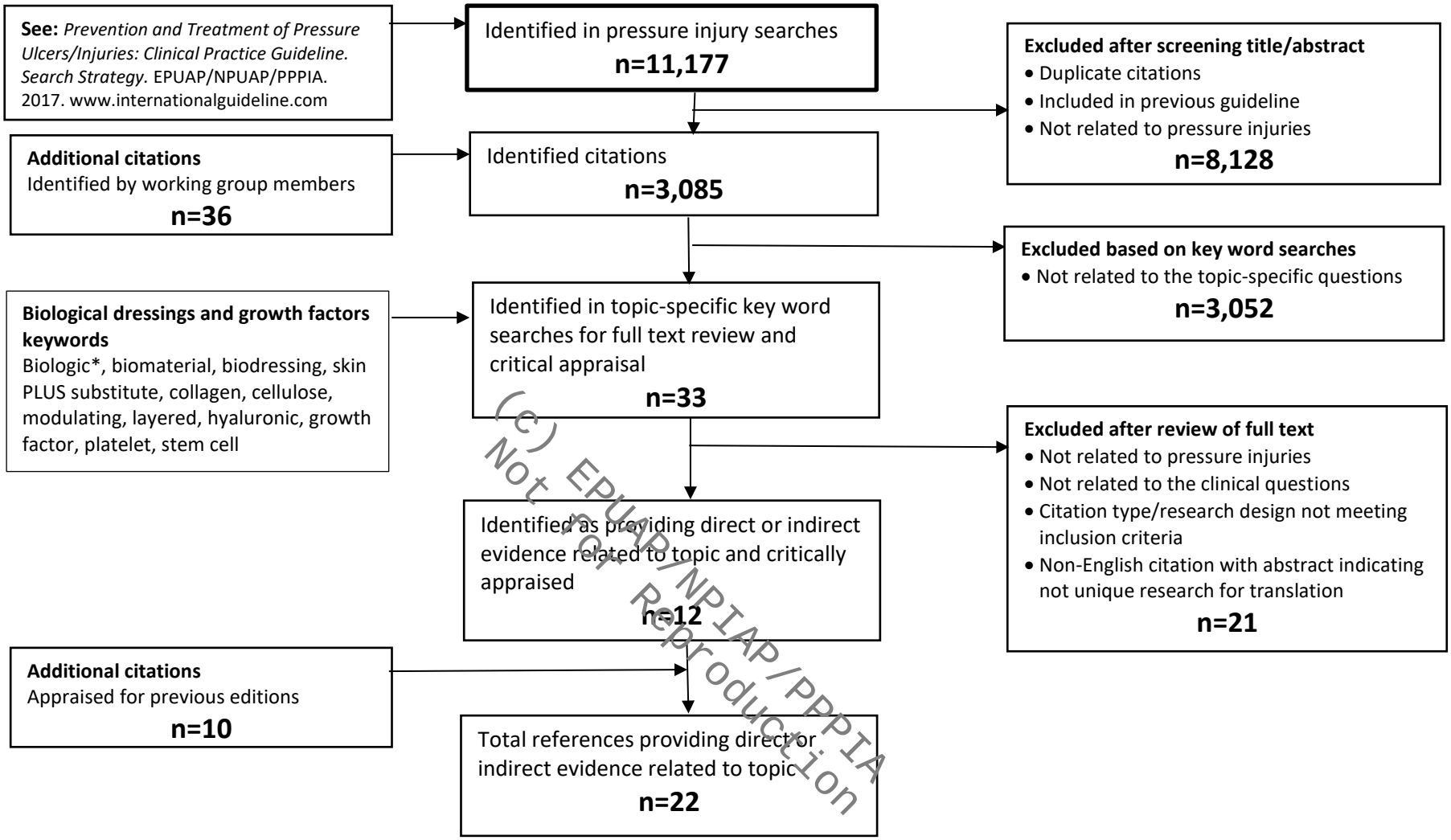
Search results for 2019 International Pressure Injury Guideline: Growth factors and biological dressings



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	
Growth factors: Platelet rich plasma for healing pressure injuries							
Ramos-Torrecillas, Garcia-Martinez, Luna-Bertos, Ocana-Peinado, & Ruiz, 2015	Non-blinded RCT **investigating effectiveness of platelet rich plasma with an without hyaluronic acid for healing pressure injuries (PI)**	Participants were recruited in a hospital and 5 geriatric centers in Spain (n=115, n=100 completed study, n=124 PIs in study) **Inclusion criteria:** • PI Stage II or III of at least 8 weeks duration • Largest diameter ≤ 10cm • Presence of granulation tissue • No local infection and necrosis **Exclusion criteria:** • HIV, cancer, hepatitis, systemic or local infection, systemic erythmatous lupus, active vasculitis, cryoglobulinemia, immunosuppressants **Characteristics:** • Mean age 82.5 years • 82% receiving statins and 50% receiving non-steroidal anti-inflammatory drugs (NSAIDs) • Control group had more heel PI (44% vs 41.1%, 36% and 35%) • Control group had longer duration (6.3 months [mths] vs 4.8, 5.0 and 4.0) • Group C had more Grade II PI and less Grade III PI)	All participants received 3rd daily dressing change and saline cleanse, debridement, liquid hydrogel and polyurethane dressing, 2 hourly repositioning Randomized to receive: • Group A: PRP day 0 (n=34 PIs) • Group B: PRP day 0 and 15 (n=25) • Group C: PRP and hyaluronic acid day 0 and 15 (n=40 PIs) • Control group: nothing additional (n=25 PIs)	**Outcome measures** • % surface area healed • % PI completely healed in each group **Assessment** • every 3rd day for 36 days • Pressure Ulcer Scale of Healing (PUSH) tool • PI surface area (cm^2) determined using calipers to measure width and length • The types of tissue (e.g. epithelial, granulation sphacelus, or necrotic) and the presence of exudate	• No infection occurred in the study period in any groups. • Adverse effects are not reported in the trial. **% reduction in surface area at day 36 versus baseline** • Control 10.3% (95% confidence interval [CI] 4.8 to 15.8) • Group A 48.3% (95% CI 39.3 to 57.4, p=0.001 compared to control) • Group B 54.8% (95% CI 36.3 to 73.3, p=0.001 compared to control) • Group C 80.4% (95% CI 71.8 to 89.1, p=0.001 compared to control) **% PIs completed healed at day 36** • Control 0% • Group A 8% (p=ns vs control, p=0.023 vs group B, p=0.004 vs group C) • Group B 32% (p=0.001 compared to control, p=ns vs group C) • Group C 37.5% (p≤0.001 compared to control) **Study conclusions: PRP is effective in promoting healing. Effectiveness is enhanced through application in two fortnightly doses and when used in combination with hyaluronic acid**	• No statistical comparison of groups at baseline • Analyzed at PI level, randomized at patient level • No ITT, information on dropouts is unclear	**Level of evidence: 1** **Quality: low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
Singh, Dhayal, Sehgal, & Rohilla, 2015 (report on the same study below)	Quasi experiment **comparing an autologous platelet rich plasma (growth factor) dressing to a saline soaked gauze dressing for healing and reduction of bacterial burden** Another goal was to determine source of cross infection in PIs in spinal injury patients	Participants were recruited from a spinal cord injury (SCI) rehabilitation center in India (n=25) **Inclusion criteria**: • ≥ two PIs present • SCI • PIs classified as critically colonized based on delayed wound healing, increased pain and exudate, discoloration and odor **Characteristics**: • Mean age participants was 36.84±12.67 years • 100% of PIs selected for PRP dressing were Category/Stage 4 • Control dressings were administered to Category/Stage 2 (44%), 3 (16%) and 4 (40%) PIs • PRP dressing PIs were primarily located on sacrum (64%) and trochanter (20%) • Control PIs were primarily located on trochanter (72%) • No significant difference in number PIs with critical colonization at baseline (PRP dressing group 92%, control group 84%, p=0.66)	• Antimicrobials were avoided unless recommended and systemic antibiotics used with systemic signs of infection (pyrexia/foul smelling discharge from wound) • Baseline debridement was conducted (method not stated) • The largest PI was selected for intervention (PRP) dressing • PIs were dressed: ○ PRP dressing changed twice weekly ○ Saline soaked gauze dressing changed daily	• Baseline and weekly urine cultures and PI, urethral meatus, perineum swabs taken for 5 weeks	**% PIs with critical colonization (between groups: PRP dressing versus control dressing)** • Week 1: 92% vs 84%, p=0.66 • Week 2: 72% vs 76%, p=1.0 • Week 3: 60% vs 72%, p=0.55 • Week 4: 40% vs 80% p=0.009 • Week 5: 24% vs 76% p=0.0006 **% PIs with critical colonization Within group (week 1 vs week 5)** • PRP dressing group: 92% vs 24%, p=0.001 • Control dressing group:84% vs 76%, p=0.72 **Non-wound swab results** • There was no significant difference in number of patients with positive urine, urethral meatus or perineal cultures from baseline to week 5 **Study conclusions: After at least 4 weeks of treatment with a PRP growth factor dressing, wound colonization was significantly reduced compared to baseline and compared to a control saline gauze dressing.**	• Same patient served as case and control • Control dressings changed daily, PRP dressing changed twice weekly (more opportunity for infection with more frequent dressing change) • Concurrent antimicrobials and systemic antibiotics were permitted but use rate not reported • No blinded analysis • Comparison dressing was not best practice dressing • Pressure injury grading, anatomical location in case and control group is varies	**Level of evidence: 2** **Quality: low**
Singh, Rohilla, Dhayal, Sen, & Sehgal, 2014	Prospective study evaluating the local application of **platelet-rich plasma (PRP) for healing**	Participants were recruited at a tertiary level care center India (n=25) Inclusion criteria: • Spinal cord injury (SCI) below C4 due to traumatic event	• Participants acted as own control • Largest PI per participant treated with growth factor: Wound cleaned, PRP applied, and Vaseline	• Not clear who evaluated the pressure injuries • Measurement using length x width, PUSH scores, biopsy for	**PUSH scores at 5 weeks** Statistically significant decrease in mean PUSH scores of for both PRP and saline control (both groups, p<0.0001) **Wound surface area**	• Non-blinded outcome assessment • Small sample size • Different severity of PI at baseline, with all growth factor-treated PIs	**Level of evidence: 2** **Quality: low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
(report on the same study as above)	**pressure injuries.**	• At least 2 pressure injuries • PIs showed no improvement after minimum regular follow-up 6 months • Aged ≥ 18 years Exclusion criteria: • Only a single PI • Associated malignant disorder • Non-traumatic SCI Participants characteristics: • Mean age 36.84±12.67 (range 20 to 60) • Mean duration of PI on enrolment 72.76±22.59 days (range 27 to 195) • All PIs treated with growth factor were stage IV • Control PIs ranged from category/stage 2 to 4 • Primarily sacral PIs	gauze applied, secondary cotton gauze and cotton pad. Dressings 2x weekly. • Control PI: dressed daily with normal saline (no mention of types of dressing)	histopathology, clinical exam • weekly wound evaluation for 5 weeks, then monthly for 6 months • EPUAP staging system used	Statistical significant decrease in surface area for PGP group (p<0.000) but not for control group (p=0.924). **Histopathology at 5 weeks** Majority of PGP-treated PIs showed necrosis and suppuration (56%) at the time of enrollment and well-formed granulation tissue and epithelialization (60%) at the 5th week. **Overall status** • 96% of PGP-treated PIs improved and only 1 deteriorated • 68% of control PIs improved, 28% deteriorated and 1 showed no change.	being category/stage 4 and controls being category/stage 2 to 4 • Control treatment was poorly described at may not have included a contemporary dressing	
Biglari et al., 2015	Case series investigating the **effectiveness of platelet rich plasma in healing fistulas associated with category/ stage III or IV PI**	Participants recruited at one center in Germany (n=15) Inclusion criteria: • Category/Stage III PI with unsuccessful treatment of fistula following pressure injury closure • Spinal cord injury Exclusion criteria: • Malignant condition • Immunosuppressive therapy • Septicemia • Thrombocytopenia • Hypofibrinogenemia • Anemia	• All participants received 7-9mL autologous platelet rich plasma (PRP) was applied directly to fistula after sharp surgical debridement and before suture line closed • Dressing consisted of fat gauzes and sterile bandages	• Suture line observed on days 3, 7 and 21 following surgery • No formal wound assessment tool reported but used MRI to confirm fistula closure • Follow up at 6, 9 and 12 months	• Minimal wound secretion at 3 days • No secretions on bandages at 7 days • Closure of all fistulas at 3 weeks confirmed by magnetic resonance imaging • No allergic reactions • By 12 months, no participants had returned for treatment of PI **Study conclusions: PRP administered during surgery following debridement and prior to wound closure may contribute to the healing of fistula associated with stage III and IV PIs.**	• Sequential recruitment unclear • Small uncontrolled study	**Level of evidence: 4** **Quality: low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
		Characteristics: • 100% had previous unsuccessful fistula following PI closure treatments • Mean age 38.3 years [yrs] (range 31 to 67) • 100% participants had paralysis • 46.7% trochanter PI, 26.6% sacral PI, 26.6% ischial PI • 12/15 Stage III PI and 3/15 Stage IV PI • 3/15 had type II diabetes • All participants given bacterial swab during surgery and no significant differences in profiles					
Yu, Han, & Lv, 2017	RCT **comparing** the efficacy of combination therapy of **platelet rich plasma (PRP) with gelatin hydrogel sheet** & combination therapy of PRP with collagen in assessment of wound healing of PIs	Subjects were recruited from a hospital wound care center and various nursing homes in China (n=320) Inclusion criteria: • Aged 20 to 90 years • PI not healed for 6 months and not responding to conventional treatment for 2 months • 1 or 2 PIs with total surface are area ≤ 20cm Exclusion criteria: • Pregnant or breast-feeding • bleeding disorders • poorly controlled glucose level • infected wound on admission or during study • Venous incompetency • Corticosteroid, anticoagulant or anti-thrombotic medication	• All PIs were debrided • Participants were randomized to either: ○ PRP followed by gelatin hydrogen (n=160); or ○ PRP followed by a layer of 2mm thickness of collagen ointment (n=160) • Firm compression bandage or stocking to secure dressing	• Healing measured as PI depth and surface area • Time to wound closure • Quality of life measured using CIVIQ score (with 20 = bad quality and 100=best quality) • Complication & adverse effects • Assessments at day 7, week 4 and week 7	**Complete healing** There was no significant difference in percent healed within 7 weeks (51.8% PRP plus gelatin versus 53.75% PRP plus collagen, p=0.786) **Healing rate** • PRP with gelatin sheeting 20% healed within 1 week and 30% within 4 weeks • PRP with collagen group: 25% healed within 1 week and 40% healed within 4 weeks **Quality of life** No significant difference between between groups for CIVIQ score **No adverse effects** Nil reported in either groups **Author conclusions: Despite reporting low healing rates, the author concluded that both therapies were**	• Low healing rates • No blinding • No control group receiving placebo/normal therapy to determine baseline • Heterogeneity in healing outcome among different nursing homes • Concurrent medical conditions that might influence healing are not reported	**Level of evidence: 1** **Quality: low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
		Participant characteristics: • Age range 23 to 90 years • 33% were sacral PI, 28% heel PIs			**successful treatments for promoting PI healing**		
Martinez-Zapata et al., 2016	Systematic review of **RCTs exploring the efficacy of autologous platelet-rich plasma for chronic wounds**	Included mostly low quality RCTs (n=10, 4=mixed chronic wounds) comparing autologous platelet-rich plasma with placebo or control Participant characteristics: • Mixed wound types • Participants aged over 18 yrs	Autologous PRP (any method of collection and formulation) with placebo or alternative topical therapies such as standard care or protease-modulating matrix	• Proportion of chronic wounds completely healed (defined as100% epithelialization or skin closure without drainage) • Percentage of wound area healed • Wound complications: infection, necrosis • Adverse events	**PRP versus standard care: mixed wounds** • complete healing: (4 studies, n=101) relative risk [RR] 1.85, 95%CI 0.76 to 4.51, p=0.18 • percent wound healed (2 studies, n=38) RR 51.78, 95% CI 32.70 to 70.86, p<0.00001 • wound infection (2 studies, n=30) RR 0.80, 95%CI 0.05 to 12.30, p=0.81 • adverse events (1 study, n=15) RR 0.44, 95% CI 0.05 to 3.85, p=0.46 **PRP releasate versus standard care** • complete healing: (3 studies, n=204) RR 1.23, 95%CI 1.01 to 1.49, p=0.04 **PRP lysate versus standard care** • complete healing: (4 studies, n=172) RR 1.45, 95%CI 0.67 to 3.13, p=0.34 **Author conclusions: No conclusions can be made about effect of autologous PRP compared with standard treatment**	• Studies are at high risk of bias and have small participant numbers • Studies were of mixed chronic wound types – only some studies included pressure injuries	**Indirect evidence (mixed etiology)**
Rappl, 2011	Case series **reporting use of platelet- rich plasma gel for healing chronic wounds including PIs**	Participants with SCI were recruited from 11 long term care facilities, 2 outpatient wound clinics, 1 home care agency and 1 wound care equipment and service supplier in USA (n=20, 18 of the 20 wounds were PIs) Inclusion criteria: • patients with SCI • open, cutaneous wound not progressing in healing	All wounds were treated with 1.3 x platelet-rich plasma (PRP gel)	Wounds were assessed using different techniques all locations, but were possible the same person performed repeat measures. Outcomes included: • Mean per cent change from baseline of wound area	• Wounds closed on average of 47.9% in area and 56% in volume in a mean of 4.0 treatments over 3.4 weeks • Undermining closed on 31.4% using 3.5 treatments over 2.6 weeks • Sinus tracts and tunnels closed on an average of 26.1% after 2.3 treatments over 1.5 weeks • In area and volume, 90% of subjects responded positively with an average	• Diversity of sites prevented standardized measurement techniques and treatment across the 14 sites of care	**Level of evidence: 4** **Quality: moderate**

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		• wounds that could have a majority clean wound bed just prior to application of product • without clinical signs and symptoms of active infection Exclusion criteria: • malignancy in the wound bed • concurrent chemotherapy • active untreated wound infection Characteristics: • Mean age 49yrs (range 27 -75) • Mean wound duration 79.4 weeks (range 8 to 416 weeks) • 14/20 wounds were <1cm in depth, 7/20 wounds were, 2cm in depth • Mean wound area 25.6cm^2 • Mean wound volume 53.4cm^3		• mean per cent change from baseline of wound volume • Improvement in sinus tracts and undermining • Number of treatments • Number of weeks	reduction of 53.8% and 67.3% respectively • Of the four subjects with undermining 75% closed 47% on average • Of the three sinus tracts and tunnels 100% closed 26.1% on average		
Frykberg, Driver, Lavery, Armstrong, & Isenberg, 2011	Prospective case series **reporting use of platelet-rich autologous plasma gel for healing chronic wounds including PIs**	A convenience sample of participants from 8 long term care facilities and 3 outpatient foot clinics in USA were recruited (n =49, with 65 wounds, 21 of which were PIs) Inclusion: • open, cutaneous wound determined to be not progressing toward healing • wound with mostly clean wound bed • no clinical signs and symptoms of active infection Exclusion: • malignancy in the wound bed • current chemotherapy	• All participants received appropriate offloading devices. • The wound bed was cleaned thoroughly and debrided before treatment. • All participants were treated with: ○ moisture barrier preparation on intact peri-wound skin ○ Preparation of autologous platelet-rich plasma (PRP) gel from a sample of ≤20ml of the participant's blood ○ As soon as it was ready the PRP gel was applied topically to the	• Wound measurements taken weekly using disposable tape measure and cotton bud probe with the deepest part of wound taken as depth measurement. • Mean wound area • Wound volume • Length of treatment time	Results for participants with PIs (n=21 wounds) at mean follow up 2.8 weeks: • Mean wound volume decrease was 43.2%± 47.6% • Mean wound area reduction was 33.7%±38.1% • Mean undermining reduction 67.7%±32.8% • Mean decrease in sinus tract/tunneling was 38.9%±36.7% • No systemic or wound site side effects were noted Results for all participants at mean follow up 2.8 weeks **(indirect evidence):** • Mean number of PRP applications was with 3.2± 2.2 • Mean wound volume decrease was 51%±43.1%	• **this is a sub-set of the participants reported in de Leon et al 2011** • No randomization or control, no a priori power calculation • Results reported in th text are different from results in the tables, reducing clarity and confidence in the findings • Patients were not available for ongoing follow-	**Level of evidence: 4** **Quality: low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
		Characteristics of all participants (n =49, with 65 wounds): • Mean age 52.9±14.2 years • Mean wound duration 48.3weeks • Mean baseline area 21.0cm^2±18.1 • Mean baseline volume63.5cm^3±79.3 weeks • Albumin 3.3g/dL, prealbumin 21.5g/dL Participant characteristics: • 32.2% PI, 24.6% venous ulcers, 21.5% diabetic ulcers • Mean age 60.6±14.7 years • Mean wound duration 47.8weeks • Mean baseline area 19.0cm^2±29.4 • Mean baseline volume36.2cm^3±77.7 • Albumin 3.2g/dL, prealbumin 24g/dL	wound and covered with a non-absorbent contact layer dressing • PRP gel was reapplied 1 to 2 times weekly according to clinical judgement.		• Mean wound area reduction was 39.5%±41.2% • Mean undermining reduction 77.8%±28.9% • Mean decrease in sinus tract/tunneling was 45.8%±40.2% • No systemic or wound site side effects were noted	up to the endpoint of complete healing • Clinicians determined treatment and dressing change frequency • Did not use gold standard wound measurement strategies	
de Leon et al., 2011	Case series **reporting use of platelet- rich plasma gel for healing chronic wounds including PIs**	Participants were recruited from 39 long term care centers, outpatient clinics, home health agency, long term acute care and an equipment supplier (n=200 with 285 wounds of which 142 were PIs) Inclusion: • open, cutaneous wound that has failed to respond to standard wound care per each facility protocol • wound has a mostly clean wound bed just before product application	• All participants received appropriate offloading devices. • The wound bed was cleaned thoroughly and debrided before treatment. • All participants were treated with: ○ moisture barrier preparation on intact peri-wound skin ○ Preparation of autologous platelet-rich plasma (PRP) gel from a sample of	• Wound measurements taken weekly using disposable tape measure and cotton bud probe with the deepest part of wound taken as depth measurement. • Mean wound area • Wound volume • Length of treatment time	• Of the 285 wounds, in a mean of 2.2 weeks (range: 0.4 to 11) with 2.8 PRP gel treatment (range 1 to 7) 86.3% of the wounds responded with a reduction of 47.5% in area, and 90.5% of the wounds responded with a reduction of 63.6% in volume • 63 (22.9%) wounds had undermining at baseline. In a mean of 1.8 weeks (range 0.4 to 9) with mean 2.5 PRP gel treatments (range: 1 to 8), 89.4% of the wounds responded with a 71.9% reduction in undermining • 28 wounds (10.2%) had sinus tracking at baseline. In a mean of 1.8 weeks (range: 0.4 to 3.1) with 2.5	• **A sub-set population is reported in Frykberg et al, 2010** • missing data for certain variables and lack of specific comorbid patient factors that could be used to explain some of the results, but did not negatively	**Indirect evidence (wounds of mixed aetiology)**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
		• no clinical signs and symptoms of active infection Exclusion: • Malignancy in the wound bed • current use of chemotherapy • allergy to bovine products Characteristics: • Mean baseline area 26.0cm^2±50.40 • Mean baseline depth 1.40cm±1.54 • 49.8% wounds were PI, 14.3% were diabetic ulcers, 11.2% were venous ulcers	≤20ml of the participant's blood ○ As soon as it was ready the PRP gel was applied topically to the wound and covered with a non-absorbent contact layer dressing • PRP gel was reapplied 1 to 2 times weekly according to clinical judgment.		PRP gel treatment (range: 1 to 4), 85.7 % of these wounds responded with a 49.3% reduction in sinus tract/tunnelling. • 10 wounds failed to respond as a measure by reduction in area, volume, undermining, or tunnelling reduction. • Percent change of area and depth between baseline and the final PRP gel post-treatment assessment were compared the mean volume area was reduced by 40.8%±36.16% and mean wound depth by 38.5%±47.17%	affect the study analysis • no randomization, control or blinding of assessment • no clear explanation of recruitment strategy/patient selection	
Scevola et al., 2010	Prospective randomized controlled open clinical pilot trial investigating **effectiveness of allogenic platelet gel for healing PIs**	Participants with SCI were recruited from a neuro-rehabilitation ward in Italy (n=13 with 16 PIs) Inclusion: • SCI • grade III and IV PIs • no signs of necrosis or infection nutritional status stable Exclusion: • metabolic, endocrine and collagen pathologies • ischaemic cardiopathy • corticosteroid or immune-suppressive therapy • obesity • malignancies • organ failure Characteristics: • 10 sacral PIs, 6 ischial PIs	• All patients used pressure-relieving devices followed their 2 hour postural change protocol • PIs were randomized to be either: ○ study group receiving allogenic platelet gel applied directly to wound bed then covered with polyurethane sponge and semi-permeable film dressing system ○ control group receiving saline cleanse, packing with iodoform-impregnated gauze, sodium alginate foam or cadexomer iodine powder or vacuum assisted closure with zinc	• Every two weeks the PI volume, dimensions, colour and bleeding of the granulation tissue (at the instant of scraping) were checked and photographs were collected	• At the end of the study 15 out of 16 PIs clinically improved • No statistically significant difference was demonstrated in volume reduction between the two groups • A statistically significant difference was demonstrated in the onset time of granulation tissue proliferation – the wounds treated with platelet gel the healing process was triggered earlier • Platelet gel is mostly effective within the first 2 weeks of treatment while a prolonged treatment does not provide any significant advantage • Semi-quantitative data (colour and bleeding of granulation tissue) did not show significant differences between the two groups.	• Small sample size for which baseline demographics were not reported • Does not report randomization or allocation concealment methods • PI was unit of analysis (multiple PIs per participant) • Control treatments included a range of different management strategies that are not considered standard PI care	**Level of evidence: 1** **Quality: low**

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			oxide paste or silver sulfadiazine applied to peri-wound skin • PIs treated twice weekly for 8 weeks				
Platelet derived growth factor							
Rees, Robson, Smiell, and Perry (1999)	RCT exploring a **platelet-derived growth factor** (Becaplermin gel) for treating PIs	Participants (n=124) Inclusion criteria: • At least 1 but no more than 3 chronic full thickness (stage III or IV) PIs	• Participants were randomized to receive either: ○ 100 µg/g Becaplermin gel (n=31) applied daily, or ○ 100 µg/g Becaplermin gel applied twice daily (n=31) ○ 300 µg/g Becaplermin gel applied daily (n=31) or ○ placebo gel twice daily (n=31) • All groups received thin layer of gel placed on the entire exposed wound surface and wound packing with saline moistened gauze	• Relative PI volume (PI ulcer volume at the end of the study divided by PI volume at baseline) • Complete healing • 16 week trial	• Pressure ulcers treated with rPDGF were more likely to achieve complete healing compared with those treated with placebo gel (placebo gel 0%; 100 µg/g daily 23%, p = 0.005; 300 µg/g daily 19%, p = 0.008). • Pressure injuries showed significantly greater reduction in mean relative wound volume when treated with 100 µg/g PRGF gel (0.07 versus 0.27, p=0.013) or 300 µg/g PRGF gel (0.05 versus 0.27, p=0.011) compared to placebo. • Safety evaluation showed no significant differences compared to placebo groups. One participant treated with PDGF withdrew due to declining wound condition attributed to continued pressure on the wound.	•	**Level of evidence: 1** **Quality: high**
M. C. Robson et al., 1992a; M. C. Robson, Phillips, Thomason, Robson, & Pierce, 1992b	RCT investigating **recombinant platelet-derived growth factor** for full thickness PIs	Participants (n=20) Inclusion criteria: • stage III or IV PIs of area 25 to 95cm^2	• Each participant was randomly assigned to receive either: ○ placebo gel (n=7), or ○ rPDGF-BB at 1 µg/ml (n=4) and 10 µg/ml (n=4) or 100 µg/ml (n=5) • When required, debridement was performed 48hours before treatment	• Volume measurements of using alginate molds were done on days 0, 7, 14, 21 and 29; • Maximum depth • Area of PI opening • histology of biopsy samples	**PI volume at 29 days** • No significant differences between groups • the 100 µg/ml rPDGF-BB group had a better healing response than the placebo group (4% of day 1 volume vs 5.6% day 1 volume, p=0.12) **Histology** • Normal active wound-healing processes in all group	• Small group size;	**Level of evidence: 1** **Quality: low**

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					• 100 µg/ml rPDGF-BB group tended to have a greater fibroblastic and endothelial cell influx and consequently more provisional extracellular matrix and new vessels		
Mustoe et al., 1994	RCT investigating **recombinant platelet-derived growth factor-BB** (rPDGF-BB) for full thickness PIs	Participants (n=44)	• Participants were randomized to receive either: ○ 100 µg/ml aqueous rPDGF-BB (n=15), or ○ 300 µg/ml aqueous rPDGF-BB (n=14) or ○ placebo (n=14) • All groups received groups received saline gauze dressings applied daily	• Serial volume measurements using alginate molds	**Percent of PIs healed at day 29** • Placebo group remained at 83% of the initial wound volume at day 29 • PIs in the 100 µg/ml were 29% of initial wound volume at day 29 • PIs in the 300 µg/ml were 40% of initial wound volume at day 29 • Combing the PDGF groups, there was a trend toward significant reduction in wound volume compared to placebo (p=0.056).	• Small sample size • potential confounder in • interpretation of the results due to loss of 8 participants who dropped out and 3 participants without complete data	**Level of evidence: 1** **Quality: low**
Pierce et al., 1994	RCT exploring impact of **recombinant platelet-derived growth factor-BB** on tissue processes	Participants (n=20) These participants were a sub-set of participants reported in trial by Mustoe et al. (1994)	• Participants received either: ○ Placebo (n=7), ○ rPDGF-BB 100 µg/ml (1µg/cm²), or ○ rPDGF-BB 300 µg/ml (3µg/cm²)) • Treatment for 28 days	3mm full thickness punch biopsies were collected before treatment on day 0 and on days 8, 15, and 29 from approximately half of the participants	**Microscopy** Fibroblast activity was detected in all rPDGF–BB treated PIs compared with placebo (2.81 ± 0.17 vs 2.05 ± 0.24, p=0.01)	• Small sample size	**Indirect evidence (healing not an outcome measure)**
Growth factors: Fibroblast growth factor (bFGF) for healing pressure injuries							
Ohura et al., 2011	Case-control study **investigating fibroblast growth factor for PI healing**	Participants were recruited from 14 institutions in Japan (n=29 pairs were enrolled, 23 pairs were analysed) Participants were paired fo PI risk factors, levels of PI care and total scores on Pressure Ulcer Healing Process-Ohura (PUHP-Ohura) Inclusion:	• All study matched pairs had equivalent alternating pressure-relief air mattress and regular repositioning 2 to 3 hourly • Surgical debridement was carried out at least 7 days prior to study period For all participants: • PIs were washed with saline solution	Wound condition changes assessed weekly for 8 weeks using PUHP-Ohura and wound photographs. Validation and reliability of this scale is not reported. The scale included assessment of: • Exudate volume • Necrotic tissue • Granulation formation • Wound edge • Epithelialization	• bFGF group showed a significantly greater decrease in exudate volume compared with control group after 4 weeks of treatment (p<0.001) • The bFGF group showed significantly greater decrease in PI depth score compared with control group on and after week 5 of the treatment (p< 0.001) • The change in granulation formation in group x time was not significant (p=0.858) and the main effects were significant (p=0.019)	• Small study • Participant characteristics are not reported • Non-validated assessment tool • No randomization or blinding of assessors or statisticians is reported	**Level of evidence: 3** **Quality: low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
		• Level B or C on Standard of Functional Independence Measure (Japanese Ministry of Health, Labor and Welfare coding) • PI Category III or IV (NPUAP classification) • Stayed in hospital for "a long time" and rejected surgical management Exclusion: • signs of infection Characteristics: • not reported	• Foam and hydrocellular dressings were used in combination with polyurethane films for all dressings. For the study group (bFGF group): • Basic fibroblast growth factor (bFGF) spray was sprayed on the wound daily (at a dose of 1μg/cm^2) prior to applying dressing. • Study period was 8 weeks	• Undermining • Surface area and depth • Total score of PUHP-Ohura	• Change in wound edge the group x time interaction was not significant (p=0.495) and the main effects of the group and time were significant (p=0.017) • Change in epithelialization the group x time interaction was significant (p < 0.001); the bFGF group showed a significantly greater decrease in epithelialization compared with control group at and after week 3 of the treatment (p<0.001) • Total score PUHP-Ohura the group x time interaction was significant (p<0.001) the bFGF group showed significantly greater decrease in total PUHP-Ohura score compared with the control group at and after week 4 of treatment (p<0.006)	• No confidence intervals reported	
Growth factors: Other lesser explored growth factors for healing pressure injuries							
Landi et al., 2003	RCT exploring use of 2.5S **murine nerve growth factor** for treating PIs	Participants were recruited within two weeks of admission to a nursing home (n=36) Inclusion criteria: • PI of the foot	Participants were randomized to either: • 2.5S murine nerve growth factor treatment (n=18), or • a conventional topical treatment reported as balanced salt solution (n=18)	• Surface area evaluated by tracing wound perimeter onto transparency • PI staging • Follow up at 6 weeks	**Mean surface area at 6 weeks** • PIs in the treatment group were significantly smaller in surface area compared to control group (274 ± 329 mm² versus 526 ± 334 mm², p=0.022) • All PIs treated with nerve growth factor showed a statistically significant acceleration of healing **Mean reduction in surface area** PIs in the treatment group had significantly greater reduction in surface area compared to control group (738 ± 393 mm² vs 485 ± 384 mm², p= 0.034)		**Level of evidence: 1** **Quality: low**
Hirshberg, Coleman, Marchant, & Rees, 2001	RCT exploring use of TGF-beta3 for treating PIs	Participants were a subset of a larger sample (n=290). Participants with PI were n =14	• Participants were randomized to receive daily application of:	PI surface area and volume	• Only 8 patients completed the study • Group 2 (higher dose TGF-beta3) achieved significant	• Small sample size • 43% of participants did	**Level of evidence: 1** **Quality: low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
			○ 1 µg/cm² TGF-β3 (n=4, Group 1) ○ 2.5 µg/cm² TGF-β3 ○ (n=5, Group 2) ○ Topical placebo (n=5, Group 3) • All groups also received standardized wound care for 16 weeks or until the PI was healed		reduction in mean relative surface area compared with Group 3 (placebo, p<0.05) • Group 1 (lower dose TGF-beta3) achieved significant reduction in PI volume surface area compared with Group 3 (placebo, p<0.05) **Study conclusions the use of topical growth factors is a progressive adjuvant to the traditional treatment of PIs.**	not complete the trial	
Sarasúa et al., 2011	Observational study reporting preliminary data on **bone marrow mononuclear cells infusion for healing PIs**	Participants with SCI were recruited in Spain (n=22) Inclusion: • SCI • PI not responded to 4 months topical treatment • PIsize 5 to 6 cms • Free from necrotic tissue and local infection • Medical condition compatible with surgery Characteristics: • Mean age 56.4 yrs (range 29 to 79) • Stage IV PIs: ischial (4), sacral-ischial (3) ischial-trochanter (1), plantar (1). • 13/22 participants had • Had undergone prior surgery on PI and antibiotic treatment	All PIs were surgically debrided and treated with bone marrow mononuclear cells (BM-MNCs) in the OR Participants were required to lie prone for 3 weeks following surgery 5/22 participants received a second infusion	• Healing rate • Mean follow up was 19 months (range 7 to 38 months) • Follow-up sessions were conducted at 1, 3, 6 months and 1 year after cell therapy	• 5/22 participants experienced suture dehiscence and required a second surgical procedure • In 17 participants the PIs fully healed after a mean time of 21 days	• The variation among the 27 extracts in the number of isolated MNCs that was patient dependent • Small sample size • No control group, no randomization, no standard assessment methods • Unclear how participants were selected	**Level of evidence: 4** **Quality: low**
M. C. Robson, A. et al., 1994	RCT recombinant **human interleukin-1 beta (IL-1β**) for PIs	Participants (n=26) Participant characteristics: • 24/26 participants had full thickness PIs	• Therapy drug were delivered by a spray bottle after cleansing with normal saline then a saline solution-moistened gauze	Measurements performed on days 0, 7, 14, 21, 29 and at 1 and 3 months after drug application	No dose adjustments were required and no participants required discontinuance of the drug No statistical difference seen in the percentage decreases in wound		**Level of evidence: 1** **Quality: low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
			dressing was applied and changed 12 hours later • Three dosage tiers were completed in groups of 8 participants (6 actively treated and 2 treated with placebo per dose) • Dose levels were: ○ Tier 1: 0.01 µg/cm²/day ○ Tier 2: 0.1 µg/cm²/day ○ Tier 3: 1.0 µg/cm²/day	treatment until it healing or for a maximum of 28 days	volumes over the 29- day treatment evaluation period between groups or compared to placebo		
M. C. Robson et al., 2000	RCT exploring sequential cytokine therapy **(granulocyte-macrophage colony-stimulating factor [GM-CSF])**for PIs	Participants were inpatients (n=61) Inclusion criteria: • stage III or IV PIs	Participants randomized to receive: • 2.0 µg/cm² GM-CSF topically applied daily for 35 days (n=15) • 5.0 µg/cm² bFGF topically applied daily for 35 days (n=15) • 2.0 µg/cm² GMCSF applied for 10 days followed sequentially by 25 • days of topically applied 5.0 µg/cm² bFGF (n=16); or comparative placebos applied for 35 days (n=15)	The PI was measured on day 0 and weekly for 5 weeks using planimetry of the ulcer, opening and volume determination using alginate molds;	**PI mean volume at day 36** • No significant differences between groups (p=0.57) • GM-CSF group: 12.02 ± 11.88 • bFGF group: 7.24 ± 6.11 • Sequential GM-CSF/bFGF group: 16.83 ± 25.75 • Placebo group: 14.24 ± 13.66 **Percent PI closure on day 36** • No significant differences between groups (p=0.69) • GM-CSF group): 67% ± 24 • bFGF group: 75 ± 19 • Sequential GM-CSF/bFGF group: 68 ± 21 • Placebo group: 71 ± 11		**Level of evidence: 1** **Quality: high**
Growth factors: Economic analysis							
Gilligan, Waycaster, & Milne, 2018	Economic analysis exploring a **platelet-derived growth factor** (Becaplermin	Participants (n=62) Inclusion criteria: • At least 1 but no more than 3 chronic full thickness (stage III or IV) PIs	• Participants were randomized to receive either: ○ 100 µg/g Becaplermin gel (n=31) applied daily, or	• Relative PI volume (PI ulcer volume at the end of the study divided by PI volume at baseline) • Complete healing • 16 week trial	**Healing outcomes** • Incidence of complete healing over 12 months was significantly greater in treatment group (49.4% vs 9.7%, p<0.01) • Incidence of ≥90% healing over 12 months was significantly greater in	This study is an analysis of the RCT performed by Rees et al (1999), but limit to only two of the study groups	**Level of evidence: NA** **Quality: high**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
	gel) for treating PIs	Participant characteristics: Mean age 50 years (SD 13,6) for placebo group and 48 years (SD 13.1) for treatment group	○ 300 µg/g Becaplermin gel applied daily (n=31)	• Economic analysis included costs of PDGF gel at recommended dose, nursing time, physician reimbursement, saline gauze. • Costs calculated in US dollars (2016) • Markov models calculating likelihood of transitioning from PI to healed/≥ 90% healed or to death and expected cost, results extrapolated to 12 months	treatment group (82.0% vs 49.4%, p<0.01) • Estimated weeks with open sound was higher in control group (48.9 weeks vs 40.4 weeks) **Economic analysis** • Actual costs for 52 week phase was $3827 for PRGF and $1279 for placebo, amounting to incremental cost-effectiveness ratio (ICER) of $298/closed wound week or ICER = $150 per ≥90% healed weeks. (i.e. patients need to pay an extra $298 to gain one additional pressure injury free week)	Actual doses used I the clinical study were unknown Based on clinical practices from the 1990s	
Biological dressings: collagen matrix							
Kloeters, Unglaub, de Laat, van Abeelen, & Ulrich, 2016	RCT exploring efficacy of a **ORC/collagen matrix dressing** in healing PIs	Participants were recruited in a wound clinic in Netherlands (n=33) Inclusion criteria: • Aged ≥ 18 years • Chronic wound > 6 weeks but < 12 weeks • Wound >1cm^2 Exclusion criteria: • Systemic inflammatory disease • Malignant tumor • Chemotherapy • Alcohol/drug use Participant characteristics: Average 63±8 years	• All wounds debrided prior to interventions • Participants were randomized to receive either: ○ Oxidized regenerated cellulose/collagen matrix (n=23) or ○ Control dressing absorbing hydropolymer foam dressing (n=10)	• Protease activity measured as levels of elastase and plasmin, measured via wound fluid collection on admission, day 5 and day 14 • Healing rate assessed via digital photography and planimetry – reduction in surface area over 8 weeks	**Healing rate** Wounds treated with ORC/collagen matrix showed a significant reduction in wound surface area by 65±13% versus 41±11% reduction in control group (p<0.05) **Protease activity** Significant reduction in elastase activity at day 5,14,28,42 and 56 for the collagen dressing group (p<0.05 for all) Reduction in elastase activity was significant compared to the control group at day 5 and day 14 Plasmin activity was significantly reduced at days 5 and 14 compared to control group (p<0.05 for both) **Author conclusions: ORC/collagen matrix significantly reduces elastase and plasmin activity in wound exudate, thereby rebalancing wound microenvironment and promoting healing**	• Minimal patient demographics reported, no reporting of severity of pressure i • Unclear if participants had wounds of comparable size at baseline • Co-morbidities not reported • Methods of randomization and allocation concealment not reported • Unclear if there was blinded outcome measurement	**Level of evidence: 1** **Quality: low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
Piatkowski et al., 2012	Prospective, pilot RCT investigating **effectiveness of a collagen dressings for healing Category/Stage II pressure injuries**	Participants were recruited from a plastic surgery department in Germany (n=10) Inclusion: • Stagnating PI of at least 4 weeks' duration • Wound had to be granulating and had to be free of necrotic tissue and slough • No clinical signs of infection Characteristics: • Mean age 63±0.62 in foam group and in 67±0.62 collagen foam group • 60% sample diabetes in both groups • All PIs category III • Mean PI diameter 8.3cm in foam group and 11.4cm in collagen foam group	Patients were randomized to receive either: ○ foam dressing as a primary dressing (n=5) or ○ combination of a collagen dressing covered with the same foam dressing (n=5) • Dressing changes were performed every second day • All participants had foam mattress and 3 hour repositioning	**Primary outcome** • Level and expression of matrix metalloproteinases (MMPs) MMP-2 and MMP-9 and tissue inhibitors of metalloproteinases (TIMPs) TIMP-1 and TIMP-2, elastase and angiogenesis • Wound fluid was collected and evaluated prior to treatment (day 0) and on days 3, 7, 14 and 21 (study end) **Secondary Outcomes** • Time to healing and reduction in area measured with digital photography, wound tracings and planimetry • Safety of treatment • Patient-reported wound pain • Comfort of the dressing regimen	• On day 3 collagen dressing was associated with significantly decreased MMP-2 levels by compared with foam dressing ($p<0.05$) but by day 14 collagen group had higher MMP-2 levels than foam group. • MMP-9 concentrations showed a faster and higher reduction in collagen group compared to foam group and the difference was significant by day 7 ($p<0.04$) • In the collagen group TIMP-1 and TIMP-2 increased faster and levels were higher than in group A. • Collagen dressing was associated with a significant positive effect on angiogenesis compared with foam group ($p<0.05$) • On day 14, 40% of PIs (n=2) in collagen group had healed compared to 0% in foam group • On day 21, all 100% of PIs healed in collagen group compared to 80% (4/5) of foam group.	• Small number of patients in pilot study resulted in the study lacking power • No blinding • 2/5 patients withdrew in collagen foam group due to early healing but included in analysis	**Level of evidence: 1** **Quality: moderate**
Karr, 2008	Case series reporting **the benefits of a living bilayered cell therapy that includes collagen**	Recruitment of participants is not reported (n=10) Characteristics: • Age range 39yrs to 78yrs 80% were diabetic foot ulcers, 20% venous ulcers • All PIs located on heels • Ulcers ranged in size from 1.0cm^2 to 18.0cm^2 • 20% participants had osteomyelitis	• All ulcers were debrided then treated with: ○ Apligraf®, a living bilayered cell therapy. ○ 60% of participants had only one application ○ For 40% with > one application, minimum time between applications was 4 weeks.	Days to closure – standardised wound assessment is not reported	• Average days to complete healing was 44 days (range 13 to 80 days) • Average days to complete healing in participants without osteomyelitis (20% sample) was 49.5 days • Average days to complete healing in participants with osteomyelitis (80% sample) was 44 days • Average days to complete healing in non-smokers (80% sample) was 39.9 days • Average days to complete healing in smokers (20% sample) was 60.5 days	• No randomization, blinding or control • Small sample size • Selection criteria is not reported	**Indirect evidence (wounds of mixed aetiology)**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
		• Ulcer duration prior to treatment was a mean of 161.3 days	• All participants had pressure offloading.				
Graumlich et al., 2003	RCT comparing collagen dressing to a hydrocolloid dressing	Participants were recruited from 11 nursing homes in the US (n=65 recruited, n=65 analyzed) Inclusion criteria: Aged above 18 years Stage 3 or 3 pressure injury Exclusion criteria: Allergy to products Osteomyelitis, cellulitis, malnutrition Eschar or necrosis of pressure injury Participant characteristics: • Mean age approx. 80 years • Mean duration of pressure injury 3 to 6.5 weeks • Mean Braden score around 12 • About 80% had stage 2 pressure injury and 20% with stage 3	• All pressure injuries received • Participants were randomized to receive: ○ Collagen dressing: sterile saline applied, collagen sprinkled in thin continuous layer over wound bed, gauze applied (n=35), or ○ Hydrocolloid (n=35) • Treatment for 8 weeks or to complete healing (whichever first) • Stratification by diagnosis of diabetes	• Digital photography, length, width, depth • Outcomes measured by blinded clinical nurses • Cost analysis	**Wound healing outcomes at 8 weeks** • Collagen dressing was as effective as a hydrocolloid dressing in achieving complete wound healing (mean difference 1%, 95% CI –26 to 29%, p=0.893) • Collagen dressing was as effective as a hydrocolloid dressing when measured by mm^2/day (mean difference 0, 95% CI –9 to 8, p=0.942) • No adverse events were experienced • Adjustment for category/stage of pressure injury showed no significant difference between interventions **Cost analysis** • Considering dressing materials, ancillary supplies and labor costs, collagen dressing was more expensive that hydrocolloid dressing for 8 weeks (average per patient cost hydrocolloid $222 versus collagen $627) ($US in 2003) • Collagen dressings required 7 nursing interventions per week versus 2 for hydrocolloid. **Author conclusions: Collagen dressing has no advantage over hydrocolloid and is more expensive to use.**	• 17% lost to followup (equivalent between groups) but used ITT analysis • Blinded outcome measurement and analysis	**Level of evidence: 1** **Quality: high**
Nisi, Brandi, Grimaldi, Calabrò, & D'Aniello, 2005	RCT comparing **collagen dressing to viscose rayon**	Participants were recruited in a plastic surgery unit in Italy (n=80) Inclusion criteria:	• Participants were randomly assigned to: • Debridement, disinfection with povidone-iodine, saline wash and hydrogel	• Classification using NPUAP classification • Ulcer length and depth • Wound bed condition • Signs of local infection	**Wound healing rates** 90% of collagen group achieved complete healing versus 70% in control group (p=0.59) **Time to complete healing**	• Methods of recruitment are not reported • No blinding	**Level of evidence: 1** **Quality of evidence: Low**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
		• Pressure injury Category/Stage II to IV Exclusion criteria: • Decompensating diabetes • Hypertension • Arterial or venous insufficiency • Low haematocrit value • Primarily males • Mean age 45 years (range 35 to 85) • Primarily sacral or trochanter pressure injuries	dressing then commenced collagen protease matrix (Pomogran®) 2-3 times weekly based on exudate levels • Debridement, disinfection with povidone-iodine, saline wash and viscose-rayon dressing plus hydropolymer.	• Norton scale to classify risk • 6 month follow up	Collagen group time to complete healing ranged from 2-6 weeks versus 2-8 weeks in control group **Number of dressings** Collagen group required 6-15 dressings versus 14-52 in control group **Hospital time** Overall hospitalization days was 360 days for collagen group versus 1164 for control group **Author conclusions: Collagen dressings reduce time to healing and resource use.**	• Methods of randomization and allocation concealment are not reported • Comparability of groups is not discussed • No statistical analysis of resource outcomes. Overall hospitalization time may be influenced by individual participants	
Biological dressings: hyaluronic acid dressings and injections for preventing and healing							
Beniamino, Vadalà, & Laurino, 2016	Non-controlled study investigating efficacy of **hyaluronic acid injections** to prevent pressure injury	Participants were recruited in an orthopedic ward in Italy (n=15) Inclusion criteria: Admitted for fracture treatment Exclusion criteria: Not stated Participant characteristics: • Age range 78 to 94 years • BMI ranged from 22 to 31 kg/m^2 • 20% had severe spinal scoliosis • 20% had a previous, heeled PI • 20% had severe weight loss or undernutrition	• All participants received a water mattress, 3hrly repositioning and preventive skin hygiene • Skin inspections conducted at sacrum, ilium and heels • On identification of blanching erythema, HA injection performed under local anesthetic: 30 to 50cc (5 to 7cc at heels) of crosslinked HA injected 3 to 5cms at lateral side or erythema until the injected gel layer was 2 to 3 cm thick	• Daily skin inspection to evaluate local reaction • Weekly inspection by doctor to evaluate skin quality and complications • Injection-related pain on a 4 point descriptor scale • Tolerability of procedure on a 4 point descriptor scale • Adverse events	**Adverse events** • 20% experienced minor injection-site bleeding associated with taking low molecular weight heparin • 30% experienced bleeding stopping within 5 mins following procedure • All participants described the procedure as comfortable, satisfactory or good • Over 86% had no pain and the remainder had moderate pain • 20% experienced minor (2 to 3 cc) gel leak **PIoutcomes** • Erythema disappeared within 2 to 4 days • No PIs detected in weekly inspection over 3 month follow-up **Author conclusions: Injected HA strengthens the extra-cellular matrix and**	• Potential selection bias • No control group • No objective outcomes for evaluating PIs • Small trial	**Level of evidence: 4** **Quality: low** *N.b.: This study focuses on preventing PIs*

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
		• 80% had catheter			**creates a soft base in the deep dermis, contributing to PI prevention**		
Caravaggi, Grigoletto, & Scuderi, 2011	Multicentre, prospective, observational study **investigating a hyaluronic acid matrix dermal substitute for development of healthy dermal tissue at wound edges**	Participants were recruited from 70 Italian centers (n=262) I Inclusion: • chronic wound • undergone conventional treatment for at least 2 months previously that proved ineffective • medication known to interfere with healing were not excluded Exclusion: • signs of infection Characteristics: • Mean age 70 years (range 53 to 103) • 46% wounds were vascular, 25% diabetic foot ulcers, 12% trauma wounds, 2% PIs (i.e. 5 PIs) • 25% wounds were >50cm^2, 30% of PIs were >50cm^2 • 31% wounds were <15cm^2, 35% PIs were <15cm^2 • 64% of wounds were partial thickness not involving tendons or joints	• Standard wound bed preparation including debridement of necrotic, non-vital tissue and hemostasis. • Hyalomatrix PA® (HPA), a non-woven pad of hyaluronic acid derivative coupled and a layer of medical grade silicone, was applied directly to the clean ulcer. • A non-adherent dressing was placed in contact with the HPA as a secondary dressing and left undisturbed for at least 1 week • Participants with peripheral vascular disease underwent revascularization. • Offloading was recommended for patients with neuropathic planter foot ulcer	• Epithelial (edge) advancement of 10% • Secondary outcome was pain assessment • Weekly follow up and at 60 days	• Re-epithelialization of 10% was achieved in 217 (83%) of the ulcers in a mean time of 16 days • The endpoint of at least 10% or re-epithelialization within 60 days of follow-up was observed in 88% of patients affected by ulcers with onset ≤1year, while the same end point was achieved by 73% of patients affected by ulcers with onset >1 year (p<0.05) • 26% of wounds achieved at least 75% re-epithelialization within 60 days of the follow up period after treatment with HPA only • Pain intensity was reduced almost 3-fold within 30 days after the initial treatment with HPA	• The study was not randomized or controlled • Unclear if participants with PVD underwent revascularization before or during treatment in accordance with criteria established by Inter-Society for the Management of Peripheral Vascular Disease (TASD II)	**Indirect evidence (wounds of mixed aetiology)**
Biological dressings: amniotic membranes							
Dehghani, Azarpira, Mohammadkarimi, Mossayebi, &	RCT exploring **effectiveness of amniotic membrane dressing for**	Participants were recruited in a university hospital in Iran (n=24) Inclusion criteria: • Aged ≥ 18 years	• All participants were cleansed, debrided and washed with povidone-iodine • Participants were randomized to receive:	• Daily measurement of surface area • Daily evaluation of clinical signs of infection	**Healing outcomes** • Complete healing was significantly higher in amniotic membrane group (75% versus 0%, p<0.001) • Partial healing was significantly higher in control group (p=0.03)	• Treatment provided to control group is not recognized as an effective management	**Level of evidence: 1** **Quality: high**

Ref	Type of Study	Sample	Intervention(s)	Outcome Measures & Length of Follow-up	Results	Limitations and comments	
Esfandiari, 2017	**promoting PI healing**	• No clinical signs of infection • Stage 2 or 3 PI Exclusion criteria: • Stage 1 or 4 PI • Pregnant or breastfeeding • Previous biological dressing or topical growth factor use • Known/suspected malignancy Characteristics: • Mean age 44±12.7 years • >90% of participants took antibiotics • 16% received NG tube feeding • More than half participants experienced fever during hospitalization • More than 80% had stage 2 PI at baseline • Mean PI surface area at baseline ranged from 3.2 to 54 cm^2	○ Amniotic membrane allograft – cryopreserved membrane applied to cover entire PI surface, covered by moist wound dressing and balloon ring bandage, procedure repeated every 2-3 days until complete healing (n=12) or ○ Control – local phenytoin powder applied (n=12)	• Scar assessment using Modified Vancouver Scar Scale • Healing defined as complete (100% epithelialization) or partial (reduction in PI size by 50% or less) • Wound healing confirmed by an independent panel of physicians	• Complete healing in amniotic membrane group occurred at between 16 to 30 days **Other outcomes** • Scar tissue score on MVSS was significantly lower for amniotic membrane group versus control ($p<0.03$) • No infection was experienced in amniotic membrane group versus 1 infection in control group • Wound discharge decreased in 2 to 3 days for amniotic membrane group versus 10 to 12 days in control group ($p=0.03$) **Author conclusion: cryopreserved amniotic membrane is effective for promoting healing in stage 2 and 3 pressure injuries**	strategy for PI (see relevant systematic reviews on topical phenytoin) • Small sample • Size, non-blinded study • Discrepancies in reporting between table and text • Other management strategy is not reported (e.g. support surface)	

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

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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
6491	Ramos-Torrecillas et al., 2015	Y	Y	N	N	N	Y	Y	Y	N	N	Y	N	1	low
13700	Kloeters et al., 2016	Y	U	U	U	U	U	Y	U	U	NA	N	Y	1	low
14777	Dehghani et al., 2017	Y	Y	N	N	Y	Y	Y	Y	Y	NA	Y	Y	1	high
14261	Yu et al., 2017	Y	Y	N	N	Y	Y	Y	U	Y	N	U	U	1	low

QUASI EXPERIMENTAL STUDIES

	Author/year	Focussed question	Subjects and investigators blinded	Groups comparable at commencement	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
8103	Singh et al., 2015	Y	N	N	N	Y	Y	Y	NA	N	Y	2	low
2753	Singh et al., 2014	Y	N	N	Y	Y	U	Y	NA	N	Y	2	low

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
16377	Beniamino et al., 2016	Y	N	N	U	U	N	NA	U	N	Y	4	low
9002	Biglari et al., 2015	Y	N	U	U	Y	Y	NA	Y	N	Y		

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
17775	Gilligan et al., 2018	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	NA	High

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