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


Identified in pressure injury searches
n=11,177

Excluded after screening title/abstract
- Duplicate citations
- Included in previous guideline
- Not related to pressure injuries
n=8,128

Identified citations
n=3,085

Excluded based on key word searches
- Not related to the topic-specific questions
n=3,052

Biological dressings and growth factors keywords
Biologic*, biomaterial, biodressing, skin PLUS substitute, collagen, cellulose, modulating, layered, hyaluronic, growth factor, platelet, stem cell

Identified in topic-specific key word searches for full text review and critical appraisal
n=33

Excluded after review of full text
- Not related to pressure injuries
- Not related to the clinical questions
- Citation type/research design not meeting inclusion criteria
- Non-English citation with abstract indicating not unique research for translation
n=21

Identified as providing direct or indirect evidence related to topic and critically appraised
n=12

Additional citations
Appraised for previous editions
n=10

Total references providing direct or indirect evidence related to topic
n=22

Additional citations
Identified by working group members
n=36

# Growth Factors and biological dressings: Data extraction and appraisals

## 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.


<table>
<thead>
<tr>
<th>Ref</th>
<th>Type of Study</th>
<th>Sample</th>
<th>Intervention(s)</th>
<th>Outcome Measures &amp; Length of Follow-up</th>
<th>Results</th>
<th>Limitations and comments</th>
</tr>
</thead>
</table>
| Ramos-Torrecillas, Garcia-Martinez, Luna-Bertos, Ocana-Peinado, & Ruiz, 2015 | Non-blinded RCT investigating effectiveness of platelet rich plasma 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 Pls in study) | All participants received 3rd daily dressing change and saline cleanse, debridement, liquid hydrogel and polyurethane dressing, 2 hourly repositioning | 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 (cm²) determined using calipers to measure width and length  
The types of tissue (e.g. epithelial, granulation sphenus, 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)  
% Pls 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 |
### Growth Factors and biological dressings: Data extraction and appraisals

<table>
<thead>
<tr>
<th>Ref</th>
<th>Type of Study</th>
<th>Sample</th>
<th>Intervention(s)</th>
<th>Outcome Measures &amp; Length of Follow-up</th>
<th>Results</th>
<th>Limitations and comments</th>
<th>Level of evidence</th>
<th>Quality</th>
</tr>
</thead>
</table>
| **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 | 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  | % 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  | 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 |
<table>
<thead>
<tr>
<th>Ref</th>
<th>Type of Study</th>
<th>Sample</th>
<th>Intervention(s)</th>
<th>Outcome Measures &amp; Length of Follow-up</th>
<th>Results</th>
<th>Limitations and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>(report on the same study as above)</td>
<td>pressure injuries.</td>
<td>At least 2 pressure injuries • Pls 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 Pls treated with growth factor were stage IV • Control Pls ranged from category/stage 2 to 4 • Primarily sacral Pls 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&lt;0.000) but not for control group (p=0.924). Histopathology at 5 weeks Majority of PGP-treated Pls 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 Pls improved and only 1 deteriorated • 68% of control Pls 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</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biglari et al., 2015</td>
<td>Case series investigating the effectiveness of platelet rich plasma in healing fistulas associated with category/ stage III or IV PI</td>
<td>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 Pls. Level of evidence: 4 Quality: low Sequential recruitment unclear Small uncontrolled study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Data Tables: 2019 Guideline Update: Growth factors and biological dressings

© EPUAP/NPIAP/PPPIA

<table>
<thead>
<tr>
<th>Ref</th>
<th>Type of Study</th>
<th>Sample</th>
<th>Intervention(s)</th>
<th>Outcome Measures &amp; Length of Follow-up</th>
<th>Results</th>
<th>Limitations and comments</th>
</tr>
</thead>
</table>
| 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 PI s | Subjects were recruited from a hospital wound care center and various nursing homes in China (n=320) | - All PI s 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 | - 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  

---

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

---

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 PI s with total surface 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
### Growth Factors and biological dressings: Data extraction and appraisals

<table>
<thead>
<tr>
<th>Ref</th>
<th>Type of Study</th>
<th>Sample</th>
<th>Intervention(s)</th>
<th>Outcome Measures &amp; Length of Follow-up</th>
<th>Results</th>
<th>Limitations and comments</th>
</tr>
</thead>
</table>
| 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 | 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 as 100% epithelialization or skin closure without drainage)  
• Percentage of wound area healed  
• Wound complications: infection, necrosis  
• Adverse events | successful treatments for promoting PI healing | • 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 |
| Rapp, 2011 | Case series reporting use of platelet-rich plasma gel for healing chronic wounds including PI's | 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 PI's) | All wounds were treated with 1.3 x platelet-rich plasma (PRP gel) | Wounds were assessed using different techniques at 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 |
<table>
<thead>
<tr>
<th>Ref</th>
<th>Type of Study</th>
<th>Sample</th>
<th>Intervention(s)</th>
<th>Outcome Measures &amp; Length of Follow-up</th>
<th>Results</th>
<th>Limitations and comments</th>
</tr>
</thead>
</table>
| 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) | • 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.  
• Wound volume  
• Length of treatment time | • 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 | |
### Ref: de Leon et al, 2011

**Type of Study:** Case series reporting use of platelet-rich plasma gel for healing chronic wounds including PIs

**Sample:** 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

**Intervention(s):**
- All participants received appropriate off-loading 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
- PRP gel was reapplied 1 to 2 times weekly according to clinical judgement.

**Outcome Measures & Length of Follow-up:**
- 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:**
- 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 3.1) with 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

**Limitations and comments:**
- 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)**

---

**Growth Factors and biological dressings: Data extraction and appraisals**

**Data Tables: 2019 Guideline Update: Growth factors and biological dressings**

© EPUAP/NPIAP/PPPIA
<table>
<thead>
<tr>
<th>Ref</th>
<th>Type of Study</th>
<th>Sample</th>
<th>Intervention(s)</th>
<th>Outcome Measures &amp; Length of Follow-up</th>
<th>Results</th>
<th>Limitations and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scervola et al, 2010</td>
<td>Prospective randomized controlled open clinical pilot trial investigating effectiveness of allogenic platelet gel for healing Ps</td>
<td>Participants with SCI were recruited from a neuro-rehabilitation ward in Italy (n=13 with 16 Ps)</td>
<td>• All patients used pressure-relieving devices followed their 2 hour postural change protocol. • Ps 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 iodofarm-impregnated gauze, sodium alginate foam or cadexomer iodine powder or vacuum assisted closure with zinc.</td>
<td>• 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.</td>
<td>• 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%</td>
<td>• Small sample size for which baseline demographics were not reported. • Does not report randomization or allocation concealment methods. • PI was unit of analysis (multiple Ps per participant). • Control treatments included a range of different management strategies that are not considered standard PI care.</td>
</tr>
</tbody>
</table>
### Growth Factors and biological dressings: Data extraction and appraisals

<table>
<thead>
<tr>
<th>Ref</th>
<th>Type of Study</th>
<th>Sample</th>
<th>Intervention(s)</th>
<th>Outcome Measures &amp; Length of Follow-up</th>
<th>Results</th>
<th>Limitations and comments</th>
</tr>
</thead>
</table>
| Rees, Robson, Smiell, and Perry (1999) | RCT exploring a platelet-derived growth factor (Becaplermin gel) for treating PIs | Participants (n=124) | - Oxide paste or silver sulfadiazine applied to peri-wound skin  
- PIs treated twice weekly for 8 weeks | - 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. | |
| 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) | - e:  
- Each participant was randomly assigned to receive either:  
  - placebo gel (n=7),  
  - 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 48 hours before treatment | - Volume measurements of using alginate moulds 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 |
<table>
<thead>
<tr>
<th>Ref</th>
<th>Type of Study</th>
<th>Sample</th>
<th>Intervention(s)</th>
<th>Outcome Measures &amp; Length of Follow-up</th>
<th>Results</th>
<th>Limitations and comments</th>
<th>Level of evidence</th>
<th>Quality</th>
</tr>
</thead>
</table>
| 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:  
  o 100 μg/ml aqueous rPDGF-BB (n=15), or  
  o 300 μg/ml aqueous rPDGF-BB (n=14), or  
  o placebo (n=14)  
• All groups received saline gauze dressings applied daily  
• Treatment for 28 days | • Serial volume measurements using alginate molds                                                                 | • 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  
• 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 the interpretation of the results due to loss of 8 participants who dropped out and 3 participants without complete data  
• Small sample size                                                                                       | Low | 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:  
  o Placebo (n=7),  
  o rPDGF-BB 100 μg/ml (1μg/cm²), or  
  o 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) | No loss of 8 participants who dropped out and 3 participants without complete data  
• Small sample size                                                                                       | Indirect evidence (healing not an outcome measure)                                                                 | |

**Growth factors: Fibroblast growth factor (bFGF) for healing pressure injuries**

<table>
<thead>
<tr>
<th>Ref</th>
<th>Type of Study</th>
<th>Sample</th>
<th>Intervention(s)</th>
<th>Outcome Measures &amp; Length of Follow-up</th>
<th>Results</th>
<th>Limitations and comments</th>
<th>Level of evidence</th>
<th>Quality</th>
</tr>
</thead>
</table>
| 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 debridment 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  
• Small study                                                                 | 3 | low |
# Growth Factors and biological dressings: Data extraction and appraisals

<table>
<thead>
<tr>
<th>Ref</th>
<th>Type of Study</th>
<th>Sample</th>
<th>Intervention(s)</th>
<th>Outcome Measures &amp; Length of Follow-up</th>
<th>Results</th>
<th>Limitations and comments</th>
</tr>
</thead>
</table>
| 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) | Participants were randomized to either: | • Surface area evaluated by tracing wound perimeter onto transparency  
• PI staging  
• Follow up at 6 weeks | Mean surface area at 6 weeks | • No confidence intervals reported |
|  |  | Inclusion criteria:  
• PI of the foot  | • 2.5S murine nerve growth factor treatment (n=18), or  
• a conventional topical treatment reported as balanced salt solution (n=18) |  |  |  |
|  |  | Exclusion:  
• signs of infection  |  |  |  |  |
|  |  | Characteristics:  
• not reported  |  |  |  |  |
| 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 | Mean reduction in surface area  
Pls 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) | Small sample size  
43% of participants did not complete study  
Level of evidence: 1  
Quality: low |
|  |  |  | • Participants were randomized to receive daily application of:  
• TGF-beta3  
• Balanced salt solution |  |  |  |

## Growth factors: Other lesser explored growth factors for healing pressure injuries

| Level of evidence: 1  
Quality: low |
### Growth Factors and biological dressings: Data extraction and appraisals

<table>
<thead>
<tr>
<th>Ref</th>
<th>Type of Study</th>
<th>Sample</th>
<th>Intervention(s)</th>
<th>Outcome Measures &amp; Length of Follow-up</th>
<th>Results</th>
<th>Limitations and comments</th>
</tr>
</thead>
</table>
| 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) | • 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 | • 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 |

| 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) | • 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 | • 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 |

| M.C. Robson, A. et al., 1994 | RCT recombinant human interleukin-1 beta (IL-1β) for PIs | Participants (n=26) | • 24/26 participants had full thickness PIs | 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 discontinuation of the drug  
No statistical difference seen in the percentage decreases in wound | Level of evidence: 1  
Quality: low |

| M.C. Robson, A. et al., 1994 | RCT recombinant human interleukin-1 beta (IL-1β) for PIs | Participants (n=26) | • 24/26 participants had full thickness PIs | 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 discontinuation of the drug  
No statistical difference seen in the percentage decreases in wound | Level of evidence: 1  
Quality: low |
## Growth Factors and biological dressings: Data extraction and appraisals

<table>
<thead>
<tr>
<th>Ref</th>
<th>Type of Study</th>
<th>Sample</th>
<th>Intervention(s)</th>
<th>Outcome Measures &amp; Length of Follow-up</th>
<th>Results</th>
<th>Limitations and comments</th>
</tr>
</thead>
</table>
| 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) | 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 GM-CSF applied for 10 days sequentially followed 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 |
| Gilligan, Waycaster, & Milne, 2018 | Economic analysis exploring a platelet-derived growth factor (Becaplermin) | Participants (n=62) | 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 treatment group (84.6% vs 34.8%, p<0.01)  
- Incidence of ≥75% healing over 12 months was significantly greater in treatment group (59.8% vs 18.2%, p<0.01) | 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 |
# Growth Factors and biological dressings: Data extraction and appraisals

<table>
<thead>
<tr>
<th>Ref</th>
<th>Type of Study</th>
<th>Sample</th>
<th>Intervention(s)</th>
<th>Outcome Measures &amp; Length of Follow-up</th>
<th>Results</th>
<th>Limitations and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>gel) for treating PIs</td>
<td>Participant characteristics: Mean age 50 years (SD 13.6) for placebo group and 48 years (SD 13.1) for treatment group</td>
<td>300 μg/g Becaplermin gel applied daily (n=31)</td>
<td>Economic analysis included costs of PDGF gel at recommended dose, nursing time, physician reimbursement, saline gauze.</td>
<td>treatment group (82.0% vs 49.4%, p&lt;0.01)</td>
<td>Actual doses used in the clinical study were unknown. Based on clinical practices from the 1990s</td>
<td></td>
</tr>
<tr>
<td>Biological dressings: collagen matrix</td>
<td>Participants were recruited in a wound clinic in Netherlands (n=33)</td>
<td>All wounds debrided prior to interventions</td>
<td>Protease activity measured as levels of elastase and plasmin, measured via wound fluid collection on admission, day 5 and day 14</td>
<td>Healing rate</td>
<td>Healed or ≥ 90% healed or to death and expected cost, results extrapolated to 12 months</td>
<td></td>
</tr>
<tr>
<td>Kloeters, Unglaub, de Laat, van Abeelen, &amp; Ulrich, 2016</td>
<td>Inclusion criteria: • Aged ≥ 18 years • Chronic wound &gt; 6 weeks but &lt; 12 weeks • Wound &gt;1cm²</td>
<td>Control dressing absorbing hydropolymer foam dressing (n=10)</td>
<td>Protease activity was significantly reduced compared to control group at day 5 and day 14 Plasmin activity was significantly reduced at days 5 and 14 compared to control group (p&lt;0.05 for both)</td>
<td>Author conclusions: ORC/collagen matrix significantly reduces elastase and plasmin activity in wound exudate, thereby rebalancing wound microenvironment and promoting healing</td>
<td>Minimal patient demographics reported, no reporting of severity of pressure injury</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: • Systemic inflammatory disease • Malignant tumor • Chemotherapy • Alcohol/drug use</td>
<td>Participants were randomized to receive either: Oxidized regenerated cellulose/collagen matrix (n=23) or Control dressing absorbing hydropolymer foam dressing (n=10)</td>
<td>Protease activity showed a significant reduction in wound surface area by 65±13% versus 41±11% reduction in control group (p&lt;0.05)</td>
<td></td>
<td>Unclear if participants had wounds of comparable size at baseline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Participant characteristics: Average 63±8 years</td>
<td></td>
<td></td>
<td></td>
<td>Co-morbidities not reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Methods of randomization and allocation concealment not reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unclear if there was blinded outcome measurement</td>
<td></td>
</tr>
</tbody>
</table>

## Biological dressings: collagen matrix

- Kloeters, Unglaub, de Laat, van Abeelen, & Ulrich, 2016

- **RCT exploring efficacy of an 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 >1cm²

- **Exclusion criteria:**
  - Systemic inflammatory disease
  - Malignant tumor
  - Chemotherapy
  - Alcohol/drug use

- **Participant characteristics:**
  - Average 63±8 years

- **Intervention(s):**
  - All wounds debrided prior to interventions
  - Participants were randomized to receive either:
    - Oxidized regenerated cellulose/collagen matrix (n=23)
    - Control dressing absorbing hydropolymer foam dressing (n=10)

- **Outcome Measures:**
  - Protease activity measured as levels of elastase and plasmin, measured via wound fluid collection on admission, day 5 and day 14

- **Results:**
  - Healing rate showed a significant reduction in wound surface area by 65±13% versus 41±11% reduction in control group (p<0.05)
  - Protease activity was significantly reduced compared to 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

- **Limitations and comments:**
  - Minimal patient demographics reported, no reporting of severity of pressure injury
  - 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

---

**Data Tables: 2019 Guideline Update: Growth factors and biological dressings**

© EPUAP/NPIAP/PPPIA

Page 15
| Ref          | Type of Study | Sample                                                                 | Intervention(s)                                                                 | Outcome Measures & Length of Follow-up                                                                 | Results                                                                                                                                                                                                                                                                                                                                 | Limitations and comments                                                                                                                                                                                                 | Level of evidence: 1  
  Quality: moderate                                                                 |
|--------------|---------------|------------------------------------------------------------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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:  
  o foam dressing as a primary dressing (n=5) or  
  o 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 |
| 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 1.0cm² to 18.0cm²  
  • 20% participants had osteomyelitis | All ulcers were debrided then treated with:  
  o Apligraf®, a living bilayered cell therapy.  
  o 60% of participants had only one application  
  o 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) |
## Growth Factors and biological dressings: Data extraction and appraisals

<table>
<thead>
<tr>
<th>Ref</th>
<th>Type of Study</th>
<th>Sample</th>
<th>Intervention(s)</th>
<th>Outcome Measures &amp; Length of Follow-up</th>
<th>Results</th>
<th>Limitations and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graumlich et al., 2003</td>
<td>RCT comparing collagen dressing to a hydrocolloid dressing</td>
<td>Participants were recruited from 11 nursing homes in the US (n=65 recruited, n=65 analyzed)</td>
<td>All pressure injuries received. Participants were randomized to receive: o Collagen dressing: sterile saline applied, collagen sprinkled in thin continuous layer over wound bed, gauze applied (n=35), or o Hydrocolloid (n=35) Treatment for 8 weeks or to complete healing (whichever first)</td>
<td>Digital photography, length, width, depth</td>
<td>Wound healing outcomes at 8 weeks</td>
<td>• 17% lost to followup (equivalent between groups) but used ITT analysis • Blinded outcome measurement and analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inclusion criteria: Aged above 18 years Stage 3 or 3 pressure injury</td>
<td></td>
<td></td>
<td>Cost analysis</td>
<td>Level of evidence: 1 Quality: high</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exclusion criteria: Allergy to products Osteomyelitis, cellulitis, malnutrition Eschar or necrosis of pressure injury</td>
<td></td>
<td></td>
<td>Wound healing outcomes at 8 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
<td></td>
<td></td>
<td>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)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• All participants had pressure offloading.</td>
<td>• Outcomes measured by blinded clinical nurses</td>
<td>• No adverse events were experienced</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Cost analysis</td>
<td>• Adjustment for category/stage of pressure injury showed no significant difference between interventions</td>
<td></td>
</tr>
<tr>
<td>Nisi, Brandi, Grimaldi, Calabrò, &amp; D’Aniello, 2005</td>
<td>RCT comparing collagen dressing to viscose rayon</td>
<td>Participants were recruited in a plastic surgery unit in Italy (n=80)</td>
<td>Participants were randomly assigned to: o Debridement, disinfection with povidone-iodine, saline wash and hydrogel</td>
<td>Classification using NPUAP classification</td>
<td>Wound healing rates</td>
<td>• Methods of recruitment are not reported • No blinding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inclusion criteria:</td>
<td></td>
<td>Ulcer length and depth</td>
<td>90% of collagen group achieved complete healing versus 70% in control group (p=0.59)</td>
<td>Level of evidence: 1 Quality of evidence: Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Wound bed condition</td>
<td>Time to complete healing</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Signs of local infection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Growth Factors and biological dressings: Data extraction and appraisals

<table>
<thead>
<tr>
<th>Ref</th>
<th>Type of Study</th>
<th>Sample</th>
<th>Intervention(s)</th>
<th>Outcome Measures &amp; Length of Follow-up</th>
<th>Results</th>
<th>Limitations and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benimino, Vadala, &amp; Laurino, 2016</td>
<td>Non-controlled study investigating efficacy of hyaluronic acid injections to prevent pressure injury</td>
<td>Participants were recruited in an orthopedic ward in Italy (n=15)</td>
<td>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 hydrogel.</td>
<td>Norton scale to classify risk • 6 month follow up</td>
<td>Collagen group time to complete healing ranged from 2-6 weeks versus 2-8 weeks in control group</td>
<td>• 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</td>
</tr>
</tbody>
</table>

### Biological dressings: hyaluronic acid dressings and injections for preventing and healing

- **Participants**
  - 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 using local anesthetic: 30 to 50cc (5 to 7cc at heels) of crosslinked HA injected 3 to 5ccms 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
  - 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

- **Outcomes**
  - 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

---

**Data Tables:** 2019 Guideline Update: Growth factors and biological dressings
© EPUAP/NPIAP/PPPIA Page 18
# Growth Factors and biological dressings: Data extraction and appraisals

<table>
<thead>
<tr>
<th>Ref</th>
<th>Type of Study</th>
<th>Sample</th>
<th>Intervention(s)</th>
<th>Outcome Measures &amp; Length of Follow-up</th>
<th>Results</th>
<th>Limitations and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caravaggi, Grigoletto, &amp; Sauder, 2011</td>
<td>Multicentre, prospective, observational study investigating a hyaluronic acid matrix dermal substitute for development of healthy dermal tissue at wound edges</td>
<td>Participants were recruited from 70 Italian centers (n=262)</td>
<td>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</td>
<td>Epithelial (edge) advancement of 10% Secondary outcome was pain assessment Weekly follow up and at 60 days</td>
<td>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% re-epithelialization within 60 days of follow-up was observed in 88% of patients affected by ulcers with onset ≤1 year, while the same end point was achieved by 73% of patients affected by ulcers with onset &gt;1 year (p&lt;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</td>
<td>• The study was not randomized or controlled • Unclear if participants with PVD underwent revascularization before or during treatment in accordance with criteria established by the Management of Peripheral Vascular Disease (TASD II)</td>
</tr>
</tbody>
</table>

## Biological dressings: amniotic membranes

| Dehghani, Azarpira, Mohammakarimi, Mossayebi, & | RCT exploring effectiveness of amniotic membrane dressing for | Participants were recruited in a university hospital in Iran (n=24) | 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 |

### Quality: high

Data Tables: 2019 Guideline Update: Growth factors and biological dressings © EPUAP/NPIAP/PPPIA Page 19
<table>
<thead>
<tr>
<th>Ref</th>
<th>Type of Study</th>
<th>Sample</th>
<th>Intervention(s)</th>
<th>Outcome Measures &amp; Length of Follow-up</th>
<th>Results</th>
<th>Limitations and comments</th>
</tr>
</thead>
</table>
| Esfandiari, 2017 | promoting PI healing  | • No clinical signs of infection  
• Stage 2 or 3 PI                | ○ 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**

<table>
<thead>
<tr>
<th>Level 1</th>
<th>Experimental Designs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Randomized trial</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 2</th>
<th>Quasi-experimental design</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Prospectively controlled study design</td>
</tr>
<tr>
<td></td>
<td>• Pre-test post-test or historic/retrospective control group study</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 3</th>
<th>Observational-analytical designs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Cohort study with or without control group</td>
</tr>
<tr>
<td></td>
<td>• Case-controlled study</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level 4</th>
<th>Observational-descriptive studies (no control)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Observational study with no control group</td>
</tr>
<tr>
<td></td>
<td>• Cross-sectional study</td>
</tr>
<tr>
<td></td>
<td>• Case series (n=10+)</td>
</tr>
</tbody>
</table>

| 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**

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

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

<table>
<thead>
<tr>
<th>Level 1</th>
<th>A prospective cohort study.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 2</td>
<td>Analysis of prognostic factors amongst persons in a single arm of a randomized controlled trial.</td>
</tr>
<tr>
<td>Level 3</td>
<td>Case-series or case-control studies, or low quality prognostic cohort study, or retrospective cohort study.</td>
</tr>
</tbody>
</table>

**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
## Growth Factors and biological dressings: Data extraction and appraisals

### RCTS

<table>
<thead>
<tr>
<th>Endnote ID</th>
<th>Author/year</th>
<th>Focussed question</th>
<th>Assignment randomised</th>
<th>Adequate concealment method</th>
<th>Subjects and investigators blinded</th>
<th>Groups comparable at commencement</th>
<th>Only difference btw groups was treatment</th>
<th>Valid, reliable outcome measure</th>
<th>% drop out in study arms is reported and acceptable</th>
<th>Intention to treat analysis</th>
<th>Comparable results for multiple sites</th>
<th>Minimal bias</th>
<th>Reliable conclusions</th>
<th>Level of evidence</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>6491</td>
<td>Ramos-Torrecillas et al., 2015</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>low</td>
</tr>
<tr>
<td>13700</td>
<td>Kloeters et al., 2015</td>
<td>Y</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>Y</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>NA</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>low</td>
</tr>
<tr>
<td>14777</td>
<td>Dehghani et al., 2017</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>high</td>
</tr>
<tr>
<td>14261</td>
<td>Yu et al., 2017</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>U</td>
<td>Y</td>
<td>Y</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>low</td>
</tr>
</tbody>
</table>

### QUASI EXPERIMENTAL STUDIES

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Focussed question</th>
<th>Subjects and investigators blinded</th>
<th>Groups comparable at commencement</th>
<th>Only difference btw groups was treatment</th>
<th>Only reliable outcome measure</th>
<th>% drop out in study arms is reported and acceptable</th>
<th>Intention to treat analysis</th>
<th>Comparable results for multiple sites</th>
<th>Minimal bias</th>
<th>Reliable conclusions</th>
<th>Level of evidence</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>8103</td>
<td>Singh et al., 2015</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>NA</td>
<td>N</td>
<td>2</td>
<td>low</td>
</tr>
<tr>
<td>2753</td>
<td>Singh et al., 2014</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>U</td>
<td>Y</td>
<td>NA</td>
<td>N</td>
<td>2</td>
<td>low</td>
</tr>
</tbody>
</table>

### CROSS SECTIONAL/SURVEY/PREVALENCE STUDIES/OBSERVATIONAL

Data Tables: 2019 Guideline Update: Growth factors and biological dressings  © EPUAP/NPIAP/PPPIA  Page 22
## Growth Factors and biological dressings: Data extraction and appraisals

<table>
<thead>
<tr>
<th>Endnote ID</th>
<th>Author/year</th>
<th>Focussed question</th>
<th>Economic importance of question is clear</th>
<th>Choice of study design is justified</th>
<th>All costs are included and measured appropriately</th>
<th>Outcome study question are relevant and measured and valued appropriately</th>
<th>Discounting of future costs and outcome measures is performed correctly when appropriate</th>
<th>Assumptions explicit and a sensitivity analysis conducted</th>
<th>Results provide information relevant for policy providers</th>
<th>Minimal bias</th>
<th>Reliable conclusions</th>
<th>Level of evidence</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>16377</td>
<td>Beniamino et al., 2016</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>U</td>
<td>U</td>
<td>N</td>
<td>NA</td>
<td>U</td>
<td>N</td>
<td>Y</td>
<td>4</td>
<td>low</td>
</tr>
<tr>
<td>9002</td>
<td>Biglari et al., 2015</td>
<td>Y</td>
<td>N</td>
<td>U</td>
<td>U</td>
<td>Y</td>
<td>Y</td>
<td>NA</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### ECONOMIC EVALUATIONS

<table>
<thead>
<tr>
<th>Endnote ID</th>
<th>Author/year</th>
<th>Focussed question</th>
<th>Economic importance of question is clear</th>
<th>Choice of study design is justified</th>
<th>All costs are included and measured appropriately</th>
<th>Outcome study question are relevant and measured and valued appropriately</th>
<th>Discounting of future costs and outcome measures is performed correctly when appropriate</th>
<th>Assumptions explicit and a sensitivity analysis conducted</th>
<th>Results provide information relevant for policy providers</th>
<th>Minimal bias</th>
<th>Reliable conclusions</th>
<th>Level of evidence</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>17775</td>
<td>Gilligan et al., 2018</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>NA</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>NA</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>

### References


Caravaggi, C., Grigoletto, F., & Scuderi, N. (2011). Wound bed preparation with a dermal substitute (Hyalomatrix (R) PA) facilitates re-epithelialization and healing: Results of a multicenter, prospective, observational study on complex chronic ulcers (The FAST study). *Wounds: A Compendium of Clinical Research & Practice, 23*(8), 228-235


Growth Factors and biological dressings: Data extraction and appraisals


Karr, J. (2008). Utilization of living bilayered cell therapy (Apligraf) for heel ulcers. *Advances In Skin & Wound Care, 21*(6), 270-274


Growth Factors and biological dressings: Data extraction and appraisals


Yu, Q., Han, F. J., & Lv, D. S. (2017). To compare the healing of pressure sores by the use of combination therapy with platelet rich plasma and gelatin hydrogel versus platelet rich plasma and collagen. *Biomedical Research (India), 28*(3), 1216-1222