Evidence Table H-5c. Topical application trials

| **Author, yearCountryOverall Quality** | **Eligibility Criteria** | **Exclusion Criteria** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **AgeSexRace** | **Intervention Type** | **Ulcer Type/ Severity at Baseline (Intervention Onset)** | **Treatment A**  | **Treatment B** | **Treatment C** | **Duration of Treatment/ Followup** | **Study Setting** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Agren, 198593SwedenPoor | Geriatric patients with one or more necrotic PU | NR | NR/NR/28/28 | Age (Median): 84 vs. 86 years Female: 64% vs. 78%Population: elderly |  Local Wound Application: Topical | Stage IIILocation: Trochanter, ischial, knee, foot, lower leg, other | Topical streptokinase-streptodor-nase (Varidase) – 100,000 IU streptokinase + 25,000 IU streptodor-nase dissolved into 20 ml sterile isotonic saline solution and applied on a sterile gauze compressDressings changed 2x/day for 8 weeks | Zinc oxide – premedicated compresses with 400 mcg ZnO/cm2Dressings changed 1x/day for 8 weeks |  NA | 8 weeks/NR | (Mixed)Hospitals/ outpatient |

| Evidence Table H-5c: Topical Application Trials, continued |  |  |  |  |  |  |  |  |  |  |  |
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| **Author, yearCountryOverall Quality** | **Eligibility Criteria** | **Exclusion Criteria** | **Number Screened/ Eligible/ Enrolled/ Analyzed** | **AgeSexRace** | **Intervention Type** | **Ulcer Type/ Severity at Baseline (Intervention Onset)** | **Treatment A**  | **Treatment B** | **Treatment C** | **Duration of Treatment/ Followup** | **Study Setting** |
| Alvarez, 200094USFair |  >18 years of age; completed two week screening period to stabilize the wound and institute physical and supportive therapies. PU must require debridement and must have nonviable tissue attached to the base of the wound.  | Infection, cellulitis, osteomyelitis, inadequate nutrition, uncontrolled diabetes and other significant medical conditions that would impair wound healing including renal, hepatic, hematologic, neurological or immunological disease. Receiving corticosteroids, immunosuppressive agents, radiation or chemotherapy within one month prior to entry into the study.  | NR/ NR/ 22/ 21 | Age (Mean): 82 yearsFemale: 50% vs. 36.4%Race: NR | Local Wound Application: Topical | Depth-stage Partial thickness-II: 1 vs. 2 Full thickness-III-IV: 9 vs. 9 | Collagenase debriding ointment - 250 bacterial collagenase units/g applied over surface of nonviable tissue 1x/day and covered with dry gauze dressing | Papain/urea debriding ointment containing papain 1.1x106 units of activity per gram and urea 100 mg per gram  | NA | 4 weeks  | Nursing home |
| Burgos, 2000(a)95SpainGood | Hospitalized or institutionalized patients of either gender aged 55 years or over; APAUP Stage III PU for <1 year.  | End-stage diseases, localized or systemic signs and/or symptoms of infection or hypersensitivity to collagenase. | NR/NR/102/86 |  Age (Mean) 78.8 yearsFemale 64.7%Race: NR | Local Wound Application: Topical | All stage IIILocation:Sacrum: 44% (N=8) vs. 37% (N=7)Trochanter: 22% (N=4) vs. 21% (N=4)Heel: 17% (N=3) vs. 32% (N=6)Other: 14% (N=5) vs. 11% (N=2) | Collagenase ointment application - at24-hour intervals for a maximum of8 weeks (or until complete healing of the ulcer,whatever occurred first). |  Collagenase ointment application - at 48-hour intervals for a maximum of8 weeks (or until complete healing of the ulcer,whatever occurred first). | NA | 8 weeks/NR | Hospital or institution |
| Burgos, 2000(b)96SpainFair | Either gender55 years old or overPresenting stage III PU for <1 year. | End-stage organ diseaseLocalised or systemic signs and/or symptoms of infection (fever, local erythema, regional lymph node swelling) Hypersensitivity to collagenase. | NR/43/37/37 | Age (Mean): 80 (range 55-96)Female: 54% femaleRace: NR | Local Wound Application: Dressing | Stage III onlyLocation::Sacrum: 41% (N=15) Trochaner: 22% (N=8) Heel: 24% (N=9) Other: 14% (N=5) | Collagenase ointment(Iruxol® Mono, Laboratorios Knoll, SA)applied once daily in a 1 to 2mm thick layer to the ulcer bed | Application of a hydrocolloid dressing (Varihesive®, Convatec, SA) that was changed every 3 days. | NA | 12 weeks or complete healing of PU | Hospitals |
| Chuangsuwanich, 201154ThailandFair | In and out patients with PU staged II or IV (NPAUP scale) | NR | NR/NR/40/40 | Age (Mean): 66 yearsFemale: 58% Race: NR | Local Wound Application: Topical | Location:Sacrum: N=14 vs. N=16Rt. Greater Trochanteric: N= 3 vs. N=1Lt. Greater Trochanteric: N=2 vs. N=2Rt. Ischium: N=1 vs. N=2  | Silver sulfide cream covering wound, changed twice daily N=20 | Silver mesh covering wound changed every three daysN=20 | NA | 8 weeks | Siriraj Hospital |
| Felzani, 201197ItalyPoor | Hospitalized patients of both sexes, aged >18 years, with foreseen hospitalization period of >15 days, with stage I-III decubitus ulcers  | Patients unable to co-operate with hygienic measures to be adopted for treatment of sores, those with history of intolerance to hyaluronic acid, those in need of concomitant local and/or general antibiotic therapy for skin lesions or for systemic disease  | NR/59/ 50/ 50  | Age (Mean): 56 yearsFemale: 58%Race: NR  | Local Wound Application: Topical | Grouped by stages; Stage I, Stage II, Stage III | Sodium hyaluronate acid plus standard of care (nutrition supplements, patient mobilization)Stage 1: n=10 Stage 2: n=10 Stage 3: n=7 | Lysine hyaluronate acid plus standard of careStage 1: n=10Stage 2: n=10Stage 3: n=7 | NA | 15 days of treatment | Hospital |
| Gerding, 199298USPoor | Newly diagnosed stage I or II skin lesion and treatment with an emollient ordered by the attending physician. Patients with one or more lesions were included. | NR | NR/NR/74/74 patients(137 ulcers) | Age (Mean): NRFemale: NRRace: NR | Local Wound Application: Topical | Stage I: N=69Stage II: N=68(Shea stage) | Oxyquinoline-containing ointment (DermaMend)Stage I: n=29 residents, 41 lesionsStage II: n=26 residents, 45 lesions | A&D ointmentStage I: n=14 residents, 28 lesionsStage II: n=13 residents, 23 lesions | NA | 28 days after initial treatment or until wound resolution | Long term care facilities |
| Graumlich, 200399USGood |  18 years and older; at least one PU, stage II or III | Hypersensitivity to collagen or bovine products; concomitant investigational therapy; osteomyelitis; cellulites; malnutrition; ulcers covered by eschar or necrotic material; ulcers covered by orthopedic casts or devices; burn ulcers; diabetic ulcers. | NR/NR/NR/65 | Age (Mean): 81 yearsFemale: 80%Race: NR |  Local Wound Application: Topical | Stage II, III |  Topical collagen applied 1x/day for 8 weeks |  Hydrocolloid applied 2x/week for 8 weeks |  NA | 8 weeks/Median Follow-up 35 days | Nursing Home |
| Guthrie, 1989100USFair | Patients with Shea stage 1 – 4 ulcers who resided at nursing homes in Lackawanna and Luzerne counties (Pennsylvania, USA) | Patients with known sensitivity to ingredients in the test product or who suffered chronic renal disease. | NR/NR/128/58 | 78 yearsFemale: 81%Race: NR | Local Wound Application: Dressing | Stage I-IV | Combination - Dermagran Spray and Dermagran ointment applied and wound evaluated 1x/ week for 42 days | Demagran spray only | Dermagran ointment only | Placebo | Nursing home |
| Hollisaz, 2004101IranGood | Paraplegia caused by spinal cord injury; PU stage I and II (Shea classification or NPUAP); informed consent; smoothness of ulcer area to establish whether adhesive could be used at the site. | (Addiction; heavy smoking (more than 20 cigarettes a day or more than 10 packs per year); concomitant chronic disease (e.g. diabetes mellitus or frank vascular disease such as Buerger's disease). | 2015/151/83/ 83 | Age (Mean): 37 yearsFemale;’ 0%Race NR | Local Wound Application: Topical | Stage I: N=13 vs. N=9 vs. N=11Stage II: N=18 vs. N=21 vs. N=19 | Hydrocolloid |  Phenytoin cream | Simple dressing | 4 months after completion of 8 week trial | Other |
| Hsu, 2000102JapanPoor | In patients with "the largest and deepest" ulcers | NR | NR/NR/32/32 | Age (Mean): 71 yearsFemale: 59%Race: NR  | Local Wound Application: Topical | NR | Sheng-Ji-San formula plus routine medical care | Routine medical care  | NA | 3 weeks of treatment | Hospital |
| Kuflik, 2001103USPoor | Elderly, immobile patients with Stage I or Stage II ulcers | Patients with PU who also had complex underlying etiologies like venous stasis, severe diabetes | NR/NR/20/15 patients (16 ulcers) | Age (Mean): Elderly, no further details reportedFemale: Males and females, no further details reportedRace: European back-ground, no further details reported | Local Wound Application: Topical | Stage I: N=6vs. N=6Stage II: N=4 vs. N=2 | Resurfix ointment plus nutrition, n=10 patients, 11 ulcers at start; n=8 patients, 9 ulcers at end of study | Petrolatum ointment plus nutrition, n=9 patients, 9 ulcers at start; n=7 patients, 7 ulcers at end of study | NA | 6 weeks | Rehabilitation Center and Nursing Center (two sites) |
| Levasseur, 1991104AustraliaPoor | NR | NR | NR/NR/34/21 patients (21 ulcers) | Age (Mean): 82Female: 52%Race: NRPopulation: elderly | Local Wound Application: Topical | Stage 1,11 (Shea)Location:Iliac crest: N=1 vs. N=0Greater Trochanter: N=1 vs. N=0Ischium: N=4 vs. N=4Lateral Malleolus: N=2 vs. N=2Sacrum: N=0 vs. N=5Foot: N=0 vs. N=2Lower leg: N=0 vs. N=1 |  F14001 (active based cream) | Placebo (non active based cream) | NA | 6 weeks | Hospital and Long-term care |
| Muller, 2001105Germany and The NetherlandsPoor | Inpatients with stage IV pressure sores on the heel following orthopaedic surgery | Patients with a life expectancy of less than 6 months | NR/NR/24/23 | Age (Mean): 73 yearsFemale: 100% Race: NR | Local Wound Application: Topical | All patients had stage IV pressure sores on the heel | Collagenase ointment -treated once a day with a collagenase-containingointment (Novuxol®), paraffin gauze (Jelonet®)and absorbent bandages after the wound had beencleaned with saline 0.9%.N= 12 | Hydrocolloid dressing (DuoDerm®) twice a week.N=11 | NA | treatment continued until total epithelialization was achieved | Hospital |
| Nisi, 2005106ItalyPoor | NR | Decompensating diabetes, hypertension, severe hypoalbuminosis(<3.00g/100ml), clinical evidence of arterial or venous insufficiency, hematocrit values <41% for males and 36% for females, treatments with steroids or immunosuppressive drugs | NR/NR/80/80 | Age (Mean): 45 years Female: 34%Race: NR | Local Wound Application: Topical | NR |  Protease-modulating matrix BID or TID (consisting of 55% freeze-dried collagen and 45% oxidized regenerated cellulose Promogran) according to wound exudation + covering with hydropolymer patch | 50% povidone iodine solution, saline wash, positioning of viscose-rayon gauze soaked in white Vaseline and covering with a hydropolymer patch. | NA | NR | Hospital |
| Pullen, 2002107GermanyFair | Patients with Seiler stage 2,3, or 4 PU with fibrinous and/or necrotic slough | History of alcohol or drug dependency, hypersensitivity to collagenase or fibrinolysin/DNAse, planned co-medication with local antiseptics, antibiotics, occlusive wound dressings, hydrogels, or hydrocolloidsPU covered with black eschar only or whose localization did not permit parallel positioning of the reference scale | NR/NR/135/121 | Age (Mean): 79 yearsFemale: 51% vs. 47%Population: Elderly | Local Wound Application: Topical | Stage I, II, IV(Seiler stage 2, 3, or 4) | Collagenase, N= 60 | Fibrinolysin and deoxyribonuclease (DNAse), N=61 | NA | 4 weeks | Hospital |
| Rhodes, 2001108USPoor | >60 years oldStage II PU | Wound infection, anemia, malnutrition, folate deficiency, chronic use of immunosuppressant medications, receiving or having a history of adverse effect caused by oral phenytoin  | NR/NR/47/39PU N=47 | Age (Mean): 78 yearsFemale: 8%Population: elderly | Local Wound Application: Topical | Stage II | Topical Phenytoin | Collagen Dressing (DuoDerm) | Triple antibiotic ointment | 8 weeks or complete wound healing | Long-term care |
| Sayag, 1996109 FranceGood | >60 and had been hospitalized for at least 8 weeks with a stage II or IV PU (Yarkony classification) | More than half the ulcer area comprised of granulated tissue, if the PU was covered with necrotic plaque, or if there was active infection.Renal failure requiring dialysis or heel ulcers combined with end stage arteriopathy of the lower limbs.  | NR/NR/92/92PU N=92 | Age (Mean): 81 yearsFemale: 74%Race: NRPopulation: elderly, limited mobility | Local Wound Application: Topical | Yarkony's classification: Stage III: 70% (N=33) vs. 67% (N=30)Stage IV: 30% (N=14) vs. 33% (N=15) Location: Pelvis area: 30%(N=14) vs. 51% (N=23)Heel: 64%)N=30) vs. 49% (N=22)Other: N=3 (6%) | Calcium alginate, N=47 | Dextranomer, N=45 | NA | 8 weeks | Long-term care and dermatology centers |
| Shamimi Nouri, 2008(a)110 IranPoor | 18 years and older with PU;PU size must be at least 1cm² with occurrence within the last 2 weeks. | Acute infection or bone exposure; presence of disease or situation that would impair ulcer improvement;alcohol and drug abuse, dialysis and renal failure, corticosteroid consumption, use of immune suppressive agents, radiotherapy, chemotherapy and drug hypersensitivity. | NR/18/18/18 | Age (Mean): 47Female: 22%Race: NR | Local Wound Application: Topical | NR | Herbal extract, topical Semelil (Brand name ANGIPARS) 3% gel daily | Conventional treatment | NA | 1 year | Hospital |
| Sipponen, 2008111FinlandPoor | Patients with one or several severe PU (stage II-IV) with or without infection, not considered suitable for surgical treatment | NR (dropouts were not included in any data at baseline or end of study) | NR/ NR/37/ 22  | Age (Mean): 77 yearsFemale: 59%Race: NR | Local Wound Application: Topical | Stage II: 39% (N=7)vs. 45%(N=5) Stage III: 50% (N=9) vs. 45%( N=5)Stage IV: 11%(N=2) vs. 9%(N=1) | Norway spruce resin mixed with butter for 6 months Dressing changed daily if ulcer was infected or producing discharge and changed every third day otherwise n=21 patients, 27 ulcers at baseline; n=13 patients, 18 ulcers at end of study | Sodium carboxymethylcellulose hydrocolloid polymer without or with ionic silver (Aquacel+/-Ag); silver used when ulcer found to be infected on bacterial culture for 6 months Dressing changed daily if ulcer was infected or producing discharge and changed every third day otherwise for 6 months n=16 patients, 18 ulcers at baseline; n=9 patients, 11 ulcers at end of study | NA | 6 months | Primary care hospitals |
| Subbanna, 2007112 IndiaGood | Paraplegic patients aged 10 to 55 years with stage 2 PU without necrotic tissue  | Anemia, hypoalbuminemia, elevated serum creatinine, abnormal liver function tests, history of smoking, peripheral vascular disease, diabetes mellitus, malignancy, connective tissue disorders, psychiatric illness | 43/28/28/26  | Age (Mean):33Female: 12%Race: NR | Local Wound Application: Topical |  PUSH 3.0 mean rating: 13.5+/-1.16 vs. 13.21+/-1.42 | Treatment: Phenytoin solution daily for 15 daysn=14 enrolled, 12 analyzed | Comparator:Normal saline solution daily for 15 days n=14 enrolled and analyzed | NA | 15 days of treatment, measures on Day 1 before treatment and Day 16 | Hospital |
| Tytgat, 1988113BelgiumPoor | Multiple sclerosis patients with decubitus ulcers | NR | NR/NR/16/16 | Age (Mean): 59 years Female: 50% Race: NR | Local Wound Application: Topical | NR | Ketanserin 2% | Placebo | NA | 3 weeks | NR |
| Zeron, 2007114Mexico and SpainPoor |  65 years and older with stage II or III pressure ulcer | Prior surgical treatment of PU, septic state; mechanical breathing support; state of coma or brain death; ingestion of steroids; abandonment of the patient by their family. | NR/NR/NR/24 | Age (Mean): 79Female: 79%Race: NRPopulation: general | Local Wound Application: Topical  |  NR | Zinc oxide paste + collagen-polyvinylpyrrolidone (clg-pvp) - a total of 1.5 ml ofmedication was injected intradermally into the patient, equally applied at four points equidistantfrom the edges of the wound applied 1x week for 3 weeks | Zinc oxide paste +placebo (not described) - a total of 1.5 ml of placebo was injected intradermally into the patient, equally applied at four points equidistantfrom the edges of the wound applied 1x week for 3 weeks | NA  | 3 weeks/3 weeks | Hospital |

| **Evidence Table H-5c: Topical Application Trials, continued** |  |  |  |  |  |  |  |  |
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| **Author, yearCountryOverall Quality** | **Outcomes: Complete Wound Healing** | **Outcomes: Wound Surface Area** | **Outcomes: Healing Time** | **Outcomes: Infection Rate** | **Outcomes: Osteomyelitis Rate** | **Outcomes: Recurrence Rate** | **Other Outcomes: Specify** | **Harms: Pain** |
| Agren, 198593SwedenPoor | NR | Disappearance of necrotic tissue: Treatment A: 43%Treatment B: 50%Wound area reduction: Treatment A: 18.7%Treatment B: 2.4% |  NR | NR |  NR | NR | NR | NR |
| Alvarez, 200094USFair | NR | % reduction in wound area from baseline with (SD)Treatment A:Week 1: 1.9 (7.6)Week 2: 23.7 (25.8)Week 3: 34.8 (25.2)Week 4: 55.4 (33.5)Treatment B:Week 1: 5.8 (17.4)Week 2: 19.9 (29.2)Week 3: 27.3 (28.5)Week 4: 33.9(26.17) | Mean time to 50% granulation (time in days for 50% of the wounds to be covered by granulation tissue): Treatment A: 6.8Treatment B:28No significant difference in healing rates between 2 groups | Treatment A:Bacterial count at baseline5.6 CFU/mLBacterial count at 4 weeks4.6CFU/mLTreatment B:Bacterial count at baseline 5.4CFU/mLBacterial count at 4 weeks: 5.0 CFU/mL | NR | NR | Treatment A vs. B:Reduction in non-viable tissue: 2 weeks: 68.3% vs. 22.3%3 weeks: 86.5% vs. 37.3%, (p<0.05)  4 weeks: 95.4% vs. 35.8%, (p<0.01)% reduction in area of necrotic tissue (slough) from baseline:Week 3: 73.4 vs. vs. 32.7, Week 4: 93.3 vs. 34.0% reduction in area of necrotic tissue (eschar) from baseline:Week 3: 90.8 vs. 46.7Week 4: 98.5 vs. 43.1% reduction of necrotic tissue by planimetry from baseline:Week 1: 13.5 vs. 7.5 Week 2: 68.3 vs. 22.3 Week 3: 86.5 vs. 37.3 (p<0.05)Week 4: 95.4 vs. 35.8 (p<0.01 )Debridement of necrotic tissue by clinical evaluation:Week 1: 3.9 vs. 2.0Week 2 4.5 vs. 2.0 Week 34.9 vs. 2.2, Week 4 5.5 vs. 1.3 (Relative score 1=76-100%, covered with necrotic tissue, 2=51-75%, 3=26-50%, 4=11-25%, 5=1-10%, 6=none)Overall wound response 4.5 vs. 1.1 9p<0.01, (0=wound deteriorated, 1=no change, 2=minimal change, 3=average improvement, 4=significant improvement, 5=necrotic tissue resolved. | NR |
| Burgos, 2000(a)95SpainGood | Closure and epithelialization:Treatment A:n=12Treatment B:n=9: (p=0.451) | ITT analysis: Change from baseline in wound area at 8 weeks (24 hour interval): -Treatment A:5.1 cm2 Treatment B:6 cm2 Change from baseline in both groups (p<0.0005) Difference between 2 groups: (p=0.641)Per Protocol analysis: Change from baseline in wound area at 8 weeks (24 hour interval): -Treatment A: 5.4Treatment B: 7cm2 Change from baseline in both groups (p<0.0005)Difference between 2 groups: (p=0.595) | NR | NR | NR | NR | Granulation tissue formation increased p<0.0005 and exudate production decreased in both groups (Treatment A, p=0.012, Treatment B, p=0.04)  | Treatment A:ITT analysis: Pain intensity decrease from baseline (p=0.001)Difference between Treatment A and B favored 24 hour interval group: (p=0.004)Per protocol analysis: pain intensity decrease from baseline (p=0.001)Difference between treatment A vs. B=NSTreatment B:Pain intensity decrease from baseline, NS ITT and Per protocol analysis |
| Burgos, 2000(b)96SpainFair | Treatment A:N=3 Treatment B:N=3(p=0.451) | Collagenase group:Mean reduction in PU size:Treatment A: 9.1 cm2Treatment B:6.2 cm2Total ulcer area reduction:Treatment A: 44%Treatment B: 28%(p=0.369) | NR | NR | NR | NR | Decrease in pain in treatment A compared with treatment B (p=0.001) | NR |
| Chuangsuwanich, 201154ThailandFair | NR | Treatment A:18.22 cm2 at week 8Treatment B:7.96 cm2 at week 8(p=0.09) | Treatment A:Healing rate 25% Treatment B:Healing rate 37%p=value 0.51 | NR | NR | NR | PUSH Score reduction:Treatment A: 34.51%Treatment B: 28.15%  (p=0.473) | NR |
| Felzani, 201197ItalyPoor | –Treatment A: 15 days of treatment:Group 1 (stage 1 ulcers): Healing of 90% of the lesion 100% (n=10)Group 2 (stage 2 ulcers):Healing of 70% of the lesion 100% (n=10)Group 3 (stage 3 ulcers):healing of 100%(n=5) Treatment B: 15 days of treatment:Group 1 (stage 1 ulcers): Healing of 70% of the lesion in 50%(n=10)Group 2 (stage 2 ulcers):Healing of 40% of the lesion in 100%(n=10)Group 3 (stage 3 ulcers):100% (n=2)  | NR | Treatment A: treatment period necessary to reach 50%RegressionGroup 1 - 9 days Group 2 - 9.5 daysGroup 3 - 12.9 days Treatment B:treatment period necessary to reach 50%RegressionGroup 1 - 15 days, p<0.05Group 2 - 15 days, p<0.05Group 3 - 19.2 days, p<0.05 | NR | NR | NR | NR | NR |
| Gerding, 199298USPoor | Treatment A:Resolved lesions (%)Stage I: 58.5%Stage II: 44.5%Treatment B:Resolved lesions (%)Stage I: 57.1%Stage II: 21.8%, (p<0.03) | NR | Treatment A:Day to resolveStage I: 6.2Stage II: 7.8Treatment B:Days to resolveStage I: 7.3Stage II: 13.0, (p<0.05) | NR | NR | NR | Treatment A vs. B: No change lesions (%)Stage I: 9.8 vs. 14.3Stage II: 11.1 vs. 30.4Worse lesions (%)Stage I: 0 vs. 7.2Stage II: 2.2 vs. 13.0No change/worse (%)Stage I: 9.8 vs. 21.5Stage II 13.3 vs. 43.4 | NR |
| Graumlich, 200399USGood | Treatment A: 51%Treatment B: 50%(p=0.89) |  NR | Area healed per day: (mm2/day, mean, SD) Treatment A: -6Treatment B: 6(p=0.94) |  NR | NR | NR | NR | NR |
| Guthrie, 1989100USFair | NR | Decrease in size:Treatment A:90.7%Treatment B:6.7%Treatment C:25.9% | NR |  NR |  NR |  NR |  NR |  NR |
| Hollisaz, 2004101IranGood | All stages:Treatment A compared to Treatment B. [74.19% (n=23) vs. 12/30 (40%); difference 34.19% (p < 0.01)].Stage I: Treatment A [11/13 (85%)] was also better than Treatment C [5/11 (45%); difference 40%, 95% (p < 0.05)] or Treatment B [2/9 (22%); difference 63%, 95%, (p < 0.005)].  Stage II:Treatment A [12/18 (67%)] than in the Treatment C [3/19 (16%); difference 51%, 95% (p<0.005], but there was no significant difference from Treatment B [10/21 (48%); difference 19%; 95% CI, -11.47 to 49.47 (p >0.05). | NR | NR | NR | NR | NR | NR | NR |
| Hsu, 2000102TaiwanPoor | Effective treatment=complete or incomplete healing:Treatment A: Effective treatment- 83 % (n=20), Complete healing- 5% (n=1)Treatment B:Effective treatment - 37% (n=3)Complete healing- 0% (n=0) | Treatment A:Decreased surface area from 26.71+/-29.37 cm2 to 18.33+/-28.28 cm2, (p<0.005)Reduction ratio of surface area (RSA) = (initial area - final area) / initial area x 100%RSA = 33.83%=/-33.32%Treatment B:Increased surface area from 35.09+/-40.35 cm2 to 41.59+/-53.11 cm2, not significantRSA = -2.85%+/-47.54%, (p<0.05) compared to Treatment A | NR | NR | NR | NR | Effective ratio (ER) = Number effectively treated / Number treated x 100%Treatment A: 83% Treatment B: 38% (p<0.05)Multivariate analysis performed to account for age, gender, disease type and SJS as independent variables; only SJS had significant correlation with RSA, p=0.03 and ER, OR 9.5, 95% CI, 1.41 to 64.6  | NR |
| Kuflik, 2001103USPoor | Treatment A:50% (n=10)5/10 (4 Stage I, 1 Stage II) Treatment B:22% (n=2)(both Stage I)  | Mean size after treatment, cm/diam: Treatment A: 0.9 (those who terminated treatment not included, n=2)Treatment B:1.8 (those who terminated treatment not included, n=2) | NR | NR | NR | NR | Erythema noted in tables by ulcer, but no collapsed data available | NR |
| Levasseur, 1991104AustraliaPoor | NR | Based on repeated measures over six weeks there was reduction in both groups (size not specified)(p <.001)  | Treatment A: 18 daysTreatment B: 29 days (p=0.08)  | NR | NR | NR | NR | NR |
| Muller, 2001105Germany and The NetherlandsPoor | Treatment A:91.7%(N=11) Treatment B: 63.6%(N=7) | NR | Treatment A: wound healing ranged from 6 to 12 weeks, mean 10 weeksTreatment B:wound healing ranged from 11-16 weeks, mean 14 weeks | NR | NR | NR | NR | NR |
| Nisi, 2005106ItalyPoor | Treatment A: 90%Treatment B: 70%(p=0.59) | NR | Time to wound healing (2nd phase results) Treatment A: 2-6 weeksTreatment B: 2-8 weeks | NR | NR | NR | Treatment A vs. B: 2nd phase resultsNo. of dressings performed: n= 6-15 vs. 14-52Overall hospitalization (days): 360 vs. 1164 | NR |
| Pullen, 2002107GermanyFair | NR | Decrease in necrotic wound area Treatment A: 61.7%(n=37)Treatment B: 57.4%(n=35) | NR | NR | NR | NR | NR | NR |
| Rhodes, 2001108USPoor | NR | NR | Mean time to healing in days:Treatment A: 35,Treatment B: 52Treatment C: 54(p=0.005) | NR | NR | Treatment A: One patient had ulcers that continually recurred after healing | New healthy granulation tissue appearance:Treatment A: 2-7 daysTreatment B: 6-21 days  | NR |
| Sayag, 1996109FranceGood | 75% healed at 8 weeks: Treatment A: 32%Treatment B: 13% | Treatment A: 40% reduction in wound area: 74%Treatment B: Dextranomer: 40% reduction in wound area: 42% | Mean reduction in surface area per week: Treatment A: 2.39 cm2Treatment B:.27cm2 (p=0.0001) | Treatment A: N=2Treatment B: N=2  | NR | NR | NR | Treatment A: 0 patients reported painTreatment B:5 patients reported pain |
| Shamimi Nouri, 2008(a)110IranGood | Treatment A:67% of wounds healedTreatment B:0% | Treatment A: Mean surface area reduced to 7.8cm²Treatment B: Mean surface area reduced to 16.7cm²(p=0.008) | Treatment A: 67% healed completely in 1 year33% healed by 50-80% in 1 yearTreatment B: 11% of patients had PU that healed by 50-80% in 1 year | NR | NR | NR | NR | NR |
| Siponnen, 2008114FinlandPoor | Treatment A:94% ulcersTreatment B:44%(n=4), p=0.003  | NR | Authors report: Speed of ulcer healing was significantly faster in treatment A group (p=0.013)   | Treatment A:1 month10 ulcers with positive cultures, 1 patient given antibioticsNote: although not routinely done, 2 ulcers were positive for bacteria at 6 monthsTreatment B: 1 month14 ulcers with positive cultures, 6 patients given antibioticsNote: no results shown at 6 months | NR | NR | Treatment A vs. Treatment B6 monthsWidth, mean (cm): 0.2 vs. 1.8 (p=0.011)Depth, mean (mm): 0.6 "Significantly better": 6% (n=1) vs.55% (n=6) "unimproved":0%( n=0) vs. 9% (n=1), (p=0.003) | NR |
| Subbanna, 2007112IndiaGood | NR | NR | NR | NR | NR | NR | Reduction in PUSH 3.0 rating (%), Treatment A vs. Treatment B19.53vs. 11.39 difference 8.14), (p=0.261)Reduction in ulcer size (%), Treatment A vs. Treatment B47.83vs. 36.03, difference 11.8 (p=0.132)Reduction in ulcer volume (%), Treatment A vs. Treatment B53.94vs. 55.76, difference -1.81 (p=0.777) | NR |
| Tytgat, 1988113BelgiumPoor |   Mean epithelialization comparison with baseline:Treatment A:Week 1-1.8 (p=significant)Week 2-2.2 ( (p=significant)Week 3- 2.3 (p=significant)Treatment B:Week 1-1.4 Week 2-:1.4 (p=significant)Week 3- 1.3  | Treatment A:Reduction in wound area at 3 weeks: 81%(p=significant)Mean wound area (comparison with baseline) mm2Week 1--1255 (p=significant)Week 2- -2776 (p=significant)Week 3-3080 (p=significant)Treatment B:PlaceboReduction in wound area at 3 weeks: 16%Wound area (comparison with baseline) mm2Week 1-155 Week 2--263 (p=significant)Week 3-195  | NR | NR | NR | NR | Treatment A vs. Treatment BMean change from baseline in granulation:Week 1- vs. 1.0Week 2-1.6 vs. 1.0 Week 3-1.9 vs. 0.0 % of patients with pronounced granulation at Week 3: 75% vs. 0Mean change from baseline in ErythemaWeek1- 0.5 vs. 0.2 Week 2- 0.4 vs. 1.3 ( (p=significant)Week 3- 0.0 vs. 0.5  | NR |
| Zeron, 2007114Mexico and SpainPoor | Treatment A: 42% Treatment B: 33% | Reduction in ulcer size (mean):Treatment A: from 3.4 to 1.14 cmTreatment B: 2.9 to 1.58 cm(p= nonsignificant) | Treatment A: Mean ulcer reduction of 6.6mm/weekTreatment B:NR | NR | NR | NR | NR | NR |

| **Evidence Table H-5c: Topical Application Trials, continued** |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, yearCountryOverall Quality** | **Harms: Dermatologic Complications** | **Harms: Bleeding** | **Harms: Infection** | **Other Harms: Specify** | **Severe Adverse Events** | **Withdrawal due to Adverse Events** | **Overall Adverse Events Rate** | **Funding Source** |
| Agren, 198593SwedenPoor | NR | NR | NR | NR | NR | NR | NR |  NR |
| Alvarez, 200094USFair | NR | NR | Treatment A:Bacterial count at baseline5.6 CFU/mLBacterial count at 4 weeks4.6 CFU/mLTreatment B:Bacterial count at baseline 5.4CFU/mLBacterial count at 4 weeks: 5.0 CFU/mL | NR | NR | 0  | 0 | NR |
| Burgos, 2000(a)95SpainGood | Treatment A: 6.5% (n=3) in presentedone adverse reaction each (rash, one patient;necrosis in ulcer bed,Treatment B:24 hour grouprash, necrosis in ulcer bed, ulcer worsening: 2.2% (each)48 hour groupnecrosis in ulcer bed: 4.3% | NR | Treatment A: 0% (n=0)Treatment B: 2.2%(n=1) | NR | NR | Treatment A: n=1Treatment B:N=2 | Treatment A: 6.5% Treatment B 6.5% | Knoll SA, Madrid |
| Burgos, 2000(b)96SpainFair | Treatment A: Dermatistis in 5.6% (n=1) of patientsTreament B: Erythema and exudates increase in 5.2% (n=1) of patients | NR | Treatment A:Treatment B: | Treatment B:Erythema and odor increase in 5.2% (n=1) patients | NR | 0 | Relative risk of adverse reaction occurrence(RRC/H) was 0.500 (95% CI, 0.041 to 6.048) | NR |
| Chuangsuwanich, 201154ThailandFair | NR | NR | NR | NR | NR | NR | NR | NR |
| Felzani, 201197ItalyPoor | NR | NR | NR | NR | NR | NR | NR | NR |
| Gerding, 199298USPoor | NR | NR | NR | NR | NR | NR | NR | Supported in part by grant from InnoVisions, Inc. |
| Graumlich, 200399USGood | NR | NR | NR | NR | NR  | NR | NR | Retirement research foundation |
| Guthrie, 1989100USFair | NR | NR | NR | NR | NR | NR | NR | NET/Ben Franklin Technology Center |
| Hollisaz, 2004101IranGood | NR | NR | NR | NR | NR | NR | NR | Jaonbazan Medical and Engineering Research Center |
| Hsu, 2000102TaiwanPoor | NR | NR | NR | NR | NR | NR | NR | Funding from Department of Health |
| Kuflik, 2001103USPoor | NR | NR | NR | NR | NR | Treatment A:One patient with Stage II ulcer discontinued due to non-improvement without deterioration Treatment B:Two patients with Stage I ulcers terminated due to worsening | NR | Topix Pharmaceuticals, Inc. |
| Levasseur, 1991104AustraliaPoor | NR | NR | NR | NR | NR | NR | NR | Schumacher Pharmaceuticals |
| Muller, 2001105Germany and The NetherlandsPoor | NR | NR | NR | NR | NR | NR | NR | Knoll AG, Ludwigshafen, Germany |
| Nisi, 2005106ItalyPoor | NR | NR | NR  | NR | NR | NR | NR  | NR |
| Pullen, 2002107GermanyFair | Treatment A: 6 skin related adverse events reported in 5 patientsTreatment B:5 skin related adverse events reported in 5 patients | NR | NR | NR | NR | NR | Treatment A:118 adverse events reported in 45 patients in the Treatment B:103 in 34 patients  | NR |
| Rhodes, 2001108USPoor | NR | NR | NR | NR | NR | NR | NR | NR |
| Sayag, 1996109FranceGood | Treatment A: NRTreatment B: 1 patient had skin irritation, 1 reported pruritus | Treatment A: NRTreatment B: 3 patients had bleeding during dressing changes | Treatment A: 2 patients had infectionTreatment B:2 patients had infection | Hypergranulation: Treatment A: 1 patient Treatment B:3 patients Deterioration of PU or stagnation after four weeks of treatment:Treatment A: 2 patients Treatment B:15 patients | NR | NR | Treatment A: 4 Treatment B: 15  | Les Laboratories Brothier |
| Shamimi Nouri, 2008(a)110IranGood | NR | NR | NR | NR | NR | NR | NR | ParsRoos Co. |
| Sipponen, 2008111FinlandPoor | Allergic skin reaction: Treatment A: NRTreatment B: 13% (n=1)  | NR | See outcomes | Number of wound revisions: Treatment A vs. Treatment B28% (n=5) vs. 64% (n=7), (p=0.078) | NR | Treatment A:13% (n=1) due to allergic skin reaction | NR | Lappish Cultural Foundation grant to A.S. (author) |
| Subbanna, 2007112IndiaGood | NR | NR | NR | NR | NR | NR | NR  | Intramural research funds from Christian Medical College, Vellore |
| Tytgat, 1988113BelgiumPoor | NR | NR | NR | NR | NR | NR | NR | NR |
| Zeron, 2007114Mexico and SpainPoor | NR | NR | NR | NR | NR | NR | NR | NR |