TREATMENT OF PRESSURE ULCERS: AN OVERVIEW

Many treatments for pressure ulcers are promoted, but their relative efficacy is unclear. The objective of this review was to systematically review published randomized controlled trials (RCTs) evaluating therapeutic interventions for pressure ulcers.

Data Sources and Study Selection

The databases of MEDLINE, EMBASE, and CINAHL were searched (from inception through August 23, 2008) to identify relevant RCTs published in the English language. Methodological characteristics and outcomes were extracted by 3 investigators.

Conclusions

Little evidence supports the use of a specific support surface or dressing over other alternatives. Similarly, there is little evidence to support routine nutritional supplementation or adjunctive therapies compared with standard care.

Context

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Data Extraction

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Data Synthesis

A total of 103 RCTs met inclusion criteria. Of these, 83 did not provide sufficient information about authors’ potential financial conflicts of interest. Methodological quality was variable. Most trials were conducted in acute care (58 [37%]), mixed care (25 [24%]), or long-term care (22 [21%]) settings. Among 12 RCTs evaluating support surfaces, no clear evidence favored one support surface over another. No trials compared a specialized support surface with a standard mattress and repositioning. Among 7 RCTs evaluating nutritional supplements, 1 higher-quality trial found that protein supplementation of long-term care residents improved wound healing compared with placebo (improvement in Pressure Ulcer Scale for Healing mean [SD] score of 3.55 [4.66] vs 3.22 [4.11], respectively; P < .05). Other nutritional supplement RCTs showed mixed results. Among 54 RCTs evaluating absorbent wound dressings, 1 found calcium alginate dressings improved healing compared with dextranomer paste (mean wound surface area reduction per week, 2.39 cm² vs 0.27 cm², respectively; P < .001). No other dressing was superior to alternatives. Among 9 RCTs evaluating biological agents, several trials reported benefits with different topical growth factors. However, the incremental benefit of these biological agents over less expensive standard wound care remains uncertain.

Conclusions

Little evidence supports the use of a specific support surface or dressing over other alternatives. Similarly, there is little evidence to support routine nutritional supplementation or adjunctive therapies compared with standard care.

METHODS

The databases of MEDLINE, EMBASE, and CINAHL were searched from inception through August 23, 2008, to identify relevant RCTs. The following search terms were used: pressure ulcer, pressure sore, decubitus, bedsore, chronic wound, treatment, therapy, management, randomized, and controlled study.
TREATING PRESSURE ULCERS

clinical trials. A hand search also was performed to identify any other articles. Inclusion criteria were RCTs published in the English language that reported objective, clinically relevant outcome measures such as healing rates or wound size. When the search was not limited to studies published in the English language, 2 non-English-language trials were found: one in Italian (294 participants) and another in Japanese (19 participants). Because few non–English-language trials were found and the total number of participants in these trials was small, this study was limited to RCTs published in the English language. Studies that evaluated chronic wounds other than pressure ulcers or assessed only adverse events or secondary outcomes (eg, pain) were excluded. There was too much clinical heterogeneity in the individual RCTs to permit meaningful pooling of the data in a meta-analysis.

Sources of funding were extracted from the trials using a method described by Als-Nielsen et al. We also determined if the RCTs reported any potential author conflicts of interest.

Information was extracted regarding participant age, population studied, and treatment setting. Trials used different terms to describe treatment settings. These terms were grouped as follows: acute care, long-term care, palliative care, rehabilitation, ambulatory care, and home care. Pressure ulcers at the beginning of each trial are described by stage unless the trial used different terminology (such as superficial or deep).

The included RCTs were categorized into 3 groups depending on whether they investigated the management of underlying contributing factors, the effects of local wound care, or adjunctive therapies. This approach was selected because wound specialists approach pressure ulcer management sequentially; first, reduce or eliminate underlying contributing factors (support surfaces and nutritional supplementation), then provide local wound care (wound dressings and biological agents), and finally consider adjunctive therapies (eg, vacuum therapy).

A criterion standard for quantifying outcomes in ulcer healing has not been established. Surrogate end points (eg, amount of granulation tissue, degree of debridement, and bacterial burden) do not directly measure healing and may not correlate with healing. Measurement of wound surface area, including wound depth and undermining (ie, tunneling under the skin), is a reliable and valid method of assessing wound healing. Therefore, only studies that calculated wound size with wound volume and/or surface area, used evaluation tools that incorporated these measurements, or used complete wound healing as end points were included.

Individual trials used various terms to describe outcomes. Some trials used scales such as Pressure Ulcer Scale for Healing or Pressure Sore Status Tool. For simplicity, remaining terms were classified into 3 categories: complete wound healing (ie, proportion of individuals whose wounds healed), time to healing (ie, time to complete wound healing), and wound surface area (ie, changes over time).

Methodological quality of the RCTs was determined using 6 elements from the checklist to evaluate a report of a nonpharmacological trial (CLEAR NPT) that are relevant to therapies for pressure ulcers: (1) adequate allocation sequence generation (ie, use of an appropriate method to generate the randomization sequence); (2) concealed treatment allocation; (3) adequate participant blinding; (4) adequate outcome assessor blinding; (5) comparable rates of other treatments and care in each randomized group (eg, frequency of dressing changes); and (6) intention-to-treat analysis. If these elements were not explicitly reported, they were considered not performed. Three authors (M.R., S.R.K., W.W.) independently rated each RCT and reached consensus. Trials meeting 4 or more of the CLEAR NPT criteria were considered good quality. Trials meeting 3 or less of the CLEAR NPT criteria were considered suboptimal. We also assessed which articles reported a sample size justification to determine whether RCTs were adequately powered to detect either clinically important differences or equivalence of compared treatments.

Specialized support surfaces such as mattresses and cushions redistribute a patient’s weight over skin and subcutaneous tissues as it presses against a bed or chair surface. A reduction of pressure between the body and the support surface is considered helpful in healing pressure ulcers. The distinction between types of support surfaces is important because costs vary widely. Support surfaces were categorized using the National Pressure Ulcer Advisory Panel classification system: nonpowered (support surfaces such as foam that do not need electricity, previously known as static) and powered (support surfaces such as rotating beds that require electricity, previously known as dynamic). An overlay is a support surface designed to be placed on top of another support surface. Powered support surfaces are generally more expensive than nonpowered surfaces. Standard hospital mattresses (ie, not a specialized support surface) usually incur a 1-time cost of less than $200, but specialized support surfaces (frequently rented) can range from less than $5 per month for nonpowered mattress overlays to more than $3250 per month for some powered support surfaces.

Randomized controlled trials that described nutritional supplementation by any method (eg, enterally or parenterally) were included. Local wound care dressings were categorized by function rather than form (eg, films or gels). Because many dressings perform more than 1 function, they were categorized based on their primary purpose: exudate absorbing (eg, foams), debriding (eg, collagenase), hydrating (eg, hydrocolloids), antimicrobial (eg, silver, povidone-iodine), and other (eg, did not fit any of these categories, fit in >1 category, or function was unclear). Adjunctive therapies were defined as modalities that neither directly address the underlying contributing factors nor primarily address local wound care (eg, vacuum therapy).
RESULTS
The search identified 872 abstracts, from which 103 relevant RCTs were selected. The flow diagram shows an overview of the study selection process (FIGURE). The 103 RCTs included 5889 participants. Only 15 trials involved more than 100 participants and 22 provided a sample size justification.

Thirty-eight of the 103 trials took place in acute care centers (37%), 25 in mixed settings (24%), 22 in long-term care (21%), 6 in rehabilitation (6%), 4 in ambulatory care (4%), 3 in home care (3%), 1 in palliative care (1%), and 4 did not mention their treatment setting (4%). Twenty-two trials (21.4%) included only participants older than 60 years or described participants as elderly and 11 trials (10.7%) included only participants with spinal cord injuries.

Forty-five trials reported funding by the for-profit manufacturers of the products under evaluation (43.7%), 15 reported funding from nonprofit peer-reviewed granting agencies only (14.6%), 14 reported funding from for-profit and nonprofit organizations (13.6%), and 29 did not indicate sources of funding (28.2%). Eighty-three trials (80.6%) did not provide sufficient information about authors’ potential financial conflicts of interest.

Three authors (M.R., S.K., W.W.) independently rated each RCT on CLEAR NPT items. Initial agreement was 83% (92% for adequate description of generation of allocation sequences, 81% for treatment allocation concealment, 82% for adequate participant blinding, 87% for adequate blinding of outcome assessors, 68% for co-interventions same in each group, and 90% for intention-to-treat analysis). Differences were resolved by consensus. Sixteen of the 103 trials (15.5%) met 4 or more of the CLEAR NPT criteria.

Nineteen RCTs (1572 participants) evaluated nutritional supplements (TABLE 2). All were oral supplements, but contents varied in each trial. Lee et al compared ulcer healing over 8 weeks in long-term care residents randomized to either a collagen protein supplement or placebo combined with standard care. Healing was measured with the Pressure Ulcer Scale for Healing (0 = healed, 17 = worst possible score). Individuals randomized to the supplement had better healing than those randomized to placebo (mean [SD] improvement in Pressure Ulcer Scale for Healing score, 3.55 [4.66] vs 3.22 [4.11], respectively; P < .05).

Six RCTs directly compared powered (eg, alternating pressure) with nonpowered (eg, foam) support surfaces.28,41,42,45,58,59 Russell et al and Day and Leonard found no differences in pressure ulcer healing between powered and nonpowered support surfaces.28,41,42,45,58,59 Although 1 RCT did not report statistical significance,59 Inconsistent findings in these 6 studies result in persistent uncertainty regarding the benefit of powered support surfaces.

Five RCTs compared different types of powered mattresses. Evans et al compared nutritional supplements with low-dose (10 mg twice daily) vitamin C given for either 12 weeks or until pressure ulcer healing (whichever came first) and found no differences in wound closure rates or mean change in ulcer surface area per week. In contrast, Taylor et al found that 500 mg of vitamin C twice daily was better than placebo (mean reduction in pressure ulcer area, 84% vs 42.7%; P < .005). Several factors may explain the disparate findings. The study by ter Riet et al included more patients (88 vs 20 in Taylor et al), was multicentered, and had longer follow-up (12 vs 4 weeks, respectively). Thus, the value of vitamin C supplementation in pressure ulcer treatment remains uncertain.

Two other trials that found beneficial effects for nutritional supplements had suboptimal quality.62,63 One of these did not report statistical significance.63 Desnave et al compared 3 diets in a study of 16 patients: standard hospital diet, standard hospital diet plus high protein, and standard hospital diet plus high protein with arginine, zinc, and antioxidants. The first 2 groups did not achieve significant improvements in pressure ulcer healing as measured by the Pressure Ulcer Scale for Healing, but the third group did.

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(Reprinted JAMA, December 10, 2008—Vol 300, No. 22) 2649
Eleven of 19 studies (57.9%) evaluating underlying contributing factors adequately described the generation of random allocation sequences. Of the 19 studies, 8 indicated that participants were randomized using concealed allocation (42.1%). Because blinding may be difficult when studying support surfaces, ratings for the CLEAR NPT item regarding participant blinding were not powered.

Table 1. Randomized Controlled Trials Evaluating Support Surfaces as an Underlying Contributing Factor to Pressure Ulcer Severity

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Completed Study Age</th>
<th>Setting Duration of Treatment</th>
<th>Pressure Ulcer Severity at Baseline Intervention</th>
<th>Primary Outcome Measures and Quantitative Estimate of Treatment Effect</th>
<th>Quality of Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groen et al, 1999</td>
<td>120; 101; ≥60 y</td>
<td>Long-term care; 2-4 wk</td>
<td>III or IV; specialized foam mattress vs water mattress</td>
<td>Complete wound healing: 45% for specialized foam mattress vs 48.3% for water mattress; this difference is not significant</td>
<td>2</td>
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<tr>
<td>Rosenthal et al, 2003</td>
<td>207; 204; mean age; LAL mattress, 69.0 y; SFMO, 65.6 y; APM, 70.4 y</td>
<td>Long-term care; 4-24 wk</td>
<td>III or IV; APM vs FMO</td>
<td>Mean (SD) Pressure Sore Status Score improvement: 18.4 (1.5) for LAL mattress vs 34.3 (1.5) for APM (P &lt; .001); mean (SD) time to complete healing: 4.38 (0.14) mo (95% CI, 4.10-4.65) for LAL mattress vs 4.55 (0.02) mo (95% CI, 4.13-4.98) for SFMO vs 3.33 (0.12) mo (95% CI, 3.09-3.58) for APM</td>
<td>3</td>
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<tr>
<td>Russell et al, 2003</td>
<td>199; 158; mean age; APM, 80.4 y; FMO, 79.9 y</td>
<td>Acute care; mean: 3 wk</td>
<td>I, II, III, or IV; APM vs FMO</td>
<td>Wound surface area overall ulcer progress: 72.3% for APM vs 74.7% for FMO (P = .67)</td>
<td>4</td>
</tr>
<tr>
<td>Brann et al, 2001</td>
<td>20; 18; age range: 36-100 y</td>
<td>Acute and long-term care; 3-8 wk</td>
<td>III or IV; LAL mattress vs air and foam mattress</td>
<td>Wound surface area mean (SD) rate of wound closure per week: 5.0% (3.7%) for LAL mattress vs 9.0% (4.8%) for air and foam mattress</td>
<td>1</td>
</tr>
<tr>
<td>Mulder et al, 1994</td>
<td>49; 39; NA</td>
<td>Long-term care; ≤12 wk</td>
<td>III or IV; LAL mattress vs SFMO</td>
<td>Wound surface area reduction in wound size: 77% more for LAL mattress vs SFMO (P &lt; .04)</td>
<td>1</td>
</tr>
<tr>
<td>Day and Leonard, 1993</td>
<td>118; 83; &gt;18 y</td>
<td>Acute care; 1-104 wk</td>
<td>II, III, or IV; LAL mattress vs foam overlay</td>
<td>Wound surface area (P &lt; .05)</td>
<td>3</td>
</tr>
<tr>
<td>Ferrell et al, 1993</td>
<td>84; NA; &gt;75 y</td>
<td>Long-term care; 1-82 wk</td>
<td>II, III, or IV; LAL mattress vs specialized foam mattress</td>
<td>Wound surface area median reduction: 9.0 mm²/d for LAL mattress vs 2.55 mm²/d for specialized foam mattress (P &lt; .001)</td>
<td>3</td>
</tr>
<tr>
<td>Nixon et al, 2006</td>
<td>NA; 113; ≥55 y</td>
<td>Acute care; 60 wk</td>
<td>III or IV; APM vs alternating pressure overlay</td>
<td>Complete wound healing: 10.3% for APM vs 10.7% for alternating pressure overlay (P = .75)</td>
<td>3</td>
</tr>
<tr>
<td>Evans et al, 2000</td>
<td>NA; 32; ≥65 y</td>
<td>Acute and long-term care; ≤67 wk</td>
<td>II or III; APM No. 1 vs APM No. 2</td>
<td>Wound surface area median absolute reduction per day: 0.12 cm² for APM No. 1 vs 0.08 cm² for APM No. 2 (P = .57)</td>
<td>5</td>
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<tr>
<td>Land et al, 2000</td>
<td>17; NA; age range: 66-99 y</td>
<td>Acute and long-term care; ≤2 wk</td>
<td>II, III, or IV; APM vs APM or overlay</td>
<td>Wound surface area: no significant difference in healing sores</td>
<td>3</td>
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<tr>
<td>Russell et al, 2000</td>
<td>183; 112; age described as elderly</td>
<td>Acute care; 72 wk</td>
<td>II, III, or IV; 2 types of APM and cushion combination</td>
<td>Complete wound healing: improvement in heel ulcers only (P = .02)</td>
<td>1</td>
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<tr>
<td>Allman et al, 1987</td>
<td>72; 65; &gt;18 y</td>
<td>Acute care; 1-11</td>
<td>I, II, III, or IV; air-fluidized mattress vs APM covered with foam</td>
<td>Wound surface area median changes in surface area: –1.2 cm² for air-fluidized mattress vs 0.5 cm² for APM covered with foam (P = .01)</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: APM, alternating pressure mattress; CI, confidence interval; FMO, fluid mattress overlay; LAL, low air loss; NA, data not available; SFMO, specialized foam mattress overlay.

*Nonpowered vs Nonpowered, does not require electricity (eg, foam mattress); powered, requires electricity (eg, rotating bed).

1. Eligible age to participate in study is provided unless participant age is only available.
2. Duration of treatment is expressed as nearest week.
3. Different systems were used in the studies to stage pressure ulcer severity, but most systems rely on 4-stage categorization with higher numbers representing more severe ulcers.
4. Complete wound healing defined as the proportion of ulcers in the study group that healed during the intervention period; time to healing defined as the time to complete wound healing; wound surface area change defined as surface area measurements before and after treatment.
5. Maximum score of 5 and determined by the criteria on the checklist to evaluate a report of a nonpharmacological trial. See “Methods” section for description of criteria.
6. Indicates effective intervention for treatment of pressure ulcers.
7. A total of 1972 patients were enrolled in this trial, 113 were studied for treatment of pressure ulcers and the rest were studied for prevention purposes.
included in Table 1. It is feasible, however, to blind participants in nutritional supplement trials but this was done in only 4 of 7 trials. In all 19 RCTs evaluating underlying contributing factors, it was feasible to perform blinded outcome assessments, and this was described in 11 trials (57.9%).

Co-interventions were described as consistent in all treatment groups among 14 of the 19 studies (73.7%). In-intention-to-treat analyses were described in only 3 of these 19 studies (15.8%). One support surface study met all 5 CLEAR NPT criteria, 1 nutrition study met 5 of 6 criteria, and two of the 19 RCTs met 4 criteria.

### Table 2. Randomized Controlled Trials Evaluating Nutritional Supplementation as an Underlying Contributing Factor to Pressure Ulcer Severity

<table>
<thead>
<tr>
<th>Source</th>
<th>No. Eligible; No. Completed Study; Age</th>
<th>Setting; Duration of Treatment</th>
<th>Pressure Ulcer Severity at Baseline; Intervention</th>
<th>Primary Outcome Measures and Quantitative Estimate of Treatment Effect</th>
<th>Quality of Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al, 2006</td>
<td>89; 71; NA</td>
<td>Long-term care; 8 wk</td>
<td>II, III, or IV; collagen protein vs placebo</td>
<td>Mean (SD) changes in PUSH at 8 wk: 3.55 (4.66) for collagen protein vs 3.22 (4.11) for placebo (P &lt; .05)</td>
<td>4</td>
</tr>
<tr>
<td>Desneves et al, 2005</td>
<td>16; 13; age range: 37-92 y</td>
<td>Acute care; 3 wk</td>
<td>II, III, or IV; standard hospital diet vs standard hospital diet plus high protein vs standard hospital diet plus high protein plus arginine, zinc, and vitamin C</td>
<td>Mean (SD) PUSH score reduction from baseline to week 3: 8.7 (1.0) to 7.0 (1.5) for standard hospital diet vs 8.0 (0.5) to 6.0 (1.2) for standard hospital diet plus high protein vs 9.4 (1.2) to 2.6 (0.6) for standard hospital diet plus high protein plus arginine, zinc, and vitamin C (P &lt; .05)</td>
<td>3</td>
</tr>
<tr>
<td>Benati et al, 2001</td>
<td>36; NA; age range: 72-91 y</td>
<td>Acute care; 2 wk</td>
<td>NA; standard hospital diet vs standard hospital diet plus high protein vs standard hospital diet plus high protein plus arginine, zinc, and antioxidants</td>
<td>Pressure Sore Status Tool score: NA</td>
<td>1</td>
</tr>
<tr>
<td>ter Riet et al, 1995</td>
<td>88; 77; NA</td>
<td>Acute and long-term care; 12 wk</td>
<td>II, III, or IV; vitamin C (10 mg twice daily) plus placebo ultrasound vs vitamin C (10 mg twice daily) plus ultrasound vs vitamin C (500 mg twice daily) plus placebo ultrasound vs vitamin C (500 mg twice daily) plus ultrasound</td>
<td>Wound surface area mean absolute healing rates: 0.21 cm²/wk for intervention group vs 0.27 cm²/wk for control group</td>
<td>5</td>
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<tr>
<td>Myers et al, 1990</td>
<td>95; 80; age range: 22-102 y</td>
<td>Acute care; 1 wk</td>
<td>I, II, III, or IV; standard care vs standard diet vs consistent wound care vs controlled nutritional support vs consistent wound care plus controlled nutritional support</td>
<td>Adjusted mean change in ulcer size on wound surface area: 2.70 for standard care plus standard diet vs 2.76 for consistent wound care vs 2.60 for controlled nutritional support vs 2.34 for consistent wound care plus controlled nutritional support; there were no group differences in healing</td>
<td>1</td>
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<tr>
<td>Taylor et al, 1974</td>
<td>20; NA; age range: 54-88 y</td>
<td>Acute care; 4 wk</td>
<td>NA; vitamin C (500 mg twice daily) vs placebo twice daily</td>
<td>Mean reduction in wound surface area after 1 mo: 84% for vitamin C (500 mg twice daily) vs 42.7% for placebo twice daily (P &lt; .005)</td>
<td>3</td>
</tr>
<tr>
<td>Norris and Reynolds, 1971</td>
<td>14; 3; age range: 23-88 y</td>
<td>Long-term care; 24 wk</td>
<td>NA; zinc sulfate vs placebo</td>
<td>Wound surface area mean net change of ulcer volume: 10.1 mL for zinc sulfate vs 6.0 mL for placebo (P &lt; .80)</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviations: NA, data not available; PUSH, Pressure Ulcer Score for Healing.

*aEligible age to participate in study is provided unless participant age is only available.

*bDuration of treatment is expressed to nearest week.

*cDifferent systems were used in the studies to stage pressure ulcer severity, but most systems rely on 4-stage categorization with higher numbers representing more severe ulcers.

*dPUSH score range: 0, healed and 17, worst possible score. Wound surface area defined as changes of surface area measurements before and after treatment.

*eMaximum score of 6 and determined by the criteria on the checklist to evaluate a report of a nonpharmacological trial. See “Methods” section for description of criteria.

*fStandard care refers to various topical treatments in accordance with the participating institution and/or guidelines.
<table>
<thead>
<tr>
<th>Source</th>
<th>No. Eligible; No. Completed Study; Age&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Setting; Duration of Treatment&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Pressure Ulcer Severity at Baseline; Intervention&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Primary Outcome Measure and Quantitative Estimate of Treatment Effect&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Quality of Trial&lt;sup&gt;e&lt;/sup&gt;</th>
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<tr>
<td>Alvarez et al&lt;sup&gt;46&lt;/sup&gt; 2002</td>
<td>28; 26; &gt;18 y</td>
<td>Long-term care; 4 wk</td>
<td>II, III, or IV; collagenase vs papain-urea- chlorophyllin copper</td>
<td>Wound surface area: no significantly different rate of reduction in wound area</td>
<td>2</td>
</tr>
<tr>
<td>Püllen et al&lt;sup&gt;31&lt;/sup&gt; 2002</td>
<td>135; 78; &gt;54 y</td>
<td>Acute care and rehabilitation; ≤4 wk</td>
<td>II, III, or IV; collagenase vs fibrinolytic or deoxyribonuclease</td>
<td>Wound surface area reduction of 61.7% for collagenase vs 57.4% for fibrinolysis or deoxyribonuclease</td>
<td>4</td>
</tr>
<tr>
<td>Burgos et al&lt;sup&gt;45&lt;/sup&gt; 2000</td>
<td>102; 63; ≥55 y</td>
<td>Acute care; ≤8 wk</td>
<td>III; collagenase daily vs collagenase every 2 d</td>
<td>Mean (SD) reduction in wound surface area from 17.7 (18.6) cm&lt;sup&gt;2&lt;/sup&gt; to 12.6 (17.0) cm&lt;sup&gt;2&lt;/sup&gt; for collagenase daily vs from 21.4 (20.4) cm&lt;sup&gt;2&lt;/sup&gt; to 15.4 (19.9) cm&lt;sup&gt;2&lt;/sup&gt; for collagenase every 2 d</td>
<td>3</td>
</tr>
<tr>
<td>Müller et al&lt;sup&gt;46&lt;/sup&gt; 2001</td>
<td>24; 23; age range: 65-79 y</td>
<td>Acute care; 6-16 wk</td>
<td>IV; collagenase&lt;sup&gt;1&lt;/sup&gt; vs hydrocolloid</td>
<td>Complete wound healing: 91.7% for collagenase vs 63.6% for hydrocolloid (P&lt;.005)</td>
<td>0</td>
</tr>
<tr>
<td>Burgos et al&lt;sup&gt;35&lt;/sup&gt; 2000</td>
<td>43; 37; &gt;55 y</td>
<td>Acute care; ≤12 wk</td>
<td>III; collagenase vs hydrocolloid</td>
<td>Wound surface area reduction of 83.3% for collagenase vs 73.7% for hydrocolloid (P=.75)</td>
<td>4</td>
</tr>
<tr>
<td>Motta et al&lt;sup&gt;76&lt;/sup&gt; 1999</td>
<td>10; NA; age range: 93-76 y</td>
<td>Home care; 8 wk</td>
<td>II or III; hydrogel vs hydrocolloid</td>
<td>Mean reduction in wound surface area per week of 8.0% for hydrogel vs 3.3% for hydrocolloid vs 5.1% for moist saline gauze (P=.89)</td>
<td>1</td>
</tr>
<tr>
<td>Parish and Collins&lt;sup&gt;71&lt;/sup&gt; 1979</td>
<td>NA; 17; age range: 28-70 y</td>
<td>Long-term care; 4-16 wk</td>
<td>NA; collagenase vs dextranomer&lt;sup&gt;4&lt;/sup&gt; vs sugar and egg white</td>
<td>Wound surface area reduction of 45.5% for collagenase vs 85.7% for dextranomer vs 0% for sugar and egg white (collagenase vs dextranomer, P&lt;.02; dextranomer vs sugar and egg white, P&lt;.001)</td>
<td>2</td>
</tr>
<tr>
<td>Amione et al&lt;sup&gt;72&lt;/sup&gt; 2005</td>
<td>32; 28; &gt;18 y</td>
<td>Acute and ambulatory care; ≤6 wk</td>
<td>II or III; foam vs foam with wound-contact layer</td>
<td>Wound surface area: no significant differences in percentage decrease in ulcer area</td>
<td>2</td>
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<tr>
<td>Sayag et al&lt;sup&gt;49&lt;/sup&gt; 1996</td>
<td>92; 60; &gt;60 y</td>
<td>Ambulatory care; &lt;8 wk</td>
<td>III or IV; calcium alginate&lt;sup&gt;1&lt;/sup&gt; vs dextranomer</td>
<td>Mean reduction in wound surface area per week of 2.39 cm&lt;sup&gt;2&lt;/sup&gt; for calcium alginate vs 0.27 cm&lt;sup&gt;2&lt;/sup&gt; for dextranomer (P&lt;.001)</td>
<td>5</td>
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<tr>
<td>Sipponen et al&lt;sup&gt;47&lt;/sup&gt; 2008</td>
<td>37; 22; age range: 58-98 y</td>
<td>Acute care; 24 wk</td>
<td>II, III, or IV; resin salve&lt;sup&gt;3&lt;/sup&gt; vs sodium carboxymethylcellulose hydrocolloid polymer</td>
<td>Complete wound healing of 92% for resin salve vs 44% for sodium carboxymethylcellulose hydrocolloid polymer (P&lt;.003)</td>
<td>1</td>
</tr>
<tr>
<td>Price et al&lt;sup&gt;73&lt;/sup&gt; 2000</td>
<td>173; 50; mean age: radiant heat, 75.7 y; alginic acid, 69.9 y</td>
<td>Acute and home care; 3-6 wk</td>
<td>III or IV; radiant heat dressing&lt;sup&gt;3&lt;/sup&gt; vs alginate</td>
<td>Wound surface area mean reduction (P=.08)</td>
<td>3</td>
</tr>
<tr>
<td>Engdahl&lt;sup&gt;48&lt;/sup&gt; 1990</td>
<td>23; NA; age range: 69-94 y</td>
<td>Acute care; 2-13 wk</td>
<td>NA; dextranomer powder vs moist saline gauze</td>
<td>Wound surface area reduction of 43.5% for dextranomer powder vs 28.2% for moist saline gauze; this difference is not statistically significant</td>
<td>0</td>
</tr>
<tr>
<td>Brown-Etris et al&lt;sup&gt;48&lt;/sup&gt; 2008</td>
<td>72; 72; &gt;18 y</td>
<td>Long-term, home, and ambulatory care; &lt;8 wk</td>
<td>II or III; transparent absorbent acrylic dressing vs hydrocolloid</td>
<td>Complete wound healing of 60.0% for transparent absorbent acrylic dressing vs 59.5% for hydrocolloid (P=.96)</td>
<td>0</td>
</tr>
<tr>
<td>Motta et al&lt;sup&gt;76&lt;/sup&gt; 1999</td>
<td>10; NA; age range: 93-76 y</td>
<td>Home care; 8 wk</td>
<td>II or III; hydrogel dressing vs hydrocolloid</td>
<td>Complete wound healing of 40% for hydrogel dressing vs 40% for hydrocolloid; the overall healing rates of wounds were not statistically significant between the 2 groups</td>
<td>1</td>
</tr>
<tr>
<td>Seeley et al&lt;sup&gt;77&lt;/sup&gt; 1999</td>
<td>40; 39; &gt;18 y</td>
<td>Ambulatory care; 1-8 wk</td>
<td>II or III; hydrocolloidal dressing vs hydrocolloid</td>
<td>Wound surface area mean reduction of 50% for hydrocolloidal dressing vs 52% for hydrocolloid (P=.31)</td>
<td>1</td>
</tr>
<tr>
<td>Day et al&lt;sup&gt;76&lt;/sup&gt; 1995</td>
<td>103; 96; ≥18 y</td>
<td>Acute care; 1 wk (mean)</td>
<td>II or III; hydrocolloid (triangle-shaped) vs hydrocolloid (oval-shaped)</td>
<td>Wound surface area reduction in ulcer width of 32% for triangle-shaped vs 17% for oval-shaped hydrocolloid (P=.03)</td>
<td>1</td>
</tr>
</tbody>
</table>

(continued)
Table 3. Randomized Controlled Trials Evaluating Absorbent Wound Dressings for Local Wound Care (continued)

<table>
<thead>
<tr>
<th>Source</th>
<th>No. Eligible; No. Completed Study; Age</th>
<th>Setting; Duration of Treatment</th>
<th>Pressure Ulcer Severity at Baseline; Intervention</th>
<th>Primary Outcome Measure and Quantitative Estimate of Treatment Effect</th>
<th>Quality of Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honda et al, 1994</td>
<td>168; 129; &gt;65 y</td>
<td>Acute care; 1-8 wk</td>
<td>Hydrating vs Hydrating</td>
<td>Complete wound healing of 8.3% for hydrocolloid vs 25.8% for copolymer membrane (P = .03)</td>
<td>2</td>
</tr>
<tr>
<td>Darkovich et al, 1990</td>
<td>90; NA; age range: 30-98 y</td>
<td>Acute and long-term care; &lt;8 wk</td>
<td>Hydrating vs Absorbent</td>
<td>Complete wound healing of 43% for hydrogel dressing vs 24% for hydrocolloid</td>
<td>1</td>
</tr>
<tr>
<td>Belmin et al, 2002</td>
<td>110; 77; ≥65 y</td>
<td>Acute care; 8 wk</td>
<td>Hydrating vs Absorbent</td>
<td>Mean (SD) reduction in wound surface area of 1.6 (4.9) cm² and 3.1 (7.2) cm² for hydrocolloid vs 5.4 (5.7) cm² and 7.6 (7.1) cm² for sequential group, at 4 and 8 wk, respectively (P &lt; .001)</td>
<td>2</td>
</tr>
<tr>
<td>Sopata et al, 2002</td>
<td>34; 29; age range: 24-58 y</td>
<td>Palliative care; &lt;8 wk</td>
<td>Hydrating vs Antimicrobial</td>
<td>Complete wound healing of 80.8% for hydrocolloid vs 77.8% for moist povidone-iodine gauze; the healing rates of the 2 groups were not statistically significant</td>
<td>0</td>
</tr>
<tr>
<td>Colin et al, 1996</td>
<td>135; 96; age range: 25-98 y</td>
<td>Acute care; 1-3 wk</td>
<td>Hydrating vs Other</td>
<td>Mean PUSH of 3.24 for polymeric membrane dressing vs 1.61 for antibiotic ointment (P &lt; .001)</td>
<td>1</td>
</tr>
<tr>
<td>Yastrub, 2004</td>
<td>50; 44; ≥65 y</td>
<td>Long-term care; 4 wk</td>
<td></td>
<td>Complete wound healing of 74.2% for hydrocolloid vs 40% for phenytoin cream vs 26.7% for moist saline gauze (P &lt; .005)</td>
<td>3</td>
</tr>
<tr>
<td>Kim et al, 1996</td>
<td>44; NA; mean age: hydrocolloid, 50.5 y; moist gauze, 46.9 y</td>
<td>Rehabilitation: 3 wk (mean)</td>
<td></td>
<td>Complete wound healing of 51% for collagen vs 50% for hydrocolloid (P &lt; .05)</td>
<td>4</td>
</tr>
<tr>
<td>Holisaz et al, 2004</td>
<td>83; 83; mean age: 36.6 y</td>
<td>Long-term and home care; 8 wk</td>
<td></td>
<td>Complete wound healing of 35% for change indicator vs 6% for hydrocolloid alginate (P = .04)</td>
<td>3</td>
</tr>
<tr>
<td>Graumlich et al, 2003</td>
<td>65; 54; ≥18 y</td>
<td>Long-term care; &lt;8 wk</td>
<td></td>
<td>Complete wound healing of 25% for hydrogel vs 15% for moist saline gauze (P &lt; .05)</td>
<td>1</td>
</tr>
<tr>
<td>Saaman et al, 2000</td>
<td>35; 33; mean age: change, 78 y; hydrogel, 66 y</td>
<td>Long-term and home care; 2 wk</td>
<td></td>
<td>Mean (SD) reduction in wound surface area of 26% (20%) for hydrogel vs 64% (16%) for moist saline gauze (P = .02)</td>
<td>0</td>
</tr>
<tr>
<td>Matzen et al, 1999</td>
<td>32; 12; age range: 32-97 y</td>
<td>Ambulatory care; &lt;12 wk</td>
<td></td>
<td>Complete wound healing of 89% for hydrogel vs 86% for moist saline gauze; median time to healing: 9 d for hydrogel vs 11 d for moist saline gauze (P = .12)</td>
<td>0</td>
</tr>
<tr>
<td>Chang et al, 1998</td>
<td>34; NA; ≥18 y</td>
<td>Acute care; 3-8 wk</td>
<td></td>
<td>Complete wound healing of 63% for hydrogel vs 64% for moist saline gauze (P = .02)</td>
<td>1</td>
</tr>
<tr>
<td>Thomas et al, 1998</td>
<td>41; 30; ≥18 y</td>
<td>Long-term and home care; ≤10 wk</td>
<td></td>
<td>Complete wound healing of 42% for polyurethane foam vs 21% for moist saline gauze</td>
<td>0</td>
</tr>
<tr>
<td>Colwell et al, 1993</td>
<td>94; 70; age range: 15-100 y</td>
<td>Acute care; 1-8 wk</td>
<td></td>
<td>Complete wound healing of 89% for hydrocolloid vs 86% for moist saline gauze; median time to healing: 9 d for hydrogel vs 11 d for moist saline gauze (P = .12)</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 3. Randomized Controlled Trials Evaluating Absorbent Wound Dressings for Local Wound Care (continued)

<table>
<thead>
<tr>
<th>Source</th>
<th>No. Eligible; No. Completed Study; Age</th>
<th>Setting; Duration of Treatment</th>
<th>Pressure Ulcer Severity at Baseline; Intervention</th>
<th>Primary Outcome Measure and Quantitative Estimate of Treatment Effect</th>
<th>Quality of Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brod et al,93 1990</td>
<td>43; 38; age described as elderly</td>
<td>Long-term care; 6 wk (median)</td>
<td>II or III; hydrocolloid vs polyethelene</td>
<td>Complete wound healing of 62% for hydrocolloid vs 52% for polyethelene (P= .54)</td>
<td>0</td>
</tr>
<tr>
<td>Oleske et al,91 1986</td>
<td>16; 15; age range: 52-93 y</td>
<td>Acute care; 1 wk</td>
<td>I or II; occlusive polyurethane dressing vs moist saline gauze</td>
<td>Mean wound surface area of 2.0 cm² for occlusive polyurethane dressing vs 7.7 cm² for moist saline gauze (P&lt;.05)</td>
<td>1</td>
</tr>
<tr>
<td>Sebern,92 1986</td>
<td>NA; 48; mean age: transparent dressing, 76.3 y; moist gauze, 72.4 y</td>
<td>Home care; 8 wk</td>
<td>II or III; transparent moisture-permeable dressing vs moist saline gauze</td>
<td>Median reduction in wound surface area of 100% for transparent moisture-permeable dressing vs 52% for moist saline gauze (P&lt;.01)</td>
<td>1</td>
</tr>
<tr>
<td>Rhodes et al,93 2001</td>
<td>47; 39; &gt;60 y</td>
<td>Long-term care; 2-13 wk</td>
<td>II; phenytoin suspension vs hydrocolloid vs triple antibiotic ointment</td>
<td>Mean (SD) time to healing of 35.3 (14.3) d for phenytoin suspension vs 51.8 (19.6) d for hydrocolloid vs 53.8 (8.5) d for triple antibiotic ointment (P=.005)</td>
<td>0</td>
</tr>
<tr>
<td>Yapucu Gunes and Eser,94 2007</td>
<td>36; 26; &gt;18 y</td>
<td>Acute care; ≤5 wk</td>
<td>II or III; ethyoxadilminoaacide and nitrofurazone vs honey dressing</td>
<td>Mean changes in PUSH from 14.52 to 12.62 for ethyoxadilminoaacide and nitrofurazone vs from 15.00 to 6.55 for honey dressing (P&lt;.001)</td>
<td>2</td>
</tr>
<tr>
<td>Kaya et al,95 2005</td>
<td>27; 27; age range: 16-56 y</td>
<td>Acute care; 2-12 wk</td>
<td>II, III, or IV; povidone-iodine gauze vs hydrogel</td>
<td>Wound surface area epithelialization of 54% for povidone-iodine gauze vs 84% for hydrogel (P=.04)</td>
<td>0</td>
</tr>
<tr>
<td>Gerding and Browning,96 1992</td>
<td>NA; 74; NA</td>
<td>Long-term care; ≤4 wk</td>
<td>II or III; oxyquinoline vs lanolin or petrolatum</td>
<td>Complete stage II wound healing of 44.5% for oxyquinoline vs 21.8% for lanolin or petrolatum (P&lt;.05)</td>
<td>4</td>
</tr>
<tr>
<td>Moberg et al,97 1983</td>
<td>45; 34; age range: 52-97 y</td>
<td>Acute care; 3-8 wk</td>
<td>Deep or superficial; cadexomer iodine vs standard care</td>
<td>Mean decrease of wound surface ulcer area of 30.9% for cadexomer iodine vs 19.6% for standard care (P&lt;.02)</td>
<td>0</td>
</tr>
<tr>
<td>Shamimi et al,98 2008</td>
<td>18; 18; &gt;18 y</td>
<td>Acute care; 8 wk</td>
<td>NA; semelil gel vs standard care</td>
<td>Mean (SD) reduction in wound surface area of 48.2 (85.3) cm² for semelil gel (78.3%) vs 2.8 (6.2) cm² for standard care (6.3%) (P&lt;.001)</td>
<td>1</td>
</tr>
<tr>
<td>Subbanna et al,99 2007</td>
<td>28; 26; mean age: phenytoin, 34.3 y; saline, 31.6 y</td>
<td>Rehabilitation; 2 wk</td>
<td>II; phenytoin solution vs normal saline</td>
<td>Mean (SD) reduction in PUSH of 19.53 (17.70) for phenytoin solution vs 11.39 (11.09) for normal saline (P=.26)</td>
<td>4</td>
</tr>
<tr>
<td>Thomas et al,100 2005</td>
<td>41; 31; mean age: radiant heat, 74.1 y; hydrocolloid and/or alginate, 77.0 y</td>
<td>Rehabilitation, long-term, and ambulatory care; ≤12 wk</td>
<td>III or IV; radiant heat dressing vs hydrocolloid and/or alginate</td>
<td>Complete wound healing of 57% for radiant heat dressing vs 44% for hydrocolloid and/or alginate (P=.46)</td>
<td>4</td>
</tr>
<tr>
<td>Measne et al,101 2003</td>
<td>38; NA; ≥65 y</td>
<td>Long-term care; ≤8 wk</td>
<td>II; soft silicone vs hydrogel</td>
<td>Complete wound healing of 44% for soft silicone (6/18) vs 50% for hydrogel (10/20)</td>
<td>2</td>
</tr>
<tr>
<td>Kloth et al,102 2002</td>
<td>53; 40; mean age: radiant heat, 78.1 y; standard care, 77.9 y</td>
<td>Acute and long-term care; ≤12 wk</td>
<td>III or IV; radiant heat dressing vs standard care</td>
<td>Wound surface area reduction of 0.52 cm²/wk for radiant heat dressing vs 0.23 cm²/wk for standard care (P&lt;.02)</td>
<td>1</td>
</tr>
<tr>
<td>Small et al,103 2002</td>
<td>58; 41; ≥18 y</td>
<td>Home care; ≤6 wk</td>
<td>II, III, or IV; hydrogel or foam or transparent film vs standard care</td>
<td>Complete wound healing (P=.15)</td>
<td>1</td>
</tr>
<tr>
<td>Kuflik et al,104 2001</td>
<td>19; 15; age described as elderly</td>
<td>Long-term care and rehabilitation; 6 wk</td>
<td>I or II; active ointment (with live yeast cell derivative) vs placebo</td>
<td>Complete wound healing of 90% for active ointment (9/10) vs 33% for placebo (1/3)</td>
<td>3</td>
</tr>
<tr>
<td>Whitney et al,105 2001</td>
<td>40; 29; ≥18 y</td>
<td>Acute, long-term, and home care; ≤8 wk</td>
<td>III or IV; radiant heat dressing vs standard care</td>
<td>Wound surface area mean reduction of 0.012 cm²/d for radiant heat dressing vs 0.004 cm²/d for standard care (P=.02)</td>
<td>1</td>
</tr>
</tbody>
</table>
Sixty-three RCTs (3330 participants) evaluated interventions targeting local wound care. Fifty-four RCTs (2857 participants) evaluated wound dressings (Table 3).31,32,34-36,46,55,57,66,105 Five of the 7 highest-quality RCTs of wound dressings found no difference in wound healing with the products they compared: collagenase vs fibrinolysin or deoxyribonuclease, collagenase vs hydrocolloid, radiant heat dressing vs hydrocolloid and/or alginate and phenytoin solution vs normal saline.31,30,36,60,97 Sayag et al60 performed a multicentered trial of 92 patients aged 60 years or older with pressure ulcers in acute care. They found that mean wound surface area reduction per week was 2.39 cm² (SD, 3.54) in wounds treated with calcium alginate and 0.27 cm² (SD, 3.21) in wounds treated with dextranomer paste (P<.001). Gerding and Browning64 found oxyquinoline improved wound healing compared with lanolin or petrolatum. However, lanolin may cause allergic contact dermatitis and has fallen out of favor in chronic wound treatment.106,107 No debriding agent was consistently superior to other dressings for wound healing.31,48,68,69,71

In another trial, nerve growth factor improved healing when compared with placebo at 6-week follow-up (mean [SD] reduction in pressure ulcer area, 738 [393] vs 485 [384] mm²; P = .03).112

Of the 63 studies examining local wound care, 22 adequately described the generation of random allocation sequences (34.9%) and 13 reported that participants were randomized using concealed allocation (20.6%). Only 15 of the 63 studies (23.8%) described adequate participant blinding. Adequate blinding of outcome assessors was described in 23 studies (36.5%). Co-interventions were equally applied in 28 studies (44.4%), and intention-to-treat analyses were performed in only 10 studies (15.9%). None of the 63 studies examining local wound care fulfilled all 6 CLEAR NPT criteria.

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### Table 4. Randomized Controlled Trials Evaluating Biological Agents for Local Wound Care

<table>
<thead>
<tr>
<th>Source</th>
<th>No. Completed Study; Age</th>
<th>Setting; Duration of Treatment</th>
<th>Wound-Environment Modulators</th>
<th>Primary Outcome Measure and Quantitative Estimate of Treatment Effect</th>
<th>Quality of Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nisi et al, 2005</td>
<td>80; NA; age range: 35-85 y</td>
<td>Acute care; 2-8 wk</td>
<td>II, III, or IV; protease-modulating matrix vs petrolatum-soaked gauze</td>
<td>Complete healing of 90% for protease-modulating matrix vs 70% for petrolatum-soaked gauze (P = .59)</td>
<td>0</td>
</tr>
<tr>
<td>Payne et al, 2004</td>
<td>34; 10; &gt;18 y</td>
<td>NA; 12-24 wk</td>
<td>III; fibroblast-derived dermal replacement plus standard care vs standard care</td>
<td>Complete wound healing of 11% for fibroblast-derived dermal replacement plus standard care vs 13% for standard care (P &gt; .05)</td>
<td>3</td>
</tr>
<tr>
<td>Rees et al, 1999</td>
<td>124; 103; &gt;18 y</td>
<td>NA; ≤16 wk</td>
<td>III or IV; recombinant platelet-derived growth factor BB (100 µg/g once daily) alternated with placebo every 12 h vs recombinant platelet-derived growth factor BB (300 µg/g once daily) alternated with placebo every 12 h vs recombinant platelet-derived growth factor BB (100 µg/g every 12 h) vs placebo every 12 h</td>
<td>Complete wound healing of 23% for 100 µg/g of recombinant platelet-derived growth factor BB vs 0% for placebo (P = .005 and P = .006, respectively)</td>
<td>4</td>
</tr>
<tr>
<td>Mustoe et al, 1994</td>
<td>52; 41; age described as elderly</td>
<td>Acute and long-term care; 4 wk</td>
<td>III or IV; recombinant platelet-derived growth factor BB (100 µg/mL) vs placebo vs petrolatum-soaked gauze</td>
<td>Wound surface area for ulcers in the 2 recombinant platelet-derived growth factor BB groups were significantly smaller in volume vs placebo group (P = .009)</td>
<td>3</td>
</tr>
<tr>
<td>Robson et al, 1992</td>
<td>20; 20; age range: 21-56 y</td>
<td>Acute care; 4 wk</td>
<td>I or II; recombinant platelet-derived growth factor BB (1 µg/mL) vs recombinant platelet-derived growth factor BB (10 µg/mL) vs recombinant platelet-derived growth factor BB (100 µg/mL) vs placebo</td>
<td>After 28 d, mean volume of ulcer on wound surface area (vs day 0); 0.4% for recombinant platelet-derived growth factor BB (100 µg/mL) vs 21.8% for placebo</td>
<td>3</td>
</tr>
<tr>
<td>Landi et al, 2003</td>
<td>38; 36; age range: 75-93 y</td>
<td>Long-term care; ≤6 wk</td>
<td>II, III, IV, or V; nerve growth factor vs placebo</td>
<td>Mean (SD) wound surface area reduction at 6 wk: 738 (393) mm² for nerve growth factor vs 485 (384) mm² for placebo (P = .03)</td>
<td>4</td>
</tr>
<tr>
<td>Hirshberg et al, 2001</td>
<td>14; 8; ≥18 y</td>
<td>Ambulatory care; ≤16 wk</td>
<td>III or IV; transforming growth factor beta 3 (1 µg/cm²) vs transforming growth factor beta 3 (2.5 µg/cm²) vs placebo</td>
<td>Mean relative wound surface area: 0.3 cm² for transforming growth factor beta 3 (1 µg/cm²) vs 0.4 cm² for transforming growth factor beta 3 (2.5 µg/cm²) vs 0.7 cm² for placebo (P &gt; .05)</td>
<td>3</td>
</tr>
<tr>
<td>Robson et al, 2000</td>
<td>NA; 61; age range: 28-70 y</td>
<td>Acute care; 5 wk</td>
<td>III or IV; granulocyte-macrophage/colony-stimulating factor for 10 d and then basic fibroblast growth factor vs granulocyte-macrophage/colony-stimulating factor vs basic fibroblast growth factor vs placebo</td>
<td>Wound surface area: basic fibroblast growth factor had significantly more patients than placebo with &gt;85% closure (P = .02) and &gt;90% closure (P = .04)</td>
<td>3</td>
</tr>
<tr>
<td>Robson et al, 1992</td>
<td>50; 49; age range: 18-65 y</td>
<td>Acute care; 4 wk</td>
<td>III or IV; basic fibroblast growth factor vs placebo</td>
<td>Wound surface area: 60% of patients achieved a 70% volume reduction for basic fibroblast growth factor vs 29% for placebo (P = .05)</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviation: NA, data not available.

1 Eligible age to participate in study is provided unless participant age is only available.
2 Duration of treatment is expressed to nearest week.
3 Different systems were used in the studies to stage pressure ulcer severity, but most systems rely on 4-stage categorization with higher numbers representing more severe ulcers.
4 Complete wound healing defined as the proportion of ulcers in the study group that healed during the intervention period; and wound surface area defined as changes of surface area measurements before and after treatment.
5 Maximum score of 6 and determined by the criteria on the checklist to evaluate a report of a nonpharmacological trial. See “Methods” section for description of criteria.
6 Standard care refers to various topical treatments in accordance with the participating institution and/or guidelines.
7 Indicates effective intervention for treatment of pressure ulcers.
Table 5. Randomized Controlled Trials Evaluating Adjunctive Therapies for Local Wound Care

<table>
<thead>
<tr>
<th>Source</th>
<th>No. Eligible; No. Completed Study; Age</th>
<th>Setting; Length of Follow-up</th>
<th>Pressure Ulcer Severity at Baseline; Intervention</th>
<th>Primary Outcome Measures and Quantitative Estimate of Treatment Effect</th>
<th>Quality of Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wanner et al,116 2003</td>
<td>22; NA; age range: 34-77 y</td>
<td>Rehabilitation; mean: 4 wk</td>
<td>II, III, or IV; vacuum therapy vs moist gauze</td>
<td>Wound surface area: no difference in time to reach 50% of initial wound volume between groups</td>
<td>0</td>
</tr>
<tr>
<td>Ford et al,117 2002</td>
<td>28; 22; age range: 18-80 y</td>
<td>Acute and ambulatory care; 6 wk</td>
<td>III or IV; vacuum therapy vs cadexomer iodine or papain-urea-chlorophyllin copper</td>
<td>Wound surface area mean reduction in ulcer volume of 51.8% for vacuum therapy vs 42.1% for cadexomer iodine or papain-urea-chlorophyllin copper (P = .46)</td>
<td>2</td>
</tr>
<tr>
<td>Adunsky and Ohry,54 2005</td>
<td>63; 38; &gt;18 y</td>
<td>Long-term care and rehabilitation; 8-20 wk</td>
<td>III; direct current vs placebo direct current</td>
<td>Complete wound healing of 25.7% for direct current vs 35.7% for placebo direct current (P = .28)</td>
<td>5</td>
</tr>
<tr>
<td>Adegboye and Badmos,118 2001</td>
<td>7; 6; age range: 21-60 y</td>
<td>Acute care; ≤4 wk</td>
<td>IV; interrupted direct current vs placebo interrupted direct current</td>
<td>Wound surface area reduction of 22.2% for interrupted direct current vs 2.6% for placebo interrupted direct current</td>
<td>2</td>
</tr>
<tr>
<td>Wood et al,119 1993</td>
<td>74; NA; age range: 42-95 y</td>
<td>Acute care and rehabilitation; ≤6 wk</td>
<td>II or III; pulsed low-intensity direct current vs placebo pulsed low-intensity direct current</td>
<td>Wound surface area reduction of 80% within 8 wk (72.9% for pulsed low-intensity direct current vs 12.9% for placebo pulsed low-intensity direct current); P &lt; .001</td>
<td>3</td>
</tr>
<tr>
<td>Griffin et al,120 1991</td>
<td>20; 17; age range: 10-74 y</td>
<td>Rehabilitation; 1-3 wk</td>
<td>II, III, or IV; high-voltage pulsed direct current vs placebo high-voltage pulsed direct current</td>
<td>Wound surface area reduction at day 20 of 84.7% for high-voltage pulsed direct current vs 9 for placebo high-voltage pulsed direct current (P = .05)</td>
<td>3</td>
</tr>
<tr>
<td>Asbjornsen et al,121 1990</td>
<td>20; 16; age range: 75-94 y</td>
<td>NA; 4-6 wk</td>
<td>NA; transcutaneous electrical nerve stimulation vs placebo transcutaneous electrical nerve stimulation</td>
<td>Wound surface area reduction in size of 4 for transcutaneous electrical nerve stimulation vs 9 for placebo transcutaneous electrical nerve stimulation</td>
<td>3</td>
</tr>
<tr>
<td>Kloth and Feedar,122 1988</td>
<td>16; NA; age range: 20-89 y</td>
<td>NA; 4-16 wk</td>
<td>IV; high-voltage pulsed current vs placebo high-voltage pulsed current</td>
<td>Wound surface area reduction per week of 45% for high-voltage pulsed current vs −11.6% for placebo high-voltage pulsed current</td>
<td>3</td>
</tr>
<tr>
<td>ter Riet et al,123 1995</td>
<td>88; NA; median age: 61 y</td>
<td>Long-term care; 12 wk</td>
<td>II; ultrasound vs placebo ultrasound</td>
<td>Wound surface area reduction of 40% for ultrasound vs 44% for placebo ultrasound (P = .61)</td>
<td>4</td>
</tr>
<tr>
<td>McDermid et al,124 1985</td>
<td>40; 18; &gt;18 y</td>
<td>Acute care; ≤9 wk</td>
<td>NA; ultrasound vs placebo ultrasound</td>
<td>Median healing time of 32 d for ultrasound vs 38 d for placebo ultrasound (P = .82)</td>
<td>3</td>
</tr>
<tr>
<td>Salzberg et al,125 1995</td>
<td>30; 29; age range: 24-69 y</td>
<td>Acute care; ≤12 wk</td>
<td>II or III; electromagnetic therapy vs placebo electromagnetic therapy</td>
<td>Complete wound healing of 84.0% for electromagnetic therapy vs 40% for placebo electromagnetic therapy at 1 wk (P = .01)</td>
<td>3</td>
</tr>
<tr>
<td>Comorosan et al,126 1993</td>
<td>30; 20; age range: 60-84 y</td>
<td>Long-term care; ≤2 wk</td>
<td>II or III; standard care vs standard care plus electromagnetic therapy vs standard care plus placebo</td>
<td>Complete wound healing of 0% for standard care vs 85% for standard care plus electromagnetic therapy vs 0% for standard care plus placebo after 2 wk</td>
<td>3</td>
</tr>
<tr>
<td>Taly et al,127 2004</td>
<td>35; 25; age range: 8-65 y</td>
<td>Rehabilitation; ≤5 wk</td>
<td>II, III, or IV; laser and moist saline gauze vs moist saline gauze</td>
<td>Mean (SD) complete wound healing of 2.45 (2.06) wk for laser and moist saline gauze vs 1.78 (2.13) wk for moist saline gauze (P = .33); PSST score (P = .57)</td>
<td>5</td>
</tr>
<tr>
<td>Lucas et al,128 2003</td>
<td>86; 79; age range: 49-100 y</td>
<td>Long-term care; ≤6 wk</td>
<td>II; low-level laser vs standard care</td>
<td>Wound surface area absolute wound size reduction (P = .23)</td>
<td>2</td>
</tr>
<tr>
<td>Dehn et al,129 2003</td>
<td>201; 164; &gt;65 y</td>
<td>Acute and ambulatory care; ≤12 wk</td>
<td>II or III; monochromatic phototherapy vs placebo</td>
<td>Complete wound healing reduction in ulcer area (P = .18); time to healing (P = .93)</td>
<td>3</td>
</tr>
<tr>
<td>Iordanou et al,130 2002</td>
<td>55; 32; age range: 37-85 y</td>
<td>Acute care; 2 wk</td>
<td>I, II, or III; polarized light vs standard care</td>
<td>Mean reduction in wound surface area from 2.84 to 2.26 cm² for polarized light vs from 2.10 to 2.04 cm² for standard care</td>
<td>1</td>
</tr>
</tbody>
</table>

(continued)
One study of dressings met 5 of the 6 criteria, 6 studies of dressings met 4 of the 6 criteria, and 2 studies of biological agents met 4 of the 6 criteria. Fourteen of the 63 RCTs (22.2%) did not meet any of the CLEAR NPT criteria. 33,112 of biological agents met 4 of the 6 criteria, and 2 studies met 4 of the 6 criteria, and 2 studies met 4 of the 6 criteria.

**COMMENT**

Fundamental to chronic wound care are managing the underlying contributing factors, local wound care, and adjunctive therapies. Guidelines for the practical management of pressure ulcers are available from the Wound Healing Society (http://www3.interscience.wiley.com/journal/118605275/issue). Management of underlying contributing factors is likely
more valuable in treating pressure ulcers than either topical or adjunctive therapies. Thus, priority should be given to addressing underlying causes. However, only 19 of 103 studies focused on management of underlying contributing factors, while the remaining 84 trials examined local wound care and adjunctive therapies. Overall, few RCTs demonstrated meaningful outcome differences between specific treatment strategies.

We did not find evidence that powered mattresses were superior to nonpowered mattresses. Support surfaces only address 1 aspect of pressure ulcer formation (ie, pressure), and not other important forces associated with immobility and ulcer formation (such as shear, friction, temperature, and moisture). To address the forces that contribute to ulcer formation, regular turning and transferring schedules may provide a less expensive alternative to costly support surfaces. No trial examined optimal turning or transferring regimens.

We found little evidence that nutritional supplements improve pressure ulcer healing in patients without specific nutritional deficiencies. Protein supplementation of long-term care residents may be beneficial. None of the included RCTs documented nutritional deficiencies prior to nutrient supplementation, so it is uncertain whether the benefits of protein supplementation are limited to individuals who have protein deficiencies.

No single dressing was consistently superior to other dressings in the trials of pressure ulcers we examined. Similar results exist for other chronic wounds. Cochrane reviews have concluded that there is insufficient evidence to show any 1 dressing type better than others for arterial ulcers, venous stasis ulcers, or surgical wounds healing by secondary intention. Standard local wound care for a healable pressure ulcer (ie, 1 with reversible underlying factors) should satisfy the 3 criteria of moisture balance, bacterial balance, and debridement.

Standard local wound care for a maintenance or nonhealable pressure ulcer may require antiseptics. Controversy persists in the literature regarding the efficacy and safety of antiseptics (such as povidone-iodine solution). Two of the RCTs we examined compared antiseptics with moist dressings. Neither of these trials met any CLEAR NPT criteria. Antiseptics are inexpensive and non-RCT evidence supports their continued use in maintenance or nonhealable wounds to help prevent wound deterioration. Because no single dressing was superior to others, clinicians should select dressings that fulfill criteria for standard local wound care, while considering cost, ease of use, goals of care, and patient comfort.

Our results suggest recombinant human platelet–derived growth factor and nerve growth factor may improve healing, but further study is needed to confirm that these expensive agents provide value over standard care in clinical practice.

We found no evidence that adjunctive therapies improve pressure ulcer healing. A recent systematic review of vacuum therapy concluded that there is insufficient evidence to demonstrate clinical benefit, and the large number of prematurely terminated and unpublished trials of vacuum therapy is concerning. No RCTs of hyperbaric oxygen therapy met our inclusion criteria. Two recent systematic reviews could not conclude if there was any benefit of hyperbaric oxygen therapy on pressure ulcers. Another systematic review found insufficient evidence to reach conclusions regarding the contributions of laser therapy, therapeutic ultrasound, electrotherapy, and electromagnetic therapy to chronic wound healing. Overall, there are limited data to support routine use of these expensive adjunctive therapies in managing pressure ulcers.

The methodological quality of the RCTs in our review was often inadequate. Only 1 of the 103 RCTs met all of the quality standards we selected from the CLEAR NPT checklist. This may partly reflect the evolving understanding of how best to design and report RCTs evaluating nonpharmacological interventions. The RCTs published after 1992 met many of the CLEAR NPT quality criteria. Only 22 of the 103 RCTs provided a sample size justification. Many negative trials were likely underpowered to detect either clinically important differences or equivalence of the treatments they compared.

The paucity of high-quality RCTs evaluating pressure ulcer may reflect differences between regulatory requirements for medications vs pressure ulcer treatments such as dressings. Prescription medications must have demonstrated efficacy and safety in RCTs prior to attaining approval for marketing. In contrast, since passage of the 1997 Food and Drug Administration Modernization Act, dressing manufacturers are not required to submit evidence of safety or effectiveness to the US Food and Drug Administration before marketing a new product. Similar regulations are in place in other countries. This situation raises concerns analogous to those highlighted by the lack of regulation for vitamins and herbal supplements since passage of the 1994 Dietary Supplement Health and Education Act.

Future RCTs will need to address the methodological deficiencies highlighted in this review. Studies also are needed to develop standardized methods for measuring wounds and reporting healing rates. Pressure ulcers may be too complex to successfully treat using a single modality. Trials of multifactorial wound care interventions (eg, a combination of repositioning and local wound care) should be considered to determine whether they offer advantages over simpler interventions.

Our review has limitations. First, it was restricted to RCTs because they provide the best evidence of treatment efficacy. This is especially important...
given the multifaceted nature of pressure ulcer treatments and the importance of controlling for co-interventions. Nonetheless, evidence from nonrandomized trials also may provide insights into treatment benefits and risks. Second, we also restricted our review to trials published in the English language. Our examination of non-English trials suggests that including these trials would not have altered our results.

Third, we examined RCTs in a variety of settings. Results of some RCTs may not be generalizable to other populations. Comparing trials was complicated by the fact that different staging systems were used to categorize pressure ulcer severity. Finally, we likely underestimated information about potential conflicts of interest because many journals only recently began publishing this information.

CONCLUSIONS
Relatively few RCTs evaluating pressure ulcer treatments follow standard criteria for reporting nonpharmacological interventions. High-quality studies are needed to establish the efficacy and safety of many commonly used treatments. There is little evidence from RCTs to justify the use of 1 support surface or dressing over alternatives. Similarly, there is little evidence to justify the routine use of nutritional supplements, biological agents, and adjunctive therapies compared with standard care. Clinicians should make decisions regarding pressure ulcer therapy based on fundamental wound care principles, cost, ease of use, and patient preference.

Author Contributions: Dr Reddy had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Reddy, Gill, Rochon.

Acquisition of data: Reddy, Kalkar, Wu, Anderson, Rochon.


Drafting of the manuscript: Reddy.

Critical revision of the manuscript for important intellectual content: Gill, Kalkar, Wu, Anderson, Rochon.

Statistical analysis: Gill, Kalkar, Wu.

Obtained funding: Rochon.

Administrative, technical, or material support: Kalkar, Wu, Anderson.

Study supervision: Rochon.

Financial Disclosures: Dr Reddy reported receiving honoraria or consulting fees from Smith and Nephew, Molnylycke, and Merck. No other authors reported financial disclosures.

Funding/Support: This work was supported by Canadian Institute of Health Research Interdisciplinary Capacity Enhancement grant HTA-80075. Dr Gill was supported by an Ontario Ministry of Health and Long-Term Care Career Scientist Award.

Role of the Sponsors: The funding organizations did not participate in the design or conduct of the study, in the collection, analysis, or interpretation of the data, or in the preparation, review, or approval of the manuscript.

Additional Contributions: We thank Gary Sibbald, BSc, MD, MED, FRCP(C) (Division of Dermatology, University of Toronto, and Women’s College Hospital, Toronto, Ontario, Canada) and Joyce Black, PhD, RN (National Pressure Ulcer Advisory Panel and University of Nebraska Medical Center College of Nursing, Omaha) for their review of the manuscript. Neither Dr Sibbald nor Dr Black received any compensation for their contributions. Dr Sibbald reported being a consultant, speaker, or researcher for Smith and Nephew, SM, Convatec, Molnylycke, Coloplast, Tyco, Johnson & Johnson, and KCI. Dr Black reported being a consultant for Gaymar Industries, HillRom, and Sage Products.

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