Treatment of Pressure Ulcers: A Systematic Review

Madhuri Reddy; Sudeep S. Gill; Sunila R. Kalkar; et al.

JAMA. 2008;300(22):2647-2662 (doi:10.1001/jama.2008.778)

http://jama.ama-assn.org/cgi/content/full/300/22/2647

Treatment of Pressure Ulcers
A Systematic Review

Madhuri Reddy, MD, MSc
Sudeep S. Gill, MD, MSc
Sunila R. Kalkar, MBBS, MD
Wei Wu, MSc
Peter J. Anderson, BA
Paula A. Rochon, MD, MPH

Context Many treatments for pressure ulcers are promoted, but their relative efficacy is unclear.

Objective To systematically review published randomized controlled trials (RCTs) evaluating therapies 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.

Data Extraction Methodological characteristics and outcomes were extracted by 3 investigators.

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 (38 [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 cm^2 vs 0.27 cm^2, 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. No clear benefit was identified in 21 RCTs evaluating adjunctive therapies including electric current, ultrasound, light therapy, and vacuum therapy.

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.

JAMA. 2008;300(22):2647-2662 www.jama.com

PRESSURE ULCERS ARE REGIONS OF localized damage to the skin and underlying tissues that usually develop over bony prominences such as the sacrum or heels.[1-3] These lesions are an important source of suffering for patients and their caregivers. Pressure ulcer prevalence varies widely depending on patient factors (eg, age, physical impairments) and treatment setting.[4-7]

Treatment strategies for pressure ulcers can be both costly and complex. Hundreds of different mattresses and local wound care products are currently promoted,[4] and few have been evaluated in randomized controlled trials (RCTs). It remains unclear which of the many available treatments promote the most effective healing of pressure ulcers.[8-11]

While several effective strategies to prevent pressure ulcers exist,[6] many patients continue to develop them. This is especially true in high-risk settings such as acute care hospitals, in which patients have reduced mobility.[12,13] Thus, clinicians require an understanding of effective treatment options. We examined the evidence supporting interventions for the treatment of pressure ulcers.

CME available online at www.jamaarchivescme.com and questions on p 2681.

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

Author Affiliations: Department of Medicine, Hebrew Rehabilitation Center, Division of Gerontology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts (Dr Reddy); Division of Geriatric Medicine, Departments of Medicine and Community Health and Epidemiology, Queen's University, Kingston, Ontario, Canada (Dr Gill); Kunin-Lunenfeld Applied Research Unit-Baycrest, Toronto, Ontario, Canada (Drs Kalkar and Rochon and Messrs Wu and Anderson); Department of Medicine, University of Toronto, Toronto, Ontario, Canada (Dr Rochon); and Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada (Dr Rochon).
Corresponding Author: Madhuri Reddy, MD, MSc, Hebrew Rehabilitation Center, 1200 Center St, Boston, MA 02131 (Madhuri.Reddy@hrca.harvard.edu).
Clinical Review Section Editor: Mary McGrae McDermott, MD, Contributing Editor. We encourage authors to submit papers for consideration as a Clinical Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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)[14] and another in Japanese (19 participants).[15] 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.[16] 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).[17]

A criterion standard for quantifying outcomes in ulcer healing has not been established.[18,19] 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.[20,21] 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.[19] 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[22] or Pressure Sore Status Tool.[23] 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) (http://www.bichat.inserm.fr/equipes/Emi0357/docs/usersguidelines.pdf)[24] 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.[25]

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.[26] 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[26]: 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.[6] 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.[27]

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).[28] 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[29-43] and 22 provided a sample size justification.[29-32,35,39,40,42,44-57]

Thirty-eight of the 103 trials took place in acute care (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 interventions for underlying contributing factors. Twelve RCTs (1214 participants) evaluated support surfaces (TABLE 1).[29,30,39-42,44-46,58-60] None evaluated the effects of repositioning alone.

Six RCTs directly compared powered (eg, alternating pressure) with nonpowered (eg, foam) support surfaces.[30,41,42,45,58,59] Russell et al[30] and Day and Leonard[41] found no differences in pressure ulcer healing between powered and nonpowered support surfaces. The remaining 4 studies, which met fewer quality criteria than Russell et al,[30] suggested that powered support surfaces were superior to nonpowered support surfaces,[42,45,58,59] although 1 RCT did not report statistical significance.[58] Inconsistent findings in these 6 studies result in persistent uncertainty regarding the benefit of powered support surfaces.

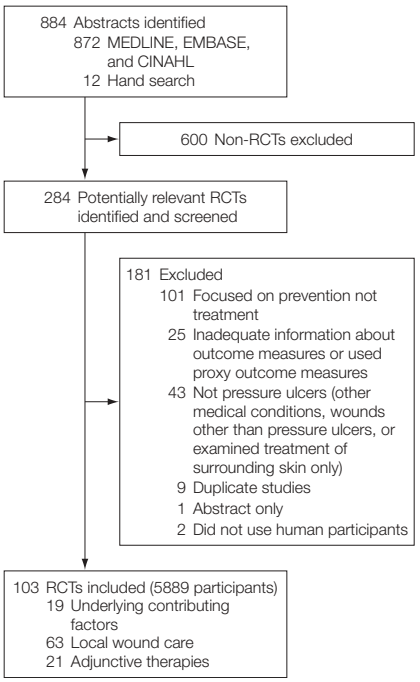
Five RCTs compared different types of powered mattresses. Evans et al[60] and Nixon et al[40] found no differences in ulcer healing between the 2 powered support surfaces they compared. Allman et al[44] found that ulcer surface area decreased with an air-fluidized mattress but increased on an alternating pressure mattress (median changes, −1.2 vs 0.5 cm^2 [95% confidence interval for the difference, −9.2 to −0.6 cm^2]; $P=.01$).

Seven RCTs (358 participants) evaluated nutritional supplements (TABLE 2).[61-67] All were oral supplements, but contents varied in each trial. Lee et al[61] evaluated 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).[18] 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; $P<.05$).

ter Riet et al[64] compared high-dose (500 mg twice daily) 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[66] 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,[64] but not the study by Taylor et al,[66] provided an adequate description of generation of allocation sequences and used an intention-to-treat analysis. In addition, the study by ter Riet et al[64] included more patients (88 vs 20 in Taylor et al[66]), 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] Desneves et al[62] 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.

Figure. Flow Diagram of Included and Excluded Studies



RCT indicates randomized controlled trial.

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

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

Source	No. Eligible; No. Completed Study; Age[b]	Setting; Duration of Treatment[c]	Pressure Ulcer Severity at Baseline; Intervention[d]	Primary Outcome Measures and Quantitative Estimate of Treatment Effect[e]	Quality of Trial[f]
			Nonpowered vs Nonpowered		
Groen et al,[29] 1999	120; 101; ≥60 y	Long-term care; 2-4 wk	III or IV; specialized foam mattress vs water mattress	Complete wound healing: 45% for specialized foam mattress vs 48.3% for water mattress; this difference is not significant	2
			Powered vs Nonpowered		
Rosenthal et al,[42] 2003	207; 204; mean age: LAL mattress, 69.0 y; SFMO, 68.6 y; APM, 70.4 y	Long-term care; 4-24 wk	III or IV; LAL mattress vs SFMO vs APM[g]	Mean (SD) Pressure Sore Status Score improvement: 18.4 (1.5) for LAL mattress vs 34.3 (1.5) for APM ($P<.001$); mean (SD) time to complete healing: 4.38 (0.14) mo (95% CI, 4.10-4.65) for LAL mattress vs 4.55 (0.22) mo (95% CI, 4.13-4.98) for SFMO vs 3.33 (0.12) mo (95% CI, 3.09-3.58) for APM	3
Russell et al,[30] 2003	199; 158; mean age: APM, 80.4 y; FMO, 79.8 y	Acute care; mean: 3 wk	I, II, III, or IV; APM vs FMO	Wound surface area overall ulcer progress: 72.3% for APM vs 74.7% for FMO ($P = .67$)	4
Branom,[58] 2001	20; 18; age range: 36-100 y	Acute and long-term care; 3-8 wk	III or IV; LAL mattress vs air and foam mattress[g]	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	1
Mulder et al,[59] 1994	49; 39; NA	Long-term care; ≤12 wk	III or IV; LAL mattress[g] vs SFMO	Wound surface area reduction in wound size: 77% more for LAL mattress vs SFMO ($P<.04$)	1
Day and Leonard,[41] 1993	118; 83; >18 y	Acute care; 1-104 wk	II, III, or IV; LAL mattress vs foam overlay	Wound surface area ($P>.05$)	3
Ferrell et al,[45] 1993	84; NA; >75 y	Long-term care; 1-82 wk	II, III, or IV; LAL mattress[g] vs specialized foam mattress	Wound surface area median reduction: 9.0 mm^2/d for LAL mattress vs 2.5 mm^2/d for specialized foam mattress ($P<.001$)	3
			Powered vs Powered		
Nixon et al,[40] 2006	NA; 113; ≥55 y[h]	Acute care; 60 wk	II; APM vs alternating pressure overlay	Complete wound healing: 10.3% for APM vs 10.7% for alternating pressure overlay ($P = .75$)	3
Evans et al,[60] 2000	NA; 32; ≥65 y	Acute and long-term care; ≤67 wk	II or III; APM No. 1 vs APM No. 2	Wound surface area median absolute reduction per day: 0.12 cm for APM No. 1 vs 0.08 cm for APM No. 2 ($P = .57$)	5
Land et al,[46] 2000	17; NA; age range: 66-99 y	Acute and long-term care; ≤2 wk	II, III, or IV; APM vs APM or overlay	Wound surface area: no significant difference in healing sores	3
Russell et al,[39] 2000	183; 112; age described as elderly	Acute care; 72 wk	II, III, or IV; 2 types of APM and cushion combination	Complete wound healing: improvement in heel ulcers only ($P = .02$)	1
Allman et al,[44] 1987	72; 65; >18 y	Acute care; 1-11	I, II, III, or IV; air-fluidized mattress[g] vs APM covered with foam	Wound surface area median changes in surface area: −1.2 cm^2 for air-fluidized mattress vs 0.5 cm^2 for APM covered with foam ($P = .01$)	3

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.
[a] Support surface groups: nonpowered, does not require electricity (eg, foam mattress); powered, requires electricity (eg, rotating bed).
[b] Eligible age to participate in study is provided unless participant age is only available.
[c] Duration of treatment is expressed to nearest week.
[d] 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.
[e] 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 changes defined as surface area measurements before and after treatment.
[f] 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.
[g] Indicates effective intervention for treatment of pressure ulcers.
[h] 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%). Intention-to-treat analyses were described in only 3 of these 19 studies (15.8%). One support surface study[60] met all 5 CLEAR NPT criteria, 1 nutrition study[64] met 5 of 6 criteria, and two[30,61] of the 19 RCTs met 4 criteria.

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

Source	No. Eligible; No. Completed Study; Age[a]	Setting; Duration of Treatment[b]	Pressure Ulcer Severity at Baseline; Intervention[c]	Primary Outcome Measures and Quantitative Estimate of Treatment Effect[d]	Quality of Trial[e]
Lee et al,[61] 2006	89; 71; NA	Long-term care; 8 wk	II, III, or IV; collagen protein[f] vs placebo	Mean (SD) changes in PUSH at 8 wk: 3.55 (4.66) for collagen protein vs 3.22 (4.11) for placebo ($P<.05$)	4
Desneves et al,[62] 2005	16; 13; age range: 37-92 y	Acute care; 3 wk	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[f]	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 ($P<.05$)	3
Benati et al,[63] 2001	36; NA; age range: 72-91 y	Acute care; 2 wk	NA; standard hospital diet vs standard hospital diet plus high protein vs standard hospital diet plus high protein plus arginine, zinc, and antioxidants[f]	Pressure Sore Status Tool score: NA	1
ter Riet et al,[64] 1995	88; 77; NA	Acute and long-term care; 12 wk	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	Wound surface area mean absolute healing rates: 0.21 cm^2/wk for intervention group vs 0.27 cm^2/wk for control group	5
Myers et al,[65] 1990	95; 80; age range: 22-102 y	Acute care; 1 wk	I, II, III, or IV; standard care[g] plus standard diet vs consistent wound care vs controlled nutritional support vs consistent wound care plus controlled nutritional support	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	1
Taylor et al,[66] 1974	20; NA; age range: 54-88 y	Acute care; 4 wk	NA; vitamin C (500 mg twice daily)[f] vs placebo twice daily	Mean reduction in wound surface area after 1 mo: 84% for vitamin C (500 mg twice daily) vs 42.7% for placebo twice daily ($P<.005$)	3
Norris and Reymolds,[67] 1971	14; 3; age range: 23-88 y	Long-term care; 24 wk	NA; zinc sulfate vs placebo	Wound surface area mean net change of ulcer volume: 10.1 mL for zinc sulfate vs 6.0 mL for placebo ($P<.80$)	2

Abbreviations: NA, data not available; PUSH, Pressure Ulcer Score for Healing.
[a] Eligible age to participate in study is provided unless participant age is only available.
[b] Duration of treatment is expressed to nearest week.
[c] 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.
[d] PUSH score range: 0, healed and 17, worst possible score. Wound surface area defined as changes of surface area measurements before and after treatment.
[e] Maxiumum 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.
[f] Indicates effective intervention for treatment of pressure ulcers.
[g] Standard care refers to various topical treatments in accordance with the participating institution and/or guidelines.

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

Source	No. Eligible; No. Completed Study; Age[a]	Setting; Duration of Treatment[b]	Pressure Ulcer Severity at Baseline; Intervention[c]	Primary Outcome Measure and Quantitative Estimate of Treatment Effect[d]	Quality of Trial[e]
			Debriding vs Debriding		
Alvarez et al,[68] 2002	28; 26; >18 y	Long-term care; 4 wk	II, III, or IV; collagenase vs papain-urea-chlorophyllin copper	Wound surface area: no significantly different rate of reduction in wound area	2
Püllen et al,[31] 2002	135; 78; >54 y	Acute care and rehabilitation; ≤4 wk	II, III, or IV; collagenase vs fibrinolysin or deoxyribonuclease	Wound surface area reduction of 61.7% for collagenase vs 57.4% for fibrinolysin or deoxyribonuclease (P=.12)	4
Burgos et al,[38] 2000	102; 63; ≥55 y	Acute care; ≤8 wk	III; collagenase daily vs collagenase every 2 d	Mean (SD) reduction in wound surface area from 17.7 (18.6) cm^2 to 12.6 (17.0) cm^2 for collagenase daily vs from 21.4 (20.4) cm^2 to 15.4 (19.9) cm^2 for collagenase every 2 d (P=.64)	3
			Debriding vs Hydrating		
Müller et al,[48] 2001	24; 23; age range: 65-79 y	Acute care; 6-16 wk	IV; collagenase[f] vs hydrocolloid	Complete wound healing: 91.7% for collagenase vs 63.6% for hydrocolloid (P<.005)	0
Burgos et al,[69] 2000	43; 37; >55 y	Acute care; ≤12 wk	III; collagenase vs hydrocolloid	Wound surface area reduction of 83.3% for collagenase vs 73.7% for hydrocolloid (P=.75)	4
			Debriding vs Hydrating vs Other		
Mulder et al,[70] 1993	67; 64; ≥18 y	Acute and ambulatory care; ≤8 wk	II or III; hydrogel vs hydrocolloid vs moist saline gauze	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)	1
			Debriding vs Absorbent vs Other		
Parish and Collins,[71] 1979	NA; 17; age range: 28-70 y	Long-term care; 4-16 wk	NA; collagenase vs dextranomer[f] vs sugar and egg white	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<.02; dextranomer vs sugar and egg white, P<.001)	2
			Absorbent vs Absorbent		
Amione et al,[72] 2005	32; 28; ≥18 y	Acute and ambulatory care; ≤6 wk	II or III; foam vs foam with wound-contact layer	Wound surface area: no significant differences in percentage decrease in ulcer area	2
Sayag et al,[49] 1996	92; 60; >60 y	Ambulatory care; <8 wk	III or IV; calcium alginate[f] vs dextranomer	Mean reduction in wound surface area per week of 2.39 cm^2 for calcium alginate vs 0.27 cm^2 for dextranomer (P<.001)	5
			Absorbent vs Other		
Sipponen et al,[57] 2008	37; 22; age range: 58-98 y	Acute care; 24 wk	II, III, or IV; resin salve[f] vs sodium carboxymethylcellulose hydrocolloid polymer	Complete wound healing of 92% for resin salve vs 44% for sodium carboxymethylcellulose hydrocolloid polymer (P=.003)	1
Price et al,[73] 2000	58; 50; mean age: radiant heat, 75.7 y; alginate, 69.8 y	Acute and home care; 3-6 wk	III or IV; radiant heat dressing[g] vs alginate	Wound surface area mean reduction (P=.08)	3
Engdahl,[74] 1980	23; NA; age range: 69-94 y	Acute care; 2-13 wk	NA; dextranomer powder vs moist saline gauze	Wound surface area reduction of 43.5% for dextranomer powder vs 28.2% for moist saline gauze; this difference is not statistically significant	0
			Hydrating vs Hydrating		
Brown-Etris et al,[75] 2008	72; 72; ≥18 y	Long-term, home, and ambulatory care; <8 wk	II or III; transparent absorbent acrylic dressing vs hydrocolloid	Complete wound healing of 60.0% for transparent absorbent acrylic dressing vs 59.5% for hydrocolloid (P=.96)	0
Motta et al,[76] 1999	10; NA; age range: 34-76 y	Home care; 8 wk	II or III; hydrogel dressing vs hydrocolloid	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	1
Seeley et al,[77] 1999	40; 39; >18 y	Ambulatory care; 1-8 wk	II or III; hydrocellular dressing vs hydrocolloid	Wound surface area mean reduction of 50% for hydrocellular dressing vs 52% for hydrocolloid (P=.31)	1
Day et al,[36] 1995	103; 96; ≥18 y	Acute care; 1 wk (mean)	II or III; hydrocolloid (triangle-shaped)[f] vs hydrocolloid (oval-shaped)	Wound surface area reduction in ulcer width of 32% for triangle-shaped vs 17% for oval-shaped hydrocolloid (P = .03)	1

(continued)

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

Source	No. Eligible; No. Completed Study; Age[a]	Setting; Duration of Treatment[b]	Pressure Ulcer Severity at Baseline; Intervention[c]	Primary Outcome Measure and Quantitative Estimate of Treatment Effect[d]	Quality of Trial[e]
			Hydrating vs Hydrating		
Hondé et al,[37] 1994	168; 129; >65 y	Acute care; 1-8 wk	II, III, or IV; hydrocolloid vs copolymer membrane[f]	Complete wound healing of 8.3% for hydrocolloid vs 25.8% for copolymer membrane (P = .03)	2
Darkovich et al,[78] 1990	90; NA; age range: 30-98 y	Acute and long-term care; <8 wk	I or II; hydrogel dressing[f] vs hydrocolloid	Complete wound healing of 43% for hydrogel dressing vs 24% for hydrocolloid	1
			Hydrating vs Absorbent		
Belmin et al,[35] 2002	110; 77; ≥65 y	Acute care; 8 wk	III or IV; hydrocolloid for 8 wk vs calcium alginate for 4 wk and then hydrocolloid for 4 wk[f]	Mean (SD) reduction in wound surface area of 1.6 (4.9) cm^2 and 3.1 (7.2) cm^2 for hydrocolloid vs 5.4 (5.7) cm^2 and 7.6 (7.1) cm^2 for sequential group, at 4 and 8 wk, respectively (P < .001)	2
Sopata et al,[79] 2002	34; 29; age range: 24-88 y	Palliative care; <8 wk	II or III; polyurethane foam vs hydrogel wafer	Mean (SD) healing rate for wound surface area ulcers of 1.23 (1.33) cm^2/d (stage II) and 0.44 (0.27) cm^2/d (stage III) for polyurethane foam vs 0.67 (0.37) cm^2/d (stage II) and 0.31 (0.21) cm^2/d (stage III) for hydrogel wafer (P > .05)	1
Colin et al,[32] 1996	135; 96; age range: 25-98 y	Acute care[h]; 1-3 wk	I, II, III, or IV; hydrogel[f] vs dextranomer	Wound surface area median reduction in wound area of 35% for hydrogel vs 7% for dextranomer (P = .03)	0
			Hydrating vs Antimicrobial		
Yastrub,[80] 2004	50; 44; >65 y	Long-term care; 4 wk	II; polymeric membrane dressing[f] vs antibiotic ointment	Mean PUSH of 3.24 for polymeric membrane dressing vs 1.61 for antibiotic ointment (P<.001)	1
Kim et al,[81] 1996	44; NA; mean age: hydrocolloid, 50.5 y; moist gauze, 46.9 y	Rehabilitation; 3 wk (mean)	I or II; hydrocolloid vs moist povidone-iodine gauze	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	0
			Hydrating vs Other		
Hollisaz et al,[53] 2004	83; 83; mean age: 36.6 y	Long-term and home care[h]; 8 wk	I or II; hydrocolloid[f] vs phenytoin cream vs moist saline gauze	Complete wound healing of 74.2% for hydrocolloid vs 40% for phenytoin cream vs 26.7% for moist saline gauze (P < .005)	3
Graumlich et al,[50] 2003	65; 54; >18 y	Long-term care; <8 wk	II or III; collagen vs hydrocolloid	Complete wound healing of 51% for collagen vs 50% for hydrocolloid (P = .89)	4
Seaman et al,[82] 2000	35; 33; mean age: change, 78 y; hydrocolloid, 66 y	Long-term and home care; 2 wk	II, III, or IV; change indicator[f] vs hydrocolloid alginate	Complete wound healing of 35% for change indicator vs 6% for hydrocolloid alginate (P = .04)	3
Matzen et al,[83] 1999	32; 12; age range: 32-97 y	Ambulatory care; <12 wk	III or IV; hydrocolloid gel vs moist saline gauze[f]	Mean (SD) reduction in wound surface area of 26% (20%) for hydrocolloid gel vs 64% (16%) for moist saline gauze (P < .02)	1
Chang et al,[84] 1998	34; NA; ≥18 y	Acute care; 3-8 wk	II or III; hydrocolloid vs moist saline gauze	Wound surface area mean reduction of 34% for hydrocolloid vs –9% for moist saline gauze (P = .23)	0
Thomas et al,[85] 1998	41; 30; ≥18 y	Long-term and home care; ≤10 wk	II, III, or IV; hydrogel vs moist saline gauze	Complete wound healing of 63% for hydrogel vs 64% for moist saline gauze (P = .92)	1
Colwell et al,[86] 1993	94; 70; age range: 18-100 y	Acute care; 1-8 wk	II or III; hydrocolloid[f] vs moist saline gauze	Wound surface area complete wound healing of 22% for hydrocolloid vs 2% for moist saline gauze	0
Kraft et al,[55] 1993	38; 17; age range: 28-78 y	Acute and long-term care; ≤24 wk	II or III; polyurethane foam[f] vs moist saline gauze	Complete wound healing of 42% for polyurethane foam vs 21% for moist saline gauze	0
Xakellis and Chrischilles,[87] 1992	39; 34; mean age: hydrocolloid, 77.3 y; moist gauze, 83.5 y	Long-term care; 10 wk	II or III; hydrocolloid vs moist saline gauze	Complete wound healing of 89% for hydrocolloid vs 86% for moist saline gauze; median time to healing: 9 d for hydrocolloid vs 11 d for moist saline gauze (P = .12)	0

(continued)

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

Source	No. Eligible; No. Completed Study; Age[a]	Setting; Duration of Treatment[b]	Pressure Ulcer Severity at Baseline; Intervention[c]	Primary Outcome Measure and Quantitative Estimate of Treatment Effect[d]	Quality of Trial[e]
			Hydrating vs Other		
Brod et al,[88] 1990	43; 38; age described as elderly	Long-term care; 6 wk (median)	II or III; hydrocolloid vs polyhema	Complete wound healing of 62% for hydrocolloid vs 52% for polyhema ($P=.54$)	0
Oleske et al,[89] 1986	16; 15; age range: 52-93 y	Acute care; 1 wk	I or II; occlusive polyurethane dressing vs moist saline gauze	Mean wound surface area of 2.0 cm^2 for occlusive polyurethane dressing vs 7.7 cm^2 for moist saline gauze ($P>.05$)	1
Sebern,[90] 1986	NA; 48; mean age: transparent dressing, 76.3 y; moist gauze, 72.4 y	Home care; 8 wk	II or III; transparent moisture-permeable dressing[f] vs moist saline gauze	Median reduction in wound surface area of 100% for transparent moisture-permeable dressing vs 52% for moist saline gauze ($P<.01$)	1
			Antimicrobial vs Hydrating vs Other		
Rhodes et al,[91] 2001	47; 39; >60 y	Long-term care; 2-13 wk	II; phenytoin suspension[f] vs hydrocolloid vs triple antibiotic ointment	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 ($P=.005$)	0
			Antimicrobial vs Other		
Yapucu Günes and Eser,[92] 2007	36; 26; >18 y	Acute care; ≤5 wk	II or III; ethoxydiaminoacridine and nitrofurazone vs honey dressing[f]	Mean changes in PUSH from 14.52 to 12.62 for ethoxydiaminoacridine and nitrofurazone vs from 15.00 to 6.55 for honey dressing ($P<.001$)	2
Kaya et al,[93] 2005	27; 27; age range: 16-56 y	Acute care[h]; 2-12 wk	I, II, or III; povidone-iodine gauze vs hydrogel[f]	Wound surface area epithelialization of 54% for povidone-iodine gauze vs 84% for hydrogel ($P=.04$)	0
Gerding and Browning,[94] 1992	NA; 74; NA	Long-term care; ≤4 wk	I or II; oxyquinoline[f] vs lanolin or petrolateum	Complete stage II wound healing of 44.5% for oxyquinoline vs 21.8% for lanolin or petrolateum ($P<.05$)	4
Moberg et al,[95] 1983	45; 34; age range: 52-97 y	Acute care; 3-8 wk	Deep or superficial; cadexomer iodine[f] vs standard care[i]	Mean decrease of wound surface ulcer area of 30.9% for cadexomer iodine vs 19.6% for standard care ($P<.02$)	0
			Other vs Other		
Shamimi et al,[96] 2008	18; 18; >18 y	Acute care; 8 wk	NA; semelil gel[f] vs standard care[i]	Mean (SD) reduction in wound surface area of 48.2 (85.3) cm^2 for semelil gel (78.3%) vs 2.8 (6.2) cm^2 for standard care (6.3%) ($P<.001$)	1
Subbanna et al,[56] 2007	28; 26; mean age: phenytoin, 34.3 y; saline, 31.6 y	Rehabilitation[h]; 2 wk	II; phenytoin solution vs normal saline	Mean (SD) reduction in PUSH of 19.53 (17.70) for phenytoin solution vs 11.39 (11.09) for normal saline ($P=.26$)	4
Thomas et al,[97] 2005	41; 31; mean age: radiant heat, 74.1 y; hydrocolloid and/or alginate, 77.0 y	Rehabilitation, long-term, and ambulatory care; ≤12 wk	III or IV; radiant heat dressing[f] vs hydrocolloid and/or alginate	Complete wound healing of 57% for radiant heat dressing vs 44% for hydrocolloid and/or alginate ($P=.46$)	4
Meaume et al,[98] 2003	38; NA; ≥65 y	Long-term care; ≤8 wk	II; soft silicone vs hydropolymer	Complete wound healing of 44% for soft silicone (8/18) vs 50% for hydropolymer (10/20)	2
Kloth et al,[99] 2002	53; 40; mean age: radiant heat, 78.1 y; standard care, 77.9 y	Acute and long-term care; ≤12 wk	III or IV; radiant heat dressing[f,g] vs standard care[i]	Wound surface area reduction of 0.52 cm^2/wk for radiant heat dressing vs 0.23 cm^2/wk for standard care ($P<.02$)	1
Small et al,[52] 2002	58; 41; ≥18 y	Home care; ≤6 wk	II, III, or IV; hydrogel or foam or transparent film vs standard care[i]	Complete wound healing ($P=.15$)	1
Kuflik et al,[100] 2001	19; 15; age described as elderly	Long-term care and rehabilitation; 6 wk	I or II; active ointment (with live yeast cell derivative)[f] vs placebo	Complete wound healing of 90% for active ointment (9/10) vs 33% for placebo (1/3)	3
Whitney et al,[101] 2001	40; 29; ≥18 y	Acute, long-term, and home care; ≤8 wk	III or IV; radiant heat dressing[f,g] vs standard care[i]	Wound surface area mean reduction of 0.012 cm^2/d for radiant heat dressing vs 0.004 cm^2/d for standard care ($P=.02$)	1

(continued)

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

Source	No. Eligible; No. Completed Study; Age[a]	Setting; Duration of Treatment[b]	Pressure Ulcer Severity at Baseline; Intervention[c]	Primary Outcome Measure and Quantitative Estimate of Treatment Effect[d]	Quality of Trial[e]
			Other vs Other		
LeVasseur and Helme,[102] 1991	34; 21; mean age: active cream, 82.5 y; placebo, 81.5 y	Acute and long-term care; 6 wk	I or II; active cream (extract of barley) vs placebo	Mean (SD) time to healing of 18.4 (4.4) d for active cream vs 29.1 (3.6) d for placebo ($P=.08$)	2
Guthrie,[34] 1988	128; 105; mean age: 77.9 y	Long-term care; ≤6 wk	Deep or superficial; zinc salt spray and aluminum hydroxide or vitamin A ointment[f] vs zinc salt spray vs aluminum hydroxide or vitamin A ointment vs placebo spray and ointment	Wound surface area reduction of 90.2% for zinc salt spray and aluminum hydroxide or vitamin A ointment vs −0.1% for zinc salt spray vs 28.7% for aluminum hydroxide or vitamin A ointment vs −2.3% for placebo	2
Agren and Stromberg,[51] 1985	28; 28; age range: 46-92 y	Acute and ambulatory care; ≤8 wk	NA; streptokinase-streptodornase vs zinc oxide	Wound surface area median reduction of −18.7% for streptokinase-streptodornase vs 2.4% for zinc oxide ($P>.05$)	1
Knudsen et al,[103] 1982	16; 8; age range: 20-57 y	Acute care[h]; 3 wk	NA; dialysate[f] vs placebo	Wound surface area reduction on 10th and 20th days, respectively, of 39% and 80% for dialysate vs 28% and 59% for placebo ($P<.05$)	3
Gerber and Van Ort,[104] 1979	31; 29; age range: 68-96 y	Long-term care; 2 wk	NA; topical insulin vs standard care[i]	Wound surface area ($P=.42$)	1
Van Ort and Gerber,[105] 1976	14; 14; age range: 19-94 y	Long-term care; 2 wk	NA; topical insulin[f] vs standard care[i]	Complete wound healing ($P=.05$)	1

Abbreviations: NA, data not available; PUSH, Pressure Ulcer Score for Healing.
[a] Eligible age to participate in study is provided unless participant age is only available.
[b] Duration of treatment is expressed to nearest week.
[c] 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.
[d] PUSH score range: 0, healed and 17, worst possible score. Wound surface area defined as changes of surface area measurements before and after treatment; complete wound healing defined as the proportion of ulcers in the study group that healed during the intervention period; and time to healing defined as the time to complete wound healing.
[e] 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.
[f] Indicates effective intervention for treatment of pressure ulcers.
[g] Radiant heat dressing has been removed from the market due to safety concerns.
[h] Indicates treatment for spinal cord injuries.
[i] Standard care refers to various topical treatments in accordance with the participating institution and/or guidelines.

Sixty-three RCTs (3330 participants) evaluated interventions targeting local wound care. Fifty-four RCTs (2857 participants) evaluated wound dressings (TABLE 3).[31,32,34-38,48-53,55-57,68-105] 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.[31,50,56,69,97] Sayag et al[49] 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 cm^2 (SD, 3.54) in wounds treated with calcium alginate and 0.27 cm^2 (SD, 3.21) in wounds treated with dextranomer paste ($P<.001$). Gerding and Browning[94] 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]

Nine RCTs (473 participants) evaluated biological agents (TABLE 4).[33,108-115] Three trials examined the effects of platelet-derived growth factors. The trial that met the most CLEAR NPT criteria was performed by Rees et al,[33] which compared 3 doses of recombinant human platelet–derived growth factor with placebo. The incidence of complete healing was greater in all 3 recombinant human platelet–derived growth factor groups ($P<.03$ in all groups) compared with placebo.

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] mm^2; $P=.03$).[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%). Cointerventions 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.

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

Source	No. Eligible; No. Completed Study; Age[a]	Setting; Duration of Treatment[b]	Pressure Ulcer Severity at Baseline; Intervention[c]	Primary Outcome Measure and Quantitative Estimate of Treatment Effect[d]	Quality of Trial[e]
Wound-Environment Modulators					
Nisi et al,[108] 2005	80; NA; age range: 35-85 y	Acute care; 2-8 wk	II, III, or IV; protease-modulating matrix vs petrolatum-soaked gauze	Complete healing of 90% for protease-modulating matrix vs 70% for petrolatum-soaked gauze (*P* = .59)	0
Skin Substitutes					
Payne et al,[109] 2004	34; 10; >18 y	NA; 12-24 wk	III; fibroblast-derived dermal replacement plus standard care[f] vs standard care[f]	Complete wound healing of 11% for fibroblast-derived dermal replacement plus standard care vs 13% for standard care (*P* > .05)	3
Platelet-Derived Growth Factors					
Rees et al,[33] 1999	124; 103; >18 y	NA; ≤16 wk	III or IV; recombinant platelet-derived growth factor BB (100 µg/g once daily) alternated with placebo every 12 h[g] vs recombinant platelet-derived growth factor BB (300 µg/g once daily) alternated with placebo every 12 h[g] vs recombinant platelet-derived growth factor BB (100 µg/g every 12 h[g]) vs placebo every 12 h	Complete wound healing of 23% for 100 µg/g of recombinant platelet-derived growth factor BB vs 19% for 300 µg/g of recombinant platelet-derived growth factor BB vs 0% for placebo (*P* = .005 and *P* = .008, respectively)	4
Mustoe et al,[110] 1994	52; 41; age described as elderly	Acute and long-term care; 4 wk	III or IV; recombinant platelet-derived growth factor BB (100 vs 300 µg/mL)[g] vs placebo	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)	3
Robson et al,[111] 1992	20; 20; age range: 21-56 y	Acute care; 4 wk	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)[g] vs placebo	After 28 d, mean volume of ulcer on wound surface area (vs day 0): 6.4% for recombinant platelet-derived growth factor BB (100 µg/mL) vs 21.8% for placebo	3
Other Growth Factors					
Landi et al,[112] 2003	38; 36; age range: 75-93 y	Long-term care; ≤6 wk	II, III, IV, or V; nerve growth factor[g] vs placebo	Mean (SD) wound surface area reduction at 6 wk: 738 (393) mm^2 for nerve growth factor vs 485 (384) mm^2 for placebo (*P* = .03)	4
Hirshberg et al,[113] 2001	14; 8; ≥18 y	Ambulatory care; ≤16 wk	III or IV; transforming growth factor beta 3 (1 µg/cm^2) vs transforming growth factor beta 3 (2.5 µg/cm^2) vs placebo	Mean relative wound surface area: 0.3 cm^2 for transforming growth factor beta 3 (1 µg/ cm^2) vs 0.4 cm^2 for transforming growth factor beta 3 (2.5 µg/cm^2) vs 0.7 cm^2 for placebo (*P* > .05)	3
Robson et al,[114] 2000	NA; 61; age range: 28-70 y	Acute care; 5 wk	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[g] vs placebo	Wound surface area: basic fibroblast growth factor had significantly more patients than placebo with >85% closure (*P* = .02) and >90% closure (*P* = .04)	3
Robson et al,[115] 1992	50; 49; age range: 18-65 y	Acute care; 4 wk	III or IV; basic fibroblast growth factor[g] vs placebo	Wound surface area: 60% of patients achieved a 70% volume reduction for basic fibroblast growth factor vs 29% for placebo (*P* = .05)	3

Abbreviation: NA, data not available.
[a] Eligible age to participate in study is provided unless participant age is only available.
[b] Duration of treatment is expressed to nearest week.
[c] 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.
[d] 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.
[e] 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.
[f] Standard care refers to various topical treatments in accordance with the participating institution and/or guidelines.
[g] Indicates effective intervention for treatment of pressure ulcers.

Table 5. Randomized Controlled Trials Evaluating Adjunctive Therapies for Local Wound Care

Source	No. Eligible; No. Completed Study; Age[a]	Setting; Length of Follow-up[b]	Pressure Ulcer Severity at Baseline; Intervention[c]	Primary Outcome Measures and Quantitative Estimate of Treatment Effect[d]	Quality of Trial[e]
			Vacuum Therapy		
Wanner et al,[116] 2003	22; NA; age range: 34-77 y	Rehabilitation[f]; mean: 4 wk	II, III, or IV; vacuum therapy vs moist gauze	Wound surface area: no difference in time to reach 50% of initial wound volume between groups	0
Ford et al,[117] 2002	28; 22; age range: 18-80 y	Acute and ambulatory care; 6 wk	III or IV; vacuum therapy vs cadexomer iodine or papain-urea-chlorophyllin copper	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)	2
			Electric Current		
Adunsky and Ohry,[54] 2005	63; 38; >18 y	Long-term care and rehabilitation; 8-20 wk	III; direct current vs placebo direct current	Complete wound healing of 25.7% for direct current vs 35.7% for placebo direct current (*P* = .28)	5
Adegoke and Badmos,[118] 2001	7; 6; age range: 21-60 y	Acute care[f]; ≤4 wk	IV; interrupted direct current[g] vs placebo interrupted direct current	Wound surface area reduction of 22.2% for interrupted direct current vs 2.6% for placebo interrupted direct current	2
Wood et al,[119] 1993	74; NA; age range: 42-95 y	Acute care and rehabilitation; ≤8 wk	II or III; pulsed low-intensity direct current[g] vs placebo pulsed low-intensity direct current	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* < .001	3
Griffin et al,[120] 1991	20; 17; age range: 10-74 y	Rehabilitation[f]; 1-3 wk	II, III, or IV; high-voltage pulsed direct current vs placebo high-voltage pulsed direct current	Wound surface area reduction at day 20 of 8 for high-voltage pulsed direct current vs 9 for placebo high-voltage pulsed direct current (*P* = .05)	3
Asbjornsen et al,[121] 1990	20; 16; age range: 73-94 y	NA; 4-6 wk	NA; transcutaneous electrical nerve stimulation vs placebo transcutaneous electrical nerve stimulation	Wound surface area reduction in size of 4 for transcutaneous electrical nerve stimulation vs 9 for placebo transcutaneous electrical nerve stimulation	3
Kloth and Feedar,[122] 1988	16; NA; age range: 20-89 y	NA; 4-16 wk	IV; high-voltage pulsed current[g] vs placebo high-voltage pulsed current	Wound surface area reduction per week of 45% for high-voltage pulsed current vs −11.6% for placebo high-voltage pulsed current	3
			Ultrasound		
ter Riet et al,[123] 1995	88; NA; median age: 81 y	Long-term care; 12 wk	II; ultrasound vs placebo ultrasound	Wound surface area reduction of 40% for ultrasound vs 44% for placebo ultrasound (*P* = .61)	4
McDiarmid et al,[124] 1985	40; 18; >18 y	Acute care; ≤9 wk	NA; ultrasound vs placebo ultrasound	Median healing time of 32 d for ultrasound vs 36 d for placebo ultrasound (*P* = .80)	3
			Electromagnetic Therapy		
Salzberg et al,[125] 1995	30; 29; age range: 24-69 y	Acute care[f]; ≤12 wk	II or III; electromagnetic therapy[g] vs placebo electromagnetic therapy	Complete wound healing of 84.0% for electromagnetic therapy vs 40% for placebo electromagnetic therapy at 1 wk (*P* = .01)	3
Comorosan et al,[126] 1993	30; 20; age range: 60-84 y	Long-term care; ≤2 wk	II or III; standard care[h] vs standard care plus electromagnetic therapy[g] vs standard care plus placebo	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	3
			Laser		
Taly et al,[127] 2004	35; 25; age range: 8-65 y	Rehabilitation[f]; ≤5 wk	II, III, or IV; laser and moist saline gauze vs moist saline gauze	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)	5
Lucas et al,[47] 2003	86; 79; age range: 49-100 y	Long-term care; ≤6 wk	III; low-level laser vs standard care[h]	Wound surface area absolute wound size reduction (*P* = .23)	2
			Light		
Dehlin et al,[43] 2003	201; 164; >65 y	Acute and ambulatory care; ≤12 wk	II or III; monochromatic phototherapy vs placebo	Complete wound healing reduction in ulcer area (*P* = .18); time to healing (*P* = .93)	3
Iordanou et al,[128] 2002	55; 32; age range: 37-85 y	Acute care; 2 wk	I, II, or III; polarized light[g] vs standard care[h]	Mean reduction in wound surface area from 2.84 to 2.26 cm^2 for polarized light vs from 2.10 to 2.04 cm^2 for standard care	1

(continued)

Table 5. Randomized Controlled Trials Evaluating Adjunctive Therapies for Local Wound Care (continued)

Source	No. Eligible; No. Completed Study; Age[a]	Setting; Length of Follow-up[b]	Pressure Ulcer Severity at Baseline; Intervention[c]	Primary Outcome Measures and Quantitative Estimate of Treatment Effect[d]	Quality of Trial[e]
			Light		
Schubert,[129] 2001	74; 59; ≥65 y	Acute care; ≤10 wk	II or III; monochromatic light plus cadexomer iodine or hydrocolloid[g] vs cadexomer iodine or hydrocolloid	Wound surface area reduction per week of 29.8% for monochromatic light plus cadexomer iodine or hydrocolloid vs 20.0% for cadexomer iodine or hydrocolloid; there was a 49% higher healing rate for monochromatic light (*P* = .05)	2
Wills et al,[130] 1983	18; 16; age range: 62-103 y	Acute care; ≤10 wk	Superficial; UV light[g] vs placebo UV light	Mean time to complete healing of 6.3 wk for superficial UV light vs 8.4 for placebo UV light (*P* < .02)	2
			Hydrotherapy		
Burke et al,[131] 1998	42; 42; NA	Acute care; ≥2 wk	III or IV; moist saline gauze plus whirlpool[g] vs moist saline gauze	Wound surface area: 14 of 24 wounds improved with moist saline gauze plus whirlpool vs 5 of 18 wounds improved with moist saline gauze only (*P* < .05)	2
			Other		
Shamimi et al,[132] 2008	18; 18; mean age: 46 y	Acute care; 4 wk	NA; intravenous semelil[g] vs intravenous normal saline	Mean (SD) reduction in wound surface area of 43.2 (57.4) cm^2 (80.3%) for intravenous semelil vs 2.8 (6.2) cm^2 (6.3%) for intravenous normal saline (*P* < .001)	0
Nussbaum et al,[133] 1994	20; 16; age range: 15-61 y	Rehabilitation[f]; 2-20 wk	NA; laser and standard care[h] vs ultrasound and UV-C plus standard care[g] vs standard care	Mean weekly reduction in wound surface area of 23.7% for laser and standard care vs 53.5% for ultrasound and UV-C plus standard care vs 32.4% for standard care (*P* = .03)	1

Abbreviations: NA, data not available; PSST, Pressure Sore Status Test.
[a] Eligible age to participate in study is provided unless participant age is only available.
[b] Duration of treatment is expressed to nearest week.
[c] 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.
[d] The PSST score range is between 13 and 65 with lower total score indicating better wound appearance. 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; and wound surface area defined as changes of surface area measurements before and after treatment.
[e] 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.
[f] Indicates treatment for spinal cord injuries.
[g] Indicates effective intervention for treatment of pressure ulcers.
[h] Standard care refers to various topical treatments in accordance with the participating institution and/or guidelines.

One study[49] of dressings met 5 of the 6 criteria, 6 studies[31,50,56,69,94,97] of dressings met 4 of the 6 criteria, and 2 studies[33,112] 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.*

Twenty-one RCTs (987 participants) evaluated adjunctive therapies (TABLE 5).[43,47,54,116-133] Among the good-quality RCTs examining adjunctive therapies, there were no benefits to the interventions, which included electric current (vs placebo electric current),[54] laser[127] (vs moist saline gauze), and ultrasound[123] (vs placebo ultrasound).

Two RCTs examined electromagnetic therapy and found improvements in wound healing compared with placebo or standard care,[125,126] but 1 of these RCTs did not report statistical significance.[126] Four trials examined light therapy,[43,128-130] with the highest-quality trial[43] demonstrating no improvement in healing with light therapy compared with placebo therapy.

Two RCTs studied vacuum therapy and found no improvement in wound healing compared with cadexomer iodine, papain-urea-chlorophyllin copper, or moist gauze.[116,117] Of the 21 studies evaluating adjunctive therapies, 5 adequately described the generation of random allocation sequences (23.8%) and 2 provided information indicating that participants were randomized with concealed allocation (9.5%). Thirteen of the studies (61.9%) blinded participants adequately. Adequate blinding of outcome assessors was described in 14 of the 21 studies (66.7%).

Co-interventions were balanced between groups in 16 of the 21 studies (76.2%). Intention-to-treat analyses were performed in only 2 studies (9.5%). None of the 21 studies examining local wound care fulfilled all 6 criteria from the CLEAR NPT checklist. Two studies[54,127] of adjunctive therapies met 5 of the 6 criteria and 1 study[123] met 4 of 6 CLEAR NPT 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[3] are available from the Wound Healing Society (http://www3.interscience.wiley.com/journal/118605275/issue). Management of underlying contributing factors is likely

*References 32, 48, 55, 74, 81, 84, 86-88, 91, 93, 95, 108.

more valuable in treating pressure ulcers than either topical or adjunctive therapies. Thus, priority should be given to addressing underlying causes.[17] 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.[136] 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,[8] venous stasis ulcers,[9] or surgical wounds healing by secondary intention.[11] 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.[17,134,135] Controversy persists in the literature regarding the efficacy and safety of antiseptics (such as povidone-iodine solution).[134,137] Two of the RCTs we examined compared antiseptics with moist dressings.[81,93] 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.[134] 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.[33,112]

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.[138] 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.[139,140] Another systematic review[141] 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[60] 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.[24] The RCTs published after 1992 met many of the CLEAR NPT quality criteria.† Only 22 of the 103 RCTs provided a sample size justification.[29-32,35,39,40,42,44-57] Many negative trials were likely underpowered to detect either clinically important differences or equivalence of the treatments they compared.[25]

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.[142] Similar regulations are in place in other countries.[143] 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.[144]

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.[19] Pressure ulcers may be too complex to successfully treat using a single modality.[145] 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

†References 30, 31, 33, 38, 49, 50, 54, 56, 61, 64, 94, 97, 112, 123, 127.

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.
Analysis and interpretation of data: Reddy, Gill, 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, Molynlycke, and Merck. No other authors reported financial disclosures.
Funding/Support: This work was supported by Canadian Institutes of Health Research Interdisciplinary Capacity Enhancement grant H0A-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, FRCPC (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, 3M, ConvaTec, Molnlycke, Coloplast, Tyco, Johnson & Johnson, and KCI. Dr Black reported being a consultant for Gaymar Industries, HillRom, and Sage Products.

REFERENCES

1. European Pressure Ulcer Advisory Panel. European guidelines for pressure ulcer treatment. http://www.epuap.org/gltreatment.html. Accessed October 29, 2007.
2. Cuddigan J, Frantz RA. Pressure ulcer research: pressure ulcer treatment: a monograph from the National Pressure Ulcer Advisory Panel. *Adv Wound Care*. 1998;11(6):294-300.
3. Whitney J, Phillips L, Aslam R, et al. Guidelines for the treatment of pressure ulcers. *Wound Repair Regen*. 2006;14(6):663-679.
4. Woodbury MG, Houghton PE. Prevalence of pressure ulcers in Canadian healthcare settings. *Ostomy Wound Manage*. 2004;50(10):22-24, 26, 28, 30, 32, 34, 36-38.
5. Brandeis GH, Berlowitz DR, Katz P. Are pressure ulcers preventable? a survey of experts. *Adv Skin Wound Care*. 2001;14(5):244,245-248.
6. Reddy M, Gill SS, Rochon PA. Prevention of pressure ulcers: a systematic review. *JAMA*. 2006;296(8):974-984.
7. Ferrell BA, Josephson K, Norvid P, Alcorn H. Pressure ulcers among patients admitted to home care. *J Am Geriatr Soc*. 2000;48(9):1042-1047.
8. Nelson EA, Bradley M. Dressings and topical agents for arterial leg ulcers. *Cochrane Database Syst Rev*. 2003;1(1):CD001836.
9. Palfreyman SJ, Nelson EA, Lochiel R, Michaels JA. Dressings for healing venous leg ulcers. *Cochrane Database Syst Rev*. 2006;3:CD001103.
10. Adderley U, Smith R. Topical agents and dressings for fungating wounds. *Cochrane Database Syst Rev*. 2007;2(2):CD003948.
11. Vermeulen H, Ubbink D, Goossens A, de Vos R, Legemate D. Dressings and topical agents for surgical wounds healing by secondary intention. *Cochrane Database Syst Rev*. 2004;2(2):CD003554.
12. Reddy M, Cabico L, Rochon P. The prevalence of skin breakdown in long-term care residents when transferred to acute care. *Can J Geriatr*. 2005;8(2):50-54.
13. Kuhn BA, Coulter SJ. Balancing the pressure ulcer cost and quality equation. *Nurs Econ*. 1992;10(5):353-359.
14. Di Giulio P, Saiani L, Laquintana D, et al. A double blind randomised clinical trial to assess the efficacy of the treatments of the superficial pressure sores [in Italian]. *Assist Inferm Ric*. 2004;23(4):201-208.
15. Toba K, Sudoh N, Nagano K, et al. Randomized prospective trial of gentian violet with dibutyryl cAMP and povidone-iodine with sugar as treatment for pressure sores infected with methicillin-resistant *Staphylococcus aureus* in elderly patients [in Japanese]. *Nippon Ronen Igakkai Zasshi*. 1997;34(7):577-582.
16. Als-Nielsen B, Chen W, Gluud C, Kjaergard LL. Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events? *JAMA*. 2003;290(7):921-928.
17. Sibbald RG, Williamson D, Orsted H, et al. Preparing the wound bed-debridement, bacterial balance, and moisture balance. *Ostomy Wound Manage*. 2000;46(11):14-35.
18. Thomas DR, Rodeheaver GT, Bartolucci AA, et al. Pressure ulcer scale for healing: derivation and validation of the PUSH tool. *Adv Wound Care*. 1997;10(5):96-101.
19. Flanagan M. Improving accuracy of wound measurement in clinical practice. *Ostomy Wound Manage*. 2003;49(10):28-40.
20. van Rijswijk L. Full-thickness leg ulcers: patient demographics and predictors of healing. *J Fam Pract*. 1993;36(6):625-632.
21. Lassere MN, Johnson KR, Boers M, et al. Definitions and validation criteria for biomarkers and surrogate endpoints: development and testing of a quantitative hierarchical levels of evidence schema. *J Rheumatol*. 2007;34(3):607-615.
22. Stotts NA, Rodeheaver GT, Thomas DR, et al. An instrument to measure healing in pressure ulcers: development and validation of the pressure ulcer scale for healing (PUSH). *J Gerontol A Biol Sci Med Sci*. 2001;56(12):M795-M799.
23. Bates-Jensen BM, Vredevoe DL, Brecht ML. Validity and reliability of the Pressure Sore Status Tool. *Decubitus*. 1992;5(6):20-28.
24. Boutron I, Moher D, Tugwell P. A checklist to evaluate a report of a nonpharmacological trial (CLEAR NPT) was developed using consensus. *J Clin Epidemiol*. 2005;58(12):1233-1240.
25. Halpern SD, Karlawish JHT, Berlin JA. The continuing unethical conduct of underpowered clinical trials. *JAMA*. 2002;288(3):358-362.
26. National Pressure Ulcer Advisory Panel Support Standards Initiative. Terms and definitions related to support surfaces. http://www.npuap.org/pdf/NPUAP_S3I_TD.pdf. Accessed September 22, 2008.
27. Schaum KD. Special report: payment perspective: pressure-reducing support surfaces. *Ostomy Wound Manage*. 2005;51(2):36,96.
28. van Rijswijk L. Ingredient-based wound dressing classification: a paradigm that is passé and in need of replacement. *J Wound Care*. 2006;15(1):11-14.
29. Groen HW, Groenier KH, Schuling J. Comparative study of a foam mattress and a water mattress. *J Wound Care*. 1999;8(7):333-335.
30. Russell L, Reynolds TM, Towns A, Worth W, Greenman A, Turner R. Randomized comparison trial of the RIK and the Nimbus 3 mattresses. *Br J Nurs*. 2003;12(4):254,256-259.
31. Püllen R, Popp R, Volkers P, Fusgen I. Prospective randomized double-blind study of the wound-debriding effects of collagenase and fibrinolysin/deoxyribonuclease in pressure ulcers. *Age Ageing*. 2002;31(2):126-130.
32. Colin D, Kurring PA, Yvon C. Managing sloughy pressure sores. *J Wound Care*. 1996;5(10):444-446.
33. Rees RS, Robson MC, Smiell JM, Perry BH. Becaplermin gel in the treatment of pressure ulcers: a phase II randomized, double-blind, placebo-controlled study. *Wound Repair Regen*. 1999;7(3):141-147.
34. Guthrie M. A randomized double-blind clinical study of Dermagran dual therapeutic system in the

treatment of decubitus ulcers. *Wounds*. 1988; 1:142-154.
35. Belmin J, Meaume S, Rabus M, Bohbot S. Sequential treatment with calcium alginate dressings and hydrocolloid dressings accelerates pressure ulcer healing in older subjects: a multicenter randomized trial of sequential vs nonsequential treatment with hydrocolloid dressings alone. *J Am Geriatr Soc*. 2002; 50(2):269-274.
36. Day A, Dombranski S, Farkas C, et al. Managing sacral pressure ulcers with hydrocolloid dressings: results of a controlled, clinical study. *Ostomy Wound Manage*. 1995;41(2):52-65.
37. Hondé C, Derks C, Tudor D. Local treatment of pressure sores in the elderly: amino acid copolymer membrane vs hydrocolloid dressing. *J Am Geriatr Soc*. 1994;42(11):1180-1183.
38. Burgos A, Gimenez J, Moreno E, et al. Collagenase ointment application at 24- vs 48-hour intervals in the treatment of pressure ulcers: a randomised multicentre study. *Clin Drug Investig*. 2000;19(6): 399-407.
39. Russell L, Reynolds TM, Carr J, Evans A, Holmes M. Randomised controlled trial of two pressure-relieving systems. *J Wound Care*. 2000;9(2):52-55.
40. Nixon J, Cranny G, Iglesias C, et al. Randomised, controlled trial of alternating pressure mattresses compared with alternating pressure overlays for the prevention of pressure ulcers: PRESSURE (Pressure Relieving Support Surfaces) trial. *BMJ*. 2006;332 (7555):1413-1415.
41. Day A, Leonard F. Seeking quality care for patients with pressure ulcers. *Decubitus*. 1993;6(1): 32-43.
42. Rosenthal MJ, Felton RM, Nastasi AE, Naliboff BD, Harker J, Navach JH. Healing of advanced pressure ulcers by a generic total contact seat: 2 randomized comparisons with low air loss bed treatments. *Arch Phys Med Rehabil*. 2003;84(12): 1733-1742.
43. Dehlin O, Elmstahl S, Gottrup F. Monochromatic phototherapy in elderly patients: a new way of treating chronic pressure ulcers? *Aging Clin Exp Res*. 2003;15(3):259-263.
44. Allman RM, Walker JM, Hart MK, Laprade CA, Noel LB, Smith CR. Air-fluizided beds or conventional therapy for pressure sores: a randomized trial. *Ann Intern Med*. 1987;107(5):641-648.
45. Ferrell BA, Osterweil D, Christenson P. A randomized trial of low-air-loss beds for treatment of pressure ulcers. *JAMA*. 1993;269(4):494-497.
46. Land L, Evans D, Geary A, Taylor C. A clinical evaluation of an alternating-pressure mattress replacement system in hospital and residential care settings. *J Tissue Viability*. 2000;10(1):6-11.
47. Lucas C, van Gemert MJC, de Haan RJ. Efficacy of low-level laser therapy in the management of stage III decubitus ulcers: a prospective, observer-blinded multicentre randomised clinical trial. *Lasers Med Sci*. 2003;18(2):72-77.
48. Müller E, van Leen MW, Bergemann R. Economic evaluation of collagenase-containing ointment and hydrocolloid dressing in the treatment of pressure ulcers. *Pharmacoeconomics*. 2001;19 (12):1209-1216.
49. Sayag J, Meaume S, Bohbot S. Healing properties of calcium alginate dressings. *J Wound Care*. 1996; 5(8):357-362.
50. Graumlich JF, Blough LS, McLaughlin RG, et al. Healing pressure ulcers with collagen or hydrocolloid: a randomized, controlled trial. *J Am Geriatr Soc*. 2003;51(2):147-154.
51. Agren MS, Stromberg H. Topical treatment of pressure ulcers. *Scand J Plast Reconstr Surg*. 1985; 19(1):97-100.
52. Small N, Mulder M, Mackenzie MJ, Nel M. A comparative analysis of pressure sore treatment modalities in community settings. *Curationis*. 2002;25 (1):74-82.
53. Hollisaz MT, Khedmat H, Yari F. A randomized clinical trial comparing hydrocolloid, phenytoin and simple dressings for the treatment of pressure ulcers. *BMC Dermatol*. 2004;4(1):18.
54. Adunsky A, Ohry A. Decubitus direct current treatment (DDCT) of pressure ulcers: results of a randomized double-blinded placebo controlled study. *Arch Gerontol Geriatr*. 2005;41(3):261-269.
55. Kraft MR, Lawson L, Pohlmann B, Reid Lokos C, Barder L. A comparison of Epi-Lock and saline dressings in the treatment of pressure ulcers. *Decubitus*. 1993;6(6):42-48.
56. Subbanna PK, Margaret Shanti FX, Tharion G, et al. Topical phenytoin solution for treating pressure ulcers: a prospective, randomized, double-blind clinical trial. *Spinal Cord*. 2007;45(11):739-743.
57. Sipponen A, Jokinen JJ, Sipponen P, Papp A, Sarna S, Lohi J. Beneficial effect of resin salve in treatment of severe pressure ulcers: a prospective, randomized and controlled multicentre trial. *Br J Dermatol*. 2008; 158(5):1055-1062.
58. Branom R. "Constant force technology" vs low-air-loss therapy in the treatment of pressure ulcers. *Ostomy Wound Manage*. 2001;47(9):38-46.
59. Mulder GD, Taro N, Seeley JE, Andrews K. A study of pressure ulcer response to low air loss beds vs conventional treatment. *J Geriatr Dermatol*. 1994; 2(3):87-91.
60. Evans D, Land L, Geary A. A clinical evaluation of the Nimbus 3 alternating pressure mattress replacement system. *J Wound Care*. 2000;9(4):181-186.
61. Lee SK, Posthauer ME, Dorner B, Redovian V, Maloney MJ. Pressure ulcer healing with a concentrated, fortified, collagen protein hydrolysate supplement: a randomized controlled trial. *Adv Skin Wound Care*. 2006;19(2):92-96.
62. Desneves KJ, Todorovic BE, Cassar A, Crowe TC. Treatment with supplementary arginine, vitamin C and zinc in patients with pressure ulcers: a randomised controlled trial. *Clin Nutr*. 2005;24(6):979-987.
63. Benati G, Delvecchio S, Cilla D, Pedone V. Impact on pressure ulcer healing of an arginine-enriched nutritional solution in patients with severe cognitive impairment. *Arch Gerontol Geriatr*. 2001 (suppl 7):43-47.
64. ter Riet G, Kessels AG, Knipschild PG. Randomized clinical trial of ascorbic acid in the treatment of pressure ulcers. *J Clin Epidemiol*. 1995;48(12): 1453-1460.
65. Myers SA, Takiguchi S, Slavish S, Rose CL. Consistent wound care and nutritional support in treatment. *Decubitus*. 1990;3(3):16-28.
66. Taylor TV, Rimmer S, Day B, Butcher J, Dymock IW. Ascorbic acid supplementation in the treatment of pressure sores. *Lancet*. 1974;2(7880):544-546.
67. Norris JR, Reymolds RE. The effect of oral zinc sulfate therapy on decubitus ulcers. *J Am Geriatr Soc*. 1971;19(9):793-797.
68. Alvarez OM, Fernandez-Obregon A, Rogers RS, Bergamo L, Masso J, Black M. A prospective, randomized, comparative study of collagenase and papain-urea for pressure ulcer debridement. *Wounds*. 2002; 14(8):293-301.
69. Burgos A, Gimenez J, Moreno E, et al. Cost, efficacy, efficiency and tolerability of collagenase ointment vs hydrocolloid occlusive dressing in the treatment of pressure ulcers: a comparative, randomised, multicentre study. *Clin Drug Investig*. 2000;19 (5):357-365.
70. Mulder GD, Altman M, Seeley JE, Tintle T. Prospective randomized study of the efficacy of hydrogel, hydrocolloid, and saline solution-moistened dressings on the management of pressure ulcers. *Wound Repair Regen*. 1993;1(4):213-218.
71. Parish LC, Collins E. Decubitus ulcers: a comparative study. *Cutis*. 1979;23(1):106-110.
72. Amione P, Ricci E, Topo F, et al. Comparison of allevyn adhesive and biatain adhesive in the management of pressure ulcers. *J Wound Care*. 2005; 14(8):365-370.
73. Price P, Bale S, Crook H, Harding KG. The effect of a radiant heat dressing on pressure ulcers. *J Wound Care*. 2000;9(4):201-205.
74. Engdahl E. Clinical evaluation of Debrisan on pressure sores. *Curr Ther Res Clin Exp*. 1980;28(3): 377-380.
75. Brown-Etris M, Milne C, Orsted H, et al. A prospective, randomized, multisite clinical evaluation of a transparent absorbent acrylic dressing and a hydrocolloid dressing in the management of stage II and shallow stage III pressure ulcers. *Adv Skin Wound Care*. 2008;21:160-174.
76. Motta G, Dunham L, Dye T, Mentz J, O'Connell-Gifford E, Smith E. Clinical efficacy and cost-effectiveness of a new synthetic polymer sheet wound dressing. *Ostomy Wound Manage*. 1999;45(10):41,44-49.
77. Seeley J, Jensen JL, Hutcherson J. A randomized clinical study comparing a hydrocellular dressing to a hydrocolloid dressing in the management of pressure ulcers. *Ostomy Wound Manage*. 1999;45 (6):39-47.
78. Darkovich SL, Brown-Etris M, Spencer M. Biofilm hydrogel dressing: a clinical evaluation in the treatment of pressure sores. *Ostomy Wound Manage*. 1990; 29:47-60.
79. Sopata M, Luczak J, Ciupinska M. Effect of bacteriological status on pressure ulcer healing in patients with advanced cancer. *J Wound Care*. 2002; 11(3):107-110.
80. Yastrub DJ. Relationship between type of treatment and degree of wound healing among institutionalized geriatric patients with stage II pressure ulcers. *Care Manag J*. 2004;5(4):213-218.
81. Kim YC, Shin JC, Park CI, Oh SH, Choi SM, Kim YS. Efficacy of hydrocolloid occlusive dressing technique in decubitus ulcer treatment: a comparative study. *Yonsei Med J*. 1996;37(3):181-185.
82. Seaman S, Herbster S, Muglia J, Murray M, Rick C. Simplifying modern wound management for non-professional caregivers. *Ostomy Wound Manage*. 2000;46(8):18-27.
83. Matzen S, Peschcardt A, Alsbjorn B. A new amorphous hydrocolloid for the treatment of pressure sores: a randomised controlled study. *Scand J Plast Reconstr Surg Hand Surg*. 1999;33(1):13-15.
84. Chang KW, Alsagoff S, Ong KT, Sim PH. Pressure ulcers-randomised controlled trial comparing hydrocolloid and saline gauze dressings. *Med J Malaysia*. 1998;53(4):428-431.
85. Thomas DR, Goode PS, LaMaster K, Tennyson T. Acemannan hydrogel dressing vs saline dressing for pressure ulcers: a randomized, controlled trial. *Adv Wound Care*. 1998;11(6):273-276.
86. Colwell JC, Foreman MD, Trotter JP. A comparison of the efficacy and cost-effectiveness of two methods of managing pressure ulcers. *Decubitus*. 1993; 6(4):28-36.
87. Xakellis GC, Chrischilles EA. Hydrocolloid vs saline-gauze dressings in treating pressure ulcers: a cost-effectiveness analysis. *Arch Phys Med Rehabil*. 1992; 73(5):463-469.
88. Brod M, McHenry E, Plasse TF, Fedorczyk D, Trout JR. A randomized comparison of poly-hema and hydrocolloid dressings for treatment of pressure sores. *Arch Dermatol*. 1990;126(7):969-970.
89. Oleske DM, Smith XP, White P, Pottage J, Donovan MI. A randomized clinical trial of two dressing methods for the treatment of low-grade pressure ulcers. *J Enterostomal Ther*. 1986;13(3):90-98.
90. Sebern MD. Pressure ulcer management in home health care: efficacy and cost effectiveness of moisture vapor permeable dressing. *Arch Phys Med Rehabil*. 1986;67(10):726-729.
91. Rhodes RS, Heyneman CA, Culbertson VL, Wilson

SE, Phatak HM. Topical phenytoin treatment of stage II decubitus ulcers in the elderly. *Ann Pharmacother*. 2001;35(6):675-681.
92. Yapucu Günes U, Eser I. Effectiveness of a honey dressing for healing pressure ulcers. *J Wound Ostomy Continence Nurs*. 2007;34(2):184-190.
93. Kaya AZ, Turani N, Akyuz M. The effectiveness of a hydrogel dressing compared with standard management of pressure ulcers. *J Wound Care*. 2005; 14(1):42-44.
94. Gerding GA, Browning JS. Oxyquinoline-containing ointment vs standard therapy for stage I and stage II skin lesions. *Dermatol Nurs*. 1992; 4(5):389-398.
95. Moberg S, Hoffman L, Grennert ML, Holst A. A randomized trial of cadexomer iodine in decubitus ulcers. *J Am Geriatr Soc*. 1983;31(8):462-465.
96. Shamimi NK, Karimian R, Nasli E, et al. Topical application of Semelil (ANGIPARS) in treatment of pressure ulcers: a randomized clinical trial. *DARU*. 2008; 16(suppl 1):54-57.
97. Thomas DR, Diebold MR, Eggemeyer LM. A controlled, randomized, comparative study of a radiant heat bandage on the healing of stage 3-4 pressure ulcers: a pilot study. *J Am Med Dir Assoc*. 2005; 6(1):46-49.
98. Meaume S, Van de Looverbosch D, Heyman H, Romanelli M, Ciangherotti A, Charpin S. A study to compare a new self-adherent soft silicone dressing with a self-adherent polymer dressing in stage II pressure ulcers. *Ostomy Wound Manage*. 2003;49(9):44-51.
99. Kloth LC, Berman JE, Nett M, Papanek PE, Dumit-Minkel S. A randomized controlled clinical trial to evaluate the effects of noncontact normothermic wound therapy on chronic full-thickness pressure ulcers. *Adv Skin Wound Care*. 2002;15(6):270-276.
100. Kuflik A, Stillo JV, Sanders D, Roland K, Sweeney T, Lemke PM. Petrolatum vs resurfix ointment in the treatment of pressure ulcers. *Ostomy Wound Manage*. 2001;47(2):52-56.
101. Whitney JD, Salvadalena G, Higa L, Mich M. Treatment of pressure ulcers with noncontact normothermic wound therapy: healing and warming effects. *J WOCN*. 2001;28(5):244-252.
102. LeVasseur SA, Helme RD. A double-blind clinical trial to compare the efficacy of an active based cream F14001 against a placebo non-active based cream for the treatment of pressure ulcers in a poplulation of elderly subjects. *J Adv Nurs*. 1991;16 (8):952-956.
103. Knudsen L, Sovhoj L, Christensen B. The use of a haemodialysate in the treatment of decubital ulcer: a double-blind randomized clinical study. *Curr Ther Res Clin Exp*. 1982;32(3):498-504.
104. Gerber RM, Van Ort SR. Topical application of insulin in decubitus ulcers. *Nurs Res*. 1979;28(1): 16-19.
105. Van Ort SR, Gerber RM. Topical application of insulin in the treatment of decubitus ulcers: a pilot study. *Nurs Res*. 1976;25(1):9-12.
106. Reichert-Pénétrat S, Barbaud A, Weber M, Schmutz JL. Leg ulcers: allergologic studies of 359 cases [in French]. *Ann Dermatol Venereol*. 1999;126 (2):131-135.
107. Saap L, Fahim S, Arsenault E, et al. Contact sensitivity in patients with leg ulcerations: a North American study. *Arch Dermatol*. 2004;140(10):1241-1246.
108. Nisi G, Brandi C, Grimaldi L, Calabro M, D'Aniello C. Use of a protease-modulating matrix in the treatment of pressure sores. *Chir Ital*. 2005;57(4):465-468.
109. Payne WG, Wright TE, Ochs D, et al. An exploratory study of dermal replacement therapy in the treatment of stage III pressure ulcers. *J Appl Res*. 2004; 4(1):12-23.
110. Mustoe TA, Cutler NR, Allman RM, et al. A phase II study to evaluate recombinant platelet-derived growth factor-BB in the treatment of stage 3 and 4 pressure ulcers. *Arch Surg*. 1994;129(2):213-219.
111. Robson MC, Phillips LG, Thomason A, Robson LE, Pierce GF. Platelet-derived growth factor BB for the treatment of chronic pressure ulcers. *Lancet*. 1992; 339(8784):23-25.
112. Landi F, Aloe L, Russo A, et al. Topical treatment of pressure ulcers with nerve growth factor: a randomized clinical trial. *Ann Intern Med*. 2003; 139(8):635-641.
113. Hirshberg J, Coleman J, Marchant B, Rees RS. TGF-beta3 in the treatment of pressure ulcers: a preliminary report. *Adv Skin Wound Care*. 2001;14 (2):91-95.
114. Robson MC, Hill DP, Smith PD, et al. Sequential cytokine therapy for pressure ulcers: clinical and mechanistic response. *Ann Surg*. 2000;231(4): 600-611.
115. Robson MC, Phillips LG, Lawrence WT, et al. The safety and effect of topically applied recombinant basic fibroblast growth factor on the healing of chronic pressure sores. *Ann Surg*. 1992;216(4): 401-406.
116. Wanner MB, Schwarzl F, Strub B, Zaech GA, Pierer G. Vacuum-assisted wound closure for cheaper and more comfortable healing of pressure sores: a prospective study. *Scand J Plast Reconstr Surg Hand Surg*. 2003;37(1):28-33.
117. Ford CN, Reinhard ER, Yeh D, et al. Interim analysis of a prospective, randomized trial of vacuum-assisted closure vs the healthpoint system in the management of pressure ulcers. *Ann Plast Surg*. 2002; 49(1):55-61.
118. Adegoke BO, Badmos KA. Acceleration of pressure ulcer healing in spinal cord injured patients using interrupted direct current. *Afr J Med Med Sci*. 2001; 30(3):195-197.
119. Wood JM, Evans PE, Schallreuter KU, et al. A multicenter study on the use of pulsed low-intensity direct current for healing chronic stage II and stage III decubitus ulcers. *Arch Dermatol*. 1993;129(8): 999-1009.
120. Griffin JW, Tooms RE, Mendius RA, Clifft JK, Vander Zwaag R, el-Zeky F. Efficacy of high voltage pulsed current for healing of pressure ulcers in patients with spinal cord injury. *Phys Ther*. 1991; 71(6):433-442.
121. Asbjornsen G, Hernaes B, Molvaer G. The effect of transcutaneous electrical nerve stimulation on pressure sores in geriatric patients. *J Clin Exp Gerontol*. 1990;12(4):209-214.
122. Kloth LC, Feedar JA. Acceleration of wound healing with high voltage, monophasic, pulsed current. *Phys Ther*. 1988;68(4):503-508.
123. ter Riet G, Kessels AG, Knipschild P. Randomised clinical trial of ultrasound treatment for pressure ulcers. *BMJ*. 1995;310(6986):1040-1041.
124. McDiarmid T, Burns PN, Lewith GT, Machin D. Ultrasound and the treatment of pressure sores. *Physiotherapy*. 1985;71(2):66-70.
125. Salzberg CA, Cooper-Vastola SA, Perez F, Viehbeck MG, Byrne DW. The effects of non-thermal pulsed electromagnetic energy on wound healing of pressure ulcers in spinal cord-injured patients: a randomized, double-blind study. *Ostomy Wound Manage*. 1995;41(3):42-51.
126. Comorosan S, Vasilco R, Arghiropol M, Paslaru L, Jieanu V, Stelea S. The effect of Diapulse therapy on the healing of decubitus ulcer. *Rom J Physiol*. 1993; 30(1-2):41-45.
127. Taly AB, Sivaraman Nair KP, Murali T, John A. Efficacy of multiwavelength light therapy in the treatment of pressure ulcers in subjects with disorders of the spinal cord: a randomized double-blind controlled trial. *Arch Phys Med Rehabil*. 2004;85(10): 1657-1661.
128. Iordanou P, Baltopoulos G, Giannakopoulou M, Bellou P, Ktenas E. Effect of polarized light in the healing process of pressure ulcers. *Int J Nurs Pract*. 2002; 8(1):49-55.
129. Schubert V. Effects of phototherapy on pressure ulcer healing in elderly patients after a falling trauma: a prospective, randomized, controlled study. *Photodermatol Photoimmunol Photomed*. 2001; 17(1):32-38.
130. Wills EE, Anderson TW, Beattie BL, Scott A. A randomized placebo-controlled trial of ultraviolet light in the treatment of superficial pressure sores. *J Am Geriatr Soc*. 1983;31(3):131-133.
131. Burke DT, Ho CH, Saucier MA, Stewart G. Effects of hydrotherapy on pressure ulcer healing. *Am J Phys Med Rehabil*. 1998;77(5):394-398.
132. Shamimi NK, Heshmat R, Karimian R, et al. Intravenous Semelil (ANGIPARS) as a novel therapy for pressure ulcers: a randomized clinical trial. *DARU*. 2008; 16(suppl 1):49-53.
133. Nussbaum EL, Biemann I, Mustard B. Comparison of ultrasound/ultraviolet-C and laser for treatment of pressure ulcers in patients with spinal cord injury. *Phys Ther*. 1994;74(9):812-823.
134. Banwell H. What is the evidence for tissue regeneration impairment when using a formulation of PVP-I antiseptic on open wounds? *Dermatology*. 2006; 212(suppl 1):66-76.
135. Schultz GS, Sibbald RG, Falanga V, et al. Wound bed preparation: a systematic approach to wound management. *Wound Repair Regen*. 2003;11(suppl 2):S1-S28.
136. Ayello EA, Braden B. How and why to do pressure ulcer risk assessment. *Adv Skin Wound Care*. 2002; 15(3):125-131.
137. Niedner R. Cytotoxicity and sensitization of povidone-iodine and other frequently used anti-infective agents. *Dermatology*. 1997;195(suppl 2): 89-92.
138. Gregor S, Maegele M, Sauerland S, Krahn JF, Peinemann F, Lange S. Negative pressure wound therapy: a vacuum of evidence? *Arch Surg*. 2008; 143(2):189-196.
139. Kranke P, Bennett M, Roeckl-Wiedmann I, Debus S. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev*. 2004;2 (2):CD004123.
140. Roeckl-Wiedmann I, Bennett M, Kranke P. Systematic review of hyperbaric oxygen in the management of chronic wounds. *Br J Surg*. 2005;92(1): 24-32.
141. Cullum N, Nelson EA, Flemming K, Sheldon T. Systematic reviews of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy. *Health Technol Assess*. 2001;5(9):1-221.
142. US Food and Drug Administration. Information from FDA on dressings with drugs (April 1, 2007). http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005. Accessed November 3, 2007.
143. Medicines and Healthcare Products Regulatory Agency. How we regulate. http://www.mhra.gov.uk/Howweregulate/index.htm. Accessed August 18, 2008.
144. De Smet PA. Herbal remedies. *N Engl J Med*. 2002;347(25):2046-2056.
145. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. *J Am Geriatr Soc*. 2007;55(5):780-791.

