Comparative Effectiveness Review
Number 90

Effective Health Care Program

Pressure Ulcer Treatment Strategies: Comparative Effectiveness

Executive Summary

Background

Uninterrupted pressure exerted on the skin, soft tissue, muscle, and bone can lead to the development of localized ischemia, tissue inflammation, shearing, anoxia, and necrosis. Pressure ulcers affect up to three million adults in the United States. Areas of the body prone to the development of pressure ulcers are depicted in Figure A. Estimates of the incidence of pressure ulcers vary according to the setting, with ranges of 0.4 to 38.0 percent in acute care hospitals, 2.2 to 23.9 percent in long-term nursing facilities, and 0 to 17 percent in home care settings.[1,2] The prevalence of pressure ulcers in acute and long-term care settings was 9.2 to 11.1 percent between 1989 and 1995 and 14.7 to 15.5 percent between 1999 and 2005.[3]

Pressure ulcer healing rates—which depend on comorbidities, clinical interventions, and ulcer severity—vary considerably. Ulcer severity is assessed using a variety of different staging or grading systems, but the National Pressure Ulcer Advisory Panel (NPUAP) staging system is the most commonly used (Figure B). Comorbidities predisposing toward pressure ulcer development and affecting ulcer healing include those affecting patient mobility (e.g., spinal cord injury), wound environments (e.g., incontinence), and wound healing (e.g., diabetes and vascular disease). Delayed healing can add to the length of hospitalization and impede return to full

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm**.

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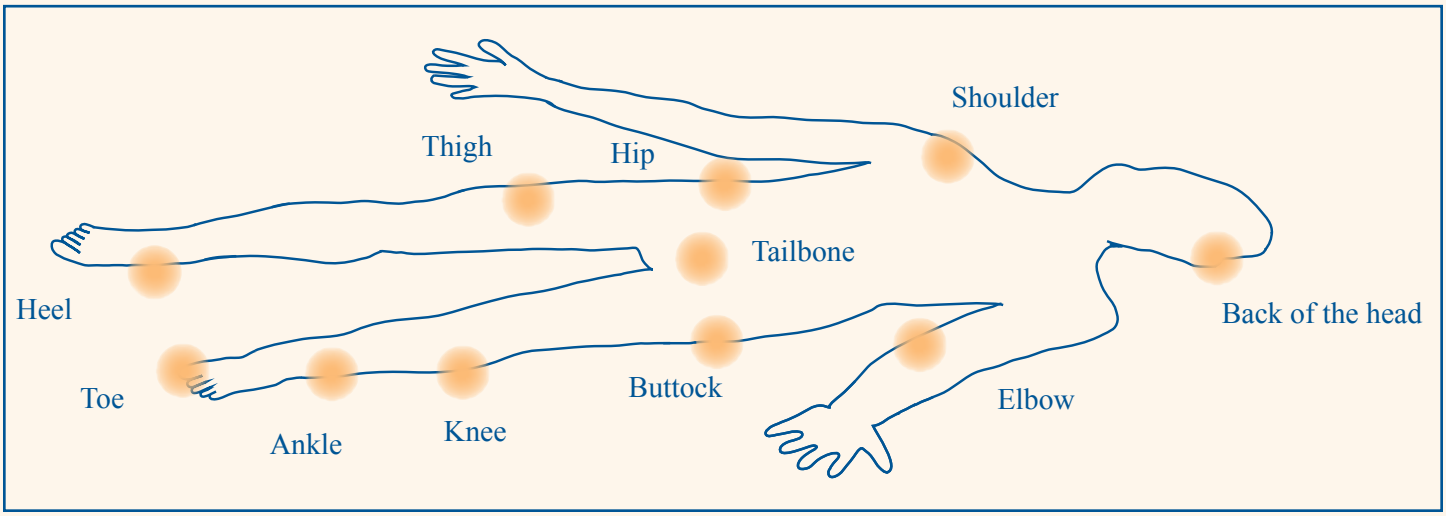
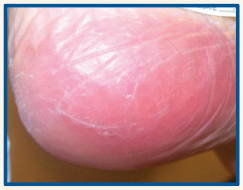
Figure A. Common pressure ulcer sites



Oregon EPC

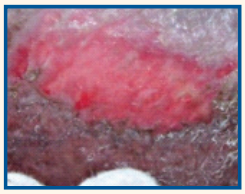
Figure B. National Pressure Ulcer Advisory Panel pressure ulcer stages/categories

Stage: I



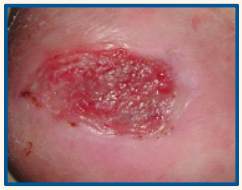
Intact skin with non-blanchable redness of a localized area usually over a bony prominence. Darkly pigmented skin may not have visible blanching; its color may differ from the surrounding area.

Stage: II



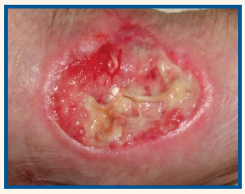
Partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or open/ruptured serum-filled blister.

Stage: III



Full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon or muscles are not exposed. Slough may be present but does not obscure the depth of tissue loss. May include undermining and tunneling.

Stage: IV



Full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present on some parts of the wound bed. Often includes undermining and tunneling.

Suspected Deep Tissue Injury[a]

Purple or maroon localized area of discolored intact skin or blood-filled blister due to damage of underlying soft tissue from pressure and/or shear. The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer or cooler as compared to adjacent tissue.

Unstageable[a]

Full thickness tissue loss in which the base of the ulcer is covered by slough (yellow, tan, gray, green or brown) and/or eschar (tan, brown or black) in the wound bed.

[a]Not pictured.

functioning.[2] Data on the costs of treatment vary, but some estimates range between $37,800 and $70,000 per ulcer, with total annual costs for pressure ulcers in the United States as high as $11 billion.[1,4] Prevalence of pressure ulcers is used as an indicator of quality for long-term care facilities, and progression of pressure ulcers in hospitalized patients is often considered an avoidable complication representing failure of inpatient management.

Given the negative impact pressure ulcers have on health status and patient quality of life, as well as health care costs, treatments are needed that promote healing, shorten healing time, and minimize the risk of complications. Pressure ulcer treatment involves a variety of different approaches, including interventions to treat the conditions that give rise to pressure ulcers (support surfaces and nutritional support); interventions to protect and promote healing of the ulcer (wound dressings, topical applications, and various adjunctive therapies, including vacuum-assisted closure, ultrasound therapy, electrical stimulation, and hyperbaric oxygen therapy); and surgical repair of the ulcer.[1,4] Most ulcers are treated using a combination of these approaches. Standards of care for pressure ulcer treatment are typically guided by clinical practice guidelines, such as those developed by NPUAP, but also are informed by patient-related factors such as comorbidities and nutritional status,[5] local practice patterns, and the stage and features of the wound. Current guidelines primarily reflect expert opinions. An examination of the comparative effectiveness and harms of different therapies and approaches to treating pressure ulcers is important to guide clinical practice.

Scope and Key Questions

The following Key Questions are the focus of our report.

Key Question 1. In adults with pressure ulcers, what is the comparative effectiveness of treatment strategies for improved health outcomes, including but not limited to: complete wound healing, healing time, reduced wound surface area, pain, and prevention of serious complications of infection?

Key Question 1a. Does the comparative effectiveness of treatment strategies differ according to features of the pressure ulcers, such as anatomic site or severity at baseline?

Key Question 1b. Does the comparative effectiveness of treatment strategies differ according to patient characteristics, including but not limited to: age, race/ethnicity, body weight, specific medical comorbidities, and known risk factors for pressure ulcers, such as functional ability, nutritional status, or incontinence?

Key Question 1c. Does the comparative effectiveness of treatment strategies differ according to patient care settings, such as home, nursing facility, or hospital, or according to features of patient care settings, including but not limited to nurse/patient staffing ratio, staff education and training in wound care, the use of wound care teams, and home caregiver support and training?

Key Question 2. What are the harms of treatments for pressure ulcers?

Key Question 2a. Do the harms of treatment strategies differ according to features of the pressure ulcers, such as anatomic site or severity at baseline?

Key Question 2b. Do the harms of treatment strategies differ according to patient characteristics, including age, race/ethnicity, body weight, specific medical comorbidities, and known risk factors for pressure ulcers, such as functional ability, nutritional status, or incontinence?

Key Question 2c. Do the harms of treatment strategies differ according to patient care settings, such as home, nursing facility, or hospital, or according to features of patient care settings, including but not limited to nurse/patient staffing ratio, staff education and training in wound care, the use of wound care teams, and home caregiver support and training?

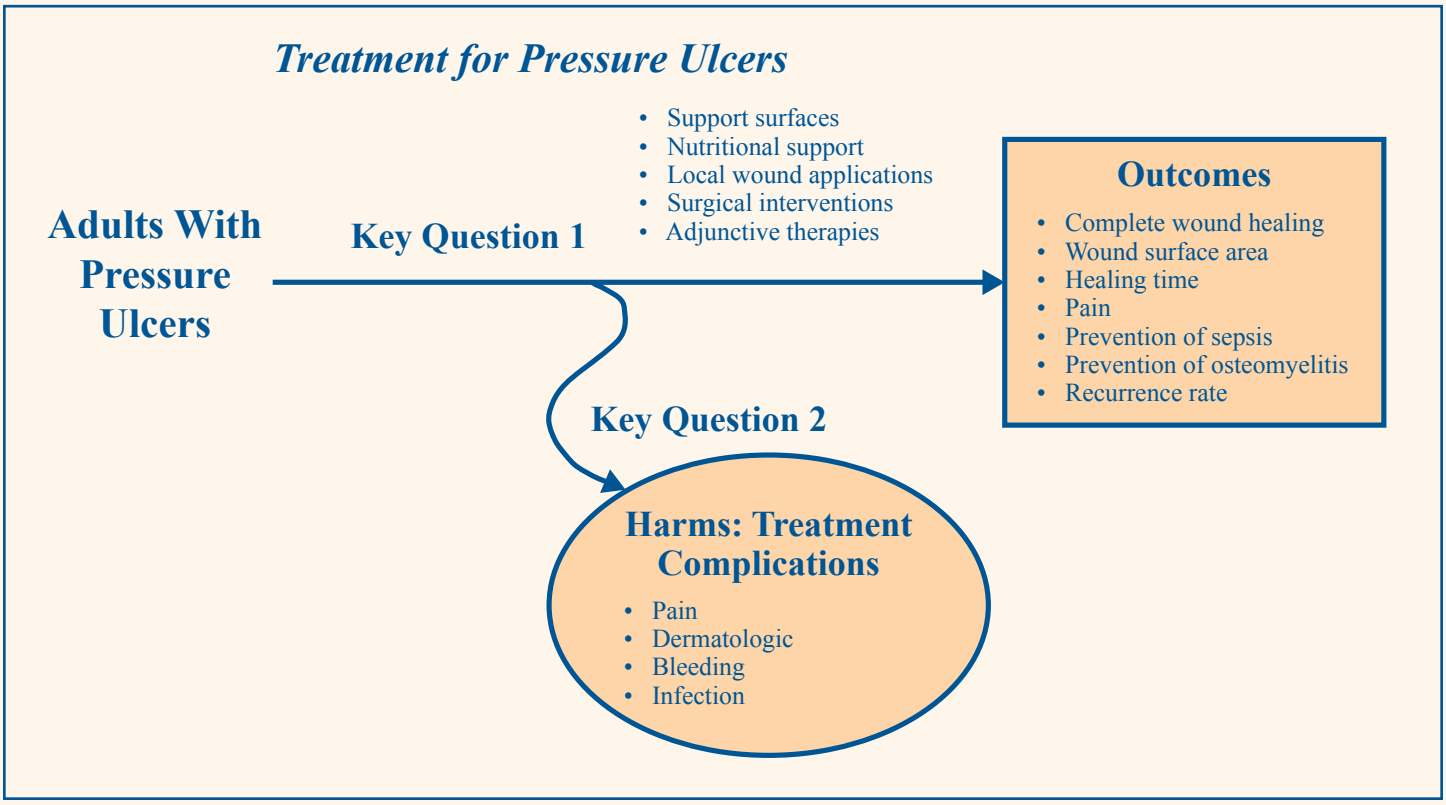
Analytic Framework

The analytic framework (Figure C) depicts the Key Questions and the population, interventions, outcomes, and harms considered in the review.

Population and Conditions of Interest

The population studied was adults ages 18 and older with a pressure ulcer. Patients with pressure ulcers usually also have limited or impaired mobility and suffer from other chronic illnesses. Pressure ulcers are most common in the elderly or people with spinal cord injuries or other conditions that restrict mobility. Patients with nonpressure-related ulcers, including but not limited to venous ulcers and diabetic foot ulcers, were excluded because treatment considerations for these patients may differ significantly from those for pressure ulcers. A systematic review of treatment for chronic venous ulcers, sponsored by the Agency for Healthcare Research and Quality (AHRQ),

Figure C. Analytic framework: pressure ulcer treatment strategies



is in progress. We excluded children because this topic was originally nominated and scoped for adults[a]. Key Informants agreed with the broadly defined proposed population of interest, but they also noted that "adults with pressure ulcers" is a heterogeneous group and that variability in the comparative effectiveness of pressure ulcer treatments may be related to a large number of patient characteristics. In addition to age, sex, race/ethnicity, socioeconomic status, and diverse specific medical comorbidities (e.g., diabetes, end-stage renal disease, dementia), many Key Informants suggested that we include specific known risk factors for pressure ulcers (e.g., nutritional status, incontinence, peripheral vascular disease, mobility limitations, and functional ability).

Interventions and Comparators

Various treatment strategies for pressure ulcers were reviewed, including but not limited to therapies that address the underlying contributing factors (e.g., support surfaces and nutritional supplements), therapies that address local wound care (e.g., wound dressings, topical therapies, and biological agents), surgical repair, and adjunctive therapies (e.g., electrical stimulation). The comparative effectiveness and harms of other interventions (e.g., repositioning, wound debridement, and wound cleansing) were considered but not reviewed, based on input from the Technical Expert Panel (TEP) that these modalities either were considered standard care or lacked comparative studies.

Combined treatment modalities (cointerventions), such as comparison of two treatments in combination compared with a single treatment, were also evaluated.

Comparators included placebo or active control, usual care, and other interventions. In some cases, particularly in older studies, newer interventions were compared with older ones that might no longer be considered standard care in the field. However, in many care settings these applications (e.g., gauze dressings, standard hospital beds) are still used, and we therefore included studies using those types of comparators because of their continued relevance in some treatment settings.

Outcomes

The most commonly examined outcomes were measures of wound improvement. Some studies examined complete

[a]Although treatment approaches for children with pressure ulcers may be similar to those for adults, other factors may influence the effectiveness differently in this population, including setting, caregiver attention, healing potential, and comorbidities.

wound healing as the primary outcome, although many studies evaluated wound size reduction. Based on input from the TEP, we considered complete wound healing to be the principal health outcome of interest. However, we also considered other indicators of "wound improvement" in synthesizing evidence. Notably, many studies reported findings in terms of wound size reduction rather than complete wound healing. We considered wound size reduction to be an important outcome for two reasons. First, it represents a necessary intermediate step toward the principal outcome of complete wound healing: that is, complete wound healing can be considered 100-percent wound size reduction. Second, the likelihood of complete wound healing is lower for larger or higher stage ulcers, and therapies deployed for more advanced ulcers may not be expected to achieve complete wound healing over the course of several weeks, which was the duration of most of the studies in our review. Thus, in summarizing the evidence about a given treatment, we considered wound size reduction to be part of the continuum of wound healing. Some studies used composite outcome measures commonly employed to monitor pressure ulcer status. The Pressure Ulcer Scale for Healing (PUSH) tool combines wound surface area, amount of wound exudate, and tissue appearance.[6] The Pressure Sore Status Tool (PSST) considers multiple ulcer characteristics, including dimensions, exudate, and tissue appearance.[7] Other studies reported outcomes in terms of wound healing rate. We included these outcomes, when reported in studies, as indicators of "wound improvement" but prioritized findings for complete wound healing, as noted above, based on input from the TEP. Other outcomes included pain and avoidance of serious complications of infection. For harms of treatment, we evaluated pain, dermatologic complications, bleeding, infection, and other adverse outcomes as reported in included studies.

Timing

We did not apply minimum followup duration for studies.

Setting

Settings were patient care settings, including home, nursing facility, or hospital.

Methods

The methods for this Comparative Effectiveness Review (CER) follow the methods suggested in the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews"[8] and the standards suggested by the Institute of Medicine for conducting systematic reviews.[9]

Topic Refinement and Review Protocol

The Key Questions for this CER were developed with input from Key Informants, representing clinicians, wound care researchers, and patient advocates. The Key Informants helped refine Key Questions, identify important methodological and clinical issues, and define parameters for the review of evidence. The revised Key Questions were then posted to the AHRQ public Web site for a 4-week comment period. AHRQ and the Evidence-based Practice Center (EPC) agreed on the final Key Questions after reviewing public comments and receiving additional input from a TEP convened for this report. TEP members were selected to provide high-level content and methodological expertise throughout the development of the review, and the TEP consisted of a multidisciplinary group of clinicians, researchers, and patient advocates with expertise in pressure ulcer treatment and research. TEP members disclosed all financial or other conflicts of interest prior to participation. The AHRQ Task Order Officer and the authors reviewed the disclosures and determined that the panel members had no conflicts of interest that precluded participation. The protocol for the CER was reviewed by the TEP and is available from the AHRQ Web site: (www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=838&pageaction=displayproduct).

Search Strategy

The primary literature search was conducted through June 2012 in MEDLINE® (Ovid), Embase (Elsevier), CINAHL (EBSCOhost), EBM Reviews (Ovid), Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and Health Technology Assessment. (See Appendix A of the full report for details.) The most relevant evidence about modalities and procedures currently used for treating pressure ulcers is found in studies conducted within the last 25 years. For this reason we set the search start date at 1985. This decision was affirmed by the Key Informants and TEP. Gray literature was identified by soliciting stakeholders, TEP recommendations, and searching relevant Web sites, including clinical trial registries (ClinicalTrials.gov, Current Controlled Trials, ClinicalStudyResults.org, and the World Health Organization International Clinical Trials Registry Platform), regulatory documents (Drugs@FDA and Devices@FDA), conference

proceedings and dissertations (Conference Papers Index [ProQuest CSA]), Scopus (Elsevier), Dissertations & Theses (ProQuest UMI), and individual product Web sites. An additional focused search strategy on hyperbaric oxygen for the treatment of pressure ulcers was conducted at the recommendation of the TEP due to the paucity of evidence for this treatment obtained from the original search. Scientific information packets (SIPs) were requested from identified drug and device manufacturers, and a notice inviting submission of relevant scientific information was published in the "Federal Register" in an effort to identify any relevant unpublished literature that may contribute to the body of evidence. All interested parties had the opportunity to submit data for this review using the AHRQ Effective Health Care publicly accessible online SIP portal (effectivehealthcare.ahrq.gov/index.cfm/submit-scientific-information-packets/). Reviewers evaluated the SIPs received for data relevant to our review.

Additional studies were identified by reviewing the reference lists of published clinical trials, systematic reviews, and review articles.

Inclusion and Exclusion Criteria

The criteria for inclusion and exclusion of studies were based on the Key Questions and the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) approach. We used the following inclusion criteria. (See Appendix B of the full report for details.)

Populations: Studies were limited to subject populations of adults ages 18 years and older being treated for existing pressure ulcers. Subgroups were defined by age, sex, race/ethnicity, socioeconomic status, and diverse specific medical comorbidities (e.g., diabetes, end-stage renal disease, and dementia), as well as patients with specific known risk factors for pressure ulcers (e.g., nutritional status, incontinence, peripheral vascular disease, mobility limitations, and functional ability). Studies conducted in populations including children, adolescents, and patients with nonpressure-related ulcers (including but not limited to venous ulcers and diabetic foot ulcers) were excluded because treatment considerations for these patients may differ significantly from those for adults with pressure ulcers.

Interventions: For efficacy and effectiveness assessments, all studies of interventions for treatment of pressure ulcers meeting the requirements of the PICOTS and Key Questions were included. Treatments for pressure ulcers included but were not limited to support surfaces, nutritional supplementation, wound dressings, topical therapies, biological agents, and surgical repair. Adjunctive therapies included electrical stimulation, electromagnetic therapy, ultrasound, negative pressure wound therapy, light therapy, laser therapy, hydrotherapy, and hyperbaric oxygen therapy.

Comparators: Comparators included usual care, placebo or sham treatment, no treatment, and different treatment interventions. Studies that did not have a comparator were not considered in our evaluation of comparative effectiveness. They were included for the assessment of harms if they reported on harms of treatments for which data on comparative effectiveness were available in other studies.

Outcomes: Studies reporting clinical outcomes of complete wound healing, wound size (surface area, volume, depth) reduction, pain, prevention of sepsis, prevention of osteomyelitis, recurrence rate, and harms of treatment (including but not limited to pain, dermatologic complications, bleeding, and infection) were included. Studies of nonpressure-related ulcers were not included. We excluded studies that evaluated only nonclinical outcomes, including ease of use, comfort, or nursing time required to administer the intervention.

Timing: No minimum followup time was required. We limited our search to publications and investigations conducted from 1985 to June 2012.

Setting: We included studies conducted in patient-care settings such as home, nursing facility, or hospital. We excluded studies in hospice settings if complete wound healing was not an outcome measured.

Study Design: We included randomized trials, cohort studies, and case-control studies pertinent to all Key Questions. If such studies were not available, we included cross-sectional studies and intervention series studies. Systematic reviews were used as background information or to ensure completeness of the literature search. Case studies of only one patient were not included.

For studies of surgical interventions, we initially planned to include controlled trials, observational studies with at least two comparison groups, and noncomparative intervention series only if they were multicenter series with a population of 100 patients or more. An initial scan of the literature, however, revealed that studies of surgical interventions revealed primarily small series of specific surgical techniques performed at single centers. Because surgical outcomes are heavily influenced by individual surgeons, local practice patterns, and other contextual factors, the TEP raised concern that data from these small ($n < 50$) single-site studies would have limited generalizability and that they would not provide a sound

basis for making indirect comparisons across studies. We therefore excluded small ($n < 50$) single-site studies reporting the results of specific surgical techniques for pressure ulcer management but expanded our inclusion criteria to include single-center intervention series reporting a large series ($n \geq 50$) of patients undergoing surgery for pressure ulcer. We included studies of any size that provided direct head-to-head comparisons of different surgical techniques.

Non–English-language studies were included in the abstract triage, but translation for full-text review was not feasible. In an effort to identify any relevant unpublished literature that may contribute to the body of evidence, gray literature, including unpublished data, abstracts, dissertations, and SIPs, were reviewed to determine if they added additional and meaningful data beyond the literature included in this review and should also be included.

Study Selection

To calibrate reviewer agreement and consistency in study selection, kappa values were calculated to estimate inter-reviewer reliability. After reconciling disagreements between reviewers, this process was repeated with additional sets of studies until a kappa value of greater than 0.50 for each pair of reviewers was reached. The remaining references were evaluated at the title and abstract level for inclusion, using the pre-established inclusion/exclusion criteria to determine eligibility for inclusion in the evidence synthesis. Excluded titles were reviewed again by a senior investigator/clinician for accuracy. All citations included by one or both of the reviewers were retrieved for full-text review.

Full-text articles were independently reviewed by two team members and included when consensus occurred between the reviewers. If consensus was not reached by the two initial reviewers, a senior investigator reviewed the article and adjudicated the decision on inclusion or exclusion.

Data Extraction

Data from included studies were extracted into evidence tables and entered into electronic databases using Microsoft Excel® and DistillerSR systematic review software. The data extracted into evidence tables included study design; year, setting, duration, and study inclusion and exclusion criteria; population and clinical characteristics, including sex, age, ethnicity, comorbidities, functional ability, and ulcer stage; intervention characteristics; results for each outcome of interest; and withdrawals due to adverse events. Outcomes of interest for effectiveness were wound improvement, as determined by complete wound healing, healing rate or time, or reduction in wound size (surface area, volume, depth); reduction in pain; prevention of serious complications of infection such as sepsis or osteomyelitis; and ulcer recurrence rates. Outcomes of interest for harms were pain; dermatologic reactions; bleeding; and complications, including but not limited to infection and need for surgical intervention. Data on settings included patient-care settings such as long-term care or nursing facility, hospital, and community. If available, we also extracted the number of patients randomized relative to the number of patients enrolled, how similar those patients were to the target population, and the funding source. Noncomparative observational studies were included if they evaluated harms of treatments for which comparative effectiveness evidence was available in other studies. These noncomparative observational studies were used for Key Question 2 (evaluation of harms) and were rated for study quality but were not formally extracted into evidence tables due to the paucity of data they contained. We recorded intention-to-treat results when available. All summary measure data were collected as available and presented in the individual studies, including but not limited to percentage of complete wound healing, relative risk and risk ratios, confidence intervals, and significance values. A second team member verified all study data extraction for accuracy and completeness.

One challenge in extracting data from pressure ulcer studies is that various systems have been used to assess the severity of pressure ulcers. Most use a four-stage categorization, with higher numbers indicating higher severity.[10] In 2007 NPUAP redefined their four-stage classification system that defines the pressure ulcer based on depth and tissue involvement (Figure B). Stage I is defined as superficial erythema, stage II as partial thickness ulceration, stage III as full thickness ulceration, and stage IV as full thickness with involvement of muscle and bone. A corresponding four-stage classification system was adopted by the European Pressure Ulcer Advisory Panel (EPUAP). Given that the stages are based on depth and tissue involvement, when an ulcer has overlying purulent material or eschar prohibiting the ability to determine the depth or extent of tissue involvement, it is classified as unstageable, or stage X. Discolored localized areas of intact skin that may indicate pressure-related injury to subcutaneous tissue are categorized as suspected deep tissue injuries. The most commonly used systems to classify pressure ulcers prior to adapting the NPUAP system are reviewed in Appendix C of the full report and aligned with the current corresponding NPUAP stage.

In order to allow comparability across studies, we extracted the stage or grade reported but used the corresponding NPUAP stage in summary tables and text when possible.

Quality Assessment of Individual Studies

In this report, risk of bias is denoted as quality, with the following summary categories:

- Good quality is defined as a low risk of bias.
- Fair quality is defined as a moderate risk of bias.
- Poor quality is defined as a high risk of bias.

Using predefined criteria to assess the quality of controlled trials and observational studies at the individual study level, we adapted criteria from methods proposed by Downs and Black[11,12] (observational studies) and methods developed by the U.S. Preventive Services Task Force.[12,13]

We rated the quality of each controlled trial based on the methods described in the published reports about randomization and allocation concealment; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; the use of intention-to-treat analysis; and ascertainment of outcomes.[12] Individual studies were rated as "good," "fair," or "poor."

Studies rated "good" have the least risk of bias, and results are considered valid. Good-quality studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates and clear reporting of dropouts; appropriate means for preventing bias; and appropriate measurement of outcomes.

Studies rated "fair" do not meet all the criteria for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The fair-quality category is broad, and studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid.

Studies rated "poor" have significant flaws that imply biases of various types that may invalidate the results. They have a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of these studies are at least as likely to reflect flaws in the study design as they are to reflect the true differences between the interventions that were compared. We did not exclude studies rated poor quality a priori, but poor-quality studies were considered to be less valid than higher quality studies when synthesizing the evidence, particularly when discrepancies between studies were present.

Data Synthesis

Due to the heterogeneity of outcomes reported and the limited number and quality of studies for specific treatment comparisons, quantitative analysis was not appropriate for most bodies of literature included in this review. For most comparisons, we synthesized data qualitatively.

We evaluated the appropriateness of meta-analysis based on clinical and methodological diversity of studies and statistical heterogeneity. We conducted meta-analysis in selected instances (when the number, quality, and homogeneity of studies permitted) for comparisons examining the outcome of complete wound healing. We chose to limit meta-analysis to the outcome of complete wound healing because of (a) wide variability in the measurement of other outcomes, including wound size reduction, and (b) indication from the TEP that complete wound healing was the principal health outcome of interest. When meta-analysis was conducted, we used relative risk as the effect measure. We assessed the presence of statistical heterogeneity among the studies using standard χ^2 tests and the magnitude of heterogeneity using the I^2 statistic.[14] We used random-effects models to account for variation among studies[15] and fixed-effects Mantel-Haenszel models when variation among studies was estimated to be zero. Sensitivity analysis was conducted to assess the impact of quality on combined estimates, and metaregression was conducted to assess the association of effect measure with study duration. However, exploration of heterogeneity was typically limited by the small number of studies for each treatment category. All quantitative analyses were performed using Stata 11.0® (StataCorp, College Station, Texas, 2009).

Strength of the Body of Evidence

Within each Key Question, we graded the strength of evidence for effectiveness and for harms by intervention/comparator pair, and for harms by intervention, using an approach adapted from the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[8] Our approach considers four major categories to rate the strength of evidence:

- Quality of studies (good, fair, or poor)
- Consistency (low, moderate, or high)

- Directness (direct or indirect)
- Precision (low, moderate, or high).

As with our ratings of individual study quality, we used the term "quality" in lieu of "risk of bias" in rating the overall strength of evidence of a given finding. Good quality is defined as low risk of bias, fair quality is defined as moderate risk of bias, and poor quality is defined as high risk of bias. Our ratings for consistency and precision were trichotomous (low, moderate, high) rather than dichotomous (consistent vs. inconsistent, precise vs. imprecise) to allow for a more graded assessment of those domains.

We did not incorporate the domain of "dose-response association" into our strength-of-evidence ratings because few, if any, studies in our review included varying levels of exposure. We also did not include the domain "plausible confounding that would decrease observed effect" because this domain is relevant primarily for observational studies and nearly all of our findings were based on the results of clinical trials. We considered "strength of association" in rating strength of evidence but did not assign explicit scores for strength of association in the strength-of-evidence ratings due to variability in strength of association for the different measures of wound improvement used across studies.

We were not able to assess publication bias using a quantitative approach for most treatments because, in many instances, we were not able to perform a formal pooled analysis due to the heterogeneity of interventions, comparators, or outcomes, or due to the poor quality of studies. We evaluated the possibility of publication bias by qualitatively examining the directionality of study findings by sample size for a given intervention and by looking for unpublished studies through the gray literature search.

The strength of evidence was assigned an overall grade of high, moderate, low, or insufficient according to a four-level scale:

- High—High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate—Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low—Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- Insufficient—Evidence either is unavailable or does not permit a conclusion.

Applicability

Applicability is "the extent to which the effects observed in published studies are likely to reflect the expected results when a specific intervention is applied to the population of interest under 'real-world' conditions."[16] We developed our review to provide evidence that might be useful to clinicians, policymakers, patients, and other decisionmakers interested in pressure ulcer treatment. Applicability depends on context, and there is no generally accepted universal rating system for it. We described features of the included studies that are relevant to applicability in terms of the PICOTS elements. These elements are the features embedded in the Key Questions that inform clinical decisionmaking and the degree to which the evidence is likely to pertain to the subpopulations. For example, it is important to determine whether techniques described in studies are representative of current practice. We extracted from studies included in our review key information that might affect applicability of findings, including characteristics of ulcers (e.g., stage), populations (e.g., spinal-cord–injured patients), study duration, cointerventions, comparators, and care setting. We based our approach to applicability on the guidance described by Atkins and colleagues.[12,16]

Peer Review

Experts in prevention and management of pressure ulcers, geriatric medicine, wound care research, and epidemiology, as well as individuals representing important stakeholder groups, were invited to provide external peer review of this CER. The AHRQ Task Order Officer and a designated EPC associate editor also provided comments and editorial review. To obtain public comment, the draft report was posted on the AHRQ Web site for 4 weeks. A disposition-of-comments report detailing the changes made to address the public and peer review comments will be made available 3 months after the Agency posts the final CER on the AHRQ Web site.

Results

Searches of databases, reviews of reference lists of published studies, and reviews of gray literature resulted in 7,274 potentially relevant articles. After dual review of abstracts and titles, 1,836 articles were selected for full-text review. Gray literature was assessed but did not meet the inclusion criteria for this report or provide data that were not already available in the peer-reviewed literature.

One hundred seventy-four studies (with results published in 182 full-text articles) were included in this review. These studies examined a wide range of interventions, but sample sizes often were small. We found moderate-strength evidence that some interventions improved healing of pressure ulcers, but no interventions were found to be effective with a high strength of evidence. Several other interventions had limited evidence of effectiveness (strength of evidence rated as low). A minority of studies examined complete wound healing as an outcome. In general, the evidence about the harms of any of these treatments was limited.

Overall Effectiveness of Pressure Ulcer Treatment

Pressure ulcer treatment encompasses numerous intervention strategies: alleviating the conditions contributing to ulcer development (support surfaces, repositioning, nutritional support); protecting the wound from contamination, creating a clean wound environment, and promoting tissue healing (local wound applications, debridement, wound cleansing, various adjunctive therapies); and surgically repairing the wound. We evaluated evidence addressing the comparative effectiveness and harms in treatment categories for which significant uncertainty exists about the best therapeutic options. Results for each Key Question are presented within the following specific treatment categories: support surfaces, nutrition, local wound applications (including wound dressings, topical therapies, and biological agents), surgical interventions, and adjunctive therapies. Although we evaluated multiple outcomes, only measures of wound improvement (complete wound healing, wound size reduction, healing rate) were consistently reported. Other outcomes, including pain, were reported sporadically. Ulcer recurrence was used as an outcome in some studies of surgery and is reported in the sections of this report covering those studies. Prevention of serious infectious complications was not reported as an outcome in any included study. There was no body of literature from which it was possible to synthesize evidence for the impact of a given intervention on outcomes other than wound improvement. In reporting results of wound improvement, when a body of literature allowed conclusions about a particular measure of wound improvement (e.g., complete wound healing), we report those findings. In many cases, however, the use of different measures of wound improvement allowed us to report only on the overall effect of an intervention on wound improvement, which included complete wound healing, wound size reduction, and healing rates.

The overall findings of this review and a summary of the strength of the evidence for the key findings are presented in Table A.

Table A. Summary of evidence: impact of pressure ulcer treatment strategies on wound improvement and harms

Key Question and Treatment Strategy	Strength of Evidence	Conclusion
Key Question 1. In adults with pressure ulcers, what is the comparative effectiveness of treatment strategies for improved health outcomes, including but not limited to: complete wound healing, healing time, reduced wound surface area, pain, and prevention of serious complications of infection?		
	Support	
Air-fluidized beds	Moderate	Air-fluidized beds produced better healing in terms of reduction in ulcer size compared with other surfaces (5 studies conducted in the late 1980s and 1990s).
Alternating pressure beds	Moderate	Complete wound healing and reduction in ulcer size were similar across different brands and types of alternating pressure beds (4 studies).
Alternating pressure beds compared with other surfaces	Low	Wound improvement was similar for alternating pressure beds when compared with air, fluid, or standard beds (4 studies).
Alternating pressure chair cushions	Insufficient	Evidence about alternating pressure chair cushions did not permit conclusions due to differences in the patient populations studied (2 studies).
Low-air-loss beds	Low	Wound improvement was similar for low-air-loss beds compared with foam surfaces (4 studies) and for low-air-loss beds compared with low-air-loss bed overlays (1 study).

Table A. Summary of evidence: impact of pressure ulcer treatment strategies on wound improvement and harms (continued)		
Key Question and Treatment Strategy	**Strength of Evidence**	**Conclusion**
Key Question 1. In adults with pressure ulcers, what is the comparative effectiveness of treatment strategies for improved health outcomes, including but not limited to: complete wound healing, healing time, reduced wound surface area, pain, and prevention of serious complications of infection? (continued)		
Nutrition		
Protein-containing nutritional supplements	Moderate	When used in addition to other measures for treating pressure ulcers, protein-containing nutritional supplementation resulted in wound improvement (12 studies).
Vitamin C	Low	Vitamin C used as a single nutritional supplement did not result in wound improvement (1 study).
Zinc	Insufficient	The evidence did not allow conclusions as to whether zinc supplementation improves pressure ulcer healing (1 study).
Local Wound Applications		
Hydrocolloid dressings compared with conventional care	Low	Wound improvement was superior with hydrocolloid compared with gauze dressings (10 studies).
Hydrocolloid compared with foam	Moderate	Wound improvement was equivalent with hydrocolloid and foam dressings (8 studies).
Comparisons of different wound dressings	Insufficient	Evidence regarding the comparative effectiveness of hydrogel (compared with standard care or other dressing types; 7 studies), transparent film (4 studies), silicone (2 studies), and alginate dressings (1 study) was inconclusive due to limitations in the number, size, and quality of studies.
Radiant heat compared with other dressings (healing rate)	Moderate	Radiant heat dressings produced more rapid wound healing rates than other dressings for stage III and IV ulcers (4 studies).
Radiant heat compared with other dressings (complete wound healing)	Moderate	Radiant heat dressings were similar to other dressings in terms of complete wound healing of stage III and IV ulcers (4 studies).
Debriding enzymes compared with dressings or other topical therapies	Insufficient	Evidence about the effectiveness of collagenase and other debriding enzymes was inconclusive due to differences in the enzymes studied and outcomes measured (5 studies).
Dextranomer paste compared with wound dressings	Low	Dextranomer paste was inferior to wound dressings (alginate, hydrogel) in promoting wound area reduction (2 studies).
Topical collagen compared with hydrocolloid dressings or standard care	Low	Wound improvement was similar with topical collagen applications compared with hydrocolloid dressings or standard care (3 studies).
Topical phenytoin	Insufficient	Three studies of the effectiveness of topical phenytoin used different comparators and produced inconsistent results.
Maggot therapy	Insufficient	Evidence about the effectiveness of maggot therapy was inconclusive due to poor study quality (3 studies).

Table A. Summary of evidence: impact of pressure ulcer treatment strategies on wound improvement and harms (continued)		
Key Question and Treatment Strategy	**Strength of Evidence**	**Conclusion**
Key Question 1. In adults with pressure ulcers, what is the comparative effectiveness of treatment strategies for improved health outcomes, including but not limited to: complete wound healing, healing time, reduced wound surface area, pain, and prevention of serious complications of infection? (continued)		
Local Wound Applications (continued)		
Platelet-derived growth factor	Low	Platelet-derived growth factor was superior to placebo in producing wound improvement in stage III and IV pressure ulcers (4 studies).
Biological agents other than platelet-derived growth factor (fibroblast, nerve, and macrophage suspension)	Insufficient	Evidence about the effectiveness of other biological agents used for the treatment of pressure ulcers was inconclusive due to limitations in the number, size, and quality of studies (7 studies of various biological agents).
Surgery		
Surgical techniques	Insufficient	Evidence was inconclusive as to whether one approach to closure of stage III to IV pressure ulcers was superior to others due to poor-quality studies and heterogeneity in patient populations and surgical procedures (4 studies).
Adjunctive		
Electrical stimulation	Moderate	Electrical stimulation was beneficial in accelerating the rate of healing of stage II, III, and IV pressure ulcers (9 studies).
Electromagnetic therapy	Low	Wound improvement of stage II, III, or IV pressure ulcers was similar with electromagnetic therapy compared with sham treatment (4 studies).
Therapeutic ultrasound	Low	Wound improvement was similar with ultrasound compared with standard care or sham treatment (3 studies).
Negative pressure wound therapy	Low	Wound improvement was similar with negative pressure wound therapy compared with standard care (3 studies).
Hydrotherapy	Insufficient	Evidence on the effectiveness of hydrotherapy was insufficient based on 2 randomized trials evaluating different treatment modalities (1 of whirlpool therapy and 1 of pulsatile lavage).
Light therapy (complete wound healing)	Low	Light therapy was similar to sham light therapy in producing complete wound healing based on 2 randomized trials.
Light therapy (wound surface area reduction)	Low	Light therapy reduced wound surface area over time compared with standard care or sham light therapy (5 studies).
Laser therapy	Low	Wound improvement was similar with laser therapy compared with sham treatment or standard care (4 studies).
Key Question 1a. Does the comparative effectiveness of treatment strategies differ according to features of the pressure ulcers, such as anatomic site or severity at baseline?		
Support		
Support, all strategies	Insufficient	Only 4 studies reported results by ulcer stage or location, and the interventions, characteristics, and results varied and did not permit conclusions.
Nutrition		
Nutrition, all strategies	Insufficient	Only 3 of the 16 studies analyzed results by ulcer characteristics, and the impact on the conclusion was inconsistent.

Table A. Summary of evidence: impact of pressure ulcer treatment strategies on wound improvement and harms (continued)		
Key Question and Treatment Strategy	**Strength of Evidence**	**Conclusion**
Key Question 1a. Does the comparative effectiveness of treatment strategies differ according to features of the pressure ulcers, such as anatomic site or severity at baseline? (continued)		
Local Wound Applications		
Local wound applications, all strategies	Insufficient	Few studies conducted subgroup analyses by ulcer characteristics (7 studies). Indirect comparisons of results across studies were limited due to heterogeneity of studies.
Surgery		
Sacral compared with ischial pressure ulcers	Low	Sacral pressure ulcers had lower recurrence rates after surgery than ischial pressure ulcers (4 studies).
Adjunctive		
Adjunctive, all strategies	Insufficient	Evidence did not permit determination as to whether the effectiveness of adjunctive therapies varied based on pressure ulcer characteristics due to heterogeneity of studies (6 studies).
Key Question 1b. Does the comparative effectiveness of treatment strategies differ according to patient characteristics, including but not limited to: age, race/ethnicity, body weight, specific medical comorbidities, and known risk factors for pressure ulcers, such as functional ability, nutritional status, or incontinence?		
Support		
Support, all strategies	Insufficient	No studies were identified that allowed conclusions about the impact of patient characteristics on the effectiveness of different support surfaces in pressure ulcer wound improvement. Indirect comparisons of results across studies were limited due to heterogeneity of studies.
Nutrition		
Nutrition, all strategies	Insufficient	Evidence did not permit determination as to whether patient characteristics, including baseline nutritional status, modified the effect of nutritional support on pressure ulcer healing due to a limited number of studies reporting outcomes by baseline nutritional status (2 studies).
Local Wound Applications		
Local wound applications, all strategies	Insufficient	Studies generally did not report outcomes by patient characteristics, including incontinence and mobility (1 study). Indirect comparisons of results across studies were limited due to heterogeneity of studies.
Surgery		
Surgical flap closure	Low	Spinal cord–injured patients had higher rates of recurrent pressure ulcer after surgical flap closure than other patients with pressure ulcers (1 study).
Adjunctive		
Electrical stimulation	Low	The effectiveness of electrical stimulation was similar in spinal-cord–injured patients compared with others (4 studies).
Electromagnetic therapy Therapeutic ultrasound Negative pressure wound therapy Light therapy Laser therapy	Insufficient	Evidence did not permit determination as to whether the effectiveness of electromagnetic therapy compared with sham electromagnetic therapy (2 studies), ultrasound therapy compared with sham ultrasound therapy, negative pressure wound therapy, light therapy, or laser therapy varied based on patient characteristics due to heterogeneity of studies and lack of reporting of specific patient characteristics.

Table A. Summary of evidence: impact of pressure ulcer treatment strategies on wound improvement and harms (continued)		
Key Question and Treatment Strategy	**Strength of Evidence**	**Conclusion**
Key Question 1c. Does the comparative effectiveness of treatment strategies differ according to patient care settings, such as home, nursing facility, or hospital, or according to features of patient care settings, including but not limited to nurse/patient staffing ratio, staff education and training in wound care, the use of wound care teams, and home caregiver support and training?		
Support		
Support, all strategies	Insufficient	Only 1 study provided data on results by setting and none provided information on setting characteristics. Indirect comparisons of results across studies were limited due to heterogeneity of studies.
Nutrition		
Nutrition, all strategies	Insufficient	No studies reported results by patient care settings. Indirect comparisons of results across studies were limited due to heterogeneity of studies.
Local Wound Applications		
Local wound applications, all strategies	Insufficient	No studies reported results by patient care settings. Indirect comparisons of results across studies were limited due to heterogeneity of studies.
Surgery		
Surgery, all strategies	Insufficient	No studies reported results by patient care settings. Indirect comparisons of results across studies were limited due to heterogeneity of studies.
Adjunctive		
Electrical stimulation	Low	Electrical stimulation produced similar results in a hospital compared with a rehabilitation center (9 studies).
Electromagnetic therapy Therapeutic ultrasound Negative pressure wound therapy Light therapy Laser therapy	Insufficient	Due to a lack of studies comparing different settings, evidence did not permit determination as to whether the effectiveness of electromagnetic therapy compared with sham electromagnetic therapy (2 studies), ultrasound therapy compared with sham ultrasound therapy, negative pressure wound therapy, light therapy, or laser therapy varied based on features of the patient care settings.
Key Question 2. What are the harms of treatments for pressure ulcers?		
Harms: Support		
Support, all strategies	Insufficient	Few of the identified studies (7 out of 24) explicitly addressed harms attributable to support surfaces. In those where harms were mentioned, most reported no significant differences in harms across the different support surfaces. However, as the harms studied were different and were associated with different support surfaces, we were unable to summarize across studies.
Harms: Nutrition		
Nutrition, all strategies	Insufficient	Harms or adverse events were reported in about half of the studies (8 of 16), but the studies reported different harms, did not describe the harm, or did not specify if it was related to treatment.

Table A. Summary of evidence: impact of pressure ulcer treatment strategies on wound improvement and harms (continued)		
Key Question and Treatment Strategy	**Strength of Evidence**	**Conclusion**
Key Question 2. What are the harms of treatments for pressure ulcers? (continued)		
Harms: Local Wound Applications		
Dressings and topical therapies	Moderate	Harms reported with dressings and topical therapies for pressure ulcers most commonly included skin irritation and inflammation and tissue damage and maceration. Variability in study populations, interventions, adverse event measurement, and reporting precluded an estimate of adverse event rates for dressings and topical therapies (30 studies).
Dressings and topical therapies	Insufficient	Evidence was inconclusive as to whether specific dressing types or topical therapies were associated with fewer harms than others due to poor study quality and differential reporting of harms across studies (7 studies).
Biological agents	Insufficient	Few harms were reported with biological agents, but evidence did not permit determination of the incidence of harms due to lack of precision across studies (5 studies).
Harms: Surgery		
Recurrence or flap failure	Low	Reoperation due to recurrence or flap failure ranged from 12 to 24 percent (2 studies).
Adjunctive		
Electrical stimulation	Low	The most common adverse effect of electrical stimulation was local skin irritation (3 studies).
Electromagnetic therapy Therapeutic ultrasound Negative pressure wound therapy	Insufficient	Due to a lack of reporting, evidence did not permit conclusions about the harms of electromagnetic therapy (1 study), ultrasound (3 studies), or negative pressure wound therapy (2 studies).
Light therapy	Low	Light therapy caused no significant adverse events based on 4 randomized studies (4 studies).
Laser therapy	Low	Short-term use of laser therapy caused no significant adverse events based on 3 randomized studies (4 studies in all).
Key Question 2a. Do the harms of treatment strategies differ according to features of the pressure ulcers, such as anatomic site or severity at baseline?		
Harms: Support		
Support, all strategies	Insufficient	None of the identified studies reported if differences in harms of support surfaces varied based on features of the pressure ulcers. Indirect comparisons of harms across studies were limited due to heterogeneity of studies.
Harms: Nutrition		
Nutrition, all strategies	Insufficient	No studies reported harms by ulcer characteristics. Indirect comparisons of harms across studies were limited due to heterogeneity of studies.
Harms: Local Wound Applications		
Local wound applications, all strategies	Insufficient	No studies reported harms by ulcer characteristics. Indirect comparisons of harms across studies were limited due to heterogeneity of studies.

Table A. Summary of evidence: impact of pressure ulcer treatment strategies on wound improvement and harms (continued)		
Key Question and Treatment Strategy	**Strength of Evidence**	**Conclusion**
Key Question 2a. Do the harms of treatment strategies differ according to features of the pressure ulcers, such as anatomic site or severity at baseline? (continued)		
Harms: Surgery		
Surgery, all strategies	Low	Wound dehiscence was more common if bone was removed at time of surgical procedure (1 study).
Ischial ulcer surgery	Low	Complication rates after surgery were higher for ischial ulcers than for sacral or trochanteric ulcers (2 studies).
Harms: Adjunctive		
Adjunctive, all strategies	Insufficient	Due to a lack of reporting, there was inconclusive evidence to determine if differences in harms of any adjunctive therapies varied based on features of the pressure ulcers (3 studies of electrical stimulation).
Key Question 2b. Do the harms of treatment strategies differ according to patient characteristics, including age, race/ethnicity, body weight, specific medical comorbidities, and known risk factors for pressure ulcers, such as functional ability, nutritional status, or incontinence?		
Harms: Support		
Support, all strategies	Insufficient	None of the identified studies reported if differences in harms of support surfaces varied based on patient characteristics. Indirect comparisons of harms across studies were limited due to heterogeneity of studies.
Harms: Nutrition		
Nutrition, all strategies	Insufficient	No studies reported harms by patient characteristics. Indirect comparisons of harms across studies were limited due to heterogeneity of studies.
Harms: Local Wound Applications		
Local wound applications, all strategies	Insufficient	No studies reported harms by patient characteristics. Indirect comparisons of harms across studies were limited due to heterogeneity of studies.
Harms: Surgery		
Surgery, all strategies	Insufficient	No studies reported harms by patient characteristics. Indirect comparisons of harms across studies were limited due to a lack of studies and reporting.
Harms: Adjunctive		
Electrical stimulation	Low	Frail elderly patients experienced more adverse events with electrical stimulation compared with a younger population (3 studies).

Table A. Summary of evidence: impact of pressure ulcer treatment strategies on wound improvement and harms (continued)		
Key Question and Treatment Strategy	**Strength of Evidence**	**Conclusion**
Key Question 2c. Do the harms of treatment strategies differ according to patient care settings, such as home, nursing facility, or hospital, or according to features of patient care settings, including but not limited to nurse/patient staffing ratio, staff education and training in wound care, the use of wound care teams, and home caregiver support and training?		
Harms: Support		
Support, all strategies	Insufficient	None of the identified studies reported if differences in harms of support surfaces varied by patient care setting. Indirect comparisons of harms across studies were limited due to heterogeneity of studies.
Harms: Nutrition		
Nutrition, all strategies	Insufficient	No studies reported harms by patient care setting. Indirect comparisons of harms across studies were limited due to heterogeneity of studies.
Harms: Local Wound Applications		
Local wound applications, all strategies	Insufficient	No studies reported harms by patient care setting. Indirect comparisons of harms across studies were limited due to heterogeneity of studies.
Harms: Surgery		
Surgery, all strategies	Insufficient	No studies reported harms by patient care setting. Indirect comparisons of harms across studies were limited due to heterogeneity of studies and surgical procedures.
Harms: Adjunctive		
Adjunctive, all strategies	Insufficient	No studies reported harms by patient care setting. Indirect comparisons of harms across studies were limited due to heterogeneity of studies and a lack of studies comparing different settings.

Key Findings and Strength of Evidence

We identified evidence addressing a variety of different support surfaces, including air-fluidized (AF) beds, alternating pressure (AP) beds and chair cushions, and low-air-loss (LAL) beds. Other types of support surfaces were evaluated only in small single studies. We found evidence of moderate strength that reductions in wound size were better with AF beds from studies that compared AF beds with other support surfaces, including standard hospital beds. Studies found no difference in wound improvement when different types of AP mattresses were compared (moderate strength of evidence). Evidence about the effectiveness of AP seat cushions was insufficient, as only two studies with very different populations were identified. There was low-strength evidence that AP beds or LAL beds led to similar wound improvement when compared with other surfaces, usually standard mattresses. The reported harms of different support surface options were minimal, although harms were infrequently and inconsistently reported in support surface studies.

Studies of nutritional support evaluated protein-containing nutritional supplementation and specific nutrient supplementation with vitamins or minerals, such as ascorbic acid (vitamin C) or zinc. Studies provided moderate strength of evidence that protein supplementation resulted in wound improvement. There was low strength of evidence indicating similar results with vitamin C compared with placebo. Evidence about zinc supplementation was insufficient to draw conclusions. There was insufficient evidence to adequately describe the harms of nutritional supplementation in this patient population.

A wide variety of modern wound dressings have been compared with each other or with standard care, usually with gauze dressings. We found low-strength evidence that hydrocolloid dressings were superior to gauze and moderate-strength evidence that hydrocolloid and foam (hydrocellular or polyurethane) dressings produced similar wound improvement. Evidence about the comparative effectiveness of other dressings—hydrogels, transparent

films, silicone, and alginates—was insufficient to draw conclusions. We found moderate-strength evidence from four studies that radiant heat dressings accelerated the rate of healing of stage III and IV ulcers compared with other dressings, but we did not find evidence of a benefit of radiant heat dressings in terms of complete wound healing.

The most commonly evaluated topical therapies were debriding enzymes (primarily collagenase), phenytoin solution, dextranomer paste, and collagen applications. There was low-strength evidence that dextranomer was less effective than wound dressings. Evidence about enzymes and phenytoin was inconsistent and insufficient to draw conclusions. Collagen applications did not produce wound improvement compared with standard care based on low-strength evidence.

The most commonly evaluated biological agent was platelet-derived growth factor (PDGF), for which there was low-strength evidence of benefit compared with placebo in promoting wound improvement in severe (stage III or IV) ulcers. There was insufficient evidence about the effectiveness of other biological agents.

There was moderate-strength evidence that the most common harms of wound dressings and topical agents were dermatologic complications, including irritation, inflammation, and maceration. However, variability across studies precluded an estimate of adverse events for specific dressings or topical therapies, and evidence was insufficient to determine whether certain types of dressings or topical therapies were more likely to cause these complications than others. Few harms were reported with biological agents, but the evidence about the harms of these agents was insufficient to reach conclusions about adverse event rates. Evidence was insufficient to make conclusions about the effectiveness or harms of local wound applications across different ulcer characteristics, patient characteristics, or settings.

Surgical interventions for pressure ulcers identified in studies meeting our inclusion criteria were primarily surgical flaps, most commonly myocutaneous and fasciocutaneous flaps. Studies of surgical interventions were nearly all observational, and most were conducted in single centers. There was insufficient evidence that one approach to closure of stage III to IV pressure ulcers was superior to others due to heterogeneity in patient populations and surgical procedures. There was low strength of evidence that sacral ulcers had a lower rate of ulcer recurrence when compared with ischial ulcers, that a higher rate of recurrent ulcers occurred among patients with spinal cord injury compared with others, that a greater wound dehiscence rate occurred with surgeries in which bone was removed as part of the operation, and that more adverse events occurred with surgery for ischial compared with sacral or trochanteric ulcers. Surgical flap failures requiring reoperation ranged from 12 percent to 24 percent.

Adjunctive therapies identified in our review included electrical stimulation, electromagnetic therapy, ultrasound, negative pressure wound therapy, hydrotherapy, light therapy, and laser therapy. Evidence about other adjunctive therapies—including vibration, shock wave, and hyperbaric oxygen—was limited to small single studies. There was moderate-strength evidence that electrical stimulation improved healing rates, but there was insufficient evidence about the effect of electrical stimulation on complete wound healing due to heterogeneous findings across studies. Low-strength evidence indicated that the most common adverse effect of electrical stimulation was local skin irritation and that harms were more common in frail elderly compared with younger populations. There was also low-strength evidence indicating that electromagnetic therapy, therapeutic ultrasound, and negative pressure wound therapy were similar to sham treatment or standard care in wound improvement outcomes; there was insufficient evidence to evaluate the harms of those adjunctive therapies due to a lack of reporting of harms. Light therapy provided benefit in terms of wound area reduction, but not in terms of complete wound healing, and it was not associated with significant adverse events based on low-strength evidence. There was low-strength evidence that laser therapy was not associated with significant adverse events, but also that it did not provide wound improvement over sham or standard treatment. There was insufficient evidence to draw conclusions about hydrotherapy due to the paucity of studies.

Discussion

Findings in Relationship to What Is Already Known

Treatments for pressure ulcers have been described and evaluated with varying degrees of rigor in the past (e.g., Lyder, 2003[4]). A recent systematic review by Reddy and colleagues, published in December 2008, evaluated 103 randomized trials published during or prior to August 2008.[10] The review included studies evaluating support surfaces, nutritional supplements, wound dressings, biological agents, and adjunctive therapies. Our review included evaluations of those treatment categories and

additionally evaluated surgical interventions. We included observational studies of pressure ulcer treatments, included assessments of treatment harms, and expanded the search to include studies published through June 2012. We assessed treatment harms in studies published through June 2012. Our review also included observational studies in addition to clinical trials in an effort to more comprehensively review the relevant literature.

The findings of the prior systematic review were qualitatively similar to ours, with a few exceptions. In the support surface category, Reddy and colleagues reported that AP surfaces and LAL beds were not superior to standard nonpowered surfaces, which is similar to our findings.[10] They did not, however, report specifically on AF beds, as only one of the five studies of AF beds we included in our review was retrieved in their literature search. Our finding that there was moderate-strength evidence that AF beds were more effective than other surfaces in achieving wound area reduction is based on the findings from these additional studies. Additional systematic reviews on the use of support surfaces have been published by the Cochrane Collaboration. A recent report[17] updated earlier versions[18-20] and separated treatment from prevention. This review summarized 18 trials. (Observational studies were not included.) This review, like ours, found some evidence that AF beds led to reductions in pressure ulcer size and no significant effect of LAL beds on healing. Unlike our review, the Cochrane review reported some benefit from the use of sheepskins, but this was based on a study that was excluded from our review because it was published in 1964. Finally, the authors of this review found, as we did, that the evidence base was weak, with studies that were small, had serious methodological limitations, and often did not report key elements such as variance data, p-values, and the characteristics of the surfaces used as the comparators.

Reddy and colleagues reported that, overall, nutritional supplements did not provide benefit in terms of ulcer healing, but that protein supplementation may have produced wound improvement.[10] Our findings were similar. We found moderate-strength evidence that protein supplementation resulted in wound size reduction, but studies did not provide evidence of an effect on complete wound healing. The Cochrane Collaboration published a 2008 systematic review on nutritional interventions to treat and prevent pressure ulcers. The authors were unable to draw conclusions about the effectiveness of nutritional interventions in the treatment of pressure ulcers due to the small number and poor quality of the available studies.[21]

We found limited evidence to support the use of certain dressings and topical therapies over others in terms of wound improvement. Our findings were similar to the conclusions drawn by Reddy and colleagues.[10] Our finding that hydrocolloid dressings are likely to be superior to gauze in promoting wound improvement was similar to the conclusion in two other systematic reviews.[22,23] A review by Chaby and colleagues[22] found equivalence between hydrocolloid and foam dressings in promoting wound improvement, a finding supported by our meta-analysis of eight studies comparing those dressing types. Both Reddy and colleagues and Chaby and colleagues highlighted a study demonstrating the superiority of alginate dressings to dextranomer paste.[10,22] We also found dextranomer paste to be inferior to dressing but considered the evidence for this to be low strength. We found moderate-strength evidence that radiant heat dressings accelerated the rate of wound area reduction, but we did not find evidence of a benefit of radiant heat dressings in terms of complete wound healing. Like Reddy and colleagues, we found a potential benefit, based on low-strength evidence, for platelet-derived growth factor in promoting wound improvement in stage III and IV ulcers.[10]

We found evidence to evaluate the comparative effectiveness of eight adjunctive therapies used in the treatment of pressure ulcers. Of these, none demonstrated consistent effectiveness in complete wound healing. Electrical stimulation, electromagnetic therapy, and light therapy showed a tendency for wound improvement, while other adjunctive therapies showed no evidence of effectiveness. Our findings are consistent with the findings of two prior systematic reviews of electrical stimulation for pressure ulcers,[10,24] two systematic reviews of therapeutic ultrasound,[10,25] one prior systematic review of negative pressure wound therapy,[10] and two systematic reviews of laser therapy.[10,26] Our findings of no significant difference in wound improvement with electromagnetic therapy (EMT) are consistent with those of a prior Cochrane review.[27] Although a trend toward improvement in rate of healing with EMT has been observed, consistent with prior systematic reviews,[10,28] we found that the clinical significance of this trend remains unknown.

Applicability

The applicability of our findings to real-world clinical settings is supported by several features of the body of literature we reviewed. First, the populations studied included a broad representation of patients with pressure ulcers—elderly patients, general populations of patients

with limited mobility, and patients with spinal cord injury—cared for in a wide variety of settings, including hospitals, nursing homes, wound care clinics, and at home. Second, the interventions represented most of the therapeutic modalities commonly used in clinical settings. Comparators were also commonly used therapies and often included standard care as defined by local practice patterns. In some studies this included use of comparators that may not be considered best practices, such as standard hospital beds and plain gauze dressings. However, as these treatment strategies remain in use in many settings, both in the United States and other countries, we retained these studies in our review.

Other features of the studies we identified, however, limited the applicability of our findings. First, the outcome in many studies was wound size (area, volume, or depth) reduction as opposed to complete wound healing. Although wound size reduction is a reasonable measure of therapeutic effect, in clinical practice the goal of therapy is almost always complete wound healing, making wound size reduction a surrogate outcome with less clinical significance than complete wound healing. A principal reason for findings of wound size reduction without complete wound healing was the short duration of most trials. Complete healing takes time. Interventions lasting only a few weeks (as was the case for most of the trials included in our review) are less likely to achieve complete wound healing than interventions carried out for periods long enough for complete healing to occur (as would be the case in clinical practice). A second reason that applicability is limited is that the treatment of pressure ulcers in clinical practice often involves multiple concurrent therapies, such as support surfaces, nutritional supplementation, biological or topical therapies, and adjunctive interventions. No studies compared one combination of concurrent or sequential therapies with another, and no conclusions can be drawn regarding the effectiveness of one compared with another.A second issue affecting applicability is that treatment of pressure ulcers is typically multimodal and often involves the sequential use of different therapies. In practice, the relevant question is often not "Which therapy works best?" but rather "Which combination of therapies works best?" and "When is a specific treatment indicated?" Most comparative studies of pressure ulcer treatments examined head-to-head comparisons of single treatment modalities. Although contextual data and cointerventions were sometimes reported, integrating those data to answer questions about treatment combinations and timing was difficult.

Studies of surgery are additionally limited by the fact that most were observational and conducted in one or, at most, a few centers. Since surgical technique and quality are often operator and/or site dependent, and because outcomes are influenced by local practices, staffing, and other features of the environment, it is difficult to generalize the findings of studies of surgery included in this review.

Implications for Clinical and Policy Decisionmaking

The limitations in applicability discussed above, as well as the limitations of the evidence base discussed below, make it difficult to draw firm conclusions with implications for clinical and policy decisionmaking. Notably, we generated no findings that were supported by high-strength evidence and only a few findings supported by moderate-strength evidence. Most findings were based on low-strength evidence, and for many issues there was insufficient evidence to draw any conclusions.

The finding that AF beds promote wound improvement compared with other surfaces might warrant consideration of this technology. However, it is important to point out that while the five studies of these beds had consistent findings, they are somewhat dated and most compared AF beds with standard beds rather than with other specialized options. Decisions about investments in support surfaces would benefit from head-to-head trials of current technologies that measure effectiveness in terms of complete wound healing, not only reduction in wound size.

Nutritional supplementation may provide benefit in terms of wound improvement, although the effects of nutritional supplementation were not dramatic and it was not clear from the studies in our review whether nutritional supplementation was beneficial to all patients or only those with evidence of nutritional deficiencies. Because nutritional support is commonly prescribed for ill or debilitated patients with evidence of malnutrition, it is not clear whether nutritional support affects ulcer healing and whether patients without evidence of malnutrition might benefit from nutritional supplementation.

Decisions about dressings and topical applications are often guided by matching the primary functions of different dressings (e.g., absorbent and hydrating) with the primary considerations for treatment of individual ulcers (e.g., dryness, contamination risk, and exudate). Given the wide array of options, comparative effectiveness and harms data have great potential to guide individualized

decisionmaking. We found limited evidence, however, to provide such guidance. Overall, we did not find substantial evidence to support certain local wound applications over others. There was evidence to suggest that radiant heat improved the pace of wound healing, but not complete wound healing. Some biological agents showed promise for the treatment of severe ulcers, but the evidence was not substantial. In light of the cost of these agents, more and better evidence is likely needed before they are widely adopted.

Surgery is typically reserved for refractory ulcers unlikely to heal with conservative management. Evidence about surgery is limited to mainly single-center observational studies. However, we found some evidence to inform decisions and expectations about which ulcers

will fare best with surgical intervention and which surgeries are likely to produce the lowest complication rates. The influence of those findings on clinical decisionmaking should be tempered by the low quality of the studies that produced the findings and the potentially limited generalizability of the findings across sites and surgeons.

Adjunctive therapies include therapies that are variably used in the treatment of pressure ulcers. Our review revealed moderate-strength evidence that electrical stimulation accelerated healing but did not otherwise produce findings that would support greater use of adjunctive therapies for the goal of wound healing.

Limitations of the Comparative Effectiveness Review Process

The most important potential limitation of our review is that important studies whose findings might influence clinical and policy decisionmaking may not have been identified. We conducted a comprehensive, broadly inclusive search that produced 7,274 study titles and abstracts. Although we excluded studies published before 1985, we do not believe that important studies of therapies used in current practice were missed. The general consistency of our findings with those of other systematic reviews, which included studies published prior to 1985, provides some assurance that our review was not biased by our timeframe selection. Although we did not include foreign-language studies, we identified these studies and, based on review of their abstracts, found that none would have altered our conclusions. Our review focused on clinical outcomes of pressure ulcer treatments, particularly wound improvement. Other outcomes, such as ease of use and nursing/staff time, might also influence treatment decisions but were beyond the scope of our review. Finally, we excluded studies of the treatment of nonpressure ulcers. To the extent that evidence for interventions studied in other types of wounds, including venous ulcers, is applicable to the treatment of pressure ulcers, our review may have underestimated the quantity and quality of the body of evidence for these interventions.

There may have been biased reporting of results in the literature such that only selected studies were published and retrievable, and that published studies may have been affected by conflicts of interest. Reporting bias and conflicts of interest are concerns with any systematic review. We were not able to conduct quantitative analyses to evaluate the possibility of reporting bias for most of our findings because the heterogeneity across studies in our review, and in many cases the lack of key information needed to perform quantitative syntheses, generally precluded meaningful comparison of effect sizes. Mitigating against the likelihood of reporting bias in our review, however, is the fact that the majority of studies in our review were small (most fewer than 100 patients, many fewer than 50), and most reported no significant effect of the intervention. Reporting bias typically results in selective publication of larger studies and/or those with positive findings, and studies biased by conflicts of interest would also be more likely to report positive findings. We also conducted gray literature searches to look for unpublished data and did not find evidence of unreported studies.

We took several measures to guard against the influence of bias in our identification and evaluation of studies. Abstracts were reviewed by at least two team members, including a clinician/senior investigator. Studies were extracted based on prespecified data elements, extraction done by one team member was checked by another, and quality rating of studies was performed by two team members, with disagreements adjudicated by consensus. Rating of elements of strength of evidence was discussed and calibrated among team members.

Limitations of the Evidence Base

The main limitation of the evidence base in our review was poor study quality. Most trials did not specify randomization method, did not conceal allocation, and did not mask outcomes assessment. Most studies were small, and many were underpowered to detect significant differences. Studies were also highly variable in terms of patient populations; ulcer characteristics (e.g., anatomic site, duration, and stage); interventions (even within a given intervention category such as different types of foam

dressings); and comparators (especially in implementation of standard, or usual, care), limiting our ability to combine or compare results across studies.

Another major limitation of the evidence base relates to the most common outcome measure: wound size reduction. Comparing changes in the size of pressure ulcers poses several measurement issues. For example, reduction in the size of larger and smaller pressure ulcers is hard to compare. Healing could involve "bridges" that split a large ulcer into two. In addition, measurement in person or from tracings or photographs can be difficult, especially when measurement and photographic techniques are not standardized across studies.

Finally, a major limitation of studies in our review was the duration of interventions and followup periods, typically a few weeks. Many pressure ulcers, especially more severe ulcers, may take months, or even years, to heal. Many of the studies in our review were implemented over a period that did not necessarily allow for complete ulcer healing, and therefore detection of significant differences in ulcer healing across groups. However, one strength in this body of literature was that most studies used intention-to-treat analyses.

Research Gaps

The major gaps in research identified by our review relate to the limitations of the evidence base, as described above. Future studies with larger sample sizes, more rigorous adherence to methodological standards for clinical trials or observational studies, longer followup periods, standardization of comparators, and more standardized and clinically meaningful outcome measures (including more patient-centered outcomes, such as quality of life and pain) are needed to inform clinical practice and policy. Inclusion of information about cointerventions and the timing of studied interventions in relation to other interventions would improve the applicability of study findings. Similarly, stratification of findings by patient characteristics (e.g., comorbidities, ulcer stage) would help determine the applicability of different interventions for specific patients and situations. It is particularly important for future studies to report findings according to ulcer stage, as the rate of healing, conditions necessary to promote healing, and therefore treatment choices may differ for partial- and full-thickness ulcers. Decisions about defining other aspects of patient populations, interventions, comparators, outcomes, study timing and duration, and study settings should be guided by clinical practice, expertise, and factors most relevant to decisionmakers, including patients, clinicians, and policymakers.

For several interventions, there was insufficient evidence to reach conclusions due to small sample sizes or mixed results across studies. These interventions included AP beds compared with other surfaces, topical debriding enzymes, phenytoin, and growth factors. Future studies should clarify the comparative effectiveness of these interventions and identify possible reasons for disparate results. For other interventions, findings indicated a possible benefit, but the strength of evidence was low due to study quality, duration, sample size, and measured outcomes (wound size reduction rather than complete wound healing). These interventions included platelet-derived growth factor and light therapy. Future studies are needed to confirm or refute the effectiveness of these interventions.

As mentioned, further study is warranted comparing AF beds with more modern support surfaces and evaluating comparative effectiveness in terms of complete wound healing. Similarly, in light of findings suggesting a benefit for radiant heat dressings and electrical stimulation in terms of wound healing rate, further study should compare these technologies with other treatments, with sufficient followup to evaluate complete wound healing. There was limited evidence to support the use of nutritional supplements as a component of pressure ulcer care, but few studies examined whether supplementation might have a differential effect for patients with and without baseline nutritional deficiencies. Future studies should address this issue.

Hyperbaric oxygen therapy is one clinical area that our TEP identified as high priority but for which we found limited evidence. Although studies and systematic reviews have evaluated this treatment in chronic wounds generally, its utility among patients with pressure ulcers specifically has undergone limited evaluation.

Conclusions

Choices of treatments for pressure ulcers are often guided by product availability, local practice patterns, and individualized decisionmaking based on specific patients and the features of a given pressure ulcer. Our review did not generate many findings to guide those choices based on evidence.

We found limited evidence to draw firm conclusions about the best approaches for treating pressure ulcers. This finding is consistent with that of a prior systematic review addressing most of the same treatment categories included in our review.[10] We found evidence from five studies indicating greater wound improvement with AF beds

over other support surfaces, from four studies indicating a benefit of radiant heat dressings over other dressings, and from nine studies indicating a benefit of electrical stimulation. However, the benefit observed in all cases was wound size reduction or better healing rates rather than completely healed wounds, and evidence for the benefit of support surfaces in promoting wound improvement was based primarily on comparisons of AF beds with hospital beds that may not be considered the standard of care in the field. The balance of costs and potential harms of those technologies against the benefits observed is unclear.

Studies generally did not provide evidence to support the use of one type of commonly used wound dressing over another. There was evidence that hydrocolloid and foam dressings performed similarly, but evidence for other dressing types—hydrogels, alginates, transparent films, and silicone dressings—compared with each other or with standard gauze dressings was limited. Similarly, there was low-strength or insufficient evidence to judge the balance of effectiveness and harms for nutritional supplementation, topical therapies, biological agents, surgical interventions, and adjunctive therapies other than electrical stimulation.

Advancing pressure ulcer care will require more rigorous study to solidify the evidence base for this widely used set of treatments.

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Full Report

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