Technology Assessment

Technology Assessment Program

Usual Care in the Management of Chronic Wounds: A Review of the Recent Literature

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BACKGROUND

The Center for Medicare and Medicaid Services (CMS) requested a technology assessment (TA) report from the Agency for Healthcare Research and Quality (AHRQ) summarizing the usual care for chronic wound management in patients presenting with decubitus ulcers due to pressure, or foot or leg ulcers due to diabetes, or arterial or venous disease. This report will be used to inform a meeting of the Medicare Coverage Advisory Committee (MCAC) in March 2005. This committee will use the information in this report, in conjunction with other data, to deliberate on the trial designs that will be needed to support the development of sufficient evidence to determine the appropriate treatment of chronic wounds. This report is not intended to support the development of clinical practice guidelines. In this report, chronic wounds are defined as wounds that do not heal completely after receiving standard medical treatment for 30 days.

The UK NHS R&D Health Technology Assessment Programme published a set of comprehensive TA reports on the management of chronic wounds between 1997-2000.[1-4] The NHS TA reports were systematic reviews of treatments for chronic wounds assessing the efficacy of mechanical and non-mechanical debridement, dressings and topical agents, antimicrobial agents, beds, compression, laser therapy, therapeutic ultrasound, electrotherapy, and electromagnetic therapy. These TA reports reviewed the comparative efficacy of treatment modalities but they did not make specific recommendations for standard of care. Table 1 summarizes the interventions assessed for various types of chronic wounds in these TA reports. The purpose of the NHS TA was to provide a comprehensive review of the evidence of different wound care interventions. The purpose of the current report (described in further detail below) is to

look at the trial design, and specifically the elements of usual care, in recent clinical trials of wound care interventions.

The FDA published a draft document in 2000 providing guidance on study designs and related issues for the industry developing products for treatment of chronic cutaneous ulcers and burn wounds.[5] Relevant to the present TA report, the draft document provided recommendations on the outcome measures and trial designs. However, the draft FDA document represents the view of only one government agency and it was not intended to provide recommendations for routine clinical practice.

The purpose of this report is to review the studies of chronic wound treatments published in the clinical trial literature since the NHS TA reports. Specifically, the questions to be addressed for arterial, decubitus, diabetic, and venous ulcers are:

1. What is the usual care given to patients in clinical trials of chronic wound management?
2. What are the common elements of wound care across different types of wounds? Include when possible information on: type of treatment, frequency of treatment, duration of treatment, setting, providers (caregivers), age range. Summarize information from 20 largest studies for diabetic, pressure, and venous ulcers according to recommendations in the FDA Draft Guidance Document for the Industry.
3. What treatment modalities are unique for each type of chronic wounds?
4. Analyze and discuss the evidence and rationale for each of the treatment modalities used in usual care.

In this TA, CMS is interested in understanding the various specific treatment modalities that are currently used as usual care for healing of chronic wounds (e.g., compression bandaging improves venous ulcer healing compared with no bandaging). CMS is not interested in learning about specific comparative efficacy between specific treatment modalities (e.g., one type of bandage compare with another type), as performed in the NHS TAs.

Rationale for Various Treatment Modalities for Chronic Wounds

The etiology of a chronic wound (ulcer) can generally be determined by the patient's history and physical examination. Some ulcers occur in patients with multiple conditions (e.g., a patient with diabetes and ischemic arterial disease) and it may be necessary to receive definitive treatment for one condition before the treatment for the other can become effective. Certain diagnostic tests may be useful to confirm the etiology of the ulcer (e.g., measurement of the arterial/brachial index to diagnose ischemic arterial disease versus a neurotrophic cause; blood glucose or glycosylated hemoglobin to diagnose diabetes mellitus).

The depth of the wound determines the overall type of process by which healing takes place. Partial Thickness wounds involve the epidermal and dermal layers only and heal by regeneration, whereby the same tissue replaces the tissue that has been lost. Epithelial cells migrate into the wound from the wound margin. Full Thickness wounds are devoid of both the epidermis and dermis and reach the level of subcutaneous tissue or muscle. At this level wound repair must proceed by granulation, contraction, and re-epithelialization.

The Biology of Wound Healing

A chronic wound is a wound "that has failed to proceed through an orderly and timely series of events to produce a durable, structural and cosmetic closure."[2] Obviously, this definition depends upon a timeline whereby the normal or acute wound is usually closed by four weeks. The various types of dressing treatments for chronic wounds can best be understood by first relating the dressing types to the phase during which they might act. The biological phases of wound healing have traditionally been divided into 3 progressive segments[6]:

- inflammatory phase
- proliferative phase
- maturational phase

During the inflammatory phase platelets play a central role in wound healing, initially through stabilization of the wound by clot formation. Platelets then activate the complement cascade, and the released cytokines (specific growth factors) attract and stimulate cells essential to wound healing. This process attracts the chief scavenger cell, the neutrophil, to the wound, thus initiating autogenous debridement. In contrast to the normal progression of wound healing to the next phase, chronic wounds appear to be stuck in the inflammatory phase.

In the second phase of wound healing, the proliferative phase, another critical cell, the macrophage, subsequently orchestrates several important processes including: 1) further wound debridement, 2) migration of fibroblasts into the wound with subsequent collagen synthesis, 3) angiogenesis, and 4) formation of granulation tissue

from the collagen and new blood vessels in the wound. Methods for stimulating angiogenesis have been the focus of more recent wound therapies because new capillary growth provides wound nutrients and helps to develop the granulation tissue bed. In the latter steps of the proliferative phase, the wound contracts due to myofibroblasts while epithelial cells from the margin of the wound start to migrate across the wound surface.

The third phase of wound healing, the maturational phase, is associated with further formation of granulation tissue and progressive epithelialization from the wound margin so that the wound surface becomes totally covered. This process involves a symphony of cytokines, such as platelet derived growth factor (PDGF), insulin-like growth factor (ILGF) and epithelial growth factor (EGF). During this phase the wound is remodeled by simultaneous synthesis and breakdown of collagen. Collagen becomes organized into bundles as the tensile strength of the wound is increased.

Clinical Considerations

Table 2 summarizes the major types of wound dressings, their mechanism of action, wound healing phase affected, and specific examples of that dressing type. Wound dressings serve a number of purposes including preventing physical and bacterial contamination of the wound, while maintaining the viability of the cells both within the wound and at the wound margin. This is accomplished by providing a moist and warm wound environment and facilitating migration of cells at the wound margin to provide wound coverage.

In addition to the type of dressing used in treating chronic wounds, several common principles apply to the management of most chronic wounds: 1) removal of dead and devitalized tissue which provides a nidus for bacterial infection (not colonization), 2) aggressive antibiotic treatment of peri-wound and wound infections, 3) mechanical measures which may favorably alter local hemodynamics or ameliorate adverse physical forces, and 4) optimization of general nutrition.

Most wounds are colonized by bacteria. Debridement of necrotic tissue is generally carried out to reduce the potential for delayed wound healing by gross active bacterial infection that produces persistent inflammation. For example, diabetic ulcers typically undergo sharp debridement of eschar and hypertrophic callus by scalpel, which has been shown to be an independent contributing factor to healing of diabetic ulcers.[7] Antibiotics are employed for obvious cellulitis or gross infection of the wound. Finally, mechanical measures are essential to counteract regional contributory factors adverse to wound healing. These include “pressure offloading" for diabetic foot ulcers and elastic compression for chronic venous ulcers.

The diabetic foot develops not only a gross sensory loss but also an impairment of proprioception. By redistributing the weight off the bony prominences (i.e., metatarsal heads) – offloading – chronic excessive pressure is reduced on these sites.[7] Offloading minimizes callus formation and subcallosal hemorrhage with subsequent ulcer formation at these sites.

Several studies have shown that in advanced chronic venous insufficiency, elastic compression bandages reduce the peak venous systolic pressure achieved during walking, thereby modifying deleterious ambulatory venous hypertension.[8,9] In

addition, interstitial fluid collection producing edema is reduced by the action of elastic compression on interstitial fluid pressure with resultant reduction of capillary leakage.[10]

Wound Dressings

Over the last quarter century there has been a major shift in the type of dressing used for wounds. Earlier it was common practice to leave a wound as dry as possible so that the dressing principally served to keep infections out and reduce trauma to the wound. The pioneering experiments of Winter and Associates[10] showed in a porcine wound model a markedly increased healing rate when an occlusive dressing was used. This experimental finding was subsequently validated in a clinical study.[12] Limbs with occlusive dressings that promote a moist wound-healing environment had a 40% increased epithelialization rate over dry bandaged wounds. Based on these findings the type of dressings slowly shifted in the 1970's and 1980's to semi-occlusive and occlusive dressings. This marked a major advance in wound therapy as stated by Falanga: "The composition and properties of a dressing itself now play a major role in modifying the wound micro-environment."[13] In addition to wound dressings, which promote a warm moist wound environment by reducing water evaporation and heat loss as well as preventing crust formation, a new approach involving biologic dressings is being developed. This class of dressings stimulates important growth factors that are necessary in promoting wound healing.

Winter has classified wound dressings as to their degree of activity with the wound: passive, interactive and active dressings.[11] Dressing types have been further divided into four classes: 1) nonocclusive, 2) semi-occlusive, 3) occlusive, and 4)

biologic. The first three types are based on the degree that the wound dressing reduces water vapor and heat loss from the wound. By contrast, the fourth type, biological dressings, comprise those dressings which either provide directly a growth factor that accelerates wound healing or a factor that indirectly stimulates important growth substances.

One working principle is that no wound dressing may be ideal for all wounds, and the type of dressings may change as wound healing and other local wound factors progress. Nonocclusive dressing, such as topical antibiotics covered with dry gauze, simply protects the wound from trauma and potential infection and is classified as a passive dressing. By contrast, the interactive types of wound dressings (semi-occlusive and occlusive dressings) maintain a moist wound environment and may help to control the amount and composition of wound exudate. The most common example of a semi-occlusive dressing is the saline wet to dry gauze dressing. This dressing may facilitate moist healing if the gauze is kept wet, but when the gauze is dried out the dressing is non-occlusive and serves to debride the wound. Unfortunately, the dry gauze also may remove cells important in wound healing. The wet gauze also has the potential for macerating the peri-wound skin.

Common Types of Semi-Occlusive and Occlusive Dressing: Dressing Properties and Mechanism of Action

Reviewed in this section are different types of dressings and their mechanism of action.[14] Film dressings are composed of transparent and adherent polyurethane that transmit water vapor, oxygen, and carbon dioxide from the wound. These dressings

both protect and insulate the wound as well as providing autolytic debridement of the eschar. Unfortunately, film dressings do not absorb drainage and maceration of the surrounding skin can occur. Examples of this are Opsite®, and Tegaderm®.

Hydrocolloid dressings are composed of a water-impermeable outer layer, containing pure polyurethane and an inner hydrocolloid layer. These dressings have the properties of debridement and protection---similar to the film dressings---but allow some absorption of wound drainage. They are probably less permeable than film dressings. Examples of this type are Duo Derm®, Comfeel®, and SignaDress®.

Hydrogel dressings are semi-transparent non-adherent hydrogels that are generally provided in sheets. These dressings are composed of insoluble polymers with hydrophilic substitutes that absorb water like Tegagel®.

Foam dressings absorb significant quantities of exudate from the wound and are comprised of siolastic or polyurethane foam. These dressings are permeable to gases and water vapor while the hydrophobic properties of the back of the dressings mitigate penetration of liquid. An example of this type is Allevyn®.

Alginate dressings are composed of sodium alginate, which is extracted from brown seaweed. This type of dressing has excellent absorptive capabilities and can be used in infected wounds as exemplified by Sorbsan®.

Biologic dressings, the fourth type of wound dressings, can be subdivided into: 1) living human dermal equivalent (artificial skin), 2) platelet products (either autologous or recombinant DNA technology), and 3) other growth factors. There are currently two types of living human dermal equivalent. The first type contains kerotinocytes (cells occupying the outer layer of the skin or epidermis) as well as fibroblasts (the dermis) on

a collagen matrix (Apligraf®). Both types of cells (keratinocytes and fibroblasts) are derived from cultured neonatal foreskins. Dermagraft®, the second type of living human dermal equivalent, contains no epithelial layer (kerotinocytes) but is constructed of dermis (fibroblasts) alone on a collagen matrix. While these skin equivalents provide temporary coverage of the wound, their main mode of action is through secreting and stimulating wound growth factors. Endogenous cells migrate into the wound to promote healing. Clinical studies with Apligraf® have shown an approximately 40% “take” of the fetal derived kerotinocytes.

The most commonly used topical biologic “growth factor” is a platelet derived growth factor, Regranax® (becaplermin), which is produced by recombinant DNA technology. The gel is applied topically to the wound and promotes chemotactic recruitment and proliferation of cells as well as increasing angiogenesis. Other growth factors such as autologous platelet-thrombin, epidermal growth factor, fibroblast growth factor, and granulocyte macrophage colony stimulation factor, have been explored recently in small trials.

METHODS

We performed a systematic review of the literature to extract information about the background care given to patients in the control group in randomized controlled trials (RCTs) as a proxy for standard of care. Analyses were restricted to RCTs because these studies generally have the most complete description of the background care information compared with other less rigorous study designs. In this report, treatment modalities prescribed in the control groups will be referred to as “usual care.” Clinical practice guidelines and selected surgical textbooks were reviewed for recommendations from authoritative bodies or opinion leaders on chronic wound management to identify major chronic wound treatment modalities and to complement our review of RCTs.

Literature Search

We searched clinical practice guidelines, surgical textbooks, and RCTs in June and July of 2004. Searches for guidelines and textbooks were not meant to be exhaustive. They were intended to provide guidance on the range of treatment modalities generally recommended. We searched for clinical trial articles published since 1997, because the goal of this report is to summarize the usual care practice in recent clinical trials of chronic wound treatments.

Clinical Practice Guidelines

We searched the National Guidelines Clearinghouse (www.ngc.gov) and MEDLINE for clinical practice guidelines on the management of chronic wounds and these were examined for information pertaining to standard of care. In addition, our

surgical consultant contacted several major surgical societies in the US for potential guidelines not included in the Clearinghouse but found none.

Surgical Textbooks

We examined chapters on wound care in a convenient sample of textbooks available on the surgical textbook shelves at the Tufts and Harvard medical school libraries for specific recommendations about usual care for chronic wounds.

Randomized Controlled Trials

We searched for English-language studies in MEDLINE, CINAHL, and the Cochrane Controlled Trials Registry databases on June 30 of 2004. Following consultation with AHRQ and CMS, we limited our literature search to articles published since 1997, which was the publication year of the first UK NHS chronic wounds TAs. A total of 2,762 unique citations were identified. After screening titles and abstracts, 277 articles were retrieved for review.

Inclusion Criteria

As a set of minimum inclusion criteria, we accepted English language RCTs evaluating treatments of chronic wounds with any number of human subjects. In general, chronic wounds are defined as wounds that do not heal completely after receiving standard medical treatment for 30 days. Because the focus of this report is not on the evaluation of clinical outcomes, there is less concern about the potential bias that may be introduced by including studies that did not clearly state the duration of wound.

Therefore, we accepted RCTs that included mixed duration ulcers in which some of the ulcers might have received standard medical treatment for less than 30 days, as well as studies that did not clearly specify wound duration. In our judgment most of the ulcers were likely to have been treated for at least 30 days.

Types of Chronic Wounds

In this report we considered the following types of chronic wounds: ischemic ulcers due to peripheral arterial occlusive disease, ulcers due to venous disease, diabetic foot ulcers (usually neurotrophic), and decubitus ulcers due to pressure. Ulcers secondary to ischemic arterial occlusive disease usually undergo revascularization to correct inadequate regional perfusion and in general are not the subject of RCTs. An exception to this is the concomitant use of hyperbaric oxygen, a form of treatment outside the realm of usual care. Because the focus of this report is not on the outcomes of treatments, we accepted trials of any duration of treatment. For completeness, studies that included different types of ulcers and did not provide clear delineation of subgroups of wound types are reported in a separate table of mixed wounds. However, this group of studies was not analyzed because of the uncertainty of the wound category and duration.

Usual Care Treatment Modalities

Specific treatments in the control arms of the RCTs were categorized into one of the following 6 treatment modalities: debridement, cleansing, dressing, compression bandage, antibiotics, and pressure offloading. Debridement methods were further

categorized into surgical and non-surgical (i.e., enzymatic) debridement. In addition, dressings were categorized into non-occlusive, semi-occlusive, and occlusive. Non-occlusive dressing includes ointment/cream and dry gauze. Semi-occlusive dressing includes saline wet-to-dry, wet dressing, paraffin gauze, and Vaseline gauze. Occlusive dressings include Unna boot and various hydrocolloids. Management of chronic wounds should include treating the underlying condition and co-morbidities, which might include optimizing blood glucose control in patients with diabetic ulcers, ensuring adequate nutrition status in debilitated patients, revascularization in patients with ischemic artery disease, and pain management. While these treatments modalities are important aspects of total patient management, they are not directed at the treatment of the wound and are not considered in this report.

Study Design

RCTs, non-randomized controlled comparison studies, and cohort studies were initially included in the analysis. We found after preliminary assessment of the literature that 84% of the retrieved studies were RCTs. Excluding the small number of non-randomized studies would have little impact on the results. Focusing on RCTs, as they most likely represent the highest quality of evidence, will improve the reliability of the conclusions. Therefore, after consultation with CMS and AHRQ, only RCTs were included in this report.

We also included RCTs without a clear control group (e.g., RCTs that compare one type of dressing with another type of dressing, or trials that compare one type of compression bandage with another type of compression bandage). In that case,

treatments in all arms of the RCT were extracted, and the usual care for the modality in comparison consisted of more than one treatment (e.g., 2 different types of bandages for compression).

Analysis of the Literature

The review of RCTs focused on determining the frequency of specific treatment modalities that had been used in the control arms for each of the 4 different types of wounds. We also sought to describe the characteristics of the RCTs by wound type. Because authors often do not completely report information about the trial, the lack of description of treatment modalities in an article should not be interpreted as a lack of use of a specific treatment modality. For example, some authors might have taken certain basic treatment modalities for granted (e.g., antibiotics treatment for infected wounds). Therefore, the information on the frequency of various treatment modalities as a proxy of standard of care should be interpreted accordingly.

Conformance of RCTs to Recommendations in the FDA Draft Guidance Document for the Industry

The FDA Draft Guidance Document for the Industry was used as another source of recommendations for usual care in clinical trials testing wound care products. This document also discussed certain design issues that should be addressed in future trials. We reviewed the FDA draft guidance document for the industry to identify recommended elements of outcomes assessment and trial design in the evaluation of wound care products.

For outcomes assessment, these elements include: assessment of partial or complete wound closures, and measurement of wound size pre- and post-debridement. According to the FDA document, prospectively defined partial wound healing (including wound size change) may be used as supportive evidence for the beneficial biological activities of a product or procedure. However, this is not an acceptable surrogate for complete wound healing. An exception is partial wound healing that facilitates surgical closure. Assessment of the wound size and infection status should be conducted after surgical debridement. Enzymatic debridement agents should be avoided because these are applied as topical agents and may confound the results of wound product trials. Measurement of wound size should be standardized with photographic imaging procedures at each clinic visit.

Systemic antibiotic therapy may be necessary during the course of the trial because wounds do not heal in the presence of infection. A trial should document the antimicrobial usage in the study population before and during the trial and the FDA Draft Guidance Document recommends that the study protocol discuss whether the study treatment should be continued in the event of an infection.

In consultation with AHRQ and CMS, we selected approximately 20 of the largest RCTs from each of the diabetic ulcer, pressure ulcer, and venous ulcer categories for additional analyses according to several outcomes recommended in the FDA Draft Guidance Document. The frequency of reporting of the following items were noted:

- partial wound closure
- complete wound closure
- 2 months post-wound closure assessment

- wound size pre- and post-debridement
- photographic imaging methods to assess wound size

In addition, CMS also requested an analysis of the reporting of wound care provider.

RESULTS

Treatment Modality Recommendations in Clinical Practice Guidelines

The search of the National Guideline Clearinghouse using the word “wound” yielded 117 guidelines. After examination, it was determined that 11 guidelines provided usual care information on chronic wounds of interest.[15-25] The other 106 guidelines did not deal with chronic wounds or mentioned wounds only peripherally. Table 3 summarizes information from these guidelines including the type of wound, guideline organization, year of publication, definition of wound, and treatment modality recommendations.

Eight of the 11 guidelines covered pressure ulcers, 2 dealt with diabetic ulcers, and one discussed lower extremity arterial ulcers. None covered venous ulcers. The guidelines were published in the US, Canada, New Zealand, and Singapore by patient and professional organizations, and government agencies. These guidelines almost universally recommended all the basic treatment modalities: debridement, cleansing, dressing, antibiotics, and offloading. Some guidelines also recommended appropriate nutritional support. Since none of these guidelines dealt with venous ulcers, compression bandages were not mentioned.

Recommendations in Surgical Textbooks

From more than 30 textbook titles examined, we identified only 5 recent editions of surgical textbooks that contained specific recommendations about chronic wound management.[26-30] Table 4 summarizes the recommendations of the authors of these 5 textbook chapters. The descriptions of wound care in these chapters were uniformly

terse, lacked specificity, and generally supported the basic treatment modalities recommended in the guidelines.

Usual Care in Randomized Controlled Trials

Eligible Studies

We found 148 qualifying studies involving 12,233 patients. There were 43 diabetic ulcer trials with a total of 3,959 patients, 33 pressure ulcer trials with 1,593 patients, 66 venous ulcer trials with 6,335 patients, 5 trials with mixed type of ulcers including 315 patients, and one arterial ischemic ulcer trial with 31 patients. The details of these studies are described in the evidence tables (appendices B – F).

Study Characteristics

Table 5 summarizes the characteristics of the included studies. The average number of patients enrolled in these studies was less than 100. Among the diabetic ulcer trials, the largest study was a multi-center trial that included 922 patients. Seven other diabetic ulcer studies enrolled more than 100 patients each, and none recruited more than 276 patients. One RCT on pressure ulcers provided only the number of ulcers (28 ulcers) without the corresponding number of patients. Seventeen venous ulcer trials had sample sizes larger than 100 patients but only one reported a sample more than 300 patients. More than half of the diabetic ulcer studies as well as almost half of the pressure ulcer trials were conducted in the US. Among venous ulcer RCTs, almost one-third were conducted in UK and one-fifth in the US. Multi-center trials involving more than one country were rare; these include one pressure ulcer and 6

venous ulcer trials. The average age of patients in diabetic ulcer studies was less than 60 years while in pressure ulcer and venous ulcer trials patients enrolled had a mean age over 66 years old. Males were predominant in diabetic ulcer studies and comprised almost 50% of pressure ulcer and venous ulcer trials. Half of the studies on diabetic ulcer pertained to ambulatory patients. More than 70% of the venous ulcer trials were conducted in an outpatient setting. The majority of pressure ulcer studies were performed in hospitalized patients or nursing home residents.

Forty percent of the diabetic ulcer articles and 45% of the pressure ulcer trials did not specify ulcer duration. One-third of pressure ulcer studies reported ulcer duration either longer or shorter than 30 days. Less than one-third of the diabetic ulcer studies mentioned explicitly that ulcer duration was more than 30 days. Among venous ulcer RCTs, 65% clearly studied chronic wounds defined as an ulcer duration longer than 30 days.

Treatment Modalities for Usual Care

Table 6 and Figure 1-4 summarize the frequency of reported uses of various treatment modalities for diabetic, pressure, and venous ulcers. About 80% of the diabetic ulcer and more than one-third of pressure ulcer trials reported surgical debridement. Non-surgical debridement was reported in only one out of 43 diabetic ulcer studies. Twelve (18%) venous ulcer RCTs mentioned surgical debridement. Non-surgical debridement was reported in less than 10% of pressure ulcer and venous ulcer studies. About 30% of diabetic ulcer RCTs reported on cleansing while more than half of the pressure ulcer and venous ulcer studies reported cleansing as part of the usual

care. Compression was described in 6 (14%) of diabetic ulcer studies while it was not mentioned at all for pressure ulcers. Compression was the most popular (83%) modality for venous ulcers. Thirty-five percent of diabetic ulcer studies described the use of antibiotics to treat wound infections in their trial protocol. Mention of antibiotics was much less common in pressure ulcer (12%) and venous ulcer (15%) trials. Descriptions of antibiotic use generally do not include the route of administration or the specific drugs. Finally, usual care included pressure offloading in most (79%) diabetic ulcer trials, in almost half (48%) of the pressure ulcer trials, but in only 3 (5%) of venous ulcer trials.

Types of dressings were specifically delineated for each wound type and then grouped into 3 categories (Table 7 and Figure 5): 1) non-occlusive, 2) semi-occlusive, and 3) occlusive. There was significant variability in the type of wound dressings employed in the control groups of the diabetic, venous, and pressure wounds. In the diabetic ulcer trials, 51% used saline wet-to-dry dressings but only 14% used hydrocolloid dressings in the control group. Hydrocolloid and saline wet-to-dry dressings were used equally at about 40% in pressure ulcer trials. Unlike the control group in diabetic ulcer trials, saline wet-to-dry was an infrequent dressing type for venous ulcers (3 trials), while in 16 other trials additional forms of non/semi-occlusive dressings were used--dry gauze, Vaseline gauze, and ointment. The Unna boot, a combination of a rigid compression device and topical medication for the ulcer, was used in 10 studies. An occlusive type of dressing, usually hydrocolloid, was the most frequently employed dressing in venous ulcer trials—25 studies.

Frequency of Dressing Changes

Twenty-three of the 43 diabetic ulcer trials (53%) reported the frequency of dressing changes. In most of these studies (17/23) dressings were changed once or twice daily. Dressings were changed every 2 days in 5 studies and twice weekly in one study. Among the 15 pressure ulcer studies that described the frequency of dressing changes, 10 reported once or twice daily, 2 every other day, and 3 once or twice per week. In the venous ulcer studies, dressing changes of once or twice weekly was mentioned in the 28 out of the 38 RCTs that provided this information. Venous ulcer dressings were changed every 2 days in 7 trials, and once or twice per day in only 3 trials. Forty-seven percent of diabetic ulcer trials, 55% of pressure ulcer trials, and 42% of venous ulcer trials did not report the frequency of dressing changes.

Conformance of RCTs to Recommendations in the FDA Draft Guidance Document

We selected the 20 largest trials from each of the diabetic, venous, and pressure ulcer categories and assessed the frequency with which these studies conformed to the recommendations in the FDA Draft Guidance Document. The results are summarized in Table 8 and Figure 6. Evidence tables for these studies are in appendices G – I.

Among the outcomes that the FDA suggested in its Draft Guidance Document, partial wound closure was included as an outcome in 9 (45%) diabetic ulcer and 5 (25%) venous ulcer trials. Complete wound closure was reported in 19 (95%) of the diabetes ulcer, 17 (85%) of the pressure ulcer, and 18 (90%) of the venous ulcer studies we sampled. Post-closure assessment of the wound after 3 months was included in 8 (40%) of the diabetic ulcer trials and in 3 (15%) of the venous ulcer trials in our sample.

One diabetic ulcer RCT reported wound size before and after debridement and one venous ulcer RCT reported pre-debridement wound size. Antimicrobial treatment was described only in pressure ulcer and in venous ulcer trials in our sample. Assessment of wound size using photographic or digital imaging techniques was reported in 25% of diabetic ulcer, 60% of pressure ulcer, and 35% of venous ulcer studies.

In the majority of the studies, the care provider was not specified. Nonetheless, a health care provider was described in 5 (25%) diabetic ulcer, 3 (15%) pressure ulcer, and 10 (50%) venous ulcer trials of the sample. In 3 papers – one diabetic ulcer and 2 pressure ulcer – the patient was the only care provider mentioned. The length of the diabetic ulcer trials typically lasted about 12 weeks, while pressure ulcer trials typically lasted 8 weeks. None of the pressure ulcer trials reported treatment duration of more than 12 weeks, whereas venous ulcers were invariably treated for a longer period. Almost half of the venous ulcer trials reported 24-week maximum treatment duration. Only 2 venous ulcer trials had treatment duration of less than 12 weeks.

SUMMARY

The basic concepts of chronic wound care appear to be well understood. There appears to be general consensus about the use of the basic treatment modalities for chronic wound care among authoritative bodies issuing clinical practice guidelines and opinion leaders writing surgical textbook chapters. However, their recommendations often are vague, not comprehensive, and lacking in specific details. There is also considerable variation in the frequency of reported use of treatment modalities across different types of ulcers and in the use of specific treatment modalities for specific ulcers. The findings suggest that certain elements of usual care will vary with ulcer type. Most common are offloading and debridement for diabetic ulcers and compression for venous ulcers while other treatment modalities such as cleansing and antibiotics are common to a certain degree across ulcer types. These observations are consistent with generally accepted clinical principles and based on sound pathophysiological rationales. We did not review dermatological, nursing, and podiatry textbooks. However, given the general consensus in the literature on the basic treatment modalities, it is unlikely that there will be significant variations in their recommendations.

We analyzed over 140 RCTs published from 1997 onward. The largest number of trials was found for venous ulcers, followed by diabetic ulcers and pressure ulcers. There was only one trial of arterial ischemic ulcers, so no reliable conclusions can be drawn. Dressings are universally used in all types of wounds as they were reported in about 90% of all the trials. However, saline wet-to-dry dressings were used in 50% of the diabetic ulcer trials, in 40% of the pressure ulcer trials, but in only 5% of the venous ulcer trials. Hydrocolloid dressings were used in about 40% of both venous ulcer and

pressure ulcer trials but in less than 15% of the diabetic ulcer trials. As expected, the rate of compression bandage use was high (83%) in venous ulcer trials although they were also used in several diabetic ulcer trials. The rate of debridement is high (81%) in diabetic ulcer trials but mentioned in less than one-half of the venous and pressure ulcer trials. A high rate (79%) of prescribing pressure offloading was reported in diabetic ulcer trials but only in 48% of pressure ulcer trials. Cleansing was reported in 30 to 52% of trials of various wound types. The use of antibiotics was reported in about one-third of the diabetic ulcer trials and much less often in trials of other types of ulcers.

The large number of RCTs available for diabetic, pressure, and venous ulcers is deceptive in that they yielded limited information about the usual care, how different treatment modalities should be used and how they should be used in combination. Many of the trials compared one product against the product of another manufacturer (i.e., one dressing versus another dressing). Practical clinical information such as the frequency of application, or combination or sequencing of treatment modalities is generally inadequately reported in these trials.

Other than the reporting of complete wound closure, the conformance with the FDA Draft Guidance Document recommendations on outcome assessment of the 20 largest trials that we examined was low in each of the 3 wound categories of diabetic, pressure, and venous ulcers.

The quality of information provided in the RCTs of chronic wound management we examined for this report is generally poor. There is a large degree of variation in the reporting of the use of different basic wound treatment modalities. Not a single wound treatment modality, among those evaluated, was uniformly reported in all the trials.

Compression bandages are considered the cornerstone treatment for venous ulcers, yet only 83% of the trials reported it as usual care in the control group. It is difficult to ascertain whether the relatively low rate of reporting of treatment modalities was indeed because the investigators did not use it as part of usual care in the trials or if the information simply was not reported. It is possible that some of these treatment modalities might have been considered to be so basic and essential to chronic wound care that the investigators did not bother to include them in their report. Over 40% of the trials did not report information about the duration of chronic wounds. Incomplete information from these trials makes it difficult to determine the reliability of these data and interpret their results.

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References for the 148 RCTs examined in this report appear in appendix A. The actual number of citations listed is 153 because of duplicate and complementary publications.

Figure 1. Frequency of reported wound care modalities in control groups of RCT
Number of studies: 43 diabetic, 33 pressure, 66 venous

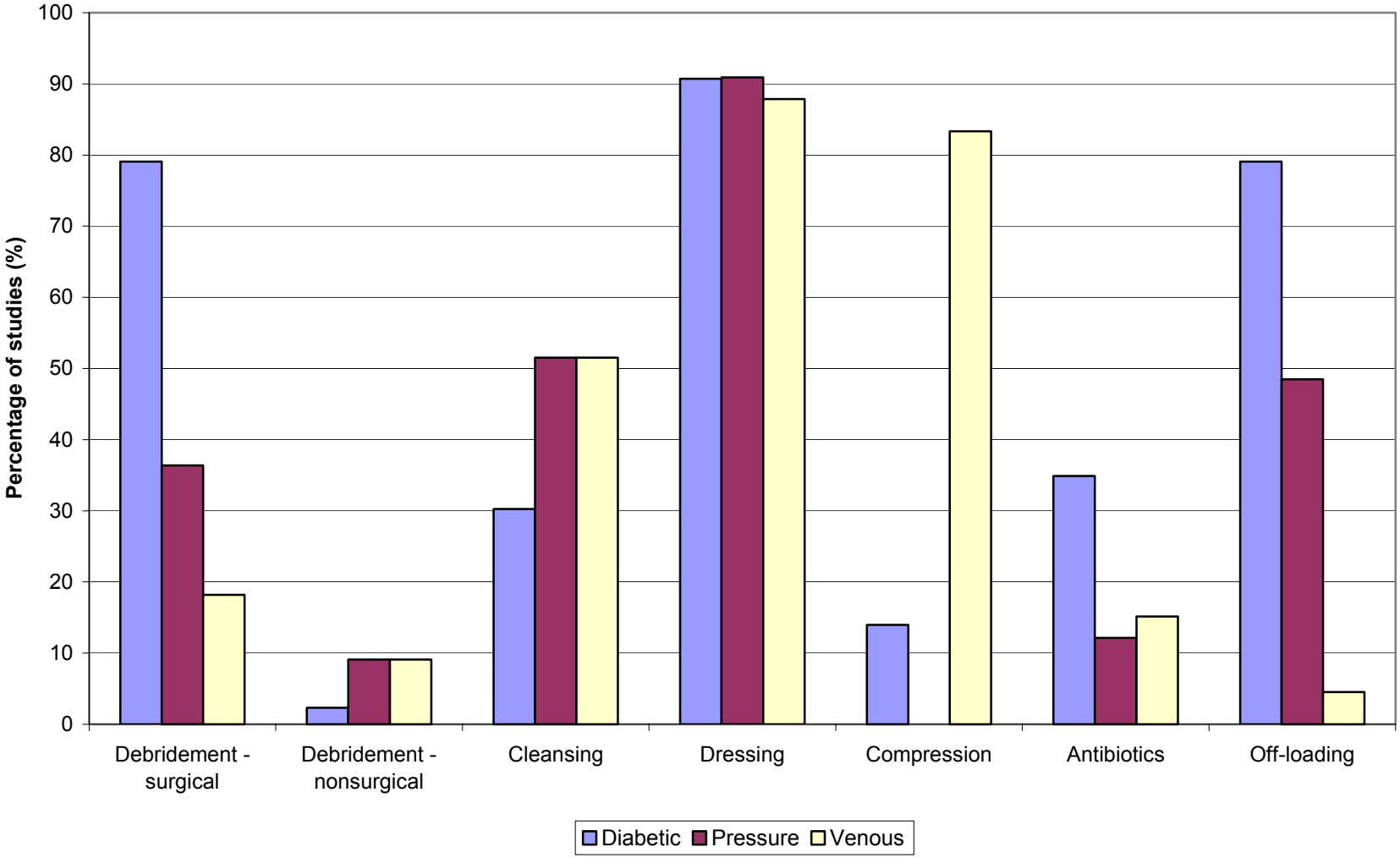

Figure 2. Frequency of reported wound care modalities in control groups of 43 RCTs of diabetic ulcers

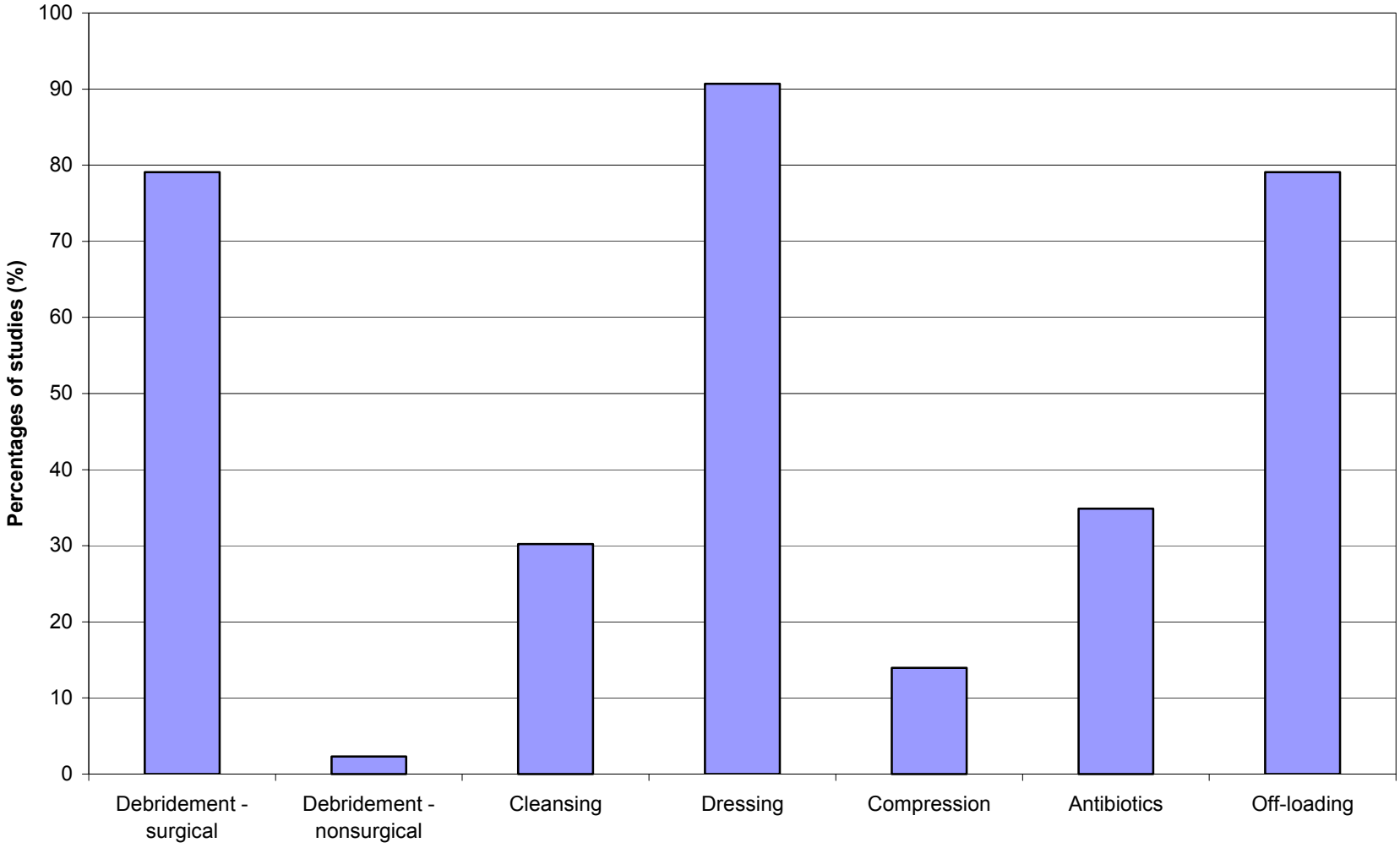

Figure 3. Frequency of reported wound care modalities in control groups of 33 RCTs of pressure ulcers

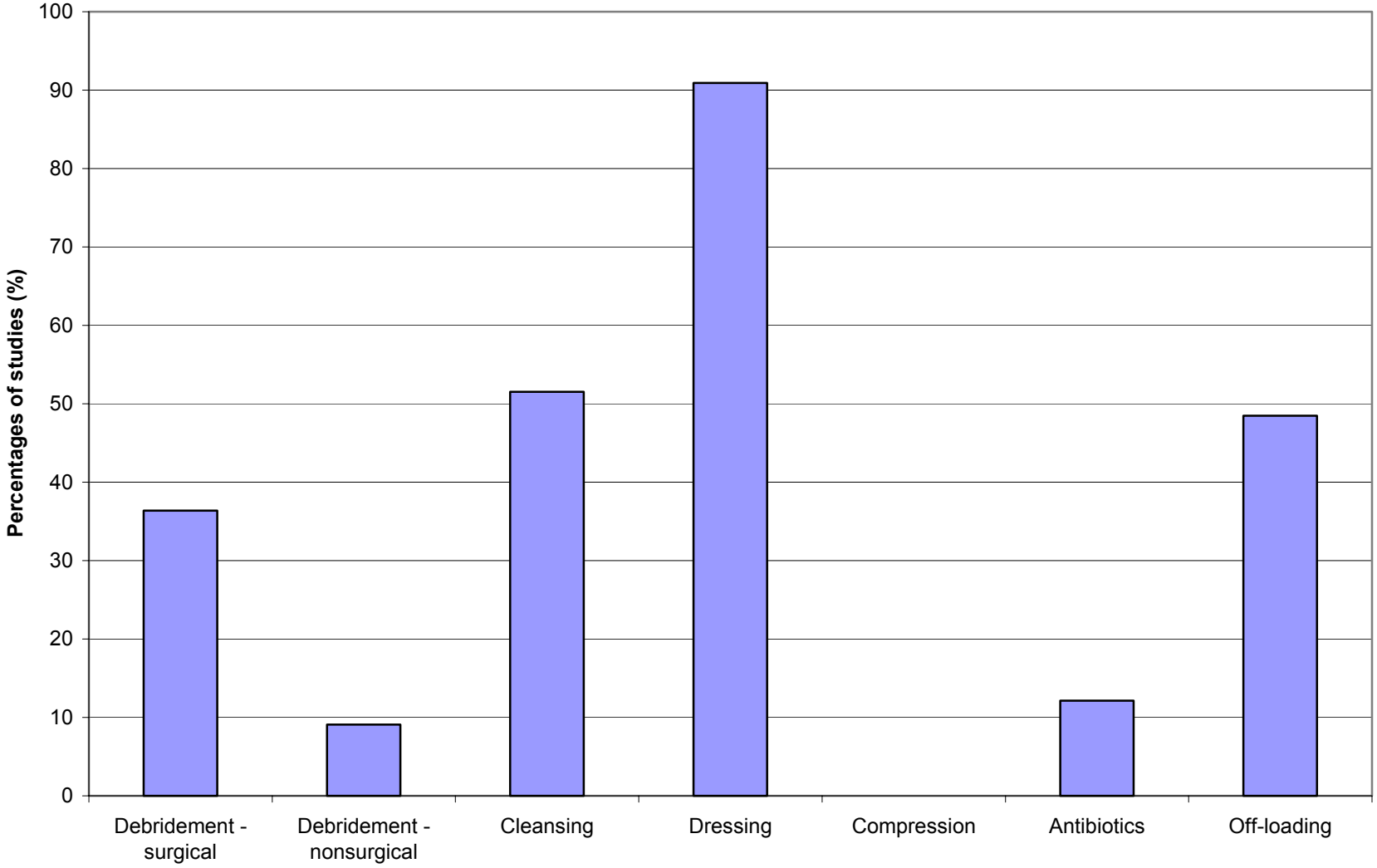

Figure 4. Frequency of reported wound care modalities in control groups of 66 RCTs of venous ulcers

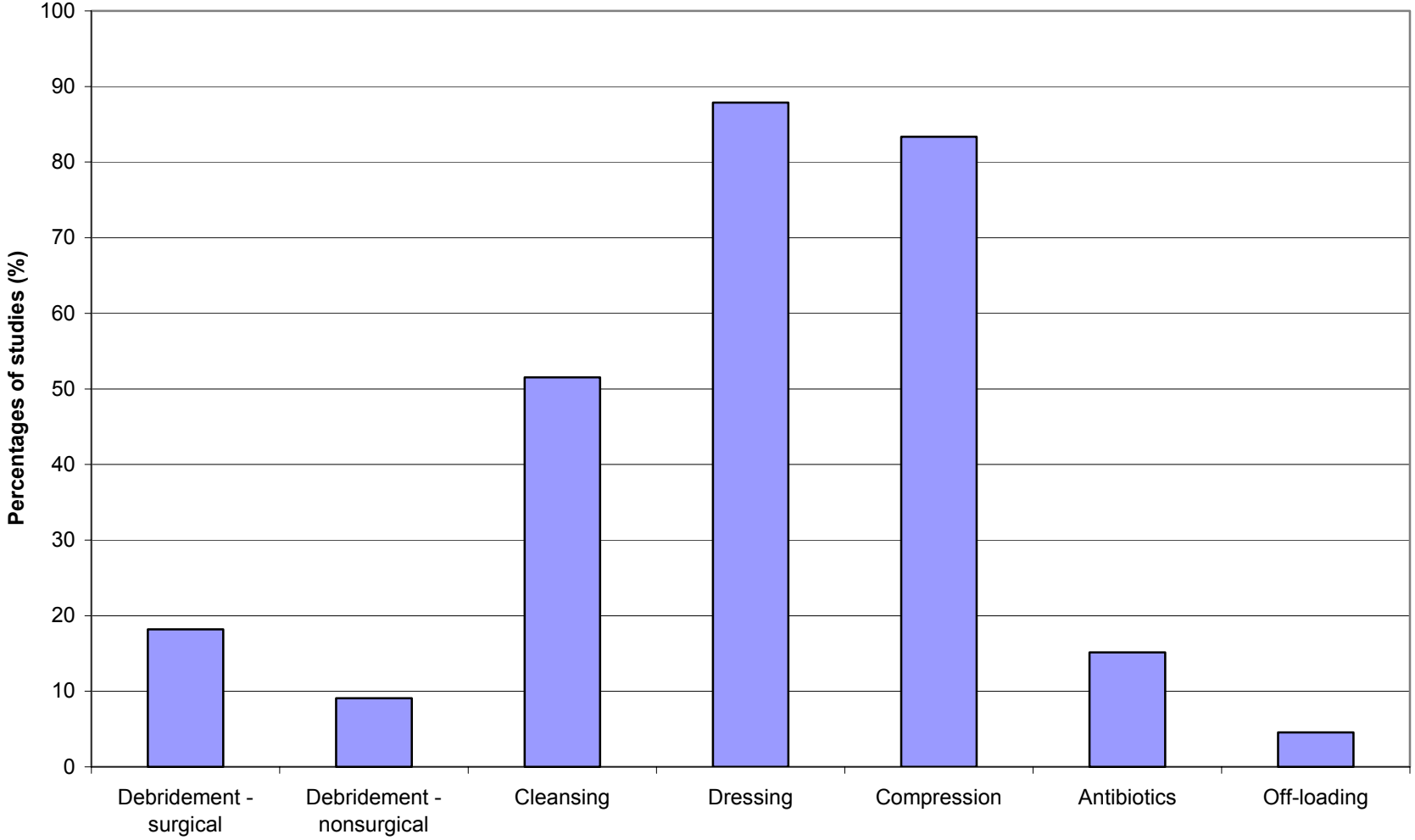

Figure 5. Distribution of specific wound dressings in various types of ulcers

Number of trials: 43 diabetic, 33 pressure, 66 venous ulcer trials

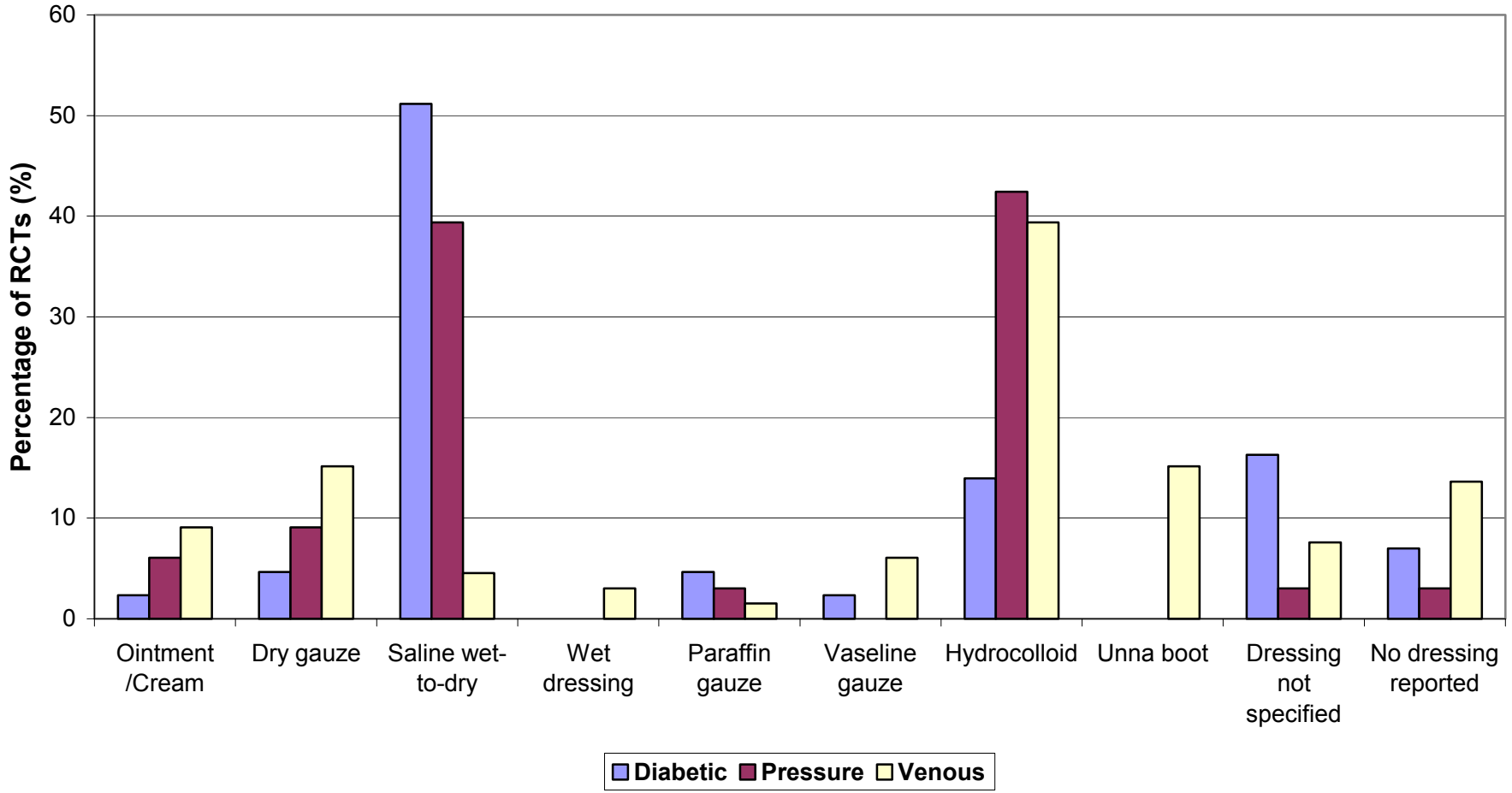

Figure 6. Frequency of reported data conforming to FDA Draft Guidance Document
20 selected largest studies each of diabetic, pressure, and venous wounds

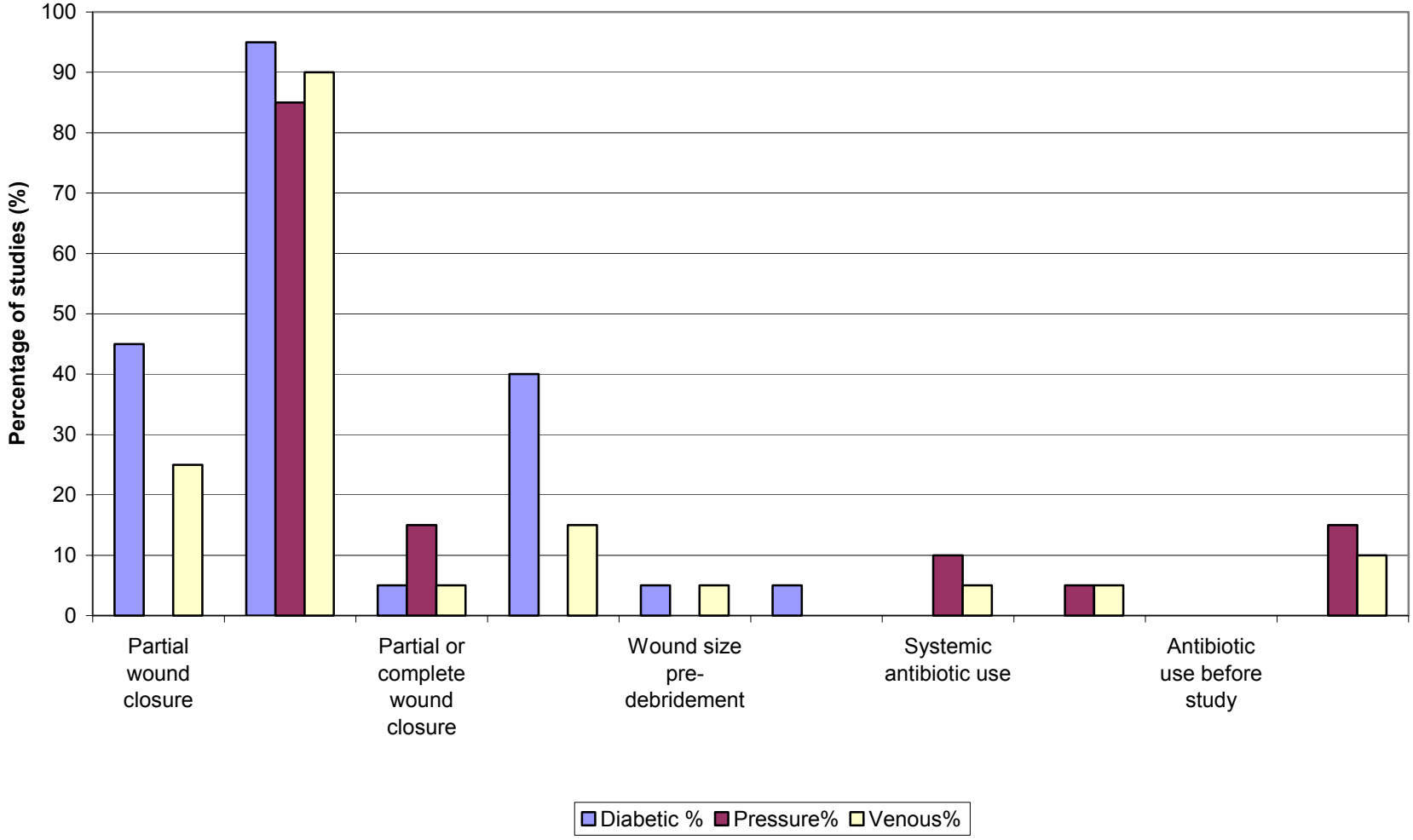

Table 1. Summary of the UK NHS Technology Assessment Reports on Chronic Wounds

Technology assessed	Number of studies, design, wound type	Date search completed	Conclusions
Dressings and topical agents used in arterial and venous ulcers			
Surgical wounds healing by secondary intervention	**5** studies	October 1997	There is little evidence to indicate which dressings or topical agents are the most effective in the treatment of chronic wounds. There is evidence that hydrocolloid dressings are better than wet-to –dry dressings for the treatment of pressure scores. In the treatment of venous ulcers, low adherent dressings are as effective as hydrocolloid dressings beneath compression bandaging
Pressure sores	**28** trials –31 comparisons of treatments		
Leg ulcers Compared Hydrocolloids with traditional dressings	**60** studies –evaluated dressings or topical agents in arterial and venous ulcers **- 9** trials –compared with Hydrocolloids - **2** trials compared hyaluronic acid with control - **4** trials compared biological dressings with traditional therapies **- 2** trials compared dressings with topical preparations - **11** trials compared dressing with dressing		

Technology assessed	Number of studies, design, wound type	Date search completed	Conclusions
Antimicrobials			
Antimicrobials	**30** studies (**25** RCTs) **-9** evaluations of systemic antimicrobials **-21** evaluations of topical agents.	January 2000	There is no existing evidence to support the use of systemic agents for chronic wound healing. Even with interventions that appear to be promising, existing trials are general small and many have other methodological problems. The methods of measuring outcomes being poorly developed, with little use of quality-of –life measures and widespread use of unblinded, subjective outcome measures. Several topical agents may be helpful, but further research is required.

Technology assessed	Number of studies, design, wound type	Date search completed	Conclusions
Diabetic foot ulceration			
Prevention modalities	**10 trials** **-** footwear (2) **-** hosiery (1) **-** education (5) - screening and foot protection (1) - podiatry (1)	End of 1998	Much uncertainty remains over the most effective interventions for the prevention and treatment of diabetic foot ulcers. Certain treatments (e.g. growth factors and offloading techniques such as total contact casting) show promise but need further, more rigorous evaluation.
Treatment modalities	**29 trials** **-** footwear (1) **-** skin replacement (2) **-** hyperbaric oxygen (2) - ketanserin (3) - Prostaglandins (3) **-** growth factors (5) - dressings and topical applications (9) - debridement (2) - antibiotics (2)		

Technology assessed	Number of studies, design, wound type	Date search completed	Conclusions
Bed, mattresses, and cushions for pressure score prevention and treatment			
Bed, mattresses, and cushions for pressure score prevention and treatment	**45** RCTs **-3** different operating – table surfaces **-6** evaluated different surfaces in intensive care units **-7** evaluated to orthopedic patients **-2** evaluated cushions **-1** evaluated the use of sheepskins **-2** looked at turning beds/kinetic therapy The remaining evaluated different mattresses, mattress overlays and beds	April 2000	Foam alternatives to the standard hospital foam mattress can reduce the incidence of pressure sores in people at risk, as can pressure-relieving overlays on the operating table. One study suggests that air-fluidised therapy may increase pressure score healing rates. There is insufficient evidence to draw conclusions about the value of seat cushions, various CLP devices (either overlays, mattresses or replacement beds) and sheepskin as pressure sore prevention strategies
Compression for leg ulcers			
Compression bandages	**24** Trials (reporting 26 comparisons) -2 prevention -24 treatment strategies	December 1999	Compression is more effective in healing venous leg ulcers than is no compression, and multi-layered high compression is more effective than single-layer compression. High-compression hosiery was more effective than moderate compression in preventing ulcer recurrence

Technology assessed	Number of studies, design, wound type	Date search completed	Conclusions
Laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy			
Low-level Laser therapy (for venous leg ulcers)	**4** RCTs	December 1999	There is insufficient reliable evidence to draw conclusions about the contribution of laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy to chronic wound healing.
Therapeutic ultrasound (for pressure sores and venous leg ulcers)	**10** RCTs **-** 7 RCTs for venous leg ulcers - 3 RCTs for pressure sores		
Electrotherapy (for ischaemic and diabetic ulcers, and chronic wounds generally)	**14** RCTs - 2 RCTs for chronic wounds - 5 trials for ischaemic ulcers -1 study for diabetic ulcers -3 RCTs for pressure sores -3 trials for venous ulcers		
Electromagnetic therapy	**5** studies - 3 RCTs with a total of 92 patients for the treatment of venous leg ulcers - 2 trials with a total 55 patients for the treatment of pressure sores		

Table 2. Mechanisms of Various Wound Treatments

Dressing Classification	Mechanism	Wound Healing Phase Affected	Examples
Non-occlusive	**Anti-infective**		
Antibacterials (topical or systemic)	Control or eradicate infection to permit healing	Inflammatory	Neosporin, Betadine, Silvadene, systemic antibiotics
	Debridement		
Debriding agents/methods	Remove necrotic tissue which interferes with healing response	Inflammatory	Saline "wet to dry" Accuzyme®, Panafil®
Semi-occlusive /occlusive			
Films Hydrocolloids Hydrogels Alginates Foams	Provide moist and warm wound environment Absorb exudate	Inflammatory & Proliferative	Opsite®, Tegaderm®, Duo Derm®, Tegagel®, Sorbsan®, Allevyn®
Biological treatments (mostly experimental)			
Living human dermal equivalent	Wound coverage – stimulate growth factors	Proliferative	Dermagraft® - neonatal foreskin derived fibroblast on a matrix Appligraft® - cultured neonatal foreskin fibroblasts and keratinocytes
Growth Factors	Promote recruitment and proliferation of cells	Proliferative	Regranex®
Platelet Concentrates	Stimulate the activation of key wound healing mechanism	Proliferative	
Stem Cells	Multiple		

Table 3. Clinical practice guidelines (2 diabetic ulcers, 1 arterial ulcers, 1 venous ulcers, and 8 pressure ulcers) examined for the management of chronic wounds

Type of Wound	Guideline Organization (Year)	Definition of Chronic Wound	Recommendations						Additional Recommendation
			Debridement	Wound Cleansing	Dressing	Pressure offloading	Infection Control	Surgical management	
Diabetic Ulcers									
Foot Ulcerations	American college of foot and Ankle Surgeons 2000	No Data	X		X	X	X	X	- management of ischemia - medical management of comorbidities
Foot ulcers	New Zealand Guidelines Group 2003	No Data			X		X		- close monitoring - prompt referral as appropriate
Arterial Ulcers									
Lower-extremity arterial	Wound Ostomy and Continence Nurses Society (WOCN) 2002	No Data	X	X	X	X	X	X	- nutrition - pain management - management of edema - adjunctive therapies - patients education
Venous Ulcers									
Chronic leg ulcers (mostly venous)	New Zealand Guidelines Group 1999	> 6 weeks	X	X	X		X	X	- compression bandages

Type of Wound	Guideline Organization (Year)	Definition of Chronic Wound	Recommendations						Additional Recommendation
			Debridement	Wound Cleansing	Dressing	Pressure offloading	Infection Control	Surgical management	
Pressure Ulcers									
Pressure Ulcers	Wound, Ostomy, and Continence Nurses Society (WOCN) 2003	No Data	X	X	X	X	X	X	- reduce friction and shear (keeping skin dry, using lift sheets or turning devices, overhead trapeze bars) - management of incontinence (bowel and bladder program; skin cleansing, skin barriers, etc) - nutrition management - educate patients caregivers and health care providers - adjunctive therapies
Stage I to IV Pressure Ulcers	Registered Nurses Association of Ontario (RNAO) 2002	No Data	X	X	X	X	X	X	- management of nutritional needs - positioning - use static and dynamic support surfaces (e.g. special beds, mattresses, seat cushions that reduce pressure while sitting or lying) - referrals to interdisciplinary team members - pain management - education - adjunctive therapies

Type of Wound	Guideline Organization (Year)	Definition of Chronic Wound	Recommendations						Additional Recommendation
			Debridement	Wound Cleansing	Dressing	Pressure offloading	Infection Control	Surgical management	
Pressure Ulcers	University of Iowa Gerontological Nursing Interventions Research Center 2002	A pressure ulcer is any injury usually caused by unrelieved pressure that damages the skins and underlying tissue.	X	X	X	X	X	X	- management of tissue loads (pressure, friction, and shearing) - nutritional assessment and support
Pressure Ulcer	Singapore Ministry of Health 2001	No Data	X	X	X	X	X	X	-Implementation of appropriate medical nutritional therapy -patient education -provision of effective pain alleviation and comfort measures
Pressure ulcers prevention and treatment (following spinal cord injury)	Paralyzed Veterans of America, 2000	No Data	X	X	X	X	X	X	- adjunctive therapies (electrical stimulation) - continue assessment - preoperative and postoperative care - support surfaces and positioning (bed positioning, bed support surfaces, wheelchair positioning, wheelchair support surfaces)
Pressure ulcers	American Medical Directors Association (AMDA) 1999	No Data	X	X	X	X	X	X	

Type of Wound	Guideline Organization (Year)	Definition of Chronic Wound	Recommendations						Additional Recommendation
			Debridement	Wound Cleansing	Dressing	Pressure offloading	Infection Control	Surgical management	
Pressure Ulcers	American Medical Directors Association (AMDA) 1996	No Data	X	X	X	X	X	X	- preventive measure - bed and chair therapeutic positioning and tissue load management - management of comorbid conditions - education and rehabilitation of the patient/caregiver
Pressure Ulcers	Agency for Health Care Policy and Research (AHCPR) 1994	No Data	X	X	X	X	X	X	- positioning techniques - support surfaces - controlling factors that impair healing - postoperative care - adjunctive therapies

Table 4. Summaries of recommendations from selected surgical textbooks on treating chronic wounds

Textbook Author, Year	Recommendations to treat chronic wounds
Surgical Infections Fry DE 1995	Diabetic foot infections: vascular assessment if debridement is necessary; culture specific antibiotics
Principles of Surgery 7th ed., Schwartz SI 1999	Chronic wounds: cleansing to reduce microbial load, debridement to remove damaged or necrotic tissue, irrigation with normal sterile saline, dressings
Surgery: Basic Science and Clinical Evidence Norton JA 2001	Open wounds: debridement; moist sterile environment, dressing that prevents pressure (e.g., plain gauze and saline with or without antibiotic ointment)
Textbook of Surgical Practice 6th ed., Rakel RE 2002	Pressure ulcers: removing pressure and friction; surgical debridement depending on stage of ulcer; saline soaked gauze and exogenous local enzymes; moist environment; occlusive dressings
Chronic Wound Management—the evidence for change Mani R, ed. 2003	Diabetic wounds: debridement, dressings, stimulation of wound healing Venous ulcer: dressings, application of bandages

Table 5. Characteristics of RCTs of diabetic, pressure and venous ulcers

Characteristics of included studies	Type of ulcers		
Diabetic N=43	**Pressure N=33**		**Venous N=66**
Sample size (mean, range)	97 (6-922)	51 (7-207)	97 (9-500)
Country			
USA n (%)	22 (52)	16 (48)	14 (21)
UK n (%)	2 (5)	5 (15)	19* (29)
Italy n (%)	7 (17)	0 (0)	7* (11)
other** n (%)	12 (29)	12 (36)	26 (39)
not specified n (%)	0 (0)	0 (0)	1 (2)
Average age (mean, range)	59 (50-73)	70 (44-88)	66 (50-76)
Average %male (mean, range)	70 (42-93)	47 (13-100)	45 (16-85)
Setting			
outpatient n (%)	23 (53)	7 (21)	49 (74)
inpatient n (%)	14 (33)	23 (70)	9 (14)
mixed n (%)	3 (7)	3 (9)	3 (5)
not specified n (%)	3 (7)	0 (0)	5 (8)
Ulcer duration			
>30 days n (%)	13 (30)	7 (21)	43 (65)
Mixed n (%)	13 (30)	11 (33)	15 (23)
not specified n (%)	17 (40)	15 (45)	8 (12)

* One study recruited patients both from UK and Italy

** None of the countries in this category reported more than 3 RCTs. Countries in this category include: Australia, India, Japan, Mexico, Thailand, and Western and Eastern European countries

Table 6. Number of RCTs reporting various treatment modalities as part of usual care for diabetic, pressure, and venous ulcers

Treatment modality	Type of ulcers		
	Diabetic n (%) N=43	Pressure n (%) N=33	Venous n (%) N=66
Surgical debridement	34 (79)	12 (36)	12 (18)
Non-surgical debridement	1 (2)	3 (9)	6 (9)
Cleansing	13 (30)	17 (52)	34 (52)
Dressing*	40 (93)	32 (97)	57 (86)
Compression	6 (14)	0 (0)	55 (83)
Antibiotics	15 (35)	4 (12)	10 (15)
Offloading	34 (79)	16 (48)	3 (5)

* Detailed dressing information appears in Table 7.

Table 7. Number of RCTs reporting specific types of wound dressings as part of usual care for diabetic, pressure, and venous ulcers

Wound dressing	Types of wounds		
	Diabetic n (%) N=43	**Pressure n (%) N=33**	**Venous n (%) N=66**
Non-occlusive			
Ointment /Cream	1 (2)[a]	2 (6)[c]	6 (9)[d,e]
Dry gauze	2 (5)	3 (9)	10 (15)[d,g,h]
Semi-Occlusive			
Saline wet-to-dry	22 (51)[a]	13 (39)[b]	3 (5)
Wet dressing	0 (0)	0 (0)	2 (3)[e]
Paraffin gauze	2 (5)	1 (3)[c]	1 (2)[f]
Vaseline gauze	1 (2)	0 (0)	4 (6)
Occlusive			
Unna boot	0 (0)	0 (0)	10 (15)[h]
Hydrocolloid	6 (14)	14 (42)[b]	25 (40)[f,g,h]
Dressing not clearly specified	7 (16)	1 (3)	5 (8)
No dressing reported	3 (7)	1 (3)	8 (12)

a: One diabetic study used both cream and saline wet-to-dry gauze
b: One pressure study used either saline wet-to-dry gauze or hydrocolloid
c: One pressure study used both ointment and paraffin gauze
d: One venous study used cream, dry gauze
e: One venous study used cream, wet dressing
f: One venous study used paraffin gauze, hydrocolloid
g: One venous study used dry gauze, hydrocolloid
h: One venous study used dry gauze, hydrocolloid, Unna boot

Table 8. Frequency of studies conforming to recommendations proposed in the FDA Draft Guidance for Industry (based on 20 selected articles for each wound type)

FDA Draft Guidance Document Recommendations	Type of ulcers		
	Diabetic n (%) N=20	Pressure n (%) N=20	Venous n (%) N=20
Outcome assessment			
Partial wound closure	9 (45)	0 (0)	5 (25)
Complete wound closure	19 (95)	17 (85)	18 (90)
Partial or complete (unclear)	1 (5)	3 (15)	1 (5)
3 months post-wound closure assessment	8 (40)	0 (0)	3 (15)
Wound size pre- & post-debridement	1 (5)	0 (0)	1 (5)
Method of assessing wound size			
Photographic/digital imaging	5 (25)	12 (60)	7 (35)
Planimetry (computerized or mechanical)	7 (35)	3 (15)	10 (50)
Not specified	8 (40)	5 (25)	5 (25)
Antimicrobial treatment			
Pre- versus during study	0 (0)	3 (15)	3 (15)
Systemic versus topical	0 (0)	3 (15)	2 (10)
Provider			
Health care provider	5 (25)	3 (15)	10 (50)
Patient	1 (5)	1 (5)	0 (0)
Both	4 (20)	1 (5)	0 (0)
Not specified	10 (50)	15 (75)	10 (50)
Maximum treatment duration			
1 – 3 weeks	0 (0)	1 (5)	0 (0)
4 weeks	0 (0)	5 (25)	1 (5)
5 – 7 weeks	3 (15)	2 (10)	0 (0)
8 weeks	1 (5)	6 (30)	0 (0)
9 – 11 weeks	1 (5)	3 (15)	0 (0)
12 weeks	8 (40)	2 (10)	4 (20)
13 – 23 weeks	4 (20)	0 (0)	1 (5)
24 weeks	0 (0)	0 (0)	5 (25)
25 – 52 weeks	3 (15)	0 (0)	9 (45)
not specified	0 (0)	1 (5)	0 (0)