Evidence-based Practice Center Systematic Review Protocol

Project Title: Chronic Venous Ulcers:
A Comparative Effectiveness Review of Treatment Modalities

Amendment Date(s) if applicable: September 4, 2012

(Amendments Details–see Section VII)

I. Background and Objectives for the Systematic Review

Background

Venous leg ulcers are extremely common in the United States and affect between 500,000 to 2 million people annually.[1] Venous leg ulcers constitute the majority of all ulcers seen in the United States. Individuals with venous leg ulcers tend to be older and more obese, with the incidence increasing with age or female sex. In the United Kingdom, where more comprehensive information is available, the mean duration of ulcers was 9 months, 20 percent of ulcers had not healed within 2 years, and 66 percent of patients had a history of ulcerations lasting longer than 5 years.[2] According to Bergan et al., "Overall, chronic venous disease has been estimated to account for 1% to 3% of total health care budgets in countries with developed health care systems."[3]

Venous leg ulcers are caused by elevated venous pressure, turbulent flow, and inadequate venous return. The latter can be due to venous occlusion or venous reflux. Risk factors for chronic venous disease include underlying illnesses where there is poor venous return (such as congestive heart failure and obesity), primary destruction of the venous system (such as prior history of deep venous thrombosis), injecting drug users (skin poppers), phlebitis, and venous valvular dysfunction.

The diagnosis of venous ulcers is made clinically on the basis of anatomic location, morphology, and a series of characteristic skin changes. The diagnosis is confirmed by the appropriate laboratory studies, which may include functional assessment of the venous system. The "gold standard" for diagnosing venous disease is venography, which is performed infrequently because of expense, morbidity, and the availability of noninvasive tests. Today venous duplex is the method used most often to diagnose venous abnormalities.[4]

Venous leg ulcers also have a series of well-defined intermediate and final outcomes. Wound healing rates, observational parameters of wound base quality, quality of life tools, and pain measurements have been proposed as reasonable surrogates for final outcomes. Final outcomes, such as percentage of wounds healed based on intent to treat and durability of healing over specified periods of time, have gained acceptance by organizations such as the U.S. Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid Services. However, the literature on chronic wounds and emerging science in the field also consider intermediate measures, such as effects on epithelization (area reduction), granulation (depth reduction), and/or vascularization of a wound. We need to consider in this review both the intermediate and final

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outcomes.

The current standard clinical approach to therapy includes lower limb compression and debridement, which heals 50 to 60 percent of venous leg ulcers.[3] If compression therapy and debridement fail, there is no widely accepted standard for second-line treatment. Below is an overview of the interventions we will evaluate in our comparative effectiveness review of the management of chronic venous ulcers. Note that our approach is more inclusive than previously published reviews, and we plan to compare classes of therapeutic agents as opposed to drawing distinctions between individual therapeutic agents.

Advanced Wound Dressings

Over the past 20 years, much evidence has been generated in the literature to support the premise that a moist wound environment is essential for wound healing. This has caused a proliferation of expensive new wound dressings, leading to confusion as to appropriate use among wound care providers. Furthermore, since many wound dressings are classified as devices and not drugs, the FDA does not require rigorous clinical trial testing. This further compounds prescriber confusion.

Advanced wound dressings regulate moisture found at the wound surface through moisture retention or exudate absorption, thereby protecting the wound base and periwound tissue. Additionally, maintaining moisture balance minimizes patient discomfort before, during, and after dressing changes. Many dressings inherently support autolytic debridement by providing added moisture, while others supply enzymatic debriding agents to rid the wound of necrotic tissue. Choice of dressings may change during the course of therapy concomitant with the changing nature of the wound base and exudate. Therefore, selection of particular dressings requires training and expertise in wound care. Evaluating the efficacy of dressings in treating venous ulcer disease may have high relevance to morphologically similar ulcers found in patients with diabetes, arterial disease, pressure ulcers, postsurgical chronic wound ulcers, and ulcers consequent to internal diseases.

Antibiotics

Antibiotic use is prevalent in the management of skin ulcers, even in the absence of clinical signs or symptoms of infection. The indications for the use of systemic or topical antibiotics are not defined, but antibiotics have profound side effects including the development of resistant organisms, the growth of undesirable organisms, and iatrogenic disease. Moreover, newer antibiotics are very expensive and may account for a substantial portion of the $25 billion spent each year for wound care.

Surgical Interventions

Most patients with venous ulcers have significant reflux on duplex scanning. Reflux is defined as retrograde blood flow lasting greater than 0.5 seconds in the greater or lesser saphenous veins or in the perforator veins with the Valsalva maneuver. As a general rule, Duplex scanning, which is now considered routine in most vascular laboratories, is essential in venous

ulcer classification. Modern ultrasonography routinely demonstrates valvular incompetence and large perforating veins. However, there is still a debate about the necessity of performing venous Duplex on every patient with a venous ulcer. Invasive venography and ambulatory venous pressure are obtained when clinical and Duplex findings are insufficient to confirm the diagnosis.

The current surgical practice is to eliminate documented reflux in patients with chronic venous ulcer that failed a 3-month period of compression dressing, debridement, and antibiotics. The minimally invasive endovenous approach has gained popularity and has been used routinely instead of vein stripping. However, each underlying pathology has several surgical treatment options with no clear evidence about which is the safest and most effective in healing the ulcer. In addition, the indications for surgery have not been standardized.

To define the Key Questions (KQs) further, we will use the PICOTS approach, taking into consideration the most important populations, interventions, comparisons, outcomes, timing, and settings of interest.

II. The Key Questions

Our draft KQs were posted on the Agency for Healthcare Research and Quality's Effective Health Care Program Web site for public comment in October 2011. Based on the public feedback, we revised our KQs by clarifying the language used to describe the interventions and comparators. We have also added biological dressings as an intervention for KQ 1. The finalized KQs are presented below.

Question 1

For patients with chronic venous leg ulcers, what are the benefits and harms of using dressings that regulate wound moisture with or without active chemical, enzymatic, biologic, or antimicrobial components in conjunction with compression systems when compared with using solely compression systems?

Question 2

a. For patients with chronic venous leg ulcers that do not have clinical signs of cellulitis that are being treated with compression systems, what are the benefits and harms of using systemic antibiotics when compared with using solely compression systems?

b. For patients with chronic venous leg ulcers that do not have clinical signs of cellulitis that are being treated with dressings that regulate wound moisture with or without active chemical, enzymatic, biologic, or antimicrobial components, what are the benefits and harms of using systemic antibiotics when compared with using dressings alone?

Question 3

a. For patients with chronic venous leg ulcers, what are the benefits and harms of surgical procedures aimed at the underlying venous abnormalities when compared with using solely

compression systems?

b. For patients with chronic venous leg ulcers, what are the comparative benefits and harms of different surgical procedures for a given type of venous reflux and obstruction?

PICOTS Framework
Population(s)

- The population will include adult patients with chronic venous leg ulcers. We will use the standard definition of a chronic venous leg ulcer, which is the presence of an active ulcer for 6 weeks or more with evidence of earlier stages of venous disease such as varicose veins, edema, pigmentation, and venous eczema. We will include studies of patients with or without other major comorbidity.
- By focusing on chronic venous leg ulcers (for the reasons mentioned in the Background section) we will exclude arterial ulcers (defined by an ankle brachial index less than 0.6 or a toe brachial index less than 0.5 or other clinical criteria), pressure ulcers, postsurgical ulcers, and neuropathic ulcers.
- We will exclude the following less common types of venous ulcers: genetically determined ulcers (e.g., congenital venous disease, sickle cell disease, and inherited thrombophilias); ulcers resulting from trauma in patients without signs of previous venous disease; ulcers in the setting of collagen vascular disease or inflammatory bowel disease; ulcers occurring in atypical locations (e.g., soles, toes, above mid-calf); and ulcers complicated by active infection (e.g., cellulitis, fasciitis).

Interventions

- For KQ 1, we will review all types of wound dressings with or without active chemical, enzymatic, biologic, or antimicrobial components, categorizing them by function (see Table 1 for a description of the functional categories, classifications, and characteristics of each group). These dressings are defined as those with biological activity, debridement activity, antimicrobial activity, or enhanced absorptive/barrier properties.

- For KQ 2, we will review systemic antibiotic use, in the context of managing chronic wounds, including the application of case definitions for infection and for initiating therapy. The antimicrobials of interest are listed below (see Table 2 for more details of these interventions).

    - Acceptable cointerventions would be compression systems for KQ 2a and dressings that regulate wound moisture with or without active chemical, enzymatic, biologic, or antimicrobial components for KQ 2b.

- For KQ 3, we will include surgical interventions by type of venous reflux and obstruction (Table 3).

- For superficial reflux (greater or small saphenous vein):
  - Vein stripping (physically removing the vein to eliminate the reflux) and vein ligation
  - Radiofrequency ablation (RFA)
  - Endovenous laser treatment
- For perforator reflux (the principle is interruption of the incompetent perforator vein):
  - Subfascial Endoscopic Perforator Surgery (SEPS)
  - Duplex-guided RFA
  - Sclerotherapy of perforator vein
- For reflux in the deep system:
  - Valvuloplasty (either internal or external)
  - External banding
  - Valve transplantation
  - Valve transposition
  - Valve substitution
- Obstructive deep system (usually at the level of the femoral and iliac veins and vena cava):
  - Endovascular approach:
    - Thrombolysis
    - Mechanical thrombectomy
    - Angioplasty and stenting
  - Open bypass using:
    - Dacron® grafts
    - Externally supported polytetrafluoroethylene (PTFE) grafts
    - Greater saphenous vein
    - Incorporating arteriovenous fistula

Comparators

- For KQs 1, 2a, and 3, the comparator of interest will be compression systems alone. Compression systems include the following components:
  - Debridement of necrotic tissue which may be by sharp, autolytic, enzymatic, mechanical (which includes pulse jet and ultrasound), or biologic debridement that leads to a clean wound base. Simple dressings containing nonactive components such

as moisturizers
- At least moderate compression described either qualitatively or quantitatively (>30 mm), so that the leg does not swell significantly during the day.

- For KQ 2b, the comparator of interest will be dressings that regulate wound moisture with or without active chemical, enzymatic, biologic, or antimicrobial components.

- For KQ 3b, the comparator of interest will be other surgical interventions of interest for a given type of venous reflux and obstruction.

- Within each intervention domain (active dressings, antimicrobials, and surgery), there are multiple possible options. Besides assessing effectiveness of each to standard conservative management, they can be compared with each other (See Figures 2–4). Within the context of this review, we will assess the availability of evidence for these intervention comparisons. Comparisons will be made both within and across classes of therapies.

Outcomes

- Intermediate outcomes

  - Wound healing rates (defined as percent area reduction from baseline) over a 4-week period of time as measured by planimetry (photos, etc,)
  - Pain using the standard pain scales
  - Quality of the wound bed as measured objectively using photographs and patient questionnaires

- Final outcomes

  - Time to achieve complete wound closure
  - Proportion of ulcers healed at 12 weeks
  - Rate of wound recurrence after 24 weeks and at 1 year
  - Development of new wounds at different anatomical locations
  - Quality of life

    - General
    - Disease-specific

  - Mortality
  - Functional status

- Harms of intervention(s)

  1. General harms for KQs 1–3

a. Maceration
b. Infection
c. Contact dermatitis
d. Venous or arterial impairment
e. Cellulitis

2. Harms for topical antibiotics contained in dressings (KQ 1)

   a. Hypersensitivity, contact dermatitis, and sensitization (e.g., neomycin)
   b. Promotion of antibiotic resistance
   c. Systemic absorption (rare)
3. Harms for systemic antibiotics (KQ 2)

   a. Allergic and hypersensitivity reactions
   b. Drug toxicity (not allergic)

      i. Major—renal toxicity, hepatic toxicity, gastrointestinal upset

   c. *Clostridium difficile* diarrhea
   d. For intravenous antibiotics, peripherally inserted central catheter (PICC) line and access infections
   e. Promotion of antibiotic resistance
   f. Selection of resistant organisms

4. Harms for surgical interventions (KQ3)

   a. Surgical site infection
   b. Bleeding
   c. Skin irritation and burn
   d. Deep vein thrombosis
   e. Long-term recurrent reflux and ulceration

Timing

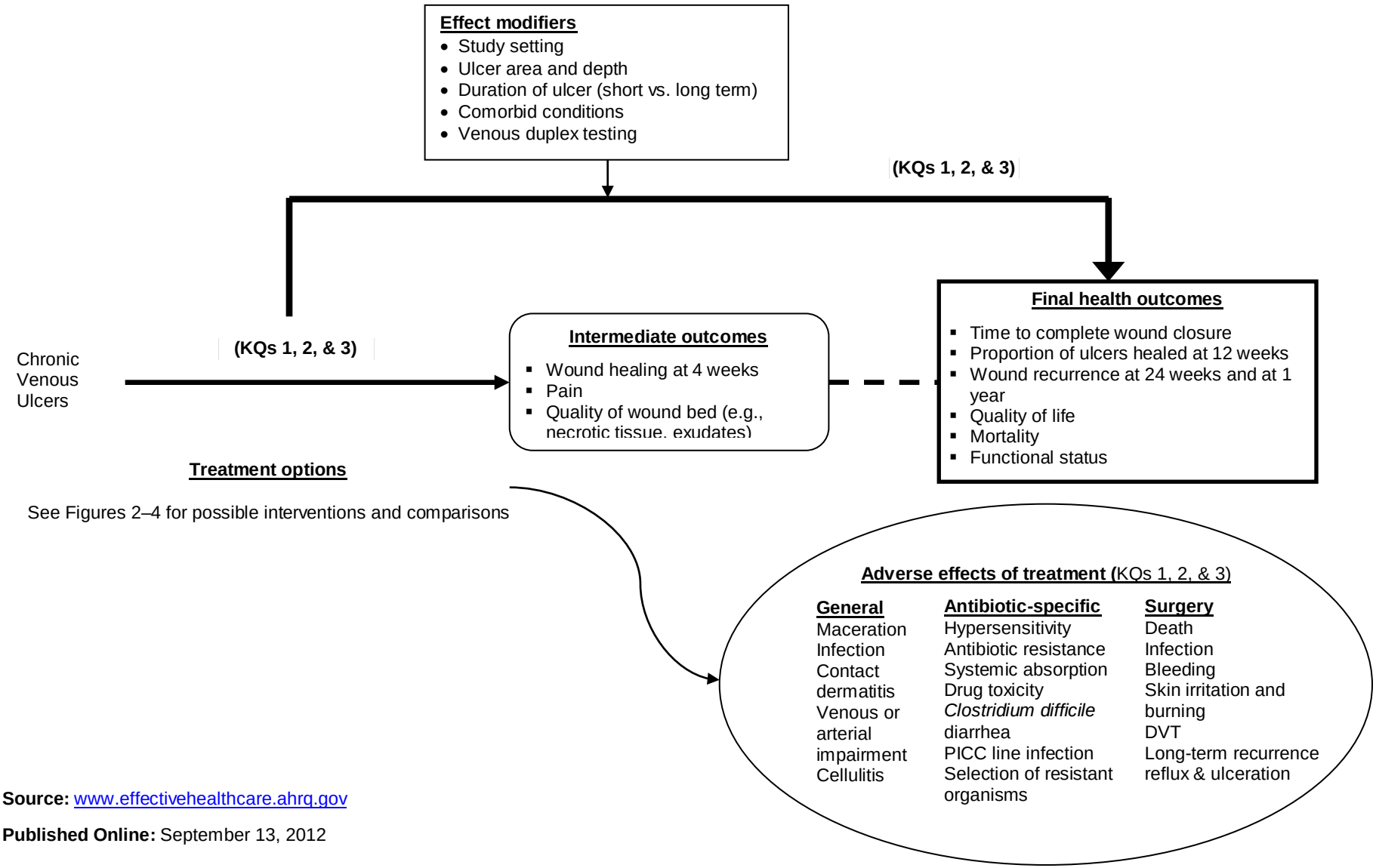
- Durations with 4 or more weeks of followup.

Setting

- All study settings (e.g., wound centers, long-term care facilities) will be included.

III. Analytic Framework

Figure 1. Analytic framework for the treatment of chronic venous ulcers.



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Abbreviations: DVT = deep vein thrombosis; KQ = key question; PICC = peripherally inserted central catheter

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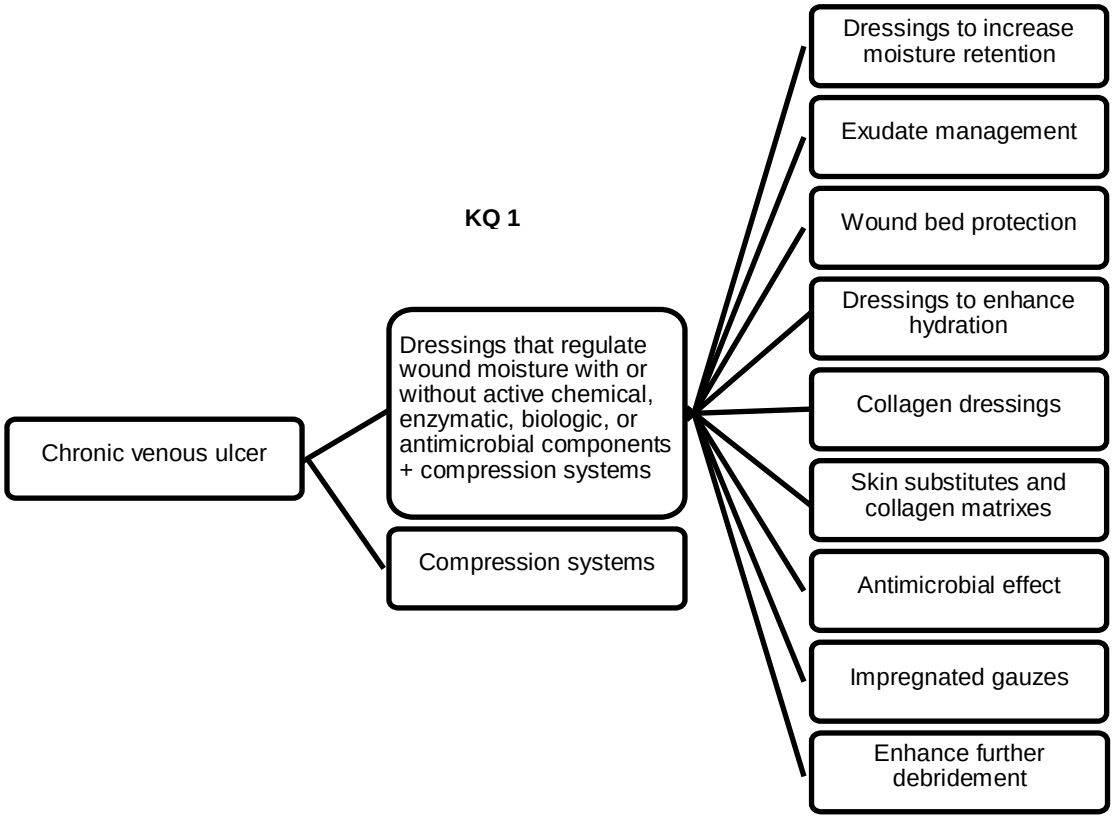
Figure 2. Potential options for wound dressings with active chemical, enzymatic, or antimicrobial components for the treatment of chronic venous ulcers



Compression systems include the following elements:

- Debridement of necrotic tissue that may be by sharp, autolytic, enzymatic, mechanical (which includes pulse jet and ultrasound), or biologic debridement that leads to a clean wound base. Debridement will be classified, when possible, into wound bed debridement and excisional debridement.

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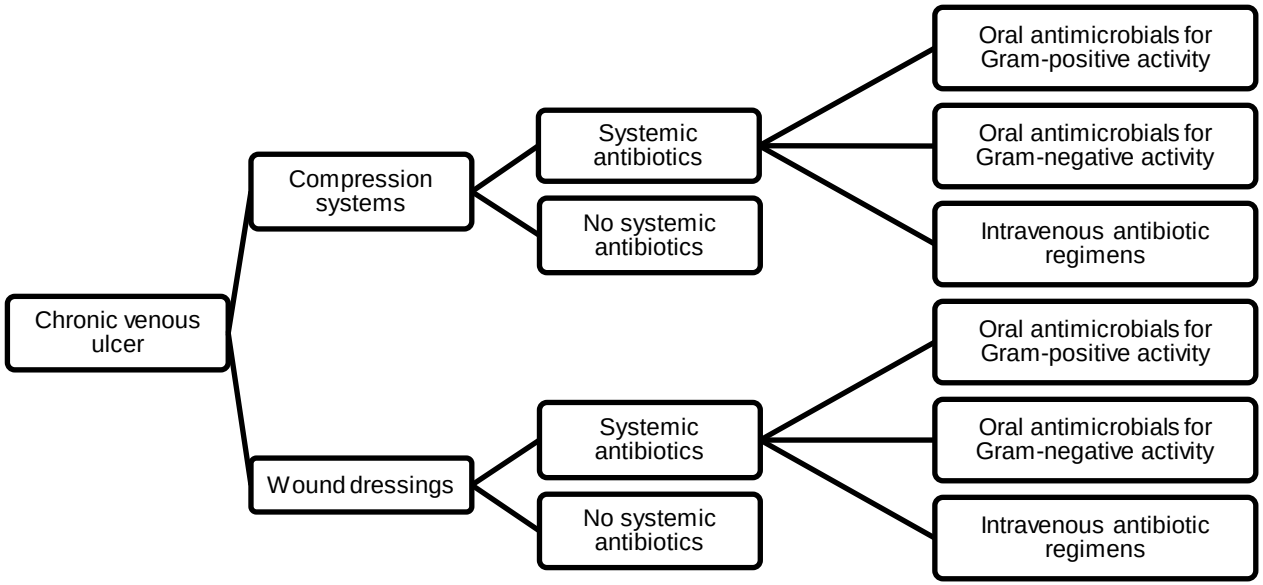
- Simple dressings containing nonactive components such as moisturizers.
- At least moderate compression described either qualitatively or quantitatively (>20 mm), so that the leg does not swell significantly during the day.

Figure 3. Potential systemic antibiotic treatment options for chronic venous ulcers



See Table 2 for a list of antibiotics.

Compression systems include the following elements:

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- Debridement of necrotic tissue that may be by sharp, autolytic, enzymatic, mechanical (which includes pulse jet and ultrasound), or biologic debridement that leads to a clean wound base. Debridement will be classified, when possible, into wound bed debridement and excisional debridement.
- Simple dressings containing nonactive components such as moisturizers.
- At least moderate compression described either qualitatively or quantitatively (>20 mm), so that the leg does not swell significantly during the day.

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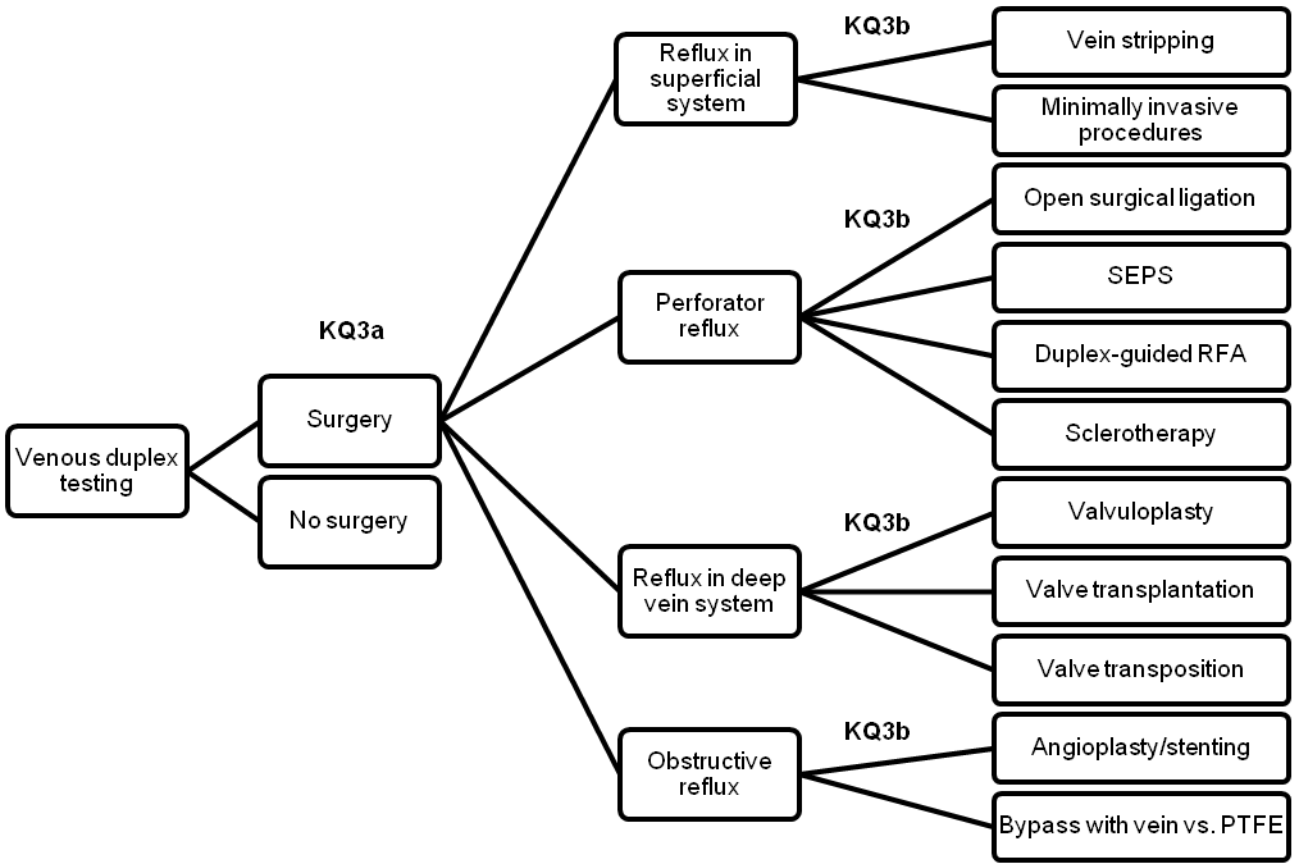
Figure 4. Potential surgical treatment options for chronic venous ulcers



Abbreviations: KQ = key question; PTFE = polytetrafluoroethylene; RFA = radiofrequency ablation; SEPS = subfacial endoscopic perforator surgery

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IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

The inclusion/exclusion criteria are presented in Table 4.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

We will search the following databases for primary studies: MEDLINE®, EMBASE®, the Cochrane Central Register of Controlled Trials, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL®). We will develop a search strategy for MEDLINE, accessed via PubMed®, based on an analysis of medical subject headings (MeSH®) and text words of key articles identified a priori. Our search strategy for MEDLINE is presented in Tables 5–7. The search will be updated during the peer review process.

Additionally, the team will search clinicaltrials.gov to identify relevant registered trials. We will review the Scientific Information Packets provided by the pharmaceutical manufacturers.

C. Data Abstraction and Data Management

Two independent reviewers will conduct title scans. For a title to be eliminated at this level, both reviewers will need to indicate that the study was ineligible. If the reviewers disagree, the article will be advanced to the next level, which is abstract review.

The abstract review phase will be designed to identify studies reporting the effects of treatment options for chronic venous leg ulcers. Abstracts will be reviewed independently by two investigators and will be excluded if both investigators agree that the article meets one or more of the exclusion criteria (see the inclusion and exclusion criteria listed in Table 4). Differences between investigators regarding the inclusion or exclusion of abstracts will be tracked and resolved through consensus adjudication.

Articles promoted on the basis of the abstract review will undergo another independent parallel review to determine if they should be included in the final qualitative and quantitative systematic review and meta-analysis. The differences regarding article inclusion will be tracked and resolved through consensus adjudication.

We will use a systematic approach to extract all data to minimize the risk of bias in this process. We will create standardized forms for data extraction, which will be pilot tested. By creating standardized forms for data extraction, we seek to maximize consistency in identifying all pertinent data available for synthesis.

Each article will undergo double review by the study investigators for data abstraction. The second reviewer will confirm the first reviewer's abstracted data for completeness and accuracy. Reviewer pairs will be formed to include personnel with both clinical and methodological expertise. A third reviewer will audit a random sample of articles to ensure consistency in the data abstraction of the articles. Reviewers will not be masked to the authors of the articles, their respective institutions, nor the journals in which their articles were published.

For all articles, the reviewers will extract information on general study characteristics (e.g.,

study design, study period, and followup), study participants (e.g., age, sex, duration of ulcer, smoking status, diabetes status, other systemic diseases, concomitant use of immunosuppressants or steroids, prior treatment), characteristics of the wound (e.g., size, whether wound was cleaned before dressing, nature of wound base), interventions (including usual care/placebo such as compression types and debridement types, advanced wound dressings, antimicrobials used, and surgical interventions, the duration of use), comparisons (including type of compression used [e.g., two-layer, short stretch, long stretch, multi-layer, Unna boot, and compression pump]), outcome measures, definitions, and the results of each outcome, including measures of variability. We expect that many studies will include patients with different types of venous disease and will use the CEAP classification of venous disease based on: clinical severity, etiology, anatomy, and pathophysiology.[5] In this classification scheme, the highest grade of clinical severity is an open venous ulcer. We will only include studies if we can extract data on those patients who were classified as having an open ulcer. We will collect data on subgroups of interest, including age, presence of comorbid conditions (e.g., diabetes, obesity), and setting.

All information from the article review process will be entered into a DistillerSR database (Evidence Partners Inc., Ottawa, Canada) by the individual completing the review. Reviewers will enter comments into the system whenever applicable. The DistillerSR database will be used to maintain the data and to create detailed evidence tables and summary tables.

D. Assessment of Methodological Quality of Individual Studies

Article quality will be assessed differently for randomized controlled trials (RCTs) and observational studies during the final qualitative and quantitative review. For RCTs, the dual, independent review of article quality will be based on the Cochrane Collaboration's Risk of Bias Tool.[6] For nonrandomized observational studies, we will use the Downs and Black quality assessment tool.[7] We will supplement these tools with additional quality-assessment questions based on recommendations in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter *Methods Guide*).[8] For both the RCTs and the nonrandomized studies, the overall study quality will be assessed as:

- **Good (low risk of bias).** These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
- **Fair.** These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.
- **Poor (high risk of bias).** These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Differences between reviewers will be resolved through consensus adjudication.

E. Data Synthesis

We will conduct meta-analyses when there are sufficient data (at least three studies) and studies are sufficiently homogenous with respect to key variables (population characteristics, study duration, and treatment). For instance, we expect studies to differ in terms of the inclusion of patients with comorbid conditions or the exact composition of compression stockings used in the comparison group. We plan to conduct analyses by treatment or drug class where possible.

For continuous outcomes, we will calculate a weighted mean difference by using a random-effects model with the DerSimonian and Laird formula.[9] For dichotomous outcomes, we will calculate a pooled effect estimate of the relative risk between the trial arms of RCTs, with each study weighted by the inverse variance, by using a random-effects model with the DerSimonian and Laird formula for calculating between-study variance.[9]

Heterogeneity among the trials in all the meta-analyses will be tested by using a standard chi-squared test with a significance level of alpha ≤0.10. Heterogeneity will also be examined among studies by using an I^2 statistic, which describes the variability in effect estimates that is due to heterogeneity rather than random chance.[10] A value greater than 50 percent may be considered to have substantial variability. If we find substantial heterogeneity, we will attempt to determine potential reasons for this by conducting meta-regression analyses using study-level variables, such as presence of comorbid conditions or setting.

We anticipate that wound dressings will change throughout the wound healing process. We may limit the analysis to only those wound dressings that are used for at least 75 percent of the time.

Publication bias will be examined by using Begg's test and Egger's test, including evaluation of the asymmetry of funnel plots for each comparison of interest for the outcomes for which meta-analyses are conducted.[11 12]

STATA statistical software (Intercooled, version 9.2, StataCorp, College Station, TX) will be used for all meta-analyses.

Studies that are not amenable to pooling will be summarized qualitatively.

F. Grading the Evidence for Each Key Question

At the completion of our review, at least two reviewers will independently assign evidence grades. Conflicts will be resolved through consensus or third-party adjudication. We will grade the strength of evidence based on the quantity, quality, and consistency of the best available evidence, addressing KQs 1, 2, and 3 by adapting an evidence grading scheme recommended in the *Methods Guide*.[13] We will apply evidence grades to the bodies of evidence about each intervention comparison for each outcome. We will assess the risk of bias of individual studies according to study design characteristics, such as confounding and selection and information biases. We will assess the strength of the best available evidence by assessing the limitations to individual study quality (using individual quality scores), consistency, directness, precision, publication bias, and the magnitude of the effect.

We will classify evidence pertaining to the KQs into four basic categories: 1) "high" grade (indicating high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of the effect); 2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of the effect and may change the estimate); 3) "low" grade (indicating low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and 4) "insufficient" grade (evidence is unavailable).

G. Assessing Applicability

We will assess the applicability of studies in terms of the degree to which the study population (age, duration of ulcer, comorbidities), interventions (treatment, cointerventions, duration of treatment), outcomes, and settings (nursing home, wound care center, primary care, hospital/inpatient) are typical for the treatment of individuals with chronic venous leg ulcers who are receiving treatment. For example, if the study included a very old population in nursing homes, then it may have limited applicability to patients in other settings.

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VI. Definition of Terms

FDA = U.S. Food and Drug Administration
PTFE = polytetrafluoroethylene
RCT = randomized controlled trial
RFA = radiofrequency ablation
SEPS = subfascial endoscopic perforator surgery

VII. Summary of Protocol Amendments

The following protocol amendments were made on September 4, 2012.

Date	Section	Original Protocol	Revised Protocol	Rationale
9/4/12	II, IV.A	We will exclude studies that do not have a concurrent comparison group.	For surgical interventions, we included studies without a concurrent comparison group if the study (a) included at least 30 patients with chronic venous leg ulcers for at least 6 weeks; (b) described the sampling frame; (c) provided demographic and baseline characteristics for the patients with chronic venous ulcers; and (d) assessed ulcer healing rates.	Because the volume of comparative studies of surgical interventions was scant, noncomparative studies will be included to assess both benefits and harms of KQ 3. While we recognize the potential bias due to the absence of a concurrent comparison group, these studies will provide useful information about available surgical procedures.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end-users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published 3 months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

One of the Coprincipal Investigators has received research support from Healthpoint Corporation to study the effect of neonatal karatinocytes and libroblasts in a fibrin matrix on wound healing; enrollment for this study ended in March 2011. He is also a member of the Board of Directors for Tridien Corporation. He is on the editorial board for the *Journal of Investigative Dermatology*, a member of the Society for Advanced Wound Care, and a trustee of George Washington University.

The other Coprincipal Investigator is the chair of Scientific and Safety Monitoring for a large phase III vaccine trial.

None of the other investigators had any disclosures.

XIII. Role of the Funder

This project was funded under Contract No. HHSA-290-2007-10061-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Table 1. Functional categories, classifications, characteristics, and Healthcare Common Procedure Coding System classification of wound dressings with active chemical, enzymatic, biologic, or antimicrobial components

Functional category	Classification	Characteristics	HCPS classification
Dressings to increase moisture retention	Hydrocolloids	• Adhesives and hydrophilic polymers (cellulose, gelatin, pectin) attached to a water-resistant polyurethane film or sheet • Polymers form a gel on contact with wound exudate: allows for wound hydration and autolytic debridement	• Hydrocolloid dressing, wound cover, sterile
	Transparent films	• Transparent sheets of polyurethane coated with an adhesive • Act as a "blister roof" to provide a moist wound-healing environment, promotes autolysis, and protects the wound and periwound tissues from external trauma	• Transparent film, sterile
Exudate management	Alginates	• Derived from seaweed and spun into a rope or sheet dressing • Fibrous and highly absorbent and can become gel-like when coming into contact with exudate to maintain a moist wound-healing environment • Are primary or secondary dressings	• Alginate or other fiber gelling dressing, wound cover • Alginate or other fiber gelling dressing, wound filler
	Foams	• Sterile, nonlinting, absorptive dressing made of open cell, medical grade expanded polymer • It is nonadherent	• Foam dressing, wound cover, sterile (with/without adhesive border) • Foam dressing, wound filler, sterile
	Composites	• Combine physically distinct components into a single dressing that provides multiple functions: 1) bacterial barrier; 2) absorptive layer other than an alginate, foam, hydrocolloid, or hydrogel; 3) either semi-adherent or nonadherent property; and 4) adhesive border	• Composite dressing, sterile with adhesive border
	Specialty absorptive dressings	• Unitized, multilayer dressings that provide either a semi-adherent quality or nonadherent layer and highly absorptive layers of fibers such as absorbent cellulose, cotton, or rayon	• Specialty absorptive dressing, wound cover, sterile with/without adhesive border
Wound bed protection	Contact layer	• Thin, nonadherent sheets placed directly on an open wound bed to protect the tissue from direct contact with other agents or dressings	• Contact layer, sterile
Dressings to enhance hydration	Hydrogels	• A polymer gel composed mostly of water in a complex network of fibers • Water is released to keep the wound moist • Can be hydrophilic	• Hydrogel dressing, wound cover, sterile with/without adhesive border • Hydrogel dressing, wound filler
Collagen dressings	Sheets, wound filler gels or powder	• Freeze-dried bovine, porcine, or equine collagen • Can contain cellulose or alginate for absorption	• Collagen-based wound filler, dry form • Collagen-based wound filler, gel/paste • Collagen dressing, sterile, pad

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Table 1. Functional categories, classifications, characteristics, and Healthcare Common Procedure Coding System classification of wound dressings with active chemical, enzymatic, or antimicrobial components

Functional category	Classification	Characteristics	HCPS classification
Skin substitutes and extracellular matrixes	Acellular	• Extracellular matrixes that support new tissue growth • Animal derived extracellular matrix (Oasis®) • Cryopreserved human skin allograft (TheraSkin®) • Three-dimensional porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan (Integra™)	
	Cellular	• Bioengineered, bilayered, living cell-based skin substitute (Apligraf®) • Cryopreserved human fibroblast-derived dermal substitute (Dermagraft®)	
Antimicrobial effect	Alginates, foams, hydrocolloids, hydrogels, transparent films, absorptive specialty dressings, collagens	• See individual dressing characteristics • Dressings containing silver, sodium chloride, polyhexamethylene biguanide, bismuth, muka honey, iodine, gentian violet, polyvinyl alcohol with methylene blue, cadexomer iodine, and chlorhexidine	• HCPS classifications as listed above
Gauzes	Impregnated	• Made of woven and nonwoven fibers of cotton, polyester, or a combination in which substances have been added such as: iodinated agents, petrolatum, zinc compounds, crystalline sodium chloride, chlorhexadine gluconate, bismuth tribromophenate, aqueous saline, hydrogel, and other agents	• Gauze, impregnated with other than water, normal saline, or hydrogel, sterile, pad • Gauze, impregnated, water or normal saline, sterile, pad • Gauze, impregnated, hydrogel, for direct wound contact, sterile, pad
Enhance further debridement	Biologic enzymatic debriding agent (collagenase santyl)	• Derived from fermentation by *Clostridium histolyticum* • Sterile enzymatic debriding ointment that contains 250 collagenase units per gram of white petrolatum USP is able digest collagen in necrotic tissue	

Abbreviations: HCPS = Healthcare Common Procedure Coding System

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Table 2. Antibiotic treatments for chronic venous ulcers

Class	Indications	Drug names	Benefits	Disadvantages
Oral antimicrobials (used primarily for Gram-positive activity)	Susceptible Staph (MSSA) and streptococci	Cephalosporins (e.g., cephalexin, Keflex®); amoxicillin/clavulanate; dicloxacillin	Inexpensive	Usually require multiple doses/day; major adverse events include rash, intolerance, allergy
	MRSA	Clindamycin	Also can treat anaerobes; allergy is rare; good bone and tissue penetration	Effective against only 50% of MRSA; requires multiple daily dosing; GI intolerance
		Trimethoprim/sulfamethoxazole	Inexpensive; good bone and tissue penetration	Interacts with warfarin; not effective against streptococci; high rate of allergy for sulfamethoxazole
		Linezolid	Effective against enterococci and streptococci; high bioavailability	Multiple contraindications (e.g., patients taking an SSRI); expensive; high rate of symptomatic side effects; thrombocytopenia
Oral drugs used for Gram-negative activity	Gram-negative organisms	Quinolones (ciprofloxacin, levofloxacin, moxifloxacin)	Effective against most community acquired GNRs and Pseudomonas; rarely anaphylactoid reaction; can dose once daily; high bioavailability	GI intolerance; increased risk for C. diff; prolonged exposure can result in resistance
		Beta lactams (augmentin, ceflixime, cefpodoxime)	Usually effective first-round for community-acquired organisms	Requires multiple dosing
Intravenous antibiotic regimens	Gram-positive sensitive Staph (MSSA)	Cefazolin, unasyn		Requires multiple dosing; requires prolonged IV access (usually PICC line); requires weekly monitoring
		Ceftriaxone	Can be dosed once daily	Requires prolonged IV access (usually PICC line); requires weekly monitoring
	Gram-positive organisms (MRSA)	Vancomycin	Inexpensive; effective against MRSA; can be dosed postdialysis	Requires weekly monitoring for drug toxicity; requires frequent adjustment of dosing
		Daptomycin	Used when intolerant to vancomycin; dosed once daily; can be dosed postdialysis	Expensive; toxicity is myositis; requires weekly CK monitoring
	Gram-negative organisms (B-lactams)	Ertapenem	Can be dosed once daily; broad spectrum for enteric gram-negative bacteria and anaerobes; requires minimal monitoring	Not effective for Pseudomonas or many MDR organisms
		Ceftriaxone		No anaerobic activity
	Pseudomonas	Piperacillin tazobactam, cefipime	Minimal toxicity profile	Requires multiple daily doses
	Aminoglycosides	Gentamicin, tobramycin, amikacin	Can be dosed once daily	Major renal toxicity; requires close monitoring of dose, drug levels, renal function

Abbreviations: C. diff = *Clostridium difficile*; CK = creatine kinase; GI = gastrointestinal; GNR = Gram-negative rods; IV = intravenous; MDR = multidrug resistant; MSSA =

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methicillin-sensitive *Staphylococcus aureus*; MRSA = methicillin-resistant *Staphylococcus aureus*; PICC = peripherally inserted central catheter; Staph = Staphylococcus; SSRI = selective serotonin reuptake inhibitor

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Table 3. Surgical treatments for chronic venous ulcers

Pathology	Treatment
Superficial veins reflux	Vein stripping RFA EVLT
Deep veins reflux	Internal valvuloplasty External valvuloplasty External banding Valve transplantation Valve transposition Valve substitution
Perforator veins reflux	Ligation SEPS RFA Sclerotherapy
Deep veins obstruction	Acute: Thrombolysis Thrombectomy PTA/Stenting Chronic: Bypass (with vein vs. PTFE)

Abbreviations: EVLT = endovenous laser therapy; PTA = percutaneous transluminal angioplasty; PTFE = polytetrafluoroethylene; RFA = radiofrequency ablation; SEPS = subfacial endoscopic perforator surgery

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Table 4. Inclusion and exclusion criteria

Population and condition of interest	• All studies will include human subjects exclusively. • We will include studies of patients with chronic venous leg ulcers. We will use the standard definition of chronic venous leg ulcer: o Presence of an active ulcer for six weeks or more with evidence of earlier stages of venous disease such as varicose veins, edema, pigmentation, and venous eczema o We will include studies of patients with or without other major comorbidity. o We will exclude arterial ulcers (defined by ankle brachial index less than 0.6 or toe brachial index less than 0.5 or other clinical criteria), pressure ulcers, post-surgical ulcers, and neuropathic ulcers. o We will exclude the following less common types of venous ulcers: genetically determined ulcers (e.g., congenital venous disease, sickle cell disease, and inherited thrombophilias); ulcers resulting from trauma in patients without signs of previous venous disease; ulcers in the setting of collagen vascular disease or inflammatory bowel disease; ulcers occurring in atypical locations (e.g., soles, toes, above mid-calf); and ulcers complicated by active infection (e.g., cellulitis, fasciitis). • We will exclude studies that have a mixed population of patients with chronic wounds (i.e., not all patients have chronic venous ulcers) unless the study presents a subgroup analysis of patients with chronic venous ulcers.
Interventions	• We will include studies that evaluate advanced wound dressings, systemic antibiotics, and surgical interventions. o We will include all types of advanced wound dressings, defined with either biological activity, debridement activity, antimicrobial activity, or enhanced absorptive/barrier properties. o We will include systemic antibiotics in the context of managing chronic wounds, including the application of case definitions for infection and initiating therapies. The antimicrobials of interest include oral antimicrobials used primarily for Gram-positive activity, oral drugs used for Gram-negative activity, and intravenous antibiotic regimens. o We will include surgical interventions, including interventions for superficial reflux, perforator reflux, and reflux in the deep system. o We will exclude topical or hyperbaric oxygen because it is not FDA approved.
Comparisons of interest	• We will include studies that compare the interventions with conservative care or with each other. Conservative care includes: o Debridement of necrotic tissue which may be by sharp, autolytic, enzymatic, mechanical (which includes pulse jet and ultrasound), or biologic debridement which leads to a clean wound base. Simple dressings containing non-active components such as moisturizers o At least moderate compression described either qualitatively or quantitatively (<20mm), so the leg does not swell significantly during the day. • We will exclude studies that do not have a concurrent comparison group. Both the treatment and comparison groups must receive the same type of compression. • We will exclude studies that use pneumatic intermittent compression as a comparison group.
Outcomes	• We will include studies that evaluate one of the following outcomes: o Intermediate outcomes – Wound healing rates – Pain – Quality of the wound bed – Relationship of intermediate healing rates to complete healing o Final outcomes – Time to achieve complete wound closure – Proportion of ulcers healed at 16 weeks – Rate of wound recurrence after 1 year – Development of new wounds at different anatomical locations – Death

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	– Quality of life (general, disease-specific) – Mortality – Functional status o Adverse events – For topical antibiotics contained in dressings: hypersensitivity, contact dermatitis, sensitization, promotion of antibiotic resistance, systemic absorption – For systemic antibiotics: allergic and hypersensitivity reactions, drug toxicity, Clostridium difficile diarrhea, promotion of antibiotic resistance, selection of resistant organisms – For intravenous antibiotics: peripherally inserted central catheter line and access infections – For surgical interventions: surgical site infection, bleeding, skin irritation and burn, deep vein thrombosis, and long-term recurrent reflux and ulceration
Type of study	• We will exclude articles with no original data (reviews, editorials, and commentaries). • We will include randomized controlled trials and observational studies with a concurrent comparison group. • We will not place any restrictions based on sample size or language. • We will exclude studies published before 1980 because most interventions were not available prior to 1980.
Timing and Setting	• We will include studies with at least 4 weeks of followup • We will include all study settings

Abbreviations: FDA = U.S. Food and Drug Administration

Table 5. PubMed search string to capture studies on wound dressings

Search	String	# Hits
#1	"Leg ulcer"[mh]	15508
#2	"Varicose ulcer"[mh]	3460
#3	"chronic leg"[tiab]	724
#4	"chronic venous"[tiab]	3035
#5	"lower extremity"[tiab] OR "lower extremities"[tiab] OR "lower limb"[tiab] OR "lower limbs"[tiab]	43707
#6	Ulcer[tiab] OR ulcers[tiab] OR ulceration[tiab]	108582
#7	(#3 OR #4 OR #5) AND #6	3298
#8	"leg ulcer"[tiab] OR "leg ulcers"[tiab] OR "leg ulceration"[tiab]	4478
#9	"venous ulcer"[tiab] OR "venous ulcers"[tiab] OR "venous ulceration"[tiab]	1528
#10	"venous stasis ulcer"[tiab] OR "venous stasis ulcers"[tiab] OR "venous stasis ulceration"[tiab]	180
#11	"chronic wound"[tiab] OR "chronic wounds"[tiab]	2243
#12	#1 OR #2 OR #7 OR #8 OR #9 OR #10 OR #11	19209
#13	Bandages[mh]	17438
#14	"Bandages, hydrocolloid"[mh]	523
#15	"Iodine compounds"[mh]	14492
#16	"Iodine/therapeutic use"[mh]	3506
#17	Iodophors[mh]	2347
#18	Collagen[mh]	87537
#19	"Skin, artificial"[mh]	1539
#20	Dressing*[tiab] or bandag*[tiab]	16094
#21	Hydrocolloid*[tiab]	1140
#22	Film*[tiab]	89949
#23	Alginate*[tiab]	7799
#24	Foam*[tiab]	14413
#25	Composite*[tiab]	64785
#26	Absorb*[tiab] OR absorpt*[tiab]	251302
#27	Gauze*[tiab]	2625
#28	Antibacterial*[tiab]	36039
#29	iodine*[tiab]	32706
#30	"silver"[tiab]	35472
#31	"polyhexamethylene biguanide"[tiab]	175
#32	"bismuth"[tiab]	5126
#33	honey[tiab]	4485
#34	collagen*[tiab]	139731
#35	oasis*[tiab]	1633
#36	"extracellular matrix"[tiab]	53496
#37	Iodosorb[tiab]	18
#38	Polyurethanes[mh]	6464
#39	Allograft*[tiab]	46451
#40	Bilayer*[tiab] OR bi-layer*[tiab]	30728
#41	Bioengineer*[tiab] OR bio-engineer*[tiab]	2860
#42	Biological*[tiab]	419280
#43	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42	1214185
#44	(animal[mh] NOT human [mh])	3616211
#45	Addresses[pt] OR Autobiography[pt] OR Bibliography[pt] OR Biography[pt] OR "Case Reports"[pt] OR "Classical Article"[pt] OR "Clinical Conference"[pt] OR "Collected Works"[pt] OR Comment[pt] OR Congresses[pt] OR "Consensus Development Conference"[pt] OR "Consensus Development Conference, NIH"[pt] OR Dictionary[pt] OR Directory[pt] OR Editorial[pt] OR "Legal Cases"[pt] OR Legislation[pt] OR News[pt] OR "Newspaper Article"[pt] OR Portraits[pt]	2625858

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#46	(#12 AND #43) NOT #44 NOT #45 AND PUBLICATION DATE LIMIT OF 1980/01/01	3269
#47	#46 AND PUBLICATION DATE LIMIT OF 1980/01/01	2955

Table 6. PubMed search string to capture studies on systemic antibiotics

Search	String	# Hits
#1	"Leg ulcer"[mh: noexp]	6997
#2	"Varicose ulcer"[mh]	3460
#3	"chronic leg"[tiab]	726
#4	"chronic venous"[tiab]	3040
#5	"lower extremity"[tiab] OR "lower extremities"[tiab] OR "lower limb"[tiab] OR "lower limbs"[tiab]	43833
#6	Ulcer[tiab] OR ulcers[tiab] OR ulceration[tiab]	108730
#7	(#3 OR #4 OR #5) AND #6	3302
#8	"leg ulcer"[tiab] OR "leg ulcers"[tiab] OR "leg ulceration"[tiab]	4484
#9	"venous ulcer"[tiab] OR "venous ulcers"[tiab] OR "venous ulceration"[tiab]	1530
#10	"venous stasis ulcer"[tiab] OR "venous stasis ulcers"[tiab] OR "venous stasis ulceration"[tiab]	180
#11	"chronic wound"[tiab] OR "chronic wounds"[tiab]	2258
#12	#1 OR #2 OR #7 OR #8 OR #9 OR #10 OR #11	14297
#13	"Anti-infective agents"[mh]	439058
#14	"beta-Lactams"[mh]	101178
#15	Clindamycin[mh]	4523
#16	"Trimethoprim-Sulfamethoxazole Combination"[mh]	5228
#17	Oxazolidinones[mh]	5452
#18	Quinolones[mh]	31049
#19	Lactams[mh]	106332
#20	Vancomycin[mh]	8771
#21	Daptomycin[mh]	887
#22	Gentamicins[mh]	16101
#23	Tobramycin[mh]	3491
#24	Antibiotic*[tiab] OR antimicrobial*[tiab] OR antibacterial*[tiab]	278690
#25	Cephalosporin*[tiab]	15693
#26	Cephalexin*[tiab] OR Cefalexin*[tiab]	2249
#27	Amoxicillin*[tiab] OR Clavulanate*[tiab]	9661
#28	Linezolid*[tiab]	2530
#29	Dicloxacillin*[tiab]	585
#30	Clindamycin*[tiab]	7092
#31	Trimethoprim*[tiab] OR sulfamethoxazole*[tiab]	12301
#32	Quinolone*[tiab]	9200
#33	Levofloxacin*[tiab]	3869
#34	Moxifloxacin*[tiab]	2244
#35	"Beta lactam"[tiab] OR "beta lactam"[tiab] OR beta-lactam*[tiab]	26142
#36	Augmentin*[tiab]	7609
#37	Cefixime*[tiab]	1087
#38	Cefpodoxime*[tiab]	607
#39	Cefazolin*[tiab]	3029
#40	Ceftriaxone*[tiab]	6241
#41	Vancomycin*[tiab] OR Daptomycin*[tiab]	15709
#42	Ertapenem*[tiab]	543
#43	Piperacillin*[tiab] OR tazobactam*[tiab] OR cefipime*[tiab]	4454
#44	Gentamicin*[tiab] OR tobramycin*[tiab] OR amikacin*[tiab]	24482
#45	aminoglycoside*[tiab]	13605
#46	Neomycin*[tiab]	8022
#47	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41	683835

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	OR #42 OR #43 OR #44 OR #45 OR #46	
#48	#12 AND #47	1094
#49	(animal[mh] NOT human [mh])	3616211
#50	Addresses[pt] OR Autobiography[pt] OR Bibliography[pt] OR Biography[pt] OR "Case Reports"[pt] OR "Classical Article"[pt] OR "Clinical Conference"[pt] OR "Collected Works"[pt] OR Comment[pt] OR Congresses[pt] OR "Consensus Development Conference"[pt] OR "Consensus Development Conference, NIH"[pt] OR Dictionary[pt] OR Directory[pt] OR Editorial[pt] OR "Legal Cases"[pt] OR Legislation[pt] OR News[pt] OR "Newspaper Article"[pt] OR Portraits[pt]	2628097
#51	#48 NOT #49 NOT #50	800

Table 7. PubMed search string to capture studies on surgical interventions

Search	String	# Hits
#1	"Leg ulcer"[mh: noexp]	7008
#2	"Varicose ulcer"[mh]	3463
#3	"chronic leg"[tiab]	728
#4	"chronic venous"[tiab]	3045
#5	"lower extremity"[tiab] OR "lower extremities"[tiab] OR "lower limb"[tiab] OR "lower limbs"[tiab]	56951
#6	Ulcer[tiab] OR ulcers[tiab] OR ulceration[tiab]	108856
#7	(#3 OR #4 OR #5) AND #6	3747
#8	"leg ulcer"[tiab] OR "leg ulcers"[tiab] OR "leg ulceration"[tiab]	4488
#9	"venous ulcer"[tiab] OR "venous ulcers"[tiab] OR "venous ulceration"[tiab]	1533
#10	"venous stasis ulcer"[tiab] OR "venous stasis ulcers"[tiab] OR "venous stasis ulceration"[tiab]	180
#11	"chronic wound"[tiab] OR "chronic wounds"[tiab]	2265
#12	"Venous Insufficiency/Surgery"[mh]	
#13	#1 OR #2 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	14554
#14	Endoscopy[mh]	223926
#15	"Catheter ablation"[mh]	16737
#16	"Laser therapy"[mh]	44566
#17	"Balloon dilation"[mh]	56081
#18	Ligation[mh]	16406
#19	Sclerotherapy[mh]	3878
#20	Thrombectomy[mh]	2491
#21	Angioplasty[mh]	48660
#22	Endoscop*[tiab]	120179
#23	Stripping[tiab]	7280
#24	Ablat*[tiab]	56368
#25	Ligat*[tiab]	65068
#26	Laser*[tiab]	157792
#27	Valvuloplast*[tiab]	3411
#28	Valve*[tiab]	88489
#29	Sclerotherap*[tiab]	4984
#30	Thrombolys*[tiab]	15026
#31	Thrombectom*[tiab]	3787
#32	Angioplast*[tiab]	34149
#33	Stent*[tiab]	52339
#34	(Vein[tiab] OR venous[tiab]) AND (surgery[tiab] OR surgeries[tiab])	27029
#35	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	
#36	#13 AND #35	
#37	(animal[mh] NOT human [mh])	3624654
#38	Addresses[pt] OR Autobiography[pt] OR Bibliography[pt] OR Biography[pt] OR "Classical Article"[pt] OR "Clinical Conference"[pt] OR "Collected Works"[pt] OR Comment[pt] OR Congresses[pt] OR "Consensus Development Conference"[pt] OR "Consensus Development Conference, NIH"[pt] OR Dictionary[pt] OR Directory[pt] OR Editorial[pt] OR "Legal Cases"[pt] OR Legislation[pt] OR News[pt] OR "Newspaper Article"[pt] OR Portraits[pt]	1113744
#39	#36 NOT #37 NOT #38	1875
#40	#39 WITH PUBLICATION DATE LIMIT OF 1980.	1763

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