Practice of Wound Care Guidelines

2nd Edition

SerenaGroup, LLC
125 Cambridge Park Dr, Suite 301
Cambridge, MA 02140
Phone 888-960-1343

SerenaGroup
Building the Nation's Leading Wound Care Team

"SerenaGroup® is dedicated to providing the best wound care education for clinicians and the best care for the patients we serve. The evidence-based Practice of Wound Care™ guides the clinician in a step-by-step fashion through the evaluation of a patient with a nonhealing wound. In addition, guidelines give rise to quality measures which in turn form the foundation of a center of excellence."

— Dr. Serena

PREFACE

SerenaGroup® Quality Driven Guidelines for the Practice of Wound and Hyperbaric Medicine, "The Practice of Wound Care,™" serve as an educational tool for clinicians practicing in advanced wound care centers managed by SerenaGroup®. It is the responsibility of the contracting facility, free-standing or hospital outpatient department to adopt these guidelines.

Guidelines, as the name implies, function as a resource to guide clinicians in treatment choices. They are in no way absolute: patients are unique individuals and no guideline will meet every patient need.

All information contained here is the property of SerenaGroup® and shall not be shared with any outside party without the written consent.

The SerenaGroup Approach

SerenaGroup® encourages an interdisciplinary approach to the evaluation and treatment of patients suffering from nonhealing wounds. We recommend that all clinicians and staff familiarize themselves with the **"The Practice of Wound Care™** In addition, delivering the highest quality care requires treating patients in all care settings. Close collaboration between inpatient, outpatient and home health clinicians is essential. The judicious use of resources fosters the delivery of value-based care. SerenaGroup® works with its hospital partners to promote the health and wellness of the wound community in a fiscally responsible manner.

Disclosure

Dr. Serena's conflict of interest statement is after the reference section (Appendix A).

ABBREVIATIONS

ABI	Ankle-Brachial Index
BPA	Bacterial Protease Activity
CMS	Centers for Medicare Services
CRO	Chronic Refractory Osteomyelitis
CTP	Cellular or Tissue-based Product for wound care.
DFU	Diabetic Foot Ulcer
DP	Dorsalis Pedis Artery
DVT	Deep Venous Thrombosis
EPA	Elevated Protease Activity
FDA	Food and Drug Administration
HbA1C	Hemoglobin A1C
HBOT	Hyperbaric Oxygen Therapy
HNE	Human Neutrophile Elastase
MliX	MolecuLight Procecure
MMP	Matrix Metalloprotease
MNA	Mini Nutritional Assessment
MRI	Magnetic Resonance Imaging
NIRS	Near Infrared Reflectance Spectroscopy
NPWT	Negative Pressure Wound Therapy
NSAID	Non-steroidal anti-inflammatory drugs
ORC	Oxidized Regenerated Cellulose
PCR	Polymerase Chain Reaction
PDGF	Platelet Derived Growth Factor
PrU	Pressure Ulcer
PT	Posterior Tibial Artery
RCT	Randomized Controlled Clinical Trial
SPP	Skin Perfusion Pressure
TBI	Toe-Brachial Index
TCC	Total Contact Casting
TNF	Tumor Necrosis Factor alpha
VLU	Venous Leg Ulcer

THE 14-STEPS TO HEALING

The Practice of Wound Care™ employs a 14 step process supported by current literature and leading professional organizations, such as the Association for Advancement of Wound Care (AAWC), the American Professional Wound Care Association (APWCA) and Wound Healing Society (WHS).

- Step 1: Assess vascular status on physical examination and using objective screening tests
- Step 2: Assess tissue oxygenation using objective testing
- Step 3: Consider a biopsy if the diagnosis is uncertain
- Step 4: Debridement: remove nonviable tissue
- Step 5: Antimicrobial stewardship: Assess bacterial burden
- Step 6: Control inflammation
- Step 7: Treat edema
- Step 8: Offload the ulcer
- Step 9: Maintain proper moisture balance
- Step 10: Evaluate nutritional status and diabetic control
- Step 11: Evaluate co-morbidities (host factors)
- Step 12: Develop a plan of care, follow the patient weekly then revaluate after 4 weeks
- Step 13: If the wound fails to progress toward healing over 4 weeks, reassess the treatment plan
- Step 14: Consider advanced modalities for wounds that do not reduce in size after four weeks of standard wound care

Step 1: Assess vascular status on physical examination and using objective screening tests.

- Examination of pulses can be inaccurate[1]. Supplement clinical examination with an objective test.

Assess all patients with lower extremity skin breakdown for arterial disease using a validated screening tool (Quality Metric)

Screening Tools:

Ankle-Brachial Index (ABI):

- Easily performed at the bedside. All clinics need this capability.
- High sensitivity and specificty[2].
- If the ABI <0.65 refer to vascular service for evaluation.
- Patients with venous disease and ABI >0.8 can have standard multilayer compression. Patients with venous disease and an ABI <0.8 but >0.65 can have compression designed for moderate vascular insufficiency (e.g. Light wraps).
- Drawback- Patients with calcified vessels, commonly seen in diabetics, may have false elevations of the ankle pressures invalidating the test. If the ABI >1.2 the patient has non-compressible vessels. Order an alternative screening test.
- Reimbursement for the procedure requires a printout of the waveform.

Ankle-Brachial Index Technique:

Technique: Place the patient in the supine position, with the arms and legs at the same level as the heart, for a minimum of 10 minutes before measurement. Select an appropriately sized blood pressure cuff for both the ankle and the arms (figure 1); the cuff width should be, at a minimum, 20% greater than the diameter of the extremity. The ankle cuff should be placed on the leg between the malleolus and the calf. Enough room should be left below both cuffs to permit placement of the ultrasound gel, so that the Doppler device can adequately detect the brachial, dorsalis pedis, and posterior tibial arteries. Obtain the brachial systolic pressures of both arms. Use the higher of the arm pressures in the ABI calculation. Obtain the pressure in the dorsalis pedis and posterior tibial arteries for the extremity with the target ulcer (Figure 1). Use

both pressures for the ABI calculation (DP and PT arteries). Ankle-Brachial Index = DP and PT ankle pressures/ Highest brachial pressure. Document both ABI values. Care should be taken to cover the ulcer during the ABI measurement. In addition, patients should be informed that they may experience discomfort during the test secondary to the pressure exerted by the cuff in the area of skin breakdown.

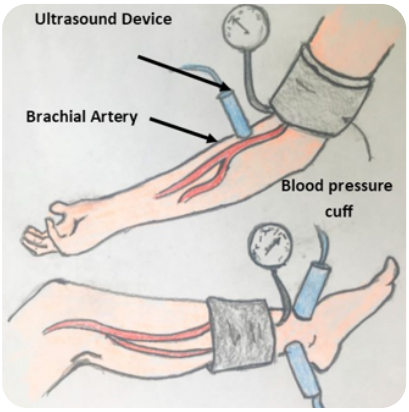


Figure 1: ABI

Toe-Brachial Index (TBI)

- One option if the ABI >1.2, indicating non-compressible vessels, is to order a TBI through the vascular lab.
- Clinical note: Arteriosclerosis, hardening of the arteries, occurs when the medial elastic layer of an artery becomes calcified (figure 2).[3] However, the digital vessels in the toes do not have a medial elastic layer. Therefore, they are not affected by calcification. The great toe is used for TBI measurement in most cases.
- TBI <0.5 refer to vascular service for evaluation.
- Drawbacks:
  - Requires referral to a vascular lab.
  - Toe amputations are common in wound clinic patients making the test impossible to perform.

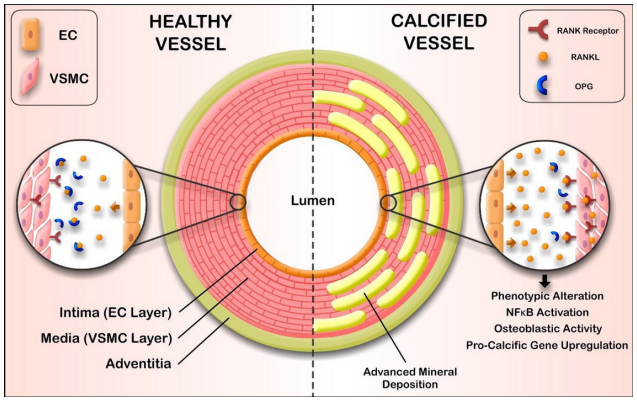


Figure 2: Arteriosclerosis (Medial Calcinosis) in an artery

Calcification in the elastic layer of an artery: medial Calcinosis (aka hardening of the arteries, arteriosclerosis).

Skin Perfusion Pressure (SPP)

- SPP is another option if the ABI value is above 1.2.
- A bedside procedure but the center must have a Sensilase® Device.
- An SPP <30mmHg refer to vascular service for critical limb ischemia.[4]
- An SPP <40mmHg in a wound with delayed wound healing consider referral to the vascular service.[4]
- An SPP >40 mmHg should heal without vascular intervention.[4]
- Drawback - Specialized equipment required.

SPP Technique

1. Secure the laser Doppler flow sensor within the bladder of a blood pressure cuff equipped with a transparent polyvinyl chloride window for measuring microcirculatory perfusion during cuff inflation and deflation.
2. Place the subject in supine position and keep still for 5 minutes.
3. Apply the cuff to the proximal margin of the ulcer and inflate to 20 mmHg above the brachial systolic pressure. A stable laser Doppler output value near zero (<0.1 volume %) should be reached before deflating.
4. Deflate the cuff, first in 10 mmHg-stepwise decrements every 5 seconds to a pressure of 50 mmHg, and then in 5-mmHg decrements every 15 seconds until the laser Doppler output increased for 2 consecutive pressure values.
5. The pressure at which this first occurred is considered the SPP value (figure 3).

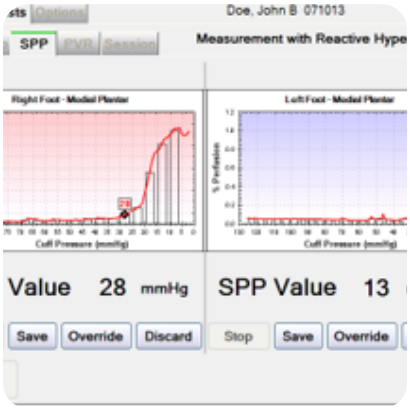


Figure 3: SPP Readout

Assess vascular status on all patients before applying multilayer compression [Safety Measure]

Step 2 Assess tissue oxygenation using objective testing.
Step 1 measured perfusion. Step 2 focuses on oxygenation. The two measures are related but not the same. Perfusion assesses arterial flow whereas oxygenation relates to the oxygen content in the periwound skin and wound bed. It is possible to have adequate arterial inflow but have a poorly oxygenated wound.

Clinical Note: An Australian Plastic Surgeon, Ian Taylor, postulated that each section of the skin ("some") received blood flow from a specific artery ("angio"). He named the concept, angiosomes.[5]* A woundologist needs to know the arterial inflow to the extremity (Step 1, perfusion) but also must know the amount of oxygen reaching the angiosome in which the wound is located (step 2, oxygenation). Transcutaneous oximetry (TCOM) and near infrared reflectance oximetry (NIRS) measure oxygenation in the periwound skin. NIRS can also measure oxygenation in the wound bed.

* For a complete description of angiosomes and their importance in wound care please see reference number 5 by Attinger et. al.

Measuring Oxygenation

Transcutaneous Oximetry (TCOM)

- Typically, the procedure is performed in the wound and hyperbaric center by the hyperbaric technician.
- TCOM measures oxygenation in the periwound skin using a heated electrode. Therefore, it measures oxygen tension in the wound angiosomes.
- The test is performed by a certified hyperbaric technician (CHT).
- A value of >40mmHg in nondiabetics suggest that the wound will heal.[6]
- A value of >30mmHg in diabetics suggests that the wound will heal.[6]
- TCOM can also predict the level of amputation.[7]
- TCOM can also predict healing for patients undergoing hyperbaric oxygen therapy (HBOT).[8]
- Drawbacks
  - The procedure is labor and time intensive;
  - It is highly operator dependent;
  - The room temperature must be kept between 68 and 72 degrees;
  - The probes cannot be applied directly to the wound bed or over boney prominences;
  - The disposable fixation rings that hold the electrodes are expensive

TCOM Technique

Place the patient in the supine position, with the arms and legs at the same level as the heart. Electrodes must be in contact with the tissue through the contact liquid. If there is air between the tissue and an electrode, TCOM values will be questionable. Erroneous readings may also occur if electrodes are placed directly over a bone or there is severe edema around the wound. For best results, tests should be conducted at ambient temperature (21-23^0), and the patient should not have smoked nor had caffeine for several hours prior. Avoid placing the electrodes over major vessels.

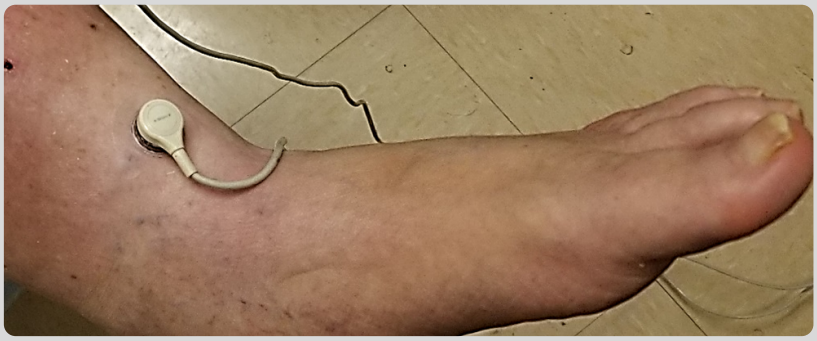


Figure 4: TCOM electrode in place.

Photo Courtesy SerenaGroup®

1. Calibrate the TCOM electrode—this takes about 15-20 minutes.
2. Clean the selected measuring site with alcohol or other skin-preparation solution.
3. Dry the site well with a gauze pad.
4. Take a standard fixation ring.
5. Remove the fixation ring from the protective film.
6. Apply the fixation ring to the measuring site as follows:
7. Press the center of the fixation ring onto the measuring site with a finger.
8. Run a finger around the rim circumference.
9. Press firmly to prevent leaks.
10. Fill the hole in the fixation ring with 3-5 drops of the contact liquid.
11. Affix the electrode into the fixation ring as follows:
    a. Align the arrow on the electrode with one of the marks on the fixation ring.
    b. Turn the electrode 90° clockwise to fasten it in the fixation ring.
12. Repeat steps 1 to 8 if more electrodes are to be applied; note, several electrodes can be calibrated at the same time.
13. It is sometimes advantageous to simultaneously use several electrodes placed strategically around the wound and calculate mean values from individual readings.

- In choosing patients for HBOT the clinician can perform an oxygen challenge with the TCOM examination. The patient breaths 100% oxygen through a mask. An increase of 100 mmHg suggests that the patient will heal with HBOT. Similarly, performing a TCOM in the hyperbaric chamber at depth breathing 100% can predict the patient's response to HBOT: an increase in the in-chamber TCOM value of >200 mmHg corresponds to a 70-80% success rate with HBOT.[8]
- Clinical Note: At one time all candidates for HBOT underwent TCOM with an oxygen challenge and in-chamber measurement. This practice fell out of favor in the last decade. In addition to the drawbacks listed above, if the oxygen challenge or in-chamber TCOM suggested that a patient with a diabetic foot ulcer might not heal, there was still a 5-10% chance of healing. A diabetic foot ulcer has a 47% annual mortality—worse than most common cancers.[9] I believe that withholding HBOT when there was still a 5-10% chance of preventing amputation and subsequent death in this population equates to denying what may be lifesaving therapy.

Near Infrared Reflectance Oximetry (NIRS)

- Near infrared spectroscopy (NIRS) is a new method for measuring tissue oxygen saturation (S_tO_2).
- Clinical Note: Oxygenated and deoxygenated hemoglobin molecules differentially absorb light in the near infrared portion of the electromagnetic spectrum (700nm-2500nm). At these wavelengths, they are the main absorbers of light or chromophores (Melanin is also a chromophore in the near infrared spectrum but to a lesser extent than hemoglobin). The device uses six wavelengths to measure the absorbance of oxygenated and deoxygenated hemoglobin. Comparing the relative ratios of oxygenated and deoxygenated hemoglobin allows the calculation of tissue oxygen saturation[10] The measurements have a strong correlation to TCOM.[11]
- NIRS has several advantages over TCOM: There is no contact with patient, images are obtained in real time at the patient's bedside, it is far less operator dependent, takes a fraction of the time and does not require expensive electrodes.
- Drawbacks
  - A specialized device is required.
  - The saturation numbers have not been correlated to healing rates although, this research is ongoing in SerenaGroup® centers.

Technique

The technique is divided into set up (figure 4) and operation (figure 5).

Figure 4: Start Up

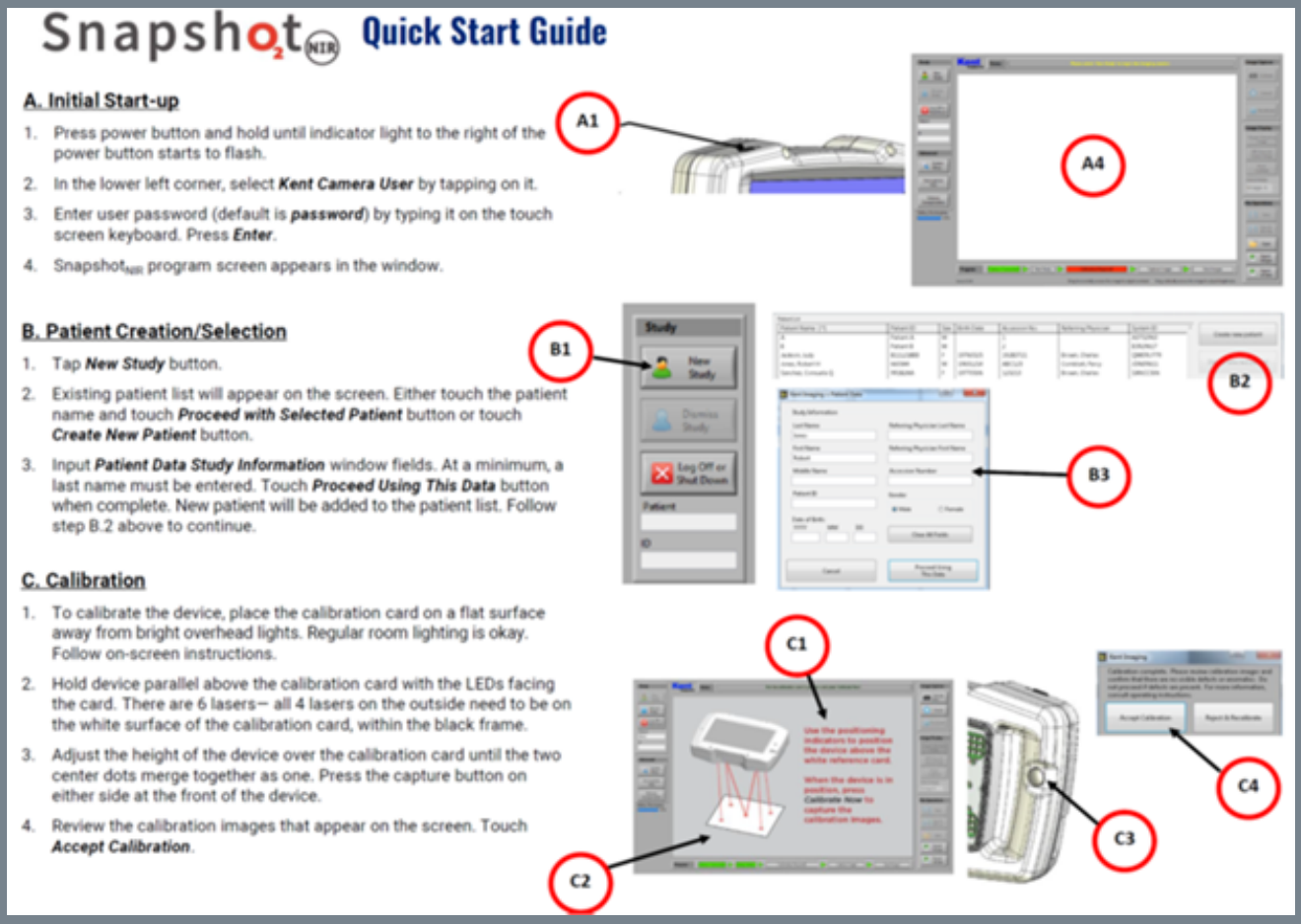
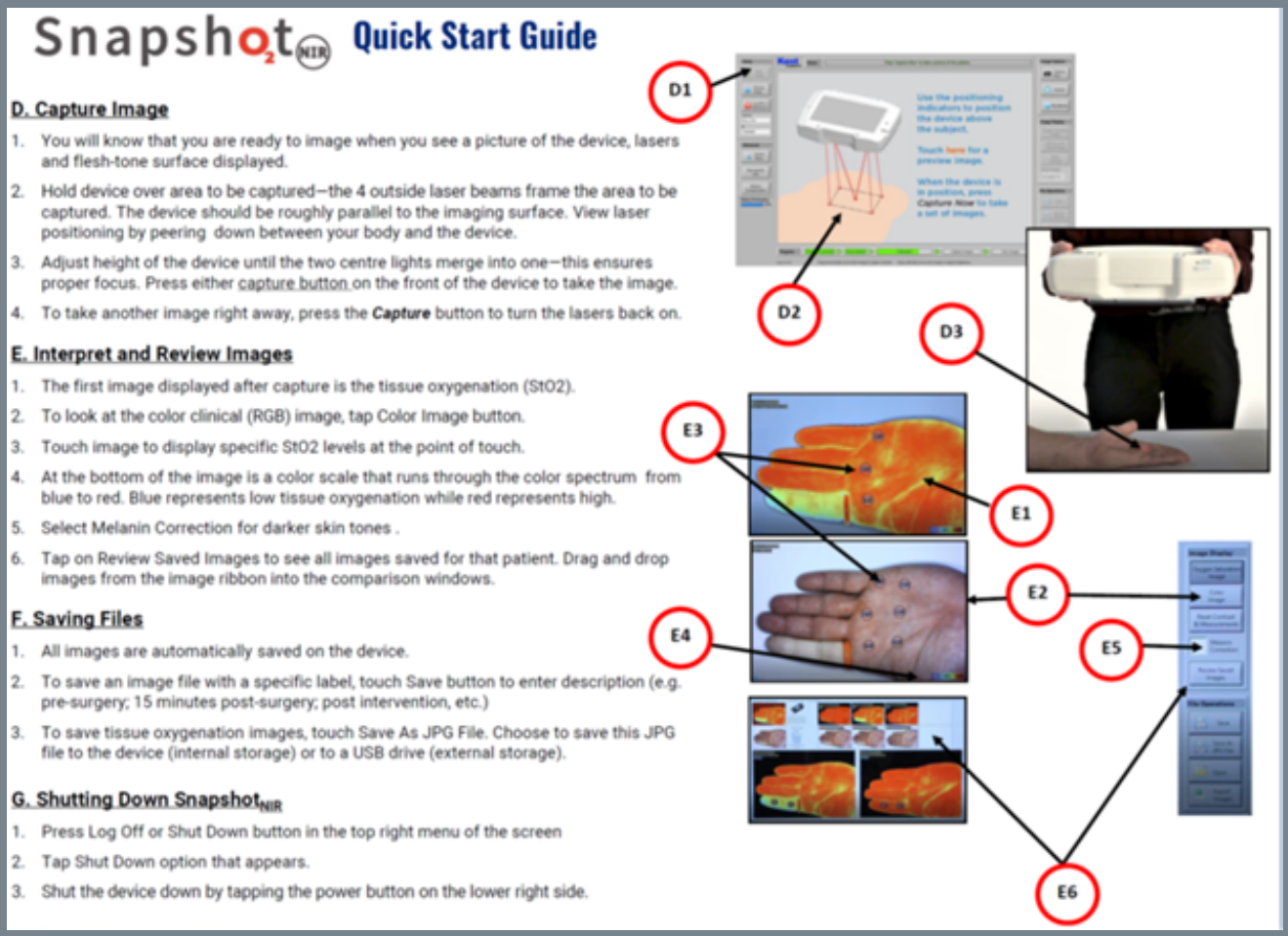


Figure 5: Imagine Capture



Step 3: Consider punch biopsy if diagnosis is uncertain

- Consider performing a punch biopsy of a patient's wound for pathologic examination if the presentation is unusual,
  - A young patient with Crohn's Disease develops what looks like a venous leg ulcer. Her inflammatory bowel disease suggests a diagnosis of pyoderma gangrenosum.
- Biopsy wounds in which cancer is suspected.
- Consider biopsy of wound that has failed to heal after repeated interventions.
- Punch biopsies are easy and safe.[12]
- Take a 2-3mm punch biopsy from the margin of the wound under local anesthetic and send the specimen to pathology in formalin.
- A biopsy may also be performed for quantitative tissue culture. In this case place the specimen in saline or culture medium rather than formalin. In addition, before obtaining a tissue sample for quantitative culture make sure the microbiology lab can analyze it. Many labs do not perform quantitative tissue cultures.

Technique

1. Obtain informed consent from the patient.
2. Prepare for the biopsy procedure by placing an antiseptic, gauze, the punch biopsy instrument (figure 6), forceps and scissors on a bedside stand.
3. Clean technique is observed. The area of interest is prepped with antiseptic.
4. Typically, 1% or 2% lidocaine with or without epinephrine is injected into the area as an anesthetic. Most clinicians avoid using epinephrine in the digits, but in other parts of the body, it hastens the anesthetic effect of the Lidocaine and decreases bleeding. For rare patients who report an allergy to Lidocaine, Tetracaine can be substituted.
5. Unless there is a suspicious area in the wound bed, the margin of the wound including a portion of intact skin is chosen for biopsy.
6. A 2-3 mm punch biopsy instrument suffices in most cases.
7. Holding the punch perpendicular to the skin (figure 7), press it into the wound with a circular motion. The specimen will separate from the surrounding tissues in most cases.
8. Using forceps, grasp the specimen and cut the base with scissors.
9. The specimen is placed in the appropriate container: formalin for histology and saline or culture medium for microbiology.
10. Direct pressure achieves hemostasis in the majority of cases. Occasionally, silver nitrate cauterization or suturing is required.
11. A dressing suited to the wound is applied.
12. In most patients the biopsy site heals in one week.

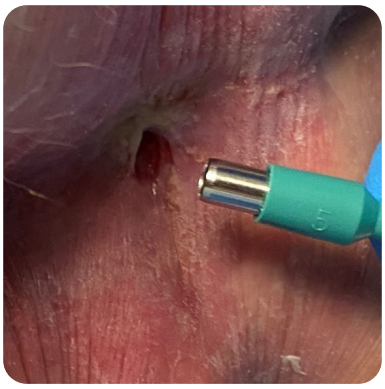


Figure 6: Punch Biopsy Tool

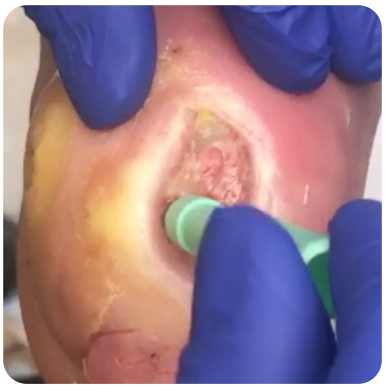


Figure 7: Taking a Punch Biopsy

Photos courtesy SerenaGroup®

Step 4: Debridement

- Weekly debridement improves wound healing.[13] The goal is to remove nonviable tissue and slough from the would bed and in the case of excisional debridement remove senescent cells from the wound margin.[14]
- Debridement is indicated for all wound types except arterial ulcers and wounds secondary to autoimmune diseases, such as pyoderma gangrenosum.
- Clinical note: Debridement increases the oxygen demand of the skin and soft tissues three-fold.[15] Arterial ulcers develop secondary to inadequate blood flow to the skin. Therefore, debriding arterial ulcers may result in an increase in ulcer size and depth. Similarly, ulcers that develop secondary to autoimmune disease worsen with debridement, although, the reason is different. Autoimmune ulcers exhibit a phenomenon called pathergy: the dermis breaks down in response to injury. Debriding an autoimmune ulcer causes it to enlarge.[15] Anecdotally, I have used enzymatic debridement (Collagenase, Santyl®, Smith and Nephew) for ischemic and autoimmune ulcers with some success.
- Caution: Debridement procedures are frequently scrutinized by payers. It is essential to understand the differences between the types of debridement and the appropriate CTP codes. When in doubt consult SerenaGroup®.

Types of Debridement

<u>Non-Selective Debridement:</u>

- Often called “mechanical debridement.”
- It is defined as the removal nonviable tissue by cleansing or the use of an instrument designed for non-select debridement (e.g. EZ Debride).
- The procedure in not considered a skilled service. It fits under general supervision and does not require physician oversight.

- Historically, wet-to-dry dressings were used to mechanically debride wounds. However, wet-to-dry dressings injure the skin and soft tissues and cause pain; therefore, they are no longer recommended to debride wounds.

Enzymatic Debridement:

- The application of topical enzymes can aid in wound debridement.
- At present, only one topical enzyme is commercially available in the United States (Collagenase, Santyl®, Smith and Nephew).
- A randomized clinical trial demonstrated superior debridement of pressure ulcers with collagenase compared to a hydrogel.[16]
- Clinical Note: The commercially available collagenase ointment is a metalloproteinase derived from Clostridium histolyticum. It does not injure healthy tissue.[16]
- One of the drawbacks of enzymatic debridement is that it is considerably slower than sharp debridement. However, there are clinical settings, such as nursing homes, in which sharp debridement may not be practical.

Biologic Debridement:

- The application of larvae to the wound to debride nonviable tissue dates to at least the 16th century.[17]
- Several anectodical and small studies demonstrate a beneficial effect on wound healing.[17] Randomized clinical trial evidence is absent.
- Maggot or larval debridement is used occasionally in the United States. It requires a good deal of preparation and wound clinic time without any demonstrable benefits over sharp debridement. At present it is a novelty.
- Clinical note: The greenbottle blowfly (Lucilia sericata), the most common species used in maggot debridement or larval therapy, eats nonviable tissue in the wound bed, secretes ammonia that inhibits bacterial growth and is believed to secrete substances that promote wound healing (figure 8).[17]

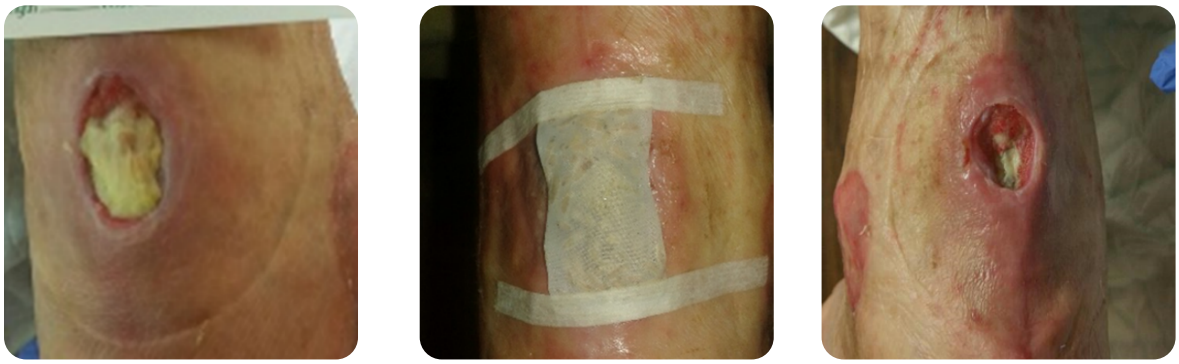


Figure 8: Maggot Debridement Therapy (before during and after).
Courtesy Joy Hall CRNP

Selective Debridement:

- The removal of devitalized or necrotic tissue or slough from the wound bed using a curette, scissors, or scalpel and forceps. Document the instruments utilized in the procedure.
- This procedure typically requires minimal or no anesthesia and has minimal associated bleeding.
- Typically, this is not the first debridement performed in an episode of care but a subsequent debridement.
- Coding note: the CPT code for selective debridement is 97597 with an add on of 97598 for greater than 20 cm.[2]

Surgical Debridement (Excisional Therapy):

- Surgical debridement removes nonviable tissue, necrosis, and eschar.
- In addition, the margin of the wound is "excised." This gives rise to the term excisional debridement. If the periwound tissue is not removed during the procedure it is not excisional debridement.
- Sharp excisional debridement is the preferred initial debridement for acute and chronic nonhealing wounds.
  - Diabetic foot ulcers require excisional debridement more frequently than other wound types.
  - Perform excisional debridement as the initial debridement for a venous leg ulcer (VLU) and prior to the application of Cellular or Tissue-based Products (CTPs).
- Clinical note: Research suggests that the excision of at least 2mm of periwound skin and subcutaneous tissue (figure 9) is required to get back to normal skin.[18]
- Coding Note: For excisional debridement use CPT codes 11042-11047. 11042, the excision of skin subcutaneous tissue is the most commonly used excisional debridement code in the wound clinic.
- Coding Caution: If the physician uses codes 11042-11047 the post debridement measurements of the wound must be larger.
- Documentation Advice: Use the SerenaGroup® templates when documenting procedures. The latest excisional debridement template is below.

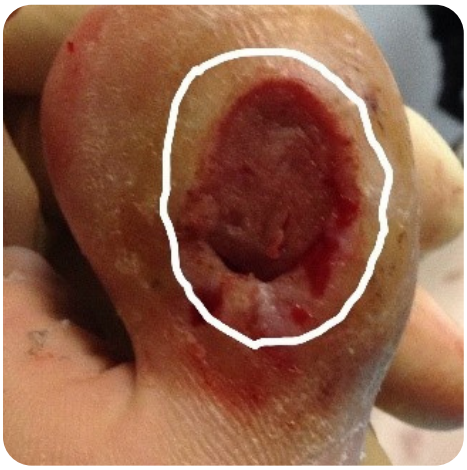


Figure 9: Excisional debridement of a DFU. Remove back to the white line.

SerenaGroup Template

Prior to the procedure, consent was obtained. I explained the risk and benefits to the patient and they wish to proceed. The site was marked, prepped and draped. The team took a time-out, confirmed the location of the procedure. The ulcer was anesthetized with (type). I performed the debridement with (blade/curette/ scissors and pick-ups); there was (minimal/scant/__cc) of blood loss. Hemostasis was obtained (how) & the patient experienced (scale) pain. Post procedure assessment was performed, and the measurements are ____x___x____ (must be larger than pre). The patient tolerated the procedure well. The following dressing (type) was applied. The patient was educated regarding the signs and symptoms of infection, such as purulent drainage, edema, cellulitis, and significant pain, and to notify healthcare personnel if any of these things occur.

Step 5: Antibiotic stewardship; reduce bacterial burden.

Assess all patients for the presence of moderate-to-heavy bacterial load.
{Antibiotic Stewardship}

Presence of bacteria in wounds impedes healing. Studies suggest that a total bacterial load of 10^4 or greater inhibits wound healing.[19] Examine the wound for clinical signs and symptoms of infection. The International Wound Infection Institute checklist serves as a reminder (table 1).[20]

Table 1: International Wound Infection Institute Checklist

Covert signs	Classic signs
❑ Hypergranulation ❑ Bleeding, friable granulation ❑ Epithelial bridging and pocketing in granulation tissue ❑ Wound breakdown and enlargement ❑ Delayed wound healing beyond expectation ❑ New or increased pain ❑ Increasing malodor	❑ Erythema ❑ Local warmth ❑ Swelling ❑ Purulent discharge ❑ Delayed wound healing beyond expectations ❑ New or increasing pain ❑ Increased malodor

Presence of 3 or more signs listed above indicates infection

- The clinical signs and symptoms are not reliable in making the diagnosis of moderate-to-heavy bacterial load.[21] Bacterial levels may reach clinically significant levels before clinical signs and symptoms appear.[22]
- Swab cultures are inaccurate in the diagnosis of bacterial burden and infection in nonhealing wounds.[23]
- Effective antibiotic stewardship demands the use of objective measures of bacterial burden in addition to clinical examination.[24]
- There is no evidence for the effectiveness of topical antiseptics in the reduction of bacterial burden.
- The use of topical antibiotics is discouraged due to the risk of bacterial resistance and limited spectrum. Given the topical antiseptics available, there is no reason to use topical antibiotics in nonhealing wounds.
- Do not use systemic antibiotics without a definitive diagnosis (punch biopsy for quantitative analysis, swab for polymerase chain reaction (qPCR), fluorescence imaging (MLiX), bacterial protease activity (BPA).

The Diagnosis of moderate-to-heavy bacterial load

- **Clinical signs and symptoms**, as noted above, fail to diagnose clinically significant bacterial loads in nonhealing wounds.
- **Swab Cultures** are also inaccurate and have a limited role in the advanced wound and hyperbaric center.

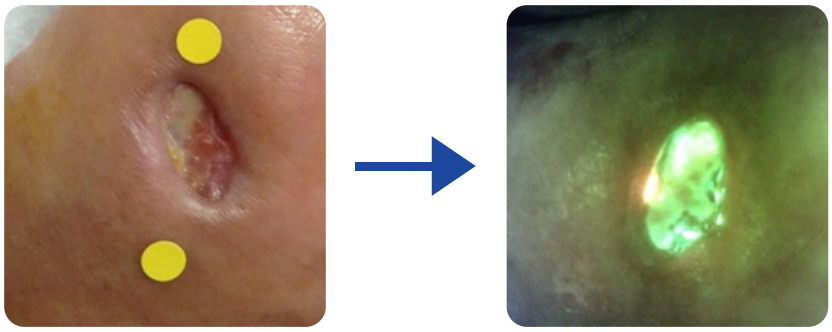
MolecuLight Procedure (MLiX):

- The MolecuLight Imaging Device is a point-of-care diagnostic that provides real-time evidence of bacterial load in the wound bed and on the periwound skin.
- Two randomized controlled clinical trials found that the device detects moderate-to-high bacterial levels (>10^4 CFU/gm of tissue) in nonhealing wounds as confirmed by quantitative tissue culture biopsies and qPCR testing.[25,26]
- Clinical Note: The majority of bacterial cells contain porphyrin molecules that become excited when exposed to a narrow band of violet light (405nm). The violet excitation causes the porphyrins to fluoresce in wavelengths between 600 -665 nm, which appear red in color.[27] LEDs in the device illuminate the wound bed with violet light. If greater than 10^4 bacteria are present, red fluorescence will appear on the image (figure 10). Pseudomonas is an exception: it contains pyoverdines rather than porphyrins. As a result, it fluoresces a cyan-white (figure 11).

Figure 10: Red Fluorescence

Standard Image Fluorescence Image

Figure 11: Cyan



Standard Image Fluorescence Image

The Advantages of MLiX

- Rapid point-of-care diagnostic test allows for decision making in real time.
- If fluorescence is visualized there is high probability that clinically significant bacterial levels are present in the wound (high positive predictive value).
- Does not require contact with the patient.
- Identifies the location of bacteria within the wound bed permitting more accurate tissue or PCR cultures.
- Bacterial identification also permits focused debridement and skin cleansing.
- When bacteria reach a level that impedes wound healing, the signs of infection are frequently absent. This has been termed the “Period of Pathogenicity."[25] It is, therefore, important to detect and treat bacterial burden early before the infection becomes more serious. MLiX identifies moderate-to-heavy bacterial load allowing the physician to use antiseptics and debridement rather than antibiotics.

Disadvantages of MLiX

- Required specialized device.
- It does identify the bacterial species in the wound. In some cases, additional tissue culture or PCR may be necessary.
- The fluorescence image capture requires a darkened room. A drake drape is available from the manufacturer but an exam room without windows is ideal.
- Does not yet have reimbursement for hospital outpatient departments.

Points about image interpretation

- A moderate-to-heavy bacterial load will appear red or Cyan.
- Collagen appears green in color.
- Dry skin on the periwound may be confused with the cyan of pseudomonas; however, pseudomonas tends to have white halo.
- Blood also fluoresces. It is a deeper red than bacteria; however, it is best to achieve hemostasis in the wound bed and clean any blood off the periwound skin before taking the fluorescence image.

The MLiX template for documentation (Add to electronic health record)

Patient has _____ (number/anatomical location/wound type) that is nonhealing or suspicious for moderate-to-heavy bacterial load. This ulcer/wound has been present for (duration)_____.The patient's plan of care includes debridement(s), off -loading, compression, glycemic control as evident by HgBA1C of_____, a vascular assessment as evident by (ABI/toe pressure or other quantitative measure) (mention all that apply). Today the goal is to determine presence of moderate-to-heavy bacterial load present using the MLiX procedure.
After consenting the patient, the patient was positioned to expose the _____(number or anatomical location) wound(s), the area around the ulcer was draped to remove background clutter. Approved MLi:X dots were placed above and below the ulcer. A first image was taken on standard imaging mode. The MLi:X green light illuminated indicating the proper distance from the wound for imaging. The MLi:X procedure reported the surface area, length and width. The dots were removed. The room lights were turned off in preparation for the fluorescent image. A dark drape was attached to the device to eliminate ambient light that could interfere with the procedure. The device was placed in Fluorescence mode. Watching the ML i:Xgreen light indicator for the appropriate distance from the wound, the fluorescence image was captured. The room lights were turned back on. I reviewed the image. Red/Cyan fluorescence was positive in the wound _____(add location) indicated **(1)that the wound contained moderate-to-heavy bacteria in that area. (2) No fluorescence was detected indicating that wound did not contain moderate-to-high bacterial load.**

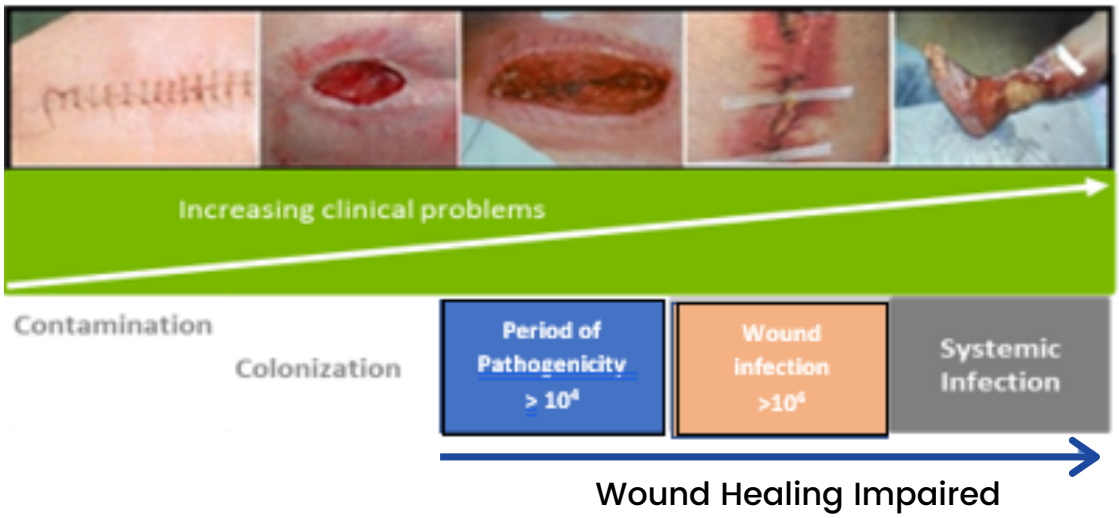
SerenaGroup Template

Quantitative Tissue Culture Biopsy

- The traditional definition of infection in a wound was greater than 10^6 colony forming units per gram of tissue (CFU/g). The value came largely from the work of the man who helped me get started in clinical research, Marty Robson MD. Marty found that flaps and grafts did not survive if there were high levels of bacteria: ≥1 × 10^6 CFU/g of tissue or any tissue level of beta hemolytic streptococci on biopsy.[26]
- Subsequent research found that a total bacterial load exceeding 10^4 impeded wound healing.

- Clearly, a continuum of bacteria exists in a nonhealing wound with clinically significant levels starting around 10^4 progressing to higher levels that indicate infection (Figure 12).

Figure 12: Bacterial continuum in nonhealing wounds



- **Advantages of quantitative tissue biopsy:**
  - The "gold standard" in making the diagnosis of infection.
  - Punch biopsies are safe and easy.[12]
- **Disadvantages of quantitative tissue biopsy:**
  - Tissue biopsies may require anesthesia and cause patient discomfort.
  - It takes 3 days to receive the microbiology report. The patient is treated with antibiotics or antiseptics they may not need during that time.
  - Quantitative tissue culture analysis requires the time-consuming serial dilution of the specimen. The majority of hospital labs do not perform quantitative cultures+ necessitating the use of a central microbiology lab.
  - In larger wounds there is an increased risk of a sampling error: taking the tissue biopsy in an area that does not have high bacterial levels (The use of MLiX guidance can eliminate this disadvantage by identifying the location of bacterial burden in the wound bed).

Technique

1. Obtain informed consent from the patient.
2. Prepare for the biopsy procedure by placing an antiseptic, gauze, the punch biopsy instrument (figure 6), forceps and scissors on a bedside stand.
3. Clean technique is observed. The area of interest is prepped with antiseptic.
4. Typically, 1% or 2% lidocaine with or without epinephrine is injected into the area as an anesthetic. Most clinicians avoid using epinephrine in the digits, but in other parts of the body it hastens the anesthetic effect of the Lidocaine and decreases bleeding. For rare patients who report an allergy to Lidocaine, Tetracaine can be substituted.
5. Unless there is a suspicious area or directed by the MLiX procedure in the wound bed, the margin of the wound including a portion of intact skin is chosen for biopsy.
6. A 2-3 mm punch biopsy instrument will suffice.
7. Holding the punch perpendicular to the skin (figure 7), press it into the wound with a circular motion. The specimen will separate from the surrounding tissues in most cases.
8. Using forceps, grasp the specimen and cut the bass with scissors.
9. The specimen is placed in the appropriate container (culture medium for microbiology).
10. Direct pressure achieves hemostasis in most cases. Occasionally, silver nitrate cauterization or suturing is required.
11. A dressing suited to the wound is applied.
12. In most patients the biopsy site heals in one week.

DNA identification of micro-organisms

- Often referred to as polymerase chain reaction (PCR), this technique extracts DNA from the microorganisms in a swab specimen and matches the sequence codes to a library of 50,000+ known microbial species. It is not a culture technique.[27]
- Advantages of PCR techniques
  - A tissue biopsy is not required.
  - The results can guide antibiotic choice.
  - Anaerobes are identified far more often than in traditional cultures.
  - Bacterial load results are available in 24 hours for some labs (MicroGen, Lubbock, TX).
- Disadvantages of PCR techniques
  - The delay in receiving the report requires the use of empiric therapy.
  - The report identifies all of the bacteria in the wound making it difficult to pinpoint an organism to treat.
  - The test is more expensive than other techniques and may not be covered by insurance.

Bacterial Protease Activity

- In the later part of 2019, the FDA approved a point-of-care test (WoundChek® Bacterial Status, Gargrave: North Yorkshire, United Kingdom) that detects the presence of bacterial proteases, called virulence factors, in nonhealing wounds.
- The test is simple and noninvasive.
- In a large multicenter clinical trial, the presence of BPA significantly impeded wound healing. It is the first biomarker diagnostic available in the U.S.28
- Clinical note: The test is a lateral flow test designed to detect bacterial proteases from commonly known wound pathogens: Staphylococcus aureus, Enterococcus faecalis, Proteus mirabilis, and Pseudomonas aeruginosa.
- The test is scheduled for commercial launch in the US in 2020.
- Advantages of BPA testing
  - BPA testing is simple, easy and provides real time information eliminating the need for empiric therapy.
  - The only test that correlates with wound healing at 12 weeks.
- Disadvantages
  - The test requires 15 minutes to obtain results.
  - Blood can interfere with the test.

The Serena Technique[29]

1. Before collecting the specimen, cleanse the wound with saline removing all the loose debris and the remains of therapeutic agents.
2. It is best not to debride the wound before swabbing. Blood interferes with the test by discoloring the test strip and blood contains tissue inhibitors of matrix metalloproteases (TIMPs) that could lead to false negative results.
3. If bleeding does occur, hemostasis must be achieved before obtaining the specimen.
4. The next step is to moisten the wound with saline such that the surface glistens. Excessive use of saline should be avoided.
5. Other wash solutions should also be avoided as they may interfere with the activity of the proteases and thereby lead to false results.
6. Use only the sterile swab provided with the kit.
7. Press the head of the swab flat against the wound base in a parallel alignment and gently rotate or roll the swab several times while applying pressure. Continue rotating the swab with pressure in this manner until the swab head is full coated with and discolored by the wound fluid.

8. Areas with thick slough or necrotic or nonviable tissue should not be swabbed. Otherwise, the swab should be rolled across the entire surface of the wound. This usually takes up to 2 minutes.
9. The swab is placed in the testing card, the reagent added and then turned five times.
10. Wait 10 minutes
11. Close the card.
12. Wait five minutes
13. The purple control line marked "C" will appear if the test is valid.
14. If the sample is + for BPA, a lower line marked "T" will appear.

Treat Wagner 3 or greater diabetic foot ulcers (Full thickness ulcers down to deeper structures with infection or history of infection) with Hyperbaric Oxygen Therapy.

Osteomyelitis

- Osteomyelitis is defined as an infection of the bone due to bacteria. It can present acutely of chronically.
- Referrals to the woundologist most commonly have chronic osteomyelitis that developed from the contiguous spread of bacteria from a soft tissue infection. The diabetic foot ulcer complicated by osteomyelitis of an underlying metatarsal head or calcaneus is a classic example.
- Chronic refractory osteomyelitis is a chronic osteomyelitis that has failed to respond to antibiotics and surgical intervention. CRO is an indication for hyperbaric oxygen therapy.
- Staphylococcus aureus remains the most common organism found in osteomyelitis, although, older patients may have gram negative bacteria.[28]
- Plain films are indicted for all patients with diabetic foot ulcers; however, plain X-rays may fail to image osteomyelitis due to a 2-3-week lag time between the development of osteomyelitis and X-ray findings. If osteomyelitis is suspected and plain films are negative, consider another imaging modality. [30]
- MRI is the best imaging modality to detect osteomyelitis.[31]

- Probing a wound like a diabetic foot ulcer to determine if bone is exposed was thought to be diagnostic of osteomyelitis. This is not true. However, if you cannot probe down to bone, there is less than a 5% chance of osteomyelitis. The probe is a good negative test for osteomyelitis, but a positive probe test is unreliable. [32]
- Infectious disease specialists prefer to prescribe antibiotics based on a bone biopsy; however, in chronic osteomyelitis the biopsies are frequently negative.
- The traditional course of antibiotic therapy for osteomyelitis is 6 weeks of intravenous antibiotics, although, a recent multicenter clinical trial published in the New England Journal of Medicine demonstrated that oral antibiotics were equally as effective. [33]
- Hyperbaric oxygen therapy (HBOT) is indicated for chronic osteomyelitis that has failed to respond to antibiotics or surgery. Patients with chronic osteomyelitis and multiple co-morbidities will benefit from adjuvant HBOT.

Current Recommendations for SerenaGroup® Centers for the Treatment of Infection

1. Avoid relying solely on clinical signs and symptoms in identifying bacterial load in nonhealing wounds.
2. Do not swab chronic wounds!
3. Choose a point-of-care diagnostic to screen patients for bacterial load (At the time of this writing only the MoleculLight device is available. In the future bacterial protease testing will also be available).
4. Treat moderate-to-heavy bacterial load early with topical antiseptics. Antibiofilm agents are preferred based on clinical evidence (e.g. BlastX™ Next Science, Jacksonville, FL).
5. Perform tissue biopsy or PCR in wounds that are actively infected to guide antibiotic use.
6. Consider HBOT for Wagner 3 diabetic foot ulcers that are infected or have been infected.
7. Perform diagnostic studies if osteomyelitis is suspected. (Plain films are routine for all foot ulcers. MRI is the most sensitive imaging modality for osteomyelitis.
8. Consider HBOT as an adjunct to surgery and antibiotics in patients with chronic refractory osteomyelitis.
9. Stay informed. These recommendations will change.

Step 6: Control inflammation

- Chronic wounds are characterized by excessive inflammation caused by elevated host proteases such as matrix metalloproteases (MMPs) and Human Neutrophil Elastase (HNE).[34]
- Roughly, 30% of patients who present to the wound clinic will have elevated protease activity (EPA) in their wounds. If a wound has EPA there is a 90% chance that it will not heal.[35]
- Bacteria will elevate host proteases in the wound but are not the sole cause of EPA.
- At present in the Unites States, there is no test available for EPA. A point-of-care test (WoundChek Protease Status™, Gargrave, North Yorkshire, United Kingdom) is on the market in Europe and there are plans to obtain US FDA approval.
- Consider protease modulation for wounds that have failed to progress in a timely fashion. Collagen acts as a sacrificial substrate for proteases. Collagen dressing will decrease protease levels. Oxidized regenerated cellulose (ORC) binds to the zinc in the metalloproteases causing them to change shape and lose effectiveness. ORC/Collagen dressings (Promogran, Prisma, 3M, Minneapolis, Minnesota) are designed to reduce wound proteases and promote wound healing.[36] Oral doxycycline also reduces proteases at doses below the antimicrobial levels. A typical dose is 50mg po BID. You can also prescribe doxycycline at 100mg po BID.
- The woundologist will also encounter ulcers of inflammatory origin. The protease levels in these ulcers are markedly elevated. Suspect an inflammatory etiology in ulcers:
  - A wound with an unusual presentation requires further investigation. (Case example: a 30-year-old woman presents with an ulcer in the medial gaiter region of 3 weeks duration. On examination the classic signs of venous disease are absent and the ulcer is 4mm in depth. On further questioning she reports a history of Crohn's disease. This inflammatory ulcer is pyoderma gangrenosum.)
  - If an ulcer worsens with debridement or was caused by minor trauma, suspect pathergy, an abnormal reaction leading to skin breakdown.
  - Pyoderma is frequently seen in peristomal wounds (figure 12).
  - Pathologic arterial inflammation can lead to the development of a vasculitic ulcer. These patients complain of pain, severe pain. Often, they refuse dressings due to the pain.

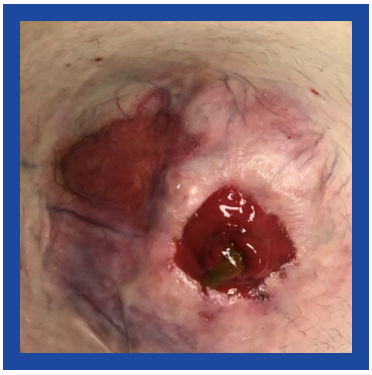


Figure 13: Peristomal Pyoderma

- The diagnosis of an inflammatory ulcer begins with a thorough history and physical examination. Biopsy of the wound using a 3mm punch can provide an answer. However, the biopsy of the most frequently encountered inflammatory ulcer, pyoderma gangrenosum, may not provide a definitive diagnosis.
- The treatment of inflammatory ulcers requires the collaboration of several medical specialists, such as rheumatology, gastroenterology and hematology.

Step 7: Control Edema

- "Edema is the enemy."
- History and physical examination reveal the etiology of the patient's edema.
  - Suspect chronic venous insufficiency if the patient is of advanced age, female, obese, or has a history of deep venous thrombosis (DVT), a family history of venous disease, a previous lower extremity orthopedic procedure, or an occupation that requires prolonged standing.
  - Chronic venous insufficiency is also accompanied by the classic signs of venous disease: Hemosiderin deposits (reddish brown discoloration beginning in the medial gaiter region of the leg), absence of hair, thickening of the nails, lipodermatosclerosis (thickened skin that has the appearance of a cobble stone street) and atrophie blanche (white scarred areas). (Figure 14).

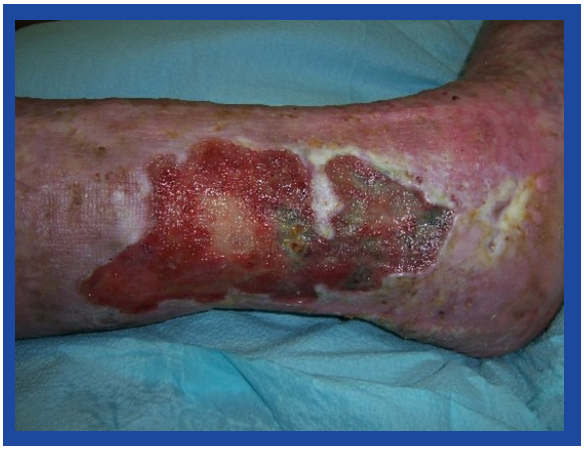


Figure 14: Chronic Venous Insufficiency with ulceration

- "Patients can have as many diseases as they want." The average patient in the wound clinic has 10 co-morbidities. The woundologist will encounter numerous edema etiologies: congestive heart failure, renal failure, hepatic insufficiency, protein-calorie malnutrition and recent cellulitis.
- Lymphedema will cause lower extremity swelling. The clinical picture is different from venous insufficiency, although, many patients suffer from both disorders. In lymphedema the dorsum of the foot and toes will swell and the classic signs of venous disease may be absent (Figure 15).
- Lipodema may masquerade as lymphedema or venous edema. It is the accumulation of excess fat in the lower extremities.

Figure 15: Lymphedema; dorsal foot swelling and an advanced case of lymphedema.

- Clinical Note: Why does venous insufficiency lead to skin breakdown? There are several competing theories. I favor the leukocyte trap theory which states that leukocytes get trapped in the swollen capillary beds releasing free oxygen radicals causing skin breakdown.[36] If interested, other hypothesis include the fibrin cuff theory[38] and a dysregulation of host proteases.[39]
- Multilayer compression is the primary treatment for edema. It is the standard of care for venous leg ulcers.
- Multilayer compression wraps provide 40 mmHg at the ankle.
- Prior to applying multilayer compression, perform a vascular assessment. Standard compression wraps require an ABI >0.8.The light versions of the wraps can be applied down to an ABI >0.6.
- Take caution in applying multilayer compression.
  - Pad the ankle area in patients with thin ankles to avoid excessive compression.
  - Start the wrap at the base of the toes to avoid foot swelling.
  - Place the patient's ankle at 90 degrees.

Adequate compression for patients with venous leg ulcers at each visit [Quality Metric]

- Prevention of venous leg ulcers is challenging with a reported recurrence rate of 67%.[39]
  - Compression stockings are the mainstay in the prevention of venous leg ulcers. CMS covers 80% of the cost of compression stockings; however, they only cover socking with compression 30-40mmHg. Most patients cannot don these stockings. We performed an exercise in a skilled nursing facility to determine how many of the residents could don a 30-40 stocking. The answer is zero. The cost of 20-30 mmHg runs around $40.00 USD.
  - If the patient fails multilayer compression, CMS will cover custom stockings with zippers or self-adhesive stockings such as Farrow Wraps (Jobst USA; Charlotte, NC).
  - If the patient cannot don any of the above stockings, consider lymphedema pumps. There are several commercially available devices.
- What is the role of venous ablation surgery in preventing the recurrence of venous leg ulcers?
  - The endovenous ablation procedure uses radiofrequency or laser therapy to close off the greater saphenous vein just below its juncture with the common femoral vein.
  - The ESCHAR clinical trial demonstrated that ablation does not increase the healing of venous leg ulcer, but it reduced recurrence by roughly 50% after one year.[41]
  - Clinicians frequently ask when to refer healed venous leg ulcer patients for ablation. Unfortunately, there are no evidenced-based criteria. I tend to refer patients who had large ulcers >10cm^2 and recurrent ulcers. SerenaGroup® hopes to develop these criteria. Stay tuned.

Step 8: Offloading

There is more evidence for off-loading than any other modality in wound care.

- **Diabetic Foot Ulcers (DFU)**
  - Total contact casting (TCC) is the gold standard for offloading the diabetic foot.[42]
  - Clinical note: The effectiveness of TCCs stems from several factors: it forces compliance with offloading, shortens stride length during ambulation, reduces activity and lowers pressure on the foot.
  - Contraindications to TCC include a highly draining wound, infection and arterial insufficiency. In addition, patients find it difficult to drive with a TCC in place.

Offload diabetic and pressure ulcers at every visit.
[Quality Metric]

- Alternatively, fixed ankle walkers provide effective offloading. The obvious problem is that patients can remove them. For this reason, several studies have demonstrated the superiority of TCC over removable boots.[43]
- Shoe inserts and half shoes do not provide adequate offloading.
- The recurrence rate of DFUs is as high as 56%.[44] After a DFU has healed, patients should be fitted with custom shoe wear. CMS will cover 80% of the cost of diabetic shoe wear and two shoe inserts annually. A local orthotist can fit the patient. There are also national companies that make custom made shoes and inserts.

- Pressure Ulcers (PrU)
  - Offloading is essential in the prevention and treatment of pressure ulcers.
  - Avoid placing patients on bony prominences. Periodic turning and repositioning reduces the risk of pressure ulcer formation; however, there is no evidence for a q2hr turning schedule. The ideal turning and repositioning timetable depends upon the patient and the situation.
  - The American College of Physicians Recommendations for offloading pressure ulcers with the strength of evidence ratings:[45]
    - Clinicians should perform a risk assessment to identify patients who are at risk of developing pressure ulcers (Grade: weak recommendation, low quality evidence).
    - Clinicians should choose advanced static mattresses or advanced static over-lays in patients who are at increased risk of developing pressure ulcers (Grade: Strong recommendation, moderate quality evidence).
    - ACP recommends against using alternating air mattresses or alternating-air overlays in patients who are at an increased risk of developing pressure ulcers (Grade: weak recommendation. Moderate-quality evidence).
- Once a PrU has developed, consider an offloading mattress such as a low air loss mattress. Use a wheelchair cushion and for heel ulcers float the heels or use offloading boots.
- For NPIAP stage 3 or 4 ulcers CMS will cover the use of an air-fluidized bed (e.g. Clinitron, Hillrom;Chicago,IL). However, there are no clinical trials that show that beds promote healing.

Step 9: Maintain proper moisture balance

- Grandma was wrong when she advised leaving a wound open to air. The importance of moisture in promoting wound healing dates to the 1960s.[46]
- Utilize a primary dressing to maintain in appropriate moisture balance.

"If the wound is dry, wet it. If the wound is wet, dry it."

- The simple statement, borrowed from our dermatology colleagues, is the best advice in dressing choice. If a patient has a dry diabetic foot ulcer add a moisture retentive gel. If a patient has a draining venous leg ulcer apply an absorptive dressing such as an alginate, foam or super absorbing dressing.
- Utilize dressings that are atraumatic that do not injure the wound or periwound skin on removal.[47]
- Avoid the use of wet-to-dry dressings.
- In my experience, Wound Source produces the best reference for dressing choice. It is found on-line at www.woundsource.com.

Step 10: Evaluate Nutritional Status and Diabetic Control

- Healing requires optimization of nutritional status.
  - Perform a nutritional assessment using a validated tool.[48] SerenaGroup® uses the Mini Nutritional Assessment (MNA) shown in Figure 14.
  - Hepatic enzymes, albumin and prealbumin, do not accurately reflect nutritional status. They are of limited use to the woundologist.[49] Elderly patients may have low albumin and prealbumin levels secondary to their age with no correlation to their nutritional status.[50]
  - High protein oral supplements are readily available.
  - Use protein supplementation with caution in patients with renal insufficiency. Consider consulting a renal dietician or if unavailable a standard dietician.
  - In patients with protein calorie malnutrition who do not respond to oral supplements, obtain a dietary consult and consider parenteral nutritional supplementation.
- Diabetic control is important in wound healing.
  - Obtain fasting glucose and HbA1C on all diabetics seen in the wound clinic.
  - It is important to note that HbA1C values do not correlate with wound healing.[51]
  - For patients undergoing HBOT, test finger stick blood sugar before and after each treatment. If the pre-treatment blood sugar is less than 120mg/dl, consider giving carbohydrates and retesting in 15 minutes.
  - Consider consulting the diabetic teaching nurse for patients with poorly controlled diabetes.

Figure 14

Mini Nutritional Assessment MNA®

Nestlé NutritionInstitute

Last name: First name:

Sex: Age: Weight, kg: Height, cm: Date:

Complete the screen by filling in the boxes with the appropriate numbers.
Add the numbers for the screen. If score is 11 or less, continue with the assessment to gain a Malnutrition Indicator Score.

Screening

A Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
0 = severe decrease in food intake
1 = moderate decrease in food intake
2 = no decrease in food intake ☐

B Weight loss during the last 3 months
0 = weight loss greater than 3kg (6.6lbs)
1 = does not know
2 = weight loss between 1 and 3kg (2.2 and 6.6 lbs)
3 = no weight loss ☐

C Mobility
0 = bed or chair bound
1 = able to get out of bed / chair but does not go out
2 = goes out ☐

D Has suffered psychological stress or acute disease in the past 3 months?
0 = yes 2 = no ☐

E Neuropsychological problems
0 = severe dementia or depression
1 = mild dementia
2 = no psychological problems ☐

F Body Mass Index (BMI) (weight in kg) / (height in m²)
0 = BMI less than 19
1 = BMI 19 to less than 21
2 = BMI 21 to less than 23
3 = BMI 23 or greater ☐

Screening score (subtotal max. 14 points) ☐☐
12-14 points: Normal nutritional status
8-11 points: At risk of malnutrition
0-7 points: Malnourished
For a more in-depth assessment, continue with questions G-R

Assessment

G Lives independently (not in nursing home or hospital)
1 = yes 0 = no ☐

H Takes more than 3 prescription drugs per day
0 = yes 1 = no ☐

I Pressure sores or skin ulcers
0 = yes 1 = no ☐

J How many full meals does the patient eat daily?
0 = 1 meal
1 = 2 meals
2 = 3 meals ☐

K Selected consumption markers for protein intake
- At least one serving of dairy products (milk, cheese, yoghurt) per day yes ☐ no ☐
- Two or more servings of legumes or eggs per week yes ☐ no ☐
- Meat, fish or poultry every day yes ☐ no ☐

0.0 = if 0 or 1 yes
0.5 = if 2 yes
1.0 = if 3 yes ☐.☐

L Consumes two or more servings of fruit or vegetables per day?
0 = no 1 = yes ☐

M How much fluid (water, juice, coffee, tea, milk...) is consumed per day?
0.0 = less than 3 cups
0.5 = 3 to 5 cups
1.0 = more than 5 cups ☐.☐

N Mode of feeding
0 = unable to eat without assistance
1 = self-fed with some difficulty
2 = self-fed without any problem ☐

O Self view of nutritional status
0 = views self as being malnourished
1 = is uncertain of nutritional state
2 = views self as having no nutritional problem ☐

P In comparison with other people of the same age, how does the patient consider his / her health status?
0.0 = not as good
0.5 = does not know
1.0 = as good
2.0 = better ☐.☐

Q Mid-arm circumference (MAC) in cm
0.0 = MAC less than 21
0.5 = MAC 21 to 22
1.0 = MAC 22 or greater ☐.☐

R Calf circumference (CC) in cm
0 = CC less than 31
1 = CC 31 or greater ☐

Assessment (max. 16 points) ☐☐.☐
Screening score ☐☐.☐
Total Assessment (max. 30 points) ☐☐.☐

Malnutrition Indicator Score
24 to 30 points ☐ Normal nutritional status
17 to 23.5 points ☐ At risk of malnutrition
Less than 17 points ☐ Malnourished

References
1. Vellas B, Villars H, Abellan G, *et al.* Overview of the MNA® - Its History and Challenges. *J Nutr Health Aging.* 2006; **10**:456-465.
2. Rubenstein LZ, Harker JO, Salva A, Guigoz Y, Vellas B. Screening for Undernutrition in Geriatric Practice: Developing the Short-Form Mini Nutritional Assessment (MNA-SF). *J. Gerontol.* 2001; **56A**: M366-377
3. Guigoz Y. The Mini-Nutritional Assessment (MNA®) Review of the Literature - What does it tell us? *J Nutr Health Aging.* 2006; **10**:466-487.

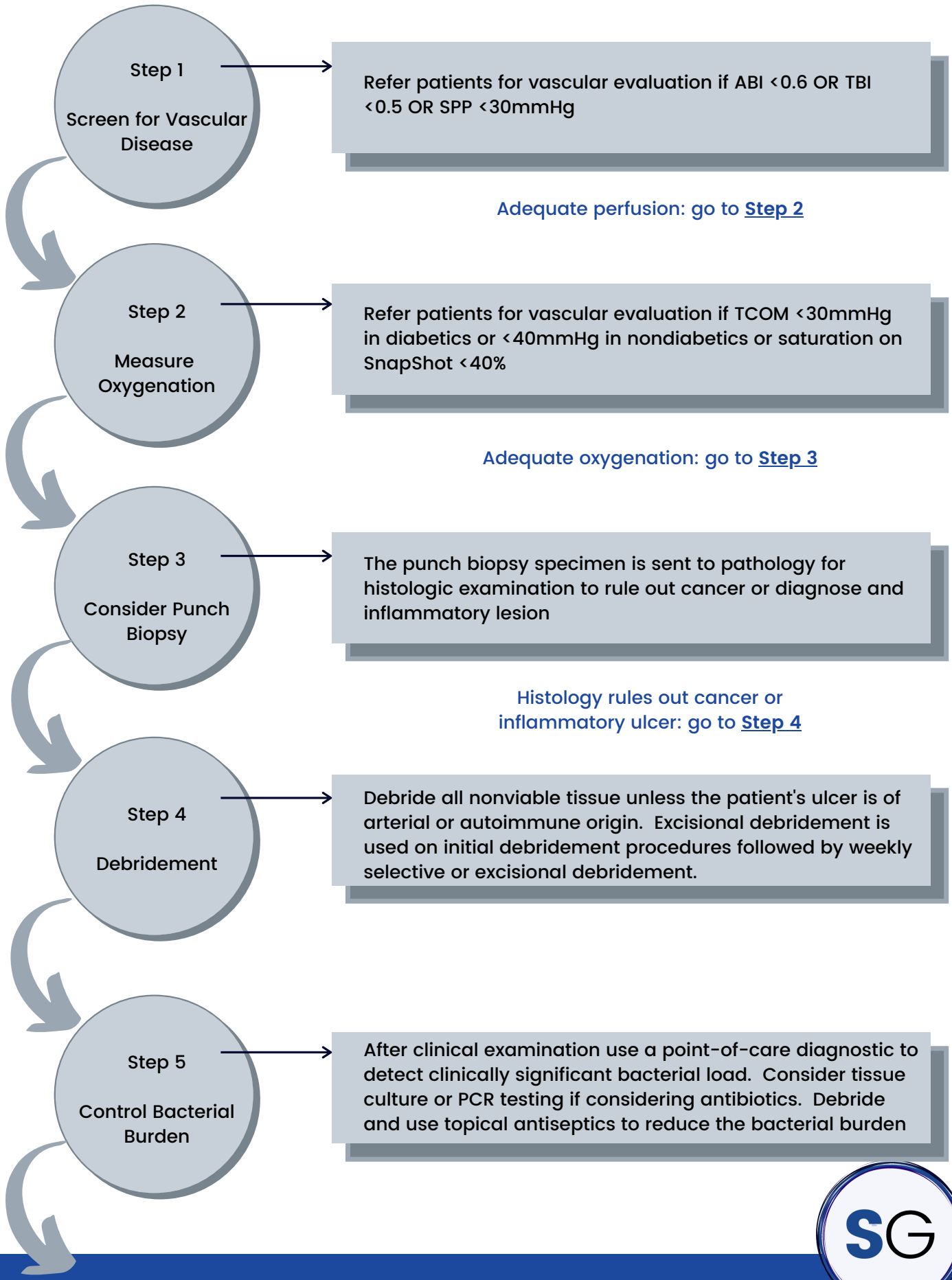
For more information: www.mna-elderly.com

Step 11: Evaluate host factors

- Patient comorbidities may affect healing.
- Perform a complete history and physical examination.
- Review the patient's medication list including herbal supplements and home remedies.
- Coordinate care with the patient's other physicians.
- The woundologist frequently encounters conditions or medications that adversely affect wound healing. In addition, treating a patient's underlying disease can promote wound healing.
    - Chemotherapy for the treatment of cancer or other conditions inhibits wound healing. It is best to focus wound healing efforts before or after chemotherapy.
    - Statins decrease the risk of amputation in diabetics.[52] Consider consulting the patient's primary care physician for patients with DFUs.
    - TNF Alfa Inhibitors (etanercept, certolizumab, infliximab, adalimumab, golimumab) suppress tumor necrosis factor alpha (TNF) an inflammatory protein produced by white blood cells. Today, TNF alpha inhibitors are used in a variety of inflammatory illnesses: such as rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, and psoriasis. The action of these medications early in the inflammatory process may inhibit wound healing. Discuss a drug holiday with the prescribing physician.
    - High dose corticosteroids impede wound healing. In patients on chronic steroids discuss with prescribing physician lowering the dose to a Prednisone equivalent of 5mg/day.
    - Immunosuppressants, such as medications to prevent organ rejection, impair wound healing; however, in most cases these medications cannot be discontinued.
    - In several studies Non-steroidal anti-inflammatory drugs (NSAIDs) were shown to suppress wound healing.[53]
    - Anticoagulants, such as low-weight-molecular heparin, may interfere with healing; However, at present the evidence is conflicting. SerenaGroup® does not recommend stopping anticoagulant therapy.
- Tabaco use, vaping and illicit drug use hinder healing. Smoking cessation is an important part of the treatment plan.

Step 12: Develop a goal

- Utilizing the previous steps, develop a plan to promote wound healing that includes weekly visits and follow the SerenaGroup® Guidelines.


Step 1
Screen for Vascular Disease
Refer patients for vascular evaluation if ABI <0.6 OR TBI <0.5 OR SPP <30mmHg
Adequate perfusion: go to Step 2
Step 2
Measure Oxygenation
Refer patients for vascular evaluation if TCOM <30mmHg in diabetics or <40mmHg in nondiabetics or saturation on SnapShot <40%
Adequate oxygenation: go to Step 3
Step 3
Consider Punch Biopsy
The punch biopsy specimen is sent to pathology for histologic examination to rule out cancer or diagnose and inflammatory lesion
Histology rules out cancer or inflammatory ulcer: go to Step 4
Step 4
Debridement
Debride all nonviable tissue unless the patient's ulcer is of arterial or autoimmune origin. Excisional debridement is used on initial debridement procedures followed by weekly selective or excisional debridement.
Step 5
Control Bacterial Burden
After clinical examination use a point-of-care diagnostic to detect clinically significant bacterial load. Consider tissue culture or PCR testing if considering antibiotics. Debride and use topical antiseptics to reduce the bacterial burden

Step 6
Control Inflammation

Suspect elevated protease activity in nonhealing wounds. A trial of protease modulation is indicated when other reasons for delayed wound healing have been ruled out.

Step 7
Treat Edema

Determine the etiology of edema. The standard of care is multilevel compression wraps applied at least weekly.

Step 8
Offloading

The gold standard for offloading is Total Contact Casting (TCC). Alternatively, a fixed ankle walker is acceptable. Reduce pressure over boney prominences in the prevention and treatment of pressure ulcers.

Step 9
Maintain Proper Moisture Balance

Choose a dressing that maintains moisture balance. Avoid dressing that traumatize the wound.

Step 10
Evaluate Nutritional Status and Diabetic Control

Screen patients for protein calorie malnutrition using the MNA. Evaluate glucose control in diabetics. Consider dietary or diabetic teaching consult.

Step 11
Evaluate Comorbidities

Perform a history & physical to evaluate co-morbidities that influence wound healing. Review medication list. Work collaboratively with other medical specialists.

Step 13: Revaluate after 30 days

- A robust body of evidence suggests that if a wound does not progress toward closure after four weeks of therapy, the current treatment regimen is ineffective.[54] However, the majority of this evidence comes from clinical trials and the percentages of healing may not extrapolate to the real world wound care population.
- The SerenaGroup® recommendations found in table 2 provide a guideline for the reduction in surface area expected in a four-week time frame. Guidelines do not apply to every patient, they serve as a reference point to assist clinicians with treatment decisions.
- If an ulcer does not progress as expected review the previous steps (1-11).
- If the healing process remains stalled go to step 14, advanced care.

Ulcer Type	Expected Reduction in Surface Area in Four Weeks
Diabetic Foot Ulcers	30%
Venous Leg Ulcers	30%
Pressure Ulcers	10%

Step 14: Consider advanced modalities for wounds that do not reduce in size after four weeks of standard wound care.

- If the wound fails to progress as expected in four weeks, consider advanced wound care therapies.
- Advanced Therapies:
  - Cellular and Tissue-based Products for wound care (CTPs) have randomized clinical trial (RCT) evidence for Wagner 2 DFUs and VLUs. [55,56]
  - Negative pressure wound therapy (NPWT) has RCT evidence.57 I use it for large defects with depth to promote granulation tissue. Our recent research demonstrates that the results with NPWT can be improved by adding antibiofilm agents.[58]
  - Growth Factor Therapy accelerates healing in DFUs.[59] The only commercially available product in the US, platelet derived growth factor (PDGF, Becaplermin, Regranex® Smith and Nephew Fort Worth, TX), has several RCTs demonstrating benefit in DFUs. However, since its launch in the late 1990's PDGF use has fallen. The wound bed in the everyday DFU is a hostile environment. PDGF works best when the wound bed is well prepared. In my opinion, the use of PDGF in DFUs in which the steps

above were not followed prior to application led to the perception that PDGF was not effective. I believe PDGF is effective in treatment of DFUs. In addition, in my experience, the combination of PDGF with HBOT accelerates the healing of Wagner 3 DFUs.

- Physical modalities such as electric stimulation and noncontact ultrasound promote wound healing.[60] These are not commonly used in most wound clinics despite their efficacy.
- Hyperbaric oxygen therapy (HBOT) is indicated for Wagner 3 DFUs, chronic refractory osteomyelitis, compromised flaps and grafts, the late effects of radiation therapy, and necrotizing soft tissue infections. Please refer to the SerenaGroup® Practice Manual for the Use of Hyperbaric Oxygen Therapy for a complete review of the indications for HBO and how to determine if a patient will benefit from HBOT.

References

1. Moffatt CJ. Palpating ankle pulses is insufficient in detecting arterial insufficiency in patients with leg ulceration. Phlebology 1994;9:170-172.
2. Baumgartner I, Schainfeld R, Graziani L. Management of peripheral vascular disease. Annu Rev Med. 2005;56:249-72
3. Zemaitis MR, Boll JM, Dreyer MA. Peripheral Arterial Disease. [Updated 2019 Nov 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430745/SPP
4. Attinger CE, Evans KK, Bulan E, Blume P, Cooper P. Angiosomes of the foot and ankle and clinical implications for limb salvage: reconstruction, incisions, and revascularization. Plast Reconstr Surg. 2006 Jun;117(7 Suppl):261S-293S.
5. Padberg FT, Back TL, Thompson PN, Hobson RW., 2nd Transcutaneous oxygen (TcPO2) estimates probability of healing in the ischemic extremity. Journal of Surgical Research. 1996;60:365
6. Blake DF, Young DA, Brown LH. Transcutaneous oximetry: variability in normal values for the upper and lower limb. Diving Hyperb Med. 2018;48(1):2–9. Published 2018 Mar 31. doi:10.28920/dhm48.1.2-9.
7. Ercengiz A, Mutluoglu M. Hyperbaric, Transcutaneous Oximetry. [Updated 2019 Jun 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470590/
8. Fife, C. et. al. Factors influencing the outcome of lower extremity diabetic ulcers treated with hyperbaric oxygen therapy. Wound Rep. Reg. (2007) 17 322 – 331.
9. Wersen, et al. Hazard risk calculated with compression analyses, adjusted for chemographic and lifestyle factors.Diabetes Care. 2009; 32:2193-9.
10. Lima A and Bakker J. Near-infrared spectroscopy for monitoring peripheral tissue perfusion in critically ill patients. Revista Brasileira de Terapia Intensiva, 2011: 23(3), 341-351. https://doi.org/10.1590/S0103-507X2011000300013.
11. Serena TE, Yaakov R, Serena LM, Mayhugh TA, Harrell K. A Pilot Study Comparing Near Infrared Spectroscopy (NIRS) and Transcutaneous Oxygen Measurement (TCOM) in Patients with Chronic Wounds. Journal of Wound Care. Accepted for publication.
12. Serena TE, Cole W, Coe S, Harrell K, Serena L,Yaakov R, Rennie M. The safety of punch biopsies on hard-to-heal wounds: a large multicentre clinical trial Journal of Wound Care, Feb. 2020, Vol. 29, Issue 2.
13. Wilcox J. Cater M., Covington S. Frequency of Debridements and Time to Heal: A Retrospective Cohort Study of 312 744 Wounds. JAMA Dermatol. 2013;149(9):1050-1058. doi:10.1001/jamadermatol.2013.4960.
14. Steed DL et. al. The effect of extensive Debridement and Treatment on the Healing of Diabetic Foot Ulcers. J Amer Coll Surg 1996; 183:61-64
15. Serena TE. Debridement in Wound Care: A Collaborative Practice Manual for Health Professionals Editors Bates-Jensen B, Sussman C. Fourth Edition. Lippincott; New York, NY.
16. Milne CT, Ciccarelli AO, Lassy M. A Comparison of Collagenase to Hydrogel Dressings in Wound Debridement. WOUNDS, 2010, 22, 270-274.
17. Wolff H & Hansson C 2003. Larval therapy – an effective method of ulcer debridement.
18. Clin Exp Dermatol 28: 134-137.
19. Tomic-Canic M, Ayello EA, Stojadinovic O, et al. Using gene transcription patterns (bar coding scans) to guide wound debridement and healing. Adv Skin Wound Care. 2008; 21:487–92.
20. Xu L, McLennan SV, Lo L, Natfaji A. Bolton T, Liu Y, Twigg SM, Yue KD. Bacterial load predicts healing rate in neuropathic diabetic foot ulcers. Diabetes Care, Vol 30; no.2; February 2007.

21. International Wound Infection Institute (IWII) Wound infection in clinical practice. Wounds International 2016
22. Serena TE, Robson MC, Cooper DM, Ignatius J. Lack of Reliability of Clinical/Visual Assessment of Chronic Wound Infection: The Incidence of Biopsy-Proven Infection in Venous Leg Ulcers. WOUNDS 2006; 18(7): 197-202.
23. Serena TE et al. A multicenter randomized controlled trial evaluation Fluorescence Assessment And Guidance (FLAAG). Manuscript in progress.
24. Serena TE, Rennie M. The accuracy of semiquantitative swabs vs quantitative tissue biopsies. Manuscript in progress.
25. Serena TE, Chi-Tyan S, Yaakov R, DaCosta R. The Role of Point-of-Care Bacterial Fluorescence Imaging in Diagnostic and Antimicrobial Stewardship. Submitted to Advances in Wound Care.
26. Serena TE. A New Term: The Point of Pathogenicity. Advances in Skin and Wound Care. December 2019.
27. Robson MC, Stenberg BD, Heggers JP. Wound healing alterations caused by infection. Clin Plast Surg 1990; 17: 485–92.
28. Schultz G, Bjarnsholt T, James GA, Leaper DJ, McBain AJ, Malone M, Stoodley P, Swanson Y, Tachi M, Wolcott RD, for the Global Wound Rep Reg. 2017;25, 744–757. VC 2017 by the Wound Healing Society.
29. Abdulrazak A, Bitar ZI, Al-Shamali AA, Mobasher LA. Bacteriological study of diabetic foot infections. J Diabetes Complications. 2005;19(3):138–141.
30. Serena TE.Development of a Novel Technique to Collect Proteases from Chronic Wounds. Adv Wound Care. 2014; 3(12): 729-732.
31. Pineda C, Vargas A, Rodríguez AV. Imaging of osteomyelitis: current concepts. Infect Dis Clin North Am. 2006;20(4):789–825.
32.. Pineda C, Espinosa R, Pena A. Radiographic imaging in osteomyelitis: the role of plain radiography, computed tomography, ultrasonography, magnetic resonance imaging, and scintigraphy. Semin Plast Surg. 2009;23(2):80–89.
33. Lavery LA, Armstrong DG, Peters EJ, Lipsky BA Probe-to-bone test for diagnosing diabetic foot osteomyelitis: reliable or relic? Diabetes Care. 2007 Feb;30(2):270-4.
34. .Li HK, Rombach I, Zambellas R, Walker AS, McNally MA, Atkins BL, Lipsky BA, Hughes HC, Bose D, Kümin M, Scarborough C, Matthews PC, Brent AJ, Lomas J, Gundle R, Rogers M, Taylor A, Angus B, Byren I, Berendt AR, Warren S, Fitzgerald FE, Mack DJF, Hopkins S, Folb J, Reynolds HE, Moore E, Marshall J, Jenkins N, Moran CE, Woodhouse AF, Stafford S, Seaton RA, Vallance C, Hemsley CJ, Bisnauthsing K, Sandoe JAT, Aggarwal I, Ellis SC, Bunn DJ, Sutherland RK, Barlow G, Cooper C, Geue C, McMeekin N, Briggs AH, Sendi P, Khatamzas E, Wangrangsimakul T, Wong THN, Barrett LK, Alvand A, Old CF, Bostock J, Paul J, Cooke G, Thwaites GE, Bejon P, Scarborough M, OVIVA Trial Collaborators. Oral versus Intravenous Antibiotics for Bone and Joint Infection. N Engl J Med. 2019 Jan 31; 380(5):425-436.
35. Dissemond J, Dowsett C, Schultz G, Serena TE EPA made Easy..Wounds International. Volume 4. Issue 2. May 2013.
36. Serena TE, Cullen BM, Bayliff SW, Gibson MC, Carter MJ, et al. Defining a New Diagnostic Assessment Parameter for Wound Care: Elevated Protease Activity, an Indicator of Nonhealing, for Targeted Protease-modulating Treatment. Wound Repair Regen. 2016;24(3):589-95. doi: 10.1111/wrr.12431.
37. Cullen BM, Serena TE, Gibson M, Snyder RJ, Hanft JR, Yaakov RA. Randomized Control Trial Comparing Collagen/ORC/Silver to Standard of Care in the Management of Venous Leg Ulcers. Advances in Skin & Wound Care. 2017 Oct;30(10):464-468.
38. Falanga V, Eaglstein WH. The “trap” hypothesis of venous ulceration. Lancet. 1993; 341:1006–8.

39. Burnand KG, Whimster I, Naidoo A, Browse NL. Pericapillary fibrin in the ulcer-bearing skin of the leg: The cause of lipodermatosclerosis and venous ulceration. Br Med J (Clin Res Ed) 1982; 285:1071–2.
40. Higley HR, Ksander GA, Gerhardt CO, Falanga V. Extravasation of macromolecules and possible trapping of transforming growth factor-beta in venous ulceration. Br J Dermatol. 1995;132:79–85.
41. McDaniel HB, Marston WA, Farber MA, Mendes RR, Owens LV, Young ML, Daniel PF, Keagy BA Recurrence of chronic venous ulcers on the basis of clinical, etiologic, anatomic, and pathophysiologic criteria and air plethysmography.. J Vasc Surg. 2002 Apr; 35(4):723-8.
42. Barwell JR, et al; Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomized controlled trial. Lancet 2004 Jun 5;363 : 1854-9.43. Cavanagh PR, Bus SA. Off-loading the diabetic foot for ulcer prevention and healing. J Vasc Surg. 2010 Sep; 52(3 Suppl):37S-43S.
43. Armstrong D., Nguyen H., Lavery L., van Schie C. Boulton A. Harkless L. Off-loading the diabetic foot. A randomized Clinical Trial. Diabetes Care 2001 Jun; 24(6): 1019-1022.
44. Armstrong D. Boulton A. Sicco B. Diabetic Foot Ulcers and Their Recurrence. N Engl J Med 2017; 376:2367-2375.
45. Qaseem A, Mir TP, Starkey M, et al, for the Clinical Guidelines Committee of the American College of Physicians. Risk Assessment and Prevention of Pressure Ulcers: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2015;162:359–369. doi: https://doi.org/10.7326/M14-1567.
46. Winter, G.D. (1962) Formation of Scab and the Rate of Epithelialisation of Superficial Wounds in the Skin of the Young Domestic Pig. Nature, 193, 293-294. http://dx.doi.org/10.1038/193293a0.
47. Price, P.E., Fagervik-Morton, H., Mudge, E.J., Beele, H., Ruiz, J.C., Nystrøm, T.H., Lindholm, C., Maume, S., Melby-ØStergaard, B., Peter, Y., Romanelli, M., Seppänen, S., Serena, T.E., Sibbald, G., Soriano, J.V., White, W., Wollina, U., Woo, K.Y., Wyndham-White, C., Harding, K.G. Dressing-related pain in patients with chronic wounds: An international patient perspective. International Wound Journal volume 5, issue 2, year 2008, pp. 159 – 171.
48. Skates J, Anthony PS. Identifying Geriatric Malnutrition in Nursing Practice: The Mini Nutritional Assessment (MNA®)—An Evidence-Based Screening Tool. Journal of Gerontological Nursing. 2012;38(3):18-27https://doi.org/10.3928/00989134-20120207-02.
49. Fuhrman MP, Charney P, Mueller CM. Hepatic proteins and nutrition assessment. Journal of the American Dietetic Association. 104(8):1258-64, 2004 Aug.
50. Friedman FJ, Campbell AJ, Caradoc-Davies TH. Hypoalbuminemia in the elderly is due to disease not malnutrition.Clinical Experimental Gerontol. 1985;7:191-203.
51. Moffat, AD Glycosylated hemoglobin and hyperbaric oxygen coverage denials. Undersea Hyper Med 2015 May-Jun: 42(3):197-204.
52. Kokkinidis DG Arfaras-Melainis A, Giannopoulos S, Katsaros , Jawaid , Jonnalagadda , Parikh, Secemsky E, Giri , Kumbhani D, Armstrong EJ. Statin therapy for reduction of cardiovascular and limb-related events in critical limb ischemia: A systematic review and meta-analysis. Vasc Med. 2020 Jan 22:1358863X19894055. doi: 53.1177/1358863X19894055.
54. Anderson K, Hamm LR Factors That Impair Wound Healing: Review Article. Journal of the American College of Clinical Wound Specialists.Volume 4, Issue 4, December 2012, Pages 84-91. https://doi.org/10.1016/j.jccw.2014.03.001.
55. Sheehan et al. Diabetes Care. 2003;26(6):1879-1882.
56. Zelen CM, Snyder RJ, Serena TE, Li WW. The Use of Human Amnion/Chorion Membrane in the Clinical Setting for Lower Extremity Repair: A Review.. Clin Podiatr Med Surg. 2015; 32 (1): 135-46. doi 10.1016/j.cpm.2014.09.002.

57. Harding K, Kirsner R, Lee D, Mulder G, Serena TE. An international consensus document on acellular matrix products in the treatment of hard-to-heal wounds such as diabetic foot ulcers, venous leg ulcers and pressure ulcers. London. Wounds International. 2010.
58. Clare M, Fitzgibbons T, McMullen S, Stice R, Hayes D, Henkel L: Experience with the vaccum assisted closure negative pressure technique in the treatment of non-healing diabetic and dysvascular wounds. Foot Ankle Int 23(10):896-901, 2002. (RETRO S) [12398148]
59. Serena TE, Serena LM, Mynti M. Enhancing NPWT with the addition of antibiofilm agents. Manuscript in progress. Publication anticipated 2020.
60. Steed D, Webster W, Diabetic Ulcer Study Group. Clinical evaluation of recombinant human platelet derived growth factor (rhPDGF-BB) for the treatment of lower extremity diabetic ulcers. J Vasc Surg 21:71-81, 1995.
61. Kloth L: Electrical stimulation for wound healing: A review of evidence from in vitro studies, animal experiments, and clinical trials. Int J Extrem. Wounds 4(1):23-44, 2005. (LIT REV) [15860450].

Appendix A

CONFLICT OF INTEREST DISCLOSURE INDUSTRY CONSULTANT AND BOARDS ACTIVE
(activity in 2019-2020)

Andover Inc. 2015 - Present
- Research Support

3M (Formerly Kinetic Concepts Inc. (KCI) 2013 - Present
- Consultant, Research Support
- **Systagenix** (now part of 3M) 2009 - Present
- Research Support

DSM 2019 - Present
- Research Support

Kloxx 2019 - Present
- Consultant on Research

Ilkois Inc. 2019 - Present
- Research Support

Inotec Inc. 2019 - Present
- Research Support

LifeCuff Technologies 2020 - Present
- Research Support

Medline 2014 - Present
- Research Support Includes A.R.T. Device (formerly owned by Seven Oaks
- Research:

Mego Aflec/Lympha Press USA 2011 - Present
- Consultant

MFT Inc. 2016 - Present
- Research Support

Next Science 2019 - Present
- Research Support

MolecuLight Inc. 2018 - Present
Research Support, Consultant to FDA and AMA

Molnlycke 2018 - Present
- Research Support, Consultant

Organogenesis 2016 - Present
- Research including clinical trials for NuTech acquired by Organogensis during the trials

RedDress 2009 - Present
- Consultant, Research Support

TR Therapeutics 2013 - Present
- Research Support

WoundChek Labs Inc. 2015 - Present
- Consultant, Research Support, Stock paid as in kind payment for research services.

WoundKair Concepts Inc. 2017 - Present
- Royalties Total Contact Case Patents