Chronic Wounds: Evaluation and Management

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Chronic wounds are those that do not progress through a normal, orderly, and timely sequence of repair. They are common and are often incorrectly treated. The morbidity and associated costs of chronic wounds highlight the need to implement wound prevention and treatment guidelines. Common lower extremity wounds include arterial, diabetic, pressure, and venous ulcers. Physical examination alone can often guide the diagnosis. All patients with a nonhealing lower extremity ulcer should have a vascular assessment, including documentation of wound location, size, depth, drainage, and tissue type; palpation of pedal pulses; and measurement of the ankle-brachial index. Atypical nonhealing wounds should be biopsied. The mainstay of treatment is the TIME principle: tissue debridement, infection control, moisture balance, and edges of the wound. After these general measures have been addressed, treatment is specific to the ulcer type. Patients with arterial ulcers should be immediately referred to a vascular surgeon for appropriate intervention. Treatment of venous ulcers involves compression and elevation of the lower extremities, plus exercise if tolerated. Diabetic foot ulcers are managed by offloading the affected area. (*Am Fam Physician*. 2020;101(3):159-166. Copyright © 2020 American Academy of Family Physicians.)

A chronic wound is one that fails to progress through a normal, orderly, and timely sequence of repair, or in which the repair process fails to restore anatomic and functional integrity after three months.1 In 2014, wound care for Medicare beneficiaries cost an estimated \$28 billion to \$96.8 billion.² A 2012 German study found a 1% to 2% prevalence of chronic nonhealing wounds in the general population.³ Chronic wounds, typically diabetic ulcers, preceded 85% of amputations.4 Some chronic wounds can take decades to heal, thus contributing to secondary conditions such as depression, and can ultimately lead to isolation and family distress. The five-year mortality rate after developing a diabetic ulcer is approximately 40%5; therefore, proper diagnosis and treatment of wounds and management of comorbidities are imperative.

See related article at https://www.aafp.org/afp/2019/0901/ p298.html.

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Stages of Wound Healing

Wound healing is a complex sequence of events that begins with injury and ends with successful closure. It typically moves through four stages: hemostasis/coagulation, inflammation, proliferation, and maturation/remodeling (*Table 1*).⁶ These phases overlap as cytokines and growth factors guide the healing process. Chronic wounds most often do not progress past the inflammatory phase.

Causes of Chronic Wounds

All wounds have the potential to become chronic wounds. They are classified by etiology into four categories, each with its own typical location, depth, and appearance: arterial, diabetic, pressure, and venous ulcers⁷ (*Table 2*). To appropriately treat a chronic wound, an understanding of the pathophysiology of the wound is critical. Despite differences in etiology, chronic wounds share certain features, including excessive levels of proinflammatory cytokines, persistent infections, formation of drug-resistant microbial biofilms, and senescent cells that do not respond to reparative stimuli.⁸

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	Comments
The ankle-brachial index may not be accurate in patients with diabetic foot ulcers; the toe-brachial index should be used instead to screen for peripheral arterial disease. ¹⁴	с	Disease-oriented study
Compression therapy has been proven beneficial for venous ulcer treatment and is the standard of care. ²⁹	В	Cochrane review of lower-quality RCTs
Offloading with a total contact cast is the optimal treatment for diabetic foot ulcers. ^{32,33}	А	Cochrane review of RCTs and a single RCT comparing treatment outcomes
A repositioning schedule should be established to treat and prevent pressure ulcers in hospitalized patients, and patients should not be positioned on bony prominences. ^{36,37}	с	Consensus guidelines
RCT = randomized controlled trial. A = consistent, good-quality patient-oriented evidence; B = inconsistent oriented evidence, usual practice, expert opinion, or case series. For info		

org/afpsort.

Assessment and Classification

Assessment of wounds should begin with a thorough physical examination. A more focused examination of the wound itself can then help guide treatment. The wound location, size, and depth; presence of drainage; and tissue type should be documented. Based on the location and appearance, most chronic wounds can be categorized by etiology, which allows for adequate workup and treatment recommendations.

Venous ulcers are the most common type of chronic wound. They are typically shallow and located on the medial supramalleolar aspect of the lower extremity (*Figure 1*).

TABLE 1

Stages of Wound Healing			
Day	Stage	Pathophysiology	Outcome
0 to 3	Hemostasis/ coagulation	Clotting, vasoconstriction	Bleeding stops
1 to 25	Inflammation	Cytokines and growth factors released; vasodilation; phagocy- tosis (i.e., white blood cells engulf bacteria and debris); neutrophils release reactive oxygen species and proteases	Redness, swelling, warmth, and pain
1 to 25	Proliferation	Collagen (type III) synthesis, gran- ulation formation, epithelialization, angiogenesis, contraction	New blood vessel growth, wound closure
20 to 365	Maturation/ remodeling	Scar remodeling (type III to I collagen)	Scar strength increases to approximately 80% of original tissue
Information t	rom reference 6.		

There may be classic signs of venous hypertension, including edema, hemosiderin staining, and lipodermatosclerosis. Workup should include assessment of arterial status with the ankle-brachial index (ABI) and palpation of pulses to rule out mixed arterial and venous disease and to ensure adequate perfusion before compression.9 If necessary, further workup with venous duplex ultrasonography with reflux and/or arterial duplex ultrasonography will help with the diagnosis.

Arterial ulcers are typically located on the distal extremities and may be deep, with tendon or bone exposed (*Figure 2*). As with

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TABLE 2

venous ulcers, the initial workup should include ABI measurement and palpation of pulses. An ABI less than 0.8 may be a sign of arterial disease, and an ABI greater than 1.2 is consistent with noncompressible vessels. Both require further vascular assessment, which may include arterial The term pressure ulcer is preferred over bedsore, decubitus ulcer, or pressure sore. A pressure ulcer is a localized injury to the skin or underlying tissue—usually over a bony prominence such as the sacrum, coccyx, hip, or heel—that results from pressure in combination with

Doppler/duplex ultrasonography, segmental limb pressures, pulse volume recording, skin perfusion pressure, or transcutaneous oximetry.¹⁰ Referral to a specialist should be considered if vascular test results suggest poor perfusion.

Diabetic ulcers are the most common cause of lower extremity amputation. Early intervention and management are essential given the high mortality rate after amputation.⁵ Diabetic foot ulcers are caused by a combination of underlying neuropathy, peripheral arterial disease, and structural deformities that cause increased pressure on affected areas of the foot.¹¹ Diabetes mellitus affects sensory, motor, and autonomic nerve function. The combined effects result in structural deformities of the foot; dry, poorly hydrated integument; and an inability to detect pain and repetitive injury. Diabetes also causes higher rates of atherosclerotic disease.¹² Diabetic ulcers are typically located on the toes or the plantar aspect of the metatarsal heads (Figure 3). They may have the characteristic crater-like appearance, be covered in eschar or necrotic tissue at the wound bed, and have exposed deep structures including tendon and bone. These ulcers can be shallow or deep and are usually surrounded by a thick ring of callus. Workup should include palpation of pedal pulses, ABI measurement,12 and assessment for neuropathy with Semmes-Weinstein monofilament.13 Imaging is often required to rule out deeper infection such as osteomyelitis. Patients with diabetes often have calcified, noncompressible arteries that result in an abnormally high ABI. A more reliable test in these patients is the toe-brachial index because the toe arteries rarely calcify.14

Assessment of Chronic Wounds		
Wound type	Appearance	Assessment
Arterial ulcer	Deep; eschar; punched- out, well-demarcated borders; deep struc- tures may be exposed	Palpate pulses Assess macrocirculation: Angiography Ankle-brachial index or toe-brachial index Lower extremity arterial duplex ultrasonography Pulse volume recording Segmental limb pressure Assess microcirculation: Skin perfusion pressure Transcutaneous oximetry
Diabetic ulcer	Located on plantar aspect of foot, exten- sive callus formation, superficial to deep	Ankle-brachial index or toe-brachial index Bone scan if concern for osteomyelitis Lower extremity arterial duplex ultrasonography Magnetic resonance imaging if con- cern for osteomyelitis Radiography Transcutaneous oximetry Wound culture
Pressure ulcer	Located over bony prominences, superfi- cial to deep	Computed tomography if indicated Magnetic resonance imaging if con- cern for osteomyelitis Nutritional support Radiography Wound culture
Venous ulcer	Shallow, no eschar; located over medial aspect of lower extrem- ity (gaiter region)	Palpate pulses Ankle-brachial index Doppler ultrasonography Lower extremity arterial duplex ultrasonography Lower extremity venous duplex ultra- sonography with reflux Transcutaneous oximetry

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shear force (*Figure 4*). Pressure ulcers can also be caused by devices such as nasal cannulas, nasogastric tubes, and casts or splints. Risk-assessment tools such as the Braden scale¹⁵ can help minimize pressure ulcers by identifying high-risk patients. These ulcers are managed according to guidelines from the National Pressure Ulcer Advisory Panel, which classifies them into six stages based on the extent of tissue damage. Assessment may include a workup for infection,



Venous ulcer.



Arterial ulcer.

imaging to rule out deeper infection, and nutritional assessment.

When assessing a chronic wound for infection, physicians should be aware that chronic infected wounds have different signs and symptoms than acute infected wounds. Typical signs of infection such as erythema, edema, pain, and fever are not always present. Two mnemonics are used to identify chronic wounds with infectious processes:



Diabetic foot ulcer.





Stage 3 sacral pressure ulcer.

- NERDS (for wounds with biofilm or critical colonization): nonhealing, exudative, red and bleeds easily, debris, and smell. Sensitivity is 73% and specificity is 80.5% when three criteria are present.¹⁶
- STONEES (for infection): size increasing, temperature increased, os (probes to or exposed bone), new areas of breakdown, exudative, erythema/edema, and smell. Sensitivity is 90% and specificity is 69.4% when three criteria are present.16

Biopsy with quantitative processing is the best method of wound culture; a result of more than 100,000 colonyforming units is considered positive. Other options include the Levine and Z techniques. The Levine technique is superior, with several studies showing higher sensitivity and specificity compared with the Z technique.17 The Levine technique consists of debriding superficial necrotic tissue, then applying pressure with a swab while rolling it over 1 cm² for five seconds to obtain fluid from deeper in the wound. In the Z technique, the handle of a swab is rotated between the fingers in a zig-zag fashion across the wound without touching the wound edge.

A chronic wound that does not respond to appropriate care may be an atypical wound. Atypical wounds are located in abnormal locations, have an abnormal appearance, and do not heal after three to six months of standard wound care. Atypical wounds have inflammatory, infectious, vasculopathic, metabolic, genetic, malignant, or external etiologies (e.g., calciphylaxis, pyoderma gangrenosum, vasculitis, autoimmune disease). Physicians should perform a biopsy for further evaluation in patients with suspected atypical wounds.¹⁸ Referral to a wound care specialist, dermatologist, or rheumatologist may also be indicated.

Treatment

Initially, all chronic wounds should be treated according to the TIME principle: tissue debridement (in all cases except arterial ulcers), infection control, moisture balance, and edges of the wound.¹⁹ After these general measures are addressed, the ulcer must be correctly diagnosed and classified so that appropriate care can be provided.

Debridement is the removal of dead cells and is an essential part of wound care. It is the first-line treatment for chronic wounds. A 2005 study showed that healing of chronic wounds is twice as likely with aggressive debridement.²⁰ Another study of 154,664 patients with 312,744 wounds showed that consistent debridement at intervals of one week or less resulted in significantly faster healing and a 70.8% overall healing rate.²¹

In addition to removing dead cells and tissue, debridement of biofilm-multicellular communities held together by a self-produced extracellular matrix that can halt the

healing process²²—is a key factor in wound healing. The National Institutes of Health reports that 80% of wound infections are due to biofilm.²³ Biofilm is invisible to the naked eye, and detection with different techniques is currently being investigated.²⁴ Without destruction of biofilm, wound healing can stall during the inflammatory phase.²⁵

There are several different types of debridement: surgical, autolytic, enzymatic, and biologic. Surgical debridement is used most often, but other methods may be appropriate depending on the type of wound. Infection is usually controlled with topical agents, including dressings with silver, polyhexamethylene biguanide, and cadexomer iodine. Antimicrobial washes may also be beneficial if biofilm is suspected. If cellulitis or signs of systemic infection are present, oral antibiotics may also be indicated.

Moisture balance is an essential part of wound care. Chronic wounds should never be exposed to air to "dry out," as is often recommended. Moist wounds heal more quickly and have less risk of infection.²⁶ If a wound appears dry, moisture needs to be added; this is accomplished by choosing an appropriate dressing (Table 3).6 Conversely, if a

Wound Dressir	ngs
Wound appearance	Type of dressing
Draining	Calcium alginate Collagen Composite Foam Hydrocolloid (for mild to moderate drainage)
Infected/inflamed	Cadexomer iodine Polyhexamethylene biguanide Silver impregnated
Necrotic	Collagenase (enzymatic debridement) Honey impregnated (autolytic debridement) Hydrocolloid (autolytic debridement) Maggots (biologic debridement)
Nondraining/dry	Collagen gel Composite Hydrocolloid Hydrogel Transparent film

TABLE 4

Treatment of Venous Ulcers

Treatment	Comments
Compression ²⁹	After vascular evaluation, compress 30 to 40 mm Hg as tolerated (contraindicated if ankle-brachial index < 0.6)
	Stockings and wraps:
	Long stretch (> 140% extensibility)
	Short stretch (\leq 60% extensibility)
	Zinc oxide compression bandage (Unna Boot)
Elevation	Elevation above level of the heart at rest
Exercise	Walking activates calf muscle pump
Simvastatin (Zocor) ³⁰	Vasoactive and anti-inflammatory properties in addition to lipid-lowering properties Clinically significant improvement in healing time and healing rates
Wound care	TIME principle: tissue debridement, infection con- trol, moisture balance, and edges of the wound
Note: See recent	review of venous ulcer treatments at https://www.aafp.org

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Information from references 29 and 30.

TABLE 5

Treatment of Arterial Ulcers

Treatment	Comments
Exercise	Planned graduated walking program
Intervention	Angiography, angioplasty, or stents Vascular bypass surgery
Wound care	TIME principle: tissue debridement, infection control, moisture balance, and edges of the wound Apply emollients to keep skin pliable Vascular evaluation Healable (adequate perfusion): TIME Maintain moisture balance Nonhealable (ischemia): Control infection Limit debridement
Notes Comment	Maintain moisture balance

wound is draining, the drainage needs to be controlled and kept off of the periwound. The proper dressing should hold the moisture on the wound bed to prevent desiccation.

Wound edges must be free from undermining. If edges are rolled, they should be excised. This allows for epithelialization, which is the clearest sign the wound is healing.²⁷

TREATMENT BY WOUND ETIOLOGY

Venous Ulcers. Venous hypertension due to incompetent veins or venous obstruction distends the superficial veins, causing wall damage, exudation of fluid into the interstitial space, and edema of venous insufficiency. Treatment consists of exercise, which lowers venous pressures²⁸; elevation of lower extremities; and adequate compression—usually 30 to 40 mm Hg—to improve venous return²⁹ after vascular status has been proven adequate (*Table 4*).^{29,30} Patients may benefit from statin therapy for its vasoactive and anti-inflammatory effects.³⁰ Early endovenous ablation may also be beneficial.³¹

Arterial Ulcers. The first step in the management of arterial ulcers is treating the underlying cause, which may include vascular bypass, stents, or dilation by a vascular surgeon (*Table 5*). The goals of wound care before adequate perfusion is obtained are to prevent infection and minimize debridement. After vascular intervention, the TIME principle should be used.

Diabetic Ulcers. Treatment of diabetic ulcers begins with optimal control of blood glucose levels. Most patients with diabetic foot ulcers also have underlying peripheral arterial disease, which requires evaluation. The thick callus that typically surrounds diabetic foot ulcers requires surgical debridement. The preferred treatment approach for diabetic foot ulcers is offloading the foot to remove pressure from the affected area^{32,33} (*Table 6*³²⁻³⁴). This can be accomplished with certain shoes or other devices, but the recommended method is a total contact cast.^{32,33} Some diabetic foot ulcers will benefit from hyperbaric oxygen therapy.³⁵

Pressure Ulcers. Localized treatment for pressure ulcers follows the same TIME principle used for all chronic wounds, but has a greater emphasis on pressure redistribution, offloading, and microclimate control^{6,36} (*Table 7*⁶). A common mistake is the recommendation

BEST PRACTICES IN WOUND CARE

Recommendations from the Choosing Wisely Campaign

Recommendation	Sponsoring organization
Do not culture or treat clinically uninfected lower extremity wounds with systemic antibiotics.	American Podiatric Medical Association
Do not use whirlpools for wound management.	American Physical Therapy Association

Source: For more information on the Choosing Wisely Campaign, see https://www.choosingwisely.org. For supporting citations and to search Choosing Wisely recommendations relevant to primary care, see https://www.aafp.org/afp/recommendations/search.htm.

TABLE 6

Treatment of Diabetic Ulcers

Treatment	Comments
Compression	Evaluate for peripheral arterial disease Compress 30 to 40 mm Hg as toler- ated if edema is present and perfusion is adequate
Exercise	Planned graduated walking program
Hyperbaric oxy- gen therapy ³⁴	Significantly improves healing rate and quality of life
Offloading ^{32,33}	 Nonremovable offloading: Plaster/fiberglass total contact cast Roll-on total contact cast (similar to fiberglass) Total contact cast with removable boot Removable offloading: Aircast pneumatic walker CAM walker Charcot restraint orthotic walker Half-wedge shoe Heel relief shoe
Wound care	TIME principle: tissue debridement, infection control, moisture balance, and edges of the wound
CAM = controlled ar Information from rea	

TABLE 7

Management of Pressure Ulcers

Management	Comments
Appropriate movement of patient	Do not drag patient
Microclimate	Control moisture Keep skin clean and dry Use barrier creams Wash with pH-balanced skin cleanser and water
Nutritional support ⁶	Ensure adequate hydration Increase protein intake to 1.5 g per kg body weight Supplements: Vitamin A Vitamin C Zinc
Offloading	Change positions every one to two hours to limit pressure on affected area Small shifts in weight every 15 minutes
Pressure redistribution	Air- or fluid-filled mattress Air- or gel-filled seat cushions No donut-style cushions
Risk assessment	Braden scale
Wound care	TIME principle: tissue debridement, infection control, moisture balance, and edges of the wound based on wound stage

of donut-style cushions for offloading. These should not be used because they impede blood flow to the area and can actually worsen existing ulcers or increase the risk of developing a new ulcer.³⁷

Data Sources: An initial PubMed search was performed using the key terms chronic wounds, diabetic foot ulcers, venous ulcers, arterial ulcers, and pressure ulcers. The search included clinical trials, systematic reviews, randomized controlled trials, and meta-analyses published since 1990. Several other searches were done using the Cochrane database, the Institute for Clinical Systems Improvement, the National Guideline Clearinghouse, and the Agency for Healthcare Research and Quality clinical guidelines and evidence reports. The Essential Evidence summary provided by *AFP* was also used, as were several landmark articles in wound care and guidelines from the major societies involved with wound care. Search date: May 2018.

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References

- 1. Mustoe TA, O'Shaughnessy K, Kloeters O. Chronic wound pathogenesis and current treatment strategies: a unifying hypothesis. *Plast Reconstr Surg.* 2006;117(7 suppl):35S-41S.
- Nussbaum SR, Carter MJ, Fife CE, et al. An economic evaluation of the impact, cost, and Medicare policy implications of chronic nonhealing wounds. Value Health. 2018;21(1):27-32.
- Heyer K, Herberger K, Protz K, et al. Epidemiology of chronic wounds in Germany: analysis of statutory health insurance data. *Wound Repair Regen*. 2016;24(2):434-442.
- Järbrink K, Ni G, Sönnergren H, et al. The humanistic and economic burden of chronic wounds: a protocol for a systematic review. Syst Rev. 2017;6(1):15.
- 5. Jupiter DC, Thorud JC, Buckley CJ, et al. The impact of foot ulceration and amputation on mortality in diabetic patients. I: from ulceration to death, a systematic review. *Int Wound J.* 2016;13(5):892-903.
- Baranoski S, Ayello EA. Wound Care Essentials. 3rd ed. Wolters Kluwer; 2015.
- 7. Werdin F, Tennenhaus M, Schaller HE, et al. Evidence-based management strategies for treatment of chronic wounds. *Eplasty*. 2009;9:e19.
- 8. Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. *Adv Wound Care (New Rochelle).* 2015;4(9):560-582.
- 9. Mosti G, labichella ML, Partsch H. Compression therapy in mixed ulcers increases venous output and arterial perfusion. *J Vasc Surg.* 2012;55(1): 122-128.
- Holloway GA Jr. Arterial ulcers: assessment and diagnosis. Ostomy Wound Manage. 1996;42(3):46-48, 50-51.
- 11. Chen NX, Moe SM. Arterial calcification in diabetes. *Curr Diab Rep.* 2003;3(1):28-32.
- 12. Megallaa MH, Ismail AA, Zeitoun MH, et al. Association of diabetic foot ulcers with chronic vascular diabetic complications in patients with type 2 diabetes. *Diabetes Metab Syndr.* 2019;13(2):1287-1292.
- 13. Baraz S, Zarea K, Shahbazian HB, et al. Comparison of the accuracy of monofilament testing at various points of feet in peripheral diabetic neuropathy screening. *J Diabetes Metab Disord*. 2014;13(1):19.
- 14. Park SC, Choi CY, Ha YI, et al. Utility of toe-brachial index for diagnosis of peripheral artery disease. *Arch Plast Surg.* 2012;39(3):227-231.
- 15. Braden BJ, Maklebust J. Preventing pressure ulcers with the Braden scale: an update on this easy-to-use tool that assesses a patient's risk

[published correction appears in *Am J Nurs*. 2005;105(8):16]. *Am J Nurs*. 2005;105(6):70-72.

- 16. Woo KY, Sibbald RG. A cross-sectional validation study of using NERDS and STONEES to assess bacterial burden. *Ostomy Wound Manage*. 2009;55(8):40-48.
- 17. Copeland-Halperin LR, Kaminsky AJ, Bluefeld N, et al. Sample procurement for cultures of infected wounds: a systematic review. *J Wound Care.* 2016;25(4):S4-S6, S8-S10.
- Tang JC, Vivas A, Rey A, et al. Atypical ulcers: wound biopsy results from a university wound pathology service. *Ostomy Wound Manage*. 2012; 58(6):20-22, 24, 26-29.
- Leaper DJ, Schultz G, Carville K, et al. Extending the TIME concept: what have we learned in the past 10 years? *Int Wound J.* 2012;9(suppl 2):1-19.
- 20. Williams D, Enoch S, Miller D, et al. Effect of sharp debridement using curette on recalcitrant nonhealing venous leg ulcers: a concurrently controlled, prospective cohort study. *Wound Repair Regen*. 2005;13(2): 131-137.
- Wilcox JR, Carter MJ, Covington S. Frequency of debridements and time to heal: a retrospective cohort study of 312744 wounds [published correction appears in JAMA Dermatol. 2013;149(12):1441]. JAMA Dermatol. 2013;149(9):1050-1058.
- 22. López D, Vlamakis H, Kolter R. Biofilms. *Cold Spring Harb Perspect Biol.* 2010;2(7):a000398.
- 23. Davies D. Understanding biofilm resistance to antibacterial agents. *Nat Rev Drug Discov.* 2003;2(2):114-122.
- 24. James GA, Swogger E, Wolcott R, et al. Biofilms in chronic wounds. *Wound Repair Regen*. 2008;16(1):37-44.
- 25. Lebrun E, Kirsner RS. Frequent debridement for healing of chronic wounds. *JAMA Dermatol.* 2013;149(9):1059.
- 26. Field FK, Kerstein MD. Overview of wound healing in a moist environment. *Am J Surg.* 1994;167(1A):2S-6S.
- 27. Pastar I, Stojadinovic O, Yin NC, et al. Epithelialization in wound healing: a comprehensive review. *Adv Wound Care (New Rochelle)*. 2014;3(7): 445-464.
- 28. Meissner MH, Moneta G, Burnand K, et al. The hemodynamics and diagnosis of venous disease. *J Vasc Surg.* 2007;46(6 suppl):4S-24S.
- 29. O'Meara S, Cullum N, Nelson EA, et al. Compression for venous leg ulcers. *Cochrane Database Syst Rev.* 2012;(11):CD000265.
- Evangelista MT, Casintahan MF, Villafuerte LL. Simvastatin as a novel therapeutic agent for venous ulcers: a randomized, double-blind, placebo-controlled trial. *Br J Dermatol.* 2014;170(5):1151-1157.
- Gohel MS, Heatley F, Liu X, et al.; EVRA Trial Investigators. A randomized trial of early endovenous ablation in venous ulceration. N Engl J Med. 2018;378(22):2105-2114.
- 32. Lewis J, Lipp A. Pressure-relieving interventions for treating diabetic foot ulcers. *Cochrane Database Syst Rev.* 2013;(1):CD002302.
- 33. Lavery LA, Higgins KR, La Fontaine J, et al. Randomised clinical trial to compare total contact casts, healing sandals and a shear-reducing removable boot to heal diabetic foot ulcers. *Int Wound J.* 2015;12(6): 710-715.
- 34. Huang ET, Mansouri J, Murad MH, et al.; UHMS CPG Oversight Committee. A clinical practice guideline for the use of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers. Undersea Hyperb Med. 2015;42(3):205-247.
- 35. Bishop AJ, Mudge E. Diabetic foot ulcers treated with hyperbaric oxygen therapy: a review of the literature. *Int Wound J.* 2014;11(1):28-34.
- Gould L, Stuntz M, Giovannelli M, et al. Wound Healing Society 2015 update on guidelines for pressure ulcers. *Wound Repair Regen*. 2016; 24(1):145-162.
- 37. Haesler E; National Pressure Ulcer Advisory Panel; European Pressure Ulcer Advisory Panel; Pan Pacific Pressure Injury Alliance. *Prevention and Treatment of Pressure Ulcers: Clinical Practice Guideline.* 2nd ed. Cambridge Media; 2014.