Dressings, Topical Therapy, and Negative Pressure Wound Therapy

Leland Jaffe, DPM, CWSP[a,*], Stephanie C. Wu, DPM, MSc[b]

KEYWORDS

• Wounds • Dressings • Topical therapy • Negative pressure wound therapy

KEY POINTS

- Proper assessment and management of the wound-bed environment through the use of appropriate dressings can facilitate wound healing.
- The use of negative pressure wound therapy (NPWT) can accelerate wound healing through the use of subatmospheric pressure. Multiple product designs exist to allow for application of NPWT in various clinical scenarios.
- Failure of the wound to progress through the stages of wound healing should prompt the clinician to consider an alternative treatment plan including the use of advanced topical wound therapies.

INTRODUCTION

Wound management has become a significant medical necessity within the health care system because of the epidemic of chronic diseases. Chronic wounds present a significant psychological, physical, and financial burden for patients. Chronic wounds are defined as those that do not progress through the stages of healing in an organized fashion to create structural integrity of the skin.[1] It has been estimated that about 1% to 2% of the general population will develop a chronic wound during their lifetime,[2] including 6.5 million patients in the United States.[3] The economic implications of this epidemic are also growing rapidly because of the aging population as well as the increased prevalence of chronic diseases such as diabetes mellitus, heart

Disclosure Statement: No financial disclosures or conflicts of interest to report.
[a] Department of Medicine and Radiology, Dr William M. Scholl College of Podiatric Medicine at Rosalind Franklin University, 3333 Green Bay Road, North Chicago, IL 60064, USA; [b] Department of Podiatric Surgery and Applied Biomechanics, Center for Stem Cell and Regenerative Medicine, Center for Lower Extremity Ambulatory Research (CLEAR), Dr William M. Scholl College of Podiatric Medicine at Rosalind Franklin University of Medicine and Science, 3333 Green Bay Road, North Chicago, IL 60064, USA
* Corresponding author.
E-mail address: leland.jaffe@rosalindfranklin.edu

Clin Podiatr Med Surg 36 (2019) 397–411
https://doi.org/10.1016/j.cpm.2019.02.005
podiatric.theclinics.com

disease, and obesity. In addition it is estimated that in excess of 25 billion dollars are spent annually in the United States for the treatment of chronic wounds,[4] and this number is expected to continue to increase.

Proper dressing selection for a wound focuses on maintaining adequate moisture level, minimizing bacterial bioburden, controlling exudate, and temperature regulation. Observance to these fundamental principles assists with the progression toward granulation tissue formation and eventual epithelialization and closure of the wound (**Box 1**).

An intact epithelium is our body's greatest barrier to the loss of fluids. The wound-bed tissue is at significant risk of desiccation following loss of the stratum corneum, placing the wound at risk of delayed progression through the stages of healing.[5] A moist wound environment has been demonstrated to improve wound healing by assisting with cellular migration and granulation tissue formation, and reducing infection rates.[6] The wound bed can range from accumulating desiccated nonviable tissue to excessive moisture buildup and periwound maceration, both of which will compromise the formation of healthy granular tissue and eventual skin epithelialization. Chronic wound fluid is noted to have abundant matrix metalloproteinases (MMPs) and other proinflammatory cytokines,[7,8] prolonging the inflammatory stage of wound healing. By contrast, too little moisture can prevent cellular activity and keratinocyte migration across the wound surface.[5] Adequate moisture balance is essential to facilitate the normal cellular activity leading to wound closure. The type and quantity of the wound exudate will determine the specific needs of the wounds. Wounds that are dry require a hydrating dressing such as a hydrogel, Manuka honey, or a hydrocolloid dressing. In recent studies comparing the efficacy of several dressings in the healing of diabetic foot ulcers (DFUs), hydrogel dressings along with amniotic membranes were noted as the preferred solutions for healing DFUs.[9,10] Meta-analyses have confirmed that the use of hydrocolloids in comparison with standard gauze dressing results in accelerated wound healing.[11,12] Excessive moisture, by contrast, will require an absorptive dressing including an alginate, hydrofiber, or foam.[13]

The TIME (Tissue, Infection/Inflammation, Moisture, Edge of wound) principle was introduced to wound-care clinicians in 2003 as a tool to assess for proper wound-healing progression. This form of wound assessment allows the clinician to objectively and systematically evaluate the environment of the wound bed. Adherence to the

Box 1
Features of an ideal wound dressing

- Facilitate a moist environment
- Absorb excess exudate
- Prevent desiccation of the wound (donates moistures in dry wounds)
- Protect the periwound tissue
- Maintain a warm environment
- Minimize bacterial bioburden (resistant to microorganisms)
- Minimize or eliminate pain
- Cost-effective
- Eliminate odor
- Eliminate dead space

TIME principles allows for critical continual evaluation of the physiologic needs of the wound bed through the use of topical dressings. Proper wound management involves optimizing the wound bed to facilitate wound closure, which is accomplished via the use of primary and secondary dressings. The primary dressing is applied directly to the wound surface and the secondary dressing is applied to either bolster the primary dressing or provide a therapeutic function. Dressings are organized categorically based on their therapeutic effect on the wound bed and periwound tissue. As wounds progress through the predictable stages of healing (hemostasis, inflammation, proliferation, remodeling), the physiologic needs of the wound may evolve. Clinicians should continue to evaluate for specific considerations regarding wound assessment including the amount of exudate, the depth, the tissue noted in the base of the wound, and the location of the wound.

An effective topical wound dressing is designed to maintain a healthy, physiologic level of moisture, facilitate autolytic debridement through the activity of endogenous enzymes, improve granular tissue formation, and enhance bacterial bioburden management.[14] Therefore, based on the needs of the wound bed, topical dressings can range from moisture-donating, moisture-absorptive, or moisture-retention materials. A moist wound bed may be maintained with the use of occlusive, semiocclusive, absorptive, or hydrating materials. Clinical indications and instructions for clinical use of various types of wound dressings are discussed in **Table 1**.

Topical Antimicrobial Dressings

Given that 60% to 90% of chronic wounds have biofilm,[32] and a biofilm may be reestablished within 3 days following a wound debridement,[32,33] proper wound-bed management and dressing selection is critical to deterring this biofilm reformation. Dressings impregnated with silver, cadexomer iodine, honey, and polyhexamethylene biguanide (PHMB) have all been advocated for the management of wounds containing biofilm[32] (**Table 2**).

TOPICAL WOUND THERAPIES

Wounds should proceed in an unimpeded fashion through the stages of healing. If wounds fail to progress as expected despite an appreciation and adherence to the fundamental principles of wound healing, more advanced topical therapies may be indicated. A meta-analysis published in *Diabetes Care* demonstrated that 24% of DFUs healed at 12 weeks and 31% healed at 20 weeks' duration.[44] In 2003, Sheehan and colleagues[45] determined that the percent change in wound area of DFU at 4 weeks is a strong predictor of complete healing at 12 weeks. In this study it was determined that if DFU did not reduce by 53% at 4 weeks' duration, the healing rate at 12 weeks was 9%. These studies have since been replicated and reproduced, and demonstrate that a failure to achieve an acceptable initial progression of wound closure should prompt the provider to consider advanced topical wound therapies. Topical wound therapies are available as topical growth factors, placental/umbilical cord tissue allograft, acellular dermal matrices, and cell-based therapies. The clinical indications and instructions for clinical use of these therapies are discussed in **Table 3**.

NEGATIVE PRESSURE WOUND THERAPY

Negative pressure wound therapy (NPWT) is a noninvasive wound-management system that uses controlled, localized, subatmospheric pressure to promote healing in chronic and acute wounds. NPWT has been found to assist with promotion of

Table 1
Wound-care dressings

Description of Product	Indications	Contraindications	Instructions for Clinical Use
Contact layer dressings • Petroleum, silicone, polyethylene, or lipidocolloid based • Nonadherent • Semiocclusive • Porous to facilitate exudate removal • Conforms to the shape of the wound • Prevents desiccation by adding moisture to the wound bed[15]	• Partial or full-thickness wounds • Placement on incisions • Overlying split-thickness skin grafts • Overlying bioengineered alternative tissues (BATs) • Placed on donor sites • Atraumatic, painless removal of dressing	• None	• Apply directly to wound bed • Secondary dressing or topical medication placed on contact layer • Indicated to be changed weekly
Hydrogels • Composed of hydrophilic crosslinked polymers that are 80%–90% water[16] or glycerin based • Nonadherent • Facilitate autolytic debridement • Absorb minute amounts of exudate by swelling • Primarily used to donate moisture to the wound surface	• Partial or full-thickness wounds • Dry wounds with minimal exudate	• Third-degree burns • Wound with moderate to severe exudate	• Apply to wound base and use appropriate secondary dressing • Daily applications • Not to be used as a wound filler

Hydrocolloids • Contain an inner self-adhesive layer and a gel-forming agent such as gelatin or sodium carboxymethylcellulose • Inner layer of the hydrocolloid is laminated on a foam or film, typically composed of polyurethane • Absorb exudate and swell to form a gel on the wound bed • Promote autolytic debridement • Create barrier to protect from pathogens	• Partial or full-thickness wounds • Minimal to moderately exudative wounds • Granular or necrotic wound beds	• Third-degree burns • Infected wounds • Eschar	• Apply directly to wound surface • Hydrocolloid placed 2.5–5 cm onto periwound tissue • Dressing changed every 3–5 d pending amount of exudate
Foam dressings • Absorptive dressing • Open-cell polyurethane material • Hydrophilic properties allow absorption of exudate • Atraumatic/painless during dressing changes	• Partial or full-thickness wounds • Moderate to severely exudative wounds • Granular or nongranular wound beds[17] • Reduces shear in pressure skin injuries[18] • Protect wounds with friable periwound tissue	• Third-degree burns • Ischemic arterial wounds with eschar wound base • Wounds with dry/necrotic wound beds • Tunneling wounds	• Used as a primary or secondary wound dressing • Frequency of dressing change will depend of the quantity of exudate, ranging from daily to once weekly
Alginate dressings • Derived from fibers of brown seaweed • Highly absorbent • Convert to a viscous, hydrophilic gel when calcium and sodium salts within the dressing interact with exudate from the wound, providing a moist wound environment • Nonadherent because of gel-forming nature • Hemostatic properties[19] • Provide autolytic debridement	• Partial to full-thickness wounds • Moderate to heavily exudative wounds • Placed within sinus tracks and tunneling wounds	• Dry wounds with minimal exudate • Third-degree burns • Wounds with necrotic tissue present, as no moisture is donated to the wound surface	• Applied daily to weekly depending on the quantity of exudate • Apply appropriate secondary dressing overlying alginate • May be used as packing into tunneling wound

(*continued on next page*)

Table 1
(*continued*)

Description of Product	Indications	Contraindications	Instructions for Clinical Use
Hydrofiber dressings • Derived from carboxymethylcellulose • Absorption of copious exudate • Form hydrophilic gelatinous substances that adapt to the wound contour[20] • Facilitate moist wound-healing environment • Nonadherent • Facilitate autolytic wound debridement, granulation tissue formation, and wound epithelialization[21]	• Partial to full-thickness wounds • Moderate to heavy exudative wounds	• Dry wounds with minimal exudate	• Change dressing every 24–48 h pending amount of exudate • Apply appropriate secondary dressing to secure hydrofiber into place
Collagen dressings • Bovine, porcine, and ovine sources • Available in sheet, gel, or powder forms • Bioabsorbable • Chemoattractant for cells involved in wound healing • Inactivate some MMPs, elastase,[22,23] decreasing the level of inflammatory mediators[24,25] • Scaffold to increase collagen production • Bacteriostatic properties in vitro[26] • Silver-impregnated versions available[27] • Increase rate of epithelialization,[28] and accelerate wound closure in patients with recalcitrant wounds[29–31]	• Full-thickness wounds • Wounds with minimal to moderate exudate • Uninfected wounds	• Sensitivity to the tissue of origin (bovine, porcine, ovine)	• Apply to wound bed and secure with secondary dressing • Frequency of dressing change varies based on product and quantity of exudate

Table 2
Antimicrobial topical wound-care therapies

Description of Product	Indications	Contraindications	Instructions for Clinical Use
0.9% Cadexomer iodine • Contains 0.9% iodine • Functions as an antimicrobial agent through its disruption of the bacterial lipid membrane and inhibition of protein synthesis[37,38] • As exudate is absorbed, iodine is slowly released from the dressing, exerting its antiseptic effect[39] • Nontoxic to fibroblasts	• High capacity for absorbing exudate; each gram absorbs 3 mL of exudate • Partial or full-thickness wounds • Critically colonized to infected wounds • Methicillin-resistant *Staphylococcus aureus* (MRSA)	• Allergy to iodine • Hashimoto thyroiditis • Graves disease	• Frequency of application every 24–72 h • Color change from brown to yellow/gray indicates the need for dressing change
Manuka honey • As honey interacts with wound exudate, hydrogen peroxide is produced, creating a broad-spectrum antimicrobial effect[42] • Also functions by eliminating water from bacterial cells, causing lysis of these cells[43] • Promotes autolytic debridement • Anti-inflammatory	• Diabetic, venous, arterial, and pressure ulcers • First- and second-degree burns • Provides a moist wound-healing environment • Light to moderate exudative wounds	• Bee stings	• Available as a hydrogel, hydrocolloid, or alginate • Dressing change protocol varies based on dressing

(*continued on next page*)

Table 2
(*continued*)

Description of Product	Indications	Contraindications	Instructions for Clinical Use
Silver dressings and topicals • Antiseptic, anti-inflammatory, with broad-spectrum antimicrobial activity[34] • Silver cations exert antimicrobial effect by blocking cellular respiration and disturbing bacterial cell membranes • Silver can also denature bacteria DNA and RNA, preventing cell replication[35] • Activity against MRSA and vancomycin-resistant *Enterococcus* (VRE)	• Reduces bacterial bioburden	• Allergy to silver • Use with caution in the management of diabetic wounds, owing to a cytotoxic effect to dermal fibroblasts[36]	• Method of silver ion delivery varies by dressing type • Dressing change protocol varies based on dressing
PHMB Products • PHMB has a positively charged structure that binds to the negative charge of the bacterial cell membrane, disrupting the integrity of the bacteria[40] • Efficacy on both planktonic and sessile (biofilm) bacterial colonies[41] • Antiseptic • Noncytotoxic • Not irritating to viable skin • Activity against MRSA, VRE, fungi	• Reduces bacterial bioburden	• None	• Dressing change protocol varies based on dressing

Table 3
Advanced topical wound-care therapies

Category of Products	Description of Product	Clinical Indications	Instructions for Clinical Use
Topical growth factor therapy	• Platelet-derived growth factor (PDGF) • PDGF recruits and stimulates fibroblast proliferation, promoting granulation tissue formation[46]	• Lower extremity neuropathic diabetic ulcerations • Indicated for wounds that extend to the subcutaneous tissue or deeper • No evidence to support use on joints, tendons, ligaments, or bone	• Applied once daily to wound bed with moistened gauze dressing covering the area • Contraindicated in patients with neoplasm at the side of application • Contraindicated in patients with allergy to parabens
Acellular extracellular matrices	• Nonliving tissue • Derived from allogenic, xenographic, or synthetic sources • Accelerate healing with minimized scar tissue formation • Promote host cell attachment to topical therapy and migration of keratinocytes, fibroblasts • Controlled degradation of product (collagen products degrade very quickly in comparison) • Viable cells removed to minimize or prevent inflammatory/ immunogenic response	• Partial and full-thickness wounds of varying causes • Burn wounds • Traumatic wounds • Surgical wounds	• Applied directly to wound bed using sutures/staples • Acellular matrix hydrated with normal sterile saline • Nonadherent secondary dressing applied to secure acellular matrix into place

(*continued on next page*)

Table 3
(*continued*)

Category of Products	Description of Product	Clinical Indications	Instructions for Clinical Use
Placental tissue allografts	• Derived from human amnion/chorion placental membrane or umbilical cord • Deliver exogenous growth factors to the wound bed • Antimicrobial and anti-inflammatory • Collagen rich	• Acute and chronic wounds • Nonhealing wounds of varying causes	• Applied directly to wound bed • Nonadherent contact layer placed on overlying tissue as secondary dressing
Cell-based therapies	• Deliver exogenous growth factors to the wound bed • Viable cells are cultured on different bioabsorbable matrices • Cell-based therapy can be epidermal, dermal, or bilayer therapies • Cells removed from cell-based therapies include hair follicles, sweat glands, blood vessels, and immune cells	• Partial and full-thickness wounds • Chronic nonhealing wounds of differing causes • Burn wounds	• Cell-based therapy applied directly to wound bed and secured with Steri-Strips and nonadherent dressing

granulation tissue, removal of excess wound exudate, improvement in tissue oxygenation, and reduction of bacterial bioburden—all key factors that assist with wound healing.

The direct and indirect physiologic effects of NPWT have had a dramatic positive impact on wound management. The direct effects of NPWT include the use of a semipermeable dressing (enabling a moist/warm environment) and generation of a pressure gradient, which assists in removing exudate from the wound ultimately to the collection canister. NPWT has been shown through numerous studies to be highly successful in assisting with forming granulation tissue over exposed bone, tendon, or orthopedic hardware.[47,48]

From an indirect standpoint, NPWT decreases bacterial bioburden and MMP activity, increases local arterial blood flow, and induces a microstrain on the tissue.[49,50] This microstrain (or cell stretch) increases cellular and growth factor activity, including fibroblasts, vascular endothelial growth factor, and fibroblast growth factor 2.[49] NPWT dressings are often changed every 48 to 72 hours, reducing cross-contamination of the wound and deterring the regrowth of bacterial biofilms on the wound bed.

Applications and indications for the use of NPWT have been expanding, including tunneling wounds or placement over avascular tissue. The optimal subatmospheric pressure setting to maximize blood flow, evacuate exudate, reduce edema, remove bacteria, and facilitate a moist wound environment has been suggested to be 125 mm Hg of pressure alternating between 5 minutes of pressure and 2 minutes of suction.[51] However, further studies have suggested that lower subatmospheric pressure may be just as effective in achieving the desired physiologic effects of NPWT.[52] The clinician also must determine whether to proceed with intermittent or continuous pressure. Studies have suggested that the intermittent setting has been more effective at stimulating angiogenesis and granulation tissue formation.[53] Increased pain and reduced patient acceptance has limited the integration of the intermittent pressure setting into routine clinical practice.

Multiple types of NPWT devices are currently available on the market and have been divided into 4 categories. The first includes the standard NPWT devices that are used in the acute care setting. The second category includes the smaller and more portable devices designed to be used in the outpatient setting. NPWT devices from categories 1 and 2 are battery powered and require frequent charging. The third group includes disposable devices intended to deliver 7 days of NPWT to wounds without charging. The fourth category of NPWT systems has been considered the specialty group, and includes the systems that contain the instillation component as well as NPWT. NPWT with use of instillation and dwell time (NPWTi-d) has also become available in clinical practice, and has further improved the efficiency of granulation tissue formation and reduced bacterial bioburden.[54] NPWTi-d combines the intermittent instillation of a solution topically to the wound, a dwell period permitting the solution to remain on the wound, followed by negative pressure removing the solution. Different solutions have been used with NPWTi-d including normal saline and antiseptics (PHMB); however, there does not appear to be a difference in outcomes regarding a duration of hospital length of stay, number of operative visits, or the proportion of wounds closed at 30 days' duration.[55] Incisional NPWT has also been included in the fourth category of NPWT systems. Incisional NPWT has been shown to assist with the closure of complex/high-risk lower extremity incisions by reducing seroma/hematoma formation,[56] decreasing tensile forces along the incision,[57] and reducing edema[56] (**Table 4**).

NPWT is a well-tolerated therapy that has become a mainstay in wound care. The clinician, however, should be cognizant of the few contraindications to NPWT

Table 4
Negative pressure wound therapy devices

Descriptions of Products	Benefits	Drawbacks
NPWT devices designed for acute care setting	• Evidence-based results • Support heavy exudative wounds	• Device may be heavy • Charging often required
Portable NPWT devices	• Small in size/lightweight • Designed for use at home	• Not available off-the-shelf • Noise of the device can be bothersome
Disposable NPWT devices	• Light weight • Off-the-shelf availability • Some devices approved for incisional therapy	• Limited pressure levels • Not indicated for moderate to higher exudative wounds
Specialized NPWT • NPWT devices with instillation • Incisional NPWT	• Studies suggest increased proficiency of granulation tissue formation • Reduce wound bioburden • Reduce seroma/hematoma formation	• In-hospital use only (cannot be used in the outpatient setting)

including untreated osteomyelitis or infection, malignancy, exposed vital structures, necrotic tissue within the wound, and nonenteric and unexplored fistulas.

SUMMARY

Following a breach in the skin, wounds should heal in a complex but predictable fashion. When patients fail to progress through these predictable stages of healing, the health care provider must determine the cause of the stalled wound. An appreciation and adherence to the major pillars of wound care including effective offloading strategies, vascular optimization, infection management, and wound-bed preparation are critical to enhanced healing. Adhering to these principles is crucial in expecting successful and timely wound closure. Included with these mainstays of wound care is topical wound and dressing management, which can be defined as manipulating the physiologic environment of the wound bed through the use of dressings, topical therapies, and NPWT to reestablish normal functioning of tissue. There are more than 3000 types of wound-care products on the market today, which can create some confusion with dressing selection. However, appreciation of the needs of the wound along with an understanding of the categories of wound-care products will facilitate this process.

REFERENCES

1. Lazarus GS, Cooper DM, Knighton DR, et al. Definitions and guidelines for assessment of wounds and evaluation of healing. Wound Repair Regen 1994; 2(3):165–70.
2. Gottrup F. A specialized wound-healing center concept: importance of a multidisciplinary department structure and surgical treatment facilities in the treatment of chronic wounds. Am J Surg 2004;187(5A):38S–43S.
3. Crovetti G, Martinelli G, Issi M, et al. Platelet gel for healing cutaneous chronic wounds. Transfus Apher Sci 2004;30(2):145–51.

4. Brem H, Stojadinovic O, Diegelmann RF, et al. Molecular markers in patients with chronic wounds to guide surgical debridement. Mol Med 2007;13(1–2):30–9.
5. Hinman CD, Maibach H. Effect of air exposure and occlusion on experimental human skin wounds. Nature 1963;200:377–8.
6. Hopf HW, Ueno C, Aslam R, et al. Guidelines for the treatment of arterial insufficiency ulcers. Wound Repair Regen 2006;14(6):693–710.
7. Trengove NJ, Stacey MC, MacAuley S, et al. Analysis of the acute and chronic wound environments: the role of proteases and their inhibitors. Wound Repair Regen 1999;7(6):442–52.
8. Dowsett C. Exudate management: a patient-centred approach. J Wound Care 2008;17(6):249–52.
9. Zhang X, Sun D, Jiang G. Comparative efficacy of 9 different dressings in healing diabetic foot ulcer :a bayesian network analysis. J Diabetes 2018. https://doi.org/10.1111/1753-0407.12871.
10. Saco M, Howe N, Nathoo R, et al. Comparing the efficacies of alginate, foam, hydrocolloid, hydrofiber, and hydrogel dressings in the management of diabetic foot ulcers and venous leg ulcers: a systematic review and meta-analysis examining how to dress for success. Dermatol Online J 2016;22(8) [pii: 13030/qt7ph5v17z].
11. Bradley M, Cullum N, Nelson EA, et al. Systematic reviews of wound care management: (2). dressings and topical agents used in the healing of chronic wounds. Health Technol Assess 1999;3(17 Pt 2):1–35.
12. Bouza C, Saz Z, Munoz A, et al. Efficacy of advanced dressings in the treatment of pressure ulcers: a systematic review. J Wound Care 2005;14(5):193–9.
13. Salmeron-Gonzalez E, Garcia-Vilarino E, Ruiz-Cases A, et al. Absorption capacity of wound dressings: a comparative experimental study. Plast Surg Nurs 2018;38(2):73–5.
14. Kahn S. Highlights from the advanced wound healing stream at the LINK congress. Br J Nurs 2017;26(Sup20):S34–6.
15. Ovington LG. Hanging wet-to-dry dressings out to dry. Home Healthc Nurse 2001;19(8):477–83 [quiz: 484].
16. Sood A, Granick MS, Tomaselli NL. Wound dressings and comparative effectiveness data. Adv Wound Care (New Rochelle) 2014;3(8):511–29.
17. Diehm C, Lawall H. Evaluation of tielle hydropolymer dressings in the management of chronic exuding wounds in primary care. Int Wound J 2005;2(1):26–35.
18. Ohura N, Ichioka S, Nakatsuka T, et al. Evaluating dressing materials for the prevention of shear force in the treatment of pressure ulcers. J Wound Care 2005;14(9):401–4.
19. Blair SD, Jarvis P, Salmon M, et al. Clinical trial of calcium alginate haemostatic swabs. Br J Surg 1990;77(5):568–70.
20. Jones S, bowler PG, walker M. Antimicrobial activity of silver-containing dressings is influenced by dressing conformability with a wound surface. Wounds 2005;17(9):263–70.
21. Waring MJ, Parsons D. Physico-chemical characterisation of carboxymethylated spun cellulose fibres. Biomaterials 2001;22(9):903–12.
22. Lobmann R, Zemlin C, Motzkau M, et al. Expression of matrix metalloproteinases and growth factors in diabetic foot wounds treated with a protease absorbent dressing. J Diabetes Complications 2006;20(5):329–35.
23. Wainwright DJ. Use of an acellular allograft dermal matrix (AlloDerm) in the management of full-thickness burns. Burns 1995;21(4):243–8.

24. Ulrich D, Smeets R, Unglaub F, et al. Effect of oxidized regenerated cellulose/collagen matrix on proteases in wound exudate of patients with diabetic foot ulcers. J Wound Ostomy Continence Nurs 2011;38(5):522–8.
25. Smeets R, Ulrich D, Unglaub F, et al. Effect of oxidised regenerated cellulose/collagen matrix on proteases in wound exudate of patients with chronic venous ulceration. Int Wound J 2008;5(2):195–203.
26. Spangler D, Rothenburger S, Nguyen K, et al. In vitro antimicrobial activity of oxidized regenerated cellulose against antibiotic-resistant microorganisms. Surg Infect (Larchmt) 2003;4(3):255–62.
27. Gottrup F, Cullen BM, Karlsmark T, et al. Randomized controlled trial on collagen/oxidized regenerated cellulose/silver treatment. Wound Repair Regen 2013;21(2):216–25.
28. Jeschke MG, Sandmann G, Schubert T, et al. Effect of oxidized regenerated cellulose/collagen matrix on dermal and epidermal healing and growth factors in an acute wound. Wound Repair Regen 2005;13(3):324–31.
29. Liden BA, May BC. Clinical outcomes following the use of ovine forestomach matrix (endoform dermal template) to treat chronic wounds. Adv Skin Wound Care 2013;26(4):164–7.
30. Driver V, French M, Cain J, et al. The use of the native collagen dressing on chronic lower extremity wounds, case studies: presented at the symposium on advanced wound care: Presented at the Symposium on Advanced Wound Care. Tampa, FL, 2007.
31. Shah S, Chakravarthy D. A clinical safety and efficacy evaluation on seriously chronic wounds with a native collagen dressing. Puracol Plus clinical report. Internal report, 2007.
32. Wolcott RD, Fletcher J, Phillips PL, et al. Biofilms made easy. Wounds International 2010;1(3). Available at: http://www.woundsinternational.com/.
33. Wolcott RD, Rhoads DD, Bennett ME, et al. Chronic wounds and the medical biofilm paradigm. J Wound Care 2010;19(2):45–6, 48–50, 52–3.
34. Ovington LG. The truth about silver. Ostomy Wound Manage 2004;50(9A Suppl):1S–10S.
35. Fong J, Wood F. Nanocrystalline silver dressings in wound management: a review. Int J Nanomedicine 2006;1(4):441–9.
36. Zou SB, Yoon WY, Han SK, et al. Cytotoxicity of silver dressings on diabetic fibroblasts. Int Wound J 2013;10(3):306–12.
37. Reynolds J. Martindale: the extra pharmacopoeia. 29th edition. London: The Pharmaceutical Press; 1989.
38. Gordon J. Clinical significance of methicillin-sensitive and methicillin-resistant staphylococcus aureus in UK hospitals and the relevance of povidone-iodine in their control. Postgrad Med J 1993;69(Suppl 3):S106–16.
39. Selvaggi G, Monstrey S, Van Landuyt K, et al. The role of iodine in antisepsis and wound management: a reappraisal. Acta Chir Belg 2003;103(3):241–7.
40. Sorensen OE, Cowland JB, Theilgaard-Monch K, et al. Wound healing and expression of antimicrobial peptides/polypeptides in human keratinocytes, a consequence of common growth factors. J Immunol 2003;170(11):5583–9.
41. Butcher M. PHMB: an effective antimicrobial in wound bioburden management. Br J Nurs 2012;21(12):S16. S18-21.
42. Chirife J, Scarmato G, Herszage L. Scientific basis for use of granulated sugar in treatment of infected wounds. Lancet 1982;1(8271):560–1.
43. Topham J. Sugar for wounds. J Tissue Viability 2000;10(3):86–9.

44. Margolis DJ, Kantor J, Berlin JA. Healing of diabetic neuropathic foot ulcers receiving standard treatment. A meta-analysis. Diabetes Care 1999;22(5):692–5.
45. Sheehan P, Jones P, Caselli A, et al. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. Diabetes Care 2003;26(6):1879–82.
46. Heldin CH, Westermark B. Mechanism of action and in vivo role of platelet-derived growth factor. Physiol Rev 1999;79(4):1283–316.
47. DeFranzo AJ, Argenta LC, Marks MW, et al. The use of vacuum-assisted closure therapy for the treatment of lower-extremity wounds with exposed bone. Plast Reconstr Surg 2001;108(5):1184–91.
48. Lee HJ, Kim JW, Oh CW, et al. Negative pressure wound therapy for soft tissue injuries around the foot and ankle. J Orthop Surg Res 2009;4:14.
49. Huang C, Leavitt T, Bayer LR, et al. Effect of negative pressure wound therapy on wound healing. Curr Probl Surg 2014;51(7):301–31.
50. Gough A, Clapperton M, Rolando N, et al. Randomised placebo-controlled trial of granulocyte-colony stimulating factor in diabetic foot infection. Lancet 1997; 350(9081):855–9.
51. Venturi ML, Attinger CE, Mesbahi AN, et al. Mechanisms and clinical applications of the vacuum-assisted closure (VAC) device: a review. Am J Clin Dermatol 2005; 6(3):185–94.
52. Borgquist O, Gustafsson L, Ingemansson R, et al. Micro- and macromechanical effects on the wound bed of negative pressure wound therapy using gauze and foam. Ann Plast Surg 2010;64(6):789–93.
53. Borgquist O, Ingemansson R, Malmsjo M. The effect of intermittent and variable negative pressure wound therapy on wound edge microvascular blood flow. Ostomy Wound Manage 2010;56(3):60–7.
54. Goss SG, Schwartz JA, Facchin F, et al. Negative pressure wound therapy with instillation (NPWTi) better reduces post-debridement bioburden in chronically infected lower extremity wounds than NPWT alone. J Am Coll Clin Wound Spec 2014;4(4):74–80.
55. Kim PJ, Attinger CE. Reply: comparison of outcomes for normal saline and an antiseptic solution for negative-pressure wound therapy with instillation. Plast Reconstr Surg 2016;137(6):1064e–5e.
56. Pellino G, Sciaudone G, Candilio G, et al. Effects of a new pocket device for negative pressure wound therapy on surgical wounds of patients affected with Crohn's disease: a pilot trial. Surg Innov 2014;21(2):204–12.
57. Wilkes RP, Kilpad DV, Zhao Y, et al. Closed incision management with negative pressure wound therapy (CIM): biomechanics. Surg Innov 2012;19(1):67–75.