Updates in Clinical Dermatology
Series Editors: John Berth-Jones · Chee Leok Goh · Howard I. Maibach

Afsaneh Alavi
Howard I. Maibach *Editors*

Local Wound Care for Dermatologists

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ISSN 2523-8884 ISSN 2523-8892 (electronic)
Updates in Clinical Dermatology
ISBN 978-3-030-28871-6 ISBN 978-3-030-28872-3 (eBook)
https://doi.org/10.1007/978-3-030-28872-3

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To all patients with wounds with the hope to ease their suffering

Afsaneh Alavi
Howard I. Maibach

Preface

With the aging of the population, impending epidemic of chronic diseases such as diabetes, and natural and man-made disasters, there is a huge need for knowledge of wound care. Individuals with chronic wounds may suffer from social isolation, disfiguring bandages, cost, pain, odor, and many disabilities. Clinicians familiar with local wound care significantly improve the quality of life of these patients. In fact, most people classify wounds as dermatological issues since it is skin-related. Dermatologists play a pivotal role in wound healing, both diagnosis and the management. Chronic wounds are also a major financial burden. The cost of wound care in the United States is estimated at $5–$7 billion per year and is increasing at an annual rate of 10%. The chronicity and recurrence make the venous ulcers a big healthcare system cost estimated to be $3 billion per year in the United States. Diabetes is a serious, lifelong condition that is the sixth leading cause of death in North America. Lifetime risk of diabetic foot ulcers in individuals with diabetes is as high as 25%. Foot ulcers precede 85% of lower limb amputations. Evidence showed that 80% of limb amputations in diabetics are preventable.

The interdisciplinary team approach and collaboration are required for quality care for the complex wounds. Unfortunately, the dermatology educational curriculum in all levels contains very little material regarding wound care. Dermatologists dealing with wounds in their routine practice either as a sign of systemic disease or ulceration from dermatological conditions usually educate themselves. Most dermatologists are familiar with wound diagnosis and differential diagnosis of wounds as part of their training, but the wound care management is an unmet need.

Over the past 20 years, our knowledge of wound healing dramatically increased from growth factors to cellular and acellular skin substitutes. There is a need for a great emphasis on quality wound care and teaching medical students, residents, and dermatology colleagues.

This book will be an invaluable resource for clinicians and particularly dermatologist in regards to local wound care. The knowledge of wound care is rapidly expanding, but well-organized basic foundations are required to interpret the new evidence.

The clinicians should have a broad differential diagnoses and think out of the box when it comes to wounds. Wounds can have many unusual and atypical etiologies.

More than 5000 wound products and devices are available in the United States only, but there is no need to know all these products. What clinicians

require to know are the main basic categories of products, their availabilities, and estimated cost to make informed decision. It is empirical to be familiar with the main types of dressings and bandages, not the commercial brand names. It is beneficial to make yourself familiar with the main components of the dressings in order to recognize or prevent contact dermatitis.

In this time of technological advancement, an online book can be handy on any device and provide general information regarding local wound care for you whether you are involved in the research or clinical practice.

Acknowledgments

Thanks are due to all authors and contributors of this book for volunteering their time and sharing their expertise to shed light on this important topic in dermatology and to the staff at Springer for supporting the publication of this book.

Toronto, ON, Canada — Afsaneh Alavi
San Francisco, CA, USA — Howard I. Maibach

Acknowledgments

I would like to thank my family that without them I was not here today. Thanks to my mentors, Professors Gary Sibbald and Robert Kirsner and also to Professor Howard Maibach for his guidance throughout this project.

Afsaneh Alavi

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The Basic Principles in Local Wound Care

1

Afsaneh Alavi and Robert S. Kirsner

Dramatic increases in the number of patients with chronic wounds have the potential to become an overwhelming burden on the healthcare system. Currently, over six million chronic wounds occur annually in the United States, and as a result, chronic wounds have been reported in 2014 as the most expensive of all skin disorders with costs, exceeding $9.7 billion annually in direct costs alone in the United States [1]. In addition to aging, the rising incidence of type 2 diabetes mellitus will also result in an increased number of chronic wounds [2]. One in 4 patients with diabetes develops a foot ulcer during their lifetime. Diabetic foot ulcers are the most preventable and the most costly complication of diabetes, responsible for 25–50% of cost of all diabetic treatments [3, 4].

The diagnosis and treatment of challenging wounds very often falls in the dermatology scope of practice. Unfortunately, wound care education is often neglected in many dermatology academic curriculums [5]. Squarely within the realm of dermatology is the diagnosis of atypical ulcers caused by vasculitis, small vessel thrombosis, and atypical infections. However, there is an unmet need to provide more up-to-date information regarding wound care-specific treatments. Dermatologists can play a key role in the management of difficult to heal chronic wounds. Understanding the pathophysiology of wound healing may additionally help dermatologist manage the variety of skin diseases that may eventuate into ulcerations. Reviewing the cellular mechanism of wound healing also helps development of new therapies and understanding their mechanism of action.

Wound Healing

Wound healing is an integral process to maintain skin integrity. Wound healing in general includes four recognized overlapped phases that characterize the cutaneous repair process: (1) coagulation, (2) inflammatory phase, (3) proliferative and migratory phase (tissue formation), and (4) remodeling phase. Redundant pathways exist to help insure healing process [6, 7]. The cell types primarily involved in wound healing include platelets, neutrophils and macrophages, fibroblasts, endothelial cells, and keratinocytes. More recently, increasing importance is accumulating for the role of lymphocytes, either directly or indirectly [7].

After a wound occurs, a fibrin and platelet plugs trigger the coagulation cascade and

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A. Alavi, H. I. Maibach (eds.), *Local Wound Care for Dermatologists*, Updates in Clinical Dermatology, https://doi.org/10.1007/978-3-030-28872-3_1

hemostasis. Collagen exposure often due to damage to the endothelial cells activates platelet aggregation and degranulation. As a result, growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor-b (TGF-b) are released. Subsequently, these and other growth factors attract macrophages, neutrophils, fibroblasts, endothelial cells, and smooth muscle cells, which are essential for the inflammatory and proliferative phases [7].

The inflammatory phase begins as neutrophils adhere to endothelium quickly after a wound occurs with one of the goals to cleanse the wound of debris and bacteria. Neutrophils utilize elastase and collagenase to facilitate migration into the extracellular space, where they phagocytose bacteria, degrade matrix proteins, and attract additional neutrophils and macrophages [8]. Macrophages are important cells at this stage as they too phagocytose pathogenic organisms, degrade wound debris, and stimulate granulation tissue formation and angiogenesis. PDGF, TGF-B, fibroblast growth factor, interleukin-1, interleukin-6, and tumor necrosis factor are all among the various cytokines released from macrophages [9].

While the inflammatory stage is ongoing, the proliferation phase also begins typically within 24 hours and encompasses fibroplasia, granulation, epithelialization, and angiogenesis. An early fibrin matrix allows keratinocytes migrate from the wound edges in a manner described "leapfrogging" action [8]. Low oxygen tension promotes angiogenesis through a variety of mechanisms including activation of vascular endothelial growth factor (VEGF) [10]. Angiogenesis or formation of new blood vessels is a key activity in wound healing when the wound involves the dermis or other deeper structures and as such has been the target of many new therapies. Fibroblasts, which migrate in between 48 and 72 hours post injury, are important for dermal matrix proliferation, regulated by PDGF, fibroblast growth factor, and other cytokines and growth factors. Fibroblasts produce structural proteins, including collagen, elastin, extracellular matrix proteins, and matrix metalloproteinases (MMPs). Eventually a new basement membrane forms, and further growth and differentiation of epithelial cells establish the stratified epithelium. The process of epithelialization is facilitated in a moist environment, serving as the biologic basis for modern occlusive dressings.

Should epithelization proceed, the final process of wound healing is remodeling which takes weeks to years and requires a balance between apoptosis of existing cells and production of new cells [8]. Even before epithelization occurs, wound contraction begins, often by day 5, due to the phenotypic change of fibroblasts into myofibroblasts [11]. Extracellular matrix (ECM) and immature type III collagen fibers turn into a stronger network of type I collagen in this phase. Collagen reaches 20% of its tensile strength after 3 weeks and 80% strength at 12 months. With natural healing, the maximum scar strength is 80% of wounded skin [12]. Aberrant remodeling may occur as an example of altered healing that may lead to hypertrophic scar and keloid (discussed in Chap. 19 with more details). Clinically, a hypertrophic scar does not extend beyond the original wound boundaries and usually regresses with time (over the course of 1 year). On the other hand, keloids are a collection of disorganized type I collagen and type III collagen and contain more elastin compared to both hypertrophic scars and normal skin [13]. This adherent remodeling is often driven by inflammation and inflammation is affected by patient age. It has been shown that IL 6 and IL 8 are significantly increased in adult healing process compared to fetal healing. IL6, IL1 beta, and TNF-a also decrease in postmenopausal women [14]. At the same time TGF b1 and TGF b2 are seen with increased concentrations in adult healing process, while TGF b3 is decreased compared to fetus and the elderly [14].

The Wound Bed Preparation

The TIME acronym has been used to help categorize key event and potential therapeutic interventions with the aim to improve healing. TIME stands for the key cocepts of The tissue debridement, the presence of Infection and Inflammation, the Moisture balance, and the appearance of the wound Edge.

Tissue Debridement

Removal of nonviable tissue or debridement is a critical section of wound bed preparation to promote keratinocyte migration over the wound bed and facilitate healing. Recently the concept of debridement has been extended to remove less responsive cells within or at the wound edge [15–19]. Different methods of wound debridement include sharp surgical, mechanical, enzymatic, chemical, and biologic. Surgical debridement can be performed with scissors, scalpel, or curette, under topical, local, or general anesthesia, and general is the only technique that addresses genotypically and phenotypically abnormal cells at the wound edge. However, before debridement an assessment of healability is required. Arterial vascular assessment for lower extremity ulcers prior debridement may be indicated. In the presence of severe peripheral arterial disease, sharp surgical debridement should be avoided and also avoid in necrotic heel ulcers which may be close to bone due to risk of nonhealing. Sharp surgical debridement is fast and highly selective but requires an experienced person to assume pain control and ability to obtain hemostasis.

Autolytic debridement is based on providing moisture to allow endogenous enzymes to degrade nonviable tissues. It can be provided by hydrogel or hydrocolloid dressing. It is less painful than sharp debridement but allows for bacterial proliferation in the moist environment that is created and thus should not be used in the setting on an infected wound.

Enzymatic debridement is an alternative option for the painless removal of necrotic tissue. Collagenase is the only commercially available product for enzymatic debridement in North America. Collagenase ointment is derived from the bacterium *Clostridium histolyticum* and can be quite effective for dry wounds with fibrinous slough at the base.

Biologic debridement by medical grade maggots is another method of debridement by using maggots' secretions to dissolve necrotic tissue. Mechanical debridement is a nonselective method using wet to dry dressings, irrigations, and ultrasound [15–19].

Infection

All chronic wounds are colonized with bacteria without impaired wound healing. As the number of bacteria increased or host resistance diminishes (critical colonization), bacteria may impair healing and potentially cause local and systemic infection. Chapter 3 discusses the wound infection. Bacterial resistance may occur in many routinely used antibiotic and antiseptic groups, even the newer agents [20].

The bacterial resistance is a global public health concern that requires attention by wound care clinicians [21].

The clinician needs to be aware of the signs and symptoms of localized, deep, and surrounding tissue infection (Chap. 5 for more details).

Moisture Balance

Moisture balance entails selecting the appropriate dressing to absorb exudate creating an optimal moisture environment (not too dry, not too wet). However, the recent dressings have more active role than passive moisture retentive dressings. Chapter 4 discusses the wound dressings in detail.

Epithelial Edge

Reepithelialization and keratinocyte migration from wound edges require a well-vascularized wound bed, adequate oxygen and nutrients, and control of underlying systemic diseases. There is a rising focus on a variety of devices from negative pressure to cell-based therapies to oxygen therapies in the management of chronic wounds. Chapters 11, 12, 13, 14, and 15 discuss a vast variety of advanced therapies.

Summary

An effective wound healing treatment requires proper local wound care, and targeting the systemic factors of the healing process may

potentially be compromised by disease or infection in a number of ways.

The decisions regarding wound management must be based on the fundamental characteristics of each wound. A regular wound assessment is required to determine wound healing progress.

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2 Skin pH, Epidermal Barrier Function, Cleansers, and Skin Health

Sandy Skotnicki

The skin's pH plays a critical role in dermatologic health. In the last decade, science has shown the acidic nature or "acid mantle" [1] of the stratum corneum can impact SC integrity, antimicrobial defense mechanisms, and epidermal barrier homeostasis [2].

The importance of achieving and maintaining a low skin pH has been underrepresented in discussions of skin health. There is ample scientific evidence to support the necessity of an acidic skin pH for optimal SC function [3].

Physiological pH is a critical factor in epidermal differentiation and desquamation. These processes are partly due to the activity of serine protease enzymes such as kallikreins 5 and 7 which are involved in the disintegration and desquamation of corneodesmosomes. Alkalization of the skin activates the kallikrein 5 enzyme with a resulting T-helper 2 response (Th2 response) leading to inflammation and eczema [4].

In contrast, acidification of the skin of mice who have eczema reduces kallikrein 5 activity and leads to a decreased eczema response [4, 5]. Glycolic acid containing moisturizers with an acidic pH have been shown to reduce the SC pH in elderly, diabetic, and healthy subjects through induction of SC proteinases [6, 7].

The normal range for skin surface pH is 4.1–5.8 and varies slightly at different points on the body [7, 8]. The skin on the face is generally acidic while skinfold sites, like the axillae and groin, have comparatively high pH levels—a characteristic which may affect the local microbiome and could account for elevated rates of infection, colonization, and eczematous reaction in these areas [9]. Stable skin pH, by contrast, supports the local skin microbiome, which gives immunologic properties to the skin and is felt to help regulate the structure and function of the skin without penetrating the SC [10].

Science has demonstrated a link between atypical pH and skin disease. Contemporary hygiene practices, like bathing daily with water, soap, and detergents, may negatively impact the SC pH and are thought to play a role in increased rates of atopic dermatitis. Research suggests modern-day detergents in high-risk patients may also increase ones' vulnerability to food allergies [11, 12].

Environmental pH

pH reflects a logarithmic scale ranging from acidic (0) to alkaline (14) with 7 registered as neutral. It is a measure of the molar concentration of hydrogen ions in a solution. The pH scale is traceable to a set of standard solutions whose pH is established by international agreement [13].

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A. Alavi, H. I. Maibach (eds.), *Local Wound Care for Dermatologists*, Updates in Clinical Dermatology, https://doi.org/10.1007/978-3-030-28872-3_2

Environment pH varies widely from place to place. Atmospheric pollutants can alter the environmental pH which in turn can affect plant growth as plants and vegetation need a normal soil pH of 6–7 to grow. Acid rain from pollutants, as well as fertilizers used in agriculture, can cause acidification of our soil, lakes, and oceans which damage inherent organisms [14].

pH and Water

Pure water has a neutral pH of 7 at room temperature (25 °C). A study examining water from various sources determined their pH to be higher than neutral, for example, water sampled from home water filters had an approximate pH of 7.5 (the same as tap water), swimming pool water measured between 7.2 and 7.5, and seawater registered at pH of 8 [15].

Water pH can be affected by water hardness, a condition characterized by the buildup of minerals in the water supply. Accepted classifications of water hardness are shown in Table 2.1.

Water hardness has been studied in relation to skin irritation. As the mineral content of water goes up, it reduces the acid in water by acting as a buffer, resulting in water with a higher pH. Alkaline water has been thought to be a contributor to skin irritation. Additionally, more surfactants or cleansers are needed to clean the skin and hair in areas with hard water because the high concentration of cations requires a much heavier lather to dissolve. This can lead to a precipitation of the surfactant leaving a film of residue on the skin.

A report from the UK Department for Environment, Food and Rural Affairs reviewed skin irritation and tap water quality [17]. The study concluded that "currently there is insufficient evidence to evaluate the effects of domestic tap water, and its chemical constituents or parameters, on skin irritation in humans. Future studies have been outlined based on potential associations identified from experimental or epidemiological studies, in relation to water hardness, water pH, personal care products, nickel, and chloramination" [17, p1].

Table 2.1 Classification of water hardness mg/L of calcium carbonate

Classification	mg/L of calcium carbonate
Soft	0–60
Moderately hard	61–120
Hard	121–180
Very hard	180+

Data from [16]

It was the recommendation of this review that "future clinical trials focus on prevention early on in life (from birth) and control for the types of wash product used, the hardness of water and its alkalinity" [17, p1]. To facilitate future studies, the review recommends defining the effect of water hardness (the concentration of free calcium and magnesium) and the alkalinity of water and these effects with cleansers on the skin's barrier function, skin surface pH, and skin irritation [17].

Still, several observational studies suggest hard water may be associated with the development of atopic dermatitis (AD). Research conducted in the United Kingdom, Spain, and Japan shows the prevalence of AD is significantly higher in areas with the hardest water quality compared to the lowest. Increased mineral content is felt to interfere with normal epidermal calcium gradients that are necessary for corneocyte development and proper SC barrier formation as well as increasing the skin's pH from acid to alkaline [18, 19].

Skin pH Age and Racial Variations

The SC in newborns is not fully formed and has an elevated pH of approximately 6 which must acidify to reach a normal pH range of (4.1–5.8). During the first year of life, the SC does not function well and is about 30% thinner than that of an adult [20]. In adult skin, the upper layer of the corneum contains between 10 and 20 layers. In premature babies there are often no SC and therefore little barrier function with high levels of TEWL [21]. Once skin acidification occurs in newborn skin, pH remains fairly constant until the fifth decade of life, when, in postmenopausal women and the elderly, skin pH increases [22–29].

Elderly skin has been shown to have a higher activity of alkaline ceramidase which functions at a pH of 9. This reduction in ceramides observed in aged skin [29] and resulting decrease in barrier function can partially be explained by an increasing breakdown of ceramide.

It appears that skin pH also has racial differences. Darker pigmented subjects exhibit a lower pH compared with individuals of lighter skin color; this may contribute to the superior SC barrier function seen in darker skin. Increased barrier function in darker pigmented subjects has been attributed to increased lamellar body density and epidermal lipid content. Serine protease enzymes which break down SC lipids were also reduced in the more acidic SC of the darker pigmented group [30].

Stability of Skin pH

SC acidity is measured by two criteria: its documented pH value and its buffer capacity. The buffer capacity is the ability of the SC to resist acidic or alkaline assaults. This ability can be determined by the titration with bases and acids [22, 31, 32].

The skin has an incredible capacity to self-buffer and while this ability is typically underrecognized, it is equally important as the functioning pH of the skin in maintaining SC barrier function. The buffer capacity is the result of differentiated keratinocytes and is produced by fatty acids, urocanic acid, carbonic acid, lactic acid, amino acids, and likely keratins [33].

Occupational dermatology literature has shown that an alkaline-resistance test, which stresses the SC with alkaline insult, can help determine whether a patient would be prone to irritant contact dermatitis [31]. Buffer capacity of the SC is decreased in elderly skin and babies and this may explain the increased reactivity of these patients to detergents and other irritants [33, 34]. The skin's ability to buffer itself against pH insults is fairly high, but repeated washing with alkaline soap can reduce this capacity by washing away its inherent buffering components [35].

Skin pH and Epidermal Barrier Function

The skin's barrier function plays a crucial role in the body's ability to defend against microbial invasion and allergen penetration. The outer layer of the skin, or SC, is the result of a complex differentiation process of keratinocytes and is the last interface of our body to the outside world. Its makeup is akin to a brick wall of cross-linked lipids and proteins that acts as a highly effective membrane against the onslaught of dehydration stress and pollution. This "bricks and mortar" model of the SC has been proposed by Michaels et al. [36] and Elias [37].

When you consider that the SC is only 15–20 cm thick, its function as a membrane is an incredible result of human evolution. A healthy and functioning SC barrier is dependent on the complicated interaction between pH and filaggrin, lipid-processing enzymes, proteases, and the microbiome.

Filaggrin

Profilaggrin is cleaved by proteases to release filaggrin. Filaggrin then facilitates the flattening of the keratinocytes in the SC. As water content in the SC decreases, filaggrin is proteolyzed into pyrrolidine carboxylic acid and trans-urocanic acid which are components of (the SC's) natural moisturizing factors (NMF) and lead to a decrease of the pH of the SC or its acidification. NMF result in corneocyte hydration and cohesion and a healthy acid mantle [38]. When fewer filaggrin metabolites are made, the skin pH increases which leads to the activation of a variety of serine proteases and a breakdown of the skin's barrier [39].

Staphylococcus aureus microbial colonization and invasion have been shown to be affected by pH. An in vitro study demonstrated *S. aureus* growth rates were affected by the acidic filaggrin breakdown products urocanic acid and pyrrolidone carboxylic acid [40].

Filaggrin gene [FLG] mutations are a significant risk factor for the development of AD [41]. Filaggrin deficiency in AD results in increased SC pH and increased trans-epidermal water

loss, partly due to decreased hydration of the SC through activation of serine proteases. Studies now show that defects in epidermal barrier function may result in triggering as well as bolstering skin inflammation in AD [42, 43].

SC Lipid-Processing Enzymes

The mortar in the "bricks and mortar" model is composed of various lipids. These SC lipid components come from the processing of keratinocyte secreting lamellar structures in an acid environment [44]; their formation involves several pH-dependent enzymes. The two most important enzymes are acidic sphingomyelinase and B-glucocerebrosidase. Both need an acidic pH to function. These enzymes synthesize ceramides which are critical to the permeability barrier [45].

Investigations corroborate the theory that pH impacts barrier function. In vivo studies in hairless mice exposed to acetone insult or adhesive film stripping demonstrated faster barrier function recovery in the presence of acidic buffer solution compared to neutral buffer solution [46]. Studies in normal skin have shown elevation of SC pH disturbs the skin barrier via decreased activity of ceramide-producing enzymes and increased activity of serine proteases [2, 3].

SC Serine Proteases

Epidermal barrier function is highly dependent on serine protease activity. This group of enzymes cleave peptide bonds in proteins. The SC, as mentioned, is a complex cross-linking of proteins and lipids that form a functional brick wall. Although this analogy has been used extensively to explain the complex SC, it is not the only cohesive force holding the corneocytes together [47].

The other component is the presence of corneodesmosomes. These modified desmosomes play a similar role to desmosomes found in the epidermis [48]. Corneodesmosomes play an important role in providing tensile strength which results in resistance to shearing forces and the resulting physical barrier function of the skin. It is useful to think of them as "masonry tiles that act as molecular rivets between the bricks in a three-dimensional space" [49, p671–677].

Serine proteases, their inhibitors, and their involvement in SC desquamation were first postulated in 1987 by Bissett et al. [50]. Studies have led to the conclusion that serine proteases are necessary in the final stages of desquamation [51].

A potential mechanism of enhanced SC desquamation and, therefore, a decreased barrier function is related to their increased activation in association with an elevation of SC pH. Increased serine protease activity is seen in dry skin; xerosis of atopic dermatitis; inflammatory dermatosis, such as psoriasis and other genetic disorders; and most importantly subclinical barrier dysfunction induced by surfactants and environmental assaults [52].

There are many serine proteases involved in SC maintenance. The predominate enzymes are from the kallikrein family, namely, kallikrein 5 and kallikrein 7. Increases in SC pH are known to increase the activity of kallikrein-related peptidases kallikrein 5 and kallikrein 7 which are involved in the degradation of corneodesmosomes and desquamation [53–55]. In addition, the rate of desquamation induced by SC serine proteases is regulated by various groups of proteases inhibitors, the most important being the LEKTI family of inhibitors [52]. As the pH of the skin becomes more acidic, the inhibitory potential of these enzymes is reduced in the superficial layers of the SC facilitating localized desquamation.

Thus, pH is a key component that initiates both sets of enzymes and enhances or decreases their activity, which is critical to a healthy and regulated desquamation of the SC and barrier function.

Skin Microbiome

In their review of the skin microbiome, Segre et al. discuss the contribution of commensal skin organisms to skin pH [56]. Propionibacterium acnes' full genome sequencing has revealed encoded lipases that reduce the skin triglycerides present in sebum into free fatty acids. These acids contribute to the acidic pH of the skin surface [57, 58]. Many pathogenic microorganisms such as *S. aureus* and *Streptococcus pyogenes* are inhibited by the skin's acidic pH. This acidic

pH also favors the growth of coagulase-negative Staphlococcus epidermidis and corynebacteria [59, 60]. The effects of an individual's use of cosmetics, cleansers, as well as antiseptic or antibiotic use may modulate the skin microbiome. The effects of antibiotic treatment of the gut microbiome have been studied [61, 62], but this has not been done in the skin.

Studies have shown reduction in *S. aureus*, *Clostridium difficile* (*C. difficile*), and *Bacillus subtilis* (*B. subtilis*) in atopic skin with the application of acidic formulations [63, 64].

Lastly, pH also regulates the activity of antimicrobial peptides (AMP) [65]. These peptides are produced by mammalian cells such as neutrophils, mast cells, and epithelial cells. However, recently, Gallo et al. [66] have shown that commensal coagulase-negative staphylococci (CoNS) isolated from healthy skin and from patients with AD have antimicrobial activity against *S. aureus*. Furthermore, these antimicrobial CoNS strains were more common on the normal population than in patients with AD, and introduction of these strains to human subjects with AD decreased the colonization of *S. aureus* [66].

pH and Wound Healing

The reduction of skin pH is a well-known therapeutic approach for treating wounds. Using acids such as ascorbic acid, alginic acid, hyaluronic acid, and acetic acid helps wound healing and aids in controlling wound infection. These effects are felt to be the result of increased antimicrobial activity, increased barrier function, altered protease function, and reduction of bacterial end products [67, 68]. Most pathogenic bacteria that result in skin infection need a pH higher than 6 as discussed above. Furthermore, their growth can be inhibited with lower pH values [68].

The growth and re-establishment of the skin barrier is integral to wound healing and an acidic skin pH is the key component in this task. Several studies have suggested lowering skin pH can offer therapeutic advantage as well as preventative benefit in other diseases such as AD and xerosis [69–71].

pH and Skin Cleansers

Cleansing is a part of our social culture; however, there is a fine balancing act to achieving good hygiene and protecting the integrity of the skin's natural barrier. The chemical reaction between detergent, water, and the skin is complex and the full impact of this act on the skin pH and the skin microbiome is not fully understood. It is known that detergents and surfactants damage the skin barrier via removal of the NMF. Surfactants cannot determine the difference between skin debris and SC lipids which results in changes in the SC and a decrease in desquamation and increased corneocyte retention [72].

The pH of cleansers can influence damage to the skin barrier. Small and repeated pH increases from daily soap-based cleanser use have been shown to decrease barrier repair [73]. Baranda et al. [74] measured the pH of many commonly used cleansers (Table 2.2). They also found a

Table 2.2 pH of cleansers

Brand name	pH	Composition
Aderm	6.44	Syndet
Avecyde	3.61	Syndet
Avéne	6.94	Syndet
Cetaphil	7.72	Syndet
Dove white	7.53	Syndet
Dove baby	7.0	Syndet
Dove (liquid)	5.16	Syndet
Dove pink	7.23	Syndet
Johnson's baby	11.9	Soap
Johnson's baby oat	12.35	Soap
Nivea baby cream	12.35	Syndet
Nivea bath care	12.21	Syndet
Nivea bath c. almond	12.22	Syndet
Nivea bath c. oat	12.30	Syndet
Zest neutral	9.85	Soap
Zest citrus sport	9.75	Soap
Zest herbal	9.97	Soap
Zest aqua	9.89	Soap
Palmolive green	10.18	Soap
Palmolive (white)	10.23	Soap
Palmolive botanicals	10.38	Soap
Palmolive botanicals/ chamomile	10.13	Soap
Camay classic	10.38	Soap
Camay gala	10.36	Soap
Camay soft	10.26	Soap

Reproduced with permission of Baranda et al. [74]

correlation between the pH of cleansers and skin irritation. True soap is typically alkaline with a pH of approximately 10. High pH soaps produce SC swelling and a decrease in the lipid bilayer.

Understanding the proper use of detergents that do not compromise the acidic pH of the skin should be part of any treatment regime of patients with skin disease, including patients with wounds.

Soap is a cleanser, but not all cleansers are soap. Cleansers can be classified based on the type of surfactant used. Soap-based cleansers are created when either animal or vegetable fat interacts with a strong alkali, like lye. This chemical reaction, known as saponification, creates a fatty acid salt which has a high pH usually between 9 and 10. Syndet cleansers are the most commonly used cleansers today and are composed of synthetic detergents known as syndets. These cleansers have a pH formulated between 5 and 7 which is closer to normal skin pH. Combining soap-based cleansers with syndet cleansers creates a formulation called a Combar. Combars provide better cleansing with less skin barrier damage.

Cleansers can also be classified based on their charge which affects their pH and their cleansing properties. The more negative the charge, the higher the pH and the more damaging to the skin barrier. Soap is an anionic surfactant with high pH. Synthetic detergents can be anionic like sodium lauryl sulfate amphoteric or neutral charge like cocamidopropyl betaine cleansers or nonionic like the alkyl glucosides surfactants (Table 2.3).

Table 2.3 Cleanser categories

Type of cleanser	Description
Soap	Made from fat and alkali-treated salts of fatty acids, pH 9–10 Transparent, glycerine Super fatty with mineral oil, etc. Antibacterial with triclosan Example: Ivory, homemade soaps
Syndet bars	Made with synthetic detergents and small amounts of soap-based detergents, pH 5–7 Example: Dove, Cetaphil, CeraVe
Combar	Equal parts of soap-based detergent mixed with synthetic detergent Example: Irish spring
Liquid cleansers	Synthetic detergents can be ionic or nonionic in lotion, cream, oil, or gel form Example: Dove body wash
Lipid-free cleansers	Contain no soap or detergent and do not need water to cleanse. Examples: Cetaphil, CeraVe

Summary

When managing patients with local wounds, it is imperative to consider the proper use of cleansers and treatments that do not compromise the acidic pH of the skin. This is an important matter to impart to students and patients alike. Cleansers should have a pH between 4.5 and 6, which is close to normal pH of the skin. Avoidance of soap or non-pH adjusted cleansers should be recommended as part of any treatment protocol for wound patients. The effects on skin pH should also be considered when using antibacterial substances or other wound treatments. Maintaining and repairing the skin barrier is the focus of wound healing and skin pH plays an integral role in this process.

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Chronic Wounds and Infections

3

Eran Shavit and Gregory Schultz

Key Features

- Wound healing is a subfield of medicine that should be familiar to dermatologist more than any other disciplines of medicine.
- Treating chronic wounds is challenging, yet rewarding and requires knowledges, patience, and cooperation of the clinician, the patients, and his/her family.
- Wound dressings are categorized into groups: hydrogels, films, hydrocolloids, alginates, gelling fibers, foams, and superabsorbent dressings.
- The choice of dressing is based on various factors, including patients' preference and adherence, availability, and type of exudate and is not based on given paradigms.
- Chronic wounds typically have biofilm bacteria that stimulate chronic inflammation, lead to elevated levels of proteases and reactive oxygen species, and degrade proteins that are essential for healing.
- Infection is an obstacle on the path toward healing and is encountered multiple times during therapy.
- The success of therapy is determined by treating the patient in a generalized holistic approach that includes treating underlying diseases, addressing patient's concerns, and relieving any obstacle that may affect the wound healing or the adherence to therapy.

Introduction

Wound healing is a huge subfield of medicine that may be provided by physicians from various disciplines such as family physicians, geriatrician, vascular/plastic surgeons, and dermatologists, although the focus for dermatologists in the past years has shifted to expand and fill in the gap in surgery [1]. There was not enough emphasis on wound healing. However, dermatologists have an advantage over most other disciplines in their ability to discern different types of wounds as part of the clinical approach to diagnosis and as an essential part of the training to become cutane-

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A. Alavi, H. I. Maibach (eds.), *Local Wound Care for Dermatologists*, Updates in Clinical Dermatology, https://doi.org/10.1007/978-3-030-28872-3_3

ous specialists. Having said that, depending on various training programs, in-training dermatologists will most likely be exposed to some type of wound healing during their training (such as venous ulcers, ulcers caused by inflammatory diseases), but much less exposed to other types of chronic wounds (such diabetic foot wounds or pressure injury wounds). Moreover, most of the graduated dermatologist will not practice wound healing after completing their residency for various reasons. Infections and bacterial biofilms are frequently encountered in the course of treating wounds. Treating infection is not an easy task considering the wounds are opened and always covered with bacteria; therefore bacterial balance is important. Based on the solid theoretical background of dermatologists on various underlying diseases that may be related chronic wounds, we aim to provide a more practical approach to different types of wounds and discuss their management plan.

Basic Approach to Wounds

Any wound greater than 6 weeks of age is considered chronic wound [2]. However, the basic approach when dealing with wounds, regardless of the etiology, is to identify which type of wound is dealt with, namely, healable, maintenance, and non-healable [3]. Non-healable wounds may be the result of a malignancy or an irreversible ischemia (which cannot be corrected). The approach toward maintenance and non-healable wounds is generally much more conservative and puts much less emphasis on the type of dressing to be used.

The first approach to the patient with wounds must initiate with a thorough and meticulous wound history and physical examination. These will, naturally, dictate the next steps of the holistic care. Evaluation of the wound includes assessment of the anatomic location of the wound, the shape and size of the wound, the appearance of the wound bed and its borders (e.g., undermined), and the amount of exudate. MEASURE mnemonic summarizes this and is an easy way for residents to remember, where M stands for measure size, E stands for exudate amount, A for appearance, U for undermining, R for reevaluate, and E for edge of the wound [4]. Appearance of the wound may later dictate the type of dressing to be tailored to the wound.

Wound cleansing should be performed next and prior to the thorough inspection of the wound. This step is essential, as the wound may be covered with debris that may obscure the true nature of the wound. Wound cleansing can be done either via irrigation, soaking, or compression of fluids. However, broader explanation about this step is beyond the focus of this section. Debridement which follows next, in some cases, means removing nonviable tissue with various techniques. Debridement may be autolytic, surgical, mechanical, enzymatic, or biological (the utilization of maggots). The author, generally, advocates surgical debridement when it is feasible, on healable wounds. Next assessment must be done to rule out imminent infections, as open wounds are always containing bacteria; this task may not be so easy.

Moist Balance. The wound bed should not be too wet and not too dry, rather in moist state to promote the healing process. This concept is known more than 50 years already and has revolutionized the wound healing concept until then [5].

Types of Wounds

Chronic, Are Commonly Divided into Typical or Classic Wounds and a Less Common Group Known as Atypical Wounds (Table 3.1)

Surgical Wounds These ulcers include all ulcers induced post a surgical procedure. Surgical wounds can be classified into one of four categories: class I, clean wounds; class II, clean-contaminated; class III, contaminated wounds; and class IV, dirty-contaminated. The surgeon may close the wound margins primarily or leave them to close spontaneously (“secondary intention”). Postsurgical wounds may be clean or clean-contaminated [6] and may be sutured primarily or left open to heal by a natural process; this latter wound repair is termed secondary intention healing. Keeping the wound bed moist is pivotal for wound

Table 3.1 Guidance to different types of wounds and treatments [30–35]

Type of wound	Clinical location	Clinical features	Investigation	Management
Examples of typical ulcers A. Diabetic foot ulcers	Anywhere on the feet (commonly areas of most pressure like metatarsal)	Peripheral neuropathy Charcot's osteoarthropathy *Ulcer clues:* may be covered underneath callus/corn or surrounded by callus	Hx and PE Vascular evaluation-AHHD ABPI, toe pressure R/O infection (including X-ray or MRI to rule out osteomyelitis)	Control blood sugar level Vascular intervention Debridement Pressure redistribution (e.g., total contact cast, removable cast walker, etc.)
B. Venous ulcers	Medial malleolus	Edema Varicose veins Discoloration, yellow-brown Hms Pinpoint petechiae +/− SD +/− LPD *Ulcer clues:* irregular border, yellow fibrinous base, shallow	PMH PE VD	Compression bandages, e.g., Unna boot Maintenance: Compression stockings Interventional surgery (selected cases based on venous duplex)
C. Arterial ulcers	More sital extremities	Absence/weak pulses Pallor Erythematous when dependent Shiny, hairless atrophic skin *Ulcer clues:* dry necrotic base, well marginated	Assess pulses AHHD ABPI TP TOS	Smoking Cessation treat other risk factors Antiplatelet meds Angioplasty Bypass surgery Pain reduction
D. Surgical wounds	Any anatomic location operated	Usually linear Well demarcated	Hx and PE No other required	Depending on clinical scenario Secondary intention if infected
E. Pressure injury	Pressure prone areas, over bony prominences Common locations; ischial tuberosity, sacrum, etc.		Hx and PE Not required (consider CBC,LFT,RFT,Alb,protein level)	Pressure redistribution Proper diet (protein intake) Absorbent dressings if needed

(continued)

Table 3.1 (continued)

Type of wound	Clinical location	Clinical features	Investigation	Management
Examples of atypical ulcers: A. Inflammatory Atypical ulcers	Any area; limbs, breast tissue; Peristomal	Hx of IBD/rheumatic/ hematological disease Trauma induced (pathergy) PG ulcer (11): *painful*, violaceous rim, undermined borders *Vasculitis ulcers:* vasculitis lesions, palpable purpura	PMH Bx (active border of the ulcer) One Bx in the center for cultures (myc, fungal, bacterial) DIF (for suspected vasculitis, bx and DIF active lesion and perilesional)	Treat underlying disorder Corticosteroids Immunosuppressive Rx[a] Biological Rx[b] Pain reduction Consider dressing with analgesics (e.g., Biatain IBU®)
B. Neoplastic	Any anatomic location	Commonly elderly patients Nonhealing ulcer Clues to Dx: Head/neck- fair skin, sun-damaged skin, background AKs Glistening rolled border (BCC), keratin layer (SCC)	Dermoscopy Bx (avoid the central area of necrosis) +/− Imaging[d]	Surgery Radiotherapy/chemotherapy[c] Pain reduction
C. Vascular Martorell	Lateral-dorsal lower leg Achilles tendon	>50 years of age Hx of HTN, less commonly DM Early lesion: *painful* red-blue blister +/−livedo reticularis background Later: a purple to erythematous hue borders and a necrotic base *painful* ulcer	"Elliptical" deep Bx (down to the fascia)	Debridement and surgery Pain reduction

Abbreviations: *ABPI* arterial brachial pressure index, *AHHD* audible handheld Doppler, *AKs* actinic keratoses, *Alb* albumin, *BCC* basal cell carcinoma, *Bx* biopsy, *CBC* complete blood count, *DIF* direct immunofluorescence, *DM* diabetes mellitus, *Hms* hemosiderin deposition, *HTN* hypertension, *Hx* medical history, *IBD* inflammatory bowel disease, *LFT* liver function tests, *LPD* lipodermatosclerosis, *MRI* Magnetic resonance imaging, *myc* mycobacterial infections, *PE* physical examination, *PG* pyoderma gangrenosum, *RFT* renal function tests, *Rx* treatment, *R/O* rule out, *SD* stasis dermatitis, *TOS* Transcutaneous oxygen saturation, *TP* toe pressure, *VD* venous duplex scan

[a]Immunosuppressive Rx = immunosuppressive therapy including systemic corticosteroids as the mainstay therapy and corticosteroid sparing agents such as azathioprine, mycophenolate mofetil, etc.

[b]Biological Rx = biological therapies such as antitumor necrosis factor (TNF) alpha inhibitors

[c]Depending on the tumor type and other factors, for instance, BCC is usually amenable to local surgery, whereas larger tumor requires combined therapeutic regimens

[d]Imaging is seldom required if small ulcer and the suspected diagnosis is basal cell carcinoma (BCC) or squamous cell carcinoma (SCC). In cases when the diagnosis is uncertain, or the tumors are deep-seated and erode deep tissue structures (such as bone), imaging should be sought

healing because a moist wound environment allows new, non-keratinized epithelial cells to rapidly migrate across the top of the wound bed rather than having to migrate under the surface of the wound bed where they can avoid death by desiccation. However, even for secondary healing wounds, the clinician may apply certain dressings to enhance or facilitate this process, rather than just provide a cover that will prevent trauma or infection. How about when to remove the dressing? A Cochrane review was conducted to evaluate the benefits and risks of removing a dressing covering a closed surgical incision site within 48 hours permanently or beyond 48 hours of surgery permanently with interim dressing changes allowed on surgical site infection. The results were that early removal of dressings from surgical wounds appeared to have no disadvantageous impact on the outcomes. The limitations of this review were that the results were based on three small randomized controlled trials, and the confidence intervals around this estimate were wide [7].

Pressure Injuries Formerly known as pressure ulcers, these are perhaps the most challenging chronic wounds clinicians will encounter during their practice of wound healing. And indeed, this has not only a tremendous physical and psychological impact on the patient's lives and his surroundings, but it has a more financial global impact on health systems. And as the management is prolonged, so does the payments, and this is no surprise that the deeper the wounds are, the longer the treatment is and the higher the costs are. Since the risk of infection for deep seated wounds (such as category/stage III) is higher, it is recommended to evaluate more meticulously, for any sign of infection that includes smell, temperature difference, probing to bone etc. infection versus managing bacterial balance. On the other hand, the need for antibiotics will be required on more than one occasion during its therapy, so overzealous use of antibiotics is not recommended and should always be used cautiously.

Diabetic Foot Ulcers Diabetes mellitus (DM) is a systemic disease; a systematic approach is required in the evaluation and the management. Infection is always a huge threat for patients with DM and the outcomes may be devastating. The first encounter should be thorough and "systemic" aspect of the disease can be evaluated via the mnemonic "ABCDE" of DM (A for HbA1c, B stands for blood pressure monitoring, C for cholesterol for lipid profile, D for diet meaning appropriate lifestyle changes, and E for exercise). In the presence of diabetic foot ulcer, (DFU) osteomyelitis (OM) must be ruled out. Some office-based techniques to try and detect bone infection include probe to bone test with reasonable sensitivity and specificity [8–10]. Other tools to determine the likelihood for OM include the utilization of infrared thermometer [11], when higher temperature is more likely to indicate infection, and evaluation of the size of the ulcer. Measurement of the ulcer's size is performed by multiplying the longest and widest diameters of the wound; depth is graded as very deep (exposing bone), moderately deep (>3 mm, but not exposing bone), or shallow (<3 mm). Other accessory tests to determine OM are more advanced or invasive including imaging tests and bone biopsy. X-ray is a cheap and accessible imaging test that can be used, but in early phase of bone infection, it lags the clinical presentation. Other imaging possibilities include technetium-99 m phosphate bone scintigraphy, indium-111-labeled leukocyte scan, and magnetic resonance imaging (MRI). The value of laboratory tests has been reviewed by Butalia et al. that concluded based on only 2 studies that an erythrocyte sedimentation rate (ESR) >70 mm/h significantly increased the probability of OM [12].

Leg Ulcers – Venous, Arterial

Large epidemiological studies show that lower leg ulcers are comprised in almost 80% of vascular etiology in origin, including peripheral vascular disease, venous disease, and mixed arterial and venous disease [13].

Venous ulcers are the commonest type of leg ulcers. Inflammation both incites and sustains

lower limb ulceration. Explanation about the clinical presentation and morphology is beyond the scope of this chapter. These wounds as other chronic wounds tend to be secondarily infected. Moreover, inappropriate dressing change that might be the result of lack of resources and difficulties to change multiple layers of dressings under compression bandages may lead to infections as well.

Arterial ulcers are caused by impaired tissue perfusion. Should the ischemic component of the arterial ulcer not be corrected, it is irreversible, which means these are non-healable ulcers. In these cases, conservative therapy is aimed at controlling bacterial colonization and infection. Debridement is contraindicated in ischemic wounds and should be avoided. Compression generally should be avoided, but can be used in caution, in selected cases especially in mixed arterial-venous disease and even then, very lightly, not in the same fashion as for venous disease [14].

Atypical Wounds

Atypical ulcers may present clinically different in patients with *vasculitis, pyoderma gangrenosum (PG)*, and other autoimmune diseases that have chronic lower extremity wounds; these wounds play a role in roughly 20% of patients with chronic lower extremity ulcers. However, such ulcers are not restricted to the lower limbs and may be anatomically located anywhere in the body [15].

From Contamination to Infection

Infection has been defined as a continuum from contamination, colonization, critical colonization, and infection.

Contamination is the presence of nonreplicating microorganisms on the surface of the wound. All open wounds (as chronic wounds are) have some degree of bacterial burden that is generally cleared by the host. In *colonization*, bacteria attach to the wound surface and replicate but do not hinder healing or cause signs and/or symptoms of infection. All chronic wounds are colonized to varying degrees. With *critical colonization*, the bacteria attach to the wound surface, replicate, and multiply to a level that affects skin cell proliferation and tissue repair without introducing systemic signs of infection. When organisms attach to the wound surface, they begin to develop *biofilm*, which is a complex system of microorganisms fixed in an extracellular, polysaccharide matrix that makes it very tolerant to some commonly used antibiotics and antiseptics. Biofilm formation is a means to protect bacterial cells including escaping from the immune response of humans. Bacteria evolved the ability to encase themselves in the protective biofilm matrix as defense against amoebas which are their natural predators in natural environment. Unfortunately, bacteria in biofilms are also protected from being engulfed and killed by neutrophils and macrophages. This protective mechanism is believed to explain persistent chronic wound infections. Sometimes it is even possible to clearly see the biofilms and remove it partly by wiping it off. Naturally, removal of these visible portions is not enough because biofilm bacteria are often located beneath the surface of wound beds [16]. In a recent study, biofilm was detected even after wiping and cleansing and sharp debridement with a nitrocellulose membrane, which was used to collect the surface biofilm components from the wound bed [17]. These results emphasize the difficulty in removing the biofilm and therefore the bacteria from the chronic wounds.

Infection occurs when organisms in the wound bed invade the healthy tissue, reproduce, defeat the host resistance, and create cellular injury leading to local or systemic symptoms [18].

Infection, according to Kravitz, should be defined as the presence of bacteria in any quantity that impairs wound healing [19]. Development of an infection is affected by the host resistance. The latter is lowered by poor tissue perfusion, poor nutritional status, as well as by smoking and drug and alcohol abuse. Other systemic factors that impair healing include comorbidities as diabetes mellitus and immunosuppression due to

underlying illness or medications (e.g., corticosteroids). It is imperative to remember that the diagnosis of infection is based on clinical grounds. Bacterial swab and culture will identify antimicrobial agent sensitivity as well as the presence of multiresistant organisms. The five cardinal signs of infection, "rubor," "dolor," "calor," "tumor," and "functio laesa," may guide clinicians toward diagnosis of an acute infection. Systemic fever, chills, and hypotension are signs of a systemic infection (may be part of the complex severe inflammatory response syndrome) that is not always present. However, these signs are the hallmark of an acute infection. For chronic infections the findings sometimes may be subtler. Woo et al. have developed a mnemonic to evaluate the presence or absence of clinical signs of critical colonization (NERDS© = non-healing, exudate, red and friable tissue, wound with debris and smell) or infection (STONEES© = size increasing, temperature, os, new areas of breakdown, erythema/edema, exudate and smell) and validated these by comparing their results to semiquantitative swab cultures. Wounds with debris, increased exudate, and friable tissue were found to be five times more likely to have scant or light bacterial growth, whereas wounds with elevated temperature were eight times more likely to have moderate or heavy bacterial growth [20]. Laboratory tests may be used in selected cases to identify clues for signs of infection/inflammation in the blood, including elevated white blood cell count (WBC) in the complete blood count (CBC), elevated sedimentation rate (ESR), and elevated C reactive protein (CRP) level, in addition to swabs and blood cultures that may be obtained in selected cases. CBC, ESR, elevated ESR or CRP are not specific, as they are elevated in other inflammatory conditions. There is not a single laboratory tool such as a biomarker that can assist in the diagnosis. Therefore, it is advised to use these tests on individual basis and based on clinical judgment. Additional accessory tests such as imaging or other studies may be required as well (e.g., imaging studies for osteomyelitis). The utilization of additional tests may be required in selected cases when the diagnosis may not be straightforward and more challenging.

Unfortunately, a confirmatory test to conclude infection or not does not exist and to determine the presence of infection relies mainly on clinical grounds and summarizing the clinical findings. Microbiological swabs should be taken as an adjunct to determine what type of bacteria are present and whether antimicrobial resistance exists to monitor successful therapy.

Inflammation may mimic infection; one example to a challenge in the differential diagnosis is Charcot osteoarthropathy, commonly encountered in diabetic patients. In the acute phase, it is difficult to differentiate the former from cellulitis, and in the chronic phase, it may be difficult to differentiate Charcot osteoarthropathy from osteomyelitis [21]. In that case, high index of suspicion is required and is facilitated with accessory tests, such as imaging. Initially X-ray, but later magnetic resonance imaging (MRI) will be necessary. Pyoderma gangrenosum (PG), is another example of a challenging diagnosis that may mimic infection, which, like an infection, is a clinical diagnosis that requires high index of suspicion. Moreover, since it classically presents with an ulceration, it might be secondarily infected as well, more obscuring the diagnosis [22]. PG is also associated with pain, which is another nonspecific symptom that may appear in the presence of infection. Accessory tests are not helpful to diagnose PG, and biopsy is only taken to rule out other etiologies. This is another good example to the essential role of a thorough history and physical examination in the process of diagnosis (see Table 3.2).

Infections

There is an ongoing battle to try and eradicate infections. The overzealous use of antibiotics partly has contributed to antimicrobial resistance that limits our capabilities since it narrows the arsenal we have and eventually jeopardizes the treatment. Patients with open wounds are more challenging to treat, since they are more susceptible to infections, and these infections, on many occasions, lack the typical signs and symptoms of infection, so much less pronounced or obvious.

Table 3.2 A comparison of different topical agents [36–43]

Topical agent	Antimicrobial properties	Comments	Adverse effects	Summary
Silver	Broad-spectrum antibacterial, including MRSA and VRE	Caution sulfonamide sensitivity	Pseudoeschar ICD	Conflicting results Probably beneficial for short term course
Iodine	Staph. Inc. MRSA, pseudo, Anaerobes Antiviral, antifungal	Also debrides. Low potential for resistance Should not be used in allergy to iodine Caution with thyroid disease	ICD Thyrotoxicosis Or hypothyroidism	Low risk of use and effective
PHMB	Broad spectrum	Low tissue toxicity Different forms available, including foam, ribbons, and gauze Comforting, so recommended for painful wounds		May cause ICD systemic and local hypersensitivity reactions
MB-GV	Broad bacteriostatic properties	Foam autolytic debridement with a low tissue toxicity Cannot be used on dry wounds		Use in selected cases (should not be used routinely for maintenance wounds)
Honey	Broad-spectrum antibacterial, antiviral, and antifungal	May cause maceration	ACD to propolis	Should not be used routinely for maintenance wounds

Abbreviations: *ACD* allergic contact dermatitis, *GV* gentian violet, *ICD* irritant contact dermatitis, *MB* methylene blue, *MRSA methicillin-resistant Staphylococcus aureus*, *PHMB* polyhexamethylene biguanide, *VRE* vancomycin-resistant enterococci

Nosocomial Infections Postoperative wound infection is one example for a common type of nosocomial infection; fortunately, its occurrence has been steadily decreasing over the past three decades due to usage of prophylaxis antibiotics [23]. However, there is not a consensus regarding the usage of prophylaxis antibiotics for surgery, and in a recent study the timing of intravenous antibiotic prophylaxis did not appear to play a significant role in the risk of surgical site infection; rather the duration of surgery and the host factors appeared to have a much greater role [24].

Resistant Organisms Antimicrobial resistance is a universal problem [25]. Methicillin-resistant *Staphylococcus aureus* (MRSA) is an example. The emergence and spread of antimicrobial resistance are accelerated by overuse of antibiotics, but also due to inadequate infection control practices as well as carriers of these bacteria that spread it non-intentionally. It should be emphasized that wound healing clinicians, perhaps more than other clinicians, are obliged to use antibiotics to control infections in chronic wound patients and must be aware of the hazard of misuse of these agents.

Biofilms According to the concept of biofilm in medicine, bacteria are attached to surfaces and exist in vivo predominately within encapsulated surroundings which protect them and make them less susceptible to treatment. Biofilms are three-dimensional mosaic consortia of microbes, which accumulate and organize at surfaces within an extracellular polymer, or glycocalyx, with interspersed water channels [26]. Bacterial biofilm prevails in most of chronic wounds [27]. Their excessive extracellular matrix secretion and the metabolic changes that they undergo render them highly tolerant of many antibiotic and antimicrobial treatments. Biofilm is a therapeutic challenge in medicine and in particular wound healing. Therefore, debridement and physical removal are common approaches to treating wounds suspected of having bacterial biofilms [28]. There are many attempts to overcome this challenge.

Researchers are no longer seeking for a broad-spectrum antimicrobial agent, rather "biofilm-eradicating" antimicrobial drugs. Nitroxoline, an antibiotic used mostly to treat urinary tract infections, is an example of such a drug that was shown to have such an effect to remove the bacterial biofilms. Wounds must be managed carefully, as infection is always a hazard to the therapy; our task is to minimize iatrogenic infections. Currently, there is no consensus or a unified approach on which technique should be implemented. However, it will be wise to combine sterile technique and "clean" procedure (plain using gloves) with minimal touch approach, limited exposure, and sharp debridement or any specialized intervention should be probably conducted in a more "sterile technique" as used in the operation rooms.

Wound Sampling

Despite progress in wound care medicine in the past years, because of the critical research performed in academic, clinical, and industrial settings, only little change has been made in the methods of wound analysis and sample collection, resulting in the inability of researchers to accurately characterize the healing process and compare results from different studies [29]. Sampling the wound for biomarkers is still in academic research and, due to many reasons, is not yet translated into everyday practice. Perhaps in the future sampling will be not only for microbiological purposes, rather to capture the phase of wound healing due to the presence of biomarkers and to tailor the treatment accordingly.

Conclusion

Wound healing is a complex process. Infection is a recurrent barrier for wound healing that must be lifted to pave the way for wound healing. We are challenged by prevention from any type of infection and especially nosocomial infections that our task is to be on the guard and protect from, as well as emerging resistant bacteria and biofilm that make our task much more difficult. Any health system should designate personnel to facilitate in prevention of infection strategies.

The purpose of this section was to provide some tools for dermatologist to be able to identify certain types of wounds and available material to apply. The key is when to use what type of dressing, and despite the tips given, it relies also on experience that the clinician will have with more practice.

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Wound Dressings

4

Dot Weir

The application of a dressing to a wound is only part of the story for successful wound repair. One must begin with a comprehensive evaluation of the patient to determine an accurate diagnosis so that appropriate supportive management may be implemented, such as compression and offloading. Further, evaluation of the co-existing conditions and resulting medications that could impact wound repair is a critical first step to determine wound healing potential. Additionally, nutritional status, tissue perfusion, and lifestyle choices are some of the other essential components to assess the full picture of potential healing or nonhealing and have been covered in other chapters.

In the United States we are in our fifth decade of the practice of moisture balance as the basis of modern wound care creating the optimal environment for granulation, angiogenesis, and epithelial migration resulting in more rapid wound closure. The genesis of the importance of moisture dates back to the early 1960s. Dr. George Winter performed a landmark study by creating wounds on the backs of domestic pigs and covered some with a saran material and the rest he left open to air [1]. The reepithelialization rate of the covered wounds was nearly double the rate of the scabbed wounds. Other studies followed which validated Dr. Winter's findings and these findings resulted in the growth of products addressing the local environment of the wound [2–4].

A comprehensive assessment of the wound and surrounding skin is an essential component to decision making related to dressing selections. Consider the following assessment points as they relate to addressing the needs of the wound and overall care of the patient (Table 4.1).

Is the wound healing? A wound should be showing signs of healing within 2–4 weeks of attaining a well-prepared site [5]. If healing is moving in a positive trajectory with each assessment, then the current dressing regimen should be continued unless there are extrinsic factors such as the cost or availability of the current dressings that would prevent this. Frequent changes in the treatment plan and dressing orders can be difficult for the caregivers, home care, or skilled nursing facility who must order dressings for use. If the wound is not improving, then a reevaluation of the patient and wound status is warranted to assess for potential barriers to healing.

What type of tissue is exposed? Is the wound bed healthy and granulating or is there nonviable tissue present? This will determine if the goal is maintenance of the healthy wound bed and balance of moisture or creation of an environment to manage to the level of necrosis. If autolytic debridement is the goal, one would opt for a

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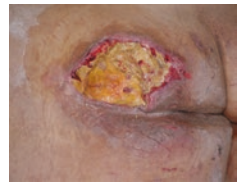
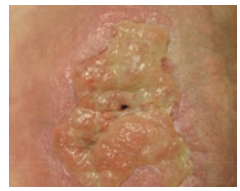
A. Alavi, H. I. Maibach (eds.), *Local Wound Care for Dermatologists*, Updates in Clinical Dermatology, https://doi.org/10.1007/978-3-030-28872-3_4

Table 4.1 Key assessment points for dressing decision making



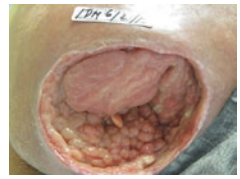
If the wound bed is dry, hydrate

- Hydrogel, osmotic dressing (honey, NaCl)
- Moistened gauze or other packing material



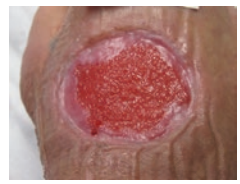
If the wound is draining, absorb

- Calcium alginate or gelling fiber dressing
- Foam
- Superabsorbent



If there is space, fill

- Calcium alginate or gelling fiber dressing
- Moistened gauze
- Superabsorbent packing material



If the wound is filled in, cover and protect

- Foam or composite dressing
- Hydrocolloid
- Contact layer or impregnated gauze with secondary dressing

dressing that ensures a continuous moist environment. If enzymatic debridement is in use, choice of a secondary dressing that is compatible with the enzyme would be necessary. If the wound surface is covered with proteinaceous thick exudates or coagulum, then consideration of a concentrated surfactant would be in order, and if the wound surface is a dry eschar and debridement is not the goal, then a completely dry dressing such as gauze would be appropriate.

The presence of exposed structure (bone, tendon, fascia) requires close attention to detail to create a protective environment to prevent trauma and desiccation of the structures.

What is the perceived bioburden? Though all chronic wounds are considered to be contaminated, as bacteria proliferate, form biofilm colonies, and invade deeper into the tissue, the risk for infection increases. Even in the absence of gross infection, wound healing can be affected because proteases, toxins, and other consequences of bacteria increase [6]. The use of topical agents and dressings to reduce local bioburden can reduce the number of bacteria before they rise to a critical level and negatively influence wound healing. Multiple dressing options exist to address bacteria while still meeting the environmental needs of the wound (see Chap. 3 on infection management).

Are there spaces to fill? If a deeper cavity (space that is unable to be visualized easily) or undermining is present, this area should be loosely filled to prevent pooling of exudates. The choice of filler dressing would be determined by the amount and type of exudate. Space should be filled with the least number of dressings possible, and notation of how many dressings may be in a space is essential so that the next caregiver is aware and able to remove them all. Notation of the number of dress-

ings packed into deep spaces would ideally be documented in the medical record as well as notated on the outside of the dressing.

What is the condition of the surrounding skin? Exquisite attention to the periwound skin is a high priority to prevent adding "insult to injury." Many wounds occur within already fragile skin which is easily denuded by wound exudate and easily stripped by the repetitive use of adhesives. Securing dressings with roll gauze whenever possible is preferable to taping. The use of self-adhering dressings utilizing silicone adherence can prevent repetitive stripping with dressing changes. If adhesive dressings or adhesive tapes are necessary, utilization of a either a polymer skin preparation or cyanoacrylate prior to the tape application can prevent medical adhesive-related skin damage [7]. In the immediate periwound area, if excessive exudate is expected or the dressing material being used is moist, the use of a petrolatum- or zinc-based skin protective ointment or long-wearing cyanoacrylate to the skin will repel the moisture and protect the skin.

How does the wound/dressing affect the patient's quality of life? As clinicians approach the treatment choice for a patient, the overall impact on their life must be considered. In addition to the other factors already discussed, a dressing choice that optimizes quality of life when able and practical is essential. One should consider patient wishes and lifestyle, work requirements, and activities of daily living. An important first consideration is the overall goal for the wound, for example, is the wound "healable"? [8] In the presence of inadequate perfusion with no intervention options, or a terminal illness, for example, the best goal may be to control pain and/or odor and infection and prevention of wound deterioration if possible.

Attributes of an Ideal Dressing

There is no one perfect dressing for all wounds and wound types. The aim of the dressing choice is to meet the needs of the wound based on a thorough assessment to drive the ideal choice. The following are important considerations:

- *Manages exudate adequately*: The ability to contain wound exudate is the primary wound dressing decision driver. A dressing should not allow the wound bed to desiccate or periwound to macerate and should provide the ideal moisture balance for wound processes.
- *Fills space*: Conforms to the wound bed, loosely filling in any cavities, undermining, tracks, and tunnels to prevent pooling of exudate without overfilling.
- *Protective*: Nontraumatic, provides a barrier to contamination from the environment and surrounding skin.
- *Prevents or mitigates pain*: Unless the location of the wound is insensate, patients have varying degrees of wound-related pain. There are enough dressing options so that repeated painful dressing changes should not be necessary or can certainly be lessened.
- *Remains in place for the desired time frame*: The anatomical location will drive how the dressing material will be attached. Wounds to the trunk must be affixed using a tape product; those on the extremities can be held in place with roll gauze or other elastic or tubular support bandages.
- *User-friendly*: Easy to apply, conducive to self-care or use by a non-skilled caregiver if necessary.
- *Cost-effective*: Covered by secondary payers or on agency or institutional formulary.
- *Compatible with support needs*: Able to be left in place for the duration of a compression wrap or total contact cast if needed.

Wound Cleansing

An important part of wound bed preparation is cleansing. Wounds should be cleansed after the previous dressing is removed as well as after wound debridement. In the world of chronic wound management, clinicians deal with residuals and exudates from dressings that are left in

place for days at a time, gelatinous and proteinaceous coagulum containing bacteria and biofilms, and necrotic material that harbors all of the above. With that visual in mind, how we clean wounds takes on new meaning.

The choice of the solution to be used for cleaning a wound should be based on the perceived need—that is, to cleanse or disinfect? If addressing bioburden is a primary factor, the use of an antimicrobial or antiseptic solution should be considered. For general cleansing of a clean wound, isotonic saline is a reasonable choice if delivered effectively. Another option is to use cleansers and antimicrobial solutions in commercially prepared dispensers.

In order to disengage most exudates, previous treatment residues, or tenacious debris, it is recommended to deliver the cleansing solution at a pounds per square inch (PSI) pressure between 4 and 15 [9]. In order to reach this delivery force requires the use of a commercially available irrigation device or a syringe and angiocath to put more force behind the stream. To that end, the literature abounds with mention of the use of a 35-cc syringe and a 19-gauge angiocath to deliver solution at 8 psi, the source of that recommendation dating from 1976 [10]. The 35-cc syringe and 19-gauge angiocath, however, are not commonly found in most clinic settings. A more recent paper describes the use of a 20-cc syringe and 18-gauge angiocath to deliver 12 psi, sizes much more readily available [11].

Commercial products in pourable containers may be delivered as described above. Those products available in a spray dispenser, many with adjustable spray/stream options, are ideal because they combine a cleanser with surface acting and wetting agents that can reduce the wound surface tension of debris, allowing for improved cleansing [12].

Effective cleansing may require that physically touching the wound bed is required to remove visible as well as non-visible debris. Avoidance of pain and trauma ranked high among wound clinicians in a multinational survey of wound clinicians looking at dressing practices [13]. The context of trauma is twofold, trauma that damages tissue and trauma that causes pain. The potential for injuring tissue must be balanced with the potential negative effects of debris and bioburden on that same tissue [12], the latter being the larger threat. Once the wound is granulating and healing, less traumatic methodology can be employed. From the pain perspective, if wound cleansing is unable to be accomplished due to the patient's intolerable discomfort, consider the use of topical anesthetics, such as lidocaine gel, solution, or ointment, to mitigate the pain. Physical cleansing of the wound bed can be accomplished using woven gauze or monofilament pads [14]. The use of gauze for scrubbing has been shown to be less effective than the use of a monofilament pad for reducing bacteria and biofilms in vitro, and in practical experience the monofilament pad is most often more frequently well tolerated for painful wounds [15]. The net result of the use of either one will usually result in a visibly cleaner wound than just flushing or irrigation alone.

Dressing Categories

Wound management is a dynamic skill, and dressing selection is both an art and a science. There are many choices, both in dressing categories and attributes of one dressing over another even within the category, making the task of selection overwhelming at times. There are numerous specialty dressings that create or enhance the wound environment to promote healing. Some have a singular function while others are combinations or composites possessing attributes of more than one category. Familiarity with the basic categories enables the clinician to understand the combination products. If one begins with a thorough assessment, sets goals based on that assessment, and then selects the product that will help to meet that goal, then the decision is made easier.

Skin Protectants

Skin protectants are formulations designed to protect the skin from the effects of mechanical

injury from tapes and adhesives. Composed of a polymer and a solvent, when applied to the skin, the solvent evaporates and the polymer dries, forming a visible transparent protective coating on the skin. Another alternative are the cyanoacrylates, which bond to the skin and are shed or lifted off with tape removal. With both options, the product is lifted with adhesive removal instead of layers of skin cells, thus avoiding mechanical injury. Skin protectants are available with and without alcohol, an important distinction when considering application to broken or irritated skin that is painful with alcohol. Skin protectors are available in foam applicators, wipes, and sprays [16].

Gauze and Cover Dressings

Gauze is without question the most recognized form of dressing material for both healthcare professionals and patients alike. It is versatile in its function as a wound cleaning tool, a wound packing material, and a wound cover and is used often as a delivery mechanism for solutions such as antiseptics, antimicrobials, or isotonic saline. As a barrier, plain woven gauze is less effective for protection from surface contamination than more modern-day dressings [17]. Gauze dressings also require more frequent dressing changes creating an increased demand on nursing time, so that although less expensive than other modern dressings, the increased cost of care and delayed healing actually may make them costlier and are associated with increased discomfort related to the pain and trauma of removal [8, 18, 19]. Gauze dressings are available impregnated with agents that can contribute to improvement of the wound environment such as hydrogel to add moisture or hypertonic sodium chloride to cause an osmotic shift of fluid enhancing autolytic debridement and moving wound exudate into a secondary dressing. Gauze dressings are available both sterile and clean, non-sterile, woven or nonwoven, and with borders of tape to be self-adhering.

Contact Layers

Contact layers are single-layer open-weave constructs that provide a low- or nonadhering material applied intimately to the surface of a wound. They be coated with an oil emulsion, silicone, or petrolatum to increase the nonadherence factor. This dressing category acts as a protective interface between the wound bed while allowing exudate to pass through the dressings into the secondary dressing [19]. Contact layer dressings are ideal to cover topical creams, ointments, and biologic products to protect from adhering or absorbing into a secondary dressing, as well as protect a wound bed from ingrowth into negative pressure wound therapy foam and prevent painful removal. Contact layers may be cut to fit the wound bed or overlapped onto the periwound skin.

Transparent Film Dressings

Transparent film dressings are self-adhering, clear polyurethane sheets. They are impervious to liquids, and bacteria, but penetrable to moisture vapor and atmospheric gasses [19, 20]. The transparency allows clear visualization of the wound and surrounding skin. They create a moist, warm environment which facilitates cellular process for wound healing and promotes autolytic debridement. Applied over early skin changes such as stage 1 pressure or suspected deep tissue injuries, easy visualization is possible to determine if these injuries are improving or degrading [16]. They can be used on primary intention surgical sites, vascular access sites, and as protection to areas exposed to friction. Films are often used as secondary dressings to allow for showering as well as protect from contamination from incontinence. They are the dressing material used with most negative pressure wound therapy devices.

Film dressings are indicated for nondraining to minimally draining wounds. Standard film dressings are not appropriate to cover infected wounds because bacteria have an ideal warm environment in which to multiply, creating a greater inflammatory response without the ability to control the increased exudate that usually accompanies an infection [16]. Buildup of exudate beyond the vapor transfer rate will migrate out of the dressing area causing maceration of the surrounding skin. When removing the dressing from fragile or macerated skin, take care to avoid

mechanical stripping leading to denuding of the periwound area. The use of a polymer skin barrier is advisable when using this category of dressing, or any dressing with an adhesive to protect from stripping of the surrounding skin.

Hydrogel Dressings

The most rapid method of hydrating an open wound is through the use of a hydrogel dressing. These dressings are high in water or glycerin content and are available in three distinctive forms: unstructured or amorphous gels, impregnated gauze, and cross-linked solid sheets. The primary purpose of hydrogel dressing products is to donate moisture to dry wound beds to aid in achieving and maintaining a moist healing environment and to soften necrotic tissue allowing for autolytic debridement [21]. These dressing may contain other ingredients such as alginate to increase viscosity or to support small amounts of absorption, antimicrobial agents which address the bioburden, and growth factors or collagen to enhance wound healing.

When using hydrogel products, protection of the periwound skin with a protective moisture barrier or skin sealant is important to prevent maceration. Hydrogels are indicated for many types of wounds including partial- and full-thickness wounds, pressure injuries, skin tears, radiation and partial-thickness burns, and vascular wounds in which a moist environment is desired. Hydrogels are not indicated for moderately or copiously draining wounds.

Hydrocolloid Dressings

Hydrocolloid dressings (HCDs) are wafer-type constructs composed of an inner, slightly adhesive layer that contacts the wound and surrounding tissue, a middle absorbent layer containing a combination of gelatin, pectin, carboxymethylcellulose, and hydrophilic particles which interact with wound fluid and an outer semiocclusive layer incorporating a moisture repellant film. The role of the middle layer is to form a gel mass over the wound bed to maintain a moist environment, support autolytic debridement, and prevent trauma upon removal. The resulting gel is reported to be acidic, therefore not conducive to bacterial growth; however, caution is advised in suspected or known wound infection as the resulting gelled dressing becomes occlusive in nature and may support bacterial proliferation [22]. The outer layer of the hydrocolloid dressings is either film- or foam-based and does not allow contamination from the outside environment to reach the wound, nor does it allow exudate to strike through from beneath the dressing. Dressings that become soiled from incontinence may be cleaned, but care should be taken to assure that residual stool or urine does not remain trapped at the edge of the dressing.

There is a visible change to the dressing appearance as the middle layer of the dressing gels signaling the clinician to assess and determine the need for a dressing change. The gel will ultimately migrate toward the edge of the dressing and may leak out from the edge. The gelatinized exudate is fairly sticky, sometimes making cleansing a challenge, and the adherent dressing may be firmly adherent to the skin and difficult to remove. HCDs may have an odor upon removal, not to be taken as a sign of infection unless the odor remains after the wound has been thoroughly cleansed.

HCDs are available in various shapes and sizes designed to fit and adhere onto almost any anatomic location such as the sacrum, elbows, and heels. Hydrocolloid material is also available in pastes, rings, strips, and powders to fill cavities and creases, as well as for use under pectin ostomy appliances. The frequency of dressing changes is dependent upon the particular manufacturers' instructions for use, but is generally between 3 and 7 days. Shearing forces over areas such as the sacrum and coccyx may cause dressing edges to roll and require more frequent changes, although many newer versions have thin borders that adhere better without rolling. In addition, the dressing can be picture framed with tape.

Calcium Alginate Dressings

Derived from algae or kelp polysaccharides [23], these dressings are composed of calcium/sodium salts of alginic acid and mannuronic and guluronic acids. Indicated for moderately to heavily exudating wounds, calcium alginates form a

moist gel through a process of sodium and calcium ion exchange within the wound exudate. Alginates are primary dressings placed in contact with the wound bed and are indicated for the all etiologies of wounds other than third-degree burns and wounds that are dry or with minimal exudate [16, 24]. This dressing conforms to the wound surface utilizing wound exudate to create a moist wound environment and can be used to tuck into spaces, pack, or fill uneven surfaces, tunnels, and undermining. Alginates support autolytic debridement and are usually painlessly removed when moist, or can be remoistened with saline or other solutions if they should dry out. In addition, they may be used to control minor bleeding [21]. Alginates require a secondary dressing to further absorb drainage, to hold the dressing against the wound bed, and to protect the wound from outside contaminants. They are available in various sizes and forms such as sheets, pads, and ropes.

Gelling Fiber Dressings

Similar in function to the calcium alginate category, gelling fiber dressings are absorbent wound dressings that fill space, absorb, and manage wound exudate. As they absorb and become hydrated, they become gelatinous on the surface creating a moist wound healing environment as well as allowing for nontraumatic removal. Gelling fibers are commonly composed of sodium carboxymethylcellulose or polyvinyl alcohol fibers and may have other materials to augment their strength, natural materials such as chitosan for its intrinsic antimicrobial and hemostatic properties [25]. Gelling fiber dressings can retain and control exudate levels to reduce the risk of periwound maceration and can also conform to various wound shapes and be removed in one piece.

Foam Dressings

Foam dressings are most commonly made of polyurethane with small, open cells capable of wicking exudates away from the wound through their hydrophilic properties, then holding exudate in the upper layers of the dressing creating a moist environment and protecting the periwound skin from maceration. This dressing category is semiocclusive, allowing for gas and vapor exchange, and may allow passage of exudate through the dressing surface or has an incorporated film layer to prevent strikethrough. Foams are a very versatile dressing category able to be used on minimally draining wounds while also able to absorb moderate to copious amounts of wound drainage. Several newer foam dressings contain absorbent particles and/or strategic cuts and tracts which enable more viscous and higher amounts of exudate to transfer into the dressing [21].

Foams are appropriate for all wound types, partial and full thickness, granulating or necrotic, and can be used under compression. Foams often have a nonadherent contact layer making them gentle on the wound bed during dressing removal. They may be bordered with an adhesive to hold the dressing in place and utilize silicone for adhesion to avoid trauma to the wound bed and surrounding skin, or they may be non-bordered requiring tape to secure the dressing. This category may function as a primary or secondary dressing and can be combined with other topical treatments to enhance protection and absorption. Foam dressings are commonly used in at-risk individuals as prophylaxis for pressure injury prevention.

It is not advisable to use foams on stable dry eschar such as on ischemic limbs or heels, as the dressing may contribute to softening of the eschar making it unstable and opening the area up to bacteria infiltration and nonhealing due to lack of blood supply. Foam dressings may have silver, PHMB, or other agents added to address the bioburden [26].

Polymembrane foam dressings are a unique specialty type of foam from which a mild, nontoxic surfactant and glycerin as a moisturizer are released when interacting with wound exudate, providing for enhanced cleansing of the wound surface while the foam contains a starch co-polymer to enhance absorption [20].

Collagen Dressings

Collagen, the major structural protein of the body, is available in dressings derived primarily

from bovine, porcine, or ovine sources [27]. These dressings are available as sheets, gels, pads, particles, pastes, and powders are indicated for partial- and full-thickness pressure ulcers, venous ulcers, donor sites, surgical wounds, vascular ulcers, diabetic ulcers, second-degree burns, abrasions, and traumatic wounds [28].

A collagen dressing's primary functions in chronic wound healing include [29]:

1. Attracting cells such as fibroblasts and keratinocytes at the wound site.
2. Providing a temporary scaffolding to help guide and support the movement and growth of cells.
3. Acting as a sacrificial substrate by binding with the excessive proteases (MMPs) found in chronic wounds that degrade the wound healing cells, cell receptors, growth factors, and extracellular matrix, allowing the patient's native collagen to perform optimally [30].

Collagen products are not intended to manage exudate or facilitate autolytic debridement, so should be placed on clean or granulating tissue in the wound bed. Collagen dressings are nonabsorbent and are biodegradable and require a secondary dressing to hold them in place and absorb exudate. Most products have increased efficacy if moistened with normal saline unless adequate ambient moisture is present in the wound bed.

When considering the use of collagen for a patient's wound, the clinician should advise the patient of the source of the collagen in the event that they have an allergy or religious or lifestyle barrier to animal-based products. Collagen dressings are not indicated for full-thickness burns. For optimal results with individual branded collagen products, read the manufacturer's information for use/package insert.

Composite Dressings

Composites are wound covers that combine different elements or combinations of products into a single dressing to provide multiple functions. They are usually comprised of multiple layers and incorporate or contact layer or nonstick pad to prevent adherence to the wound bed. They may also include an adhesive border of nonwoven fabric tape, transparent film, or silicone. Composite dressings can function as either a primary or a secondary dressing on a wide variety of wounds and may be used with topical medications.

Superabsorbent Dressings

An emerging and growing category, superabsorbent dressings utilize technology to enhance the wicking of exudate into the dressing, by binding the drainage through the use of particles or fibers to pull the exudate up and often laterally into the construct of the dressing, using larger interface pores to allow the lifting of more viscous drainage, or the use of specialized cuts and tracts within foams for more efficient movement of the drainage off of the wound surface and away from the periwound skin improving protection.

Concentrated Surfactant Gel

Concentrated surfactant gel or CSG contains the surfactant Poloxamer 188, also known as Pluronic F-68. Poloxamers are nonionic synthetic surfactants comprising one central hydrophobic chain and two outer hydrophilic chains. These molecules form loose (non-covalent) cross-links with water to form a micelle matrix. The matrix is surface active and in a dynamic system creates a "rinsing" action at a molecular level on the wound bed. The product consequently adds moisture more efficiently via the surfactant activity and essentially solubilizes dried exudate and other matters, helping to soften, loosen, and trap wound debris. These undesirable elements can then be rather easily removed at dressing change via simple rinsing or wiping with wet gauze or similar materials [31, 32].

Summary

The decision making for management of acute and chronic wounds is driven by the focused assessment of the wound for management of the moisture, the perceived condition of the wound environment for factors that can be balanced, and

then the assessed presence of the bacterial load. To achieve appropriate and successful wound management attention to detail is essential, management grounded in evidence-based guidelines is the key driver, and the patient experience is critical in developing the best treatment plan. It is, though, the evaluation of the plan along the way and alterations based on the changing needs of the wound that enable the best decision making to put the wound on the optimal healing trajectory.

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5 The Use of Antiseptic and Antibacterial Agents on Wounds and the Skin

Khalad Maliyar, Asfandyar Mufti, and R. Gary Sibbald

Introduction

As our global population ages, the prevalence and frequency of both acute and chronic wounds will rise, generating increased burden on patients, healthcare professionals, and healthcare systems. It is estimated that worldwide there are 4.5 million pressure injuries, 9.7 million venous leg ulcers (VLUs), and ten million diabetic foot ulcers [2]. Any wound that is present for greater than 6 weeks is a chronic wound. Wounds will become chronic if the inflammatory or proliferate components of the cascade stall [1]. These wounds take longer to heal and are typically not managed effectively.

Any wound that is open contains colonized bacteria, but it does not indicate the presence of an infection [3]. In fact, most appropriately treated wounds that are not infected continue to heal successfully. In this situation, the host's immune system and the bacterial bioburden are in balance. However, in situations in where the wound healing response is compromised, the balance will tilt toward the growth of bacteria. As the bacterial communities continue to expand and grow, there will be a corresponding rise in the local and systemic host response that can result in impaired wound healing, infection, and chronic inflammation [3]. These host responses that impair wound healing include an increase in cytokine release from bacteria, cellular dysfunction, and higher levels of metalloproteinases [4]. This hostile environment allows communities of bacteria and fungi to flourish and critically colonize the wound. Bacteria create an organized and encapsulated structure with a glycocalyx surrounding a core liquid interface of microbial organisms known as a biofilm [5]. It is believed that approximately 80% of the wound bed surface bacteria exist within a biofilm [6]. The presence of biofilms creates a challenge to the management of chronic wounds. Biofilms hamper tissue repair by stimulating the wound bed, prolong inflammation, and have a predilection for surrounding tissue virulence with periodic release of planktonic bacteria. Bacterial biofilms are available to initiate local infections from their ability to communicate with another via a mechanism known as quorum sensing [7]. Although one commonly utilized means of successfully removing biofilm is with sharp or mechanical debridement [8], antimicrobial agents may also play an important role in their removal. The role of antimicrobials in this regard will be discussed later in the chapter.

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A. Alavi, H. I. Maibach (eds.), *Local Wound Care for Dermatologists*, Updates in Clinical Dermatology, https://doi.org/10.1007/978-3-030-28872-3_5

Wound-related bacterial damage can be situated on either the surface compartment of the wound or the deep and surrounding compartments. Wounds that are infected on the surface component are said to have local infection and should be treated topically. Wounds infected in the deep and surrounding components should be treated systemically. One analogy used to illuminate the difference between the two compartments is to picture a soup bowl with a thin layer of soup at the top. The bottom and sides of the bowl represent the deep and surrounding infection. The thin layer of soup on the surface represents the surface compartment that has superficial critical colonization. Topical antimicrobial and antiseptic agents are used to treat superficial critical colonization and not deep and surrounding infection. Systemic antimicrobial agents are used to treat deep and surrounding infection. This chapter will address the use of topical antimicrobials and antiseptics for the treatment of the superficial compartment.

Wound Classification for Healability

Clinicians are increasingly requiring evidence-based guidelines and protocols in their wound care practices [9]. Sibbald et al. [10] and Falanga [11] were the first to describe the wound bed preparation paradigm (see Fig. 5.1). The wound bed preparation paradigm is a comprehensive, interprofessional approach for the care of chronic wounds, which necessitates the clinician to holistically treat the cause and examine the patient-centered concerns prior to addressing the wound itself. In the initial assessment, wounds were then classified as either healable, maintenance, or nonhealable. The categorization of wounds in this manner provides a more accurate diagnosis and precise treatment plan.

A healable wound is one that has adequate blood supply and the cause has been corrected [12]. Patients with wounds on their feet are considered to have adequate blood supply if they have a palpable pulse, indicating a foot arterial pressure of 80 mmHg or higher. Should the pulse be absent, a Doppler examination of the ankle-brachial pressure index (ABPI) is performed to determine if it is healable. The ABPI of the dorsalis pedis artery should be at least 0.6.

A nonhealable wound is one with inadequate blood supply and a noncorrectable cause. A maintenance wound has established blood flow that is necessary for healing, but the patient cannot ensure adequate adherence to the treatment protocol whether it be due to individual or healthcare system factors (e.g., patient that is not willing to wear compression bandages or able to afford protective footwear that is not covered by the healthcare system) [13].

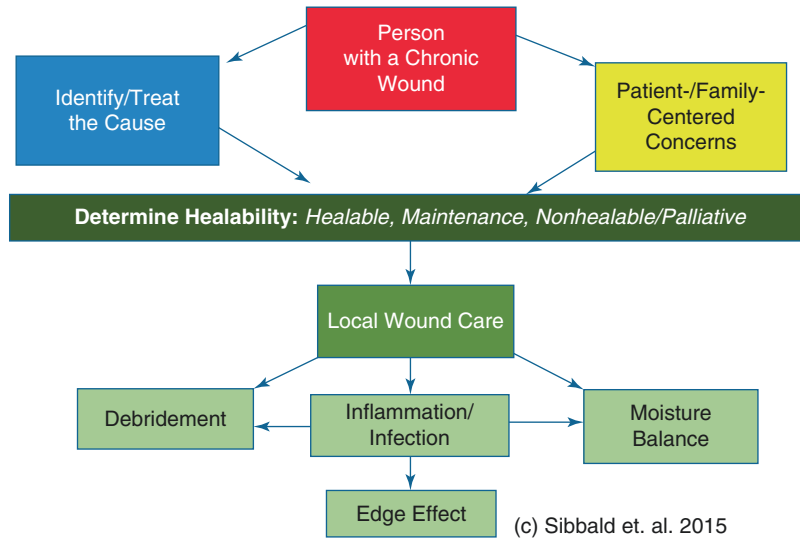

Fig. 5.1 Wound bed preparation paradigm 2015 [52]

NERDS Criteria for Local Infection

From the wound bed preparation model, a standardized clinical guide was developed for the identification and treatment of local infection (superficial critical colonized wounds). Local infection is defined as a wound surface compartment contaminated with organisms with subtle surface clinical signs of host injury but no significant deep and surrounding tissue damage [13]. The assessment model developed by Sibbald, Ayello, and Woo is a potential criterion for clinical diagnosis of local infection. NERDS is a mnemonic that stands for five clinical signs: nonhealing, increased exudate, red friable granulation tissue, debris, and smell [12]. See Table 5.1 for the defining clinical features of each NERDS clinical criterion. A validation study conducted by Woo and Sibbald [15] concluded that a wound that was positive for at least 3 of the 5 NERDS criteria (73.3% sensitive, 80.5% specific) should be diagnosed as local infection. Clinicians are encouraged to utilize topical antimicrobial agents and antiseptics for the management of these wounds, in order to lower the bacterial count and mitigate the influx of organisms entering the proximal healthy tissue [12].

In contrast, wounds can also be defined as showing signs of deep and surrounding tissue wound infection. A deep and surrounding wound infection is one in which there are significant levels of bacterial burden that has overburdened the host response, and the microorganisms have caused local clinical injury that may invade the deep and surrounding skin below the wound base prior to potential systemic sepsis [16]. Sibbald et al. [12] developed an assessment model using the mnemonic STONEES to diagnose deep wound infection. STONEES stands for 7 clinical signs: size is bigger, temperature increase, os (probes to or exposed bone), new areas of breakdown, erythema/edema, exudate, and smell. If a patient presents with 3 or more of these signs, then they must be treated with systemic antimicrobial agents.

Table 5.1 Definition for NERDS variables [12] (c) Sibbald et al. [14]

Letter	Image and variable	Defining features
N	Nonhealing wound	A wound in a healing trajectory should demonstrate a decreased size of 20–40% after 4 weeks with appropriate treatment. A wound that does not get smaller or increases in size indicates that a proinflammatory environment on the wound surface has prevented adequate wound healing. The wound size is measured by taking measurements of the longest length and the widest width perpendicular to one another.
E	Exudate from the wound base	Increase in wound exudate can be indicative of proinflammatory damage and may lead to periwound maceration. Often more than 50% of the dressing stained with exudate.
R	Red and bleeding wound surface granulation tissue	Presence of a bright red wound bed with exuberant granulation tissue. Tissue bleeds easily on the removed dressing or with gentle manipulation using a sterile instrument. This may be due to VEG-F (vascular endothelial growth factor) often secreted from surrounding surface bacteria.
D	Debris	Presence of discolored granulation tissue, slough, and necrotic/nonviable tissue. Debris is often yellow, brown, or black loose slough. It is the result of surface cell death.
S	Smell or unpleasant odor from the wound	Unpleasant or sweet, sickening, foul odor. Smell is the by-product of the proliferation of gram-negative bacteria and / or anaerobes.

Topical Antimicrobial Dressings

Topical antimicrobial dressings ideally contain antiseptic chemicals that are utilized to either kill or limit the growth of microorganisms found on the wound bed [17]. As mentioned previously, antimicrobial dressings should be used on wounds with superficial critical colonization (i.e., locally infected) and/or to prevent deep and surrounding skin infection in patients that are of increased risk

of wound infection. More specifically, they should be used in wounds that are healable, rather than nonhealable or maintenance wounds. Antimicrobial dressings are placed topically onto the wound bed, where they employ their broad-spectrum, often nonselective antibacterial activity. These dressings work on multiple sites on the microbial cell, significantly reducing the possibility of developing bacterial resistance that can more commonly occur with topical antibiotics. They may also not have the autolytic debridement or moisture-balance properties of antiseptic dressings.

Once antimicrobial therapy has begun, the effect of the dressing on the wound should be continuously monitored. The first review of the wound should be performed 1–2 weeks after a new dressing has been introduced. If the wound bed is not optimized by the dressing or if there is a greater deterioration of the wound, there should be a reassessment of the wound bed. This process will help rule out other causes of wound deterioration or the presence of deep and surrounding infection requiring systemic antimicrobial therapy. If the wound is improving, then it is recommended that the dressing should be continued for 14–28 days, after which the wound is formally assessed again by a healthcare provider [18]. The healthcare provider should recognize two salient points reported in the literature in regard to wound healing trajectories. Firstly, most wounds should establish a healing trajectory within about 4 weeks [19]. Secondly, chronic healable wounds that do not reduce in total area by 30% within 4 weeks of treatment are unlikely to heal by week 12 [20].

It is important that topical antimicrobial dressings not only be used judiciously, but topical antibiotic cream and ointment formulations should be avoided. Mupirocin and fusidic acid both have antimicrobial effects against aerobic gram-positive cocci, but recent reports have shown emerging resistance among staphylococci [21]. More specifically, mupirocin is indicated only for the topical treatment of impetigo and the elimination of nasal colonization with *S. aureus* [21]. Furthermore, fusidic acid is not available in the United States. Inexpensive, over-the-counter minor injury remedies include nonprescription topical antibiotics (e.g., bacitracin, gramicidin, neomycin sulfate, polymyxin B) that are commonly used to prevent deep/surrounding infection. Adverse reactions can occur. For example, bacitracin may cause allergic contact dermatitis and, rarely, anaphylactic reactions. Neomycin in a topical powder formulation is also used in some wound irrigating solutions and can cause systemic toxicity (it is FDA banned in the United States, and a presciption product in Canada), and hypersensitivity reactions have been seen in 1–6% of patients. There have also been reports of hypersensitivity and neurological or renal adverse reactions to polymyxin B [21].

There are currently five broad classes of topical antimicrobial agents used in chronic wounds with superficial critical colonization: polyhexamethylene biguanide (PHMB), ionized silver, slow-release iodine, methylene blue and gentian violet (MB/GV), and honey. Moreover, surfactant-based solutions will be discussed in their relation to treating biofilms. Considerable attention will be given to each agent's chemical structure, formulation, function, and clinical applicability.

Polyhexamethylene Biguanide (PHMB) Topical Dressings

Polyhexamethylene biguanide (PHMB), or polyhexanide, is composed of a synthetic mixture of polymers that resemble antimicrobial peptides (AMPs) when the molecules assembled together. AMPs are low-molecular-weight proteins, created by the immune system that have broad-spectrum antimicrobial activity [22]. PHMB is a positively charged polymer with a hydrophobic backbone and catanionic groups separated by hexamethylene chains [23]. The structure of PHMB confers its ability to bind to the negatively charged bacterial cell wall, disturb the structural integrity of the bacterial cell membrane, and precipitate dissolution of the bacterial cell [23]. PHMB has been formulated in both non-release gauze packing and foam dressings. PHMB gauze packing is best used for a deep exudative wound, whereas PHMB foam dressings are suited for healable surface

wounds with exudate. PHMB has broad-spectrum effects on bacteria, yeast, and viruses.

A recent systematic review was aimed at exploring the effectiveness of PHMB on chronic wounds [24]. The authors concluded that topical PHMB may aid in the healing of chronic nonhealing wounds, lessen bacterial burden, eradicate methicillin-resistant *Staphylococcus aureus* (MRSA), and mitigate wound-related pain. A 4-week randomized controlled trial (RCT) compared the use of PHMB foam against foam alone in 45 patients with chronic wounds. Compared with foam alone, the use of PHMB foam dressing significantly reduced wound superficial bacterial burden and demonstrated greater pain reduction [23].

Ionized Silver-Based Dressings

Due to its broad-spectrum antimicrobial activity, silver use is recommended in chronic wounds with local infection. It is capable of carrying out its antimicrobial effects once ionized. Thus, ionized silver demands an aqueous or water environment in order to carry out its function. Ionized silver has at least 3 antimicrobial mechanisms, as it can target either the cell membrane, cytoplasmic organelles, or DNA, making silver resistance highly uncommon. Ionized silver should not be utilized in maintenance wounds or nonhealable wounds as both should aim for moisture reduction and a dry surface. Furthermore, silver should not be utilized in conjunction with oil-based products (e.g., petrolatum or zinc oxide on the periphery that can creep into the wound bed), as their hydrophobic effects may impede with the ionization of silver by water. There is a wide variety of silver-based dressings to choose from (see Table 5.2) with no single silver product taking precedent over another. The dressing of choice is made based on the level of ionized silver released from the dressing and the appropriate moisture balance in the dressing. Healthcare providers must complement these dressing characteristics with the clinical attributes of the wound bed. A proper matching of dressing to wound bed will help control exudate, prevent periwound maceration, and ensure sustained release of ionized silver onto the wound bed.

Silver-based dressings are typically combined with calcium alginates, hydrofibers, hydrogels, and hydrocolloids. Acticoat, Acticoat 7, and Acticoat Absorbent (Smith & Nephew, Largo, FL) release the highest amount of silver compared to other silver-releasing dressings. Unlike silver sulfadiazine (SSD) cream formulations and silver nitrate, Acticoat does not cause permanent local staining in the dermis (i.e., argyria or blue discoloration of the skin) but can cause temporary stain in the surrounding wound edge. Moderate levels of ionized silver can be obtained by utilizing Contreet Foam (Coloplast Corp, Marietta, GA) or Acticoat Moisture control (Smith & Nephew, Largo, FL). The other silver dressings, seen in Table 5.2, all release low levels of ionized silver, with the exception of Actisorb (Johnson & Johnson, Somerville, NJ) that is non-release formulation.

Silver is capable of acting on a broad spectrum of aerobic, anaerobic, gram-positive, and gram-negative bacteria, in addition to yeast, fungi, and viruses [25–27]. Ionized silver is not utilized systemically, and the dressings have low cytotoxicity, making silver a suitable mode of treatment of wounds with increased bacterial growth in the superficial compartment [10]. Sibbald et al. [28] established that silver dressings do not reverse the impaired healing response in the deep compartment or usually treat the increased bacterial burden in the deep compartment. Systemic agents should be used for deep and surrounding infection. Furthermore, compared to other bacterial organisms, wounds locally infected with pseudomonas require greater concentrations of silver ion release in order to reduce the concentration of pseudomonas on the wound surface.

Moreover, in a meta-analysis of the efficacy of silver-releasing dressings in the management of nonhealing chronic wounds, compared to alternative wound management approaches, silver dressings significantly improved the wound healing rate, reduced odor, reduced pain-related symptoms, decreased wound exudate, and had a prolonged dressing wear time [29]. The data in

Table 5.2 Silver preparations used in wound management [12] (c) Sibbald et al. [14]

Preparation	Delivery mechanism	Product name	Benefits	Considerations
Nanocrystalline silver (NCS)				
Bilayered: NCS-coated fabric with absorptive core	Silver on 2 rayon fabric outer layers with a vicryl absorptive core or central layer	Acticoat burn (Smith & Nephew, Largo, FL) (+++)	High level of released silver in nanocrystalline clusters allows maximal antimicrobial action, with sustained release up to 72 hours Indicated for burns and chronic wounds Anti-inflammatory	Should be used with water, not saline compresses. Dressing is activated by soaking in water prior to application. May burn on contact with wound (put blue rather than silver side down and soak for a longer period in water prior to application). Temporary staining of wound edge keratin can be removed with debridement and is not associated with permanent silver deposits in the dermis (argyria). Secondary dressing is required. Do not use with petrolatum or zinc oxide products.
3 layered: NCS-coated fabric with 2 absorptive cores	Silver on 3 rayon fabric outer and middle layers with 2 vicryl absorptive cores between the silver layers	Acticoat 7 (Smith & Nephew, Largo, FL) (+++)	Sustained release of bactericidal concentrations of silver over 7 days Useful under compression therapy in venous ulcers	May provide higher initial release of silver compared with other dressings in this class. Sustained release of silver in the ionized form from the nanocrystalline structures can decrease bacterial burden in the deep wound compartment, but systemic antimicrobials are still recommended for deep tissue infection. This dressing under compression for 1 week has also exhibited an anti-inflammatory action in persons with venous ulcers and has stalled or delayed healing. Secondary dressing may not be required if wrapped under compression.
NCS-coated calcium alginate	NCS-coated calcium alginate	Acticoat Absorbent (Smith & Nephew, Largo, FL) (+++).	For moderate to highly exudating chronic wounds and post debridement Provides rapid and high fluid absorption Antimicrobial activity and silver release related to biodegrading of alginate fiber Hemostasis Autolytic debridement	Potential for staining the wound. May burn on application 8. Can form a hard crust on the wound. Surface of the wound becomes less exudative.
NCS-coated foam	Foam dressing with nanocrystalline silver	Acticoat Moisture Control (Smith & Nephew, Largo, FL) (++)	Provides absorptive polyurethane foam and silver ions	Foam may cause maceration of the surrounding normal skin; protect with film-forming liquid acrylate or cut the dressing to the wound size. Secondary dressing is required.

Silver salt-containing foam	Ionized silver in a foam dressing	Contreet Foam (Coloplast, Marietta, GA) (++), Optifoam Ag (Medline Industries)	Provides bacterial balance in a foam dressing Second-generation foam that allows partial fluid lock High absorption	Similar to all foams may give back moisture, leading to irritation and potential maceration of the surrounding skin (may need to protect surrounding skin with barrier such as film-forming liquid acrylate) (Cavilon: No Sting Barrier, 3M).
Silver salts				
Silver amorphous hydrogel	Silver chloride in an amorphous hydrogel	SilvaSorb Gel (Medline Industries, Mundelein, IL) (+)	Low cytotoxicity. Broad-spectrum antimicrobial that delivers time-released silver for 3 days	Needs secondary dressing. Limited absorption of exudate. Does not 'melt', so the product stays in place and provides autolytic debridement.
Silver sodium chloride polyacrylate sheets	Silver chloride in hydrogel sheets	SilvaSorb Sheet, Perforated Cavity (Medline industries) (+)	Low cytotoxicity Broad-spectrum antimicrobial that delivers time-released silver for up to 7 days Donates moisture or absorbs up to 5 times its weight in exudate for superficial wounds with limited exudate, but exudate absorption can be increased with alginate pad	Absorbs slowly for low to moderately exuding wounds. Good for superficial wounds to maintain bacterial balance with autolytic debridement.
Silver-calcium-sodium phosphates F film +/− Alginate pad	Co-extruded silver-calcium silver-phosphate polymer matrix (film)	Arglaes Film, Arglaes Island (Medline Industries) (+)	Residual antimicrobial activity lasts up to 7 days.	Limited absorption of fluid for film version. Good absorption for island version with calcium alginate pad. If fluid accumulates under the dressing or if wound strikethrough occurs then changing to an alternative dressing would be indicated.
Silver chloride site disc	Polyacrylate with silver chloride	SilvaSorb Site (Medline Industries) (+)	Protection for vascular and nonvascular percutaneous sites. Delivers for 7 days Translucent, flexible, low profile	Not self-adhesive, and as with other site dressings, needs a secondary adhesive product for securement.
Silver chloride and calcium alginate powder	Polymer silver chloride in alginate powder	Arglaes Powder (Medline Industries) (+)	Low cytotoxicity silver Antimicrobial activity up to 5 days with fluid management virtually any size, shape or depth of wound managed easily with this product	Needs a secondary dressing for coverage. Allows flexibility to apply silver under ostomy sites and other dressings with limited interference with adhesive.

(continued)

Table 5.2 (continued)

Preparation	Delivery mechanism	Product name	Benefits	Considerations
Silver calcium alginate/ carboxymethylcellulose dressing	Silver-impregnated calcium alginate rope or wafer	Maxorb Extra Ag (sheet or rope) (Medline Industries) (+)	Low-cytotoxicity silver Delivers silver for 4 days for superior absorption and fluid handling, vertical wicking, and one-piece removal May facilitate hemostasis and autolytic debridement	Product not differentiated by color from non-silver alginate due to low level of silver incorporated (1%). Bioresorbable and may need to have dressing changed with loss of alginate fiber; if retained fiber at dressing changed, exudate levels may be inadequate and another dressing may be more appropriate for maximal silver delivery.
Silver hydrofiber	Sodium−/silver-impregnated on a carboxymethylcellulose wafer dressing	Aquacel Ag (ConvaTec, Skillman, NJ) (+)	1.2% ionic silver released via ion exchange Provides fluid lock to prevent excess wound fluid from macerating surrounding skin Good vertical wicking May improve periwound maceration	Nonresorbable fiber that needs to be removed with dressing change. Low level of silver release.
Silver salt combined with hydrocolloid	Ionized silver in a hydrocolloid base	Contreet-HC (Coloplast) (+)	Provides odor control under hydrocolloid dressing	Low to moderate fluid absorption with a low level of ionized silver delivered from the dressing dependent on the absorption of exudate.
Silver nitrate	0.5% solution or sticks	Silver nitrate solution or sticks	Easy to use High cytotoxicity	Staining, can produce local argyria. May lead to electrolyte imbalance if large quantities are used, short half-life.
Silver sulfadiazine	1% in carrier cream	Silvadene (Monarch Pharmaceuticals, Bristol, TN) Flamazine (Smith & Nephew Lachine, Quebec, Canada) (+)	Easily available Wide clinical acceptance, though there are a few controlled studies Higher release of metallic silver and a lower relative concentration of ionized silver compared with some of the new ionized silver dressings	Cytotoxic (in vitro) and not to be used if sulfa allergy. Tends to leave heavy deposits of foreign matter (termed a pseudoeschar) in the wound bed: can be painful to remove. Temporary staining of marginal keratin known to occur but also occasional reports of argyria or permanent dermal deposits rare neutropenia. May need a secondary dressing, especially as product tends to "melt" because of cream base. Short half-life.
Metallic silver				
Silver charcoal	Charcoal and silver contained in a dressing	Actisorb (Johnson & Johnson, Somerville, NJ) (0)	Silver kills organisms, which are trapped onto the charcoal Deodorizing properties as odor molecules bind to charcoal Also traps endotoxins	Poor absorption properties. Product cannot be cut as charcoal particles will leak out. Silver particles are not released from the dressing.

Table 5.2 is arranged in order of the amount and sustained release of ionized silver to least effective.

Iodine-Based Dressings

Iodine is a natural, dark violet, nonmetallic element that is vital for thyroid hormone production. Its broad-spectrum antimicrobial activity is not completely understood. It is thought to be performed through several mechanisms including obstructing bacterial cell efflux pumps, restraining cellular respiratory processes, altering the structural integrity of DNA, inhibiting hydrogen bonding, and denaturing cellular enzymes and proteins [13]. Elemental iodine is associated with displeasing side effects including pain, irritation, and staining of the skin. Iodophors were manufactured in the 1950s to circumvent these side effects. Iodophors are preparations that deliver iodine slowly, safely, and with less pain to the body [30]. There are two commonly used wound dressing iodophors: povidone-iodine (PVP-I) and cadexomer iodine.

PVP-I is a complex chemical composed of povidone, hydrogen iodide, and elemental iodine. It can be applied through a variety of vehicles including slow-release dressings (Inadine), 7.5–10% solution formats, creams, ointments, and sprays [13]. Inadine is a 10% PVP-I dressing with an equivalent of 1% available iodine on a tulle dressing consisting of a knitted viscose fabric with a polyethylene glycol base [31]. Inadine works by releasing iodine at a rate proportional to the amount of exudate present. As exudate is absorbed by the dressing, iodine is slowly released onto the wound surface allowing for it to perform its antimicrobial action.

Cadexomer iodine is a water-soluble, absorptive starch polysaccharide that contains iodine. Cadexomer iodine is capable of absorbing exudate and five to seven times its weight in water. Similar to Inadine, as the dressing becomes moist with pus and debris, it slowly releases iodine onto the wound bed, having a dual function of autolytic debridement and bacteriocidal action [31]. Cadexomer iodine has been shown to be an effective treatment agent to inhibit the proliferation of MRSA in wounds [32].

The use of iodine in wound management is a contentious one. Despite having highly efficacious antimicrobial effects with a broad-spectrum activity, iodine is perceived to delay wound healing and have cytotoxic effects [33]. Two reviews have concluded that iodine's cytotoxic effects are limited to animal wound models, whereas human wound studies posit that PVP-I helps speed up the wound healing process by decreasing the bacterial load and the infection rates [34, 35]. PVP-I has been shown to improve the healing rates in patients with chronic venous leg ulcers and lack cytotoxicity in vivo [36]. Cadexomer iodine has also been shown to be effective in reducing signs and symptoms of local infection (i.e., exudate, erythema, edema, and pain) in patients with pressure ulcers [37] and venous leg ulcers [38]. Consensus agreement from experts supports the use of Inadine dressings on healable, nonhealable, and maintenance wounds with local infection [31].

When applied to the skin, the iodine dressing will release the iodine on the surface of the wound often with this exchange being facilitated with wound exudate. This will stain the surface of the skin brown-orange, while the dressing will turn from brown-orange to white when the iodine is depleted from the dressing. The staining on the skin however is harmless and will fade rapidly. Despite current iodine dressings providing a slow release of iodine, it is only for a relatively short period of time. Healthcare providers must frequently change the dressings to maintain a constant supply of iodine to the wound surface. Once the iodine dressing has lost its color (i.e., go from brown-orange to white), the antiseptic effect has been depleted and the dressing should then be changed [33]. Wounds with high levels of exudate should have their dressings changed daily. Furthermore, if there are lower moisture levels on the wound, then the iodine dressing can be replaced 1–3 times per week.

Iodine dressings should be used cautiously in patients with thyroid disease [39]. Patients' thyroid function should be monitored with medical supervision for an extended period of time if a

large wound area is being treated by iodine dressings. Treatment with iodine dressings should be re-evaluated continually and be discontinued should there be signs that the local infection is resolving and the wound is healing, or if the wound does not improve in 10–14 days. In the latter case, an alternative antiseptic or systemic antibiotic treatment for untreated deep and surrounding infection should be considered.

Methylene Blue and Gentian Violet Foam Dressings

Methylene blue and gentian violet are two non-cytotoxic antimicrobial dyes that are affixed with polyvinyl alcohol (PVA) foam (Hydrofera Blue, LLC, Willimantic, Connecticut). This dressing was approved by the Food and Drug Administration (FDA) and has been available to use since 2003. Unlike topical antimicrobials that release agents into the wound bed, such as iodine-impregnated or silver-impregnated dressings that cause localized burning sensation, the antibacterial effect occurs within this dressing as a non-release formulation [40]. The two antibacterial entities affixed to the dressing will bind directly with the bacterial products (e.g., endotoxins), which can help limit patient unease [40]. Methylene blue and gentian violet work by dysregulating the redox environment within the cell, alternating the tightly regulated oxidative and reductive processes necessary to keep the growth of the bacteria [41]. Before it can be used, Hydrofera Blue (polyvinyl alcohol format, not the polyurethane format) must be hydrated with either sterile saline or water and then squeezed out to remove excess water. Then it can be applied to the wound bed with a relevant secondary dressing depending on the quantity of exudate present.

The PVA dressing's physical structure is an interconnected open cell foam. This gives rise to superb wicking, moisture retention, and excellent exudation absorption. Hydrofera Blue has been shown to be effective against microbes such as MRSA and vancomycin-resistant *enterococci* (VRE) [42]. Hydrofera Blue has been shown to be compatible with the debriding enzyme *Clostridium* collagenase [43]. It also does not appear to inhibit fibroblast growth factor (FGF) activity [44]. One case series by Coutts et al. [40] established that Hydrofera Blue is an acceptable dressing to use for lower leg-chronic wounds with increased superficial bacterial burden. Moreover, the polyvinyl alcohol format provides autolytic debridement. A second case series by Woo and Heil [45] concluded that Hydrofera Blue is effective in progressing wounds toward healing and reducing clinical signs and symptoms of local wound infection.

Honey Dressings

Honey is a natural, viscous, concentrated sugar solution obtained from nectar collected and modified by the honeybee, *Apis mellifera* [46]. It is a carbohydrate-rich syrup composed of approximately 30% glucose, 40% fructose, 5% sucrose, 20% water, and other substances including amino acids, vitamins, minerals, and enzymes [47]. Honey has been utilized in wound treatment since antiquity for its antibacterial, anti-inflammatory, and antioxidant features. The antibacterial effects of honey arise from its acidity (pH 3.2–4.5), osmolarity (i.e., from its high sugar content), its ability to release hydrogen peroxide, nutritional and antioxidant content, stimulation of humoral immunity, and other unidentified compounds [48].

A recent Cochrane Collaboration conducted a systematic review on the effects of honey on minor acute wounds and chronic wounds [46]. The results of this study concluded that honey dressings may improve the healing times of superficial and partial thickness burns compared to conventional dressings and that honey may be more effective than antiseptic followed by gauze for healing infected postoperative wounds. It is unclear if honey dressings are superior or substandard to conventional dressings for the treatment of venous leg ulcers, minor acute wounds, pressure ulcers, diabetic foot ulcers, leishmaniasis, Fournier's gangrene, and mixed chronic wounds. The authors of this study concluded that it is problematic to extract a clear

conclusion on the wound effects of honey dressings due to the diverse patient populations studied and the largely low- or very low-quality evidence that is available. Therefore, there is insufficient evidence to support the routine use of honey in clinical practice.

Surfactants and Biofilms

Healthcare providers can reasonably suspect the presence of a biofilm on the wound bed if there is failure for the wound to heal despite optimal standard care and/or the wound bed is not responding as expected to either the topical or systemic antimicrobial interventions [49]. Biofilms are treated primarily with surgical and sharp debridement of the necrotic, devitalized tissue. Should surgical debridement not be an option, due to various patient-related or clinical reasons, it is recommended that topical surfactant-based wound cleansing solutions be used. These agents work by decreasing the surface tension between a liquid and the solid surface, allowing for fluids and antimicrobial agents to penetrate between the biofilm and the wound surface interfering with the ability of the biofilm to adhere to the wound surface [50]. Surfactants containing propylbetaine-polyhexanide (betaine) solution, PHMB, or poloxamer 188 have been used to aid in wound cleansing and autolytic debridement and facilitate wound closure at the cellular level [50, 51].

Topical Antiseptic Agents

Topical antiseptic agents are utilized by clinicians in wounds that do not have the ability to heal (i.e., nonhealable wound) or in a maintenance wound. Antiseptics are used for wound cleansing. This is done to advance wound healing, increased comfort with adherent dressing removal, and potential for rehydration of the wound bed [52]. Solutions that are recommended for wound cleansing should be those that are gentle to the skin and noncytotoxic to the wound. Refer to Table 5.3 for a list of antiseptic agents listed by increasing cytotoxicity.

Table 5.3 Effects of topical antiseptic agents listed by increasing cytotoxicity [52] (c) Sibbald et al. [14]

Antiseptic agent	Effects
Saline/sterile water	No antibacterial effects/ low toxicity
Chlorohexidine, PHMB	Broad spectrum/low toxicity (but avoid chlorhexidine contact with the eyes or ears)
Povidone-iodine (PVP-I)	Broad spectrum/low toxicity
Acetic acid (0.5–1%)	Effective against *Pseudomonas* and other organisms, especially gram-negatives
Dyes: scarlet red, proflavine	Effective against gram-positive bacteria, ineffective against gram-negative bacteria
Sodium hypochlorite: Dakin's EUSOL (Edinburgh University Solution of Lime)	Toxic to granulation tissue
Hydrogen peroxide	Effective only when it is effervescent
Quaternary ammonia: Cetrimide	Very high toxicity

Irrigation may be important to decrease the bacterial burden of the wound and clear any loose debris and is recommended to be a part of routine wound management [53]. A Cochrane review noted that there is very low evidence for the effectiveness of wound irrigation and vigorous procedures may cause more damage to the wound surface than the benefit achieved especially if bleeding, trauma, and pain result from the procedure [54].

Isotonic (normal) saline and sterile water are widely used as irrigating and wound dressing solutions. They are both compatible with human tissue. Furthermore, neither causes damage to new tissue, nor do they affect the functioning of fibroblasts and keratinocytes in the wound healing process [55]. There are no statistically significant differences in the infection rate for potable tap water (safe drinking water) compared to saline for cleansing acute wounds [56]. However, potable (drinkable) tap water is recommended in situations where saline and sterile water are not available. This is primarily because microbes,

including pseudomonas aeruginosa, have been reported to colonize the plumbing systems within healthcare facilities. Wounds irrigated with tap water may be exposed to this microbe inadvertently [57]. Moreover, tap water may not be appropriate for deep wounds or in patients with immunosuppression.

Chlorhexidine, a biguanide, is a commonly used antiseptic agent that has low toxic effects on granulation cells and high antimicrobial activity against gram-positive and gram-negative bacteria [55]. It does not account for all microbial infections, as it does allow for the growth of *Pseudomonas aeruginosa* and *Proteus mirabilis* [55]. Chlorhexidine is commonly used as surgical wound irrigation, hand washing, perioperative mouthwash formulations in patients receiving dental implants, and in antiseptic dressings [13]. It is able to exert its antimicrobial effects by disrupting both the inner and outer bacterial cell membranes, causing cell leakage and disruption of the membrane potential vital for ATP generation [58]. If this agent is used, it is important to recognize that it should not come in contact with the eyes, the middle ear, or meninges [59].

Similar to chlorhexidine, povidone-iodine has broad-spectrum antimicrobial activity and has low cytotoxic potential. The high iodine in PVP-I concentration may cause an irritating stinging or burning sensation and thus should be applied with discretion on sizeable wounds [31]. Furthermore, PVP-I may interfere with thyroid gland function in patients with thyroid disease due to the possibility of excess iodine absorption [31].

Lowering the wound surface pH can have an antibacterial effect. Hypochlorous acid is effective against pseudomonas and other gram-negative bacteria that thrive in alkaline environments. Pseudomonas is associated with a green colored exudate and sickeningly sweet odor. Some wound clinics have hypochlorous acid generators with 0.5–5.0% concentrations that are used as a soak or compress, typically for 5–10 minutes after dressing removal. Most gram-positive and gram-negative bacteria including pseudomonas grow best in an alkaline environment, and by lowering the surface pH of wounds, the acid pH inhibits their growth [13].

Since acetic acid does have considerable tissue cytotoxic effects, it is recommended that it be used in the short term when the bacterial colonization of the wound takes greater precedence than tissue toxicity. Dilute acetic acid can be formulated by diluting white vinegar (5%) with potable water. A 0.5–1% dilution is usually applied in a soak or compress.

There are other antiseptic agents available including dyes (e.g., scarlet red, proflavine), sodium hypochlorite (Dakin's, EUSOL), hydrogen peroxide, and quaternary ammonia compounds. However, none of these agents are recommended for use in chronic wounds as they are very high in tissue toxicity. Dyes such as scarlet red and proflavine are more active against gram-positive than gram-negative bacteria. Sodium hypochlorite (bleach) is commonly used on the surface of objects and work stations to eliminate bacterial contamination. Bleach is also formulated as Dakin solution or Edinburgh University Solution of Lime (EUSOL). Hydrogen peroxide has a limited period of antimicrobial activity on the skin surface. Bacteria contain an enzyme known as catalase. When the bacterial cell wall is damaged, and catalase is released, it interacts with the hydrogen peroxide converting it into water and oxygen. The effervescent (i.e., fizzing) that is seen on the wound bed is the indication of active hydrogen peroxide creating bubbles of oxygen gas. However, air emboli has been provoked in hydrogen peroxide used in deep cavities [60]. This is why hydrogen peroxide is not suitable for routine wound irrigation. Finally, although quaternary ammonia compounds have broad-spectrum antibacterial activity, they also have very high levels of tissue cytotoxicity. Its use in wound management is also not recommended.

Moisture-Balance Dressings

Achieving adequate moisture balance is another component of the wound bed paradigm that deserves special attention. It is important for healable wounds to be sufficiently moist to

encourage new tissue growth and enhance wound healing. Should the wound be excessively or insufficiently moist, wound healing will be impaired and the wounds may deteriorate and even enlarge [52]. Furthermore, failure to grow healthy new skin makes the wound susceptible for bacterial colonization and infection [52]. Minimal moisture levels in the wound bed environment may promote wound desiccation and formation of necrosis and eschar, all of which are impediments to wound closure and proper wound healing [61]. Moisture-balance dressings are often used in conjunction with antimicrobial dressings (previously discussed), in healable wounds depending on the clinical features of the wound. There are a variety of moisture-balance dressings to choose from (see Table 5.4). The following section will go into describing each moisture-balance dressing with respect to their chemical composition, function, and clinical applicability.

Table 5.4 Modern moisture-based dressing categories ordered by increasing absorbency [52]

Modern dressing category	Comments	Average wear time
Hydrogels	Contain 70%–90% moisture Donates moisture to the wound Bioresorbable Can be combined with silver, iodine (cadexomer) for antimicrobial action	1–3 days
Films	Protective layer Does not donate or absorb a large amount of exudate	3–7 days
Hydrocolloids	Water-binding and water-repelling components Will absorb small to moderate amount of moisture	2–7 days
Hydrofibers	Bind small to moderate amount of exudate Fluid lock, nonbioresorbable Can be combined with silver for antimicrobial action	1–3 days
Calcium alginates	Absorb small to moderate amounts of exudate onto outer surface of dressing Fibers are bioresorbable, releasing calcium (hemostasis property) and resorbing sodium to form a hydrogel with exudate fluid Can be combined with silver and honey for antibacterial action	1–3 days
Foams	Absorb moderate amounts of exudate Fluid balance with the dressing giving back some exudate that prevents wound surface from dehydrating Can be a method of delivering an antibacterial agent (silver) or containing a nonrelease antibacterial agent for antibacterial action above the wound surface (PHMB, methylene blue/gentian violet)	2–7 days
Superabsorbents	Absorb a larger amount of exudate Fluid lock technology equivalent to diapers	1–3 days

Hydrogels

Hydrogel dressings are developed from a semi-occlusive, three-dimensional cross-linked network of hydrophilic polymers (i.e., polyvinyl pyrrolidine, polyacrylamide, or polyethylene oxide) [62]. They are capable of absorbing large amounts of water while holding onto their structure as a result of the physical cross-linking of the polymer chains. Hydrogels are composed predominantly of water (70–90%), are able to hydrate a dry wound rapidly, and allow for the dressing material to adhere to the wound surface. All hydrogels are semitransparent, providing the healthcare provider the

opportunity to inspect the wound continuously without removing the dressing.

There are three types of hydrogels, each varying in physical and chemical properties: amorphous (most common), wafer, and impregnated gauze. There is no significant difference in the efficacy of the dressing subtypes in the treatment of chronic wounds. Hydrogels are capable of facilitating autolytic debridement of necrotic wound tissue, by preserving a moist environment. Hydrogels are indicated for wounds that are dry, wounds that are sloughy with mild exudate, and partial thickness wounds. They have also been shown to provide a cooling/soothing effect [61, 63]. Hydrogels are contraindicated in patients with ischemic ulcers [64]. Furthermore, the hydrogel sheets must usually be cut into the exact size of the wound, in order to prevent potential maceration of the periwound skin.

Films

Film dressings are composed of a transparent, polyurethane, or synthetic polymer sheet with either adhesive or nonadhesive coating on one side. Adhesive films have an adhesive coating on the wound side and are often onerous to apply. Film dressings have no capacity to absorb wound exudate and cannot hold onto moisture. These films are semipermeable, allowing water vapor and oxygen to permeate through the dressing, but are impermeable to water and microorganisms. It is possible for fluid to accumulate under the dressing, as a result of excessive production of wound exudate. This can give rise to an alkaline environment on the surface of the wound bed and cause superficial critical colonization. Therefore, the dressing must be replaced if the adhesive bond is undermined. Furthermore, adhesive films have been shown to be associated with increased rates of infection [65]. They should be utilized with caution in cases of suspected wound infection.

Film dressings are indicated to cover intravenous catheter sites and partial-thickness wounds [66, 67]. Moreover, they are used for wounds that are in their late re-epithelization stage or used to insulate wounds that have recently healed. Film dressings are capable of providing an additional layer of protection to the wound bed.

Hydrocolloids

Hydrocolloid dressings consist of an inner hydrocolloid gelling agent (containing carboxymethylcellulose, CMC) combined with pectin, an inner adhesive layer, and an outer water-resistant coating (e.g., polyurethane). When in contact with wound exudate, the hydrocolloid gelling agent will absorb the moisture and form a gel, creating a moist environment for the wound bed. The more moisture the hydrocolloid dressing absorbs, the more water permeable it becomes. This allows hydrocolloids to effectivity manage wound exudate.

The inner adhesive layer may be composed of a hydrogenated rosin ester under the trademark Pentalyn H. This is a common allergen that patients with chronic wounds may have a cross-reactivity to colophony [68]. Patients may experience allergic contact dermatitis as a result. Hydrocolloids may melt to different degrees when exposed to wound exudate, leaving a skin surface residue. Moreover, the gelling component of hydrocolloid dressings can incorrectly cause clinical suspicion of infection due to its foul odor and appearance [62]. Since the hydrocolloid film is impermeable to gases and water vapor, the wound may become overhydrated and result in periwound maceration [69].

Hydrocolloids may be indicated for venous ulcers, decubitus ulcers, burns, partial-thickness wounds, and diabetic foot ulcers. Furthermore, hydrocolloid gels are useful for autolytic debridement due to its hydrating properties and also due to the endogenous enzymes present within the gelling layer [70]. When used for this purpose, it is important to change the dressing more frequently. Hydrocolloid dressings are contraindicated in wounds that are ischemic, have deep and surrounding infection, or are associated with active vasculitis [52, 71]. The dressing can adhere to the wound bed, be difficult to remove, and potentially damage fragile skin upon removal.

Hydrofibers

Hydrofiber dressing, manufactured in either ropes or sheets, consists of highly absorbent CMC that spun into a fiber structure. Hydrofiber dressing is very hydrophilic and can absorb fluid and exudate, bounding it within the interior of the fiber structure (moisture retention). As the fluid is absorbed, the hydrofiber dressing will remodel into a clear, soft gel. These dressings are known to have low to moderate levels of absorbency.

Hydrofiber dressings are indicated for wounds with moderate to heavy exudate and partial- and full-thickness cavernous wounds with increased bacterial burden. It is contraindicated for dry or nonexudating wounds [61]. The fiber dressing has good tensile strength, allowing it to be removed easily in pieces and packed loosely into wounds. This dressing is not adhesive to the skin, since adhesion would impede its ability to absorb fluid. Therefore, a secondary dressing or hypoallergenic tape is necessary to keep hydrofiber dressing in place.

Calcium Alginates

Calcium alginate dressings are nonwoven biodegradable sheets (lateral fluid wicking) or ropes (vertical fluid wicking) of calcium sodium alginate polysaccharide (kelp or seaweed derivative). When the calcium in the dressing binds to the fluid in wound exudate, the calcium ion is displaced onto the wound surface, in exchange for a sodium ion to the dressing. This reaction creates a sodium alginate gel with the ability to absorb moisture of up to 20 times its weight in fluid. The dressing also has autolytic debridement potential [52].

The gel consists of units of mannuronic acid and guluronic acid, both of which determine the physical properties of the dressing. The higher the levels of mannuronic acid, the more gelling that will occur, in contrast to increased levels of guluronic acid improving fiber strength for packing. The calcium in the dressing is also useful homeostasis, as it is a component of the coagulation cascade. The calcium in the gel can be helpful in stopping bloody exudate post debridement. Calcium alginate dressings with potentiating effect on postthrombotic coagulation and platelet activation are those that contain zinc ions [72].

Calcium alginate dressings are nonadherent, a property that they share with hydrocolloids and hydrogels. They need a secondary dressing or hypoallergenic tape to hold the dressing in place. Moreover, when the dressing is hydrated with wound exudate and fluid, the gel well becomes malodorous and appears as though it is infected until the wound surface is cleansed. If there are dry, undissolved fibers remaining after dressing removal, this indicates minimal wound bed exudate that should prompt the clinician to change to a water-donating hydrogel or hydrocolloid dressing [52].

Foams

Foam dressings are composed of a bilaminate structure of a hydrophilic, semiocclusive outer layer and a porous polyurethane center. Foam dressings are high in absorbency, may be high in moisture vapor permeability, and have long wear times compared to other dressings. The hydrophilic outer surface of the dressing may become too drying on wounds with minimal to mild exudate, which may require the use of a saline soak prior to dressing removal, in order to decrease the trauma and potential pain associated with dressing change [73]. Foam dressings can be made with or without adhesives. Silicone adhesives compared to acrylate formulations cause less pain on dressing removal. The foam also provides a layer of thermal insulation not obtained with other dressings. They can also be easily cut to appropriately match the shape of the wound and be utilized in deeper cavities. Since foam dressings are opaque, continuous monitoring of the wound bed cannot be performed without dressing removal. Foam dressings are indicated in venous ulcers with exudate and deep cavity wounds. They are contraindicated in dry wounds, with minimal or no absorbable moisture.

Superabsorbents

Abundant quantity of exudate on the wound bed has impaired patient quality of life, caused severe discomfort, promoted social isolation, and caused complications including maceration and excoriation of the periwound skin [74]. Superabsorbent polymer dressings are dressings that are used for highly exudative wounds [75]. These dressings contain superabsorbent, polyacrylate particles that can retain a large amount of water and exudate within the dressing core, without the fluid leaking out back onto the wound (fluid lock), avoiding periwound maceration [76, 77]. The top layer of the dressing is composed of a nonwoven polypropylene layer, which also prevents the fluid from leaking out onto the skin. They are manufactured predominantly from acrylic acid and undergo suspension polymerization or cross-linking. This superabsorber has a high density of ionic charges that provides it with hydroactive properties and protein-binding capacity [77]. Superabsorbent polymers have also been used in personal hygiene products including diapers, feminine hygiene products, and adult incontinence products [78].

Summary

All healable wounds need moisture-balance or moisture reduction dressings. Local infection is an indication for antiseptic dressings or topical antiseptic agents for moisture reduction in maintenance or nonhealable wounds. Local wound care is futile unless the patient as a whole has been addressed with the treatment of the cause and management of patient-centered concerns as outlined in the wound bed preparation paradigm.

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Topical Anti-inflammatory Agents in Wound Care

6

Andrea Chiricozzi and Marco Romanelli

Introduction

Inflammation constitutes a crucial phase in the wound healing process. The inflammatory response occurring at the injured site is characterized by a marked infiltration of neutrophils, macrophages, and T cells. In particular, macrophages play a critical role in the inflammatory phase of tissue repair, because of their dynamic plasticity that allows these cells to mediate both tissue-destructive and tissue-reparative functions [1]. Thereby, they result relevant both for initiation and resolution of inflammation during the wound healing process. During the early inflammatory phase, macrophages are differentiated in M1 subtype, owing phagocytosis activity, scavenging, as well as the production of pro-inflammatory mediators that contribute to the healing process in response to pathogen-associated molecular patterns (PAMPs) expressed by microbes and danger-associated molecular patterns (DAMPs) produced by stressed cells. They help in removing damaged tissue and preserving from infections.

Subsequently, within the regenerative phase, macrophage phenotype is predominantly oriented toward the M2 subtype which downregulates inflammation and promotes fibroblast proliferation, collagen tissue deposition, extracellular matrix synthesis, and neoangiogenesis [2–4]. The cross talk among immune cells and tissue cells is regulated by cytokines, chemokines, and other mediators. The acute inflammatory response is crucial to promote the healing process as it anticipates and triggers the subsequent proliferative phase, once the resolution of inflammation is obtained. In physiological pro-healing conditions, neutrophils and macrophages reached the injured site through the interactions with endothelial cells mediated by adhesion molecules such as selectins, integrins, and adhesion molecules of the immunoglobulin family (intercellular adhesion molecule-1 [ICAM-1] and vascular cell adhesion molecule-1 [VCAM-1]) [5]. Inflammatory-induced tissue damage occurs through the release of proteases, cytokines, and other neutrophil- and macrophage-derived factors [6, 7], including reactive oxygen species (ROS), collagenases, elastases, matrix metalloproteinases (MMPs), and antimicrobial proteases (cathepsins, defensins, lactoferrin, and lysozyme) having protective function against pathogenic microorganisms [8]. Other mediators, such as

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A. Alavi, H. I. Maibach (eds.), *Local Wound Care for Dermatologists*, Updates in Clinical Dermatology, https://doi.org/10.1007/978-3-030-28872-3_6

tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, IL-6, IL-17A, and IL-22, derived from both immune and tissue cells sustain pro-healing inflammation, and their activity is balanced by other cytokines limiting the inflammatory response (i.e., IL-10); favoring the repairing process, such as IL-4 and IL-13, which drive macrophage differentiation into the pro-healing M2 phenotype; and stimulating keratinocyte migration and re-epithelization (i.e., the IL-20 family cytokines, namely, IL-19, IL-20, IL-22, and IL-24). The imbalance of the cytokine expression profile or the altered cell activity including the pathological effects of PMNs sustains chronic inflammation and contributes to extracellular matrix degradation, causing detrimental effects and nonhealing conditions. The exaggerated neutrophil migration and activation could generate reactive oxygen species (ROS) and proteases production, causing extracellular matrix degradation, impaired collagen deposition, and delayed re-epithelialization [6, 9]. The excessive inflammation in early wound healing phases may portend poorer clinical outcomes as suggested by higher IL-1β, IL-8, and MMP-9 levels in wound fluid associated with postoperative complications [10]. Along these lines, the altered expression of one of the abovementioned cytokines may be responsible of an impaired healing process leading to chronic ulceration. Various mice models and ex vivo evidence obtained from patients with chronic ulcers support the crucial role of cytokines in mediating signaling pathways involved in the healing process. Increased levels of TNF-α are detected in nonhealing chronic venous leg ulcers [11, 12]. TNF-α inhibits collagen deposition and stimulates extracellular matrix degradation inducing MMPs expression in in vitro keratinocytes [13, 14]. Its capability in inhibiting collagen synthesis has been proved in a nonhealing ulcer mouse model knockout for secretory leukocyte protease inhibitor (SLPI) gene [12]. In this model the severe wound healing impairment and excessive inflammation, mediated by an elevated TNFα expression, improve after topical application of anti-TNFα neutralizing antibodies, blunting leukocyte recruitment and NFκB activation, re-establishing the balance between M1 and M2 macrophages, enhancing matrix synthesis, and accelerating wound healing.

This observation is in line with other evidences showing beneficial effects of TNFα blockade in treating human refractory chronic wounds [15, 16]. IFNγ is another pro-inflammatory cytokine that inhibits wound healing in vivo and in vitro, reducing collagen synthesis and granulation tissue formation [17, 18]. IFNγ-deficient mice compared to wild-type ameliorates chronic wound lesions, obtaining a more rapid resolution, and similarly, wild-type mice treated with an anti-IFNγ more rapidly heal its skin wounds as compared to control IgG-treated wild type [19].

Likewise, the excessive expression of other pro-inflammatory cytokines, namely, IL-1 and IL-17A, is detected in nonhealing condition, and their absence, normalization, or inhibition in various mouse models shows an improvement of the repairing process [20, 21]. Conversely, for those cytokines whose activity promotes wound healing, in vitro and mouse model-based studies suggest that in chronic nonhealing conditions, their enhanced expression may favor the healing process. Particularly, IL-22 stimulates re-epithelization, AMP production against potential wound-delaying infectious agents, neoangiogenesis, and wound bed formation [20, 22–24]. The other cytokines belonging to the same cytokine family act in line, and potentially in synergism, with IL-22 [25–27]. IL-20 and IL-24 activity is reported to be predominantly pro-proliferative, inducing keratinocyte proliferation and, thus, epidermal hyperplasia [28–31]. A differential activity is related to IL-19 that owns anti-inflammatory effects, driving M2 macrophage and favoring a Th2 response [32]. Furthermore, it stimulates neoangiogenesis, fibroblast activation and proliferation, and, indirectly, epidermal hyperplasia, through KGF and EGF activity [28, 29, 32]. The milestone cytokine in mediating anti-inflammatory signals, IL-10, shows favorable effects on the wound healing process as it improves healing and scar formation, as also observed in treating hypertrophic human scars [33, 34]. Another cytokine, namely, IL-27, is proven to play a crucial role in the healing process. Increased IL-27 pro-

duction by CD301b$^+$ dendritic cells is detected after skin injury, and CD301b-depleted or IL-27 receptor knockout mice exhibit delayed or attenuated wound closure in vivo, suggesting an essential role for IL-27 signaling in skin regeneration in vivo. This evidence has been confirmed by the amelioration of nonhealing condition occurring in the CD301b-depleted mice, using topical IL-27 treatment. The IL-27 contribution to normal wound healing response is firstly due to its capability in stimulating keratinocyte proliferation and re-epithelialization and secondly to markedly increased antiviral expression [35]. Overall, leukocytes, especially macrophages, neutrophils, and T cells secreting a wide array of cytokines (i.e., IL-22, IL-8, and IL-17), regulate the inflammatory process that is crucially involved in the healing process.

Corticosteroids

The use of topical corticosteroids is not a common practice during treatment of chronic wounds. There are several controversial issues according to this topical intervention and there is no evidence or guideline regarding this treatment [36]. The main concern from caregivers is that topical corticosteroids because of the immunosuppressant effect are going to increase the risk of bacterial burden increase and particularly the development of a sensitization in the wound bed and surrounding skin, which is usually becoming a chronic status complicating the tissue repair process [37].

However, there are several conditions facilitating the use of topical corticosteroids:

- Hypergranulating wound beds
- Vasculitic ulcers
- Pyoderma gangrenosum
- Hidradenitis suppurativa
- Wounds in necrobiosis lipoidica
- Atrophie blanche

The use corticosteroids if advocated must follow several criteria like the potency of drug selected, the frequency of application, and the duration of the treatment [38]. A major advantage by using topical corticosteroids in chronic wounds has been found for the management of related pain. There were several case reports where the patients reported a beneficial effect on pain reduction after only few days of treatment [39]. Overall the use of topical corticosteroids in chronic wounds must be taken in consideration under very specific and limited restrictions and with cautious action.

Retinoids

The topical use of retinoids in wound healing is getting increased evidence particularly in chronic wounds. Topical tretinoin was found to promote the granulation tissue formation in venous leg ulcers and rheumatological ulcers as a short contact therapy [40]. The application of tretinoin 0.05% solution for 10 minutes on the wound bed was able to increase the amount of granulation tissue after 1 week of treatment by clinical judgment. Biopsies taken in the same study were demonstrating an increased angiogenesis and collagen fibers production after 3 weeks of treatment. Another study on diabetic foot ulcers demonstrated the tolerability and efficacy of short contact therapy with tretinoin compared to placebo. In this study 46% of patients achieved complete healing at 16 weeks of treatment [41]. One major concern regarding topical tretinoin is related to the irritation caused by the drug in open wounds and surrounding skin.

Protease Modulating Matrix

Matrix metalloproteinases (MMPs) have shown to play a peculiar role in chronic wound repair [42]. The exudate from chronic wounds is characterized by a very high concentration particularly of MMPs 2 and 9, which is producing a delay in tissue repair by imbalancing the function of several cytokines and growth factors [43]. The tissue inhibitors (TIMPs) for those MMPs are also crucial in the inflammatory phase of wound healing, because they limit the MMPs activity during the

extracellular matrix remodeling. Therefore, several attempts to introduce topical strategies to control the high concentration of MMPs have been proposed in the literature [44]. A topical MMPs modulating matrix has been recently presented in the list of technological advanced wound dressings. The dressing is made of a collagen/oxidized regenerated cellulose scaffold able to modify the wound microenvironment, by promoting granulation tissue formation and reactivating wound repair. The product has shown excellent results in the treatment of diabetic foot ulcers, venous leg ulcers, and pressure ulcers [44, 45].

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7 Wound Dressing Allergic Contact Dermatitis: Epidemiology and Management

John Havens Cary, Becky S. Li, Rasika Reddy, and Howard I. Maibach

Introduction

Contact dermatitis, defined as skin inflammation, results from exposure to an external agent [1]. Contact dermatitis consists of both irritant contact dermatitis (ICD), which may present on initial or multiple exposures, and allergic contact dermatitis (ACD), which requires an initial and subsequent allergen exposure, resulting in sensitization and elicitation of the clinical lesion. Aside from severe irritants, which often result in characteristic skin necrosis with acute burning and stinging, the majority of irritants and allergens are indistinguishable clinically, usually resulting in a delayed, eczematous-like reaction [2]. Chronic ICD and ACD both present with hyperkeratosis, lichenification, and fissuring [2].

Patch testing remains the diagnostic gold standard and is an attempt to reproduce the eczematous reaction of ACD on a smaller scale by applying a collection of allergens on intact skin of the affected patient under occlusion [3]. Possible allergens are applied at nonirritating concentrations in order to help distinguish between allergic and irritant reactions [3]. Clinicians may apply allergens using several different apparatuses, including the thin-layer rapid use epicutaneous (TRUE) test, chamber units (e.g., Finn chambers), or non-chamber units [4]. Allergens are applied to the patient's upper back and examined after 48 hours and 96 hours for any potential reaction that is assessed according to a defined scale.

Of the 85,000 plus chemicals present in our environment, many are potential irritants at sufficient concentrations [5]. Response to an irritant may occur to any individual with some variance. Important factors contributing to ICD include the physiochemical properties of the irritant and degree of exposure experienced by the individual [5].

An estimated 4350 chemicals act as allergens [5]. In order for a chemical to be an allergen, it

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A. Alavi, H. I. Maibach (eds.), *Local Wound Care for Dermatologists*, Updates in Clinical Dermatology, https://doi.org/10.1007/978-3-030-28872-3_7

must be capable of eliciting a type IV hypersensitivity reaction. However, allergens often also possess irritant properties and are capable of producing both ACD and ICD [4].

Modern wound dressings provide numerous benefits to patients with chronic wounds, including enhanced healing, lower rates of infections, and improved quality of life [6]. However, cumulative irritation in individuals with chronic wounds due to multiple irritants contained in wound bandages and dressings is frequent. Individuals with chronic wounds are particularly susceptible to ICD due to repeated application of wound care products with numerous irritants and removal of adhesive dressings or tape from patient's skin [7]. However, minimal literature assesses the rate of ICD due to cumulative action of multiple irritants otherwise known as "tandem" ICD. ACD is not rare in patients with chronic wounds due to the allergens often contained in wound care products; however, it is less common than ICD [8]. While it is difficult to obtain a true rate of ACD in chronic wound patients, there is both a prolonged healing time and increased treatment cost associated with these patients [9].

Current Literature

A review of current literature was performed on PubMed, Google Scholar, and Embase restricted to Jan 2008–Jan 2018 using the following keywords: "wound sensitization," "wound dermatitis," "wound dressing contact dermatitis," "wound bandage contact dermatitis," and "wound allergic contact dermatitis." Our goal in our literature search was to obtain the most relevant and recent large prospective studies documenting the rates of sensitization among chronic wound patients and identify the most commonly implicated allergens in wound care.

Larger Prospective Studies

There are three large prospective studies [6, 10–11] that we deemed particularly valuable in their possible contribution to contact sensitization with respect to wound care over the10-year period. The studies all contained 350+ patients, were published in major peer-reviewed dermatological journals (*Contact Dermatitis*), and had minimal appreciable bias. While the study design and the particular objectives among the studies varied, each analyzed the rate of contact sensitization among chronic wound patients: 44.8% (2333/5264 patients) [10], 59.6% (211/354 patients) [6], and 73% (308/428 patients) [11].

Erfurt-Berge et al. [10] quantified sensitization in patients with "stasis dermatitis/chronic leg ulcer" as the main diagnosis and/or leg/lower leg as the main localization. The authors examined data from the Information Network of Departments of Dermatology (IVDK) on 5264 patients across multiple centers in Germany, Switzerland, and Austria with the above diagnoses from the years 2003 to 2014 in the chronic leg ulcer group (CLU group), as well as 4881 chronic leg ulcer patients from 1994 to 2003 (CLU patients 1994–2003), and 55,510 age-controlled patients without CLUs (current control group). Patients from all groups were tested with the German Contact Dermatitis Research Group (DKG) Baseline series, while patients from the current CLU group were also tested with additional DKG test series for separate analysis.

The percentage of patients having an ACD final diagnosis declined from 25.9% of patients from 1994 to 2003 to 16.9% of patients in 2003–2014. Interestingly, the rate of patients with an ACD final diagnosis in the current control group (23.4%) was even higher than that of the current CLU group (16.9%). The authors found the rate of sensitization to at least one allergen in the German Contact Dermatitis Research Group (DKG) baseline series among the current CLU group to be 44.8% in comparison to 58.6% in CLU patients from 1994 to 2003 and 43.1% in the current control group. In the current CLU group, significantly more positive reactions were seen to *M. pereirae* (balsam of Peru), fragrance mix I, lanolin alcohol, fragrance mix II, colophonium, neomycin sulfate, cetearyl alcohol, jasmine absolute, ammoniated mercury, oil of turpentine, *Santalum album* (sandalwood) oil, benzocaine, paraben mix, bronopol, and zinc

diethyldithiocarbamate than in the current control group. While most allergen frequencies declined from the CLU patients from 1994 to 2003 to the current CLU group, ammoniated mercury and bronopol increased in frequency. Larger decreases in frequency were noted in propolis, bufexamac, and formaldehyde from the 1994–2003 CLU group to the current CLU group. In summary, while the authors did not necessarily find higher rates of sensitization among chronic wound patients, they identified allergens that appear to be particularly problematic in the setting of wound care.

Valois et al. [6] investigated rates of sensitization to dressings among patients with chronic leg ulcers across five centers. Unlike Erfurt-Berge et al. [10], the authors did not provide a control to compare sensitization rates in chronic ulcer patients to the general population; however, they did provide an extensive review of sensitivity to wound dressings. They patch tested 354 CLU patients with the European baseline series, a special series designed for patients with CLUs, and 10 modern dressings representative of each dressing class. The classes tested included: "charcoal dressings (Carbonet® [Smith & Nephew Laboratory, Le Mans, France]); alginate dressings (Algosteril® [Brothier Laboratory, Nanterre, France]); hydrocellular dressings, dressings with ibuprofen (Biatain® adhesive part and nonadhesive part and Biatain Ibu® [Coloplast Laboratory, Rosny-sous-Bois, France] and Mepilex® [Mölnlycke Health Care Laboratory, Wasquehal, France]); hydrogel dressings (Hydroclean® gel [Hartmann Laboratory, Selestat, France]); hydrofiber dressings (Aquacel® [ConvaTec Laboratory, Garenne-Colombes, France]); hydrocolloid dressings (Duoderm E® [ConvaTec Laboratory]); ialuset creme® (Genevrier Laboratory, Antibes, France); and interface dressings to test silver sulfadiazine, which could not be obtained in a pure form for testing (Urgotul SAG® [Urgo Laboratory, Chenove, France])." They also tested dressings used by the patients as is (Versiva® [ConvaTec Laboratory], Allevyn Heel® [Smith & Nephew Laboratory], and Intrasite Gel® [Smith & Nephew Laboratory]).

The most frequent allergens in the European baseline series were *Myroxylon pereirae* (balsam of Peru) (23.7% of patients), fragrance mix I (13.3%), nickel sulfate (6.5%), fragrance mix II (6.2%), and lanolin alcohol (4.2%). Among allergens from the special series on chronic leg ulcers, ialuset creme® (12.7%), benzalkonium chloride (7%), Amerchol® L101 (5.4%), Duoderm E® (5.1%), and sodium metabisulfite (4.8%) were the most frequent sensitizers. "Sixty-eight patients (19.2%) were sensitized by medical dressings (MDs): 45 (12.7%) by Ialuset cream®, 28 (7.9%) by hydrocellular products (1 Versiva®, 1 Allevyn heel®, 5 Mepilex®, 14 Biatain® adhesive part, 5 Biatain® non-adhesive part, and 2 Biatain Ibu®), 18 (5.1%) by a hydrocolloid (Duoderm E®), 7 (2%) by hydrogels (3 Hydroclean gel®, 3 Intrasite gel®, and 1 Urgo hydrogel®), 6 (1.7%) by alginates (Algosteril®), 5 (1.4%) by hydrofibres (Aquacel®), and 8 (2.3%) by an interface dressing (4 Urgotul SAG® and 4 Urgotul®). Regarding new components of MDs, 3 (0.8%) patients were sensitized by carboxymethylcellulose (CMC) and 4 (1.1%) were sensitized by Urgotul SAG® containing silver sulfadiazine" Valois et al. [6].

Barbaud et al. [11] determined the frequency of contact sensitization among chronic leg ulcer patients to determine whether there was a correlation with leg ulcer duration. They patch tested 423 patients from multiple centers across France with a European baseline series, a series of 34 allergens designed specially for leg ulcer patients, three commercially available products (Comfeel® transparent, Duoderm E®, and Biafine®), dressings used by the patients when possible, and EMLA® in a limited number of patients. Of 423 CLU patients, 73% had at least one positive patch test, with the most frequently involved allergens: *Myroxylon pereirae* (40.7%), fragrance mix I (26.5%), lanolin (wool alcohol) (17.7%) and its derivative Amerchol L101® (19.6%), Povidone-iodine (12.7%), benzalkonium chloride (10.4%), neomycin sulfate (9.2%), Biafine® pure (8.5%), colophonium (7.6%), and budesonide (7.1%). They found a correlation between the duration of ulcer and the number of positive tests per patient ($P < 0.01$). Among the 308 sensitized patients, they were sensitized to an average of 3.7 allergens, sug-

gesting a polysensitization as a possible factor. In addition, the authors also found the sensitization rate among CLU patients with surrounding erythema to be 78% compared to 57% in CLU patients without erythema (Chi-squared = 17.4, $P < 0.0001$).

Discussion

While evidence points toward decreasing rates of ACD in chronic wound patients, there remain several common problematic allergens among those patients. It is difficult to determine the true rate of allergen sensitivity among the general population; the North American Contact Dermatitis Group (NACDG) and the European Surveillance System on Contact Allergies (ESSCA) periodically publish group patch test studies [12, 13]. However, these studies are not representative of the general population or the dermatological patient population, as they consist of patients referred for suspected allergic contact dermatitis. Conversely, the large prospective studies patch tested patients with chronic wounds, but not necessarily suspected ACD. Table 7.1 lists the top 10 allergens in the 3 large chronic wound prospective studies [6, 10–11] along with the top 10 allergens from the North American Contact Dermatitis Group's most recent patch test results [12]. However, it is our opinion that the NACDG and ESSCA study sensitization rates are elevated in comparison to the true rate of the general population. Perhaps, the most accurate identification of problematic allergens in the setting of wound care were those with significantly higher rates in the CLU group in comparison to the control group in the Erfurt-Berge et al. [10] study (*M. pereirae* [balsam of

Table 7.1 Top allergens in 3 large prospective ACD chronic wound studies and NACDG database top allergens by percentage of patients sensitized[a]

Rank	Erfurt-Berge et al. [10] ($n = 5264$)	Valois et al. [6] ($n = 354$)	Barbaud et al. [11] ($n = 423$)	NACDG ($n = 4874$) (non-ulcer patients)
1	*Myroxylon pereirae* (balsam of Peru) (25% pet)	*Myroxylon pereirae* (balsam of Peru) (25% pet)	*Myroxylon pereirae* (balsam of Peru) (25% pet)	Nickel sulfate hexahydrate (2.5% pet)
2	Fragrance mix I (8% pet)	Fragrance mix I (8% pet)	Fragrance mix I (8% pet)	Fragrance mix I (8% pet)
3	Lanolin alcohol (50% pet)	Benzalkonium chloride (0.1% pet)	Lanolin alcohol (50% pet)	MI (0.2% aq) Methylisothiazolinone
4	Fragrance mix II (14% pet)	Nickel sulfate (5% pet)[c]	Povidone- iodine (10% water)[b]	Neomycin sulfate (20% pet)
5	Colophonium (colophony) (20% pet)	Fragrance mix II (14% pet)	Benzalkonium chloride (0.1% pet)	Cobalt (II) chloride hexahydrate (1.0% pet)
6	Methyldibromo glutaronitrile (0.3% pet)	Sodium metabisulfite (1% pet)[b]	Neomycin sulfate (20% pet)	Bacitracin (20% pet)
7	Methyldibromo glutaronitrile (0.2% pet)	Cetearyl alcohol (cetyl-stearyl alcohol) (20% pet)	Colophonium (colophony) (20% pet)	*Myroxylon pereirae* (balsam of Peru) (25% pet)
8	Nickel sulfate (2.5% pet)	Lanolin alcohol (30% pet)[d]	Budesonide (0.1% pet)	4-Phenylenediamine base (1.0% pet)
9	Neomycin sulfate (20% pet)	Colophonium (colophony) (20% pet)	Cetearyl alcohol (cetyl-stearyl alcohol) (20% pet)	Formaldehyde (2.0% aq)
10	Cetearyl alcohol (cetyl-stearyl alcohol) (20% pet)	Neomycin sulfate (20% pet)	Nickel sulfate (5% pet)[c]	MCI/MI (0.01% aq)

[a]Note: Brand names and wound dressings were omitted from the list of top allergens
[b]Not included in ACDS baseline series
[c]NACDG uses nickel sulfate hexahydrate 2.5% pet
[d]NACDG uses lanolin alcohol 50% pet

Peru], fragrance mix I, lanolin alcohol, fragrance mix II, colophonium, neomycin sulfate, cetearyl alcohol, jasmine absolute, ammoniated mercury, oil of turpentine, *Santalum album* [sandalwood] oil, benzocaine, paraben mix, bronopol, and zinc diethyldithiocarbamate).

The following discussion quantitatively compares sensitization rates among common allergens in the setting of wound care [6, 10–11] to those patients referred for suspected ACD [12, 13]. In all 3 studies examined, chronic wound patients exhibited the highest sensitivity to *Myroxylon pereirae* (balsam of Peru), with chronic ulcer patient sensitivity rates ranging from 14.8% to 40.7% [6, 10–11]. By comparison, the European Surveillance System on Contact Allergies (ESSCA) found sensitization to *Myroxylon pereirae* to be 5.7% among patients with suspected ACD. The NACDG obtained a 7.2% contact sensitivity to *Myroxylon pereirae* in tested dermatological patients [12]. Smaller studies evaluating sensitization in North America found positive patch tests to *Myroxylon pereirae* among 30% (16/54) and 10% (10/100) of chronic wound patients [8, 14]. However, it remains unclear whether there is a true causative association with wound dressing allergic contact dermatitis and balsam of Peru.

Fragrance mix I, a mixture of fragrance allergens, contains cinnamyl alcohol, cinnamal, amyl cinnamal, hydroxycitronellal, geraniol, eugenol, isoeugenol, and *Evernia prunastri* [10]. Constituents in fragrance mix I represented the second most frequent sensitizer among chronic wound patients in all 3 studies. Rates in chronic wound patients ranged from 11.4% to 26.5% of patients [6, 10–11]. The ESSCA found a 7.8% positive rate to fragrance mix I, while the NACDG database estimates sensitization to fragrance mix I to be around 11.9% of patients [12]. Despite lower rates in comparison to the NACDG database, Erfurt-Berge et al. [10] did find significantly higher rates of sensitization to fragrance mix I, as well as fragrance mix II (containing lyral, citral, citronellol, farnesol, coumarin, and hexyl cinnamic aldehyde), in comparison to their control group.

Other allergens of particular significance in the studies examined include lanolin alcohol, colophonium, neomycin sulfate, cetearyl alcohol, corticosteroids, and benzalkonium chloride.

Lanolin is commonly used as an emollient in topical agents [15]. Since 1969, lanolin has been tested in baseline patch tests as lanolin alcohol [16]. In addition, Amercholᵀᴹ L101 is a commercial derivative of lanolin alcohol, consisting of hydrolyzed wool fat with 10% wool alcohols in mineral oil [15]. Lanolin alcohol had positive patch test rates from 4.2% to 17.7% in the chronic wound patients in the examined studies, while Amercholᵀᴹ L101 had positive rates of 5.4%–19.6% [6, 10, 11]. By comparison, the ESSCA found sensitivity rates to lanolin (30% pet.) to be 1.9% [13]. The NACDG found sensitivity to lanolin alcohol (50% pet.) to be 5.4% [12]. Fransen et al. [15] analyzed the prevalence of lanolin alcohol and Amercholᵀᴹ L101 sensitivity in the general population and found a positive patch test rate of 1.2%. In addition, 26.9% of patients patch tested positive for both lanolin alcohol (30% pet.) and Amercholᵀᴹ (50% pet.), while 46.3% of patients tested positive to only Amercholᵀᴹ and 26.9% to only lanolin alcohol [15]. Differing rates of positivity suggest the possible need to include both allergen derivatives in a baseline series in order to cover all lanolin contact allergy. However, many have suspected lanolin to have irritancy potential, with some authors attributing positive patch tests to "excited skin syndrome," which is discussed further in the later section, "Patch Testing Caution" [17, 18].

Colophonium, also known as colophony in Europe and rosin in North America, consists of over 100 constituents extracted from pine trees, with individual composition varying by regional pine tree species and extraction method [19]. Most believe oxidation of modified and unmodified colophony to be responsible for the majority of sensitization [20]. Colophony has many applications at home and in the workplace and is used most frequently in hydrocolloid dressings as an adhesive in the chronic wound setting [19, 20]. Sensitization was 4–7.6% among chronic wound patients in the studies examined [6, 10–11]. The ESSCA found the sensitization rate to colophony

to be 2.9%, while the NACDG found sensitivity to be 1.9% [12].

Neomycin is often used topically for the prevention of superficial skin infections, as it is economical and particularly effective against many aerobic Gram-negative and some aerobic Gram-positive bacteria [21]. Topical antibiotics, specifically aminoglycosides, have documented allergenic properties and continue to be frequently used in chronic wounds and are, thus, potential contributors to ACD in this setting. Among the analyzed prospective studies, sensitivity to neomycin sulfate (20% pet.) was 3.7%, 5.0%, and 9.2% in chronic wound patients [6, 10–11]. Erfurt-Berge et al. [15] found the rate of 5.0% in the CLU group to be significant when compared to the control group. The ESSCA found rates of sensitivity to neomycin sulfate (20% pet.) to be 1.3% among referred patients [13]. However, the NACDG found sensitivity to neomycin sulfate (20% pet.) to be 8.4% among patients referred for patch testing [12].

In all prospective studies examined, cetearyl alcohol (cetyl-stearyl alcohol) ranked among the top 10 most common allergens, with positive patch test rates ranging from 4.4% to 5.7% of chronic ulcer patients [6, 10–11]. Cetearyl alcohol is not currently included in the European baseline series or the North American baseline series and was not among the allergens examined by the ESSCA or the NACDG in their most recent group patch test results. Cetearyl alcohol (cetyl-stearyl alcohol) is a clear example of an allergen that should be included in special patch test series for chronic wound patients and perhaps even in the standard baseline series.

Topical corticosteroids remain significant allergens among chronic wound patients. Among large prospective studies, the sensitivity to budesonide (0.1% pet.) ranged from 2.8% to 7.1% [6, 10–11]. The ESSCA found the number of sensitized patients to budesonide (0.1% pet.) to be 0.4%; the NACDG found 0.9% sensitivity to budesonide (0.1% pet.) [12, 13]. While difficult to avoid using topical corticosteroids in the treatment of chronic wounds, healthcare professionals should suspect an allergy when eczema worsens or fails to improve despite topical corticosteroid use.

Benzalkonium chloride (0.1% pet) had relatively high rates of sensitivity in both Barbaud et al. (10.4% positive patch tests) and Valois et al. (7% positive patch tests) with a considerably lower rate in Erfurt-Berge et al. (1.7% positive patch tests). Benzalkonium chloride is not contained in the European baseline series, so there was no sensitization rate obtained by Uter et al. While benzalkonium chloride is included in the ACDS (American Contact Dermatitis Society) core allergen series, it is not routinely tested by the NACDG. However, it should also be noted that the authors consider benzalkonium chloride a potential mild irritant. In addition, irritant reactions to patch testing with benzalkonium chloride often appear papular and are difficult to distinguish from allergic responses [22].

In summary, it is difficult to approximate the true rate of sensitization among chronic wound patients with/without wound dressings in comparison to patients without chronic wounds, as different studies patch test with different series, may have biased patient populations, and often lack a true control group. However, clinical experience and understanding of the pathophysiology of ACD suggests a higher rate of sensitization in patients with CLUs due to the presence of allergens in modern wound dressings, continued contact with sensitizers under occlusion, and impaired skin barrier function [11]. In our analysis, we identified particular allergens that have a higher prevalence among chronic wound patients that should be excluded by manufacturers to avoid prolonged healing times and increased treatment costs.

Additional Suggestions

While ostomy patients, surgical wound patients, chronic leg ulcer patients, and others require different healing management, most chronic wound patients have contact with potential allergens under occlusion, often have pre-existing inflammation at the wound site, and have decreased skin barrier protection. All of these factors should prompt the physician to have a high index of suspicion when eczematous changes develop in

the area surrounding the wound. In addition, the physician should also suspect ACD if the wound does not respond to treatment or when there is minimal improvement of eczematous changes around the wound despite topical corticosteroid use [10].

When ACD is suspected, healthcare professionals should remove the suspected dressing and potential causative topical formulations (e.g., topical aminoglycosides, adhesives). Physicians should prioritize testing for contact allergy with the suspected wound dressing and alternative wound dressings by placing small 1-cm squares of the dressings over the patient's back for 48 hours. Should a patient develop an allergic reaction to the suspected wound dressing and no reaction to an alternative, healthcare professionals can feel comfortable using the new alternative dressing. Should a topical formulation be suspected, a repeat open application test may be performed. In a repeat open application test (ROAT), the topical is applied twice daily for up to 28 days to an outlined area of around 4 cm to the volar aspect of the forearm, antecubital fossa, or scapular area and monitored for a potential reaction [4]. For ostomy devices, we suggest using the nonreactive side of the abdomen to test for potential sensitivity. Practitioners may add a delayed reading 96 hours later when testing for sensitization in the setting of wound care, as wound dressings are often left on patient skin for extended periods of time. Note that this suggested patch test duration is not experimental, but based upon clinical experience of the authors.

Physicians should additionally look to discern the causative allergen within the wound dressing or topical medication. An appropriate first step is to perform a literature search of the causative wound care product and examine the product ingredients for any potential allergens. However, some manufacturers are not obligated by law to disclose a complete ingredient list due to proprietary designation. As evidenced from the previously described prospective studies, the most common allergens in chronic wound patients are generally included in the American Contact Dermatitis Society's baseline series. However, patients should also be patch tested with additional specialized allergens encountered in the treatment of chronic wounds, such as that suggested in Table 7.2, and any other potential allergens listed in the ingredients or present in the product-relevant literature. In addition, DeGroot's *Patch Testing, 3rd ed*, provides testing concentrations when an allergen is not commercially available [23]. Identifying the particular allergen within the wound dressing allows patients and future healthcare workers to avoid using products with the causative ingredient. However, as discussed below, "Patch Testing Caution," it is important to consider potential marginal irritants and false positives.

Table 7.2 Suggested special series (to be used in addition to ACDS core allergen series)

Allergen type/allergen	Percentage and vehicle
Preservatives	
Sodium metabisulfite	1% pet.
Dodecyl gallate	0.5% pet.
Octyl gallate	0.3% pet.
Antiseptics	
Povidone-iodine[a]	10% aq.
Cetrimide	0.1% aq.
Silver sulfadiazine	5% pet.
Silver nitrate[a]	2% aq.
Corticosteroids	
Aclometasone-17,21-dipropionate	1% pet.
Prilocaine hydrochloride	5% pet.
Miscellaneous	
Eosin	50% pet.
Carboxymethylcellulose	2% pet.
Polyethylene glycol	"As is" (100%)
Ibuprofen[b]	10% pet.
Ethylene glycol dimethacrylate	2% pet.

[a]Povidone-iodine and silver nitrate are suspected marginal irritant in the opinion of the authors
[b]Ibuprofen is not extensively used topically in the USA

Patch Testing Caution

When patch testing, physicians should be particularly cautious about certain allergens that are suspected to be marginal irritants (e.g., propylene glycol). Several studies suggest its marginal irritancy, while many remain skeptical of

its potential as an allergen [24]. Lessmann et al. (2005) found a 2.3% positive patch test rate in the retrospective analysis of 45,138 patients patch tested with propylene glycol (20% aq) [25]. However, they found a high percentage of these to be weak positive reactions (>80% of all positive reactions) and, thus, concluded that most must be interpreted as false positives [25]. Basketter et al. (2004) recently suggested benzalkonium chloride to be a marginal irritant with questionable allergic properties [26]. Other reported allergens that are likely marginal irritants include triethanolamine, silver nitrate, the parabens, chromate, and the lanolin alcohols [17]. In short, the physician should retest weak positives, especially allergens that have a history as a suspected irritant.

Practitioners should also be cautioned regarding "excited skin syndrome" ("angry back syndrome"), which occurs when there is a strong positive regional reaction induced by a particular tested allergen, resulting in additional positive reactions to other allergens, which are negative on subsequent testing [4]. Excited skin syndrome occurs most frequently when testing with marginal irritants in the setting of atopic dermatitis or skin that is hyperirritable, such as stasis dermatitis [4]. Kligman (1998) suggested positive patch tests to lanolin to be a characteristic feature of this syndrome [18].

Extracting the Allergen (for the Experimentally Minded Physician)

For the experimentally minded physician and motivated patient, there are several methods to extract and identify the allergen from the specific causative product. This process is particularly helpful when the manufacturer does not disclose full ingredient lists and relevant literature does not identify a causative ingredient. To start, physicians can attempt to determine whether the allergen is hydrophilic or lipophilic by placing the wound dressing in a water-soluble extract (e.g., water) and a lipid soluble extract (e.g., petroleum). We suggest water to allergen and petroleum to allergen at a 1:10 ratio. In patch testing with both the lipid soluble and water soluble extracts, should the investigator obtain a negative reaction with the lipid-soluble extract and a positive reaction with the water-soluble extract, the physician should have confidence that the allergen is hydrophilic and vice versa. In cases in which there are two positive reactions, physicians may repeat the process. Whenever there are two negative reactions, the investigator can use heat or ultrasound to help extract additional allergens from the suspected wound dressing into the water and lipid-soluble extracts. Once the allergen is identified as hydrophilic or lipophilic, thin-layer chromatography (TLC) can be used to separate the hydrophilic or lipophilic compounds extracted from the wound care product even further. In this process, a drop of the allergen mixture is deposited at one end of a glass plate covered in adsorbent [27]. Next, the plate is dipped into a glass pot with a good cover, or a cell, containing a solvent. When the solvent is 1–2 cm from the top of the plate, the plate is removed from the cell. With evaporation of the solvent, the investigator can spray the plate with a reagent (such as sulfuric acid and iodine) to reveal the individual compounds within the mixture [27]. Additional patch testing using the separated allergens on the TLC strip allows identification of a specific separated band, which can then be identified using mass spectroscopy or other processes in a commercial lab.

Treatment

When the eliciting substance is avoided, topical corticosteroids have been successful in the treatment of ACD [5]. In mild to moderate cases of ACD, twice daily application of topical corticosteroids for 2 weeks has proven an effective treatment; patients should use milder corticosteroids applied over the face and intertriginous areas and higher potency corticosteroids over the torso and extremities [5]. Clinicians should select corticosteroids with few preservatives, especially in patients that have a history of positive patch tests to one or more preservatives [2]. Topical tacrolimus and pimecrolimus may aid in the manage-

ment of facial dermatitis and can be used as an alternative to lower potency steroids [28].

While topical corticosteroids have proven to be an effective treatment for ACD, topical corticosteroid use remains controversial in the treatment of ICD. Levin et al. induced ICD in six healthy patients with open application test with sodium lauryl sulfate (SLS) five times on 1 day on the hands [29]. The authors applied low (hydrocortisone 1%) and medium (0.1% betamethasone 17-valerate) potency corticosteroids to the subjects and assessed visual grading of erythema and dryness, bioengineering techniques, and squanometry, finding no significant difference with the parameters used to assess skin response between corticosteroid treated, vehicular, and untreated skin [29]. Other studies yielded similar results of no or possibly negative effect in treatment of ICD with corticosteroids [30, 31]. In contrast, other studies have yielded significant improvement in ICD treated with corticosteroids [32, 33].

Systemic corticosteroids are occasionally used in the acute phase of severe or widespread contact dermatitis; however, they should be generally avoided due to accompanying adverse side effects. In addition, oral antihistamines may be helpful in order to reduce symptomatic pruritus.

Conflict of Interest The authors declare no conflict of interest.

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8 Vascular Studies for Nonvascular Surgeons

Ali Rajabi-Estarabadi, Mahtab Forouzandeh, Ahmed Kayssi, Robert S. Kirsner, and Afsaneh Alavi

Background

Dermatologists encounter a wide variety of ulcers throughout their careers. Many of these ulcers are located on the lower extremity and are related to venous insufficiency (VI) and peripheral artery disease (PAD). Venous leg ulcers due to VI, in particular, affect 2.2 million Americans annually [1]. Moreover, data suggests that 3–4% of the US population suffers from VI, while 1.5% of the population have at least one venous leg ulcer (VLU) [2]. It is clear to see that these problems impact a large number of Americans.

Much like the problems associated with VI, PAD's effects are also wide reaching. In fact, recent data suggest that nearly ten million Americans are affected by PAD [3, 4] The presence of PAD not only worsens lower extremity wounds but potentially also leads to ineffective wound healing. It is also worth noting that, as the population of the elderly in Americans increases, the incidence of VI and PAD will continue to rise and contribute substantially to the public health burden. Therefore, prompt detection, diagnosis, and management of lower extremity ulcers are important in order to improve patient outcomes and reduce overall healthcare costs.

A patient's therapeutic plan is guided by a combination of their medical history, vascular test results, and physical examination. Diagnostic tests play an essential role in the detection of vascular disease from both a venous and arterial standpoint. The sooner vascular disease can be identified in an individual, the sooner both physicians and patients can work toward integrating therapies that will prevent or mitigate ulcer formation. Knowledge regarding the proper indications and interpretations of the various vascular studies is critical to the successful management of each patient.

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A. Alavi, H. I. Maibach (eds.), *Local Wound Care for Dermatologists*, Updates in Clinical Dermatology, https://doi.org/10.1007/978-3-030-28872-3_8

Arterial Vascular Studies: Macro-vascular Tests

The Ankle-Brachial Pressure Index (ABPI), Toe Pressure (TP), and Toe Brachial Index (TBI)

The ankle-brachial pressure index (ABPI) is an important diagnostic tool for the diagnosis of peripheral artery disease. ABPI testing is relatively uncomplicated, quick, uncostly, and noninvasive. It also has high sensitivity and even higher specificity in its detection of significant peripheral arterial disease (84.7% sensitivity, 97% specificity) [5, 6]. ABPI is also comparable to the gold standard of contrast-enhanced angiography in its ability to detect arterial stenosis of greater than 50% [7, 8] Furthermore, ABPI demonstrates superior accuracy in measuring arterial stenosis of the femoropopliteal vessels [9].

The ABPI is calculated by dividing the ankle systolic blood pressure (measured at dorsalis pedis and posterior tibialis arteries) by the highest brachial systolic blood pressure (measured at both brachial arteries) (Fig. 8.1) [9]. The systolic pressures measured in the brachial arteries and systolic pressures measured at the posterior tibialis and the dorsalis pedis arteries

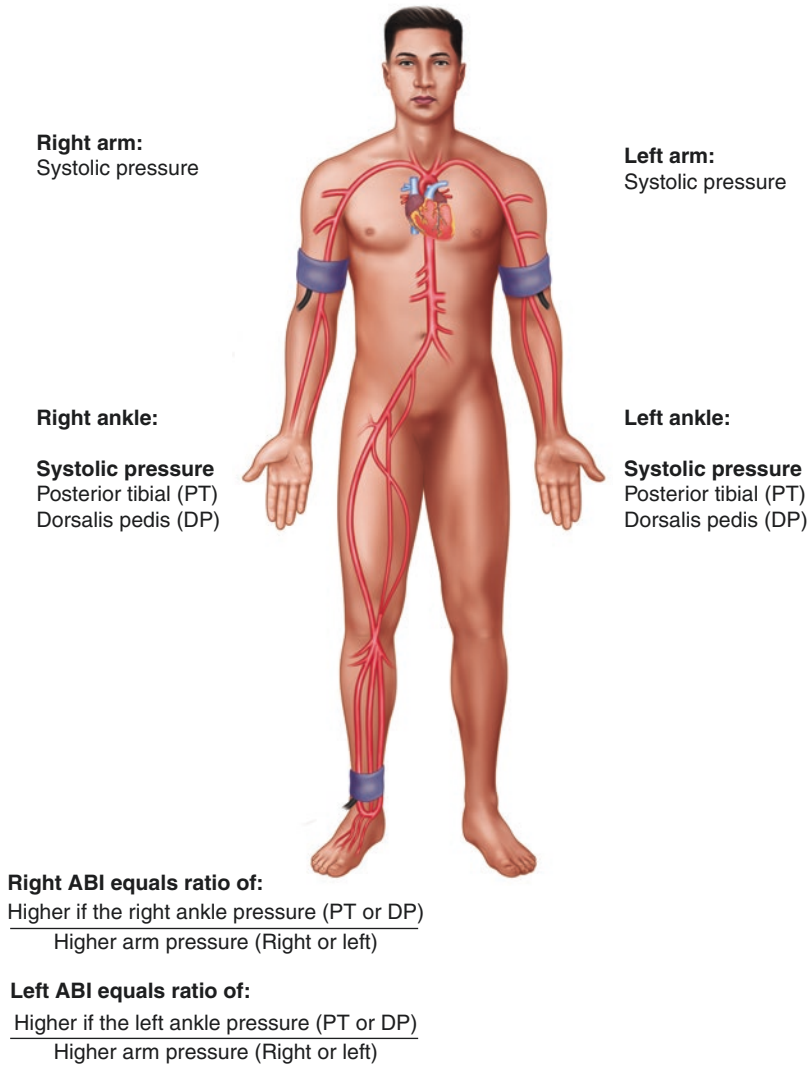

Fig. 8.1 Ankle-brachial pressure index (ABPI)

Table 8.1 Interpretation of ankle-brachial pressure index

Generally normal	0.91–1.3	
Mild-moderate disease	0.41–0.90	
Severe disease	≤0.40	Danger of limb loss
Rigid arteries	>1.3	Calcified vessels: need an ultrasound test to check for peripheral artery disease instead of an ankle-brachial pressure index

at each ankle are estimated by using a sphygmomanometer and Doppler probe. The highest pressure measurement is used in calculating the ratio (Fig. 8.1) [10].

The American Diabetes Association has defined the normal range for the ABPI to be between 0.91 and 1.3 [9]. Mild disease is defined as a ABPI of 0.7–0.9, moderate ischemic disease is defined as a ABPI of 0.41–0.69, and severe disease, also called critical limb ischemia, is defined as a ratio of less than or equal to 0.4 (Table 8.1) [11].

However, in patients with diabetes mellitus (DM) and in the elderly, ABPI calculations are less reliable and can be falsely elevated or normal due to the increased prevalence of medial calcinosis of the arteries in these populations. Calcified and noncompressible arterial vessels that are commonly encountered in elderly patients can result in an unreliable ABPI measurement [12]. Additionally, the vessel glycosylation found in patients with DM may lead to an increased frequency of noncompressible arterial vessels. Another contributor to unreliable ABPI results is leg and foot edema which can disrupt ABPI measurements [13]. Despite these limitations, the ABPI remains a cost- and time-effective, noninvasive, and accurate screening and diagnostic test for large vessel arterial disease in most circumstances.

The toe brachial index (TBI) and toe pressure (TP) measurements can be helpful in screening for PAD in patients with DM and in patients with an ABPI measurement of above 1.3 [14, 15]. Because falsely elevated or falsely normal ABPI due to vessel stiffness is prevalent in patients that are of advanced age or in patients with DM, the use of TP and TBI may be more useful in the detection of PAD in these populations [16]. This is due to the toe vessels' decreased susceptibility to vessel stiffness (Fig. 8.2).

TBI can be calculated by dividing the systolic pressure of the great toe by the greater of the two brachial pressures. This can be achieved by placing probes on the tips of both great toes and placing cuffs on the arms and legs (above the ankle or at the base of the great toes) [16].

Due to its reliability and noninvasive nature, TP is both cost and time efficient [9, 17, 18]. TP can be measured while the patient is lying flat with feet at the level of the heart, by using sphygmomanometry around the base of the toe and using optical means, such as a photocell [19].

TP can also be utilized to predict foot ulcer healing outcomes by providing physicians and patients with a quantitative assessment of lower limb vascular function. Although the cutoff values of TP and TBI vary in the literature, in general, a toe pressure of 70–110 mmHg or TBI > 0.5–0.75 is considered to be normal. A TP of less than 30 mmHg reflects an increased likelihood of a nonhealing lower limb ulcer. Because of this, the International Working Group on the Diabetic Foot currently recommends urgent imaging and potential revascularization in patients with a TP of <30 mmHg and a concurring foot ulcer [20, 21]. It is important to note that TBI also has some limitations, particularly in patients with Raynaud's or scleroderma. Unlike in ABPI testing, TBI is calculated by measuring both the large and small vessels in the foot and is consequently impacted by these conditions [24–27].

Skin Perfusion Pressure

Skin perfusion pressure (SPP) is considered to be a precise and noninvasive method in the assessment of tissue viability [22, 23]. It is a useful and independent predictor of wound healing in patients with ischemia of the limb. Moreover, its results are not affected by calcified arteries like the results seen with ABPI [23, 24]. It is especially useful in helping physicians decide

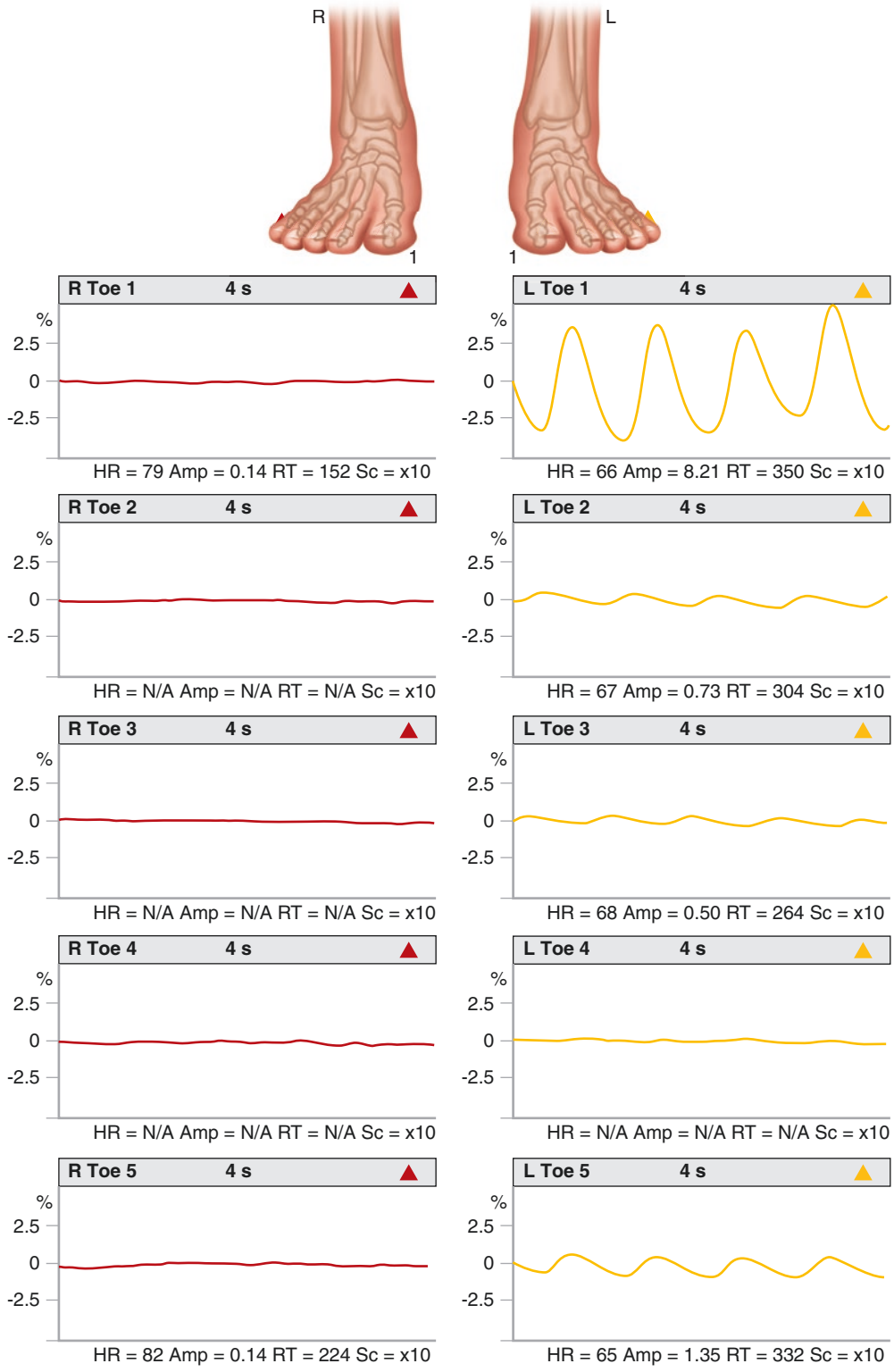

Fig. 8.2 Digit plethysmography exhibits severely dampened to unobtainable toe waveforms at room temperature characteristic of the low amplitudes associated with peripheral arterial disease, digital arteriolar occlusive disease, or vasospasm in the right foot and in the left second to fifth toes

between conservative therapy, revascularization, and the need for amputation, as well as the level of the amputation recommended [23]. By using a laser Doppler and radioisotopic clearance techniques, skin perfusion pressure can be achieved [25]. More specifically, a cuff is inflated and the pressure is subsequently released very slowly. The pressure at which the movement of red blood cells, washout of isotope, or the reappearance of pulsatile flux occurs is recorded as the SPP. [26]

30 mmHg and 40 mmHg are the most commonly used pressure cutoff points during the measurement of SPP. Recent literature has stated that the optimal SPP cutoff for predicting wound healing is 30 mmHg, with a sensitivity of 81.4% and a specificity of 69.2% [27]. The probability of wound healing with SPP values >30 mmHg, 40 mmHg, and 50 mmHg was determined to be 69.8%, 86.3%, and 94.5%, respectively.

Doppler Arterial Waveforms

Arterial Doppler blood flow can be measured by using continuous Doppler or pulse-wave ultrasound probes. These methods allow the arterial Doppler waveforms to be measured in a noninvasive fashion along the course of arteries of the lower limbs, extending from the aorta to the pedal arch [9, 28–30].

In ultrasound probes set to pulse-wave Doppler mode, the transducer emits ultrasound in pulses, and the velocity of the blood at the precise location of the probe is measured in real time [31].

In order to prevent vasoconstriction or vasodilatation of the vessels in question, the arterial measurements are recorded in the supine position and at neutral (20–25 °C) room temperature. The waveforms are measured at different levels along the arterial vessels of the lower limbs, and this can be done with or without the use of 2D mode imaging [32].

When evaluating a normal waveform, it is important to recognize its triphasic nature and its components. The first upstroke creates a sharp peak, which corresponds with the high flow of systole. The subsequent downstroke corresponds with the inverse flow created by the beginning of diastole. The final small peak of the waveform is caused by the aortic recoil present at the end of diastole (Fig. 8.3) [33].

However, when there is an interruption in blood flow within a vessel or significant atherosclerotic disease, the resultant reduction in vessel distensibility can diminish the second and third components of the normal waveform. This can result in a biphasic or monophasic wave appearance on ultrasound [34, 35].

In cases of arterial stenosis, the amplitude of the ultrasound wave can become progressively diminished, and the wave peak can become delayed, resulting in a monophasic waveform distal to the stenosis. In contrast, blood flow at the site of the stenosis is accelerated, leading to an increased wave amplitude and early wave peak [30].

Duplex Ultrasonography

Duplex ultrasonography is a noninvasive diagnostic test that is commonly used for the detection of vascular disease in peripheral and central arteries and veins [9]. This technology combines blood flow measurements, achieved by pulsed Doppler spectral analysis, and anatomic information, achieved by B-mode and color Doppler imaging.

Patient positioning is an important component of duplex ultrasound testing. The full arterial scan is performed with the patient in the supine position and the legs adducted and hips externally rotated by 10°. The scan covers the arterial anatomy from the saphenofemoral junction to the tibial arteries. In regard to the detection of significant arterial disease, duplex imaging has a sensitivity of 80% and specificity between 90% and 100%. Furthermore, it has the capability of providing important information by imaging the cross-sectional area of the vessel and longitudinally imaging the vessel walls from several angles (Fig. 8.3) [36].

Another useful aspect of duplex imaging is its ability to allow assessment of plaque morphology, which allows the differentiation of thrombi from calcified plaque. It can also identify disruption of the intimal wall following trauma, hemorrhage, and dissection [37]. However, several limitations

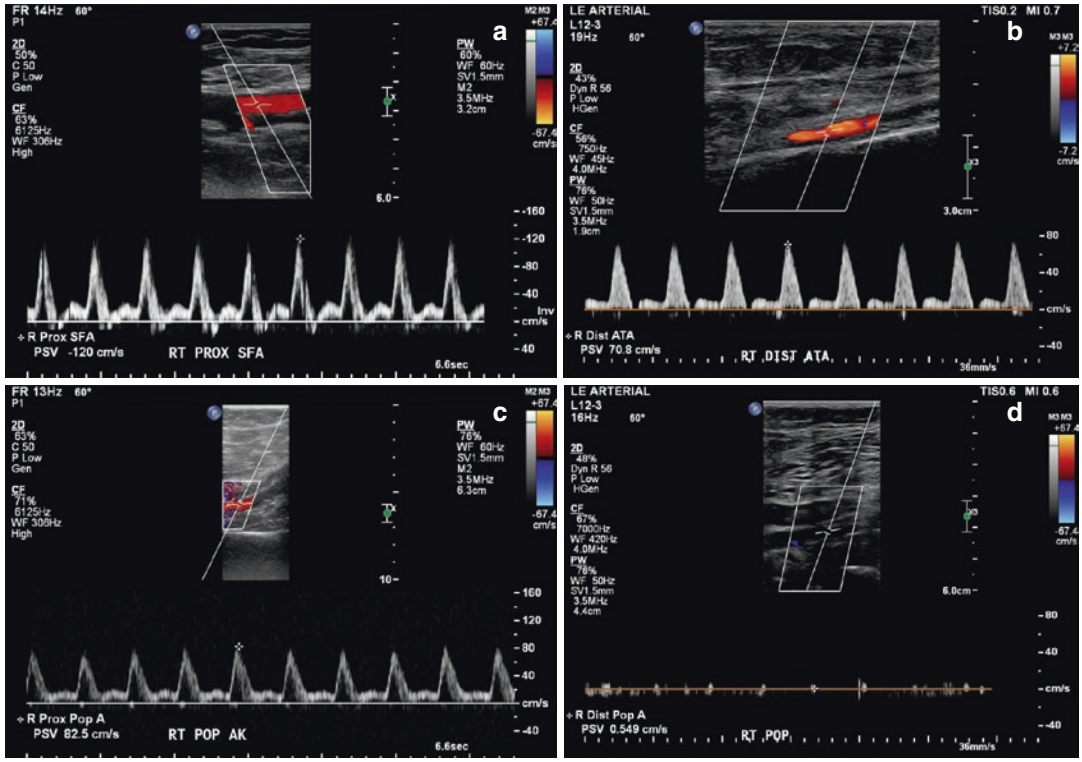

Fig. 8.3 Types of Doppler waveforms from a peripheral artery. (**a**) The triphasic waveform corresponds to a Doppler waveform morphology with three "phases." A sharp ascending branch (systolic phase) with a short rise time and then a descending branch comprising a retrograde portion and an anterograde portion during the diastolic phase. (**b**) The biphasic waveform corresponds to a Doppler waveform morphology with two "phases." A sharp ascending branch (systolic) with a short rise time and then a descending branch and a retrograde portion during the diastolic phase. (**c**) The sharp monophasic waveform corresponds to a Doppler waveform morphology with an ascending branch (systolic phase) with a short rise time, a rapid descending phase (short fall time), and no retrograde portion during the diastolic phase. (**d**) The "blunted" monophasic waveform corresponds to an extension of the ascending branch rise time (systolic phase), with no retrograde diastolic portion. This is found downstream from an "obstruction" [58]

do exist. The presence of extremity edema, vessel calcification, and excess subcutaneous fat can impede Doppler signal velocity, thus disrupting the visualization of the structural characteristic of the vessel, as well as disrupting the plaque morphology. Another limitation to duplex ultrasonography is its limited field of view. Unlike in angiography, where many branch views and vessel segments can be appreciated simultaneously, duplex ultrasonography only allows the visualization of small amounts of information at a given time. Duplex ultrasonography has been shown to correlate relatively well with its more invasive counterpart, angiography. From a diagnostic standpoint, it is important to note that there is increased agreement between duplex ultrasonography and conventional angiography above the groin and less agreement between the two tests below the groin [38].

Lastly, duplex ultrasonography is inherently operator dependent, requiring appropriate training and technological skill to optimize its effectiveness and accuracy.

Angiography

Angiography is considered the gold standard of arterial assessment; this is due to its ability to effectively outline the entire arterial system [9].

Angiography combines x-ray imaging tests with a contrast agent to allow visualization of blood flow within the arteries, allowing the detection of any blockages that may be present. A catheter is inserted into an artery (commonly the common femoral artery) and is used as port through which to inject the contrast agent. A small dose of ionizing radiation emitted through x-ray imaging provides the resultant images.

Angiography is the preferable diagnostic tool of choice in patients who are obese, have extensive vessel calcifications, have arteriovenous malformations, or have bilateral diffuse atherosclerosis disease. Not only does angiography allow visualization of the entire arterial system in question, it also aids in therapeutic decision-making. It allows for the planning of arterial bypass surgery and the treatment of any concerning vessel lesions by angioplasty or stenting. It also allows for the assessment of pressures across a vascular lesion and can be used to guide endovascular interventions [39, 40].

Although widely useful and effective, angiography is associated with a number of risks and complications. These include the risk of arterial puncture bleeding, arterial dissections, cholesterol emboli, arteriovenous fistula formation, thrombus embolization to legs, and contrast-induced allergic reactions. It is also worth noting that patients with decreased renal function should, ideally, not undergo contrast-enhanced investigations [39].

Microvascular Tests (Microcirculation Assessment): Transcutaneous Oxygen Saturation

Transcutaneous oximetry (tcPO2) is considered to be a noninvasive and simple test for the evaluation of local skin microcirculation, tissue ischemia, and peri-wound oxygenation [36]. The tcPO2 value is dependent on four variables; these are the cutaneous circulation, arterial partial pressure of oxygen (pO2), oxygen consumption by skin tissue, and oxygen infusibility through the skin. Although TCPO2 measurements can be calculated from any area of the body, the most commonly measured locations for assessment of lower extremity arterial perfusion are the dorsum of the foot, the anteromedial aspect of the calf (10 cm below the patella), and the thigh (10 cm above the patella).

TcPO2 provides specific information regarding the skin surface oxygenation using a Clark-type polarographic oxygen electrode, which measures the electrochemical reduction of oxygen on the skin surface. The Clark-type polarographic oxygen electrode measures ambient oxygen concentration using a catalytic platinum surface. During tcPO2 testing, the electrode is heated up to 43.5 C and placed on the skin [41]. The warmed electrode causes vasodilation of the arterioles and capillaries in contact with the electrode service, thereby promoting the diffusion of oxygen toward the electrode. The probe is then able to estimate the vasodilatory capacity of the microvessels by directly measuring the post-heating hyperemia.

TcPO2 measurements are impacted by regional blood flow, epidermal thickness, metabolic rate, local glands, and production and consumption of tissue gases. The stratum corneum layer of the epidermis barrier prevents oxygen diffusion [42].

A tcPO2 value greater than 40 mmHg is considered normal [43]. Pressures between 30 and 40 mmHg indicate adequate healing and mild circulation compromise. Pressures between 20 and 30 mmHg indicate moderate compromise of the oxygen saturation of the skin and would be associated with a delay in wound healing [43]. A tcPO2 of less than 20 mmHg would indicate a nonhealing wound and a risk for further ulceration [41].

As with other tests, tcPO2 has limitations. Results can be unreliable in obese patients and in patients with edema or infection [37]. Furthermore, patient position can also affect results. Skin manifestations such as inflammation, scar tissue, irradiated tissue, and sclerosis can affect oxygen diffusion and consequently impact results. The increased consumption of oxygen in the skin present in inflammatory conditions can result in decreased tcPO2. Patients with cutaneous morphea, scleroderma, and hypertro-

phic scars may also have reduced tcPO2 [44–46]. Drugs that are vasoactive can also impact tcPO2 results [47].

Aside from these limitations, tcPO2 has a number of other drawbacks. These include high equipment costs, time inefficiency, and high rates of variability among observers. Lastly, plantar surfaces in patients with neurotrophic foot ulcers cannot be tested using this modality, as the plantar aspect of the foot cannot be physically assessed.

Venous Studies

Venous Doppler

The handheld venous Doppler is considered to be a noninvasive test, which is used to assess deep and superficial veins [9]. Patient positioning during this test consists of the patient either sitting at approximately 40 degrees or the patient positioned in the reverse Trendelenburg position at 30 degrees. The patient's knees should be bent slightly and the patient's legs should be externally rotated. Subsequently, the Doppler probe is placed over the vein while the calf is compressed distally. The Doppler is then able to detect the rapid flow of the blood traveling up the leg.

It is important to note that, at rest, venous flow is described as spontaneous and phasic [48]. In a normal leg, venous valves normally close and flow halts following compression. A short retrograde flow may also be heard at this time. However, a second retrograde flow wave can be heard after compression, if the venous valves have failed. Furthermore, reverse flow that lasts for more than 1 second in the deep veins or reverse flow that lasts half a second in the superficial veins is diagnostic of venous reflux and, consequently, significant venous incompetence. In order to distinguish superficial venous reflux from deep venous reflux, tourniquets can be used to occlude the venous system around the probe. Incompetence of the great saphenous vein can be identified relatively easily using this technique. However, the diagnostic accuracy diminishes in the case of incompetence of the lesser saphenous vein or of the deep venous system. This reduction in accuracy can be attributed to anatomical variations; examiner-dependent differences may also impact the accuracy of the Doppler [49, 50].

Color Flow Duplex Ultrasonography

Color flow duplex ultrasonography is another noninvasive test used to assess veins. It provides anatomical and flow data for the assessment of reflux and patency within specific veins. Color duplex indicates the direction and velocity of blood flow, thus allowing the detection and location of venous occlusion, venous stenosis, and/or venous reflux (Fig. 8.4.) [9, 51]. In regard to patient positioning, duplex ultrasound scanning should be performed with the patient in the standing position to allow maximum venous dilation. Specific provocative maneuvers such as foot/calf compression, ankle dorsiflexion, and Valsalva may be performed to create physiologic flow [52].

Furthermore, color flow duplex ultrasonography can be used to detect clots in large vessels and is capable of visualizing the deep and superficial calf veins. By compressing the veins with an ultrasound probe, thromboembolic events in the leg veins can be diagnosed with a high degree of accuracy [53]. It is important to note that color flow duplex ultrasonography is a highly operator-dependent diagnostic tool and requires proper training.

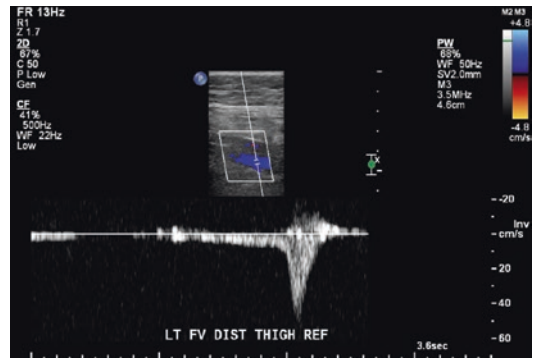

Fig. 8.4 Venous Doppler: patent and compressible flow in the femoral vein with no evidence of deep venous thrombosis, thrombophlebitis, or valvular incompetency

Venography

Venography provides a view of the entire venous system. Color flow duplex ultrasonography has largely replaced venography in the diagnosis of deep vein thrombosis. However, venography can still offer some additional information regarding thrombus age and valve damage [54]. Venography is associated with risks similar to angiography, including contrast-induced allergic reactions, pain, infection, and superficial thrombophlebitis at the access puncture site [55, 56].

See Table 8.2 for descriptions, indications, interoperations, benefits, and limitations of vascular studies.

Summary

Nearly ten million Americans are affected by peripheral artery diease [3, 4]. The presence of PAD does not only hinder lower-extremity wound healing but can also lead to ineffective wound healing. The diagnosis of PAD is based primarily on the patient's description of his/her symptoms, medical history, and physical examination in combination with vascular testing. In patients with DM, ABPI measurements are limited due to vascular stiffness as the result of glycosylation of the vessel wall; in these cases, TBI or TP measurements may be deemed necessary.

The use of a handheld, continuous-wave or pulsatile-wave Doppler should be included in every patient's clinical assessment whenever leg ulcers are present or PAD is suspected, especially if the patient does not present with palpable pedal pulses. Select patients may benefit from further investigations that confirm or assess the severity of the arterial disease. Furthermore, in patients with absent pulses or a high suspicion for significant vascular disease, a thorough vascular assessment should be obtained prior to instituting any form of compression therapy (Fig. 8.4).

Duplex ultrasonography is a noninvasive diagnostic test that is commonly used for the detection of vascular disease in the arteries of the lower extremities [37]. With regard to the detection of significant arterial disease, duplex imaging has a sensitivity of 80% and specificity between 90% and 100%. Furthermore, it has the capability of providing important anatomical information by noninvasive imaging such as the cross-sectional area of the vessel [36, 38]. Duplex ultrasonography has been shown to correlate relatively well with its more invasive counterpart, angiography. A limitation to duplex ultrasonography is its limited field of view. Unlike in angiography, where many branch views and vessel segments can be appreciated simultaneously, duplex ultrasonography only allows small amounts of visual information at a given time.

Angiography is considered the gold standard of arterial assessment; this is due to its ability to effectively outline the entire arterial system [9]. It is also the most widely used method for anatomic evaluation of PAD, when intervention is considered or planned. Angiography combines x-ray imaging tests with a contrast agent to allow visualization of blood flow within the arteries, allowing the detection of any blockages that may be present.

Transcutaneous oximetry (tcPO2) is considered to be a noninvasive, simple, and reliable test used for the evaluation of local skin microcirculation, tissue ischemia, and peri-wound oxygenation [36]. Measurement of tcPO2 is helpful, in determining the optimal level for amputation. It is especially useful in diabetic patients, as it is not affected by arterial calcification.

Up to 30% of ulcers are considered to be mixed arteriovenous ulcers; therefore, examination of venous system should be included as a part of the primary patient evaluation.

When considering the assessment of deep vein thrombosis, color flow duplex examination is the investigation of choice [57]. It also provides great value in the assessment of perforated and junctional reflux prior to varicose vein surgery. With this technique, exact localization of reflux within the superficial and deep systems is possible. Although color flow duplex provides the best method of quantification of reflux, venography can provide additional information regarding thrombus age, valve damage, and a much wider view of the venous system as a whole.

Table 8.2 Vascular studies: descriptions, indications, interoperations, benefits, limitations[59]

Study name	Description	Indication	Interpretation	Benefits	Limitation
Ankle-brachial pressure index (ABPI)	Assessing by using blood pressure at the ankle and the blood pressure in the upper arm (Fig. 8.1)	Suspected peripheral artery disease	Normal: 0.91–1.3 Mild disease: 0.7–0.9 Moderate disease: 0.41–0.69 Severe disease: ≤0.4	Noninvasive, cost effective, time effective	Falsely elevated or normal in diabetic and elderly patients Impacted by vascular stiffness and leg edema
Toe pressure (TP) and toe brachial index (TBI)	TP: assessed by using plethysmography or photocell TBI: assessed by using the systolic pressure of brachial pressure and the great toe	Peripheral artery disease Estimate lower limb ulcer healing outcomes	Normal TP: 70–110 mmHg Normal TBI: > 0.5–0.75+	Not affected by arterial stiffness	Affected by local vasoconstriction Impacted by patients with Raynaud's and/or scleroderma
Skin perfusion pressure (SPP)	Evaluates blood flow to impaired tissue using a laser Doppler	Predicts lower limb ischemia outcomes and guides therapy approach	Adequate wound healing predicted at pressure > 30 mmHg	Noninvasive Not affected by edema, anemia, callus, or wound location	Motion artifact
Arterial Doppler	Measures the velocity of the blood at the precise location of the probe	Measures degree of arterial stenosis	Dependent on amplitude of the ultrasound wave, wave peak time, and blood flow rate	Noninvasive Quick No side effects	Presence of extremity edema, vessel calcification, and excess subcutaneous fat can impede Doppler signal velocity
Angiography	Using x-ray imaging tests with a contrast agent to allow visualization of arteries' blood	Recognition of any obstructions that may be present and help in therapeutic decision-making	Exact location of stenosis, assessing the degree of stenosis	Gold standard for evaluation of arteries' blood flow Visualization of the whole arterial system	Risk of puncture bleeding, dissections, cholesterol emboli, arteriovenous fistula, and contrast-induced allergy
TcPO2	Assessed by using four variables: cutaneous circulation, arterial partial pressure of oxygen (pO2), oxygen consumption by skin tissue, and oxygen infusibility through the skin	To assess the local microcirculation, tissue ischemia, and peri-wound oxygenation	Normal: > 40 mmHg Mild circulation compromise: 30–40 mmHg Moderate compromise: 20–30 mmHg Nonhealing wound: < 20	Noninvasive, no adverse events, quick	Impacted by regional blood flow, epidermal thickness, metabolic rate, inflammation, scar tissue, irradiated tissue, and sclerosis High equipment costs, time inefficiency, and high rates of variability among observers

Because every vascular diagnostic test has its own set of limitations, vascular specialists continue to rely heavily on clinical judgment when assessing arterial and venous systems. Assessing vasculature remains an inexact science; therefore, there is ongoing research that attempts to overcome this obstacle through the development of new tools. This will ultimately allow physicians to more quickly and accurately quantify the vascular supply of any anatomical distribution.

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Compression Therapy

9

Joshua S. Mervis and Hadar Lev-Tov

Abbreviations

4LB	4-layer bandage
ABI	Ankle-brachial index
CHF	Congestive heart failure
CVI	Chronic venous insufficiency
IPC	Intermittent pneumatic compression
SSB	Short-stretch bandage
VLU	Venous leg ulcer

Introduction

Compression therapy is the primary treatment for chronic venous insufficiency (CVI) and venous leg ulcers (VLUs). In the outpatient clinic, dermatologists often use compression to treat CVI-related sequelae, such as varicose veins, edema, venous dermatitis, and lipodermatosclerosis. Compression counteracts the mechanisms that lead to the symptoms and manifestations of chronic venous disease by ameliorating venous hypertension. Various compression modalities are available, including stockings, elastic and inelastic bandages, pneumatic pumps, and specialized garments. Studies have consistently demonstrated that compression increases healing rates compared to no compression. Moreover, comparisons between specific types of compression have generally shown that multilayer elastic bandages are the most effective for healing chronic wounds. Nonetheless, the different compression systems have pros and cons that may make certain types of compression more or less appropriate depending on clinical and social factors. Patient compliance has historically been one of the biggest challenges with compression, and new devices have sought to make compression more comfortable and acceptable to patients. Finally, evidence is emerging for use of compression therapy in wounds other than VLUs and is well established for treatment of lymphedema. Thus, a thorough understanding of compression is important for all dermatologists and, in particular, those with an affinity for wound care.

Compression Therapy: Mechanism of Action

The veins of the lower extremities contain one-way bicuspid valves that ensure blood flow toward the heart and prevent pooling of blood distally [1]. Blood in the superficial venous sys-

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A. Alavi, H. I. Maibach (eds.), *Local Wound Care for Dermatologists*, Updates in Clinical Dermatology, https://doi.org/10.1007/978-3-030-28872-3_9

tem normally flows through perforator veins into the deep venous system. With ambulation, the calf muscle pump contracts to propel blood in the deep veins upward against gravity toward the heart, resulting in venous emptying and reduced venous pressure [2]. When valvular function fails, either due to genetic or acquired conditions resulting in reflux, or the calf muscle pump is ineffectual, blood pools and elevated pressures are transmitted retrograde through the venous system [3]. The resulting ambulatory venous hypertension, the defining feature of CVI, may result in lower extremity edema, pain, venous dermatitis, hyperpigmentation, lipodermatosclerosis, and, ultimately, ulceration. Compression therapy moderates venous hypertension by increasing the velocity and volume of blood flow via reduction in vein diameter, improvement in valvular function, and enhancement of calf muscle pump action. The hemodynamic benefits of compression have been corroborated by numerous studies that have demonstrated increased venous ejection fraction, reduced residual volume, and decreased reflux times [4, 5].

Other secondary effects of compression include increased microcirculation and tissue oxygenation [6], paradoxically improved arterial flow [7], and reduced pro-inflammatory cytokines and increased anti-inflammatory cytokines in VLUs [8]. Antithrombotic and fibrinolytic effects have also been demonstrated in studies, though the clinical implications of these findings are still unclear [9–12]. These effects of compression apart from its action on venous hypertension are potentially significant in relation to the possible benefits of compression therapy for various wound types.

Compression Pressure

A variety of compression modalities are available. When compression stockings, wraps, or garments are used, compression is generally applied from the base of the toes to just below the knee. The amount of external pressure, or sub-bandage pressure, can be modeled using a modified version of Laplace's law, which relates pressure as a function of number of bandage layers, tension, bandage width, and limb circumference [13]:

$$\text{Sub-bandage pressure} \propto \left[\text{number of layers} \times \text{tension}\right] / \left[\text{bandage width} \times \text{limb circumference}\right]$$

Accordingly, ankle pressure will be greater than calf pressure, assuming limb circumference increases proximally and tension is uniformly applied. This principle underlies traditional compression techniques in which graduated compression, greatest at the ankle, is applied to leg. While there exists a widely held belief that graduated pressure is necessary to drive blood upward, new research has shown that higher pressures over the calf improve venous return by augmenting calf muscle pump function. Such anti-graduated stockings and wraps have been found to improve edema and increase venous ejection fraction in patients with CVI [14, 15]. Additional research in this area, however, is still needed.

Compression Modalities

Numerous modes of compression are widely available, which are summarized in Table 9.1.

Compression Stockings

Elastic graduated compression stockings are the traditional nonsurgical intervention for CVI and prevention of venous ulcers. Compression stockings can be removed overnight when the feet are elevated in bed but should be worn throughout the day or whenever upright. In addition, stockings lose tension with repeated use and should be replaced every 6 months when used daily.

Table 9.1 Compression therapy modalities

Compression type	Examples	Strengths	Weaknesses	Practical tips
Stockings	Many brands widely available	Various strengths of compression available Can use multiple lower pressure stockings to ease application and increase total compression Provide continuous, uniform, graded compression	Difficult to apply making compliance low Often cause significant pain, discomfort, or itch May traumatize wounds or intact skin with application	Professionally fitting patients often lead to better adherence
Elastic (long-stretch) bandages	Ace™ Biflex® Dauerbinde® K SurePress®	Highly extensible High resting pressure Inexpensive Washable and reusable forms available	Low working pressure Lose elasticity with continued use Tend to unravel over time Risk of incorrect application	"50–50 rule": When applying use 50% of the stretch and overlap 50% with each repetition
Inelastic (short-stretch) bandages	Unna boot (zinc oxide paste-impregnated bandage) Comprilan® Panelast® Porelast®	Low resting pressure is more comfortable, better tolerated Generate high working pressure Unna boot can soothe itch	Low resting compression after initial application Mechanism largely dependent on calf muscle contraction Unna boot application requires training	Can help patients with severe venous dermatitis
Multicomponent bandage systems	Profore®, Profore® Lite Coban™ 2, Coban™ 2 Lite FourFlex™	Higher compression Sustained compression "Lite" or reduced compression with fewer layers for patients with arterial disease Can often be left in place for 1–2 weeks if wound drainage well controlled	Very difficult to self-apply Application requires significant training Compression pressures are very dependent on technique and vary significantly even among trained staff Can cause new wounds after initial or inappropriate application along skin fissures due to nonuniform compression	Applying petroleum jelly-based ointment to leg can help relieve itch and prevent slippage of bandages
Garments	CircAid® FarrowWrap® CoolFlex™	Compression can be easily adjusted Relative ease of application Easily removed for washing, bathing	Expensive Can be bulky	Caution with garments that do not cover the foot. These may need an adjunct device
Pneumatic compression devices	Lympha press® CircuFlow™	Intermittent pumps can be used on patient's own schedule	Expensive Must be immobile for a few hours each day	Can be used over compression bandages or stockings

Compression stockings are available in various strengths and are classified according to the interface ankle pressure. The effective pressure exerted over the leg will depend on the user's leg circumference and shape, as well as the elasticity of the particular stocking material. A minimum of 20 mm Hg at the ankle is recommended for mildly symptomatic CVI, and pressures of 40 mm or greater are recommended for treatment of VLUs [3]. While compression stockings are not generally regarded as treatment for VLUs, a recent randomized trial found that a two-layer stocking system was as effective as four-layer elastic bandages for the complete healing of VLU [16]. Though the potential for trauma to the wound, pain with application, and noncompliance risks usually make compression bandages preferable for patients with lower extremity wounds, stockings may be a reasonable first-line treatment for certain patients [17]. As a means of secondary prevention, compression stockings are recommended to prevent recurrence of VLU. While a recent meta-analysis was not able to validate this claim based on a lack of availability of highest-quality evidence, individual studies have found that compression stockings do reduce rates of VLU recurrence [18].

Compression stockings have been shown to reduce lower extremity edema and pain and to increase user activity level and quality of life in patients with CVI but without VLUs [19–21]. Studies comparing different strengths of compression stockings have found equivalence among stockings 20 mm Hg and greater for edema and symptom control [22], while compression of 10 mm Hg or less was less effective than 15–20 mm Hg [23]. Moreover, while different lengths of stockings, namely, knee and thigh high, are available, current evidence does not suggest benefit of one over the other [21].

Compression Bandages

Whereas compression stockings can be readily applied by the wearer, compression bandages are usually put on by a skilled nurse or caretaker and are typically used for patients with VLUs. Compression bandage systems typically contain multiple layers and are classified based on the elasticity of the compressive layers. Elastic, or long-stretch, bandages are 100–200% extensible and provide a constant resting recoil pressure [3]. Elastic bandages should be applied at 50% of maximal stretch with 50% overlap in bandage width. Typical elastic compression systems consist of four layers, with the first two layers providing padding and a smooth surface over which the outer two elastic compression layers can be uniformly applied (Fig. 9.1).

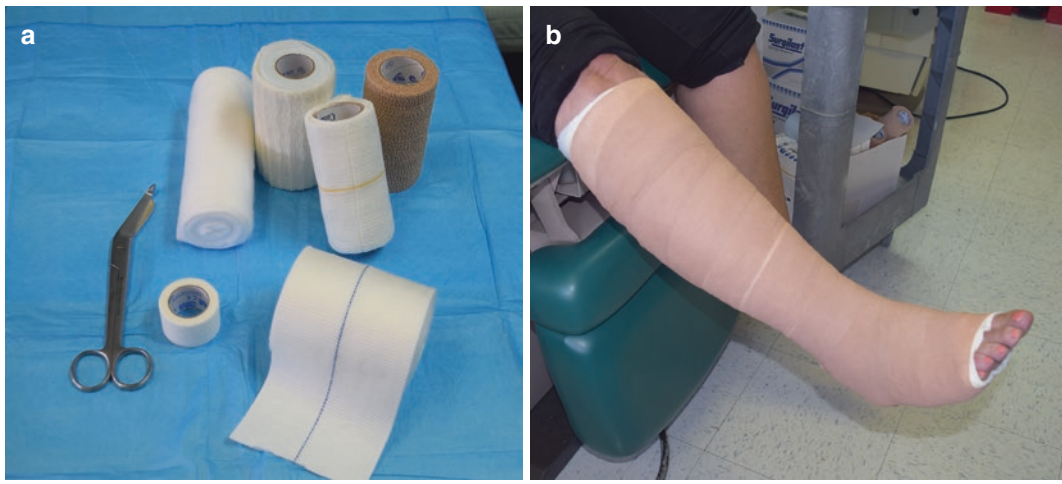

Fig. 9.1 (**a**, **b**) Four-layer elastic compression system

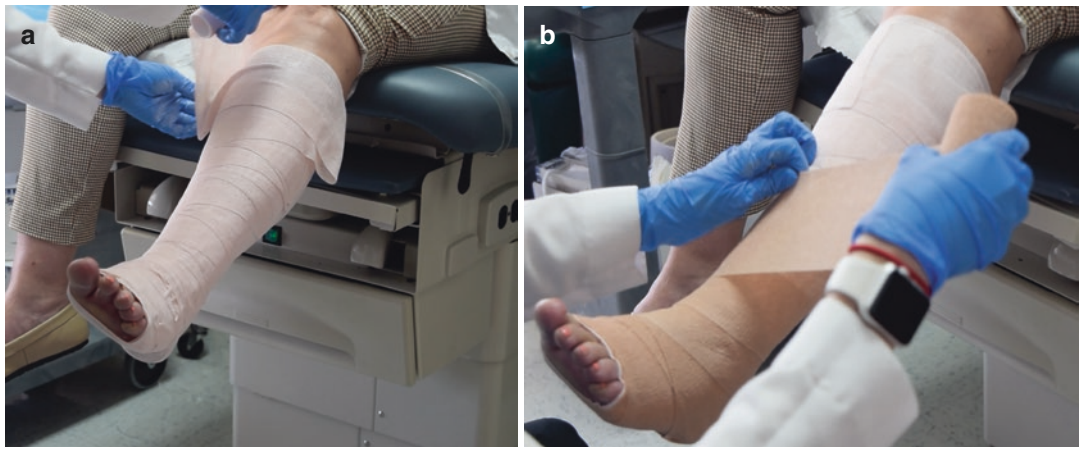

Fig. 9.2 (**a**, **b**) Inelastic compression with an Unna boot

On the other hand, inelastic, or short-stretch, bandages (Fig. 9.2) are 40–99% extensible, making them stiffer and more resistant to expansion [3]. This property of inelastic compression bandages confers higher pressures during ambulation, as contraction of the calf muscle against the rigid bandages helps propel blood toward the heart. Inelastic compression, thus, provides high working pressures with ambulation or when the legs become edematous due to blood pooling. By contrast, after application of inelastic wraps and the initial reduction in edema, resting sub-bandage pressures are quite low.

A measure of bandage stiffness, termed the "static stiffness index," describes the increase in sub-bandage pressure when standing up from a supine position [24]. Elastic bandages have a static stiffness index of <10 mm Hg, while inelastic bandages, which yield lower resting pressures and produce higher peak pressures, result in greater static stiffness indices [25]. Moreover, multicomponent elastic compression systems result in stiffer compression than the elasticity of the individual layers would suggest, as friction between the layers produces increased resistance to expansion [26].

Both elastic and inelastic compression have demonstrated efficacy in treating VLUs. Due to the centrality of calf muscle contraction in the mechanism of inelastic compression, inelastic bandages are often discouraged for people who are unable to walk or in whom calf muscle pump function is impaired. Nonetheless, the Canadian Bandaging Trial, a recent large randomized study comparing elastic 4-layer bandages (4LB) with short-stretch bandages (SSB), found that mobility was not a factor in predicting healing of VLUs [27]. Furthermore, this study found no significant difference in healing time between 4LB and SSB in the overall cohort of 424 subjects [27]. The most recent Cochrane meta-analysis to address this question found that 4LB appear to be more effective than SSB in healing VLU [28]; however, when the results of the Canadian Bandaging Trial are included in the meta-analysis, the apparent benefits of 4LB were no longer evident [29].

In addition, inelastic compression may be advantageous when lower resting pressures are desirable, such as in patients with substantial leg pain or significant arterial disease, where ischemia secondary to compression is a concern [3]. Inelastic compression is also simpler to correctly apply in that consistent and appropriate leg pressures are more easily produced. Studies have shown that pressure generated by compression bandages, especially elastic compression, is highly susceptible to inter- and intra-user variation [30–32]. Moreover, even when applied by trained nurses, both elastic and inelastic compression pressures do not meet the target range in the majority of attempts [33]. Of note, a new bandage system has been devised that seeks to overcome this challenge. This compression system is comprised of an elastic bandage with markers

that must be aligned and movable inelastic patches that confer stiffness, essentially converting the elastic bandage into an inelastic bandage that produces a consistent pressure independent of the applier [34].

Compression Devices and Garments

Pneumatic Pumps

Pneumatic compression pumps can be used to provide either sustained or intermittent compression. These devices are particularly useful for patients with restricted mobility, as they are set up in the home and can be used simultaneously with stockings or bandages. Intermittent pneumatic compression (IPC) has been shown to mimic the effects of inelastic bandages during ambulation, providing cyclic pressure that recapitulates calf muscle pump function [35]. Evidence suggests that IPC, either used alone or in combination with graduated compression for 1 hour 2–3 times per day, improves healing of VLUs [36, 37].

Compression Garments

A variety of compression garments (Fig. 9.3) are available that provide short-stretch inelastic compression, most commonly via Velcro straps that the wearer wraps around the leg. One of the major benefits of a compression garment is that it is readily adjusted or removed as desired. Thus, they provide the patient a greater degree of autonomy. Additionally, in many cases where a patient cannot tolerate compression stockings or lacks the hand strength to don them, a compression garment may be less painful and easier to put on.

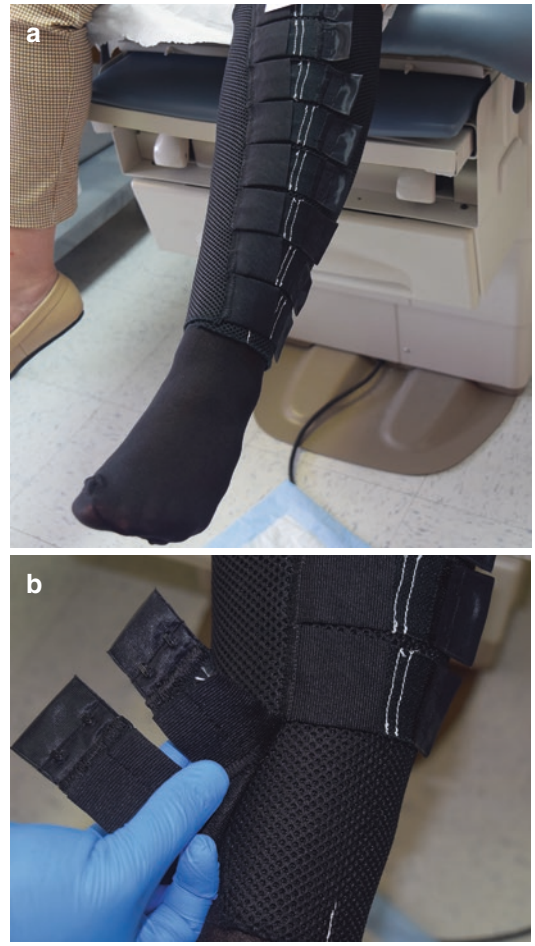

Fig. 9.3 (**a**, **b**) Compression garment that utilizes a porous mesh with adjustable hook straps

Adherence to Compression Therapy

Patient adherence rates with compression therapy are generally quite low. In one large study, only one third of patients with CVI used compression stockings on most days or a daily basis [38]. For a wide variety of reasons, compression is not easily integrated into patients' lives. When bandages are applied to patients with ulcers, they prevent the patient from bathing the leg, sometimes leading to an unpleasant odor, and get in the way of normal fitting pants and shoes. Patients instructed to wear compression stockings are often physically unable to use them due to lack of strength, flexibility, or mobility. Specialized donning and doffing devices that help to mitigate these factors are available, including the stocking "butler" or donner (Fig. 9.4), hosiery gloves (Fig. 9.5), and donning pads [39]. Stockings with lower compression are easier to put on and have demonstrated better compliance rates with no difference in efficacy compared to high compression stock-

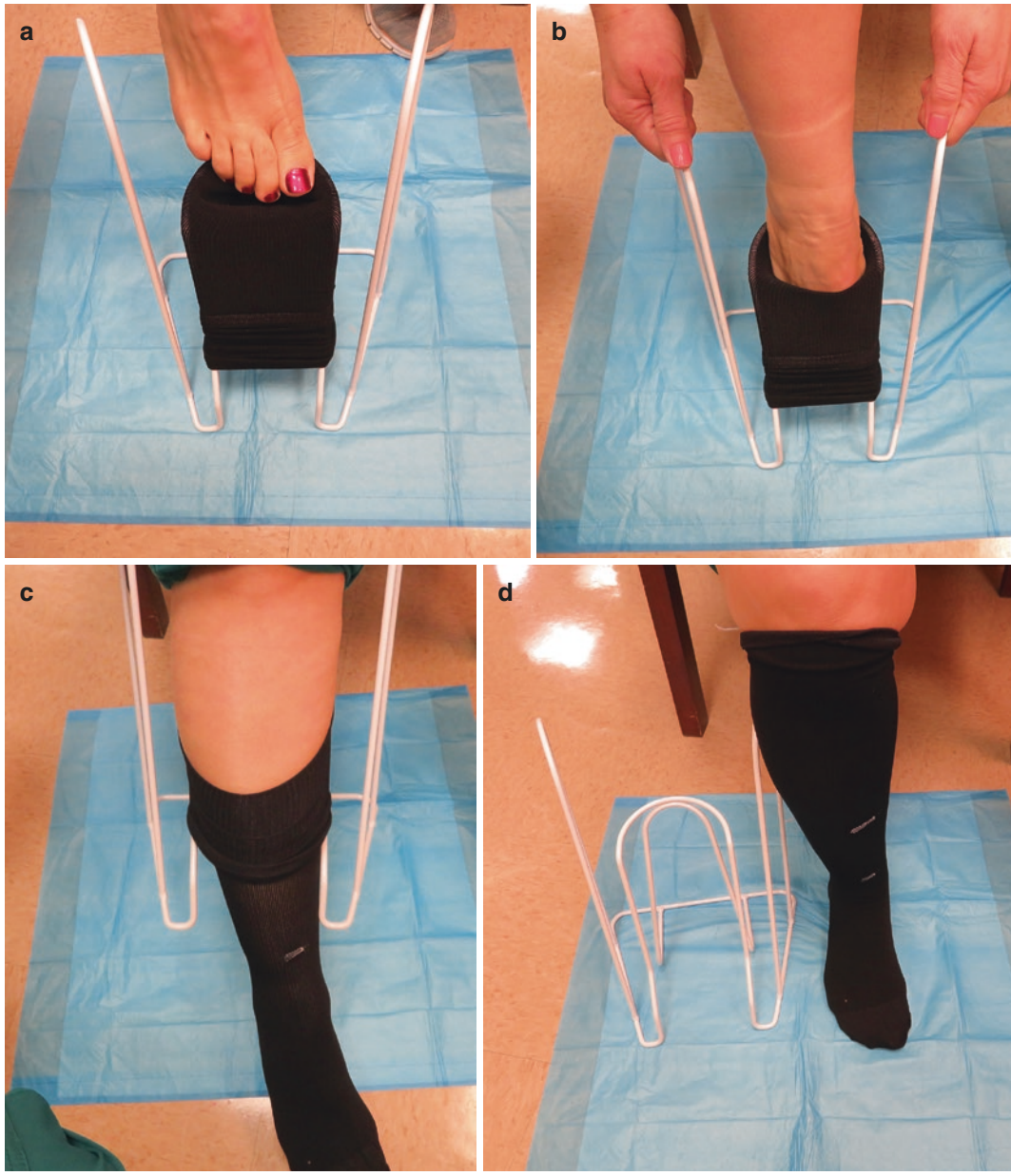

Fig. 9.4 (**a**–**d**) Stocking "butler" or donner

ings [22, 23]. Moreover, if greater compression is desired, two lower pressure stockings applied one over the other can be used to facilitate ease of application [40]. Other common reasons for non-adherence secondary to use of compression include pain, skin irritation, itch, and excessive heat [22, 38, 41]. Psychosocial reasons also play a major role in lack of patient adherence to compression therapy, as stockings or bandages may be cosmetically unacceptable and pose major social hindrances. Finally, many patients have beliefs that compression is unnecessary or not worthwhile for treating their condition [42]. Regardless of the mode of compression therapy, adherence can be increased by taking time to educate patients on the benefits of compression,

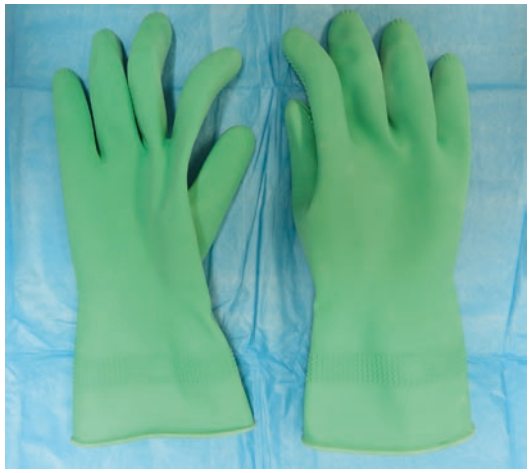

Fig. 9.5 Hosiery gloves

why it is appropriate for them, and how to properly use their compression stockings or devices.

Contraindications to Compression

Arterial Disease

Arterial blood flow must be evaluated prior to initiating compression therapy, as adding compression to already occluded vessels can lead to worsening of ischemia. Pulses can be assessed by palpation or a portable Doppler ultrasound device, but measurement of the ankle-brachial index (ABI) is a highly sensitive and specific method for identifying arterial disease [3]. The ABI is the ratio of systolic pressure at the ankle to systolic pressure at the brachial artery in the arm and can be easily measured using a blood pressure cuff and handheld Doppler [43]. An ABI of 0.9–1.2 is considered normal, while values greater than 1.2 are usually seen with arterial calcification [44]. When the ABI is above 0.8, high compression can typically be used without any concern for ischemia; however, an ABI between 0.5 and 0.8 indicates moderate arterial disease and should prompt use of compression with a lower resting pressure [3]. In such cases of mixed arteriovenous disease, four-layer compression systems can be modified by removing one of the compressive layers. "Light" compression kits with fewer components are also available. Inelastic compression, which is characterized by lower resting pressures, may be safer and more effective for patients with concomitant arterial disease [3]. Moreover, evidence exists that inelastic compression in patients with moderate arterial disease may actually improve ischemia and wound healing [45]. Regardless, compression should be used with caution in all patients with suspected arterial insufficiency. Patients should be counseled to remove compression if any signs of ischemia, such as pain, numbness, or pallor, begin to develop. An ABI less than 0.5 is indicative of severe arterial disease and is an absolute contraindication to continuous compression therapy. Even so, this population may benefit from IPC, which has been shown to improve wound healing in patients with symptomatic peripheral arterial disease or critical limb ischemia who are not surgical candidates [46, 47].

Congestive Heart Failure

Initiation of compression therapy in patients with congestive heart failure (CHF) can incite decompensation due to acutely increased preload secondary to venous decongestion [48]. For this reason, it is prudent to start with a lighter compression or compression of a single leg only [3]. Compression strength can then be increased if the patient does not experience symptomatic worsening of CHF. Compression is absolutely contraindicated in patients with decompensated CHF.

Allergy

Allergic contact dermatitis from compression materials is uncommon but can develop. Stockings and elastic bandages may contain latex, rubber, or silicone that can cause hypersensitivity reactions when in direct contact with the skin. If an allergy develops, a compression product with different material at the skin surface interface should be used.

Other Indications for Compression Therapy

Other Wound Types

Compression therapy may aid the healing of all wounds regardless of etiology, including pyoderma gangrenosum, vasculopathy, and postsurgical and diabetic foot ulcers, though the mechanisms are unclear [25, 49–54]. It must be considered that venous insufficiency is extremely common, affecting around one third of adults in the United States, and is likely to be a component of many nonhealing wounds [55]. Nonetheless, as mentioned previously, compression has a number of potentially favorable effects on wound healing independent of its effects on venous hypertension. Improved tissue oxygenation, microcirculation, and arterial flow [6, 7, 56], reduced pro-inflammatory cytokines and increased anti-inflammatory cytokines [8], and release of antithrombotic and fibrinolytic mediators [9–12] due to compression have all been demonstrated in studies. Compression bandages also provide a physical barrier that limits patients from touching their wounds and reduces likelihood of contamination. In our experience, compression accelerates healing of all wounds types and leads to better outcomes. Accordingly, we typically recommend multilayer compression bandages for anyone presenting with an ulcer on the lower extremities, except in the select instances when compression is contraindicated.

Lymphedema

Compression therapy with pneumatic pumps, multilayer wraps, stockings, and other specialized garments is a fundamental component of lower extremity lymphedema management [57, 58]. The highest strength compression that can be tolerated should be used, ideally at least 40 mm Hg [58, 59]. Compression reduces lymphatic congestion, improves lymphatic flow, maintains limb shape, and protects the skin from trauma [57].

Arm lymphedema is often seen after surgery or radiation for breast cancer due to disruption of the axillary lymphatic system. In such cases, compression with elastic sleeves and bandages or pneumatic compression pumps has been shown to be effective in reducing arm edema and improving functionality [60].

Superficial Thrombophlebitis

Superficial thrombophlebitis is the term used to describe thrombosis in the superficial venous system [61]. Compression therapy with stockings or bandages may reduce local pain and swelling [62], though evidence to support the sole use of compression without concomitant therapy is weak [63].

Post-thrombotic Syndrome

Post-thrombotic syndrome is a potential complication of deep vein thrombosis, characterized by chronic pain and swelling that can develop in the years after clot resolution [64]. A recent systematic review that included 10 randomized controlled trials found some limited evidence to suggest that elastic compression may prevent the occurrence of post-thrombotic syndrome, though large prospective trials are needed [65].

Pregnancy

Compression stockings are sometimes recommended to reduce leg swelling, heaviness, and varicosities that occur during pregnancy. Small studies have found symptomatic improvement in women using graduated compression stockings [66–68]. A systematic review, however, found little prospective data on the use of compression during pregnancy [69].

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10 Management of Diabetic Foot Ulcers: Offloading and Debridement

Chia-Ding Shih, Laura Shin, and David G. Armstrong

Introduction

Lower extremity complications due to diabetes are unfortunately common, costly, and challenging. In the USA alone, an estimated 30 million citizens have diabetes, medical cost, and lost work and wages due to diabetes and related complications total some $327 billion dollars [1]. Diabetic foot ulcers are one of the most devastating complications of this disease and are a predictor of early mortality and lower extremity amputation [2–4]. Globally the prevalence of diabetic foot ulcer is 6.3% and the prevalence in the Northern America is as high as 13% [5]. More importantly the annual mortality rate is about 11% for patients with diabetic foot ulcer and 22% among those who had amputations [6]. Physicians and surgeons around the world have recognized this devastating predicament, and there are a growing number of guidelines to treat diabetic foot ulcers and related comorbidities [7–15].

Although there is still much to learn about chronic wound healing, studies over the last few decades have shed light on the causal pathway of diabetic foot ulcer [16]. The etiology of diabetic foot ulcer is multifactorial, but one of the largest contributors to injury is trauma in the setting of diabetic peripheral neuropathy [15–18]. Increased pressure and loss of sensation can cause a relatively benign lesion such as a callus which can progress to a chronic wound if left untreated. In the presence of underlying peripheral arterial disease, these wounds can become gangrenous and ultimately lead to proximal amputations [18, 19]. Puncture wounds in patients with diabetes can also precipitate limb-threatening events [20–22]. A comprehensive understanding of pathophysiology of diabetic foot ulcer facilitates wound healing and prevents recurrence [23]. This chapter will briefly discuss the three main causative factors for diabetic foot ulcers and preventative offloading strategies for the diabetic foot.

Pathophysiology of Diabetic Foot Ulcer

Diabetic peripheral neuropathy, foot deformity, and trauma are three contributors to diabetic foot ulcerations [16, 24]. Diabetic peripheral neuropathy is perhaps the most prominent threat. The estimated prevalence of diabetic peripheral neuropathy is 50% [25]. The underlying etiology of

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A. Alavi, H. I. Maibach (eds.), *Local Wound Care for Dermatologists*, Updates in Clinical Dermatology, https://doi.org/10.1007/978-3-030-28872-3_10

diabetic neuropathy is not fully understood, but it is multifactorial and thought involves biochemical pathways associated with inflammatory responses leading to nerve dysfunction [26]. The irreversible effects of diminished peripheral nerves lead to consequences such as diminished protective sensations, autonomic dysregulation, and changes in musculoskeletal control (Table 10.1) [18, 25, 27].

Loss of protective sensation (LOPS) secondary to peripheral neuropathy marks the start of a cascade toward diabetic foot ulcer for many patients [16]. When a diabetic patient loses protective sensation (i.e., Ipswich Touch Test, Semmes-Weinstein 5.07 monofilament), the patient becomes vulnerable to continued trauma [16, 28]. A plantar ulceration can develop and lead to soft tissue infection and osteomyelitis [29].

A diabetic foot ulcer can also occur from repetitive shearing force and pressure in parts of the foot during ambulation [19]. In the advanced stage of diabetic peripheral neuropathy, the loss of integrity of the motor neurons that control intrinsic muscles of the foot can lead to digital deformities and flexion contractures [20]. Due to retrograde force from the digital deformities, peak plantar pressure under the respected metatarsal head becomes elevated [20]. Clinically callus formation can be found in these high peak plantar pressure regions [30]. Studies have found that peak plantar pressures greater than 65 N/cm^3 have a six times greater risk to developing foot ulcers [21]. Pressures greater than 200 KpA may be a prognostic factor for re-ulceration in 18 months [31].

The sudomotor innervation is also challenged when the peripheral nerve is dysfunctional. Losing autonomic control can lead to fissuring secondary to anhidrosis [27]. This combination of neuropathy, fissuring, repetitive trauma, and increased plantar peak pressure all cause skin breakdown and expose underlying soft tissues to infection. Another devastating complication associated with autonomic neuropathy and repetitive trauma is Charcot neuroarthropathy (Fig. 10.1) [32]. Charcot neuroarthropathy appears to create a local osteopenic reaction of bone leading to collapse and significant deformity (i.e., rocker bottom deformity) and ulceration if not managed and offloaded early (Figs. 10.1 and 10.2) [32].

Table 10.1 Clinical presentations in response to the neurological dysfunction

Complications of peripheral diabetic neuropathy	Clinical presentations
Sensory neuropathy	Loss of protective sensation (via Semmes-Weinstein 5.07 monofilament exam or Ipswich Touch Test or biothesiometer) Allodynia Hyperesthesia Hypothesis Loss of proprioception
Autonomic neuropathy	Charcot neuroarthropathy Anhidrosis Fissuring of the plantar skin
Motor neuropathy	Hammertoe/claw toe deformity Hallux valgus/hallux abducto valgus

Local Wound Care

Evaluation of diabetic foot ulcerations includes four main systems: vascular status, neurological findings, dermatological manifestations, and musculoskeletal presentations (Table 10.2) [18]. By focusing on these four systems, one can quickly assess the etiology, severity, and healing potential of the wound. Identifying the etiology of the wound provides perspicuous treatment plan that tailors toward a particular wound.

Wound Assessment

The diabetic foot assessment may be performed with minimal resources. Assessing limb threat is ideally performed by assessing complexity and

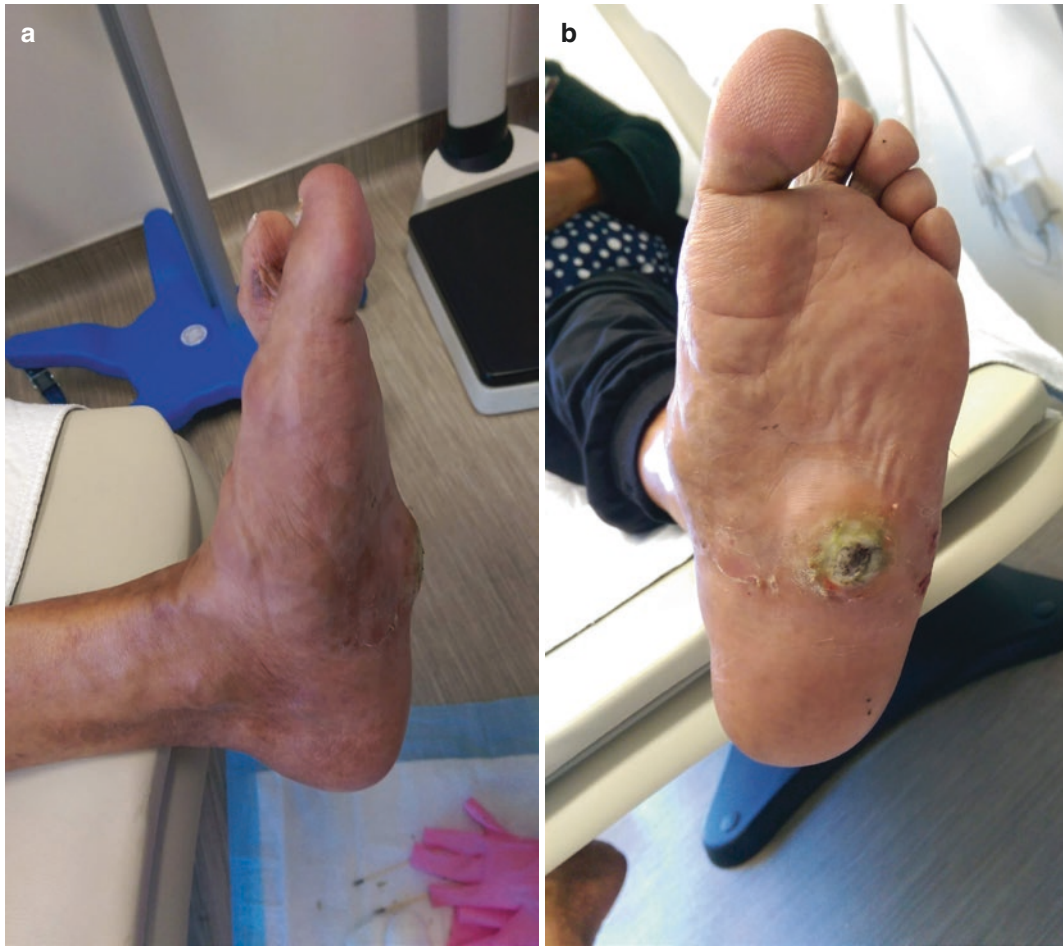

Fig. 10.1 Charcot neuroarthropathy with (**a**) collapsed midfoot (i.e., rocker bottom deformity) and (**b**) plantar ulcer

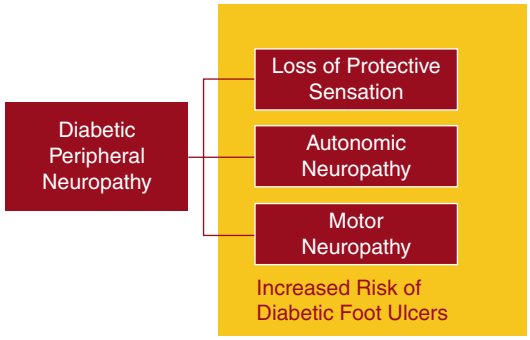

Fig. 10.2 Schematic illustration of diabetic foot ulcer pathophysiology

severity of the wound (W), ischemia (I), or foot infection (FI). This creates a limb-threat system known by the acronym WIFI [34–36]. These two systems have been well validated.

Wound Debridement

Routine debridement is essential to wound closure. Methods of wound debridement include sharp, surgical, enzymatic, autolytic, biological (larval), and mechanical [18, 37–39]. The use of different debridement technique relies on the

Table 10.2 Components of diabetic foot physical exam [18, 33]

System	Possible exam/findings	Diagnostic study
Vascularity	Palpable pedal pulses Brisk capillary refill time within 2 seconds Presence of digital hair	Ankle-brachial index (ABI) Toe-brachial index (TBI) Toe pressure Transcutaneous oxygen (TcPO2) Pulse volume recording Photoplethysmography (PPG) Skin perfusion pressure
Dermatology	Ulceration Hyperkeratotic lesions (i.e., callus) Interdigital maceration Fissuring Wound/infection assessment	Biopsy
Neurology	Loss of protective sensation via Ipswich Touch Test, Semmes-Weinstein monofilament, or biothesiometer	Epidermal nerve fiber density/nerve conduction velocity
Musculoskeletal	Deformity Strength Range of motion of the ankle and 1st metatarsophalangeal joint	

presence of infection, vascular status, tissue quality, and patient tolerance. Sharp debridement is a common clinical procedure for noninfected and well-vascularized diabetic foot ulcer. Due to increased plantar peak pressure and shearing force, hyperkeratotic skin often accumulates around the wound edges which stagnate the wound healing process [30]. Removal of the biofilm is also essential for wound healing [40, 41]. Surgical debridement is commonly performed in the case of infection [18, 37]. By debriding infected and nonviable tissue, healing process can be re-established and be treated with adjunct negative wound therapy [42].

Wound Care

Although there are many wound care dressings available to optimize the local environment, it is imperative to identify underlying etiology of each wound for successful closure. Early vascular surgery consultation and intervention are necessary for evaluation and closure of all arterial ulcers [43]. With diabetic foot ulcer, offloading is the most important factor. Reduction of peak plantar pressure by means of reconstructive surgery or shoe gear devices is necessary to prevent worsening or recurrence of the wound [15, 20, 44, 45]. If infection is present, antibiotics and proper debridements are also a key part of therapy.

Table 10.3 Comparison of removable and irremovable offloading modalities

	Irremovable	Removable
Pros	Total contact cast. Gold standard to treat diabetic foot ulcers Limiting nonadherence to therapy	Minimal application time Allow daily wound dressing change and inspection Lower learning curve for application
Cons	Cost of materials Labor intensive Demanding skills Difficult to access the wound site	Compliance Lower and slower healing rate
Examples	Total contact cast (TCC) Instant TCC (iTCC)	Removable cast walker (RCW) Half-shoe Postoperative shoe

Offloading Modalities

A wide array of offloading modalities are currently available. They can be classified into two major categories, removable vs. irremovable (Table 10.3). The literature suggests irremovable

offloading modalities are more effective than removable devices in treating diabetic foot ulcer [46, 47]. Cast applications and nonremovable offloading modalities are labor and time intensive; however, they yield better results and increase the amount of time the foot is offloaded [48]. Studies following patients whose wounds were offloaded with removable cast walkers (RCWs) spent on average only 28% of their total daily activity in the RCW [48]. The study suggests that removable offloading devices permit patient's noncompliance. A number of modified offloading devices have been developed in recent years.

Total Contact Cast (TCC)

Among available offloading devices, total contact casting (TCC) is considered the gold standard [13, 49–53]. It is widely recommended by multiple guidelines for diabetic foot ulcer management [9, 11, 13]. By applying a well-molded and well-padded plaster cast to the entire lower limb with the plantar wound, a TCC increases total contact surface area at the sole of the foot (Fig. 10.3) [54, 55]. Therefore, the plantar peak pressure, particularly at the wound site, is reduced and redistributed [56]. When applied correctly, TCC is proven to be the most effective for noninfected and nonischemic plantar diabetic foot ulcers when compared to other offloading modalities [46, 47, 57].

Despite its effectiveness in treating diabetic foot ulcer, TCC utilization is only 2% [50]. According to this national survey study, factors influencing TCC utilization include patient tolerance, the amount of time needed for application, cost of materials, reimbursement rates, lack of familiarity with the application, customizing casts for deformities, and clinician coverage [50]. TCC also limits access to wound site for dressing change or inspection for an entire week [58]. Application of TCC does require some skill and training for proper usage [55]. When these casts are applied improperly, a new lower extremity wound can develop and lead to complications [58]. The cast is also bulky and requires some coordination for ambulation. It can also increase the risk of falls and be challenging to the daily functions such as sleeping and bathing [58, 59]. As a result, these limitations may sway many clinicians to alternative offloading modalities or to modify the traditional TCC [50].

Removable Cast Walker (RCW)

The most common alternative offloading device to the TCC is perhaps the removable cast walkers (RCWs) [50]. RCWs are offloading walking boot with foam or modifiable grid insoles to

Fig. 10.3 (**a**, **b**) Total contact application and completion. Patients are allowed to weight bearing in TCC

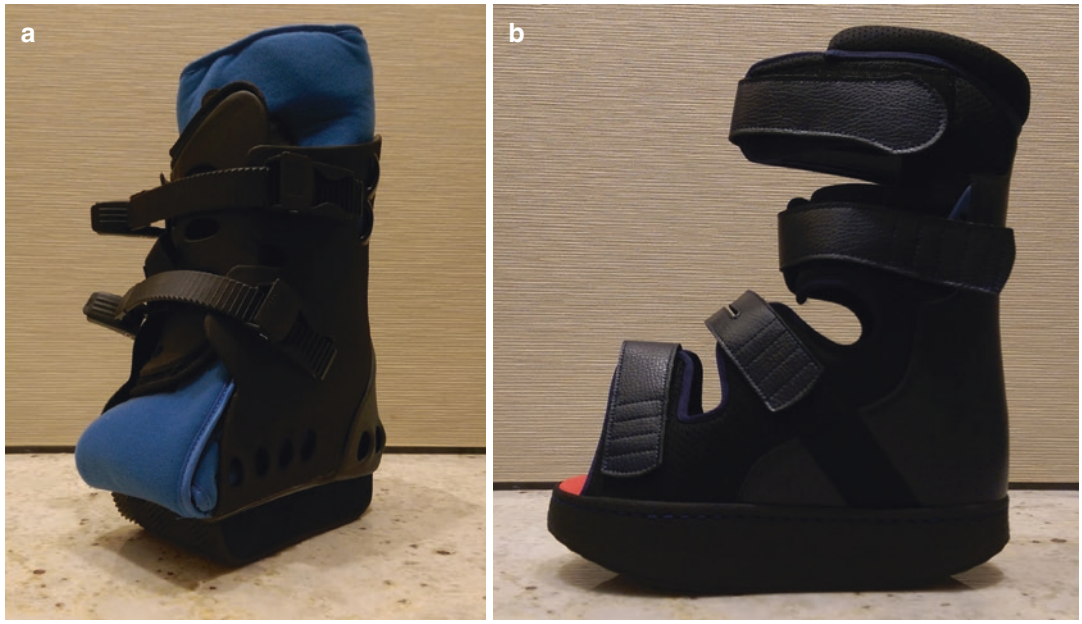

Fig. 10.4 (**a**, **b**) Examples of removable cast walker (RCW). (**b**) Demonstrates a modified version for patients who have a history of partial foot amputation

offload the plantar wound (Fig. 10.4). RCWs are relatively easy to apply and provide easy access for wound care. It is therefore a particularly useful option for patients with heavily draining wounds. RCW typically consists of Velcro straps from the forefoot to ankle as well as soft foam padding throughout that are supported by a hard plastic shell posteriorly and on the sides. Although RCW provides many advantages such as an easy application, shortened clinical visit, and comfort for the patient, its strength is also its weakness. When these devices were monitored without a patient's knowledge, these removable devices were only utilized for only 28% of daily weight bearing activity [48]. A recent systematic review further validated that TCC and irremovable cast walker had a higher rate of diabetic foot ulcer healing [60]. On the same study TCC and irremovable cast walker were less expensive than RCW, but interestingly patients reported lower cost burden with RCW [60].

While TCC and other irremovable devices appear to have higher healing rate and cost-effectiveness, RCW remains to be an ideal option particularly for wounds that require frequent dressing change or for a primary care setting where casting is impossible. As the technology evolves, a new type of connected RCW device allows clinicians to adjust parts of the devices based on the location of the wound and/or the stage of Charcot neuroarthropathy (Fig. 10.5). Selecting an appropriate offloading device is essential as it is part of the overall wound care plan. Factors such as patient tolerance and wound characteristics are important to consider.

Instant Total Contact Cast (iTCC)

To overcome the technical challenge and laborious process of TCC, an idea of instant total contact cast (iTCC) is developed. It utilized the framework of a walking cast to create a TCC [61]. This device adopts the quick and easy fit

Fig. 10.5 Image of a new RCW (Optima® Motus connected removable cast boot) that allows clinicians to change parts of the device based on clinical presentations

from the removable cast walker (RCW) and the patient compliance from the TCC. An ankle hinge design of the "Cargo Bay iTCC" allows the foot wound to be exposed without removing the cast. Studies have shown iTCC and TCC have similar wound healing rate which is likely owing to the increased compliance comparing to the counterpart, RCW [60, 62, 63].

Half Shoes/Forefoot Offloading and Postoperative Shoe

Offloading devices in this category are one of the most commonly used and readily available devices in any clinical settings [47, 59]. A variety of offloading designs are available in addition to the characteristic stiff sole post op shoe (Fig. 10.6). Although offloading shoes (i.e., half shoes) take pressure off by design, forefoot and heel offloading design can increase the risk of falls [52]. Additionally they do not provide as much pressure relief as other devices that extends beyond the ankle [64]. Nonetheless they are viable and low-unit-cost options for non-chronic wounds that require frequent dressing changes.

Felt Pad

The most simple and economical method is utilizing a felt pad [65–67]. This type of offloading is typically done by cutting an offloading area (U shape or donut hole) into the felt pad where the wound is at the center of this void and subsequently offloaded. This method allows easy access to wound dressing change. A new felt pad can offload as much as 50% of the pressure in gait [65]. Worn felt pads, however, offload 32% less pressure than the new ones [65]. Therefore to achieve proper offloading, patients should be educated on how to place and how often to change the felt pad. Anecdotally stacking the felt pads or using thicker felt pad may extend the offloading effect. As the backside of the felt pad has adhesive, it is imperative to make sure the patient does not have adhesive allergy.

Shoe Modification and Therapeutic Shoes

The offloading devices in this category are meant for wound prevention among high-risk patients who have loss of protective sensations, history of foot ulcer, and/or foot deformity [46, 68]. These shoes often consist with extra depth and multi-density insole to accommodate deformity, reduce shearing force, and evenly distribute plantar pressure. This type of device is not ideal for patients with active wounds that require strict offloading.

Prophylactic Reconstructive Surgery

As discussed above, diabetic foot ulcer often develops at the areas of high peak plantar pressure [20, 22, 69]. These high peak plantar

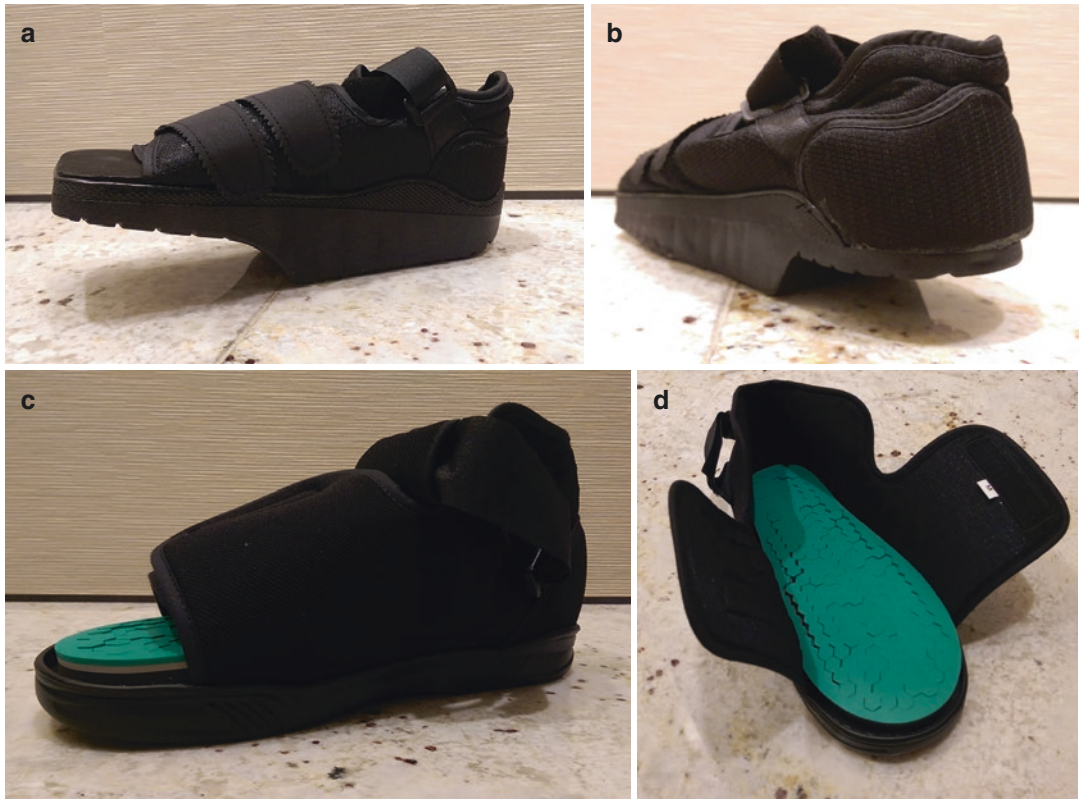

Fig. 10.6 (**a**–**d**) Examples of forefoot and rearfoot offloading postoperative shoes. It may also have the option to remove the plugs to offload the specific plantar wound site

pressure areas manifest as callus on the skin before the skin deteriorates and ulcerates. The underlying contributors to the high peak pressure areas can be the underlying bony prominence, biomechanical imbalance of the gait, or anatomical deformity of the lower extremity [70]. Therefore the idea of prophylactic reconstructive surgery is to intervene and correct the underlying causes of the peak pressure before the foot ulcer develops or worsens (Fig. 10.7) [71]. Each evaluation of prophylactic reconstructive surgical candidate should go through detailed biomechanical, musculoskeletal, and vascular evaluations. Preoperative anesthesia consult can be helpful and sometimes necessary as many diabetic patients have complex medical history. Overall prophylactic reconstructive surgery is safe with good long-term outcome [45]. Upon completion of the prophylactic reconstructive surgery, the patient should still be fitted with appropriate therapeutic shoes.

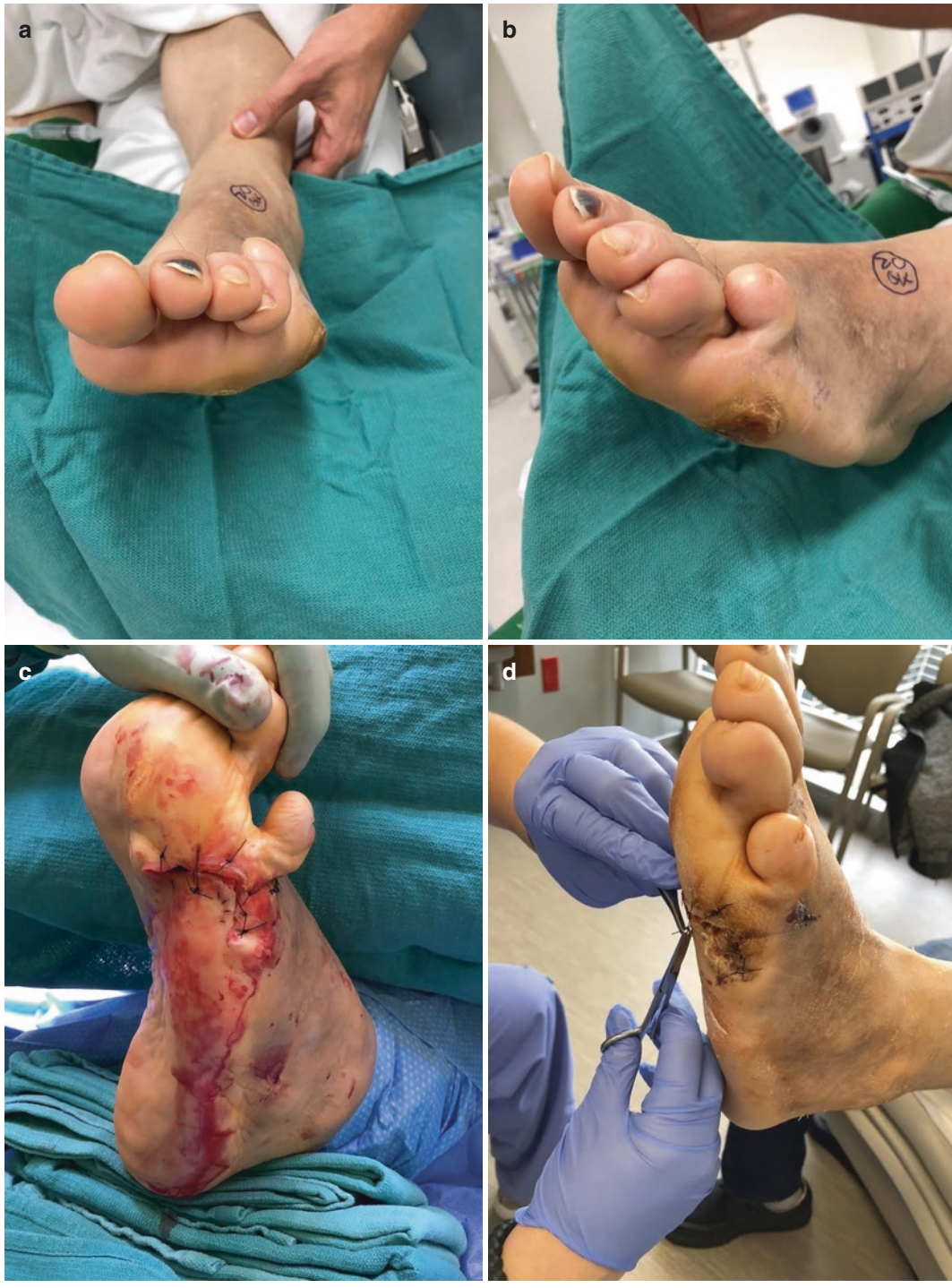

Fig. 10.7 (**a**–**d**) Hammer toe of the fifth digit on a neuropathic foot leads to an increased retrograde pressure on the fifth metatarsal head and a sub-fifth metatarsal head ulcer. By removing the metatarsal head and a V-to-Y lengthening, the contracture of the digit reduced and the bony prominence was removed

Conclusion

A hallmark of diabetic peripheral neuropathy is the manifestation of diabetic foot ulcers. Due to the loss of protective sensations and the presence of underlying deformity, these patients are at high risk of developing diabetic foot ulcers. The surrounding environment at the lower extremities subjects these wounds to become contaminated with matter from the soil and ground. Consequently amputations due to infections are not uncommon. By understanding the etiology of diabetic foot ulcer and the disease process, local wound care and offloading are imperative to ensure wound healing and are the initial steps to prevent major amputations. Additionally many of these patients have other comorbidities such as peripheral arterial disease. To comprehensively manage this population, a multidisciplinary team approach is necessary to effectively reduce major amputations [13, 43, 72].

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Negative Pressure Wound Therapy

11

Valentina Dini

Introduction

Chronic cutaneous wounds include leg ulcers, pressure ulcers (PUs), and diabetic foot ulcers (DFUs). Each of these conditions is difficult to heal within an acceptably short time, and some are harder to maintain healed. Patients suffer tremendous discomfort and pain and are often socially deprived as a result. The financial consequences of this medical problem are enormous. Chronic or nonhealing ulcers are characterized by defective remodeling of the extracellular matrix, a failure to reepithelialize, and prolonged inflammation [1]. The epidermis fails to migrate across the wound tissue, and there is hyperproliferation at the wound margins that interferes with normal cellular migration over the wound bed, probably through inhibition of apoptosis within the fibroblast and keratinocyte cell populations.

Bacterial Burden

Most clinicians are concerned about infection in healing wounds. Microorganisms are present in all chronic wounds, although numbers, virulence, species, and mixture vary. Bacterial involvement in a chronic ulcer can be divided into distinct categories predominantly based on the induced host reactions.

Contamination it is characterized by the presence of non-replicating microorganisms in the wound. Most organisms are usually incapable of developing replicative condition due to the hostile environment of the human soft tissue.

Colonization microorganisms multiply but do not cause injury to the host or necessarily delay the healing process. Bacteria can release metalloproteinases and other pro-inflammatory mediators that impair healing. Bacteria can also stimulate angiogenesis and lead to the production of a deficient or corrupt bright red matrix. *Critical colonization*: as the bacterial burden increases, the colonized wound is transformed into a covert infection, which may not involve extensive tissue invasion but is sufficient to inhibit wound healing.

Infection bacteria invade the healthy tissue and continue to proliferate so that their products elicit or overwhelm the host immune system. Signs and symptoms of infection are advancing erythema on the surrounding skin, fever, warmth, edema, pain, foul odor, and pus. In a chronic wound, the continuous presence of virulent microorganisms can lead to a massive and continued inflammatory response, which may actually contribute to host injury. Localized thrombosis and release of vasoconstrict-

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A. Alavi, H. I. Maibach (eds.), *Local Wound Care for Dermatologists*, Updates in Clinical Dermatology, https://doi.org/10.1007/978-3-030-28872-3_11

ing metabolites, which can lead to tissue hypoxia, bring about further bacterial proliferation and tissue destruction. In infected wounds, the occlusion of large vessels leads to wound hypoxia, the proliferation of small vessels leads to the formation of fragile granulation tissue, and few fibroblasts are associated with disorganized collagen production. Although diagnosis of infection may be difficult, one common feature is the failure of the wound to heal and, moreover, the progressive deterioration of the wound. The diagnosis of infection in a chronic wound is often hampered by the subtle nature of the transformation from microbial colonization to infection. Quantification of bacteria using tissue biopsy can predict host injury and wound infection. Experimental studies have shown that impairment of wound repair may occur when there are more than 10^5 microorganisms per gram within a wound bed, regardless of the species of microorganisms [2]. In chronic wounds, the pathogen species may be much more important than the number of organisms. Indeed, beta-hemolytic streptococci can induce significant injury at 10^2 to 10^3 colony-forming units (cfu) per gram of tissue, whereas wounds with more than 10^6 cfu of different bacterial species can often heal without trouble. The microbial flora of a chronic wound changes over time. In an early acute wound, gram-positive bacteria of the normal skin flora are the predominant organisms. After about 4 weeks, a chronic wound usually becomes colonized with facultative anaerobic gram-negative rods such as *E. coli*, *Proteus*, and *Klebsiella* species. As the wound deteriorates, and deeper structures become involved, anaerobic flora becomes part of the microbial population. Wounds of several-month duration will have, on average, four to five different microbial pathogens including aerobic gram-negative rods, such as *Pseudomonas* species, *Acinetobacter* species, and *Stenotrophomonas maltophilia*. These bacteria may be introduced into the wound from exogenous sources such as bath water and footwear. These microorganisms seldom cause soft tissue invasion unless the host is highly compromised.

The importance of biofilm formation as an element of wound infection has recently been stressed [3]. When bacteria proliferate in wounds, they form microcolonies, which attach to the wound bed and secrete a glycocalyx, or any kind of extracellular matrix, and take up an interdependent surface-attached existence. These microbial communities, called "biofilms," protect the organisms against antibiotics, antiseptics, and host immune defenses [4]. Almost all bacterial species form biofilm in vivo, thus representing a therapeutic challenge in many, if not most, bacterial diseases. Biofilm formation has also been linked to the emergence of a variety of opportunistic pathogens, such as *Staphylococcus epidermidis* and *Pseudomonas aeruginosa*, that contribute to persistent infections by changing environmental parameters.

Despite the recent efforts in identifying bacteria of chronic wound microflora, it is apparent that the clinical relevance resides in the structure of the bacterial community, not in the presence of particular species in the wound. Experimental biofilm measurements are developed to determine in vitro the attitude of a bacterial strain to produce biofilm. These measurements fit with the genomic presence of virulence determinants. In vivo biofilm observation using confocal laser scanning microscope is now under development [4].

Negative Pressure Wound Therapy (NPWT)

NPWT is a wound treatment provided by a mechanical device that is using a subatmospheric pressure applied to the wound bed to facilitate different biological aspects during tissue repair.

NPWT has been successfully used in several phases of the treatment of different chronic wounds [5]. Positive effects of the NPWT, such as reduction of edema, drainage of wound exudate, stimulation of angiogenesis [6], and acceleration of granulation tissue formation, are the reasons for recommending NPWT in order to improve the healing rate. The application of NPWT should be focused on the following criteria:

- To promote debridement
- To control bacterial burden
- To stimulate angiogenesis
- To control exudate

- To enhance cell proliferation – migration
- To promote oxygenation – nutrition
- To control pain

In the presence of colonized wounds and moderately to heavily secreting ulcers, a polyurethane foam should be employed with a continuous suction pressure of 125 mmHg. Because of its hydrophilic properties, the white polyvinyl alcohol foam is suitable for the support of meshed skin grafts. The compression bandage should be applied while NPWT is in progress in venous leg ulcers. Cotton bandage padding, consisting of several layers, is advisable especially in the area of the trac-pad connector to prevent pressure changes. NPWT can be useful in hard-to-heal venous leg ulcers in order to promote a faster granulation tissue formation and decrease the costs associated with the treatment of the patients with chronic wounds.

The conventional devices delivering NPWT are relatively large and complex and require an extensive interaction with the caregiver, who needs to monitor and track the clinical outcome with a relatively high frequency change of dressing, like every 2–3 days. This is also due to the potential complications of the use of NPWT, particularly in the home care setting. FDA is warning on the risks of unmonitored bleeding linked to the therapy.

Several studies have demonstrated the evidence of NPWT for treating chronic wounds, and a large number of guidelines exist today according to the various types of acute and chronic wounds [7, 8]. Diabetic foot ulcers (DFUs) are a specific target for NPWT treatment when standard therapy has not shown significant effect [9]. Several consensus documents were developed on the use of NPWT on DFUs, particularly after surgical debridement and/or reconstructive surgery in order to provide exudate balance, control bacterial burden, and promote cellular activities which are beneficial to the tissue repair process [10]. NPWT has also been applied in the treatment of hard-to-heal venous leg ulcers. Dini et al. [11] have performed an immunohistochemical evaluation in venous leg ulcers before and after the use of NPWT. The main goal of this study was to evaluate, using immunohistochemical markers, the efficacy of NPWT in terms of angiogenesis and granulation tissue formation in the management of hard-to-heal venous leg ulcers. This was a randomized study where 30 patients were included. The patients were randomized into two groups according to treatment with NPWT, polyurethane foam, and four-layer bandaging system or with moist wound dressings and four-layer bandaging system. Multiple biopsies were taken from the wound bed and wound edge in order to perform an immunohistochemical evaluation including markers for angiogenesis (CD31), lymphatic vessels (D240), macrophages (CD68), and lymphocytes (CD3). After just 1 week, there was a significant improvement of angiogenesis, lymphatic vessels, and macrophage and lymphocyte proliferation in the NPWT group compared to the control group.

Different studies have also shown a good level of evidence for the management of NPWT for the treatment of pressure ulcers (PUs) [12]. In those patients, there is always a beneficial effect on granulation tissue formation and particularly on wound exudate management [13]. The nurse workload on PUs is definitely alleviated due to less frequent dressing change and better quality of life for patients and relatives. A future opportunity will be according to more user-friendly interface dressings for NPWT in PUs.

Practical considerations in choosing an intervention with NPWT:

- Treatment setting
- Treatment provider
- Treatment payer
- Treatment availability
- Medical contraindications
- Adjunctive treatment

NPWT Ultraportable Devices

In the last year, simpler and disposable devices have started to appear (Fig. 11.1a–d), and this has been driven mainly by the need to overcome the relative complexity of the current business model such as a durable medical equipment, which requires to be managed at the hospital or healthcare facility level [14]. The current disposable

Fig. 11.1 (**a**–**d**) NPWT for different settings from hospital to homecare management

products (Smith & Nephew PICO®, KCI VAC Via®, Spiracur SNAP®) essentially solve the availability issue, making the device more accessible in different therapy settings (hospital and home care), but still deliver only NPWT and still require a relatively resource-intensive patient monitoring. The development of smart NPWT system, with the capability of actively and remotely monitoring several wound-related parameters, has the potential to extend the use of this therapy to a wider base of patients, in a safe, effective, and controlled way [15]. The real-time control of wound parameters, with the smart control of the NPWT pump and the possibility to add active second-line therapy, will allow a more controlled use of this effective therapy, even in the home care segment, overcoming the risks highlighted by the FDA.

Factors influencing treatment modality selection:

- Wound etiology
- Location
- Necrotic tissue
- Undermining
- Drainage
- Infection
- Labor

The "smart" approach has also the potential to make the therapy itself more effective, therefore

reducing the time that the patient will need to be treated with the device.

NPWT Precautions and Contraindications

There are several aspects during tissue repair which have to be considered before starting the use of a NPWT device as follows [16–19].

Precautions:

- Active bleeding
- Difficult wound hemostasis
- Taking anticoagulant medication
- Weakened, irradiated, or sutured blood vessels or organs
- Enteric fistulae
  - Protect blood vessels, organs, or exposed tendons with overlaying fascia, tissue, or other protective barriers
  - Protect barriers, vessels, or organs in the presence of sharp edge or bone fragments

Contraindications:

- Necrotic tissue/eschar present
- Direct placement over exposed (i.e., vital structures, blood vessels, and/or organs)
- Untreated osteomyelitis
- Non-enteric/unexplored fistulas
- Malignancy in the wound
- Sensitivity to silver

Ultraportable NPWT devices have other aspects to be considered when selecting a treatment compared to original and standard pumps, like no possibility to change setting between continuous and intermittent regimen, absence of an alarm system any time the canister is full, and small amount of exudate volume absorption.

Cost Evaluation of Current Products

The current cost of the NPWT goes from as low as 130–150 Euro per week for disposable devices such as Smith & Nephew PICO® to an average of 300–350 Euro per week for conventional NPWT systems such as KCI VAC® or S&N Renasys®. The general global trend is toward a reduction of prices for conventional NPWT, linked to a simplification of the devices and to an increasingly competitive environment.

The recent introduction of disposable devices has highlighted how the market is trying to move away from the current dominant business model like renting of the pump and sale of the consumables: this is mainly due to the administrative burden caused by the management of the fixed asset (the pump) and the servicing required (cleaning, electrical safety check, etc.) in the interval between two different users. Portable/disposable NPWT systems target the elimination of some key unmet needs in this market, prominently patient convenience, accessibility, and affordability. Given these features, these systems are expected to drive the NPWT equipment market in the future. The portability of NPWT systems will accelerate the penetration of this technology while simultaneously expanding the target market opportunity through new indications. Portable/disposable systems are expected to cannibalize the stand-alone NPWT equipment market, although they will contribute in expanding the overall NPWT market potential.

It's known from several publications that treating chronic wounds is the single most time-consuming use of community nurse time: studies suggest between 50% and 60% of the available district nurse time is spent in caring for patients with wounds [1]. It's also well established that the determinants of cost in wound care are split between devices and materials, typically 15–20% of total cost, nurse time which is 30–35% of total cost, and hospitalization representing at least 50% of total cost [20].

NPWT with Instillation

In the last few years, NPWT technology has introduced the concept of instillation. These devices have the option to perform a lavage on the wound bed by using wound cleansers while NPWT is ongoing. The procedure could be pro-

grammed and scheduled with different timing for the intervals of instillation activity. The main purpose of this treatment is to reduce the increased bacterial burden of wounds and to provide an option for biofilm removal and management. Several antimicrobials have been used in combination with NPWT devices with instillation, and there is evidence about efficacy and safety compared to traditional NPWT treatment [21].

Conclusion

NPWT devices have shown promising results as treatment modalities applied in conjunction with topical and systemic wound management. The therapy main indication is going to be when an individual has not shown signs of wound repair by standard treatment. Ultraportability of NPWT is increasing in use and application and should produce more evidence in the not-too-distant future. The NPWT with instillation is a specific way of biofilm and infected wound management.

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Oxygen Therapy in Wound Healing

12

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Abbreviations

ATA	Atmosphere absolute
ATP	Adenosine triphosphate
CVI	Chronic venous insufficiency
DFU	Diabetic foot ulcer
EPC	Endothelial progenitor cells
HBOT	Hyperbaric oxygen therapy
HIF	Hypoxia-inducible factor
IL	Interleukin
MOIST	Moisture balance, Oxygen balance, Infection control, Support, Tissue management
NO	Nitric oxide
NOX	NADPH oxidase
NOX-2	NADPH oxidase 2
PAD	Peripheral arterial disease
PAOD	Arterial wounds associated with peripheral arterial occlusive disease
PVD	Peripheral vascular disease
ROS	Reactive oxidative species
ROS	Reactive oxygen species
TCOM or TCPO	Transcutaneous oximetry
TIME	Tissue removal, Infection control, Moisture balance, Edge advancement
TNF	Tumor necrosis factor-alpha
TOT	Topical oxygen therapies
VEGF factor	Vascular endothelial growth

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Introduction

Oxygen is a major determinant for wound healing processes. Its existence is vital for the restoration of microcirculation, infection control, onset of epithelization, fibroplasia, and collagen deposition [1]. Particularly chronic wounds lack sufficient oxygen supply and suffer from a hypoxic microenvironment, which, in turn, prevents the wound from healing as protracted hypoxia preserves a pro-inflammatory microenvironment.

Various studies showed the beneficial effects of additional oxygen administration into chronic wounds such as diabetic foot ulcers (DFUs) or arterial wounds associated with peripheral arterial occlusive disease (PAOD) [2]. Re-oxygenation induces tissue repair in various ways, among others via increasing response to different treatments, such as growth factors and antibiotics, or even improving graft take.

A. Alavi, H. I. Maibach (eds.), *Local Wound Care for Dermatologists*, Updates in Clinical Dermatology, https://doi.org/10.1007/978-3-030-28872-3_12

Additional oxygen can be applied to wounds in addition to commonly used wound treatments such as compression therapy and revascularization in the form of topical oxygen therapies (TOT) or hyperbaric oxygen therapy (HBOT) [3].

Role of Oxygen for Wound Healing

Under usual circumstances, oxygen supply in the skin is delivered through blood circulation and diffusion from the adjacent tissue. A transcutaneous partial oxygen pressure ($TcPO_2$) below 40 mmHg is defined as tissue hypoxia [4].

There is a narrow line of essential oxygen saturation in the skin. While, on the one hand, hypoxia prevents wound healing, on the other hand, chronic and severe hyperoxia leads to cell death and thus tissue loss through oxidative damage. A temporary mild hypoxia, however, can be compensated by of the tissue through hypoxia-inducible factor (HIF)-dependent adjustments. HIF-dependent pathways, for instance, regulate erythropoietin production and are even beneficial for wound healing up to a specific amount of oxygen. Decreased oxygen supply which sustains ATP, however, leads to the activation of HIF-independent pathways which induces inhibition of protein synthesis and cell growth.

In chronic wounds, oxygen saturation is commonly compromised: edema and restriction of the micro- and macro-circulation reduce oxygen transport capacity, and bacterial infections and biofilms increase oxygen consumption. This imbalance prevents the wound from healing by entering a vicious circle [5]. Hypoxia can be further intensified by additional factors such as pain or hyperthermia. All wound healing phases (inflammation phase, proliferation and granulation phase, epithelialization phase, maturation phase) comprise various oxygen-dependent processes [1, 5, 6].

The oxygen demand in wounds is higher compared to healthy tissue, as energy in terms of ATP is required for various steps in tissue regeneration such as collagen/fibroblast/protein synthesis, cell proliferation, and angiogenesis. ATP is released by the aerobic glucose metabolism in the mitochondria under the consumption of oxygen [7].

Box 12.1

- *Aerobic glucose metabolism*
  - In the mitochondria in the presence of glucose and oxygen for the production of ATP (=energy), required for various steps in wound healing processes:

$$\text{Glucose} + 6O_2 \rightarrow 6CO_2 + 6H_2O + 30\,\text{ATP}$$

  - (in case of hypoxia → anaerobic glycolysis, production of lactate)
- *Infection control*
  - Production of reactive oxidative species (ROS) via NADPH-dependent oxygenases (NOX)
- *Collagen synthesis and fibroblast proliferation*
  - In the extracellular matrix
- *Vascular tonus regulation*
- *Protein synthesis and cell proliferation*
- *Induction of endothelial cell signaling cascades*
  - For angiogenesis, cell migration, cell mitosis, and cell death

Phagocytosis of microbes consumes oxygen via NADPH oxidase (NOX). This leads to the release of reactive oxygen species (ROS), resulting in microbial killing, cell destruction, and the so-called respiratory burst [8], which requires a specific amount of oxygen (pO_2, >300 mmHg; oxygen concentration for maximal half-ROS production, 45–80 mmHg). Infections further increase oxygen consumption (see Box 12.1).

The most common underlying diseases or causes for undersupply of oxygen are decreased vascular flow or increased tissue requirement due to healing processes.

- *Peripheral vascular disease (PVD)*
  - *Peripheral arterial disease (PAD)*
    Vascular stenosis is the complicating key factor for wound ischemia, leading to reduction of oxygen below demand levels (=hypoxia). In more than 95% of cases due to arterioscle-

rosis, stenoses result in a severely inadequate supply of blood to the lower extremity affected and thus hypoxia. This leads to gangrene, necrosis, and arterial leg ulcer.
  - *Chronic venous insufficiency (CVI)*
    Venous hypertension, venous stasis, and the resulting capillary changes such as widening or rarefaction and edema result in fibrosis with an induration of the connective tissue. As a consequence, the diffusion distance for oxygen and nutrients from the capillaries to the cells in the tissue is extended, which in turn leads to hypoxia.
- *Infection and biofilm*
  Stimulated neutrophils activate NADPH oxidase, which induces ROS production. Via NADPH oxidase 2 (NOX-2), further O_2 consumption is amplified [9–12]. As biofilms harbor an increased number of activated neutrophils, additional oxygen depletion is provoked [9, 13, 14]. Ongoing hypoxia shifts microbial colonization toward an anaerobic or facultative-aerobic spectrum [15, 16]. Therefore, sustained hypoxia prevents transition from the inflammatory into the further stages of wound healing.
- *Diabetes mellitus*
  Patients with diabetic ulcers suffer from neuropathy and angiopathy (micro and macro) in 50% and 25%, respectively, Underlying reasons are the media sclerosis and the vasomotor dysregulation which restrict the microcirculation. Both factors predispose for tissue hypoxia. This is aggravated by bacterial superinfection, which is frequently more prevalent in this patient group due to the relative immunosuppression [17].
- *Malnutrition*
  Malnutrition is associated with the development of ulcers as shown in demographic data and in various studies [18]. Wounds require increased energy metabolism for onset of repair mechanisms, but cell proliferation can be inhibited by undersupply of proteins, fatty acids, vitamins, zinc, and iron. Supplementation can support wound healing processes in malnourished ulcer patients as different studies showed [19].

Oxygen Treatment Modalities

The key role of oxygen in the wound healing process is indisputable. As mentioned before, extensive hyperoxia and hypoxia have to be carefully avoided, as both lead to cell cycle arrest and prevent the wound from regeneration. Therefore, measurement of oxygen saturation is useful for the indication of oxygen therapy and for monitoring during such a treatment. Several devices for oxygen measurement are available and mainly include pulse oximetry, hyperspectral imaging methods, transcutaneous oximetry (TcPO), or tissue oxygen tension [20–22].

Indirect Oxygen Treatment

Indirect methods to increase oxygenation of the tissue include compression therapy and revascularization. These methods are explained in the respective chapters.

Hyperbaric Therapy (HBOT)

HBOT is an established method for the treatment of decompression sickness, but it is also used for further indications. Chronic hypoxic wounds profit from a hyperbaric chamber as was shown in many studies during the last 40 years. The perfusion in the chamber with 100% oxygen with a pressurization of 2–2.5 atmosphere absolute (ATA) is performed once or twice daily for 2 hours each, five times per week with up to 40 cycles overall [23]. Due to the time-consuming and expensive nature of this treatment as well as the restriction to only a few centers worldwide, a strict pre-selection of patients and monitoring of $tcPO_2$ is mandatory.

HBOT application raises oxygenation in hypoxic wounds up to 20-fold via blood circulation. Reduction of edema and stimulation of various restorative, angiogenic, and anti-inflammatory processes are the result. It leads to antibacterial and even bactericidal conditions for both anaerobic and aerobic strains via neutrophils and further provides synergistic effects to specific antibiotics

[24–27]. In the bone marrow and perivascular tissue, nitric oxide (NO), which regulates the vascular tonus, is raised via endothelial progenitor cells and via NOS. Through increased levels of NO, perfusion is facilitated, and thus tissue regeneration is stimulated [28, 29]. Mobilization of stem cells and alteration of gene expressions encoding for interleukin (IL)-1 beta and IL-8, tumor necrosis factor (TNF)-alpha, and angiogenin have been additionally shown [26, 30].

Various clinical studies have shown significant improvement of chronic non-healing wounds in terms of wound size and healing rates. The latter are doubled compared to placebo in diabetic foot ulcers as shown in a randomized double-blind trial ($p = 0.03$) [31]. However, long-term effects seem less favorable. A reduction of amputation rates (RR about 0.29) is discussed controversially in the literature [3, 32, 33].

HBOT is well tolerated, and side effects result from increased pressure such as middle ear barotrauma and hyperoxia in terms of oxygen toxicity on the lungs or the central nervous system. Absolute contraindications include untreated pneumothorax. Relative or temporary contraindications include pregnancy, febrile conditions, claustrophobia, severe asthma or hearing insufficiency, ongoing chemotherapy, or equilibration problems in the middle ear [34].

HBOT may be applied in different diabetic or ischemic ulcers grade 1A-2C [35]. However, due to the limited availability of these devices, high costs, and questionable long-term effects, application is restricted to a few critical wound patients in specific centers. $TcpO_2$ has to be carefully monitored, as an elevated level of pO_2 can result in toxic features and thus impair wound healing [36]. This effect is even intensified in malnourished patients [37].

Topical Oxygen Therapy (TOT)

Various topical treatment modalities have been established for increasing oxygen supply in wounds.

Antibacterial effects and enhancement of growth factors which are involved in tissue regeneration processes including angiogenesis, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF-2), are one of the most important effects [38, 39]. Randomized controlled studies about the effect of these treatments are rare, and quality of study designs is often poor. It also seems evident that the pO_2 of deeper tissues will hardly benefit from topical oxygenation procedures. Although the systemic effects of HBOT are missing, the preeminent advantages of TOT compared to HBOT are foremost the practicability, safety, relative inexpensiveness, and availability outside of rare centers. Furthermore, the effects are relatively independent from macro-circulation. These facts, together with the confirmed wound healing effects, account for the rising implementation of TOT in clinical practice of hypoxic wounds.

Various devices for oxygenation delivery are available; the most common are listed as follows:

- *Topical pressurized oxygen*
  - *Low constant pressure oxygen in a contained chamber*
  - *High cyclical pressure oxygen in a contained chamber*

With the help of these devices, oxygen is supplied via a local chamber unit under the following:

- Constant pressure of up to 35 mmHg.
- Cyclic pressure of 5–50 mmHg, in combination with humidification.

These devices facilitate enhanced penetration of oxygen into deeper tissue parts as well as reduction of edema and stimulation of perfusion. Several case series and studies support this concept, but prospective randomized trials are lacking [38, 40–43].

- *Topical continuous diffusion of oxygen*
  - *Continuous diffusion of non-pressurized oxygen (CDO)*
  - *Transdermal continuous oxygen therapy (TCOT)*

A dressing is connected with a tube to a battery-powered diffusor, which continuously delivers concentrated pure normobaric oxygen (up to 98%) at low doses (3 ml per hour) 24 hours daily, 7 days a week.

Various clinical trials suggest a positive impact on wound healing, including 1 randomized placebo-controlled double-blinded multicenter study in 100 diabetic foot ulcers compared to standard treatment [44–46].

Different systems are available and are FDA approved for the treatment of skin ulcerations due to diabetes, venous stasis, postsurgical infections and gangrenous lesions, pressure ulcers, amputations/infected stumps, skin grafts, burns, and frostbite.

In some devices, continuous oxygen supply has to be controlled due to the small tubes. Pressure and oxygen supply have to be high enough to reach the targeted tissue.

- *Wound dressings with oxygen release*

There are various dressings or hydrogels, which release dissolved oxygen that can diffuse into the wound bed via different systems:

- *Pure oxygen is incorporated into dressings as bubbles and released if liquefied.*
- *Hydrogen peroxide 0.3% is embedded in hydrogel dressings and released via biochemical reaction into H2O and O2.*
- *Multi-component dressings: one component containing hydrogel/glucose/iodide (0.04%) and another one containing glucose oxidase. Via oxidation processes, dissolved O2 is produced. Additionally, the iodine has an antimicrobial effect.*

In vitro studies found increased oxygen levels and increased efficacy against different microorganisms. Various case series and small studies are available; randomized controlled trials are lacking so far [47–50].

- *Hemoglobin for oxygen transfer*
  - *Oxygen transfer*
    Wound exudate and fibrin slough act as a potent barrier to oxygen diffusion from the surrounding air into wound tissue. As hemoglobin is a known transporter of oxygen, this process can be utilized for the oxygenation of wounds in combination with standard wound treatment. It was already shown in 1960 in vitro that hemoglobin can increase diffusion rates up to eight times [51] and oxygen saturation was significantly increased in wounds with the usage of a hemoglobin spray [52].
    A prospective randomized trial in 72 chronic VLU of 36 patients found a 53% reduction of wound size and 87% improvement using 10% hemoglobin vs. no significant effect in the standard of care group after 13 weeks of treatment [53]. Further, cohort studies, case series, and retrospective evaluations revealed comparable or even better results in favor of the hemoglobin spray [54–56].
  - *Other oxygen carriers (solutions, gels)*
    Super-oxidized rinsing solutions or wound gels such as hypochlorous acid containing ROS activating factors via singlet oxygen seem to be superior for desinfection compared to povidone-iodine as shown in a randomized controlled trial in postsurgical wounds and in cohort studies in terms of healing and infection rates [57–59].

Conclusion

During the healing process, wounds require an increased amount of oxygen compared to normal skin due to the metabolic changes in the different wound healing phases and the need for restructuring of new tissue and for angiogenesis. As hypoxia is one of the main factors preventing wound restoration, monitoring of oxygenation levels and sufficient oxygen administration is mandatory for the induction and maintenance of wound healing processes.

Due to the demographic change, an even further increase of ulcers associated with decreased oxygen supply such as DFUs and PAODs is to be expected. The increased number of multiresistant bacterial infections further accentuates the necessity of immediate onset of adequate wound [60–

62]. As oxygen is a pivotal player in wound healing including infection control, adequate oxygen therapy will be a progressively fundamental player in wound treatment. Therefore, it has been suggested to complement the established TIME (Tissue removal, Infection control, Moisture balance, Edge advancement) concept for wound bed preparation with oxygen therapies – resulting in the MOIST (Moisture balance, Oxygen balance, Infection control, Support, Tissue management) model [63].

However, only selective application will lead to increased healing rates. Therefore, more study-based data are required for adequate wound and patient selection. Furthermore, selection of the proper application type is mandatory to achieve highest improvement rates. Only with the help of reliable diagnostic parameters such as transcutaneous oximetry (TCOM) [22], for instance, for evaluation of local hypoxia prior to and during therapy, this aim can be controllably reached. The so-called smart dressings with integrated oxygen sensors might further support this development. Further prospective controlled trials are warranted in order to provide best patient care in a cost-effective manner.

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The Role of Ablative Fractional Lasers in Wound Healing

13

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Abbreviations

AF	Ablative fractional
CO_2	Carbon dioxide
Er:YAG	Erbium:yttrium aluminum garnet
HSP	Heat shock protein
MMP	Matrix metalloproteinase
RCM	Reflectance confocal microscopy
TGF-β	Transforming growth factor beta

Introduction

Numerous advanced therapeutic modalities have been developed that improve healing of chronic wounds. Despite these innovations, which have undoubtedly moved the field forward, treatment for chronic wounds often still remains unsatisfactory. As the population ages, chronic wounds are becoming more common, while costs of care continue to rise, representing an ever-greater burden on both the individual and healthcare system [1–3]. Moreover, chronic wounds are associated with significant morbidity and decreased quality of life [4–7]. Thus, new treatments that efficiently improve healing of chronic wounds are still needed.

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In recent years, the potential utility of lasers in treating a variety of dermatologic conditions has been increasingly recognized [8]. One exciting new application of lasers is their potential to accelerate wound healing. In particular, ablative fractional carbon dioxide lasers have been reported to dramatically hasten healing time in a small number of cases. This chapter will review the use of these lasers in wound healing to date and discuss their potential mechanisms of action.

Background

Lasers emit light of a specific wavelength that travels through space until it is absorbed. In the skin, light-absorbing molecules, or chromophores, include hemoglobin, melanin, and water. These chromophores contain unique peak absorption spectra that can be targeted with specific wavelengths of light. As energy from light is absorbed, temperature rises and eventually causes thermal damage. By using wavelengths that target particular structures of interest, thermal damage can be confined and controlled. This concept is termed "selective photothermolysis" and is the basis for laser therapy in medicine [9].

In 2004, Manstein et al. introduced the concept of fractional lasers, whereby thermal damage is induced in a grid-like pattern by hundreds or thousands of small laser beams per cm^2 [10]. They dubbed each microcolumn of thermal injury

A. Alavi, H. I. Maibach (eds.), *Local Wound Care for Dermatologists*, Updates in Clinical Dermatology, https://doi.org/10.1007/978-3-030-28872-3_13

a "microscopic treatment zone" and called the overall process "fractional photothermolysis." Commonly used fractional lasers are the carbon dioxide (CO_2) and erbium:yttrium aluminum garnet (Er:YAG) ablative lasers, which can ablate the epidermis and superficial dermis. These lasers are now commonly used for cosmetic facial rejuvenation procedures. Non-ablative fractional lasers have also been developed for this same purpose [11]. With ablative fractional (AF) lasers, the targeted chromophore is water, making them, in effect, non-selective. Of great importance, each microcolumn of injury has been shown to heal by remodeling without evidence of residual scar tissue [12, 13]. This discovery led to the testing of AF lasers on scarred skin. Waibel and Beer used AF CO_2 laser on a woman with scarring from third-degree burns and multiple reconstructive surgeries that had been present for over 50 years [14]. Significant improvement in skin texture and appearance was noted after a single treatment with AF laser. Cervelli et al. then reported a study in which AF CO_2 laser successfully improved skin tone, texture, and appearance in all 60 patients with severe skin scarring who received this treatment [15]. AF CO_2 laser was subsequently reported to improve range of motion, gait, and flexibility in adult patients with functional limitations due to scar contracture [16, 17]. Pediatric patients with scar contractures have also benefitted from this treatment [18].

First Report of Ablative Fractional Laser for Wound Healing

In 2009, Shumaker and colleagues at the San Diego Naval Medical Center started using AF laser to treat traumatic scars and related contractures [19]. In 2011, they reported the case of a 26-year-old serviceman who presented to the dermatology clinic 5 months after being injured by an improvised explosive device while deployed in Afghanistan [20]. He had required bilateral above-knee and right above-elbow amputations, and he was suffering from scar contractures, poor skin pliability, and textural irregularity. In addition, he had multiple, painful, non-healing wounds, despite treatment with standard care, at the site of a split-thickness skin graft on the distal right lower extremity stump that were impairing his progress in a prosthetic rehabilitation program [20].

Shumaker and colleagues employed AF CO_2 (10,600 nm) laser (Deep FX laser and UltraPulse Encore system, Lumenis Ltd., Yokneam, Israel) for the treatment of scar contractures and textural irregularity. Laser settings consisted of 5% treatment density to the entirety of the graft site and 1–2 mm of normal surrounding skin with a single pulse and single pass without overlap. Pulse energy was set at 50 mJ, while microcolumn width was 120 μm, and pulse width was 250 microseconds, both of which were fixed parameters. One week after the initial laser treatment at the first follow-up visit, the team observed significant healing of the graft site wounds, as well as improved skin texture and pliability. By 2 months, nearly all wounds had healed, despite increased prosthetic use. The patient then received an identical additional course of AF laser, and improvement was noted to persist 6 months after this second treatment. The authors report comparable findings after using a similar protocol in two other patients with scar-associated chronic wounds following blast injury. All patients experienced incidental rapid healing of their chronic wounds within 2 weeks of their initial ablative fractional laser treatment (Table 13.1).

Ablative Fractional Laser for Lower Extremity Ulcers

Following the report of AF CO_2 laser stimulating wound healing in scar-related wounds, Phillips and colleagues tested this treatment in chronic post-traumatic lower extremity ulcers not associated with previous scarring. They first reported successful AF CO_2 laser treatment in three elderly individuals (Table 13.1) whose wounds had failed to heal, despite care with moisture-retentive dressings and multilayer compression therapy [21]. Two of the patients had undergone Mohs treatment for non-melanoma skin cancer, after

Table 13.1 Published cases of an ablative fractional carbon dioxide laser accelerating wound healing

Age (years)	Wound etiology	Wound description	Wound duration	Laser pulse energy, mJ	Total treatments	Healing time	Author
26	Trauma (improvised explosive device)	Multiple erosions and ulcers over distal stump	5 months	50	2 treatments 8 weeks apart	Near complete healing of all wounds after 2 months	Shumaker et al. (2012) [20]
28	Trauma (improvised explosive device)	Erosion over distal stump	6 months	30	2 treatments 8 weeks apart	Complete healing by post-op day 6	Shumaker et al. (2012) [20]
39	Trauma (detonation injury)	0.8 × 1.5 cm ulcer over forearm	60 months (time since injury)	50 and then 30	3 treatments 6 weeks apart	n/a (authors note sustained healing during follow-up)	Shumaker et al. (2012) [20]
70s	Trauma (motor vehicle accident)	3.0 × 1.7 cm ulcer on dorsal foot	3 months	30 (wound base) 50 (wound edge)	1 treatment	Complete healing by 6 weeks	Phillips et al. (2015) [21]
70s	Post-operative (Mohs surgery)	1.5 × 1.5 cm ulcer on shin	11 weeks	30 (wound base) 50 (wound edge)	1 treatment	Complete healing by 3 weeks	Phillips et al. (2015) [21]
90s	Post-operative (Mohs surgery)	2.2 × 1.7 cm on shin	7 weeks	30 (wound base) 50 (wound edge)	1 treatment	Complete healing by 6 weeks	Phillips et al. (2015) [21]
8	Chemical burn	1.2 cm linear ulcer on forearm	8 months	50	2 treatments 2 months apart	Near complete healing after 2 months; complete healing within 4 months	Krakowski et al. (2016) [22]
17	Aggressive cryotherapy followed by repeated trauma	1.5 cm and 2 cm diameter wounds on shin	6 months	50	2 treatments 1 month apart	Complete healing within 2 months	Krakowski et al. (2016) [22]
22	Recessive dystrophic epidermolysis bullosa	7 cm diameter ulcer on upper back	9 months	30	2 treatments 2 months apart	Near complete healing after 2 months	Krakowski and Ghasri (2015) [23]

which the wounds were left to heal by secondary intention. The other patient had sustained a degloving injury of her foot following a motor vehicle accident. The resulting wound had been sutured but later dehisced. They have also successfully used AF CO_2 laser treatment in a 16-year-old boy with phacomatosis pigmentovascularis who presented with a 6-month history of a non-healing post-traumatic ulcer on the left lateral ankle, which had not responded to compression, hydrocolloid dressings, or amniotic membrane dressings (Fig. 13.1).

Prior to laser treatment, topical lidocaine hydrochloride gel, 30%, was applied to all wounds for 30 minutes. In each case, one pass with AF CO_2 laser was administered at a treatment density of 5%. The pulse energy to the wound base was 30 mJ, while the entire wound edge and 1–2 cm of surrounding skin received 50 mJ. After laser treatment, a petrolatum-based ointment, non-stick

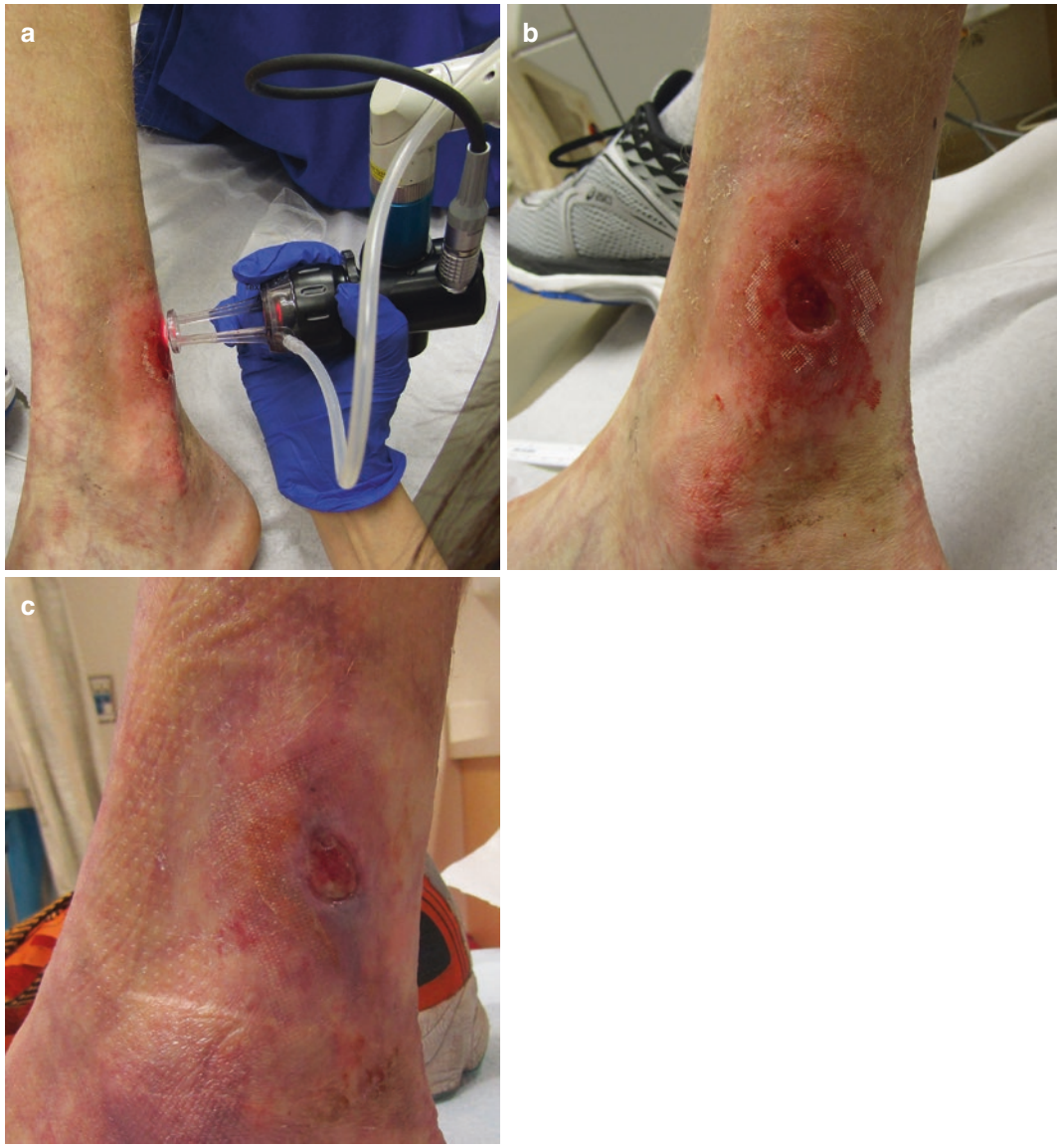

Fig. 13.1 A 16-year-old boy with a 6-month history of non-healing post-traumatic ulcer. (**a**) Patient undergoing ablative fractional CO_2 laser treatment; (**b**) 1 week after treatment; (**c**) 4 weeks after treatment

gauze, and compression wrap were applied. The procedures were very well-tolerated, and no adverse events other than mild erythema were reported following treatment. All wounds were at least 60% reduced in size after 3 weeks. Notably, all of these patients were in generally good health, without vascular insufficiency, uncontrolled diabetes, or other major risk factors for non-healing wounds. To date, no reports of laser treatment for more typical chronic wounds etiologies, such as venous, arterial, diabetic, or pressure ulcers, have been published.

Other Reports of Ablative Fractional Laser for Wound Healing

In addition to the previously discussed reports in adults, AF CO_2 laser has been successfully used on pediatric patients with chronic scar-related

wounds. Krakowski and colleagues reported treating an 8-year-old with a forearm wound at the site of a previous chemical burn and a 17-year-old with two wounds on the shin following aggressive cryotherapy and repeated trauma [22]. In a separate report, Krakowski and Ghasri reported the use of AF CO_2 laser on a 22-year-old with wounds due to recessive dystrophic epidermolysis bullosa [23]. In this case, topical lidocaine 4% cream was applied under occlusion for 1 hour prior to the procedure. The authors note a 92% decrease in wound surface area after only 4 weeks. Ultimately, given the very positive outcome seen with this ulcer, laser treatment was used on three wounds, all of which responded similarly. In all of these cases, a fractional CO_2 laser (Deep FX fractional CO_2 laser, Lumenis Ltd.) was used with a similar protocol (5% density, single pass, 30–50 mJ) to that described in earlier reports.

Mechanisms of Action

While it is poorly understood why AF laser might stimulate wound healing, a number of mechanisms of action have been postulated.

Mechanical

The fractionated pattern of injury with fenestration of the wound edge, in particular, has been suggested to play a key role [21]. Especially in wounds related to scarring and contractures, increased tension might cause tissue ischemia and increase the risk of skin breakdown [24]. Treating the wound edge and surrounding skin may improve tissue pliability and reduce skin tension, thereby facilitating healing. Nonetheless, Phillips et al. have anecdotally noted that treating the wound edge or peripheral skin alone was not as effective as treating the wound bed plus periphery [21]. If this observation is true, other nonmechanical mechanisms of stimulating healing must also be at work.

Collagen Remodeling

Evidence suggests that fractionated skin injury, the removal of microcolumns of tissue in a controlled fashion, stimulates collagen remodeling and might promote healing. In a somewhat analogous process, percutaneous collagen induction, or skin microneedling, is commonly used to stimulate collagen production and skin rejuvenation [25]. El-Domyati et al. looked at the collagen composition of healthy skin before and after treatment with AF Er:YAG laser. At 1 and 6 months after treatment, they found new dermal collagen formation with increased concentration of collagen types I, III, and VII. They also showed that there was no significant difference in effect after 6 months with three to five treatments [26]. The collagen arrangement in healthy skin typically has a regular orientation, while scarred skin has collagen that appears more disorganized or disrupted [27]. Makboul et al. treated patients with hypertrophic scars with AF CO_2 laser and demonstrated that the epidermal thickness showed significant increase after laser treatment ($P > 0.001$). There was also thinning in the stratum corneum and replacement of the irregular collagen bands with organized new collagen fibrils as demonstrated by H&E and other special stains [28]. Similar changes in collagen architecture following AF CO_2 laser have been visualized in vivo using reflectance confocal microscopy (RCM). The collagen type as seen upon RCM observed at baseline was replaced by a newly formed collagen type with long, bright, and straight fibers. These fibers were arranged in parallel and observed throughout the entire RCM mosaic.

AF laser has also been found to increase the ratio of type III collagen to type I collagen in hypertrophic scars, resulting in a collagen profile more typical of nonwounded skin or as seen in the early stages of wound remodeling [29]. By inducing durable alterations in collagen structure, AF laser may also reduce scar tension, leading to better functional and cosmetic outcomes.

Debridement

In the initial report of AF laser stimulating wound healing, Shumaker et al. propose the term "photomicrodebridement" to refer to the vaporization of skin microcolumns [20]. Debridement is generally considered an essential element of

wound care, as it removes dead tissue and phenotypically altered senescent cells, reduces bioburden and biofilm, and induces an acute injury response that promotes healing [30–32]. While Phillips et al. did not perform sharp debridement of the lower extremity wounds prior to treatment with AF laser, photomicrodebridement with AF laser may remove devitalized tissue and senescent cells, as well as break up biofilm and reduce overall bacterial burden [24]. These effects may partly account for the improved healing seen in their study.

Changes in Molecular Profile

AF laser on scarred skin has been shown to increase transcription of microRNAs involved in transforming growth factor beta (TGF-β) signaling pathways [33]. Hypertrophic burn scars treated with AF laser had significant upregulation of miR-18a and miR-19a and decreased expression of TGF-β2, TGF-β3, and basic fibroblast growth factor [33]. Likewise, in a similar study, Makboul et al. found that expression of TGF-β1 was significantly decreased, though other proteins in the TGF-β family were not studied. By contrast, when AF Er:YAG laser was used for facial rejuvenation in non-scarred photoaged skin, overall TGF-β expression was significantly increased [34]. TGF-β is an important regulator of fibroblast proliferation, collagen production, and tissue remodeling and repair in human skin, overexpression of which can lead to scarring [35, 36]. TGF-β expression also decreases in response to UV exposure, leading to decreased collagen production and contributing to skin aging [37]. Given the observed effects of AF laser on TGF-β expression in scarred and photoaged skin, AF laser seems to reset TGF-β expression to more optimal levels that promote restoration of healthy skin.

Other molecular changes seen following AF laser add further supporting evidence for its effect on collagen production. Heat shock protein (HSP) 47 has been shown to be elevated at least 3 months after treatment with AF CO_2 laser [13, 38]. HSP47 targets collagen processing and is thought to play an important role in wound healing, including scar formation [39]. Certain matrix metalloproteinases (MMPs) have also been shown to be upregulated following AF CO_2 laser. MMPs break down collagen and other extracellular matrix proteins, and their expression is known to be dysregulated in chronic wounds [40]. AF laser has been found to significantly increase expression of MMPs 1, 3, 9, 10, 11, and 13 [41] in photodamaged and scarred skin [33, 41]. Finally, growth factors, including platelet-derived growth factor and epidermal growth factor, that play principal roles in wound healing have been shown to be acutely elevated following treatment with AF CO_2 laser [42]. Vascular endothelial growth factor has also been found to be acutely elevated following similar treatment in a mouse model [43].

Other Considerations

The use of AF laser for wounds is still in the very early stages of development, and, as such, no established protocols have been developed. The particular treatment settings for use with wounds can be informed by a 2014 expert consensus report outlining guidelines for use of laser treatment on traumatic scars [44]. The guidelines note that scar thickness should be proportional to treatment depth, which is correlated with pulse energy setting. Additionally, low treatment density, narrow-beam diameter, short pulse width, and a single pass without overlap repeated every 2–3 months are recommended to decrease risk of worsening scarring. In the context of chronic wounds, these same general principles may apply for stimulating tissue remodeling and wound healing; however, it must be considered that wounds, at the least, lack an intact epidermis. Accordingly, desired treatment depth may be reduced and suitable pulse energy settings are likely decreased.

The use of other fractional laser devices for treating wounds has not been described. Nonetheless, fractional Er:YAG laser would be expected to have a similar effect [44].

Future Directions

Undoubtedly, lasers represent an exciting new modality for the treatment of chronic wounds. Though limited to a small number of case reports and case series, the cases presented herein offer compelling evidence for the effectiveness of AF CO_2 laser as an adjuvant therapy for post-traumatic chronic wounds. Certainly, clinical trials are needed to validate these early results and to establish the best treatment protocols. Most importantly, perhaps, the role for lasers in treating other types of chronic wounds, including venous, arterial, diabetic, and pressure ulcers, has yet to be explored. Efficacy for any of these other conditions for could make lasers extremely valuable tools in the future of wound care.

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Stem Cell Therapy in Wound Care

14

Makram E. Aljghami and Saeid Amini-Nik

Background

Millions of people suffer from chronic wounds which require billions of dollars annually for treatment [1]. These wounds alone make up 2% of total health-care spending, which occur due to the aging population and the increase in the prevalence of diabetes [1]. Thus, wound therapy has changed its focus from wound management to an active role in optimizing wound healing. Stem cell therapy has become a topic of interest due to the potential of stem cells to regenerate the wounded skin for ideal healing outcomes. Since different cell types have different roles during the course of wound healing, understanding the stages of wound healing and the cells that contribute to these stages is important.

Stages of Wound Healing

Wound healing after the injury occurs in three different phases known as hemostasis/inflammation, proliferation, and maturation [2, 3]. During hemostasis/inflammation, blood loss is stopped, and immune cells are recruited to the wound site. Neutrophils, macrophages, and lymphocytes infiltrate the wound bed to release cytokines and phagocytose debris from dead cells and pathogens [2]. Immune cells also release important growth factors and cytokines such as fibroblast growth factor (FGF), tumor necrosis factor (TNFα), and interleukin (IL1) to signal for fibroblasts, keratinocytes, and stem cell recruitment to the wound site [4, 5]. This stage typically lasts for a few days and is, then, followed by the proliferative phase.

The proliferative phase involves granulation tissue formation, angiogenesis, and epithelialization [6, 7]. Fibroblasts proliferate and migrate to the wound bed where they deposit collagen and fibronectin to form a matrix for epithelial cell migration [8]. Furthermore, matrix metalloproteinases (MMPs) are also released to degrade the basement membrane to facilitate keratinocyte migration [9, 10]. The keratinocytes, in turn, make up the new epidermal layer. Other released factors include TGFα, TGFβ, keratinocyte growth factor, and epidermal growth factor (EGF) which mediate the proliferation and movement of keratinocytes in the wound [11–14]. In addition, in concert with vascular endothelial growth factor (VEGF) and fibronectin growth factor-2 (FGF2), these factors promote angiogenesis which increases blood flow to the wound [15, 16]. Following the proliferative phase, the overlapping tissue remodeling phase is initiated.

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A. Alavi, H. I. Maibach (eds.), *Local Wound Care for Dermatologists*, Updates in Clinical Dermatology, https://doi.org/10.1007/978-3-030-28872-3_14

Tissue remodeling involves the reorganization of the extracellular matrix fibers, namely, collagen [17]. This stage can last from weeks to years. As the wound bed matures, type III collagen which is initially deposited during the proliferative phase is replaced with organized type I collagen by MMPs [17]. When the collagen fibers are organized, the tensile strength of the new tissue increases, despite not being able to regain the initial tensile strength of the intact skin prior to injury [18]. All stages of wound healing are important for proper repair; impairments in any of the stages could elongate the healing time of the wound resulting in chronic wounds [19]. Chronic wounds are complex and do not currently have any proper treatments, making them an attractive target for stem cell research.

Acute and Chronic Wounds

In normal wound healing, acute wounds heal within weeks in healthy individuals. However, disruptions in any of the healing stages could cause the wound to become chronic [19]. Chronic wounds are characterized as long-term wounds which fail to heal properly in time to restore their function and physical barrier [20]. Studies have shown that chronic wounds typically regress during the inflammatory phase which slows down the activation of the later healing processes [21].

Although the shift from acute wounds to chronic wounds is still not well understood, free radical production, infections, and ischemia have all been suggested to disrupt one or more stages of wound healing [22–24]. Imbalances in the production of growth factors and cytokines, cell infiltration, defective ECM components, and overexpression of proteinases have also been implicated in chronic wounds [25–27]. Understanding the mechanisms underlying chronic wounds is crucial to providing proper treatment to these wounds since conventional methods are yet to be effective. Thus, stem cell therapy may provide a new approach to address complications associated with these chronic wounds.

Current Treatments

Wound care aims to provide proper treatment to the skin injury to promote proper and scarless wound healing. The standard of care involves debridement of the necrotic tissue following injury and application of dressing to prevent infection [28, 29]. Different strategies are used to speed up wound repairs such as skin grafts, skin substitutes, and other synthetic products. The gold standard of care in burns is the use of autografts as they provide the most suitable biochemical environment for the host cells and minimize the chance of immunological rejection [30]. Although autografts have been successful in treating burn patients, larger surface areas of burn injuries proved to be problematic due to the invasiveness of the procedure which does not yield sufficient sample size.

Advancements in bioengineering brought forth the development of novel skin substitutes that help in wound closure in cases where traditional skin grafts were unavailable or inadequate. Integra® (Integra LifeSciences, Plainsboro, New Jersey, USA) is an acellular skin substitute that is most commonly used as a dermal replacement to promote wound closure [31, 32]. It is made up of a dermal analog made of collagen and a silicone layer which acts as a temporary epidermis to maintain a wet environment for optimal wound healing while providing a physical barrier to pathogens [33]. However, skin substitutes like Integra® are still not perfect as they fail to fully recapitulate the function of human skin due to lacking cellular components and are also very expensive which may burden health care.

Ulcers in diabetic patients and chronic wounds lack necessary factors for skin repair. Thus, many cellular processes that are required for normal healing are affected including cell migration, angiogenesis, proliferation, and ECM deposition. With the use of these growth factors in conjunction with the earlier treatments previously described, healing times were reduced in patients with chronic wounds [34]. Alternatively, transplantation of keratinocytes into the wound bed also promotes reepitheliza-

tion in porcine models [35]. However, many diabetic patients still do not respond to the discussed conventional methods, and, thus, newer stem cell therapy has been suggested. The purpose is to restore the dermal and epidermal components of the skin to retain full functionality of the skin. Stem cells have been thought to be able to not only replace the lost cells upon injury but also stimulate other nearby cells to contribute to wound closure by migration and secretion of factors necessary in wound repair [36]. Hence, stem cell therapy demonstrates great potential in providing a novel approach to treating chronic wounds and other complex skin injuries.

Stem Cell Therapy

Stem cell therapy aims to restore the function of the wounded area through regeneration of the skin to its original state. These stem cells require appropriate cues and methods of delivery that are necessary for optimal healing and regeneration. They have gained interest due to their ability to self-renew and differentiate into cells which could potentially integrate into the wound to replace the damaged tissue [37]. Further, they have been shown to secrete factors to promote various processes such as neovascularization, cell migration, and immunomodulation (Table 14.1) [38]. Stem cells can be derived from different sources such as embryos, the bone marrow, the adipose tissue, the umbilical cord, and the epidermis [39–41].

Stem Cells Derived from Embryos

Embryonic stem cells (ESCs) are pluripotent cells which, therefore, have the capacity to differentiate into various types of cell lineages. They are derived from the inner cell mass of blastocysts 4 or 5 days post-fertilization, which have already shown potential in the treatment of different diseases such as Parkinson's, diabetes, and severe heart failure [42–45]. However, since they are derived from embryos, ESCs are not easily obtainable and, therefore, are not commonly used in stem cell therapy compared to other types. Alternatively, adult donor cells are more commonly used as they not only are more abundant but also deal with less ethical concerns than ESCs which damages the embryonic blastocysts [46]. Despite having no approved current treatments using ESCs, new methods are being studied aim to minimize the invasiveness of ESC derivation [46, 47].

Stem Cells Derived from the Bone Marrow

The bone marrow contains different types of stem cells such as hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) [48]. HSCs play an important role in repopulating the bone marrow and blood [49]. MSCs can self-renew and differentiate into various cell lineages such as osteoblasts, chondrocytes, and adipocytes [50]. MSCs enter the wound site where they regulate the inflammatory response in order to promote

Table 14.1 Published studies on different stem cell sources. "Y" denotes that the implication has been shown in the literature, and "N" indicates that it has not been shown

	Dermis				Epidermis			
	Trophic effect (secretome)		Cellular integration (cell effect)		Trophic effect (secretome)		Cellular integration (cell effect)	
	Animal	Human	Animal	Human	Animal	Human	Animal	Human
Umbilical cord MSCs	Y	N	N	N	Y	N	N	N
BM MSCs	Y	Y	Y	Y	Y	Y	Y	Y
Adipose-derived MSCs	Y	Y	Y	N	Y	Y	N	N
Epidermal stem cells	N	N	N	N	Y	Y	Y	Y

proper wound healing, thus preventing the wound from entering a chronic state [51]. Furthermore, they act to decrease the high levels of pro-inflammatory cytokines and promotes anti-inflammatory cytokine production, attenuating prolonged inflammation seen in chronic wounds [52]. MSCs can also differentiate into specialized cells to help in wound repair. Transplanted MSCs in patients with chronic wounds and diabetic patients revealed improved healing and wound closure [53, 54]. Hence, these studies demonstrate the promising role of bone-derived stem cells in enhancing skin regeneration.

Stem Cells Derived from Adipose Tissue

Although bone marrow–derived stem cells have an advantage in their plasticity which makes them attractive in regenerative medicine, isolating these cells from patients is invasive and painful. On the other hand, adipose tissue also provides a great source of MSCs and is less invasive to isolate than bone-derived stem cells [55–57]. Adipose tissue can be harvested through debridement after surgery or through biopsies, yielding 500-fold greater number of MSCs than the bone marrow [58].

Several studies have shown that MSCs derived from adipose tissue have therapeutic potential. It was previously shown that adipose-derived MSCs injected intramuscularly relieved pain in patients with critical limb ischemia [59]. This has improved claudication walking distance in those patients after multiple intramuscular injections of MSC [59]. Since those adipose-derived stem cells have increased blood flow in ischemic tissue, they can play a potential role in treating chronic wounds by allowing for proper perfusion of the healing wound. Furthermore, studies have shown that injection of adipose-derived MSCs into acute wounds sped up wound closure, reduced inflammation, and increased epithelialization in preclinical studies [60, 61]. Another study also showed that those stem cells reduced wound size and promoted granulation tissue formation and collagen deposition in full-thickness wounds inflicted on mice [62].

The injection of MSC into the wound bed requires a large number of cells, due to poor survival and function of these cells, which is especially problematic in larger wounds. Thus, newer studies aim to design bioactive materials to maintain ideal environments for optimal cell growth, proliferation, and migration.

Stem Cells Derived from the Umbilical Cord

The umbilical cord contains a large number of stem cells in its different layers, including Wharton's jelly and the outer lining [63, 64]. Stem cells derived from the outer lining can be classified into groups of epithelial cells or mesenchymal cells. They express common stem cell markers such as Oct4 and Nanog and can differentiate into different cell types such as epithelial and endothelial cells [65]. Hence, these stem cells may have a potential function in regenerating the epithelial cells in skin wound healing. Wharton's jelly is the gelatinous supporting matrix found in the umbilical cord [66]. Transplantation of MSCs derived from this layer was found to promote reepithelialization, increase gene expression and keratinocyte differentiation, reduce scar formation, and improve wound healing [67–69].

Umbilical cord-derived stem cells may play a promising role in skin regeneration. Clinical trials are currently testing the efficacy of these stem cells in treating chronic wounds. Interestingly, no tumor formation or immune rejection was reported, suggesting no risk of transplantation to patients. Umbilical cords are readily available as they are normally discarded as waste, making them an attractive source for stem cell therapy [70].

Stem Cells Derived from the Epidermis

The epidermal layer of the skin has a reservoir of adult stem cells which can be potentially incorporated into skin substitutes to create a bioactive scaffold [71]. These stem cells are non-oncogenic

so pose fewer risks compared to other types such as embryonic or induced pluripotent stem cells [72]. Furthermore, they can also address some issues such as immunological rejection of the delivered cells and the lack of skin appendage formation. Unipotent epidermal stem cells are found in the epidermal basal layer and function to regenerate epidermal cells in adults [40, 73]. Multipotent stem cells are found in the hair follicle which is capable of repopulating the hair follicles themselves, sebaceous glands, and the epidermis [74]. Following skin injury, stem cells from the hair follicles are mobilized for skin repair in vivo to enhance reepithelization of the epidermis [75]. Although they have multipotent effects upon injury, hair follicle stem cells are unipotent under normal conditions as they constantly repopulate the hair follicle [75].

Cultured epithelial sheets which contain epidermal stem cells, keratinocytes, and a fibrin matrix are commonly used in the treatment of burn wounds [76]. These sheets of cells have also been previously shown to treat skin ulcers and deep dermal wounds [77]. Transplantation of epidermal stem cells using a collagen-chitin biomimetic membrane enhanced skin regeneration in mice with full-thickness wounds and in diabetic mice [78]. Lastly, other studies reported that epithelial cells injected into wound beds promoted reepithelization, angiogenesis, and hair growth suggesting that these cells may play an important role in facilitating wound healing [79].

Stem Cell Delivery Techniques

Although the importance of stem cell therapy has been previously demonstrated, some of the challenges in the field relate to the method of delivery of cells to the skin. Discussed below are the main techniques used in stem cell delivery: delivery by scaffold, injection, and spraying.

Delivery by Injection

The most common method of cell delivery in the clinic is through the injection of suspended cells into the wound [80]. However, without the support of a synthetic matrix, challenges remain where cell survival is low and are affected by shear pressure upon injection [81]. In addition, the delivered cells are not properly organized in the wound area which decreases the attachment of stem cell to the wound bed and results in cell death [80]. Another problem relates to the ability of the cells to migrate to other tissues or organs in the body, creating a cancer-prone environment at unintended targets. Thus, newer methods of delivery should be developed to address these challenges.

Delivery by Spraying

Stem cell delivery through spraying was developed as a convenient way to deliver cells with extracellular materials such as fibrin [82]. Stem cells are combined with fibrinogen to form fibrin by thrombin coadministration. Fibrin prevents stem cell from degradation at the wound site and facilitates the adherence of the cells to the wound bed [83]. Furthermore, the fibrin spray allowed the cells to be distributed properly over large wound areas compared to other methods and was already proven to be safe and effective in stimulating wound healing [83–85].

Delivery by Scaffold

One of the main methods of stem cell delivery that bioengineering research is focusing on is through biocompatible scaffolds, where stem cells can be incorporated to be delivered to the wound. Different materials can be used to fabricate the scaffold including collagen, gelatin, chitosan, pullulan, and hyaluronan [86–88]. These materials have similar properties as the tissue microenvironment which allows for waste and nutrient transfer. However, nutrient transfer to the scaffold is not yet sufficient due to challenges associated with optimizing the porosity of the three-dimensional matrix. Current studies continue to work on developing novel biomaterials to improve cell delivery and viability.

Delivery by 3D Printing

A new approach to stem cell delivery involves the use of 3D printing to deliver stem cells and biopolymers. Multiple studies have shown examples of bioprinted skin tissues in vitro and in vivo, but due to the novelty of this approach, challenges remain where the 3D printers are bulky, require laser scanning of the wound, work at low speeds, and are limited by their spatial control [89–94]. A new model that addresses these challenges was developed to design an extrusion-based bioprinter which allows for printing of planar biomaterials and skin tissue sheets at a relatively fast rate [95]. The device was shown to be compatible with dermal and epidermal cells embedded into cross-linked materials, which are delivered in bioinks made up of alginate, fibrin, collagen, and hyaluronic acid [95]. Proof-of-concept experiments showed the capacity of the printer to deposit material onto inclined and compliant wound surfaces in murine and porcine excisional wound models, but comprehensive in vivo studies and clinical trials are required to examine the effectiveness of this approach on wound healing [95]. This novel approach provides an innovative and promising stem cell delivery method which may also be applied to the delivery of other materials such as biopolymers as well as differentiated and non-differentiated cells.

Challenges and Future Directions

Wound healing is a complex process that requires interactions of different players such as the extracellular matrix, cells, and growth factors. Stem cell therapy plays a key role in the different wound healing stages of inflammation, proliferation, and tissue maturation. While stem cell delivery has shown potential therapeutic benefits, there are still challenges to be addressed in the field before clinical applications. There still has not been sufficient evidence that the newly formed skin cells and appendages are regenerated by the administrated stem cells. Furthermore, perfect regeneration without scarring has not been yet achieved, and whether the regenerated skin mimics the intact skin function is still unclear. Cells isolated from adults may also have decreased plasticity due to aging factors [96]. Finally, due to their plastic nature, stem cell therapy comes with the risk of giving rise to cancerous cells in suboptimal niches that may promote tumor growth [97, 98]. Therefore, more research is needed to overcome these challenges in stem cell therapy. Preclinical and clinical studies are needed to develop better methods of stem cell application to achieve optimal cell delivery for effective wound healing.

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15 Cellular- and Acellular-Based Therapies: Skin Substitutes and Matrices

Brian Cahn and Hadar Lev-Tov

Abbreviations

BLCCs	Bilayered living cellular constructs
CA	Cadaveric allograft
CDM	Collagen dermal matrix
CEAs	Cultured epidermal autografts
CPM	Cryopreserved placental membrane
DFU	Diabetic foot ulcer
DHACM	Dehydrated human amnion/chorion membrane
DRT	Dermal regeneration template
ECM	Extracellular matrix
PU	Pressure ulcer
VLU	Venous leg ulcer

Introduction

Wounds are the most common skin disease. Therefore, dermatologists should develop a thorough understanding of the etiology, natural history, principles of diagnosis, and treatment of wounds. However, even under optimal expert care, some wounds do not heal at the appropriate rate. Fortunately, advanced wound therapy with skin substitutes and matrices can often correct the healing trajectory of a stalled wound. Therefore, dermatologists should be familiar with these products and develop basic understanding of the classes available, the way they are applied, and how they work since they are simple to use and often effective.

Historically, the first written account of skin substitutes occurred in the fifteenth century BCE in *Ebers Papyrus*, where frog skin was used as a xenograft [1]. Skin allografts were first reported 3000 years later in writings from the Branca family of Sicily in the first half of the fifteenth century [2]. In the early 1900s, amnion began to be used as a biological dressing for the management of burns [3]. Over the past 40 years, there have been breakthroughs in the ability to bioengineer tissue substitutes leading to a vast array of products. The first major breakthrough was in 1975 when Rheinwald and Green cultivated keratinocyte sheets from epidermal cells allowing for the production of large quantities of keratinocytes in vitro [4]. In 1981, the first artificial skin bilayer was used to treat burn wounds, and it was found that the host tissue utilized the bilayer to synthesize neoepidermis and neodermis [5, 6]. This paved the way for the first commercially available epithelial autografts in 1988 with the development of Epicel®, a cultured epidermal

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A. Alavi, H. I. Maibach (eds.), *Local Wound Care for Dermatologists*, Updates in Clinical Dermatology, https://doi.org/10.1007/978-3-030-28872-3_15

autograft. Since then, a multitude of matrices have been made available that allows the clinician to tailor to the unique needs of each clinical encounter.

Acellular and cellular matrices, also referred to as skin substitutes, are a form of advanced wound care utilized when standard wound care fails to heal a wound. Wound recalcitrance is often due to the "edge effect" whereby the epithelium fails to migrate across the granulation tissue. Utilization of skin substitutes may be used to overcome the edge effect by providing structural support for migration, tissue regeneration, growth factors, and cytokines and via restoration of the biochemical and moisture balance within the nonhealing wound [7]. Additionally, evidence suggests that skin substitutes revert the wound's inflammatory environment back to an acute healing phenotype that promotes wound healing [5, 8]. Interestingly, these engineered tissues do not persist in the wound and are replaced by the patient's tissues. These skin substitutes afford the clinician the ability to cover larger areas than what is usually allowed with a traditional skin graft [9]. Furthermore, skin substitutes obviate the need for autografts, thus avoiding a surgical procedure, painful surgical donor site, and additional scarring, which is often the most distressing aspect of a traditional skin graft [10].

There are multiple ways to classify skin substitutes. Most broadly, they can be classified as acellular or cellular skin equivalents [11]. Acellular matrices functionally act as a scaffold by transiently functioning as an extracellular matrix (ECM), which promotes host cellular migration leading to wound healing via replacement of the skin equivalent with endogenous host tissue. They may be biologically active or inert and are produced from natural sources, manufactured, or from a combination of both. On the other hand, cellular matrices contain functional cells that are embedded into an ECM. These cells are capable of secreting cytokines, growth factors, collagen, fibronectin, and glycosaminoglycans that promote angiogenesis, granulation, and re-epithelialization [12]. Generally, acellular matrices are less expensive and easier to produce, apply, and store [9].

Skin substitutes can be further divided into epidermal grafts, dermal replacements, and composite grafts. Epidermal grafts consist of autologous cultured keratinocytes, while dermal grafts consist of cellular or acellular dermal components, mainly collagen. Composite grafts are bilayered skin equivalents and consist of an epidermal layer of keratinocytes or synthetic material on top of a dermal layer. This categorization can be further divided into allogeneic, xenogeneic, or autologous grafts.

Characteristics of an ideal tissue-engineered skin substitute [11, 13, 14]:

- Allow for endogenous cell adherence and migration
- Nontoxic
- Non-inflammatory
- Non-immunogenic
- Cost-effective
- Widely available
- Stored at room temperature
- Prolonged shelf life
- Durable
- Malleable
- Biodegradable
- Prevent water loss
- Provide coverage for unique wound characteristics including location, depth, and underlying etiology

Although no single skin equivalent meets all of these characteristics, the numerous products available afford the clinician the ability to tailor treatment to the unique clinical picture.

Principles of Selection and Use of Skin Equivalents

Skin substitutes should be applied according to manufacturer's instructions, and typically the company can readily provide technical support. Since a myriad of products are available, each with some unique features and subtleties, an overview of the principles of selection and applications is provided.

Assessment and preparation of the wound bed is the essential first step in preparing for advanced

wound therapy. This is first accomplished by a thorough history and physical examination to determine the etiology of the wound. Any underlying causes for the delayed healing such as immunosuppression, poor nutrition, infection, or systemic illness should be addressed prior to initiation of advanced wound therapy [15].

The wound should then be inspected and measured for wound size, depth, color, undermining, edema, erythema, and exudate. Often, chronic wounds contain necrotic tissue and biofilms that impede healing and should be debrided. Wound edge should be assessed, and undermined tissue should be removed to allow for re-epithelialization. Similarly, debridement of callus is essential for relieving pressure. The wound surface should be cleansed of contaminants, bacteria, and remnants of previous dressings. If erythema, tenderness, and warmth are noted at the wound, infection should be suspected, and initiation of topical or systemic antimicrobials is essential. Moisture balance should be achieved with proper dressing choice to manage exudate and avoid excessive dryness or maceration at the skin edges [16]. The importance of meticulous wound bed preparation cannot be understated as healthy granulation tissue is crucial for the success of skin substitutes' application [17, 18].

Typically, initiating treatment with advanced wound therapies should be considered when a wound fails to heal for at least a few weeks with appropriate standard wound care (i.e., multilayered compression for venous leg ulcers [VLUs] or offloading for diabetic foot ulcers [DFUs]) [9]. Contraindications to placing a skin substitute include wound infection; exposed muscle, tendon, or bone; or hypersensitivities to the matrix [19].

Following wound bed preparation, accurate measurements of the wound should be recorded to obtain a baseline by which the clinician can monitor the healing response to the skin substitute. Additionally, these measurements will help the clinician select and prepare the matrix to properly fit the wound. Careful preparation must be taken to ensure proper placement of the product as some come ready to be placed onto the wound, while others must be fenestrated to allow for exudate to permeate through the matrix [20]. Matrices that contain only one layer need not take into account orientation, while the bilayered composite grafts need to be carefully placed to ensure proper orientation [21]. Skin substitutes that are dehydrated require rehydration, and others matrices that are cryopreserved must be thawed with care according to the manufacturer's instructions. Flowable matrices that are injected into wounds are usually hydrated before use [22]. The applied product should be secured with a preferred method such as Steri-Strips® or suture. Following placement of the matrix, application of a non-adherent contact layer helps to secure the product in place and protect during secondary dressing changes. A secondary dressing can then be placed to maintain moisture balance. Throughout these steps, aseptic technique should be strictly maintained. Once application is complete, standard of care should be completed as appropriate. Increase in exudate is common after application of skin substitutes, and the patient should be advised, and proper secondary dressing should be provided. However, the clinician should be vigilant for signs of infection.

Generally, it is advised that the primary dressing should not be disturbed for a week following placement of skin substitutes. However, clinicians should be familiar with the specific post-care instructions of each product as those may differ. Once the allotted time has passed, the clinician should remove the primary dressing and thoroughly inspect the wound for evidence of healing such as advancing wound edge. If unhealed, many of the wounds will retain some residue of the skin substitute in the wound, and it is generally advised to not remove it. In this case, necrotic tissue can be removed selectively, and new primary non-adherent dressing can be applied followed by standard of care. If the clinician is still concerned about the healing progress, reapplication may be considered. Guidelines for reapplication are generally derived from pivotal trials that classically utilize weekly applications. However, evidence on the most adventitious timing for reapplication is lacking.

Cellular Matrices (Table 15.1)

Cultured Epidermal Autografts (CEA, Epicel®, Vericel, Cambridge, MA)

Indications: deep dermal or full-thickness burns greater than or equal to 30% of total body surface area [40]

The in vitro capability of skin stem cells to expand has been leveraged to create an autologous skin graft from a biopsy taken from the patient [41]. In order to obtain autologous keratinocytes for culture, two 6 cm × 2 cm full-thickness biopsies are taken within 24–48 hours of admission from the axilla and/or groin. These biopsies are placed into biopsy media tubes provided by the manufacturer and sent to Epicel® for ex vivo expansion. The grafts mature over approximately 17 days to create 4800 cm^2 sheets of keratinocytes that are 2–8 cell layers thick. This process allows expansion of a relatively small donor site into a graft that can cover a large body surface area. Additionally, if the use of the graft is not immediately necessary, the cultured autograft may be cryopreserved for future use [42].

Once the expanded cultured autograft is obtained, the graft should be arranged with the cell sheet facing down to preserve the basal-apical orientation of the keratinocyte sheets. The grafts should be placed as close together without overlap as possible and then stapled in place. Importantly, the graft material should not be stapled until the sheets are providing full coverage over the wound in case rearrangement is necessary. Once in place, the grafts should be covered with a primary nylon dressing and then an outer secondary dressing.

The disadvantages of CEAs include the high cost of the graft, sensitivity of the keratinocyte sheets to infection due to breakdown from bacterial proteases and cytotoxins, variable graft take

Table 15.1 Cellular matrices

Product	Product type	Indications	Contraindications	Level of evidence*
Epicel®	Cultured epidermal autograft	Deep dermal or full-thickness burns greater than or equal to 30% of the total body surface area	Clinically infected wounds	Level 3 [23–25]
Apligraf ®	Bilayered living cellular construct	Partial- and full-thickness VLUs >1 month Full-thickness neuropathic diabetic foot ulcers >3 weeks	Exposed muscle, tendon, or bone, infected wounds, hypersensitivities to bovine collagen or components of shipping medium	VLUs: Level 1 [26] DFUs: Level 1 [27, 28]
Dermagraft®	Collagen dermal matrix	Full-thickness neuropathic DFUs >6 weeks	Clinically infected wounds, wounds with sinus tracts, hypersensitivity to bovine products	Level 1 [29, 30]
TransCyte®	Collagen dermal matrix	Partial- and full-thickness burns	Clinically infected wounds	Level 2 [31, 32]
Epifix®	Epifix®	DFUs VLUs	Infected wounds	DFUs: Level 1 [28, 33, 34] VLUs: Level 1 [35, 36]
Grafix®	Cryopreserved placental membrane	DFUs	Acute or chronic infection, hypersensitivity to gentamicin, vancomycin, amphotericin B	Level 1 [37, 38]

*Level of evidence derived from The Oxford 2011 Levels of Evidence [39]:

1. Systematic review of randomized trials or n-of-1 trials.
2. Randomized trial or observational study with dramatic effect.
3. Non-randomized controlled cohort/follow-up study.
4. Case series, case-control studies, or historically controlled studies.
5. Mechanism-based reasoning.

rate, and the length of time it takes to culture and produce the epidermal autograft [43]. Some labs have reported using fibrin glue to decrease the culturing time to approximately 14 days. However, this has not been widely available [44]. The initial optimism for CEA has been hampered by reports of poor results from surgeons and various burn centers throughout the country [45]. Currently, its use is limited to the initial closing of the wound, but not for permanent closure [46, 47].

Similar products have recently been FDA approved such as RECELL®, which is a CEA spray [48]. There are many CEA products outside of the United States such as Celaderm, Laserskin, Autoderm, TransDerm, Myskin, Epidex, Lyphoderm, and Cryoceal, but they are not currently approved for use in the United States [49]. The level of evidence for the use and efficacy of CEAs is limited to smaller trials and case studies [44].

Bilayered Living Cellular Constructs (BLCC, Apligraf®, Organogenesis, Canton, MA, and OrCel, Ortec International, Atlanta, GA)

Indications: noninfected partial- and full-thickness VLUs that remain unhealed for greater than 1-month duration and full-thickness neuropathic DFUs that remain unhealed for greater than 3 weeks duration. In both cases, there should be no exposed tendon, muscle, or bone. Its successful use has also been reported in partial- and full-thickness burns, epidermolysis bullosa, surgical excisions, and pyoderma gangrenosum [20, 50–53].

BLCCs are tissue-engineered composite skin equivalents that have been shown to decrease wound healing time [54]. Both Apligraf® and OrCel® contain epidermis from human neonatal foreskin on top of bovine collagen [55]. Thus, it possesses both allographic and xenographic features. Of the two, Apligraf® (Fig. 15.1) is the best trialed and consists of allogeneic neonatal keratinocytes and fibroblasts derived from neonatal foreskin on top of bovine type I collagen [50, 52–55]. Since it contains both keratinocytes and fibroblast, it allows for cross talk between the different cell types. Additionally, this graft can produce its own matrix proteins and growth factors. During engineering of the Apligraf®, the epidermal layer is exposed to air, allowing the keratinocytes to stratify and create a stratum corneum [56]. Apligraf® remains viable at room temperature for 10 days from the date of shipping.

Fig. 15.1 Apligraf®, a BLCC, is shown to the left. It is important for the clinician to be prepared before graft placement as the BLCC is delicate. The easiest method to apply the Apligraf® is to place a gauze over the top of the matrix, which is contained in the center circle of the petri dish (black arrow). Wet the gauze with a few drops of saline to allow the membrane to adhere to the gauze. Then gently peel back the matrix and gauze together. If needed, fenestrate the membrane with a blade and cut to size while still attached to the gauze. Then place the matrix on the wound with the gauze side facing up so as to maintain the polarity of the matrix. The matrix can be gently separated from the gauze using a cotton-tipped applicator. It can then be affixed in place with Steri-Strips ™, a noncontact primary layer and a secondary dressing

After the wound bed is prepared, Apligraf® should be fenestrated with a blade. Fenestration allows the product to remain affixed in case of wound exudate. Care should be taken to maintain the orientation of the product such that the dermal layer is in contact with the wound bed. It should then be affixed with a preferred method such as wound glue or Steri-Strips™ at the periphery. The graft should then be covered with a primary nonadherent dressing and then covered with a secondary dressing. The wound should be inspected and redressed within 1 week [20].

OrCel® is comprised of keratinocytes derived from neonatal foreskin cross-linked to a bovine

type I collagen sponge (epidermal side) that contains human dermal fibroblasts on the opposite side of the sponge (dermal side). This composite graft also produces necessary growth factors and matrix proteins. One of the benefits of OrCel® is that it can last for up to 9 months due to cryopreservation. OrCel® should be applied in a similar fashion as the Apligraf® [49].

These composite grafts promote fibrovascular ingrowth and re-epithelialization. Studies have demonstrated a lack of cultured cell DNA when the wound heals suggesting that it is the patient's endogenous skin that heals the wound and the composite graft biodegrades [40]. The main disadvantage of the BLCCs is their high cost [57]. Contraindications to use include infected wounds or if the patient has known hypersensitivities to bovine collagen or components of the shipping medium [20].

Collagen Dermal Matrix (CDM, Dermagraft®, Organogenesis, Canton, MA TransCyte, Advanced BioHealing Inc., Westport, CT)

Indications: The best evidence is for Dermagraft®, and it has been approved for the treatment of full-thickness neuropathic DFUs that have failed to heal for more than 6 weeks without involvement of the tendon, muscle, bone, or joint capsule [29]. It has also been trialed, albeit with less success, in the treatment of VLUs and burns [58, 59]. TransCyte has been FDA approved for partial- and full-thickness burn wounds [31].

Dermagraft® is a CDM that is a bioabsorbable cryopreserved human fibroblast-derived dermal substitute. The dermal matrix is synthesized by culturing neonatal fibroblasts in a glycolic acid mesh. This mesh serves as a scaffold for the production of cytokines, growth factors, matrix proteins, and collagen into a three-dimensional matrix [29]. Aside from fibroblasts, Dermagraft® does not contain other skin cells like keratinocytes, endothelial cells, hair follicles, or white blood cells. When placed into a wound, the CDM stimulates fibrovascular growth and re-epithelialization [40].

Dermagraft® comes in a clear bag containing a single piece of 2 inch × 3 inch CDM. The product should be maintained at a temperature of −75 °C ± 10 °C. Additionally, Dermagraft® should not be kept at room temperature for more than 30 minutes. Dermagraft® should be removed from the foil packaging but kept in the clear packaging and submerged into a 34–37 °C water bath to thaw for 2 minutes. The clear bag should then be cut open, liquid should be removed, and the product should be rinsed three times with room temperature saline until ready for use. Once ready, the saline should be poured out, and the clear bag should be closed. The clear bag should then be placed over the ulcer, and a marker should be used to trace the ulcer. The bag should then be cut along the tracing, and CDM should be placed in the ulcer. After placement, it should be secured with a preferred method. It should then be covered with a non-adhesive primary dressing and then with a secondary dressing. The ulcer site should not be disturbed for 72 hours after placement of the CDM. Dermagraft® is contraindicated in infected wounds, wounds with sinus tracts, and patients that have hypersensitivity to bovine products [21].

TransCyte is synthesized from human newborn fibroblasts cultured onto a nylon mesh of Biobrane® (Dow B. Hickam, Inc., Sugarland, Tex). It is similar to Dermagraft®; however, the fibroblasts are not viable. It is prepared and applied in a similar fashion as Dermagraft®.

Dehydrated Human Amnion/Chorion Membrane (DHACM, Epifix®, MiMedx Group Inc., Marietta, GA)

Indications: VLUs, chronic vascular ulcers, DFUs, partial- and full-thickness wounds, pressure ulcers (PUs), trauma wounds, surgical wounds, and third-degree burns [28, 33, 36, 60–62]

Epifix® is an allographic cellular matrix that is composed of human amnion and chorion matrix. It contains a single layer of epithelial cells, basement membrane, and an avascular connective tissue matrix. This product is bioengi-

neered in such a way that it removes blood products but leaves intact the amniotic membrane and extracellular matrix (ECM). As a result, the product contains cytokines, growth factors, and ECM proteins [36].

Epifix® can be stored in a clean, dry environment at room temperature for up to 5 years. Multiple sizes are available in sheets or mesh from 2 cm^2 up to 49 cm^2 allowing the clinician to meet the needs of a specific clinical scenario.

After the wound bed is prepared, remove the DHACM from the packaging and carefully cut to the size of the wound allowing no more than 1 mm of overlap of the wound margins. When placing the DHACM, use the embossed letters as a guide to maintain correct orientation. If the wound is exudative, the product can be fenestrated. Additionally, the product can be wet or dry depending on the clinical picture. To wet the DHACM, apply sterile saline after it has been placed in the wound. Place a non-adherent primary dressing followed by a secondary dressing and do not disturb the wound site for several days [63]. Epifix® is contraindicated in infected wounds [64]. The company also bioengineers other DHACM products such as AminoFix® (injectable DHACM) and EpiBurn® (DHACM for burn wounds) as well as other products derived from placental tissue and amniotic fluid. However, the evidence and efficacy of these products have not been extensively studied.

Cryopreserved Placental Membrane (CPM, Grafix®, Osiris Therapeutics, Inc., Columbia, MD)

Indications: The best evidence is for use in the management of DFUs [37, 38]. It has shown benefit in the treatment of VLUs, PUs, burns, surgical wounds, pyoderma gangrenosum, and epidermolysis bullosa [62, 65].

CPM is an allogeneic graft composed of growth factors, cytokines, ECM proteins, and cells including mesenchymal stem cells, epithelial cells, and neonatal fibroblasts [38].

CPM is available in multiple sizes and should be maintained at −80 °C. When maintained at that temperature, it has a shelf life of 2 years. After wound bed preparation, warm water that does not exceed 32 °C should be placed into a basin. Place the inner plastic bag into the basin with the label side up. Once no ice crystals are visible, remove the plastic bag and cut open. Using forceps, transfer the CPM to a second basin that is filled with saline. After the wound bed is prepared, remove the top cover from the CPM and place over the wound. Gently remove the back cover from the CPM to place the CPM on the wound. Using cotton tip applicators, arrange the CPM so that it is covering the entire wound including the wound edges. Cover with a non-adherent dressing and then a secondary dressing. CPM is contraindicated in wounds with acute or chronic infection or if the patient has known hypersensitivities to gentamicin, vancomycin, or amphotericin B [65].

Acellular Matrices (Table 15.2)

Porcine Derived (Oasis®, Smith and Nephew, Largo, FL, Biobrane®, UDL Laboratories, Inc., Rockford, Illinois)

Indications: Oasis® has been studied in the management of partial- and full-thickness wounds, DFUs, VLUs, PUs, chronic vascular ulcers, tunneled or undermined wounds, trauma wounds, second-degree burns, and surgical wounds [66, 67, 84–87]. The best evidence is for VLUs and DFUs [66, 67]. Biobrane® is indicated for donor sites and partial-thickness burns [69–73, 88–90].

Oasis® is three-dimensional dermal substitute that is derived from porcine small intestinal mucosa. It provides a collagen scaffold as well as other ECM components such as glycosaminoglycans, proteoglycans, fibronectin, and growth factors [66]. It is available in multiple sizes as either a single- or tri-layered matrix. It can be stored at room temperature for up to 2 years. After the wound bed is prepared, the Oasis® sheet should be cut to the size and shape of the wound. After placement, it should be hydrated with sterile saline, and a non-adhesive

Table 15.2 Acellular matrices

Product	Product type	Indications	Contraindications	Level of evidence*
Oasis®	Porcine derived	VLUs DFUs	Hypersensitivity to porcine	VLUs: Level 2 [66] DFUs: Level 3 [67, 68]
Biobrane®	Porcine derived	Donor sites Partial-thickness burns	Hypersensitivity to porcine	Donor sites: Level 3 [69–71] Partial-thickness burns: Level 3 [72, 73]
Integra®	Dermal regeneration template	DFUs	Infected wounds, hypersensitivity to bovine or chondroitin material	Level 1 [74, 75]
AlloDerm®	Cadaveric allograft	Partial- and full-thickness burns Soft tissue defects and scars	Hypersensitivity to gentamicin, lincomycin, polymyxin, vancomycin, or Polysorbate 20	Burns: Level 2 [76] Soft tissue defects and scars: Level 4 [77–83]

*Level of evidence derived from The Oxford 2011 Levels of Evidence [39]:
1. Systematic review of randomized trials or n-of-1 trials
2. Randomized trial or observational study with dramatic effect
3. Non-randomized controlled cohort/follow-up study
4. Case series, case-control studies, or historically controlled studies
5. Mechanism-based reasoning

primary dressing should be placed followed by a secondary dressing. Its use is contraindicated in those with known porcine hypersensitivities [91]. Biobrane® is a bilaminar nylon mesh that is filled with porcine collagen type I. The product is available in multiple sizes and is placed in a similar fashion but should be secured in place with a preferred method under tension [92].

Dermal Regeneration Template (DRT, Integra®, LifeSciences, Plainsboro, NJ)

Indications: Partial- and full-thickness wounds, PUs, VLUs, repair of scar contractions, surgical wounds, chronic vascular ulcers, and second-degree burns [74, 75, 93–97]

Integra® is an acellular three-dimensional DRT that consists of a porous bilayer matrix. The temporary epidermal layer is made of a thin layer of silicone, and the dermal layer consists of a cross-linked bovine tendon collagen and glycosaminoglycan (chondroitin-6-sulfate) biodegradable matrix. This provides a scaffold for cellular migration and angiogenesis [74, 97].

It is available in sheet, mesh, fenestrated, or flowable form. These products may be stored at room temperature. Once the wound bed is prepared, remove the DRT from the packaging and peel off the cover sheet. Place the DRT in a basin with sterile saline. Cut the DRT to fit the wound and carefully place it on the wound ensuring direct contact. Care must be taken to maintain the orientation so that the dermal layer is in direct contact with the wound. This can be verified by black threads in the silicone layer, which should be facing outward (away from the wound bed). It should be affixed with a preferred method, and a non-adherent primary dressing should be placed followed by a secondary dressing [97]. For tunneled wounds, the flowable form should be utilized. This can be prepared by drawing up sterile saline into an empty syringe and connecting the syringe to the syringe that contains collagen via a Luer Lock Connector. Depress the plungers back and forth to mix together. Once mixed, disconnect the two syringes and attach the flexible injector. The product can then be injected into the wound. Place a primary dressing and then a secondary dressing over the wound [22]. DRMs are

contraindicated in infected wounds and those with known hypersensitivities to bovine collagen or chondroitin materials. Newer products such as PriMatrix® (Dermal Repair Scaffold, Integra®, LifeSciences, Plainsboro, NJ) are available, but their evidence and efficacy have not been extensively studied. Additional DRMs such as Matriderm® are available outside of the United States.

Cadaveric Allograft (CA, AlloDerm® Regenerative Tissue Matrix, LifeCell, Branchburg, NJ)

Indications: replacement of damaged or inadequate integument including surgical wounds, burns, soft tissue defects, and sinus tracts [77, 98–102].

CA is an acellular dermal allograph that is processed to remove all cellular components so as to minimize the risk of tissue and graft rejection while preserving the three-dimensional structure of the dermis as well as other biological components [100]. It is available as a sheet or in an injectable form (Cymetra® Micronized AlloDerm® Tissue) (Fig. 15.2) [103].

The CA should be stored at room temperature. Before the wound bed is prepared, remove the tissue from the packaging and place it into a basin filled with 37 °C saline for 5 minutes. Transfer the tissue into the second basin filled with rehydration fluid for approximately 40 minutes. Once it is rehydrated, place onto the wound making sure the "L" that is in the mesh pattern on the tissue is facing outward, assuring that the dermal layer is in contact with the wound. Cover with a non-adherent primary dressing and then a secondary dressing [98].

CA is contraindicated in known hypersensitivities to antibiotics listed on the packaging (gentamicin, cefoxitin, lincomycin, polymyxin, and vancomycin) or to Polysorbate 20.

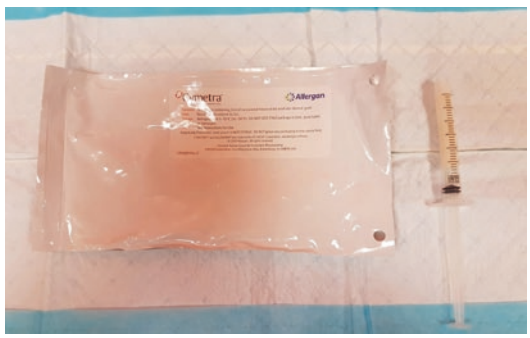

Fig. 15.2 Cymetra®, which is an acellular matrix is a micronized injectable form of AlloDerm®**.** This cadaveric allograft is a flowable matrix that comes in a syringe and is best used for the treatment of tunneling wounds

Future Research

Many new acellular and cellular skin substitutes are currently being developed, and it is hoped that new grafting sources and multipurpose products will deliver better outcomes; however, clinical evidence is still premature. For example, an acellular xenogeneic dermal matrix derived from fish skin (Kerecis® Omega3 wound matrix, Isafjordur, Iceland) is being trialed to heal various wound etiologies and has initially demonstrated efficacy in the stimulation of granulation tissue and re-epithelialization. Additionally, it has been reported to have antinociceptive and analgesic properties [104]. Hyalomatrix PA® (Fidia Advanced Biopolymers, Padua, Italy) that is a bilayer of esterified hyaluronan scaffold beneath a silicone membrane has been shown to provide a favorable environment for cellular migration and wound healing [105]. PuraPly ® Antimicrobial Wound Matrix is a collagen sheet, similar to Oasis®, that is coated with the antimicrobial agent polyhexmethylenebiguanide. It was released in 2016 and indicated for the management of wounds of multiple etiologies and is intended to provide a scaffold for cellular migration as well as protect against bacterial overload.

Conclusion

Acellular and cellular skin substitutes are an important adjunctive treatment for nonhealing wounds. These products provide key elements and scaffolding that promote healing and may be

used to treat varying wound etiologies. Many different skin substitutes are available on the market, and each product has unique characteristics, benefits, and disadvantages. For example, non-exudating wounds may benefit from sheet matrices, while exudative wounds may benefit from fenestrated or mesh forms. Additionally, flowable matrices are advantageous in tunneled or sinus wounds. Some may be able to cover wounds with exposed tendon, bone, or muscle, while others may not. Although some have been extensively trialed, further research is necessary to demonstrate the full efficacy of many of the matrices currently available. It is imperative that clinicians are familiar with the many differing products available in order to best tailor the product to the unique clinical presentation. Correct patient and product selection combined with meticulous wound bed preparation is key to successful use of these products. Future studies are needed to better understand the mechanism of action of these products, and large, well-designed, randomized controlled clinical trials are warranted to compare between products. Given the high cost of these grafts, evidence of the best application timing, number, and spacing of applications will help to develop efficient guidelines for use.

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16 Local Peristomal Cutaneous Manifestations and Their Management

Kimberly LeBlanc and Lorne Wiesenfeld

Introduction

The need for an ostomy is a life-altering event. While the exact prevalence is not known, experts estimate that there are close to 2.5 million individuals living with an ostomy globally [1]. Ostomies are surgical openings primarily from the intestine or urinary tract to the surface of the abdomen. They are required for a multitude of reasons (e.g., cancer, trauma, inflammatory bowel disease, and congenital issues) and are found across all ages [2]. Although beyond the scope of this chapter, which will focus on urinary and fecal diversions, there are a multitude of different types of ostomies other than fecal and urinary diversions (e.g., tracheostomies, gastrostomies). Fecal and urinary diversions involve the creation of an ostomy to allow for the evacuation of feces or urine from the body and require the use of a medical device (pouching system) to collect the output. The pouching system needs to be emptied throughout the day and changed regularly to guard against disruptions in skin integrity [2].

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The negative effects of living with a stoma on quality of life are well documented, and the effects are magnified in individuals experiencing stomal and peristomal skin complications (PSCs) [2]. More than 80% of individuals with an ostomy will experience some type of peristomal complication within 2 years of undergoing surgery, with a heightened risk found among those with impaired mobility and/or suffering from obesity [3–5]. The negative effects of an ostomy on health-related quality of life (HRQoL) are most severe in people who experience peristomal and stomal skin complications. The incidence of these complications varies between 30% and 67% [3]. The risk of peristomal skin complications is a continuous process. With time, the body's morphology changes with events, such as pregnancy, changes in weight, and aging. This changes the contour and properties of the peristomal skin and hence the adhesion of an ostomy appliance [6].

It has been estimated that on average, a person living with an ostomy will experience a peristomal complication within 2 years of surgery and the risk increases to 75% for those with impaired mobility or an operative performance deficit [7]. Peristomal skin complications have been linked to moisture-associated skin damage, mechanical injury, chemical irritation, infection, and comorbidities. Frequently, these complications arise from an improper fitting pouching system leading to leakage of effluent and more

A. Alavi, H. I. Maibach (eds.), *Local Wound Care for Dermatologists*, Updates in Clinical Dermatology, https://doi.org/10.1007/978-3-030-28872-3_16

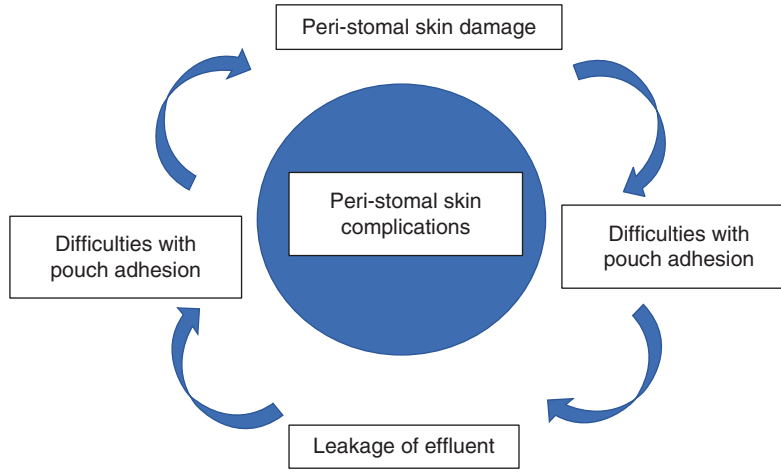

Fig. 16.1 Cycle of peristomal skin complications [3–8]

frequent pouch changes. Skin exposure to effluent and frequent removal of adhesives result in skin irritation and injury [8] (Fig. 16.1). Dermatologists are frequently called upon to assist patients and healthcare professionals in the care of peristomal skin complications. This chapter focuses on local peristomal cutaneous manifestations and peristomal skin complications and their management.

Assessment of Peristomal Skin

There are two validated tools for assessing peristomal skin: the Ostomy Skin Tool (OST) and the Study on Peristomal Skin Lesions (SACs) tool. No single instrument for assessing peristomal skin complications has achieved widespread international acceptance. The OST was developed and validated as a standardized measuring instrument for assessing the extent and severity of peristomal skin damage in terms of discoloration (D), erosion (E), and tissue overgrowth (T) (DET) [9]. The Study on Peristomal Skin Lesions (SACs) tool was developed and validated as a means of classifying peristomal skin changes according to their severity. The SACs tool defines peristomal skin lesions as any compromise in the integrity of the skin around the stoma [10].

Woo et al. [11] developed a mnemonic teaching tool (MINDS) that categorizes peristomal skin injury into classifications of tissue injury: mechanical, infection, noxious chemical irritants, diseases, and skin allergens. The MINDS framework is limited in that it restricts mechanical peristomal skin injury to skin stripping with no focus on the other aspects of skin injury related to the use and removal of medical adhesives. The authors intended the mnemonic to be used as a guide to the systematic assessment of peristomal skin [11].

M Repeated application and removal of adhesive tapes and appliances pull the skin surface from the epithelial cells which can precipitate skin damage by stripping away the stratum corneum [11].

I Infection (bacterial and fungal) [11].

N Noxious chemical irritants including feces and urine. Ileostomy effluent contains digestive enzymes and electrolytes that are extremely corrosive and damaging to the skin. Despite various containment strategies, effluent may leak and spill over to peristomal skin particularly in patients experiencing hyperactive bowels, diarrhea, and entero-cutaneous fistulas [11].

D Diseases of the skin that are common in persons with ostomies, such as pyoderma gangrenosum or psoriasis [11].

S Skin allergens [11].

Types of Common Peristomal Skin Complications

Medical Adhesive-Related Skin Injury

Medical adhesive-related skin injury (MARSI) is the change in skin integrity where erythema and/or other skin alterations such as skin tears, erosion, bulla, or vesicle persist for 30 minutes or more after removal of an adhesive product [12]. Peristomal MARSI (P-MARSI) is when it is specific to the removal of an adhesive ostomy appliance. It should be understood that an ostomy patients cannot leave their ostomy barrier off for 30 minutes or more and thus the individuals should be assessed for P-MARSI upon removal of the adhesive ostomy appliance. Medical adhesive-related skin injury, including P-MARSI, can be further divided into three main types: mechanical, dermatitis, and others (see Box 16.1) [12].

Mechanical P-MARSI

Mechanical P-MARSI can be further divided into skin (epidermal) stripping, tension injury, or tension blister or skin tears. Patient/caregiver/healthcare professional education is an essential prevention strategy for this type of peristomal complication [12]. Skin stripping consists of removing or tearing of the epidermis. These injuries are usually accidental, caused by traumatic removal of adhesive products [12] (Fig. 16.2).

Box 16.1 Medical Adhesive-Related Skin Injuries (MARSI) [12]

Types of MARSI

Mechanical
- Skin (epidermal) stripping
- Tension injury or blister
- Skin tear

Dermatitis
- Irritant contact dermatitis
- Allergic dermatitis

Others
- Maceration
- Folliculitis

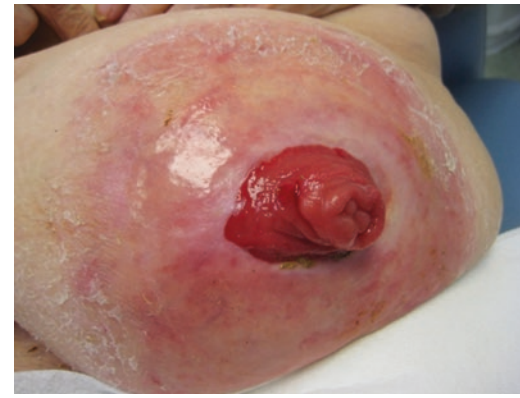

Fig. 16.2 Skin stripping

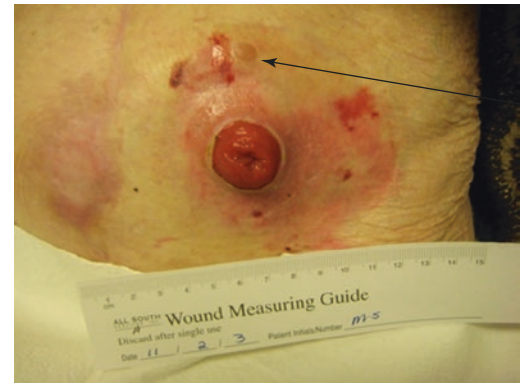

Fig. 16.3 Tension injuries

Tension injuries or blisters are often caused by shearing forces resulting from distension of the skin beneath an adhesive product that does not stretch. Peristomal tension injuries are often associated with postoperative peristomal edema [12] (Fig. 16.3).

In a recent global consensus document, the International Skin Tear Advisory Panel (ISTAP) defined skin tears as "traumatic wounds caused by mechanical forces, including removal of adhesives." The severity may vary by depth (not extending through the subcutaneous layer) [13].

Specific to P-MARSI, skin tears occur predominantly when the adhesive portion of the pouching system is removed from the skin. The amount of force required to cause a skin injury is dependent on individual's overall intrinsic and environmental risk factors [13] (Fig. 16.4).

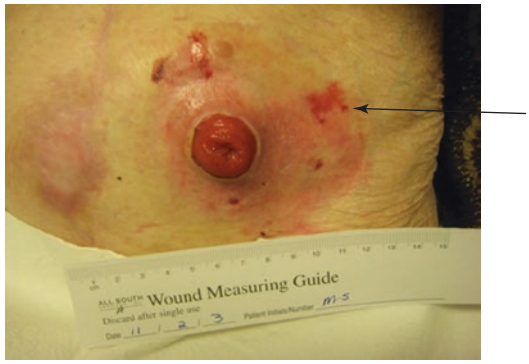

Fig. 16.4 Skin tears

Dermatitis P-MARSI

There exist two different forms of dermatitis associated with P-MARSI: irritant contact dermatitis and allergic dermatitis [12]. Dermatologists play a vital role in the diagnosis of PSCs and the management of any associated dermatitis. Corticosteroids are the medication of choice for the treatment of peristomal dermatitis and can be administered systemically or topically. It is important to note that traditional treatments with ointments and/or creams will interfere with adhesion of the pouching system [4]. Topical corticosteroid sprays and/or foams are appropriate alternative treatments which will not interfere with pouch adhesion while at the same time aid in the management of peristomal dermatitis [14].

Irritant Contact Dermatitis

Irritant contact dermatitis is development of erythema, edema, and possibly vesicles to the peristomal skin as the result of contact with chemical irritants. This could be the result of water, stool, or urine trapped under an adhesive and/or from the adhesive itself. It should be noted that irritant contact dermatitis is the most frequently found type of peristomal dermatitis [6] (Fig. 16.5).

Maceration is also a form of irritant contact dermatitis and can result from moisture being trapped under adhesive products. The entrapment of stool, urine, serosanguinous fluid, and/or perspiration under an adhesive pouching system may lead to maceration. This resulting peristomal maceration will in turn increase the risk of skin breakdown and pouching difficulties [8] (Fig. 16.6).

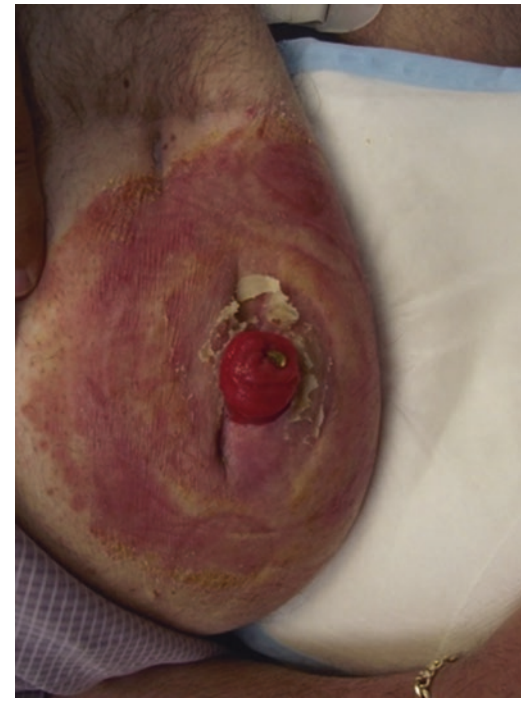

Fig. 16.5 Irritant contact dermatitis

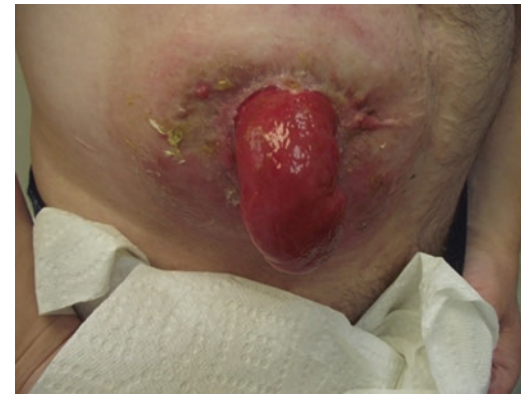

Fig. 16.6 Peristomal maceration

Allergic Dermatitis

Allergic dermatitis seen in P-MARSI is a cell-mediated immunologic response to an adhesive and may manifest as areas of erythema [6] (Figs. 16.6 and 16.7).

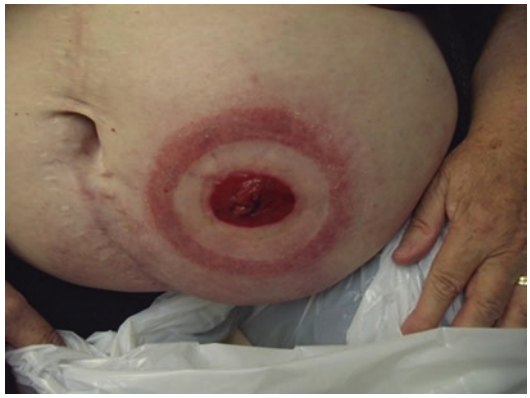

Fig. 16.7 Allergic dermatitis

Management of Common Peristomal Skin Complications

Primary management of PSCs involves determining the correct diagnosis of the type of PSC and its underlying cause. Once the cause of the PSC has been determined, it is imperative that steps be taken to break the cycle of PSCs [14] (Fig. 16.1). Ensuring a secure fit of the pouching system is one method to minimize the risk of PSCs [14] (Table 16.1). Nurses specialized in wound, ostomy, and continence (NSWOC), wound ostomy continence nurses (WOCN), enterostomal therapy nurses (ETN), and/or stomal care

Table 16.1 Common pouching issues (adapted from Almutairi, LeBlanc, and Alavi [4])

Common pouching issues		
Pouching issue	Description	Treatment
Stoma opening of pouching system is too tight	Repeated friction may lead to mechanical trauma and peristomal ulceration May lead to leakage of effluent due to broken seal around stoma secondary to friction	Regular checking of appliance size especially in postoperative period and patient weight changes Consult CNS stoma care (NSWOC, WOCN, ETN, SCN) to ensure proper fit and application
Stoma opening of pouching system is too large	Stoma output in contact with peristomal skin which leads to irritant contact dermatitis	Regular checking of appliance size especially in postoperative period and with patient weight changes Consult CNS stoma care (NSWOC, WOCN, ETN, SCN) to ensure proper fit and application
Frequent pouch changes due to leakage or over cleaning by patient/caregiver	Stoma output in contact with peristomal skin leading to irritant contact dermatitis Redness and irritation of the skin secondary to friction with over cleansing	Educate patient/caregiver to provide gentle cleansing with warm water only and to pat dry. Avoid alkaline soaps or products containing perfume. Instruct patient not to instill water into the pouch and to rinse when emptying as when water comes in contact with the seal around the stoma, the seal will break and leakage will occur Ensure proper fit of appliance Manage peristomal skin irritation/dermatitis (topical corticosteroids may be required; foam or spray versions are the best) Consult CNS stoma care (NSWOC, WOCN, ETN, SCN) to ensure proper fit and application
Stoma retraction	Stoma receding 0.5 cm below the skin level that leads to stoma leak	Convex appliance if not contraindicated Consult CNS stoma care (NSWOC, WOCN, ETN, SCN) to ensure proper fit and application
Irregular peristomal skin resulting in creases	Uneven skin surface leads to appliance leak	There are different modalities to help even the skin and reduce leaking, for example, filler or strip paste Consult CNS stoma care (NSWOC, WOCN, ETN, SCN) to ensure proper fit and application

nurses (SCN) are clinical nurse specialists (CNS) with advanced knowledge related to the assessment and management of stoma care. Such nurse specialists can collaborate with dermatologists to manage PSCs and ensure a proper fit of stoma pouching systems [14].

Infection

Folliculitis

Folliculitis is another consequence of P-MARSI consisting of an inflammatory reaction in the hair follicle caused by entrapped bacteria or by traumatic hair removal. Folliculitis presents as pustules or papules surrounding the hair. These pustules or papules will result in fluid collection under the pouching system and possible leakage or maceration [6]. Folliculitis is commonly caused by *Staphylococcus aureus* resulting from shaving or repeated pulling of the peristomal hair adhesives when changing ostomy appliances. Folliculitis clinically appears as pustule surrounding a hair follicle [15] (Fig. 16.8). Sometimes it can also appear with a similar morphology to candidiasis; in this case, a swab culture is required for definitive diagnosis [16].

Folliculitis management includes topical or oral antibacterial medications accompanied by preventative measures. Topical clindamycin or clindamycin mixed with benzoyl peroxides (in the form of lotion with alcohol base or gels) or topical alginate powder containing ionic silver particles can all be effective measures for managing folliculitis [16].

Oral antibiotics, such as first-generation cephalosporins, can be used when patients do not benefit from topical treatment. A bacterial swab for culture and sensitivity is recommended to identify the appropriate antibiotic because of the increase in incidence of multidrug resistance bacteria [16]. To reduce the recurrence of folliculitis, peristomal hair trimming is recommended [4].

Fungal Infection

Given the frequency of having a moist environment of the peristomal skin, it is not unusual that increased fungal growth is often found in the area. Candida and dermatophytes are the microorganisms most frequently identified in the peristomal area. Clinically, most individuals will present with characteristic itchy papules, pustules on an erythematous base, and peripheral papules presenting in a satellite pattern [4] (Fig. 16.9).

Treatment of peristomal fungal infections includes antifungals such as nystatin (fungicidal and a fungistatic agent) as a powder, so as to not interfere with appliance adhesion [4]. Topical alginate powder, which contains ionic silver particles, has also been shown to be an effective means of managing fungal infections [16, 17]. Prevention should include steps to decrease moisture-associated skin damage and maceration and prevent leakage.

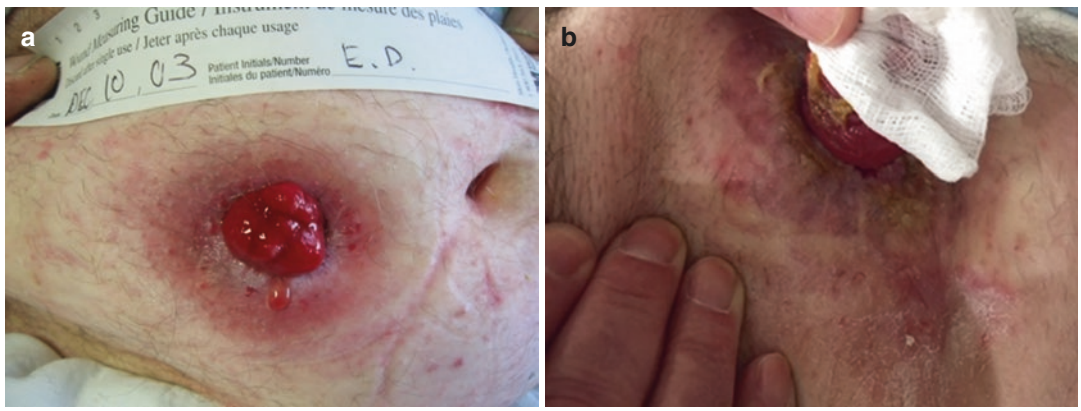

Fig. 16.8 Folliculitis. (**a**) Photo credit Tarik Alam. (**b**) Photo credit Mary Glockenar

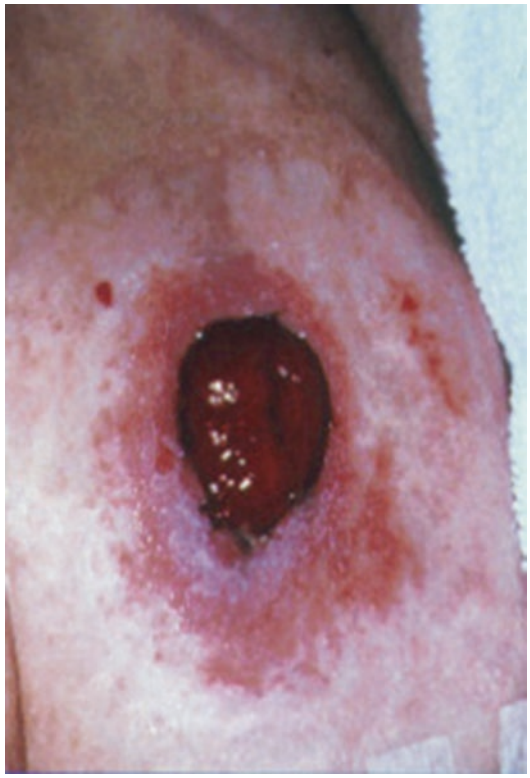

Fig. 16.9 Candida

Hypergranulation/Granulomas

Granulomas are very common lesions/papules that may appear on the surface of the stoma but more commonly occur at the mucocutaneous junction. They are considered to greatly contribute to the incidence of persistent and recurrent leakage or seepage of effluent onto the skin [4] (Fig. 16.10). They are caused by chronic inflammation from the friction and rubbing of a too small pouching opening and/or frequent leakage of urine or stool. It is a benign skin condition, but its recognition is paramount as it affects appliance adhesion and has an increased tendency to bleed. Management of granulomas includes reducing over-granulation by means of topical silver nitrate application or a topical steroid (foams or sprays). Surgical removal is rarely required [4]. Topical steroids tend to be the treatment of choice as they do not cause undue pain. Patients should be educated that in the case of bleeding, application of firm pressure with gauze at the site of bleeding should prove effective. The use of right size of stoma appliances prevents granuloma formation in these patients [4].

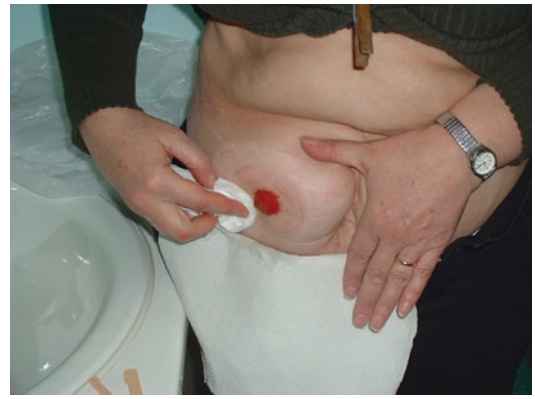

Fig. 16.10 Peristomal granuloma

Pseudoverrucous Lesions

Pseudoverrucous lesions occur in 20% of patients with a urostomy [18]. Chronic exposure of the peristomal skin to alkaline urine results in uric acid deposition on the skin. These deposits will lead to chronic inflammation that forms a thick epidermal projection or pseudo-wart-like lesions on the peristomal skin (Fig. 16.11). Leakage may occur for a variety of reasons but is primarily the result of an ill-fitting pouching system [19].

Management of pseudoverrucous lesions includes the reduction of the alkaline effect of urine through using topical compresses with diluted acetic acid. It has been reported that acidification of the urine by means of the individual drinking cranberry juice or vitamin C in combination with increased fluid intake may decrease the risk of pseudoverrucous lesion development. Surgical removal of the lesion and silver nitrate direct application to remove thickened skin are other less favorable treatment options [4].

Pyoderma Gangrenosum

Pyoderma gangrenosum (PG) is an inflammatory skin condition which is often associated with inflammatory bowel disease (IBD) and rheumatoid arthritis [4, 20]. It presents as rapidly growing painful papules or pustules which progress to form an ulcer with purple or violaceous, well demarcated, rolled wound margins [4, 20]

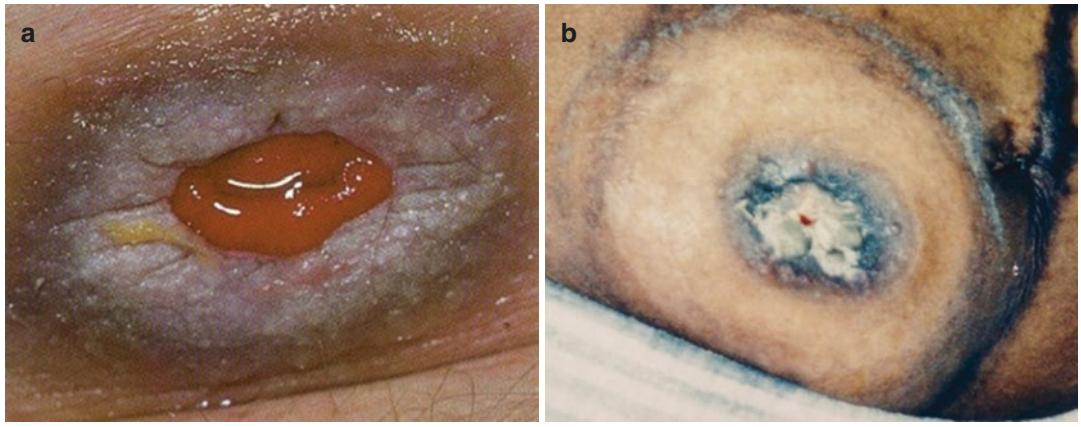

Fig. 16.11 (**a**, **b**) Pseudoverrucous lesions

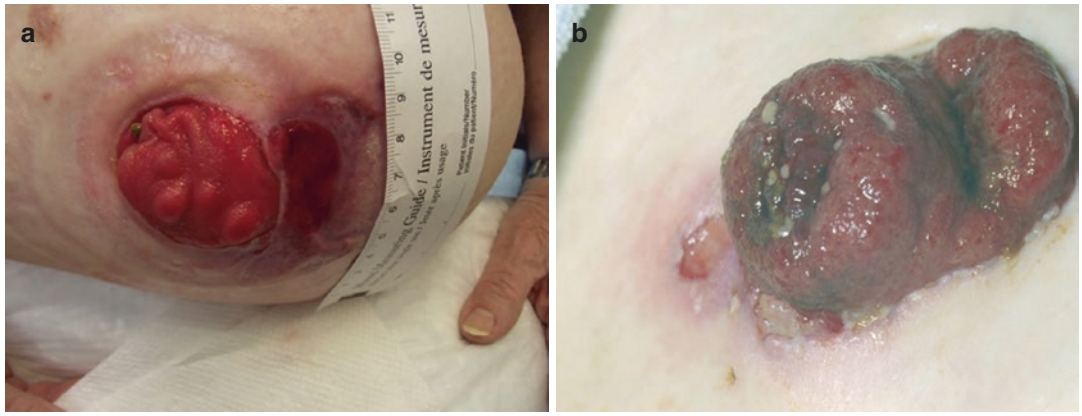

Fig. 16.12 (**a**, **b**) Pyoderma gangrenosum

(Fig. 16.12). Peristomal PG is rare with a reported prevalence of less than 10% [20]. Lesions are typically diagnosed clinically and should be treated immediately to prevent disease progression and to minimize pain [4].

The goal of first-line treatment of PG such as topical and intralesional steroids is to reduce the inflammation. Systemic steroids and immunosuppressive agents such as cyclosporine or dapsone can be used in severe cases to control the active IBD [4].

Topically absorptive silver dressings are usually recommended for their anti-inflammatory properties [17]. Up to half of all cases of PPG are recurrent and progress to heal with irregular scarring. The resulting scar tissue interferes with pouch adhesion and frequently necessitates consulting a clinical nurse specialist. Surgical treatment with stoma relocation is associated with a high chance of recurrence; however, stoma closure has been associated with no recurrence [4].

Psoriasis

The prevalence of psoriasis has been reported as occurring in 11.2% of patients diagnosed with Crohn's disease and 5.7% in patients diagnosed with ulcerative colitis [4]. Given the large number of individuals suffering from either form of IBD, it is important to consider psoriasis as a differential diagnosis when examining peristomal skin irritation. Independent of any relevant past

history, psoriasis may be seen in peristomal skin as a by-product of repeated trauma [4]. Psoriasis is treated with topical or intralesional steroids, with other topical treatments such as vitamin D analogs and, in severe cases, through the use of biologics [4] (Fig. 16.13).

Cancer

While peristomal cancers are rare, peristomal skin squamous cell carcinoma (SCC) can be found among individuals with long-standing ileostomies of 26 years or more [4] (Fig. 16.14). The exact mechanism remains unknown, but chronic inflammation, irritation, and recurrent infection are known to predispose to SCC development. Treatment includes radical excision and re-siting of the stoma. Healthcare professionals involved in stoma care should be educated to prevent chronic inflammation and to biopsy any unusual lesion in a long-standing ileostomy to rule out malignancy and prevent a late diagnosis [4].

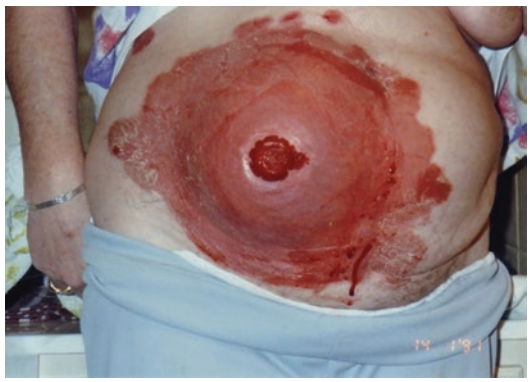

Fig. 16.13 Psoriasis. (Photo credit Dawn Christensen)

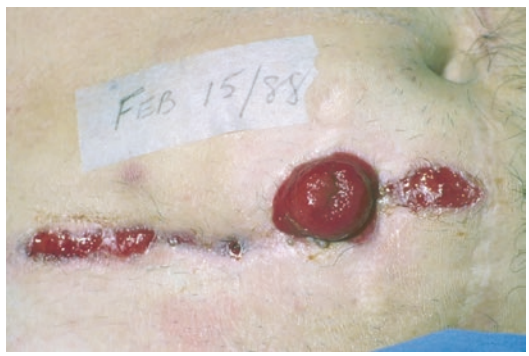

Fig. 16.14 Peristomal squamous cell carcinoma

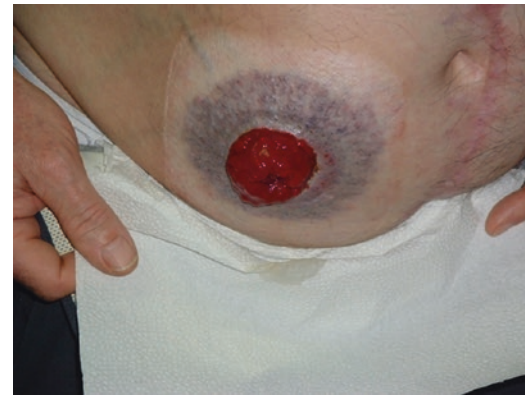

Fig. 16.15 Caput medusa

Caput Medusa/Portal Hypertension

Caput medusa is a manifestation of the dilated superficial veins surrounding the stoma as a result of advanced liver disease such as cirrhosis. Individuals typically present with a purple ring around the stoma and have a high tendency to bleed [4]. It is important for clinicians to be cognizant of this condition and to educate patients on the safe application and removal of pouching systems so as to avoid trauma and bleeding. In some cases, individuals may need medical assistance to control bleeding [4] (Fig. 16.15).

Conclusion

Traditionally peristomal skin complications are managed by clinical nurse specialists (CNS) with advanced knowledge related to the assessment and management of stoma care (NSWOCs, WOCNs, ETNs, SCNs). However, given the complex nature of the peristomal skin and the variety of potential skin-related issues, it is imperative for dermatologists to continue their pivotal role in the care of individuals with peristomal skin issues. As the recognized specialists of skin conditions, dermatologists must be cognizant of the unique challenges in managing peristomal skin complications and advocate for this vulnerable population.

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Comprehensive Wound Care for Malignant Wounds

17

Brooke E. Corbett, Nina R. Blank, and Alina Markova

Introduction

Malignant wounds (MW) are a rare complication of advanced cancer in which tumor cells infiltrate and erode through the skin [1, 2]. The prevalence of MW is unknown, but studies have estimated the prevalence in cancer patients to be approximately 5–10% [2–5]. Breast cancer, primary skin cancers, and head and neck cancers are the most common primary cancer types associated with MW [2, 3, 6, 7]. Breast cancer metastases are the most common cause of MW in women, while melanoma metastases are most common in men [2]. The most common anatomic sites for MW to occur are the anterior chest/breast (31–62%), head and neck (21–34%), and groin (3–17%) [5, 6, 8–10].

MW may develop from (1) ulceration of primary skin cancers (e.g., melanomas, keratinocyte carcinomas, angiosarcomas), (2) direct extension of visceral malignancies into the skin, (3) cutaneous metastases from distant malignancies, and (4) cutaneous involvement of hematologic malignancies [1, 11]. Tumor infiltration causes massive damage to the normal architecture and structures of the skin. Disruption of the blood supply and lymphatic drainage leads to hypoxia, loss of tissue viability, and consequent necrosis. Uncontrolled tumor proliferation, impaired wound healing, and secondary colonization perpetuate this process, leading to chronic MW [1, 5, 11, 12].

MW often first present as discrete, nontender, indurated plaques. As the malignant process progresses, MW may develop into destructive and/or proliferative lesions. Destructive wounds present as crater-like ulcerations of the skin (Fig. 17.1a), whereas proliferative wounds present as protruding nodular cauliflower-like growths (Fig. 17.1b).

MW can be extremely distressing to patients given their high symptom burden. Commonly reported symptoms include malodor, copious exudate, bleeding, pain, pruritus, and infection [8, 10, 13–16]. In addition to physical symptoms, patients with MW experience psychosocial symptoms, such as depression, shame, poor body image, low self-esteem, social isolation, and

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A. Alavi, H. I. Maibach (eds.), *Local Wound Care for Dermatologists*, Updates in Clinical Dermatology, https://doi.org/10.1007/978-3-030-28872-3_17

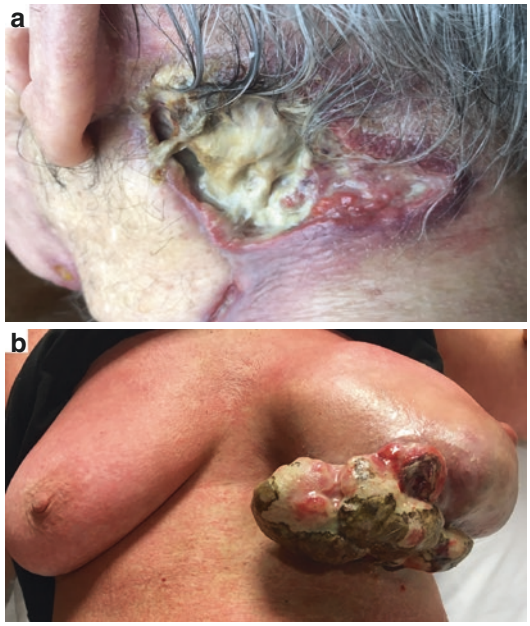

Fig. 17.1 (**a**) Erosive malignant wound (MW) on the left posterior neck in an elderly man with metastatic squamous cell carcinoma of the skin. (**b**) Proliferative MW on the left breast in a middle-aged woman with mucinous carcinoma of the breast

increased anxiety surrounding death [10, 13–20]. One cross-sectional study of 70 patients with MW demonstrated a strong inverse correlation between symptom burden – including physical and psychosocial – and quality of life (QoL) [14].

Some MW due to primary skin cancer or hematologic malignancy may be cured via surgical excision or systemic chemotherapy, respectively. However, many chronic MW are incurable (typically due to direct tumor extension or cutaneous metastasis) and are associated with an average life expectancy of approximately 6–12 months [10]. Because MW typically do not heal, management is directed at reducing symptoms and improving QoL. This differentiates management of MW from that of nonmalignant chronic wounds, for which the goal of therapy is curative. Treatment of MW requires highly individualized, multidisciplinary care based on the symptom burden, psychosocial impact, and personal values of the patient. Comprehensive local wound care is an integral component in the management of MW.

Assessment Tools

Comprehensive and individualized assessment of MW is essential to guide successful management of these complex patients. Clinicians must consider the type and severity of each symptom, as well as the functional and psychological impact of each symptom on the patient's QoL. Multiple assessment tools have been developed to evaluate MW with an emphasis on QoL. Grocott's assessment tool using the Treatment Evaluation by Le Roux's (TELER) method is a clinician-reported system to evaluate dressing performance in terms of patient experience [21, 22]. The Malignant Wound Assessment Tool (MWAT) combines both clinician- and patient-reported measurements of wound features, symptoms, and impact on QoL [23]. The Wounds Symptoms Self-Assessment Chart (WoSSAC) is a patient-reported survey designed to measure the severity of symptoms and the impact they are having on the patients' lives [24]. The WoSSAC is not yet validated.

Dressings

MW are typically dressed in two layers: primary and secondary dressings. The primary dressing should be non-adherent and maintain a moist wound bed, while the second layer should be highly absorbent and secure [25]. This two-layer system allows changing of the secondary dressing as needed while leaving on the primary dressing for longer periods of time. Depending on the condition of the wound, primary dressings may be left on for up to 7 days [25].

Table 17.1 displays characteristics of commonly used dressings in MW. Choice of dressing products should be tailored to the individual needs of each patient. Along with patient goals and wound symptoms, clinicians should consider dressing comfort, aesthetics, availability, cost, and caregiver skill level when creating a dressing regimen [9]. Minimizing frequency and duration of dressing changes is paramount as each dressing change may be associated with pain and negative burden on QoL.

Table 17.1 Characteristics and relative cost of commonly used dressings in the care of MW [10, 25, 33, 87, 88]

Dressings	Exudate level	Properties	Commercial names	Cost per dressing (dressing dimensions in inches)
Contact layers	Dry to mild	Non-adherent, allows passage of moisture to secondary dressing, can be cut to fit the size of the wound	Adaptic (Systagenix) Mepitel (Mölnlycke)	$ 3 × 3 (box of 50) $$$ 3 × 4 (box of 10)
Hydrogels/ hydrogel sheets	Dry to mild	High moisture content, best for dry or necrotic wounds with low exudate, stimulates autolytic debridement, comfortable	Elastogel (SW Technologies) Kendall Hydrogel (Covidien) KerraLite Cool (Crawford)	$$ 4 × 4 (box of 5) $$$ 4.75 diameter (box of 5) $$$ 4.7 × 3.3 (box of 5)
Hydrocolloids	Mild to moderate	Mildly absorbent, waterproof, forms gel upon contact with exudate which helps maintain a moist wound environment, may stimulate granulation tissue	DuoDerm (ConvaTec) Cutinova (Smith & Nephew) Nu-Derm (Systagenix) Tegaderm Hydrocolloid (3 M)	$$$ 4 × 4 (box of 5) $$$$ 4 × 4 (box of 5) $$$$ 4 × 4 (box of 5) $$$ 4 × 4 (box of 5)
Foams	Moderate to heavy	Moderately to highly absorbent, absorbs and retains moisture, allows passage of moisture to secondary dressing, prevents leakage, conforms to shape of the wound, comes in a variety of shapes/sizes	Allevyn Foam (Smith & Nephew) Aquacel Foam (ConvaTec) Biatain Foam (Coloplast) Cura Foam (Dynarex) Mepilex (Mölnlycke)	$$$$ 4 × 4 (box of 10) $$$ 4 × 4 (box of 10) $$$$ 4 × 4 (box of 10) $$ 4 × 4 (box of 10) $$$$ 4 × 5 (box of 5)
Hydrofibers	Heavy	Highly absorbent, wicks fluid vertically directly into the fibers, forms gel upon contact with exudate which helps maintain a moist wound environment	Aquacel Extra (ConvaTec) Durafiber (Smith & Nephew) KerraCel (Crawford) Opticell (Medline)	$$$$ 4 × 5 (box of 10) $$$$ 4 × 4 (box of 10) $$$$ 4 × 5 (box of 10) $$$ 4 × 4 (box of 10)
Alginates	Heavy	Highly absorbent, hemostatic properties, forms gel upon contact with exudate which helps maintain a moist wound environment	Algicell (Derma Sciences) Kalginate (DeRoyal) Kaltostat (ConvaTec) Melgisorb Plus (Mölnlycke) Tegaderm High Gelling (3 M)	$$$ 4 × 4 (box of 10) $$$$ 4 × 4 (box of 5) $$$$ 3 × 4.75 (box of 10) $$$ 4 × 4 (box of 10) $$$ 4 × 4 (box of 10)
Hydroconductive dressings	Heavy	Highly absorbent, wicks fluid horizontally and vertically away from wound surface, allows passage of moisture to secondary dressing	Drawtex (SteadMed)	$$$$$ 4 × 4 (box of 10)
Abdominal pads	Heavy	Highly absorbent, thick multilayer pad that absorbs and laterally disperses fluid, moisture-resistant barrier prevents fluid leakage, comes in larger sizes	ABD Pads (Medline)	$ 8 × 7.5 (box of 20)

Cost data from *Wound Care Shop* [89]. $, less than $1 per dressing; $$, between $1 and $5 per dressing; $$$, between $5 and $10 per dressing; $$$$, between $10 and $15 per dressing; $$$$$, greater than $15 per dressing

Exudate

MW often produce copious amounts of exudate. Poor control of wound exudate can lead to leakage on to clothes, malodor, and skin irritation, which may subsequently yield shame, social withdrawal, and poor QoL [13–16]. Exudate produced from MW is due to a combination of processes, including inflammatory-mediated vasodilation, tumor disruption of the normal blood and lymphatic vessel architecture, and tumor secretion of vascular permeability factor [11, 13]. MW exudate is managed by proper selection of dressings based on each patient's individual needs. The amount of exudate produced varies and may change over time. In addition to absorbing excess exudate, dressings need to maintain a balanced, moist wound environment to prevent traumatic removal.

Table 17.1 displays recommended dressings based on amount of exudate. For MW with high exudate, hydrophilic fiber and alginate dressings are recommended because they are highly absorbent. Alginates also have hemostatic properties and transform into a hydrophilic gel on contact with exudate, which helps to maintain moisture balance in the wound bed [11, 25, 26]. Hydrofiber dressings can hold up to 30 times their own weight [25]. Hydroconductive dressings (e.g., Drawtex®) or abdominal pads can also be used over the secondary dressing to capture excess leakage. Ostomy appliances and vacuum-assisted closure devices may also be considered for heavily exudative wounds [26].

For MW that are dry or have low exudate (Fig. 17.2), hydrogel sheets are preferred to moisturize the wound bed and provide a soothing, cooling sensation. For MW with low-to-moderate exudate, silicones and foam contact layers are excellent primary contact layers because of their trauma-free removal. They are highly absorbent and may also be used as secondary dressings [25].

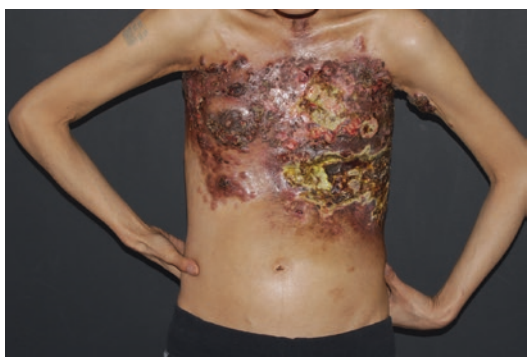

Fig. 17.2 Dry, fibrinous MW on the anterior chest of a middle-aged woman with metastatic breast cancer

Malodor and Infection

Malodor is often the most distressing symptom for patients with MW and can be detrimental to patients' QoL [14]. The smell has been described as "rotting flesh," "garbage," and "spoiled meat" [6, 10, 13]. Malodor may induce nausea, vomiting, and anorexia and is a major source of anxiety, shame, social isolation, and withdrawal [11, 13, 15, 26, 27]. Malodor is a result of metabolic byproducts (e.g. dimethyl trisulfide) produced by bacteria that colonize the necrotic tissue in MW [10, 11, 25, 28–31]. A study of bacterial flora in 25 breast cancer MW found a significant association between malodor and presence of anaerobic bacterial colonization [32]. Management of malodor focuses on targeting these bacteria and thereby reducing production of malodorous, volatile compounds.

Wound cleansing helps remove necrotic tissue, exudate, and residual dressing material [33]. Because the tissue is especially friable, clinicians should be careful not to traumatize the wound, which can lead to pain and hemorrhage. Gentle cleansing with water or normal saline is recommended [8, 31, 33]. Cleansing with antiseptic solutions such as chlorhexidine, povidone-iodine, hydrogen peroxide, acetic acid, or sodium hypochlorite solution is controversial due to their cytotoxicity and tendency to cause irritation or pain [8, 9, 31]. The cytotoxic effect may be less relevant to the treatment of MW as the therapeutic goal is palliative [25].

Similar to wound cleansing, debridement reduces risk of infection and malodor by removing bacteria-colonized necrotic tissue. Autolytic debridement and enzymatic debridement with collagenase are the preferred methods of debrid-

ing MW as they are relatively atraumatic. However, it should be noted that these methods of debridement can increase wound exudate during liquefactive necrosis [8, 25, 33]. Surgical debridement must be approached with caution due to the fragility of the tissue and tendency to bleed [8, 25, 33]. If surgical debridement is necessary in highly necrotic or acutely infected wounds, systemic and/or local anesthetics with intralesional epinephrine should precede the procedure. Maggot debridement therapy selectively debrides dead tissue with reported antibacterial and wound healing benefits [34–37].

The use of dressings impregnated with antibacterial agents may also be used to reduce wound malodor (Table 17.2). Silver-impregnated dressings are now widely available and have been shown to effectively reduce malodor in MW [38]. Honey-coated dressings inhibit bacterial growth by producing a hyperosmotic environment and assist in autolytic debridement. In one study of MW patients, honey-coated dressings were found to be just as effective at reducing malodor as silver-coated dressings [39]. Activated charcoal dressings attract and bind bacterial metabolites responsible for malodor, preventing their escape outside of the dressing. The utility of activated charcoal dressings in MW is controversial given their inactivation by high amounts of exudate, their need to achieve a perfect seal, and their high cost [9, 11, 25, 27].

Table 17.2 Types of odor-reducing dressings commonly used to treat malodor in MW [10, 25, 33, 87, 88]

Odor-reducing dressing	Commercial products
Silver-impregnated dressings	Aquacel Ag (Smith & Nephew) Durafiber Ag (Derma Sciences) Algicell with Silver (Derma Sciences) Silvercel (Systagenix) Allevyn Ag (Smith & Nephew) Mepilex Ag (Mölnlycke) Optifoam Ag (Medline) Silverseal (Alliqua)
Honey-coated dressings	Manuka (ManukaMed) Medihoney (Derma Sciences) TheraHoney (Medline)
Activated charcoal dressings	CarboFlex (ConvaTec)

Metronidazole, either topical or systemic, is the most commonly used antibiotic to treat malodor associated with MW. Metronidazole reduces malodor in MW via production of free radicals and associated cytotoxic effect on odor-producing anaerobes. Multiple case series and one randomized controlled trial (RCT) support the use of topical metronidazole in the treatment of MW malodor [40–45]. Topical metronidazole 0.75% gel is applied directly to the wound once or twice daily [9, 10, 25, 26]. Alternative methods of topical metronidazole application include direct application of crushed metronidazole tablets and compounded 1% solution (500 mg metronidazole in 100 mL normal saline) via spray bottle or solution-soaked gauze [9, 26].

The use of systemic metronidazole is supported by one RCT and one retrospective case series [46, 47]. *Ashford* et al. conducted a prospective, double-blind cross-over trial that compared the effect of oral metronidazole with placebo on MW malodor in six breast cancer patients. The study found that the malodor score was significantly lower in the metronidazole group than placebo [46]. A retrospective study of 179 patients with MW by *George* et al. compared the outcomes of patients treated with topical, oral maintenance (extended course of lower doses), and oral intermittent (short courses of higher doses) metronidazole regimens [47]. Maintenance oral metronidazole was found to be significantly more effective in reducing MW malodor when compared to topical or intermittent oral regiments. Based on their findings, the authors published the "SNIFFF" therapeutic ladder of metronidazole based on degrees of malodor [47]. Figure 17.3 displays a simple algorithm for managing MW malodor adapted from *George* et al. [47].

While most MW are chronically colonized with bacteria, secondary infections may also occur. Signs of MW infection include acute changes in erythema and edema, increased tenderness, purulent discharge, and fevers. In case of suspected wound infection, superficial wound culture should be performed and appropriate systemic antibiotics should be initiated. There is no evidence supporting the use of prophylactic antibiotics to prevent infections in MW.

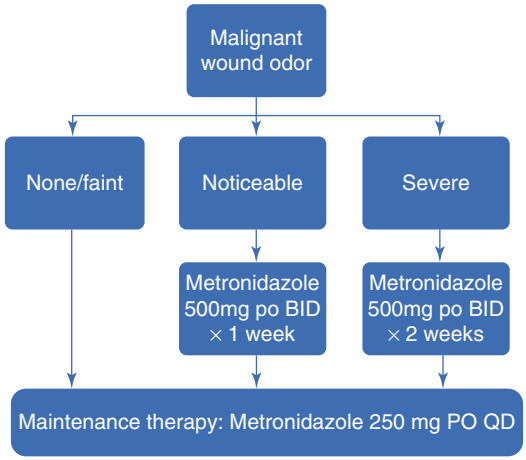

Fig. 17.3 MW malodor treatment algorithm for oral metronidazole. (Adapted from *George* et al. [47])

Bleeding

MW are prone to bleeding due to fragile granulation tissue susceptible to trauma, local tumor invasion into blood vessels, altered peri-tumor angiogenesis, and systemic coagulopathies associated with malignancies (Fig. 17.4) [1, 8, 11]. Preventative measures are important to reduce the risk of bleeding. Maintaining a moist wound bed and using non-adherent dressings in contact with skin help to prevent trauma. If a dressing is found to be adherent, the dressing should be soaked in water or saline to facilitate easy removal.

Figure 17.5 displays suggested management based on level of bleeding. Minor bleeding, typically due to slow capillary oozing, can be managed with local pressure, ice packs, aluminum chloride, and sucralfate paste. Hemostatic alginates or surgical foam sponges can also be used to stop moderate bleeding and can be left on the wound under a secondary dressing. Heavy bleeding can occur when the tumor disrupts a major blood vessel. Urgent interventions such as cauterization, radiotherapy, artery ligation or embolization, and vasoconstrictors should be used in these situations to prevent catastrophic bleeds. In MW susceptible to heavy bleeding, oral or topical antifibrinolytics (e.g., tranexamic acid) may cautiously be used for bleeding management. Hematologic consultation should be considered prior to the use of antifibrinolytics, as this population has a high risk of thrombosis [8, 11, 27, 31, 48].

Pain

Pain is a common and debilitating symptom of MW, affecting an estimated 38–77% of patients [13, 49]. The pain experienced by patients can be highly variable and may result from nerve damage from direct tumor invasion and compression, exposure of nerve endings from dermal erosion, swelling caused by impaired capillary and lymphatic drainage, and infection [11, 13, 27, 31, 50]. Some of the most severe pain experienced by patients, however, is introduced iatrogenically during dressing changes. Dressing removal, wound cleansing, and debridement can be severely painful. Preventative measures such as use of non-adherent dressings, maintenance of a moist wound bed, gentle irrigation with warm saline, dressing removal in the shower, and minimal frequency of dressing changes can all reduce potential discomfort. Pretreatment with topical anesthetics or short-acting systemic pain medications should precede dressing changes.

Clinicians should employ a stepwise approach to treating MW pain, similar to that of the World Health Organization's analgesic ladder for managing cancer (Fig. 17.6) [51]. When approaching pain management in patients with MW, clinicians should always consider co-managing with or referring to palliative care/pain management specialists. Topical analgesics are preferred for treating mild pain associated with MW as they do not have systemic adverse effects. Topical lidocaine and lidocaine/prilocaine can be used for temporary analgesia during dressing changes [9, 10, 48]. Preclinical studies and small case studies of topical opiates show that they may be efficacious at treating moderate-to-severe pain with minimal systemic exposure [48, 50, 52–55]. Common preparations of morphine 0.1% gel (1 mg morphine with 1 g hydrogel) or methadone powder (100 mg methadone with 10 g inert powder) [48,

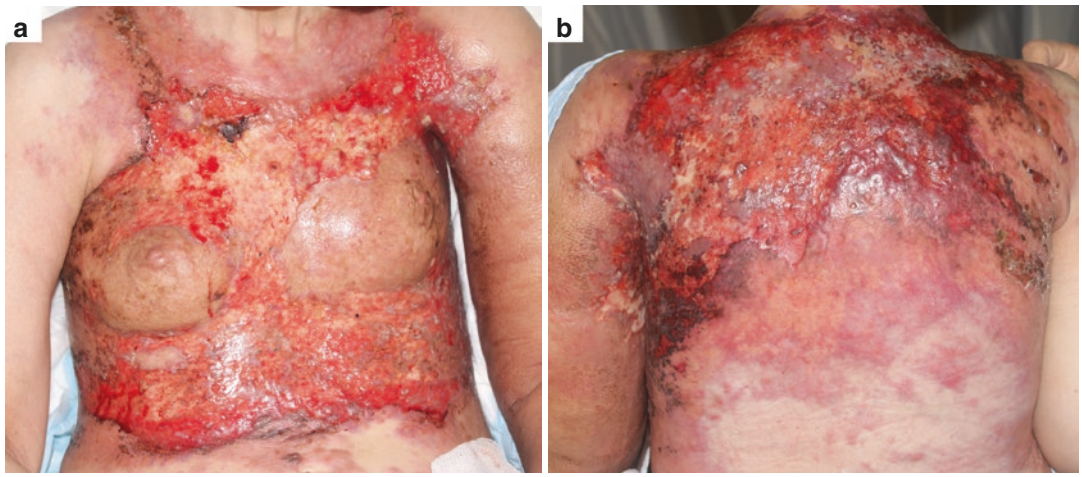

Fig. 17.4 (**a**, **b**). Erosive MW with frequent bleeding on the trunk of a middle-aged woman with metastatic breast cancer

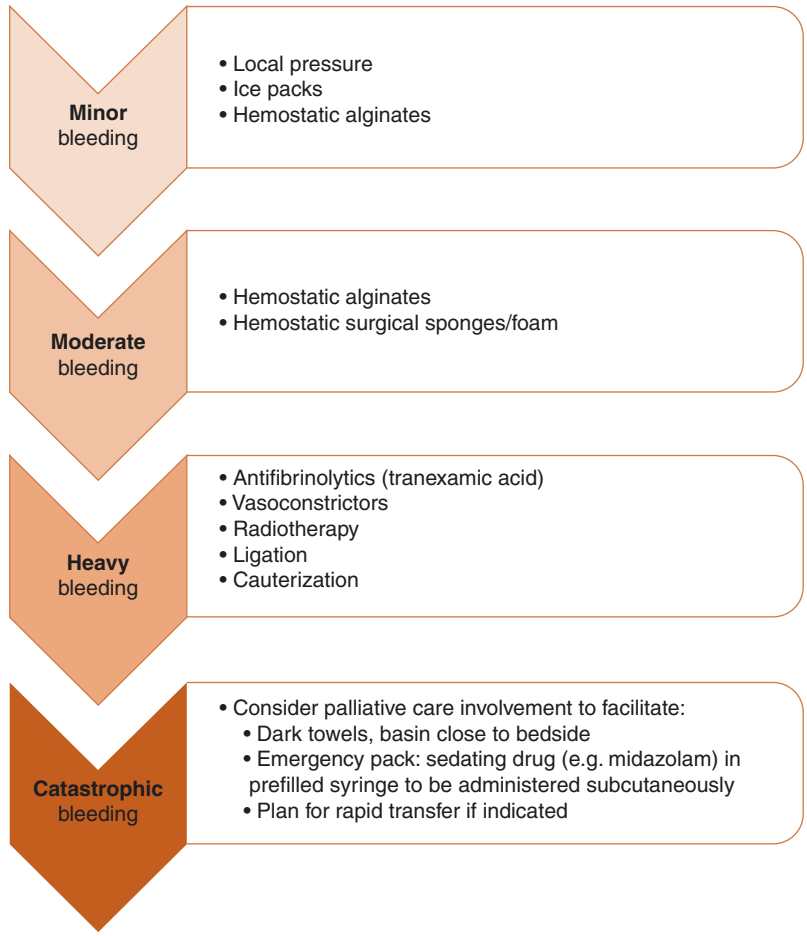

Fig. 17.5 Management strategies to control bleeding in MW [13, 48]

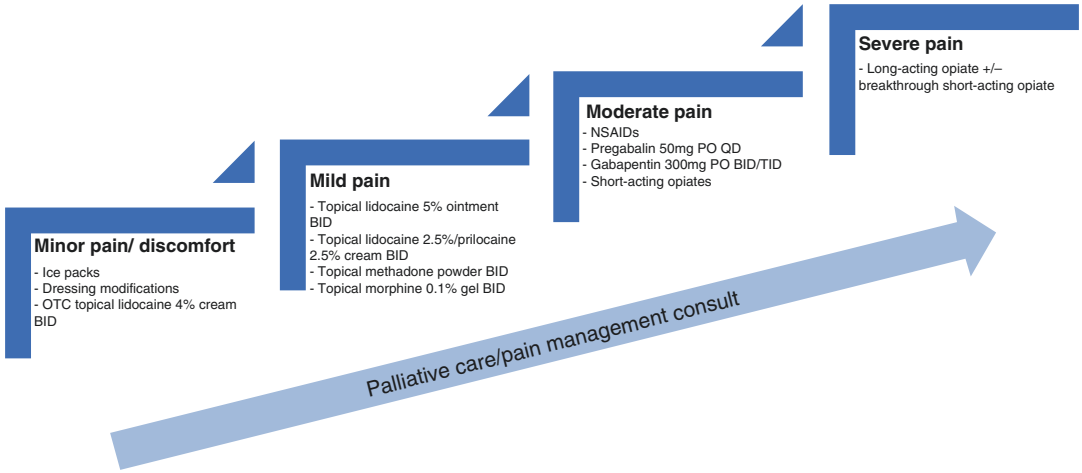

Fig. 17.6 Pain management ladder for MW-associated pain

50, 53, 55] may be prepared by a compounding pharmacy. Case reports of topical cannabinoids have also been described as effective analgesics in MW [56]. Moderate-to-severe MW pain often requires addition of a systemic pain medication. Non-opiate pain medications are preferred as they have low addictive potential. However, severe MW-induced pain may warrant use of systemic opiates. Palliative care involvement is strongly recommended in these patients.

Pruritus

Chronic pruritus is another a commonly reported symptom of MW. Pruritus is thought to arise from irritated nerve endings due to tumor stretching the skin, tumor-mediated local release of inflammatory mediators, and periwound moisture-associated dermatitis [10, 13, 57].

The literature describing treatments for pruritus in MW is limited and consists mostly of anecdotal reports. The antidepressant mirtazapine, often used as an off-label treatment for itch, was reported to effectively treat pruritus in a patient with breast carcinoma en cuirasse [57]. In combination with paroxetine, mirtazapine was also reported to improve localized pruritus from cutaneous metastatic ovarian carcinoma, though true effects of this systemic therapy may have been confounded by concurrent external beam radiation therapy to tumor sites [58].

The highly pruritic nature of both cutaneous T-cell lymphoma and burn wounds has yielded case reports and studies of antipruritic agents that might be extrapolated for use in MW. Initial antipruritic local therapy for MW consists of medium- to high-potency topical corticosteroids and temperature control measures such as ice packs and, for dry wounds, cooled hydrogel sheet dressings [9]. Topical preparations of the tricyclic antidepressant/antihistamine doxepin have been shown to reduce pruritus among patients with newly re-epithelialized burn wounds and chronic burn scars [59, 60]. Though histamine blockade is considered a hallmark of itch relief, wound-associated pruritus is thought to be poorly responsive to systemic antihistamines [9, 59–61]. Systemic gabapentin and pregabalin are often used as antipruritic agents due to their suppression of neuronal hyperexcitability. A comparative study of gabapentin and cetirizine in burn patients found gabapentin to have superior itch relief over cetirizine [62]. Anecdotal evidence of itch relief with dual therapy with gabapentin and mirtazapine for patients with cutaneous T-cell lymphoma has also been reported [61]. Finally, aprepitant and fosaprepitant are systemic neurokinin-1 receptor antagonists FDA - approved for chemotherapy-associated nausea that also prevent itch pathway

mediator substance P from binding to its neurokinin-1 receptor. Aprepitant has been demonstrated to be effective against pruritus in case reports of patients with cutaneous lymphoma and solid organ cancers [63–67].

Palliative Therapeutics

Cancer-directed therapy may have a palliative role for certain patients with MW. By destroying the malignant cells driving the MW, cancer-directed therapy can decrease MW size and reduce bleeding and pain. However, the potential palliative benefits must be weighed against the possible treatment-related adverse events. A meta-analysis of skin-directed cancer treatments (electrochemotherapy, photodynamic therapy, radiotherapy, intralesional therapy, topical therapy) reported complete and objective response rates of 35.5% and 60.2%, respectively, among cutaneous metastases [68].

Radiation therapy (RT) is the most commonly used palliative cancer-directed treatment used in MW. This noninvasive treatment may help reduce size, bleeding, and pain in MW (Fig. 17.7a). However, there is risk of radiation dermatitis, which may irritate and cause breakdown of perilesional skin (Fig. 17.7b). Delivery of hypofractionated, high-dose external beam RT has been shown to provide patients with cutaneous metastases rapid pain relief within days; maximum analgesia reportedly occurs 2–4 weeks after treatment [69]. Image-guided, intensity-modulated RT was reported to evenly and effectively distribute radiation doses in a case report of chest wall invasive breast cancer, though studies in MWs are limited [70]. Finally, RT in combination with topical or intralesional therapies showed high observed response rates in two studies of cutaneous breast cancer and melanoma metastases [71, 72].

Electrochemotherapy (ECT) uses electric, tumor-directed pulses to increase cell membrane absorption of intralesional or intravenous chemotherapy, typically bleomycin or cisplatin, and has proven more efficacious than intralesional or systemic treatment alone [73, 74]. ECT treatment requires 30 minutes; however, sequential sessions and general anesthesia may be required for intraprocedural pain. Local anesthesia may be used in select circumstances, and complications are generally limited to transient erythema and edema [75]. A recent meta-analysis estimated mean objective response of 84% among 70 studies of ECT for primary or metastatic cutaneous tumors [75]. ECT is limited, however, by its suboptimal electric current penetration to inner portions of tumors greater than 3 centimeters and through fibrotic tissue of previously irradiated fields [75]. Photodynamic therapy (PDT) uses light to activate a topical or intravenous photosensitizer to generate phototoxicity of malignant cells. One case report and early trial have shown promising efficacy and safety in palliation of

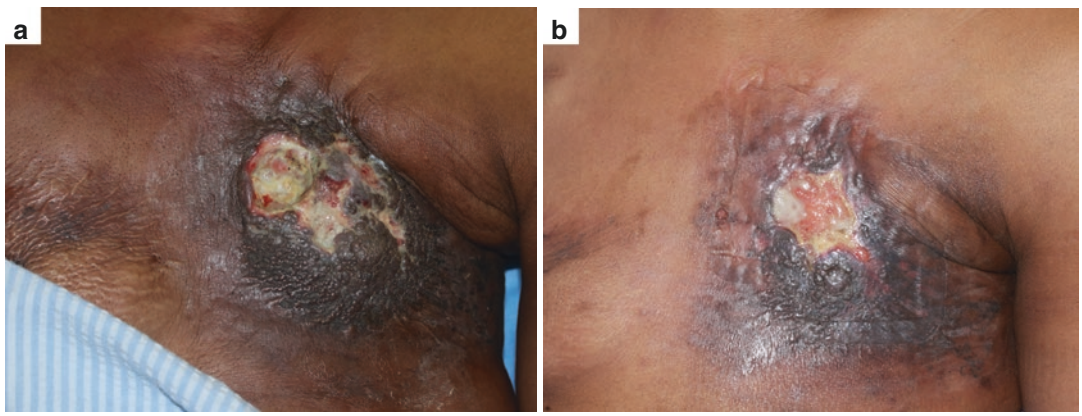

Fig. 17.7 (**a**) Elderly woman with breast cancer MW on left anterior chest before palliative radiation therapy (RT) and (**b**) after palliative RT

chest wall breast cancer metastases using PDT [76, 77].

Topical cancer-directed therapies are antineoplastic agents applied directly onto MW. Case reports using the immunomodulator imiquimod have illustrated dramatic reductions in chronic lymphocytic lymphoma skin lesions [78] and in cutaneous metastases from melanoma [79], renal cell carcinoma [80], and breast cancer [81]. A prospective trial using imiquimod, however, showed minor results: among ten patients with cutaneous breast cancer metastases, only two demonstrated partial (<50%) response after 8 weeks of treatment [82]. Combination therapy, however, appears to be more efficacious. In a study of 14 patients with cutaneous breast metastases receiving topical imiquimod in combination with systemic paclitaxel, 10 achieved partial or complete responses, for median duration of 12 weeks or 16 weeks, respectively [83]. The combination of topical 5-fluorouracil and imiquimod effectively induced partial or complete responses in 44 of 45 lesions of five patients with cutaneous melanoma metastases with one recurrence in 6 months, suggesting a synergistic effect of these two topical agents [84]. Additionally, the first and only randomized, double-blind, placebo-controlled trial using topical therapy for cutaneous metastases tested topical miltefosine in women with superficial breast lesions, showing a statistically significant – though clinically modest – difference in time to treatment failure compared to placebo (56 vs. 21 days) [85].

Finally, surgical resection may also be considered for select cutaneous metastases in appropriate patients. While excision under local anesthesia of isolated and symptomatic nodules is likely to improve patient QoL without significant morbidity, the larger, more infiltrative, and/or poorly defined plaques that tend to arise from breast cancer metastases – the large majority of cutaneous metastases in women – are likely unsuitable for surgical resection. As such, in a retrospective study of patients who underwent surgery for cutaneous metastatic lesions, the average size of resected tumor was 2.2 centimeters, and breast cancers, at only 10% of the study group, were vastly underrepresented compared to the usual breakdown of cutaneous metastases in the population at large [86].

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18 Wound Healing in Hidradenitis Suppurativa

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Abbreviations

HS	Hidradenitis suppurativa
I&D	Incision and drainage
NPWT	Negative pressure wound therapy
PHMB	Polyhexamethylene biguanide
PRP	Platelet-rich plasma

Introduction

Hidradenitis suppurativa (HS) is a chronic, inflammatory disease of the folliculopilosebaceous unit with a predilection for regions such as the axillae, groin, inguinal, and peri-anal areas. It presents as recurrent, painful, suppurative nodules that can progress to involve entire anatomic areas through the formation of tunnels that can connect lesions. HS is estimated to affect up to 1% of the global population [1]. There is often a delay in diagnosis, and it can take up to 7 years to correctly diagnose HS patients [2]. HS is commonly staged according to the Hurley staging system (Table 18.1).

The exact pathophysiology of this disease has yet to be elucidated; however, several mechanisms have been proposed. Essentially, HS stems from a problem at the level of the pilosebaceous-apocrine unit. This problem can arise as a result of a genetic mutation, altered anatomy, or variation in sweat gland proteins. The abnormality can be modified by patient factors such as stress, smoking, and obesity. Abnormality of the pilosebaceous-apocrine unit leads to follicular occlusion, perifollicular cyst development, and rupture. Initially an acute event, it can result in persistent inflammatory nodules and dermal tunnels likely due to an exaggerated response from the cutaneous innate immune system and recurrent disease activity [3]. Bacterial colonization often occurs in HS lesions, likely arising from commensal bacteria in local anatomical structures such as the hair follicle [4, 5].

Increased bacterial colonization can also create an environment favorable for biofilm growth [5]. Kathju et al. (2012) first visualized bacterial biofilms in tissue samples from a patient with HS [6].

Table 18.1 Hurley stages 1–3

Stage 1: Single or multiple abscesses with no scarring or sinus tracts
Stage 2: Recurrent abscesses with sinus tract formation
Stage 3: Diffuse involvement with interconnected sinus tracts and multiple abscesses

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A. Alavi, H. I. Maibach (eds.), *Local Wound Care for Dermatologists*, Updates in Clinical Dermatology, https://doi.org/10.1007/978-3-030-28872-3_18

Ring et al. (2017) showed that large biofilms (>50 μm) were found predominantly in sinus tracts and the infundibulum [5]. Thus, the biofilm represents both a treatment challenge and an additional therapeutic target. Debridement is the treatment of choice for the removal of biofilms in HS patients, and it can be done surgically through the opening of dermal tunnels.

The psychosocial burden for patients with this disease is quite extensive, and part of it pertains to ostracism due to the odor, drainage, and appearance of the lesions. For this reason, patients may need daily dressings to mitigate the factors that can lead to social isolation and disruption at work [7]. The unpredictability of having a lesion burst is an additional source of stress for the patient. Having absorptive dressings to cover inflamed abscesses or draining tunnels gives patients more confidence to go about their day, based on anecdotal patient feedback. Furthermore, the pain associated with HS has been reported to be one of the most debilitating symptoms of the disease. Dressings with or without topical pain medications help ameliorate some of that pain and help enhance a patient's quality of life [8].

Depending on the stage of disease, patients can require a combination of medical and surgical therapy. In an acute setting, extremely painful abscesses can be treated with incision and drainage (I&D), although the recurrence rate has been reported to be as high as 100% [9]. A lower recurrence rate has been associated with simple localized excision or de-roofing which is a simple and minimally invasive procedure where the top of an abscess or tunnel is removed. Smaller excisions may also be helpful for individual persistent lesions. Wide excision is considered to be the most effective surgical treatment for advanced disease [10, 11]. Given the chronic and recurrent nature of the disease, patients can often require repeated surgical treatments.

This chapter addresses wound healing in HS; it is important to stress that comprehensive management with combined medical and surgical therapies directed at HS will improve the non-surgical persistent lesions or wounds indirectly. Topical wound care and dressings are an adjunct to this, and the involvement of wound care nurses and pain management physicians can provide the optimal multispecialty treatment approach to patients with HS. While evidence-based practice guidelines for wound care in HS have not yet been developed, we present the current state of knowledge of options to facilitate wound healing in HS.

Wound Types in HS

There are two major wound types in HS, post-surgical and non-surgical. Post-surgical wounds encompass simple and complex or non-healing wounds. Non-surgical wounds refer to draining lesions that require management of exudate, malodor, or signs of critical bacterial colonization. Furthermore, HS lesions often present with different phenotypes and can affect a myriad of anatomical regions that may require conformable dressings to manage symptoms and/or reduce pain. Figures 18.1 and 18.2 show different wound

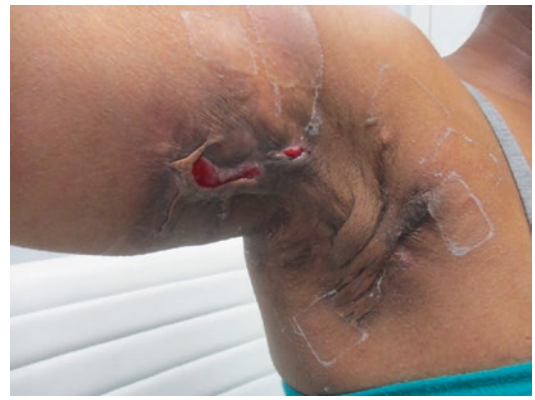

Fig. 18.1 A large HS lesion with hypertrophic scarring and ulcerating lesions

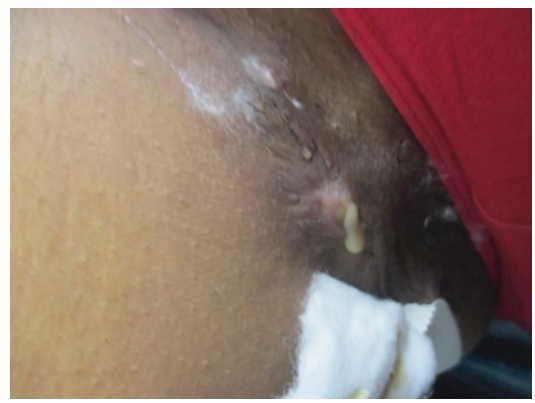

Fig. 18.2 An HS lesion with a tunnel draining purulent exudate

types in patients with HS. Atraumatic absorptive dressings that conform to flexor areas are a common choice among patients with HS.

Factors Affecting Wound Care in HS

There is currently limited evidence for optimal wound care in HS. The wound bed preparation paradigm is the framework employed for all wounds including HS wounds. It encompasses four main concets: type of tissue and the need for tissue debridement, infection/inflammation, moisture balance, and the role wound edge [12].

Tissue Debridement

The presence of a gelatinous material has been reported in HS tunnels and is thought to represent inflammation. This material consists of mixed immune cells including neutrophils, cytokines, endothelial cells, and matrix metalloproteinases (MMPs) [13]. All of these may be potential treatment targets. The changes observed may be reflective of a reactive and nonspecific chronic inflammatory process. Debridement is often utilized in HS to remove devitalized tissue and disrupt biofilms. In more acute cases of abscesses causing debilitating pain, de-roofing and simple excision will aid in the removal of biofilms. Pain from these procedures may require topical or intralesional anesthetics and form an essential part of wound care in this patient population [14].

Infection and Inflammation

The role of bacteria in HS disease progression is not well understood [15]. HS lesions can become critically colonized or secondarily infected and may require dressings with local antimicrobial properties. This will reduce the complications of bacterial colonization such as increase in inflammation, pain, and odor. However, to minimize antibiotic resistance, local antimicrobial agents should only be used when there is evidence of critical colonization and not with all lesions [14].

Moisture Balance

Moisture balance is key as the wound needs to be moist enough to promote epithelialization but dry enough to prevent maceration and an environment conducive to secondary infections. HS lesions that require wound care can be dramatically different, ranging from daily dressings for chronic, draining ulcers or tunnels to temporary dressings for a post-surgical wound. Lesions may be associated with malodor and differing amounts of exudate, and these factors are important to take into account when choosing the most appropriate dressing [14].

Edge Effect

Wound edges following either wide excision or laser therapy can be non-advancing, and additional therapies can be required to bring the edges together. Negative pressure wound therapy (NPWT), skin substitutes, and growth factors can be used to achieve advancement of the wound edges. Achieving the edge effect shortens healing time, minimizes functional limitations, and reduces scarring, particularly in patients with a large post-surgical defect [16]. There is little data on the use of these approaches in management of chronic HS wounds, although they may be helpful in post-surgical wound care.

Dressing Options for Use in HS

The dressings in this section are categorized according to the type of wounds they target (Fig. 18.3). Brief mention will also be made of advanced therapies such as cellular and acellular skin substitutes.

Superabsorbent and Absorbent Dressings

Superabsorbent and absorbent dressings can be used in the setting of simple and complex or non-healing post-surgical wounds, as well as non-surgical wounds with heavy exudate or tunnels. Superabsorbent dressings are effective at

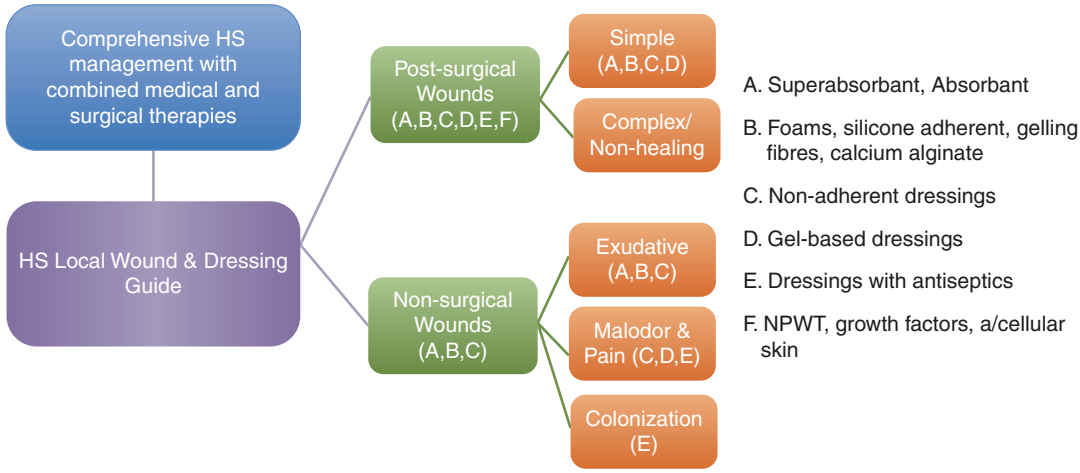

Fig. 18.3 Algorithm for providing optimal wound dressings in hidradenitis suppurativa. (Modified from Alavi, Sibbald, & Kirsner, J Dermatol Treatment, 2017 [17])

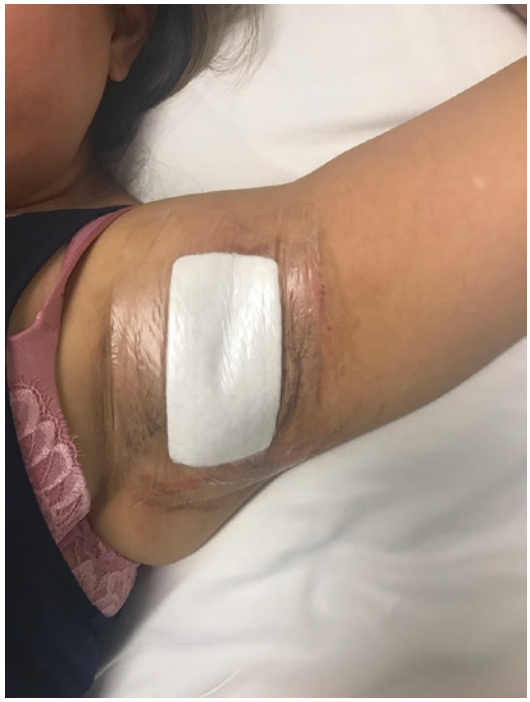

Fig. 18.4 An absorbent dressing for a wound with moderate exudate

absorbing fluid and can lock in moisture (Fig. 18.4). Their mechanism is similar to that of a diaper, and they prevent the fluid from going back to the skin surface [16]. Sanitary pads are also an inexpensive option that utilizes this technology. Absorbent dressings, on the other hand, are common items that can be ordered from surgical supply companies or online pharmacies, such as abdominal or breast pads [17].

Foam Dressings

Foam (Biatain, Allevyn) dressings can be used in many types of wounds, including those with moderate exudate. They are not as absorbent as superabsorbent or absorbent dressings and should not be used in lesions with heavy exudate. They return fluid back to the skin surface, and hence, their moisture balance favors peri-wound maceration and bacterial growth [16]. Foam dressings are helpful in maintaining the moisture on the wound surface and promote healing in both post-surgical and non-surgical wounds.

Silicone foam dressings can also be used in many types of wounds, including those with moderate exudate [16]. An example of such a dressing is the Mepilex border, which is conformable to various anatomic locations and is designed to decrease pain and trauma to the wound and surrounding skin. It is capable of absorbing exudate, thus minimizing the risk of maceration [18]. When compared to standard dressings such as self-adherent absorbent dressings and a non-sterile film dressing, the silicone

adherent dressing reduced occurrence of tape blisters and decreased the number of dressing changes needed [18, 19]. The main limitation accompanying the use of silicone dressings is their cost.

Gelling Fibers

Gelling fibers, previously known as hydrofibers, are absorptive dressings composed of carboxymethyl cellulose fibers. They can be used in many types of wounds, including those with moderate exudate. Upon contact with fluid, the cellulose fibers form a gel and can conform to various anatomic locations. They can be used in both acute and chronic settings. The moist environment allows for healing while decreasing the risk of peri-wound maceration as the fibers can control the amount of exudate they can retain. Aquacel is a gelling fiber dressing integrated with ionic silver which allows for simultaneous antimicrobial activity without compromising wound healing [20].

Calcium Alginate

Calcium alginate dressings, similar to foams, silicone, and gelling fibers, can be used in many types of wounds, including those with moderate to heavy exudate. These dressings are a combination of aqueous calcium chloride and aqueous sodium alginate. Alginate is a substance found in the walls of brown algae [21]. The consistency of this dressing is gelatinous and water-insoluble. It is available in the form of ropes, ribbons, and sheets and forms a moist pocket over the wound while the surrounding skin remains dry [21, 22]. One study showed that calcium alginate dressings are able to absorb 15–20% of their weight in exudate [23]. Furthermore, this dressing does not have to be changed daily which makes treatment adherence easier for patients. The one major drawback of these dressings is that they do not reduce the bacterial load, thus rendering them ineffective in the setting of colonized wounds [21, 24].

Non-adherent Dressings

Non-adherent dressings (i.e., Telfa) can be used for simple post-surgical wounds as well as non-surgical wounds with mild exudate [16]. These dressings can be impregnated with antiseptics or Vaseline, or they can be plain. They can be kept in place with Tegaderm, netting, tapes, Hypafix, or clothes such as biker shorts that are composed of compressive material and are capable of absorbing moisture. The benefit of using clothing to keep dressings in place is that they can be washed and re-used, thus presenting a cost-effective option for patients, and they reduce the pain associated with dressing changes [17]. Non-adherent dressings themselves are also more affordable for patients.

Gel-Based Dressings

Gel-based dressings (hydrogel) are primarily used for dry and simple post-surgical wounds. They add moisture and provide autolytic debridement which can in turn lead to epithelialization and healing of the wound [25]. The gel-based dressings are highly conformable, but care must be taken not to use these dressings on wounds with exudate or on infected wounds. This limitation restricts the use of these dressings in patients with HS [25].

Dressings with Antiseptics

Dressings with antiseptics are best suited for complex or non-healing post-surgical wounds and non-surgical wounds with malodor or critical colonization. Antiseptics that can be used include chlorhexidine derivatives such as polyhexamethylene biguanide (PHMB), silver, iodine, Manuka honey, and others. All of the above can be utilized to minimize complications from critical colonization of bacteria such as inflammation, pain, and odor. Silver-impregnated dressings also have anti-inflammatory effects and can reduce the wound size and expedite wound healing [26]. However,

silver only works in moist environments. As a result, silver dressings will not be effective in reducing the bacterial load in dry lesions, whereas PHMB will. Furthermore, chlorhexidine or PHMB does not contain alcohol and, thus, will not sting on contact with skin. Lastly, chlorhexidine-derivative preparations are much less expensive than silver and, by virtue of their cost-effectiveness alone, may represent a favorable alternative as antiseptic dressing for many patients [16].

Negative Pressure Wound Therapy (NPWT) and Other Advance Therapies

A lengthy recovery period and having to take time off work represent barriers to getting extensive surgery for patients with HS. NPWT is used primarily for complex or non-healing post-surgical wounds. It is one of the techniques employed to close large post-surgical wounds and shorten the time to complete healing. NPWT in HS promotes granulation and controls infection. It results in a short healing time and increased patient satisfaction with the aesthetic outcomes [27, 28].

Platelet preparations can also be used to accelerate wound healing by delivering growth factors and cytokines directly to the wound. Applying platelet-rich plasma (PRP) topically is a simple and inexpensive intervention that can reduce peri-surgical morbidity and pain and can speed up recovery after complex HS surgery ([29]). PRP can be placed on the wound bed directly, be applied to split-thickness skin graft, or be injected into the wound edges to accelerate wound healing though promoting neovascularization. Hyalomatrix, which stimulates neodermis regeneration, can be used to cover the PRP application. One case report used a combination of PRP and Hyalomatrix for a post-surgical wound which resulted in a completely healed wound in 2 months, with no recurrence at 1 year or scar contracture ([30]).

The studies on the role of advanced therapies in HS are limited to case reports and case series, and the use of these therapies in practice is limited. Cellular-based therapies are commonly composed of living neonatal foreskin fibroblasts along with a matrix. Commercial forms include TransCyte®, Dermagraft®, Apligraf®, and Graftskin®. These have been used for the treatment of venous and diabetic ulcers ([31]). Their use can perhaps be extrapolated to the chronic, draining ulcers found in HS. Autografts and allografts can be used in split-thickness post-surgical grafting; however, if donor tissue is in short supply, synthetic acellular skin substitutes can be used ([31]). The commercially available forms include Biobrane ®, Integra ®, and AlloDerm™. The "epidermis" is usually a silicone membrane, and the "dermis" is a nylon mesh or collagen. Two case reports described the use of Biobrane® in a wide local excision for axillary HS. They found that the patients experienced limited wound contraction, lower postoperative pain, and no increased incidence of wound infection when compared to conventional dressings with antibiotics. However, Biobrane® resulted in a long healing time, continuous wound care, and a higher cost than conventional therapy ([32]). Limitations of skin substitutes in general include decreased vascularization, poor mechanical integrity, and immune rejection. While promising as future therapies, more research needs to be done before cellular and acellular therapies can be used in everyday practice ([31]).

In addition to being categorized by the type of wound, dressings can also be categorized by tiers. Kazemi et al. (2017) proposed a tier system from one to four for wound dressings in HS where each additional tier represents enhanced difficulty of obtaining dressings and a higher cost ([17]). The authors have modified these tiers to three layers (Fig. 18.5).

Tier 1 is composed of the most affordable dressings such as adult briefs, sanitary napkins, diapers, and gauze (Fig. 18.6). These dressings can be used for lesions with a lot of exudate as they are very absorbent and can retain moisture leaving the wound dry and less subject to peri-wound maceration. The exception to this is gauze, as it is not as effective at absorbing moisture, and thus it can require several dressing changes. Gauze can also leave fibers on the wound bed, making the dressing changes quite

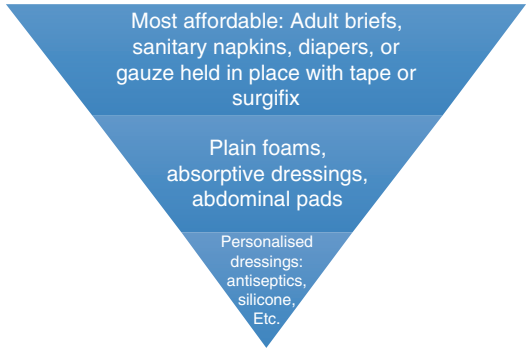

Fig. 18.5 A modified tier system for wound care

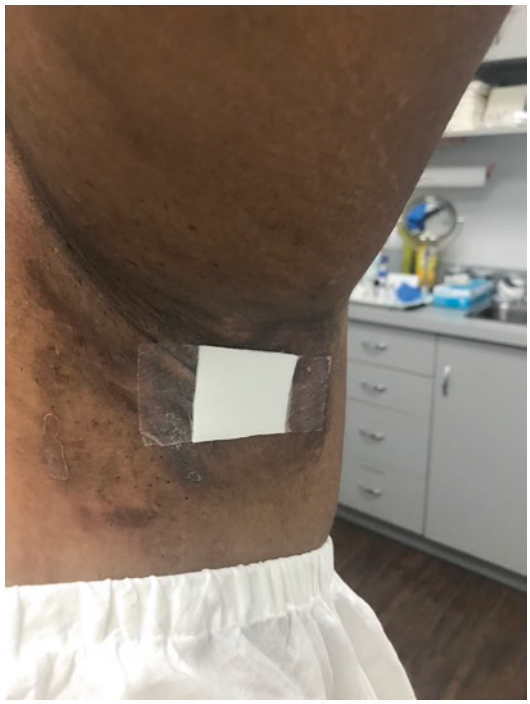

Fig. 18.6 A tier 1 dressing – gauze adhered with tape

painful. With tier 1 dressings, it is important to weigh cost savings against comfort ([17]).

Tier 2 dressings are difficult to obtain over the counter and can instead be bought via online pharmacies or surgical supply companies. Abdominal pads, superabsorbent dressings, and foams fall under this category, and they are moderately absorbent and bulky. They are also more expensive than tier 1 dressings ([17]).

Tier 3 dressings are not available over the counter and are more expensive than tiers 1 and 2 dressings. These dressings contain active ingredients such as silicone, antiseptics, or pain medications and can be modified based on individual patient needs ([17]). NPWT and cellular- and acellular-based dressings for post-surgical wounds also fall under this category.

Conclusion

In summary, the ideal wound dressing in HS is dependent on a number of factors (see Tables 18.2 and 18.3). From the perspective of the healthcare provider, features of the wound such as whether the wound is post-surgical or non-surgical and the presence of exudate, pain, odor, critical colonization, and infection play an important role. However, from a patient perspective, factors such as cost, pain with dressing changes, and the number of dressing changes required can take precedence. If the patient is not educated on appropriate wound care and is not in agreement with the treatment plan, treatment adherence will inevitably suffer, and a subsequent impairment in quality of life for the patient will ensue. Patients benefit from having knowledge and access to multiple dressings options since wounds in patients with HS are dynamic. In a disease where the diagnosis can take up to 7 years to make and where patients may require repeated surgical procedures, optimization of wound care is one important way in which a patient's comfort and quality of life can be enhanced. For this reason, when choosing the ideal HS wound dressing, one must take into consideration the ability of the dressing to absorb exudate, conform to intertriginous areas, manage odor, and reduce bacterial colonization ([17]). From a patient's perspective, factors such as ease of application, comfort, and cost should not be compromised.

For patient education and care, we provide the following tips:

1. *Manage the cost of dressings*: Dressings can be expensive, especially if you need them every day. Ask your healthcare provider for samples of different dressings to see which one is right for you. You can then buy in bulk

Table 18.2 A summary of the dressings, brand names, providers, and indications for application

Type of dressing	Examples	Providers	Application
Superabsorbent and absorbent dressings	Mesorb Xtrasorb Mextra Abdominal pads Breast pads Feminine hygiene pads Diapers	Mölnlycke Derma Sciences Over the counter Online pharmacies	Simple and complex or non-healing post-surgical wounds Non-surgical wounds with heavy exudate or tunnels Minimal adherence to the wound
Foams	Mepilex Post-op Border (silicone) Mepilex Border Biatain Silicone Tegaderm foam Restore (Silicone foam) Allevyn	Mölnlycke Coloplast 3M Hollister Smith & Nephew	Simple and complex or non-healing post-surgical wounds Non-surgical wounds with moderate exudate
Gelling fibers	BIOSORB™ AquaRite ™ Extra Aquacel® Extra Aquacel® Ribbon	Acelity DermaRite ConvaTec	Simple and complex or non-healing post-surgical wounds Non-surgical wounds with moderate exudate
Calcium alginate	Medihoney Sorbalgon Kaltostat	Derma Sciences Hartmann Smith & Nephew Hollister ConvaTec	Simple and complex or non-healing post-surgical wounds Non-surgical wounds with moderate to severe exudate
Non-adherent dressings	Non-adhesive Tegaderm Adaptic Jelonet Mepitel (silicone) Telfa	3M Acelity Smith & Nephew Mölnlycke Kendall	Simple post-surgical wounds Non-surgical wounds with mild exudate Keep secondary dressings from sticking to the wound Decreased pain with dressing changes
Gel-based dressings	Hydrogel Amerigel® Gold Dust™ Excel™	AMERX Southwest Technologies MPM Medical	Simple, dry post-surgical wounds
Dressings with antiseptics	Silver Bactigras (chlorhexidine-impregnated paraffin fabric) Inadine (iodine) PHMB	Smith & Nephew BSN Medical Acelity Silver is carried by many manufacturers	Complex or non-healing post-surgical wounds Non-surgical wounds with malodor or critical colonization Reduce bacterial burden and inflammation

Table 18.3 A summary of dressing categories and indications for application

	Simple wound	Complex/ non-healing wound	Dry	Mild exudate	Moderate exudate	Heavy exudate	Malodor	Infection
Superabsorbent and absorbent dressings	✓	✓				✓		
Foam dressings	✓	✓		✓	✓			
Gelling fibers	✓	✓			✓	✓		
Calcium alginate	✓	✓			✓	✓		
Non-adherent dressings	✓			✓				
Gel-based dressings	✓		✓					
Dressings with antiseptics		✓					✓	✓

from online pharmacies or Amazon. You can also ask your institutional pharmacy if they are willing to sell some of their stock at wholesale price. Medicare and some commercial insurance companies may cover some advanced dressings, requiring monthly application and approval.

2. *HS is a dynamic disease:* HS lesions are dynamic; they can resolve and recur and leave behind scarring or draining tunnels. Recognize the change in your disease and be proactive about requesting a new dressing recommendation for new or changing lesions.
3. *Recognize lack of treatment effectiveness:* Do you find that you are still struggling with odor and exudate despite being prescribed a dressing? Try to elucidate why that dressing is not working for you. It could be pain with changing the dressing, needing to change your dressing frequently, discomfort, or cost. Speak to your healthcare provider about what you need in a new dressing.
4. *Recognize an infected HS lesion*: If there is increased odor, pain, or temperature along with more exudate drainage than usual, your wound may be infected. If you have antiseptic dressings on hand, apply them and seek care right away.
5. *Wound healing is multifactorial:* When taking care of your wounds, it is also important to take care of yourself. Good nutrition is an important aspect of wound healing. If you have other health issues, such as diabetes, ensure that it is under optimal control as it can impair wound healing.

Conflict of Interest

- AA has consulted for AbbVie, Janssen, LEO, Galderma, Novartis, and Valeant and is also an investigator for AbbVie, Novartis, Regeneron, Pfizer, Boehringer-Ingelheim, Glenmark, Merck Serono, Roche, Xoma, and Xenon. AA received an unrestricted educational grant from AbbVie.
- MAL has consulted for AbbVie, Incyte, Janssen, BSN, and Xbiotech.
- All authors state no conflict related to this manuscript.

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19 Wound Healing in Pyoderma Gangrenosum

Asma Asif Amir Ali, Angelo Valerio Marzano, and Afsaneh Alavi

Introduction

Pyoderma gangrenosum (PG) is a chronic relapsing cutaneous disease included among the neutrophilic dermatoses, which encompass a group of forms due to accumulation of neutrophils in the skin and rarely in internal organs [1–3]. PG is nowadays regarded as autoinflammatory in origin based on its pro-inflammatory cytokine expression profile [4–7] and its association with a number of mutations involving genes regulating the innate immunity, leading to innate immunity dysfunction [6, 8]. However, a role of adaptive immunity in the pathogenesis of PG has also been demonstrated [9].

It usually presents as a sterile papule or pustule that progresses into an enlarging ulcer with an undermined necrotic border, erythematous rim, and purulent base [7]. PG is often associated with a disproportionate level of pain and is a dynamic disorder with multiple variants such as ulcerative, bullous, pustular, and superficial granulomatous. While the ulcers usually favor the lower extremities, they can be present on other sites such as trunks, breasts, face, upper extremities, and peristomal sites [10]. PG can be associated with IBD, inflammatory arthritis, plasma cell dyscrasia, and hematologic malignancies [7] and commonly affects those aged 25–54 [11]; however, there have been case reports of it affecting the pediatric population [12]. Pathergy or the development of PG lesions following minor trauma has been reported in 20–30% of patients with PG [7].

PG can also occur at the site of surgical incisions, but its close resemblance to infection can lead to delayed diagnosis and eventually destruction and deformity [13].

Treatment Options

The dynamic nature of the disease and its varying clinical presentations call for a multipronged approach to treatment. The use of topical and intralesional therapy is indicated in small and localized PG and can also be an adjuvant in more aggressive PG [14]. While first-line treatment typically includes the use of agents such as

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A. Alavi, H. I. Maibach (eds.), *Local Wound Care for Dermatologists*, Updates in Clinical Dermatology, https://doi.org/10.1007/978-3-030-28872-3_19

systemic steroids and cyclosporine [15], local wound care and compression therapy are essential adjuvants to attack the disease on all fronts. Systemic steroids can help control the inflammation; however, PG is a chronic disease, and long-term use of steroids results in adverse effects such as avascular necrosis and osteoporosis. Newer therapies are emerging for PG, such as IL-1, IL-12/23, and IL-17 antagonists as well as PDE-4 inhibitors [16]; however, all systemic therapies carry the burden of serious adverse events. In order to combat this issue, this chapter turns to explore the evidence supporting topical and intralesional agents while recognizing that these routes might make patient adherence more challenging since topical applications would require more frequent applications.

Topical and Intralesional Immunosuppressants

Topical Corticosteroids

Topical corticosteroids can help control inflammation locally by inhibiting the production of leukotrienes and prostaglandins through stimulating lipocortin [17]. High-potency steroids (class I) are most typically used for PG wounds [18]. A prospective cohort study in 2016 showed that clobetasol propionate 0.05% was the most commonly prescribed topical therapy in 66 patients at a secondary care center in the UK. Median time to healing was 145 days, and approximately 44% of patients' ulcers had healed by the 6-month mark. This study concluded that in less severe cases, topical steroids alone could be effective as first-line treatment [19].

One case report described PG ulcers that were not decreasing in size with the use of prednisone and silver sulfadiazine [20]. Topical steroids alone did not help to shorten wound healing time either; however, a mixture of both methylprednisolone and silver sulfadiazine (4 g and 400 g, respectively) resulted in complete healing within 10 weeks [20].

Patients must be counseled in judicious use of topical corticosteroids, as inappropriate use can lead to skin atrophy, purpura, steroid acne, and tachyphylaxis [21].

Topical Calcineurin Inhibitors

Topical calcineurin inhibitors are also among the first-line topical therapies for PG. These include tacrolimus, pimecrolimus, and topical cyclosporine. When compared to clobetasol 0.05%, tacrolimus proved superior with regard to a higher proportion of patients achieving complete recovery, a shorter recovery time (5.1 vs 6.5 weeks), and improved closure of wounds greater than 2 cm [22]. The efficacy of topical tacrolimus was further corroborated by Marzano et al. who successfully treated five patients with localized PG by achieving complete resolution with no reported relapse. Localized PG was defined as covering 5% or less body surface area along with three or fewer lesions. In such cases of idiopathic, localized PG, Marzano et al. postulate that topical tacrolimus can be first-line therapy [23]. Tacrolimus, like pimecrolimus, inhibits T-cell activation through blocking calcineurin and inhibiting cytokine transcription.

Pimecrolimus 1% cream was shown to be effective in a 57-year-old female with multiple sclerosis. She presented with a 4-cm infected ulcer positive for *Staphylococcus aureus* and was initiated on a treatment regimen of ciprofloxacin and gentle debridement with 0.5% silver nitrate baths. Pimecrolimus 1% cream was applied twice daily and resulted in significant improvement within 21 days and complete remission in 6 weeks with no recurrence at 8 months [24]. Similar results were obtained in another patient where systemic steroids did not result in adequate control of her disease. Pimecrolimus 1% cream resulted in significant improvement at the 15-day mark, with complete healing at week 12 and with no recurrence at the 12-month mark [25]. Pimecrolimus remains an attractive first-line option for those who are resistant to systemic corticosteroids [25].

Cyclosporine inhibits the proliferation of T-cell lymphocytes by inhibiting interleukin-2 transcription. Three of the four patients enrolled

in the study achieved complete healing at 3.5 months; the fourth patient achieved only 80% improvement in one ulcer at 6 months, but most of the other ulcers healed completely. The formulation used was 50 mg/ml of cyclosporine diluted in a 1:1 ratio of distilled water and placed under occlusive lint and Tegaderm [26]. Topical cyclosporine is both efficacious and safe; no adverse effects were noted, and systemic absorption was limited.

Pimecrolimus and tacrolimus, on the other hand, have been associated with adverse effects such as burning upon application, but placing the cream in the fridge before application can ameliorate the burning sensation. Systemic absorption has been reported with both agents but is approximately 9–10 factors less with pimecrolimus when compared with tacrolimus and 70–110 factors less than topical steroids [27]. Reduced bioavailability could translate into fewer side effects.

Intralesional Immunosuppressants

Intralesional Corticosteroids

Intralesional corticosteroids 5–10 mg/ml every 4 weeks have been used successfully in treating PG ulcers. Intralesional triamcinolone 10 mg/ml was used in two patients with ulcerative colitis in addition to systemic steroids. A mere single series of injections was sufficient to induce healing within 2 months with no recurrence at the 1.5- and 2.5-year marks [28]. Two other cases demonstrated healing within 48 hours with complete healing at 6 weeks [29], and one reported complete resolution at 3 weeks with 6 mg/ml of intralesional triamcinolone every other day for 14 days [30].

Intralesional corticosteroids have also been used in unusual sites with success. One study reported a case of retrosternal PG that developed on the background of previous PG of the back. Therapies such as prednisone, minocycline, dapsone, and 60 days of vacuum-assisted closing dressing had failed to produce a significant response. Heparin (1000 U) and normal saline (500 ml) were subsequently flushed into the site using a retrosternal catheter for 7 days. Dexamethasone (20 mg/24 hrs.) was then added to the irrigation fluid for 30 days. The drain was steadily withdrawn at 1 cm/week, and this resulted in a reduction in the size of the involved area. The same patient then went on to develop maxillary sinus PG after a tooth extraction. This case report highlights the use of intralesional corticosteroids as a prophylactic measure for patients who are prone to develop PG post-surgically [31].

Care must be taken with intralesional corticosteroids as inappropriate use can result in localized atrophy, iatrogenic Cushing's syndrome, and hypothalamic-pituitary-adrenal (HPA) axis suppression [32].

Intralesional Methotrexate

Systemic methotrexate has been proven to be efficacious in some cases of PG, as methotrexate can reduce neutrophil migration and chemotaxis [33]. One case demonstrated failure of oral methotrexate 10 mg oral weekly for 2 months in conjunction with prednisone 60 mg/day. Oral methotrexate was subsequently changed from a systemic to an intralesional route (25 mg/week), and 90% of the ulcers healed with scar formation by the 7th injection with significant improvement noticed after just the first injection; no new lesions were noticed at 10 months [34].

Adverse effects include ulceration, necrosis, pancytopenia, and hepatotoxicity if systemically absorbed [35].

Intralesional Biologics

Biologics such as IL-1 receptor antagonist, anakinra; IL-1B antibody, canakinumab; IL-12/23, ustekinumab; and TNF-a inhibitors such as infliximab, adalimumab, and etanercept have been trialed in PG. While there is no literature on intralesional biologics, the success of targeted intralesional methotrexate therapy can perhaps be extrapolated to biologics as well.

Immunomodulatory Drugs

Topical Imiquimod

Topical imiquimod has been used successfully in basal cell carcinoma, actinic keratosis, and genital warts. It modifies the innate immune system and is a cytokine inducer [36]. There is not a lot of literature on the use of topical imiquimod in PG. A case report from 2011 describes the effective use of imiquimod in a case of genital PG. Topical corticosteroids were employed initially but resulted only in partial treatment. Tapering of the corticosteroids, however, resulted in an increase in size. Imiquimod 5% cream was subsequently prescribed once daily for a period of 2–4 weeks. The lesion completely cleared within 4 weeks, and remission was maintained at the 6-month mark [37]. Inflammation, erythema, and crusting are indicative of effectiveness of treatment [38]. Common side effects include burning and itching. Larger doses of imiquimod have been associated with more serious side effects such as psoriasis, eczema, and depigmentation. Non-cutaneous side effects due to systemic absorption include headache, seizures, and constitutional symptoms (fever, myalgias) [38].

Topical Phenytoin

Topical phenytoin has been used for a variety of ulcers, wounds, and abscesses. It works by stimulating fibroblast proliferation, promoting collagen deposition, and decreasing bacterial contamination and wound exudate. Phenytoin also has the advantage of being cheap and easy to prepare [39]. Phenytoin powder can create an eschar-like coating on the wound; however, mixing phenytoin with sodium chloride and applying the solution with gauze eliminates the coating [39, 40]. Phenytoin powder (90%, 100%) can also be mixed with Polyox™ in order to maintain contact with the skin. Polyox™ is a polymer that can bind with water [39]. Fonseka et al. reported treating six patients successfully with 2% phenytoin sodium suspension daily who were previously treatment-resistant to topical betamethasone. Four of the six patients achieved complete resolution at 4 weeks. The only side effect reported in this study was a burning sensation reported in two of the patients [39].

5-Aminosalicylic Acid

5-Aminosalicylic acid can be used in mild PG, as well as in the vegetative/superficial form of the disease. 5-Aminosalicylic acid is the active component of sulfasalazine and likely works through inhibiting leukocyte motility and inducing cytotoxicity [41]. One case report about a patient with PG and concomitant Crohn's disease demonstrated successful healing of her ulcer within 5 weeks while her Crohn's disease deteriorated [42].

Sodium Cromoglycate

Sodium cromoglycate is an inhibitor of mast cells, macrophages, eosinophils, monocytes, and platelets [43]. 1% sodium cromoglycate was used successfully in five patients; initial improvement was noticed within 3–7 days, and complete healing occurred within 5–8 weeks. Systemic corticosteroids were added to patients who did not show significant initial improvement [44]. Adverse events include erythema and irritation [45].

Benzoyl Peroxide

Benzoyl peroxide has been shown to promote wound epithelialization in different rates with different concentrations; it also has antimicrobial, antipruritic, and antifungal properties [46]. 20% benzoyl peroxide-soaked gauze applied twice daily has been used successfully to clear PG lesions in 4 weeks. A barrier cream can be used to minimize irritation [47]. Topical antibiotics can be used to reduce secondary infections in PG [48].

Dressings

Dressings are an important part of local wound care. They can keep the topical agents in place and increase local absorption. The differing presentations of wounds warrant different dressings. Most of PG lesions require moisture-retentive dressings with consideration of pain on removal and application of dressings. Films and hydrocolloids have limited use in these patients due to minimal absorbency. Hydrogel dressings are a good choice regarding the pain in these patients and are appropriate for very dry wounds but not wounds with drainage. Moisture-retentive dressings such as superabsorbents, foams, gelling fibers, and calcium alginates are ideal for moist wound beds. Silicone foam is less adherent and traumatic if wound is very painful. The use of dressings containing pain medication (ibuprofen) helps minimize the pain. The routine use of antiseptics is not recommended. However, the use of silver as an anti-inflammatory agent would be beneficial in alleviating the inflammation [49].

Pain Management

PG wounds can be associated with a disproportionate amount of pain [10]. Traumatic dressings can contribute to pain, and care must be taken to prescribe an appropriate dressing. Silicone dressings, for instance, have been shown to be less traumatic than a regular adhesive hydrocellular polyurethane foam dressing [54, 55]. Furthermore, dressings impregnated with topical analgesics can also be used to manage pain locally. Topical morphine and ibuprofen have been used in this setting [54, 55]. Topical morphine is prescribed as "morphine sulfate 10 mg in Intrasite Gel 8g" in the palliative setting for painful skin ulcers. Contraindications include an infected wound, acute respiratory depression, and impairment of the central nervous system. Adverse effects include pruritus, and the risk of systemic absorption increases with a larger surface area [56]. Topical cannabis has also been reported in successfully reducing wound pain in PG ([57]).

Other Therapies

Compression Therapy

Compression therapy is part of the conservative management used for PG to reduce any associated edema [50]. It can be used as an adjunct to immunosuppression and in ulcers without an inflammatory border [50]. One report signifies the importance of combined multimodal therapy, including immunosuppressive and wound care that includes compression therapy in patients with PG [51].In a retrospective study of 29 patients with chronic leg ulcers and concurrent rheumatologic disease, 17 patients were treated with compression therapy alone. The study concluded that compression therapy was a key strategy in treating chronic leg ulcers [52]. Lastly, a systematic review of 39 randomized clinical trials showed that using compression, especially multicomponent elastic compression, improved ulcer healing rates compared with no compression [53].

Negative Pressure Wound Therapy (NPWT)

There have been multiple case reports of treating PG ulcers with NPWT, although the risk of pathergy is an ongoing concern. NPWT contributes to wound healing by inducing macrodeformation, which shrinks the wound; microdeformation which induces undulation; fluid removal which increases blood flow; and bacteria and toxin removal which contributes to wound environment stabilization ([58]). Two case reports describe the use of NPWT in conjunction with immunosuppression (oral prednisolone) – the first case saw resolution of the ulcer within 4 weeks (15 cm pads; pressure, −80 mmHg) that allowed cessation of the prednisolone. The second case saw complete epithelialization at 8 weeks (20 cm pads; pressure, −80 mmHg), and prednisolone was once again ceased; the ulcer was oval and 15 cm in size.

A case series of 15 patients treated with NPWT to secure split-thickness skin grafts in patients under immunosuppression demonstrated that healing was induced within 1 month of grafting in 67% of cases, and 27% of cases showed an improvement of more than 90% – far superior to conservative measures ([59]).

The concerns with surgical intervention are aggravating lesions or inducing new ones; however, that was not noticed in the above cases (58). NPWT with immunosuppression is thus another alternative therapy for PG.

Skin Substitutes

Pathergy can occur in up to 30% of patients with PG and can make physicians hesitant to perform surgical debridement. In patients with a history of pathergy, especially, skin substitutes can be a favorable alternative. One patient with a history of pathergy, contraindications to oral steroids and cyclosporine, and some improvement with adalimumab received an allograft from a cadaver which was fixed in place with Steri-Strips and covered with binding bacteria dressing and an inelastic bandage. The allograft was engrafted perfectly at the 3-week mark ([60]). Another case report describes a case of postsurgical PG that only worsened with subsequent surgical debridement. The patient responded to azathioprine and prednisone, but due to the large size of the wound, hyperbaric oxygen was started to aid with cicatrization and resulted in superficial neovascularization within 45 days. Incomplete re-epithelialization prompted the use of an autologous skin graft on the ulcer bed. This resulted in complete closure of the wound with no recurrence at 10 months ([61]).

In-Person Approach

PG is a chronic disease that causes both physical pain and psychological distress. A multidisciplinary team consisting of a dermatologist, family physician, wound care nurse, and perhaps even social worker is necessary to provide holistic care for the patient. A strong therapeutic relationship is necessary as it is essential for the patient to receive consistent follow-up.

Conclusion

In conclusion, PG is a dynamic disease that requires equally dynamic and creative solutions in order to provide the best care. Open communication is necessary to elucidate patient preference and find common ground to ensure patient compliance. Optimizing local wound care can result in reduced dose of systemic therapies and a more favorable side effect profile.

Conflict of Interest

- AAA and AVM have no conflict of interest to declare.
- AA has consulted for AbbVie, Janssen, LEO, Galderma, Novartis, and Valeant and is also an investigator for AbbVie, Novartis, Regeneron, Pfizer, Boehringer-Ingelheim, Glenmark, Merck Serono, Roche, Xoma, and Xenon. AA received an unrestricted educational grant from AbbVie.
- All authors state no conflict related to this manuscript.

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Scar Management

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Abbreviations

5-FU	5-Fluorouracil
DNA	Deoxyribonucleic acid
Gy	Gray
IL	Interleukin
ROS	Reactive oxygen species
TGF	Tumor growth factor
TNF	Tumor necrosis factor

Introduction

Successful wound healing always results in scar tissue. In the context of chronic wounds, the appearance of scar tissue is often less of concern to patients than scars resulting from acute wounds. Nevertheless, there can be major aesthetic and functional impairment from scars, e.g., contractures resulting from extensive wounds. This, as well as a number of subjective symptoms such as pain or itching, can result in a significantly reduced quality of life. Furthermore, scar tissue resulting from the healing of a chronic wound will usually not be as mechanically resistant as healthy tissue and therefore predispose to recurrences of the wound at the same location. The tensile strength of mature scar tissue is around 70% of the healthy tissue it replaces.

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Scar Types

After a wound with secondary wound healing is completely epithelialized, scar tissue replaces the substance defect. This scar tissue takes several more months for maturation. Scar tissue shows some important differences to normal skin: it lacks all appendages and it shows reduced tensile strength, which will never reach more than approximately 70% of the original value. The scar can be hypertrophic, i.e., the scar is raised but not extending beyond the borders of the original defect. Hypertrophic scars can still show some maturation and flatten within the ensuing 1–2 years. Among the risk factors for hypertrophic scars are prolonged inflammatory phase of wound healing and tension on the healing tissue.

If the scar tissue extends beyond the size of the original defect, a keloid has formed. Keloid scars show no spontaneous regression. Keloids mostly appear in individuals with genetic predisposition and darker skin types and in certain typical sites of predilection, i.e., chest, shoulders, and earlobes. In some instances, wound healing processes, particularly inflammatory processes, can result in a loss of volume, which results in an atrophic scar.

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Many factors influence the type and extent of scar tissue formation [1]. One important factor is the length of the inflammatory phase of wound healing. Among the cytokines involved in this process, TGF-β plays a key role. It is present in three isoforms which have both pro-fibrotic and anti-fibrotic effects. Polymorphous neutrophils and macrophages release pro-inflammatory cytokines (IL-1, TNF-a, IL-6) which lead, through their proteolytic activity, to a pro-oxidant microenvironment and increased ROS, which cause extracellular matrix and cell damage as a consequence.

Scar Prevention and Early Intervention

Longer wound healing and more inflammation tend to result in more pathologic scars. The important factors in the prevention of pathologic scars are therefore all measures that allow wounds to heal as rapidly as possible and reduce inflammation in the wound healing process. For chronic wounds, this can include the maintenance of a moist wound healing environment and measures to reduce pro-inflammatory cytokines such as matrix metalloproteinases. For postsurgical wounds, this includes the avoidance of postsurgical complications which favor pathologic scars, namely, wound dehiscence, necrosis, and wound infection. These possible complications all influence each other: wound infection often leads to necrosis and wound dehiscence and thus to a wider, possibly raised scar, and wound dehiscence or necrosis can predispose to wound infection.

After surgical interventions, several measures in the first postoperative days and weeks prove helpful in preventing pathologic scars [2]. One of the most important aspects is to immobilize the scar tissue, i.e., to reduce any movement and tensile forces on the scar. The application of paper tape immediately postoperatively can be one measure to reach this goal; its effect on achieving less raised scars has been demonstrated in one small study [3].

After the early phase of scar maturation, scar massage can also be beneficial. A large selection of creams and ointments containing ingredients such as onion extracts, allantoin, or heparin are available for this. The main mode of action for this measure might be the hydration of the scar tissue. There is mostly anecdotal evidence for scar massage, and the benefit is uncertain, but the efficacy seems to be greater in postsurgical scars [4]. The best documented topical remedy for better scar formation is silicone, in form of either a gel or sheets. Silicone sheets or gel should be applied over the entire scar area ideally 24 hours per day. Silicone increases the hydration of the stratum corneum and the oxygen saturation and reduces the hypoxia-induced angiogenesis. The production of fibroblasts and collagen is reduced in well-hydrated tissues. There is a considerable body of literature documenting the benefits of the early application of silicone in the process of scar maturation which shows that silicone is effective in preventing abnormal scaring in high-risk individuals and shows improvements in scar thickness and scar color. However, most studies are of poor quality and highly susceptible to bias [5].

One of the most effective measures both in the prevention and treatment of keloids is compression of the scar tissue. Various devices can be fitted to apply effective pressure on the scar tissue and should be worn ideally 24 hours per day [6].

Treatment of Hypertrophic Scars and Keloids

In normal scar maturation, the abovementioned treatments can be stopped after 3 months. If hypertrophic scaring begins to develop, a more active treatment regimen should be considered. Scar massage, the application of silicone sheets or gel, and pressure therapy should be continued. In addition, intralesional injection therapies or laser therapy can be considered. For keloids, cryosurgery or radiotherapy can be more effective alternatives. Surgical scar revision should only be considered if hypertrophic scars do not respond to more conservative treatment modalities after 12 months, for scar contracture with functional impairment, or if disturbing scars are the result of unsatisfactory earlier interventions. For keloids, surgical scar revision should never be performed without supporting postoperative treatments such as intralesional injections, radiotherapy, or pressure therapy [6, 7].

The most common intralesional treatment of hypertrophic scars and keloids is steroid injection. It can be used after approximately 2 months; most commonly triamcinolone is injected in a concentration of 10 mg/ml, 20 mg/ml, or 40 mg/ml in intervals of 4–6 weeks. Intralesional steroids reduce fibroblast proliferation, collagenase inhibitors, and collagen synthesis. However, there are important side effects to be considered. In particular, skin atrophy, telangiectasia, and hypopigmentation are common, depending on the concentration of the steroids injected. Furthermore, if large areas are treated, systemic effects of the steroids can be observed such as Cushing-like effects. It is therefore advisable to use the smallest effective dose. Clinical efficacy has been documented in many studies and ranges from 50% to 100%; recurrence rates are between 9% and 50% [8].

An interesting alternative for intralesional injection is the injection of 5-fluoruracil [9, 10]. 5-FU acts as a pyrimidine analog that inhibits DNA synthesis and as an irreversible inhibitor of thymidine synthetase. Fibroblasts are halted in their proliferation, causing scar degradation, and type I collagen gene expression is hindered. The effects of TGF-β1 are blocked. 50 mg/ml can be given in weekly, biweekly, or monthly intervals at a dose of 1–3 ml per session. Side effects include pain, ulceration, burning, infection, and transitory hyperpigmentation, but usually no systemic side effects are observed. However, there are important contraindications for this cytostatic drug, such as pregnancy, lactation, thrombocytopenia, anemia, leukopenia, bone marrow suppression, or infections. Many studies have shown an improvement in scar thickness and pliability with this treatment; clinical efficacy ranges from 45% to 78% with recurrence rates documented as low as 19%. The best results can be achieved with a combination of intralesional 5-FU and steroids, resulting in reduced side effects and increased clinical efficacy with lower recurrence rates. A recent randomized controlled double-blind study compared the efficacy of intralesional steroids (triamcinolone) versus 5-fluorouracil in the treatment of keloids. In a group of 43 patients with 50 keloid scars treated with intralesional steroids or 5-FU over 6 months, they found no significant difference between treatments in remission rate (46% for steroids vs. 60% for 5-FU). However, there were significantly more local adverse effects such as cutaneous atrophy and telangiectasia in the steroid group. These authors recommended to use 5-FU especially for cosmetically sensitive skin areas [11].

Another substance used for intralesional treatments with interesting results is bleomycin. It causes breakage in DNA, leading to fibroblast apoptosis, a lack of response to TGF-β1, and a reduction in lysyl oxidase levels. It can be injected in monthly intervals over 3–4 months; the total dose should remain below 9 IU to avoid risk of pulmonary and cutaneous fibrosis, renal toxicity, hepatotoxicity, and bone marrow suppression. Clinical response rates are between 53% and 84% with relatively low recurrence rates. It seems to be an interesting alternative for larger and more resistant lesions, with no systemic toxicities reported so far. Comparative studies with 5-FU and triamcinolone injections have shown slightly more efficacy with lower recurrence rates but also more pain [12].

For large hypertrophic scars and for keloids, cryosurgery can be a valuable alternative. Cryo treatment rejuvenates scar tissue and reverses the abnormal keloidal fibroblasts to the normal phenotype. Type III collagen to type I collagen ratio is increased, whereas cellular matrix is preserved and acts as a scaffold for cellular regeneration with no contraction. Cryosurgery has impressive results with a large reduction of volume (50–94%) and pain and keloid softening but usually not complete eradication, and many treatments are required for a durable effect. If sufficiently performed, cryosurgery results in extensive blisters and new wounds that take 6–8 weeks for healing. It is repeated every 2–3 months. Besides the prolonged wound healing times and pain during the application, a disturbing side effect is significant pigment loss, especially in dark skin types. Different devices exist for the application of cryosurgery: open spray, contact probe, or intralesional probes. The liquid nitrogen has to be applied until the entire scar turns white which usually requires treatment times of more than 1 minute. In most cases, cryosurgery is combined with intralesional injection of steroids which is much facili-

tated by the softening of the freshly thawed edematous tissue [13].

Surgery and Radiotherapy

Surgery is a treatment option for scars that are functionally limiting or aesthetically disturbing. However, surgical correction is only indicated if tension in the scar tissue can be redistributed and/or the pathophysiological process leading to the original scar can be avoided. For example, scars resulting from suboptimal surgical technique or postoperative complications can often be surgically corrected. Tension can be redistributed with different surgical approaches such as Z-plasties. Hypertrophic scars should only be treated surgically if the scar has fully matured and more conservative approaches have failed. Usually, the earliest time point for this is after 12 months. Keloids should never be excised without any adjuvant treatments; as the excision stimulates keloid growth, they would usually recur even larger than the original lesion. Excision without primary wound closure, so as not to create new tension, followed by injections of intralesional corticosteroids in biweekly intervals can be effective for some types of keloids.

For extensive keloids, radiotherapy can be used as an adjuvant therapy after surgical excision. A dose of usually 10 Gy in one fraction can be applied shortly postoperatively. In one study with 80 keloids, this resulted in recurrence rates after 1 year of 9% and 16% after 5 years [14].

Various laser treatments such as fractional CO2 laser or pulsed dye laser have shown to improve scar surface contour and to reduce redness and pliability of scars.

In conclusion, good surgical technique and optimal management of wound healing lead to less disturbing scars, which can greatly improve patient's quality of life. If a hypertrophic scar or keloid develops, there are a large number of treatment options, which all have relevant side effects and need to be repeated over long periods. Surgical correction of scars should not be performed as a monotherapy. For most scar treatments, a combination of different modalities will be optimal.

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