



PATIENT-CENTERED OUTCOMES OF THERAPEUTIC STRATEGIES IN TREATMENT OF CHRONIC ULCERS

Iqra Suleman^{1*}, Dr. Momina Tuz Zobia Malik², Dr. Syeda Shehar Bano³, Dr. Atiqa Ali⁴,
Mehwish Idrees⁵, Dr. Ayesha Iqbal Shehzad⁶

^{1*}M.Phil Scholar Riphah International University, Pakistan, Email: iqrasuleman576@gmail.com

²Department of Medicine, Faraz Hospital Bahawalpur, Pakistan,
Email: mominamalik108@gmail.com

³Women Medical Officer, Department of Medicine, THQ Hospital Bhalwal, Pakistan,
Email: sheharbanosyeda4109@gmail.com

⁴Resident Medical Officer, Department of Internal Medicine, Jinnah Medical and Dental College,
Pakistan, Email: atiqa.ali29@gmail.com

⁵Scholar, Doctor of Pharmacy, Shifa Tameer e Millat University, Pakistan,
Email: mehwishidrees51@gmail.com

⁶Demonstrator, Department of Pharmacology, Sharif Medical and Dental College, Lahore, Pakistan,
Email: draysha83@gmail.com

***Corresponding Author:** Iqra Suleman

*M.Phil Scholar Riphah International University, Pakistan, Email: iqrasuleman576@gmail.com

Abstract

Background: Chronic ulcers pose significant challenges in dermatological therapy. Understanding the etiology of these ulcers is pivotal for effective treatment. Local therapy is often indispensable, focusing on cleaning, debridement, infection control, and the application of various topical agents, including medications and dressings.

Methods: This review explores recent therapeutic advancements for chronic ulcers, considering both established and emerging approaches.

Results: A growing area of research focuses on the development and application of biological skin substitutes. These substitutes offer potential solutions for enhancing wound healing and tissue regeneration. Investigations into the role of growth factors in ulcer healing have shown promise. Identifying the most effective growth factors and methods for their delivery is essential to optimize treatment outcomes. Laser therapy is gaining attention as a viable option for ulcer management. Researchers are exploring the mechanisms and safety considerations associated with laser treatments for chronic ulcers. Hyperbaric oxygen therapy's potential to expedite wound healing is under scrutiny. Determining optimal treatment protocols and understanding its influence on tissue regeneration are key areas of focus. Electrical stimulation has emerged as a potential adjunctive treatment for chronic ulcers. Investigating the mechanisms by which electrical stimulation promotes healing and its parameters for effective application is a critical research area. The use of negative pressure wound therapy is showing promise in ulcer management. Research efforts are directed towards understanding its mechanisms and identifying patient populations that benefit most from this therapy.

Cost-Effectiveness Analysis: Evaluating the economic viability and accessibility of novel therapeutic strategies compared to traditional approaches is a vital component of current research.

Patient-Centered Outcomes: Studies are assessing the impact of various ulcer treatments on patient

quality of life, pain management, and overall well-being, considering patient-reported outcomes. **Combination Therapies:** Investigating the synergistic effects of combining multiple therapeutic strategies, such as growth factors with electrical stimulation or biological skin substitutes with hyperbaric oxygen therapy, is a significant area of inquiry.

Conclusion: This comprehensive review of therapeutic advances in chronic ulcer management highlights the significance of ongoing research to improve treatment efficacy, patient outcomes, and the accessibility of innovative approaches. It also underscores the enduring value of traditional therapies.

Keywords: chronic ulcers, dressings, compression cure, biological skin substitutes.

INTRODUCTION

Ulcers correspond to losses of skin substance that reach, at least, the dermis. The most superficial lesions are called erosions or ex-ulcerations. Given the definition, there is no doubt that it is a dermatological process, although it is sometimes the consequence of other types of disorders (vascular, neurological, endocrine, etc.). Despite being a frequent process, we have the impression that fewer and fewer people go to the dermatologist's office. Moreover, our specialty is rarely part of the multidisciplinary teams that treat this disease. Lack of interest, abandonment, or intrusiveness in a disease that has traditionally filled the consultation of dermatological dispensaries? The treatment of ulcers is not so easy, and it requires a correct diagnosis and continuous updating in their management; in fact, the market is saturated with different types of dressings, healing creams, or methods that promise a rapid (Carter, DaVanzo et al. 2023).

Ask for repair of the lost tissue. How many times do you receive visitors from these commercial houses for consultation? We are convinced that it is a field that eludes us and that, worse, we are, on many occasions, willing to let it slip away. That is why we believe the commission from the Editorial Board of ACTAS to review the current therapeutic situation, and this review has made us confirm our suspicion since few of the referred works are carried out by dermatologists or published in dermatology journals; They almost always do so in specialized publications, General Surgery and especially nursing (Carter, DaVanzo et al. 2023).

CONCEPT

As we have already commented, an ulcer is a loss of substance that affects the entire skin structure, the terms erosion and ex-ulceration corresponding to more superficial aggressions. Classically, the term "wound" is used to designate ulcers with an exogenous cause, generally traumatic, and the term "ulcer" for those with an endogenous cause. Still, the truth is that they are used interchangeably. Therefore, The term ulcer is purely descriptive and must always be accompanied by its etiological cause: vascular, postphlebotic, diabetic, pressure, etc. We will not go into the diagnosis of ulcers in this work, but we will directly address their treatment. However, there is no doubt that establishing the etiology or correct diagnosis is an absolute priority. Years ago, we addressed the "leg ulcers" diagnosis in a monograph that may still be useful for the uninitiated¹ (Carter, Frykberg et al. 2023). Skin ulcers can be acute or chronic. The former are generally traumatic and are usually repaired by surgical techniques or granulation by secondary intention. However, the chronicles suffer a phenomenon of stagnation in their healing mechanisms that makes them unable to complete it; in them, external manipulation using various techniques is essential to bring the repair to a successful conclusion. It is this type of technique that we will mention (Herruzo, Fondo Alvarez et al. 2023).

SIGNIFICANCE OF THE PROBLEM

There is no doubt that chronic ulcers represent a major problem if one considers their incidence, the deterioration they produce in patients' quality of life, and their economic repercussions. The prevalence of ulcers of vascular origin in the United States is established between 600,000 and 1,500,000²; annually, 3% of people with diabetes develop foot ulcers, and between 15 and 20% do so throughout their lives; 90% end up requiring limb amputation. Different studies on the quality of life

in patients with chronic ulcers have shown a significant deterioration based mainly on the pain of the lesions, loss of time necessary for their care, and repercussions on their physical, work, and social activity. The economic repercussion of chronic ulcers is truly important, not only due to healthcare costs but also due to the loss of working days. Recently, Eisenbud et al.⁶ estimate that in the United States, it represents an expense of 5 trillion dollars annually (Holubová, Chlupáčová et al. 2023).

REPAIR MECHANISM OF THE WOUNDS

As soon as the loss of substance occurs, a series of complex mechanisms are set in motion, only partially known and which can be synthesized in three phases.^{7,8}: inflammatory, proliferative, and long-lasting. The first phase, which lasts approximately 72 hours, is aimed at packing the wound (clot formation) and cleaning it; platelets and different inflammatory cells, mainly granulocytes and macrophages, participate in it. Also, during this stage, a series of soluble mediators are released that initiate the healing process. The proliferative stage has as its fundamental mission the increase of collagen and angiogenesis to constitute the granulation tissue; at this stage, the participation of endothelial cells is of great importance. The maturation stage can last for years and is fundamentally based on collagen production and subsequent destruction. In all these stages, there is a participation of keratinocytes that tend to migrate both from the edges and the epithelial remains of the wound through multiplication and maturation systems (Li, Xing et al. 2023).

In chronic ulcers, there are alterations in the healing mechanisms. Thus, in studies using exudate from these lesions, metalloproteinase levels have been shown, determining an increase in proteolytic activity and inactivation of the growth factors necessary for healing. Collagen is the main component of the dermis and of some extracutaneous structures such as tendons, bones, or ligaments. Collagen production is not essential in the creation of the new scar. Unfortunately, in this process, the skin does not recover its elasticity, reaching 70 or 80% of its original situation in the best cases. The balance between the synthesis and degradation of this dermal protein is essential in the scar's characteristics. In diabetic patients, collagen synthesis is altered, which affects healing mechanisms. In the inflammatory phase, there is great cellular activity of resident cells (epithelial cells, fibroblasts, dendritic cells), as well as the production of different mediators that attract platelets, neutrophils, lymphocytes, and macrophages to the wound area, and they favor the phenomena of angiogenesis and the production, ultimately, of granulation tissue. Many factors are released within the ulcer, but we will only comment on those that may be of interest from the point of view of their therapeutic application (Rayate, Nagoba et al. 2023):

1. Growth factors, such as platelet-derived growth factor (PDGF-B), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and nitric oxide (NO) are found in the exudate from ulcers. They promote chemotaxis, migration, stimulation, and cell proliferation.
2. Recombinant growth factor-BB derived from human platelets (PDGF-B) or bescaplermin (PDGF) is the only growth factor accepted by the Food and Drug Administration (FDA) for the treatment of diabetic ulcers of the feet. It has been established that PDGF is in
3. Low concentration in the exudate of chronic ulcers, and it has been shown that its topical application favors their healing. PDGF is a potent mitogen and chemotactic agent that increases vascularization and endothelial proliferation.⁹
4. bFGF is one of the most important factors in the inflammatory phase of healing since it is a potent mitogen that acts on many cells and, therefore, has a proven role in migration cell proliferation and endothelium¹⁰. The topical application of bFGF has shown a favorable action on forming granulation tissue and epithelial regeneration in burn patients. Still, its efficacy is not superior to placebo on diabetic ulcers.¹¹. Possibly, the failure of this monotherapy resides in the need to use more than one growth factor.
5. VEGF determines endothelial cell proliferation and migration in the wound repair process. It is secreted in different cells: keratin cells, macrophages, fibroblasts, and endothelial cells, a secretion that is usually carried out in a hypoxic environment. This secretion reaches its highest concentrations on day 7 and is the fundamental stimulus for angiogenesis.

6. NO is an important factor in fibroblast proliferation and collagen production. It is secreted by the fibroblasts themselves and fibroblasts and macrophages.

Vascular ulcers, especially venous ones, are due to the appearance of venous hypertension that leads to valve insufficiency and, therefore, to passive vasodilatation of the veins with slowing of circulation. This explains why compression dressings are the most appropriate treatment for this process. The demonstration of fibrin cuffs around the vessels results in a decrease in transcutaneous oxygen. In any event, the resulting tissue ischemia favors the entrapment of leukocytes and the release of proteolytic substances that induce skin changes (ulceration and the well-known changes of stasis dermatitis) (Saboia-Dantas, Dechichi et al. 2023).¹.

TYPES OF HEALING

Classically, two types of scarring correlate with the defect's size and reciprocate with healing time and the quality of the resulting repair. Healing by *first intention* is performed on wounds with an approximation of the edges, either because they are small or because this proximity is achieved surgically. Healing is obtained quickly, and the aesthetic and functional result is good. This type of healing usually occurs in small wounds with clean edges and no necrotic debris (Shapira, Govrin-Yehudain et al. 2023).

On the contrary, scarring *second intention* is performed on large wounds with rough edges and generally contaminated. Healing is slow since it involves a long and complex process, and the aesthetic and functional result is poor since the epithelial lining is generally fragile and very different from its original appearance. Pressure ulcers and vascular ulcers are the ones that usually perform this type of healing. Healing by primary intention requires little medical intervention. However, sluggish or chronic ulcers are favored by correct handling and are the ones that will be discussed in this paper {Wang, 2023 #28}.

RELATED FACTORS WITH THE HEALING PROCESS FROM A WOUND

Wound healing is a long, complex, and dynamic process that can be influenced by many factors, some known and others unknown. Even those labeled as known are not fully agreed upon or supported by studies of scientific evidence. It is important to know them since it is in our hands, in most cases, to correct them. We will review the most notable (Carter, DaVanzo et al. 2023).

General situation of the patient

Usually, a well-nourished, healthy, and young patient presents a greater facility to achieve adequate healing.

nutritional status

All nutritional deficiencies delay the healing of ulcers, but states of hypoproteinemia and hypovitaminosis, especially A, C, and K, have a special influence. Alcoholism is also a risk factor for chronic ulcers (Carter, DaVanzo et al. 2023).

Age

Older people have a lower capacity for cell proliferation, neovascularization, and collagenogenesis, so their capacity for tissue repair is diminished.

coagulopathy

Protein C and S deficiencies and coagulation disorders are clearly an obstacle to healing. Of all these signs, the increase in pain and Obesity, diabetes, pituitary and adrenal disorders alter the intimate mechanisms of wound healing (Carter, Frykberg et al. 2023).

Neuropathies

The presence of ulcers in neurological patients, both central and peripheral, is well known.

Drugs

Some drugs, such as steroids, cyclosporin, colchicine, and some antiseptics, paradoxically widely used in the treatment of wounds, can be toxic to macrophages and inhibit neovascularization and collagen synthesis, thereby delaying healing (Herruzo, Fondo Alvarez et al. 2023).

local factors

Humidity

The humid environment is the most appropriate, as we will discuss later, for the healing of wounds¹³ since it favors cell conservation and migration, which is not achieved in a dry environment.

oxygen tension

Hypoxia promotes wound healing^{14,15}, which determines that a closed cure is more useful than an open one. This aspect is controversial since some authors use hyperbaric chambers to treat wounds, especially arterial ones.

pH titular

The acidity benefits healing¹⁵ since it is an excellent barrier against bacterial invasion. Consequently, one of the most common maneuvers on wounds, washing with household soap and, therefore, alkaline, is detrimental to the healing process (Holubová, Chlupáčová et al. 2023).

infections

The presence of germs in wounds is a controversial topic. There is no doubt that wounds, especially chronic ones, are colonized by germs, and it is not always easy to decide if this presence results from colonization or infection. Many authors consider the presence of classic clinical signs such as erythema, edema, heat, purulent exudate, and pain as a sign of infection, to which have been added delayed healing, discoloration or friability of granulation tissue, formation of pockets in the base of the ulcer and unpleasant odor. Delayed healing is the most reliable¹⁷. The culture taking to be assessable should not be done, as usual, by taking it with a brush, but by needle aspiration or biopsy, considering the presence of infection when more than 10 are isolated—⁵ bacteria/g (Li, Xing et al. 2023).

Another important problem is the use of antibiotics in the treatment of chronic ulcers since it usually leads to the production of bacterial resistance. On the other hand, using local antiseptics is not only not useful but counterproductive. The use of topical antibiotics prophylactically is not useful, as can easily be deduced, and is a risk factor for developing resistance. Therefore, we should follow what is listed in Table 1 when suspected of a bacterial infection (Rayate, Nagoba et al. 2023).

other

The complexity of the wound itself, inadequate care, etc.

GENERAL CONCEPTS ABOUT THE TREATMENT OF CHRONIC ULCERS

Classically, two healing systems have been established in chronic ulcers: the traditional cure or dry cure, based on the use of antiseptics and "leaving the wound in the open air," and the cure in a humid environment or humid cure, which proposes the use of products that generate a humid environment in the wound bed, control exudate and stimulate more physiological healing. Most experts believe the latter method is the most appropriate and should replace the former. The treatment of chronic ulcers has two aspects: that of the underlying disease and local treatment. Etiological treatment is necessary, but it will not always solve the presence of chronic ulcers since they frequently appear as a consequence of an irreversible vascular lesion, such as diabetic ulcers (Saboia-Dantas, Dechichi et al. 2023).

Cleaning wounds is an important step in your care. It is not a purely mechanical act, but its success or failure will depend on its correct performance. The American Agency for Health Care Policy and Research (AHCPR) dictates standards for cleaning pressure ulcers that can be extended to the rest of

chronic ulcers (Table 2). The use of antiseptics is controversial since, as previously mentioned, their use can be harmful. However, some molecules, such as the calcium dexomer of iodine, have demonstrated their usefulness and an absence of toxicity, so their use in chronic ulcers is not contraindicated²². Given their known toxicity and aggressiveness on monocytes, fibroblasts, granulocytes, and granulation tissue, we consider antiseptics inappropriate. Instead, saline solution, which should be applied with a determined pressure, is recommended. In this sense, the GNEAUPP (www.gneaupp.org) recommends that the most suitable vacuum pressure is that of gravity itself or using a 35 ml syringe with a 0.9 mm needle with which a pressure is achieved of 2 kg/cm². The safety pressure for washing ulcers ranges between 1 and 4 kg/cm² (Shapira, Govrin-Yehudain et al. 2023). Debridement is necessary if debris, slough, or necrotic remains are a breeding ground for the development of bacteria and send a phagocytic response that is detrimental to wound healing. It can be done using larvae by mechanical, enzymatic, chemical, surgical, or surgical methods. Although this step is widely accepted and practiced, no studies demonstrate its efficacy. Exudate control is important since, although a humid environment in the wound is advisable, it should not be excessive, as it could cause maceration of the edges and the granulation tissue. This excessive exudate can also be a sign of infection. Today, different types of dressings on the market help control ulcer exudation. Infection control has already been discussed (Shapira, Govrin-Yehudain et al. 2023).

TABLE 1. MANAGEMENT OF A CHRONIC ULCER WITH SUSPECTED INFECTION

1. Given the clinical suspicion of infection (bad odor, abundant or purulent exudation, abnormal granulation tissue, pain, arrest of the healing phenomenon, etc.), proceed to a culture/antibiogram, taking it with aspiration or biopsy.
2. The isolation of various germs does not necessarily indicate infection or interfere with Wound healing, only isolating more than 10 ⁵ colonies/g, is the infection index and indication of treatment with systemic antibiotics.
3. Topically, we must consider the use of antibiotic therapy for ulcers that do not evolve adequately with the correct topical treatment: – Choose an effective antibiotic against gram-negatives, gram-positive and anaerobes (e.g., Argentine sulfadiazine)
– Do not use dressings that do not allow gas exchange. Today, dressings are available that
Generally contain silver or activated carbon, with bactericidal capacity.
– No study has shown the usefulness of local antiseptics in local infections. On the contrary, their use (povidone-iodine, sodium hypochlorite, hydrogen peroxide, acetic acid) is toxic to many of the cellular elements involved in the mechanisms.
healing

TABLE 2. AHCPR RECOMMENDATIONS FOR THE CLEANING OF ULCERS

Cleaning should be the first act in wound treatment and always at each dressing change. It should be performed gently, applying the least possible mechanical force to allow mechanical removal of necrotic debris without causing trauma to the wound bed.
Do not use antiseptics such as iodinated derivatives, sodium hypochlorite, hydrogen peroxide, and acetic acid.
Use an isotonic saline solution.
AHCPR: Agency for Health Care Policy and Research. Tomada de Roldán Valenzuela ²⁴

TABLE 3. ADVANTAGES OF THE WET CURE

Increased oxygen and nutrient supply endogenously through angiogenesis
Acidification of the medium
Ease of cell migration
exudate control
Maintain the right temperature, stimulating fibrinolysis.
pain reduction
Protection of wounds against infections Reduced healing time
Decrease in local cures

An ideal dressing (Table 4), but the different types available will be discussed. Dressings can be classified into passive, active, and interactive. The passive dressing only has a protective function, while the others create a suitable environment, a microclimate that favors wound healing, favoring debridement, avoiding infection, and facilitating healing. We will try to synthesize the different types of dressings, emphasizing their indication (Table 5).^{4,12,24}:

Conventional (passive)

gauze

They are the most used dressings. They are composed of cotton fibers, considered dry dressings with great absorbent capacity. They are cheap, and their main drawback is that they damage the granulation tissue during changes. This defect can be avoided by soaking the gauze in saline or paraffin solution.

made of viscose

They are a little adherent; some are infused with silicone to reduce silicone further.

Specials (active and interactive)

hydrocolloids

It is the first type of interactive dressing introduced to the market. Its basic composition is carbo.

TABLE 4.PROPERTIES OF THE IDEAL DRESSING

Create a humid environment
Promote wound healing
Do not adhere to the wound.
Being able to renew itself without causing trauma or pain Ability to absorb excessive exudate
Maintain gas exchange
Impermeability to microorganisms
Acceptability by the patient
Easy to use
acceptable cost

TABLE 5.CRITERIA FOR THE CHOICE OF DRESSING

ximethylcellulose, to which other variable substances are added to increase its absorption and adherence capacity. The polyurethane cover may be permeable to oxygen (semi-occlusive and occlusive, respectively). In contact with the exudate from the wound, they form a gel, which determines that they gradually lose permeability and efficacy and even that the edges of the wound can be macerated. They exist on the market in different presentations: plates of different sizes and thicknesses, paste for filling cavities, absorbent granules, and even in the form of ribbons known as "hydrofibers." They are indicated in pressure ulcers in the initial stages and not infected. They also act as autolytic debris and promote granulation and wound healing since different studies have shown the presence of growth factors in the exudate that remains in contact with the ulcer (Carter, DaVanzo et al. 2023)

Alginates

They are derived from natural algae(*Phaeophyceae*) and are made up of polysaccharides formed by associating mannuronic and glucuronic acids with a calcium alginate base. They are dressings with a high absorbent capacity, around 10 to 20 times their weight, and have some antibacterial action. When in contact with an exudate that contains sodium salts, calcium alginate, which is insoluble, is transformed into sodium alginate, which constitutes a hydrophilic gel that creates a humid and warm environment in the wound bed, providing conditions Ideal for the healing process. They are marketed in the form of dressings of different sizes, tapes for cavities, and are associated with hydrocolloids in the form of plates and liquids. Its indications are exudative wounds, with bad smell and even infected, and in case debridement is required (Rayate, Nagoba et al. 2023).

They are semi-permeable dressings; that is, they are impervious to liquids and permeable to water vapor. Its main properties are the absorption of exudate, the maintenance of a humid environment, and the prevention of maceration. They do not break down with exudate and are flexible and, therefore, adaptable to different types of wounds. Depending on their composition, there are different types available:

1. Nonadherent acrylic inner layer dressings, highly absorbent hydrophilic middle layer, and gas-permeable polyurethane externally.
2. Internal layer dressing of polyurethane foam or gel and externally with gas-semipermeable polyurethane.
3. Trilaminar structure dressings, internally microperforated polyurethane sheet, in the middle area hydrocellular absorbent layer and externally polyurethane.

These dressings should not be used with oxidizing agents containing hypochlorites, ether, or hydrogen peroxide.

silicones

They consist of a silicone-coated polyamide mesh. It comes in sheets of various sizes. The hydrophobic properties of silicone mean that it does not adhere to moist areas, that is, the wound, and it does adhere to dry areas, that is, to the edges of the wound. This property is known as microadhesion. They reduce the pain sensation, do not dissolve on contact with the exudate, and, by not adhering, do not cause detachment of the epidermal cells with the dressing change. The sheet can remain in the wound for about 5 days. They are indicated for any wound in the granulation phase, painful lesions, and even for fixing grafts or repairing graft-donor areas (Li, Xing et al. 2023).

charcoal dressings

Its base is activated carbon but can also contain silver, alginate, and hydrocolloids. They have great absorption capacity, especially for odours and microorganisms. They are poorly adherent. They are applied directly to the wound but require an additional fixation dressing. Logically, its indication is highly exudative, malodorous and super-infected wounds (Holubová, Chlupáčová et al. 2023).

silver dressings

They are presented with silver on carbon mesh, hydrofiber, and silver polyethylene meshes covered with nanocrystalline silver or silver on a hydrocolloid base. Although, depending on their composition, they have different properties, the antimicrobial or bactericidal effect and the control of exudate and bad odor are common characteristics. They are, therefore, indicated in wounds with a torpid evolution, suspected or not of infection, and with the production of an unpleasant odor (Holubová, Chlupáčová et al. 2023).

collagen

They are dressings that produce a suitable environment and gradually dissolve in the ulcer. It would be best if you did not make your changes until they are completely released.

Dextranomer

It is a three-dimensional network of dextran polymers in porous microspheres with a high absorption capacity when in contact with the exudate. They also absorb cellular and bacterial debris present in the wound by capillarity. They also have debridement capacity, eliminating necrotic tissue without damaging the living tissue. The large number of products present on the market is evident; each one of them has its advantages and disadvantages that we have tried to comment on, but it seems appropriate to conclude this section by summarizing some of the conclusions obtained in a study carried out by the Carlos III University, which aims to evaluate the efficacy and cost-effectiveness ratio. The use of special dressings in the treatment of pressure ulcers and vascular ulcers, both venous and arterial (Herruzo, Fondo Alvarez et al. 2023)

- Similar efficacy on the variables healing or reduction of the wound size between specific dressings, social and conventional, except in the case of hydrocolloids in pressure ulcers.
- Absence of significant differences between the different types of special dressings.
- Although the cost of material per treatment unit is higher in the case of special dressings, in general, there seems to be a decrease in indirect costs based on less use of nursing time, which favors a better cost ratio. -effectiveness.
- For further studies to validate or not these results.

TABLE 6.CHARACTERISTICS OF ELASTIC STOCKINGS

Compression DensityPressure Indications(mmHg)

Mild 70 18-22	Pregnancy without vascular risk
long trips	
Works in orthostasis	
Moderate 140 22-29	Pregnancies with vascular risk Discrete varicose veins
Prevention of deep vein thrombosis in bedridden	
Risks of venous insufficiency in orthostatic professions	
Prevention of primary varicose veins	
Strong 280 30-40	Mild chronic venous insufficiency Thrombophlebitis
Prophylaxis in healed ulcer	
Truncal or symptomatic varicose veins	
Extra strong 420 37-49	Chronic venous insufficiency with edema Active static ulcer

Protecting the skin with an insulating cream such as water-based paste or Vaseline is advisable. The ulcerated area can be treated most properly since this type of bandage is compatible with any local cure. The first layer of bandage should be made with cotton, and then an adhesive elastic bandage is applied circularly. Once the bandage is finished, it is advisable to check the color of the fingers, both when the patient walks and when he is at rest, as well as ask him if he feels too much oppression or tingling in the fingers; if so, it should be loosened until a good tolerance is found. The bandage is changed weekly, although it can be done more frequently if the exudate from the ulcer requires it (Carter, Frykberg et al. 2023).

Bota de Unna

It is also a classic system for treating skin ulcers, but no less useful. It positively affects venous hypertension during orthostatic but not during rest. Unna's boot results from the combination of a moist paste in contact with the wound and the external compression of the bandage itself. Although variable, the paste that is used can perfectly be a water-based paste with which the entire bandage is impregnated, which must be perfectly adjusted without excessive compression. Once the first layer is placed, a bandage is made with zinc glue, resulting in moist internal and hard external parts. It is advisable to check the bandage after 24 hours to verify no signs of ischemia. The patient should be informed that he should go to the clinic if he notices pain, tingling, or any other striking subjective sign. The care of the bandage is like that of any plaster, and, depending on the exudation of the wound, it must be removed between 3 and 15 days (Carter, DaVanzo et al. 2023).

Bota de Duke

It is a variation of the Unna boot in which a hydrocolloid plate is placed to absorb the exudate. We sometimes use a foam rubber plate instead of a hydrocolloid plate; the one found in surgical scrub brushes can even be used with good results. We must insist that compression therapy should only be used in venous vascular ulcers and that it is contraindicated in arterial ones. Therefore, it should not be used when there is a decrease in pulses, if oscillometry is decreased, or if the malleolar systolic blood pressure is less than 80 mmHg (Carter, DaVanzo et al. 2023).

TREATMENT THROUGH THE USE OF SKIN GRAFTS

The surgical repair of vascular ulcers is undoubtedly a provocative idea, but it clashes from the outset with an obvious fact: the poor vascularization of the area. The use of thin autologous grafts is undoubtedly a valid option. Still, it provides thin skin that can easily ulcerate again.³² There has recently been an evident development of the so-called biological skin substitutes (SBC)³³ They provide a wide therapeutic possibility to which we dermatologists will, of course, have to adapt since it will be an unquestionable help in the treatment of loss of substance in which classic skin grafts cannot be used (Shapira, Govrin-Yehudain et al. 2023).

SBCs, also known as *live skin equivalents*, are offered commercially as autologous and allogeneic substitutes; the latter is obtained from genetic engineering and can be epidermal, dermal, or mixed (epidermis and dermis). SBCs offer a series of advantages over traditional grafts: it is a non-invasive technique, does not require anesthesia or patient admission, and, of course, has no donor area, thus avoiding the production of a new wound. It is undoubtedly an expensive product, but the savings in indirect costs (consultations and hospital expenses) can compensate for this (Shapira, Govrin-Yehudain et al. 2023).

Epidermal SBC

They are available as autografts and obtained from the patient's keratinocyte cultures. It has been available in the United States since 1988 as Epicel[®] and can provide large amounts of tissue. It is used in the treatment of burns and leg ulcers. Its drawbacks lie in the delay in performing the treatment, the need for a prior biopsy and culture, and the quality of the skin obtained since it is thin and fragile. To avoid delay in treatment, cultures of allogeneic keratinocytes from neonatal foreskin skin have been performed, which are cryopreserved until implantation (Saboia-Dantas, Dechichi et al. 2023).

dermal SBCs

They are allogeneic grafts and, therefore, immediately available. They positively affect epithelial migration, differentiation, and production of adequate granulation tissue that allows the subsequent use of grafts. Classically, cadaver skin has been used as a donor, which can be chemically treated to eradicate its antigenic components (Alloderma[®]). Based on genetic engineering, a current alternative is dermal grafts made up of a polymer of bovine collagen and chondroitin-6-sulfate with a coating of human keratinocytes or fibroblasts (In tegra[®]). The FDA recently authorized Dermagraft[®] to treat diabetic ulcers; this product consists of cultured neonatal dermal fibroblasts *in vitro* and a bioabsorbable polyglactin mesh³⁴. The exact mechanism of operation of these substrates is not well known. Still, the studies carried out, especially on Derma graft[®], suggest that, although they do not survive inside the ulcer, they favor releasing a series of cytokines that stimulate healing (Rayate, Nagoba et al. 2023)

Composite grafts

They consist of bilayers made up of epidermal and dermal components. The best-known group is the Apligraf[®], containing an outer layer of allogeneic epidermal keratinocytes and an inner layer of human fibroblasts dispersed in a protein matrix; it does not contain skin appendages. Appli graft[®] Produces cytokines and growth factors that accelerate the healing process. Cel[®] is another allogeneic SBC with a structure similar to Apligraf[®], made on a porous matrix of bovine collagen I, which is also indicated in vascular ulcers, diabetics, and bullous epidermolysis³². Several studies have shown that using SBC on venous ulcers is well tolerated and produces excellent results.^{35,36}, so it is a future technique that should be considered. Table 7 lists the products that currently exist in the American market (Li, Xing et al. 2023).

OTHER THERAPIES

Other therapeutic measures have been used in the treatment of chronic ulcers. They include the laser, electrical stimulation, negative pressure, and the hyperbaric chamber. There are also some more curious among which honey or insect larvae can be considered, as well as the use of new medicines.

Hyperbaric oxygen therapy (HBO) is "physical therapy based on obtaining high partial pressures of oxygen, inside a hyperbaric chamber, in which a pressure higher than atmospheric is reached"⁴⁰. Numerous experimental and clinical studies show that hyperbaric oxygen therapy increases the partial pressure of oxygen (PO₂) in hypoxic and infected tissue, reaching figures higher than 30-40 mmHg (Holubová, Chlupáčová et al. 2023).

TABLE 7.LIST OF LEATHER REPLACEMENT PRODUCTS IN ALPHABETICAL ORDER

Indications	Other uses	Product	Company approved published	Advantages	Disadvantages by the FDA
Alloderm [®]					com Burns and grafts full thickness (allografts) None
	Celaderm [®]		Smith & Nephew Inc., 727-392-1261		
		Organogenesis Inc., 888-432-5232 www.organogenesis.com	www.smith-nephew.com		Diabetic foot ulcers; ulcers high schools and epidermolysis bullosa
Apligraf [®]	Dermagraft [®] Epicel [®]		Genzyme Biosurgery, 800-232-SKIN www.genzymebiosurgery.com		Venous and diabetic ulcers Burns deep partial and deep complete; congenital nevus
		Bertek Pharmaceuticals, 304-285-6420 www.bertek.com			
Biobrane [®] , Biobrane-L [®]					Burns partial and deep/ autointerios mottled/ donor area
	THIS is Derm [®] LifeCell Inc., 800-367-5737 www.lifecell.com		Burn Medical, Inc., 800-943-4522 www.brennenmedical.		Burns. Venous ulcers, diabetic,
and by pressure. Xenoinjector porcine other formulations (Cymetra [®] , Repliform [®]) used to fill defects of soft tissues, dental, gynecological surgeries and urological		Product cryopreserved	does not produce rejection, high incidence of permanence	and hard use	commercial; one day of life; in some patients results cosmetics poor
Epidermolysis bullous; anecdotal posts, studies of cases and pilots in many others situations	Burns thick partial or complete, ulcers venous I do not reject; no case of viral transmission after more than 100,000 applications; 2 years of duration (life)	three years of life; good barrier function and water exchange (raincoat bility)	Long life relatively Lack of components cell phones	No antibacterial property/requires change in 7-10 days	Potential answer immunological I disease transmissior (Keep going)
	Mimics the function of the dermis.	More than 6 months in duration; relatively cheap. good results in several pilot studies	Simulates the dermal function. Product cryopreserved	Not approved by the FDA	
		autologous cells; it	Duration 5 days; logistics of request	Logistics of use and distribution difficult; short life (unless reserved cryopreserved)	
				Fragile; preparation	

TABLE 7.LIST OF LEATHER REPLACEMENT PRODUCTS, BY ALPHABETICAL ORDER
(Continued)Indications Other uses Product Company approved publishedAdvantages Disadvantages by the
FDA.

Indications	Other uses	Product Company approved	publishedAdvantages	Disadvantages
Integra [®]	www.integra-ls.com	www.smith-nephew.com Burns deep partial and complete	does not produce rejection; high incidence of permanence	Potential answer immune
Laserskin [®]	Fidia Advanced Biopolymers Srl, 011-39-049-8232111 www.fidiapharma.it	thick burns partial, ulcers venous chronicles and for pressure, vitiligo	1.5 year half-life	requires stores lie cryogenic
Oasis [®]	Healthpoint, 800-441-8227 www.healthpoint.com	Burns thick partial/complete ulcers pressure, venous and diabetic	Simulates cytokine expression of healthy skin; 9 months old, cryopreserved 1.5 year refrigerator life layer removal silicone and requires auto injection	silicone men must be deleted
OrCel [®]	Ortec International Inc., 212-740-6999 www.ortecinternational.com	area wound donor. Hands in "mitten" of epidermolysis bullosa	wounds venous or diabetic Two layers; good function barrier; used in about out of 10,000 patients; moderately long life	Two days old; preparation commercial; fragile
TransCyte [®]	Integra LifeSciences Corp., 800-654-2873	Smith & Nephew Inc., 727-392-1261	partial thickness burns the complete	autologous cells; it

Tissues improve healing, angiogenesis, and the activity of fibroblasts and, therefore, collagen synthesis. It also improves the antimicrobial defense of the host, with the greater phagocytic activity of leukocytes, inhibition of the growth of anaerobic bacteria, and the effect of some antibiotics is enhanced. It is, therefore, a useful therapeutic option. High-pressure oxygen administration can be performed locally using small pressurized chambers designed to accommodate a limb. Although they have the advantage of their low cost and great manageability, they should not be considered HBO since their supposed benefits are not based on the physiological effects of breathing oxygen at high pressures. The usefulness of this system is controversial since while some authors have reported good results in diabetic foot, its use in combination with other therapies makes it difficult to know your real profit⁴¹. On the contrary, randomized studies show that not only are they not beneficial, but they can decrease the release of oxygen in the affected limb (Carter, DaVanzo et al. 2023)

Topical treatment of chronic negative pressure ulcers has been available since the late 1990s. This technique can accelerate the formation of granulation tissue, decrease the size of the edema, increase blood flow, and speed healing. It is especially useful in reducing the size and depth of ulcers.^{45,46}. Negative pressure devices (suction cups) consist of glass, metal, or rubber applicators or suction cups in the form of caps of different diameters depending on the treatment area, at the top of which is connected to the suction-compression tube attached to the vacuum-producing mechanism. Due to the risk of dissemination, its use is contraindicated in recent thrombophlebitis and phlebothrombosis, circulatory disorders of cancerous origin and acute infections (Carter, Frykberg et al. 2023).

Some antiepileptics, such as phenytoin⁵³ and the topiramate uncle⁵⁴, have shown efficacy both on the speed of healing and on the quality of it. The usefulness of becaplermin and the various growth factors in neuropathic and diabetic ulcers has already been discussed, and their usefulness may be extended to other chronic ulcers. Therefore, treating chronic ulcers is a field of great interest in whose knowledge and therapeutic possibilities are advancing rapidly. We do not doubt that it is a multidisciplinary disease in which the dermatologist must participate. Possibly, this aspect depends, to a great extent, on ourselves (Herruzo, Fondo Alvarez et al. 2023).

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