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Review Article

Hard-to-Heal Wounds

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ABSTRACT

A hard-to-heal wound or chronic wound is a wound that fails to heal in an expected time due to disruption of the normal healing process. Commonly encountered chronic wounds are those occurring in patients with diabetes, long-standing pressure injuries, and venous diseases. If not treated properly, a chronic wound might be complicated with infection, threatening limb loss, and serious psychological impacts. This review addresses the concepts of chronic wound management, emphasizing the TIMERS principle. Care for specific types of wounds and modern dressing materials used in chronic wound care are also discussed.

Keywords: chronic wound; hard-to-heal wound; TIMERS principle

INTRODUCTION

The Wound Healing Society (WHS) 2006 defines chronic wounds or hard-to-heal wounds as: A wound that occurs but does not heal over extended time periods because of the disruption of the normal wound-healing process[1]. Subsequently, several studies have been conducted to provide additional definitions and a precise timeline for providing a more definitive diagnosis of chronic wounds[2-4]. In 2019, Atkin et al. defined chronic wounds in the Journal of Wounds as a wound where the wound surface area has decreased less than a specified amount over a period of 4 weeks, which, depending on the type of wound, can be classified as follows:

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- Venous leg ulcers with less than 50% reduction in wound size in 4 weeks.
- Diabetic foot ulcers with less than 40% reduction in wound size in 4 weeks.
- Chronic pressure ulcer with less than 20–40% reduction in wound size in 4 weeks.

Types of chronic wounds' wound classification

Chronic wounds can be classified according to their cause. In general, people with chronic wounds tend to have an underlying disease that is the main cause of the chronic wound and these can be classified into three main categories:[5]

- Chronic wounds caused by pressure injuries.
- Chronic wounds caused by venous lesions (varicose ulcer, venous leg ulcer).
- Chronic wounds caused by diabetic disease (diabetic foot ulcer).

However, some studies also include radiation wounds and chronic infection wounds as chronic wounds[6].

Stages of normal wound healing

Wound healing is the process of tissue repairing to return to function as close to normal as possible. The wound-healing process can be divided into many steps. Each step can overlap in each type of wound. Also, each step period may end in a short time, but, at the same time, some periods can take years. The wound-healing processes involve chemical change, morphological change, and physical change, and can be divided into four main phases as follows (Figure 1).

1. Hemostasis phase

Here, the blood vessels constrict and the platelets come together. A clot is formed, which includes fibrin, fibronectin, vitronectrin, von-Willebrand factor and thrombospondin, platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1), epidermal growth factor (EGF), and transforming growth factor-beta. (TGF-beta), which stimulates the healing cascade and increases microvascular permeability, causing swelling at the wound site.

2. Inflammatory phase

A molecular cascade causes white blood cells to pool at the wound site. Bacteria are destroyed and there is a secretion of cytokine and growth factors, such as fibroblast, keratinocytes, and endothelial cells, to repair blood vessels and wounds.

3. Proliferative phase

Fibroblast cells are drawn to the wound site by the PDGF and TGF-beta. The fibroblasts multiply and produce extracellular matrix (ECM), which is important for cell repair. Also, the collagen that is created from the fibroblasts is an essential component of every step of the healing process. In addition, at this stage, angiogenesis and epithelial cells' migration occurs. If this phase is disrupted, it can lead to long-term chronic wound development.

4. Remodeling phase

In this final phase, the collagen bundle will be larger, which increases the strength of the wound heal. However, the strength of the wound heal is only 80% that of normal skin due to the wound-contraction process, as shown below in Figure 1.

Pathophysiology of hard-to-heal wounds

Chronic wounds are caused by a disturbance in the wound-healing process; whereby, when the normal wound-healing process is unable to proceed with the normal process, it will result in delayed wound healing and the possible development of a chronic wound. Ayello et al. found that the majority of chronic wounds are caused by a disturbance in the inflammatory or proliferative phase that results in the wound being unable to enter the re-epithelialization process[7]. The healing process can be interrupted for various reasons, including the following (Figure 2).

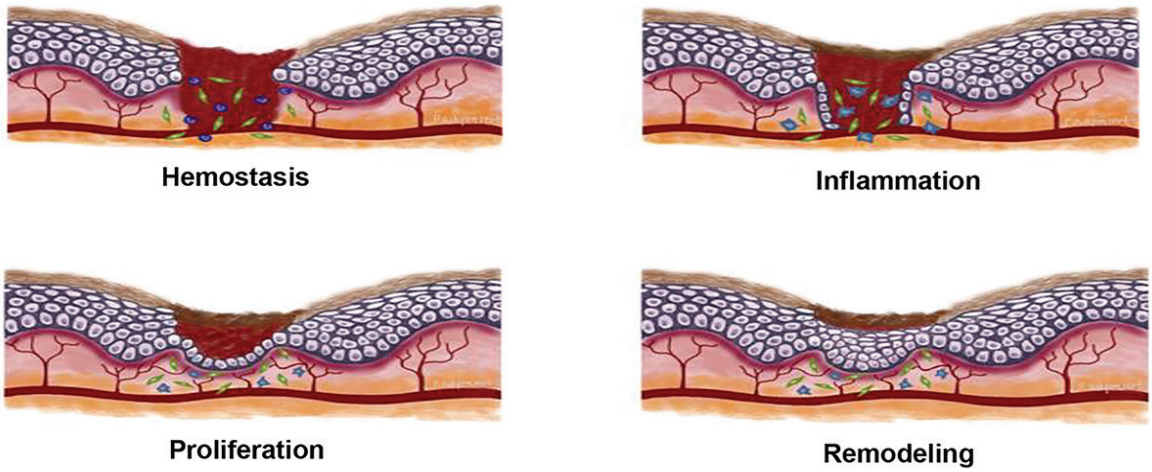
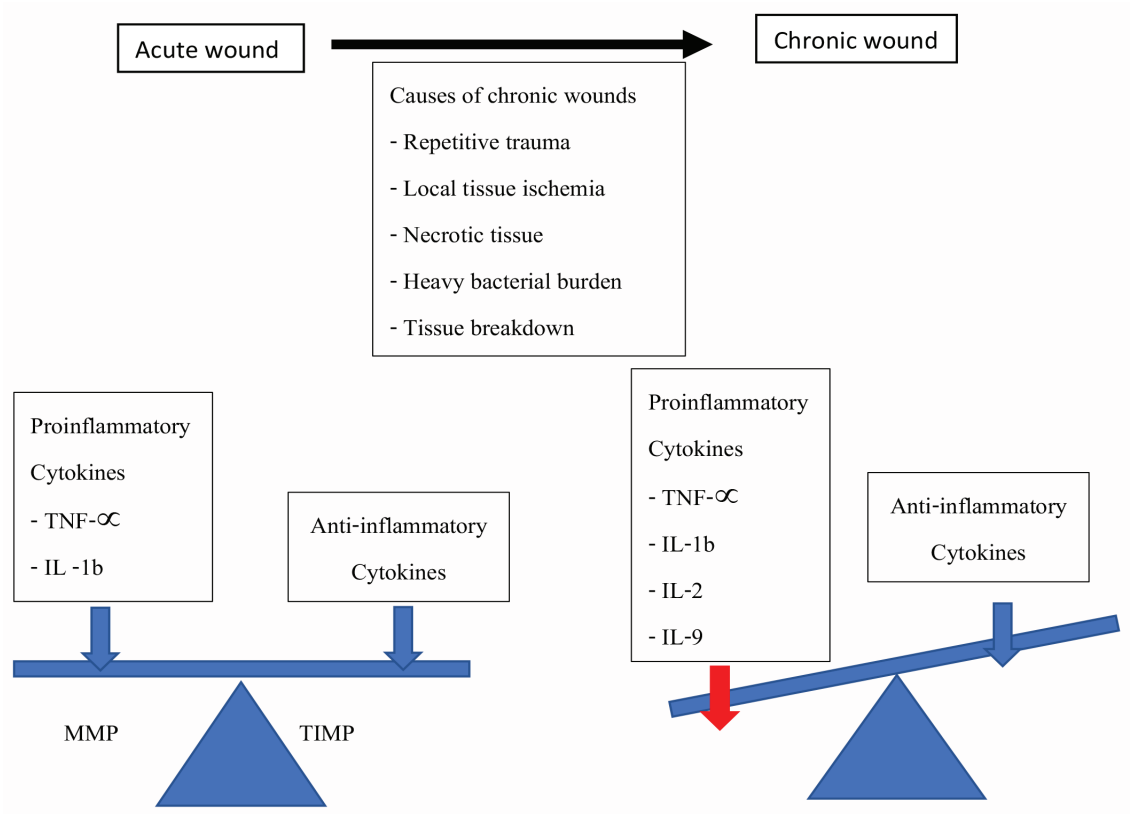


Figure 1 Illustration of the wound-healing process, begining from hemostasis, inflammation, proliferation and remodeling



MMP=metalloprotease enzyme, TIMP=tissue inhibitor of metalloprotease enzyme

Figure 2 Pathophysiology of hard-to-heal wounds

1. Local tissue hypoxia

The amount of tissue oxygen is directly related to the blood supply and tissue swelling. The swollen tissue increases the diffusion distance of oxygen from the capillaries to the tissue. When the tissue lacks oxygen, growth factor decreases and the matrix metalloproteinases (MMPs) increase[8–10]. MMPs are important mediators that can prevent the wound-healing process.

2. Bacterial colonization of the wounds

Data from a systematic review and meta-analysis study performed by Malone et al. identified bacteria as the cause of biofilm formation in chronic wounds[11]. Such wound sites are a hiding place for bacteria from the immune system and antibiotics. A high amount of bacteria of more than 10^5 cells/gram and severe bacterial infections, such as Beta-hemolytic streptococci, in combination with immunodeficiency in patients can cause severe wound infection and high mortality[12,13].

3. Repetitive ischemia-reperfusion injury

The reperfusion of oxygenation from ischemia produces reactive oxygen species (ROS), which can combine with nitric oxide (NO) to form peroxynitrate, which is a tissue-destroying agent. Further, the reduced amount of nitrous oxide prevents blood vessels dilating, even in the reperfusion stage (the no-reflow phenomenon), while the free radicals can destroy small blood vessels and tissues (Figure 2).

Table 1 Risk factors for hard-to-heal wounds

Obesity	Diabetes	Cancer
Older age	Arterial disease	Systemic medication
Poor nutrition	Venous disease	Radiation
Genetics	Neuropathy	Psychosocial
Smoking	Chronic inflammation	Patient adherence
Anemia	Lymphatic insufficiency	Patient economic status
Hypoxia	Edema	Demographic factors
Comorbidities	Immune suppression or disease	
Behavioral factors	Immobilization	

Management of chronic wound

When a hard-to-heal wound is identified by the criteria presented above, a systematic assessment of the patient's conditions, especially an accurate diagnosis of the underlying disease should be taken care of. Management of a patient with chronic wounds should be holistic care that involves not only the wound but an effective control of his/her underlying conditions. In general, a wound that does not decrease its size by 40–50% after adequate wound care, has persisting exudate, increased area of devitalized tissue, increasing pain, or has a new onset of pain should be referred to a specialized wound clinic.

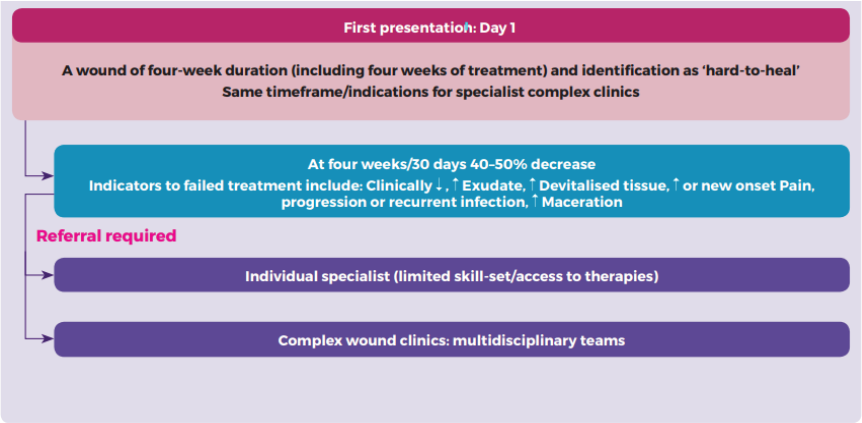


Figure 3 Timeline and indications for treatment and referral[1]

Table 2 TIMERS framework for wound bed preparation

TIME acronym (later modified to TIMERS)	Term proposed by the EWMA advisory board
T=Tissue, nonviable or deficient	Tissue management
I=Infection or inflammation	Inflammation and infection control
M=Moisture imbalance	Moisture balance
E=Edge of wound, non-advancing or undermined	Epithelial (edge) advancement
R=Repair and regeneration	Regenerative therapy: growth factors, oxygen therapy
S=Social and patient-related	Psychosocial factors

EWMA=the European wound management association

Wound care

The principles of chronic wound care comprise three main parts: wound bed preparation, wound cleansing, and wound dressing[5].

1. Wound bed preparation.

For preparation of the wound surface for faster healing, in 2003 Schultz et al.[14] first described the concept of wound bed preparation using the principles of TIME, which considers tissue debridement, infection or inflammation, moisture balance, and the edge effect. Later, the European Wound Management Association (EWMA) modified and expanded the definition of TIME more clearly until it is now accepted and applied as a guideline for the care of patients with chronic wounds and other wounds. In 2018, the International Consensus Document modified the principles to TIMERS by adding two new categories: r for regeneration and repair; and s for social factors, which includes patient factors that may impact healing, as shown in Table 2[5].

Further explanation of TIMERS

T (Tissue management): Debridement is very important in chronic wound care and is performed to devitalize the tissue or necrotic tissue or slough from the wound bed, because these narcotic tissues will disrupt the wound-healing process. James et al. (2013) reported on 154,664 patients with 312,744 chronic ulcers, and revealed that a debridement interval of less than 1 week resulted in significantly faster wound healing compared to an interval time of 1–2 weeks or more, HR 4.26 (95% confidence interval (CI), 4.20–4.31) and an overall healing rate of up to 70.8%[15].

Method of wound debridement

The two common debridement options are:

1. Surgical and sharp debridement: This involves cutting the necrotic tissues with a knife or scissors and is the fastest and most efficient debridement treatment that yields good outcomes.

2. Mechanical debridement: This involves eliminating necrotic tissue using mechanical force. This method is quick and easy, but has the potential to damage healthy tissue underneath and can cause the patient terrible pain. Some examples of mechanical debridement include:

• Hydro-surgery/ hydro-dissection, in which water pressure is used to debride necrotic tissue from the wound. This method can help to minimize the destruction of good viable tissues4.

• Ultrasonic debridement, in which acoustic waves are used in combination with saline to debride nonviable tissues and debris. Common methods include ultrasonic-assisted wound debridement (Soring) and non-contact ultrasound (MIST)[5].

I (Inflammation and infection control):

Bacteria can often be found living in chronic wounds, and their effects will have different levels of severity depending on the amount of bacteria present in the chronic wounds, which can be divided into four types:

1. Wound contamination: Bacteria content is low, with no division and no impact on the wound-healing process; these organisms are usually normal flora.

2. Wound colonization: Bacteria can divide and increase in number, but still do not affect the wound-healing process.

3. Critical colonization (Bacteria burden): Once the amount of bacteria become high enough, the bacteria can affect the wound, destroying tissue and impacting the wound-healing process. This state may be reached with a bacteria culture of more than 10^5 cell/gram tissue.

4. Wound infection: This stage is characterized by a bacteria culture of more than 10^5 cell/gram tissue with signs of local infection or systemic infection.

Signs of chronic wound infection

- Delayed healing (no evidence of improvement within 2 weeks)
- Discoloration of granulation tissue
- Friable granulation tissue that bleeds spontaneously or bleeds with little provocation
- Pocketing at the base of the wound or recessed areas with an absence of granulation tissue
- Foul odor
- Wound breakdown
- An increase in the level of pain

M (Moisture balance — exudate management):

Moisture is important for wound healing and has an effect on epithelial cell migration. Winter discussed the importance of moisture in wound healing and reported that wounds that were closed with a moisturizing dressing healed faster than dry wounds exposed to air[16]. Subsequently, a number of studies have supported the development of new wound dressings that retain moisture in the wound. However, if the wound is too wet, it will cause skin maceration, making the wound wider or worse and carrying a risk of infection. Therefore, the proper level of hydration is an important factor in wound healing.

E (Epithelial or edge advancement):

The basic principle of wound healing is epithelization from the bottom of the wound to the top and from the edge of the wound to the inside. Therefore, if the wound edge has a barrier, epithelization requires debridement until well-granulated tissue is revealed.

R (Repair and regeneration):

The focus here is encouraging wound closure by providing a matrix to support cell infiltration and activity using growth factors or oxygen therapy, including nitric oxide, hyperbaric oxygen therapy (HBOT), growth factors, bioengineered technologies, stem cells, sucrose octasulfate, tissue equivalents, placental-based grafts, negative pressure wound therapy (NPWT), and ECM-based technologies.

S (Social and patient-related factors):

This element focuses on the social situation and patient-related factors that can affect the treatment adherence, the physical and comorbidity factors, and extrinsic factors, such as the patient's economic situation. These highlight that if the patients understand and agree to their care plans, they are more likely to adhere to them, and this can lead to a better outcome of the wound management.

2. Wound cleansing

The best wound cleaner is normal saline because it is safe and does not damage good tissue, whereas other antiseptic wound dressings, such as hydrogen peroxide, iodine, and chlorhexidine, are all toxic and have a tissue-destroying effect. Therefore, the Wound Care Guideline 2018 does not recommend the use of antiseptic agents in wound dressings unless necessary.

3. Wound dressing

The main characteristic of an ideal dressing is that it must be able to maintain moisture in the wound. At the same time, it must be able to absorb excess wound exudate, eliminate bacteria, and protect the wound from

external injuries. At present, there are many types of wound dressings with different properties, with some of the key types listed below.

3.1 Gauzes. These are a basic dressing material, and commonly take two forms: woven gauzes, which are usually made from sheets of cotton fabric, and non-woven gauzes, which are made from synthetic fibers and which have the ability to absorb exudate better than the woven gauze. Moistened gauzes have historically been used for dressing wounds, and used to be called "wet to dry dressing". The Wound Healing Society (WHS) currently does not recommend this wound dressing because it can cause reinjury to tissue and also causes non-selective mechanical debridement, which also removes the healthy tissue of the wound[17].

3.2 Hydrogels. These are ideal dressings for very dry necrotic wounds (Eschar, arterial ulcers, dry venous ulcers) and consist of a water-based complex polymer with greater than 80–90% cross-linking, and which releases water molecules to the wound, thereby moisturizing the dry wound, while also promoting the formation of tissue (granulation tissue) and the epidermis layer. It can also stimulates autolytic debridement, but is not suitable for gangrenous tissue that is at risk of infection. Due to the ability to absorb exudate being less, it cannot prevent bacteria from passing through the wound bed. There are two forms of hydrogels, namely the sheet form (hydromesh) and gel form, where the gel form requires a secondary dressing to be applied over another layer to prevent the hydrogel coming in to contact with normal skin, which can cause skin deterioration. Some examples of hydrogels are Intrasite and 3M Hydrogel[17,18].

3.3 Hydrocolloids. These consist of an inner layer, in which sodium carboxymethylcellulose gelatin, pectin, and elastomers form a hydrophobic gel. The outer layer is an adhesive bonded to a transparent film (polyurethane) or foam sheet (foam), which acts to prevent bacteria and foreign matter from passing through the wound. The inner layer expands through the absorption of exudate from the wound bed and forms a "gel-like mass" on the wound, providing moisture appropriate to the wound-healing environment. By absorbing more exudate, the bottom of the wound will also have more acidic properties, thus inhibiting the growth of bacteria[17,19] (Figure 4).

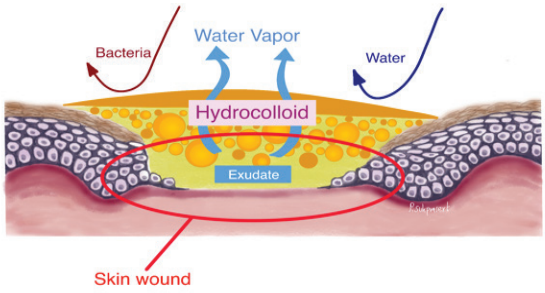


Figure 4 Mechanism of action of hydrocolloids

Hydrocolloids are suitable for wounds with a moderate to large amount of exudate, such as minor burns and pressure ulcers[20], and care should be taken with their use in patients with thin skin, because the adhesive in the patch may cause the skin around the wound to peel off and also cause an overgranulation of the lesion[21]. Contact with the dermatitis has also been reported as an issue[22]. Some example hydrocolloids include Duoderm®, DuoDERM®, Urgotul®, and UrgoStart. Hydrocolloid fibers or Hydrofibers are another form of hydrocolloids, such as Aquacel™ and Versiva™.

3.4 Alginates. These are made from sodium and calcium salts of alginic acid. When applied to a wet wound, a reaction between the calcium salts in the alginate and the sodium from the water in the wound forms calcium sodium alginate, which is a gel-like alginate, with high absorbency but less than hydrocolloids, that is able to absorb exudate 15–20 times its body weight[18]. It is suitable for wounds with high exudate, deep wounds, hollow wounds, such as deep diabetic wounds, and deep pressure ulcers. It should not

be used in dry wounds because this will dry out the wound even more. Some examples include Algisite*, Kaltostat®, Sorbsan®, and Askina® Calgitrol Ag.

3.5 Foams. Foams are suitable for granulating and low exudate wounds. Some examples include Allevyn® Adhesive, and Aquacel™ foam adhesive.

Antimicrobials

Several types of wound dressing have now been developed for use in infected wounds and to prevent infection in wounds with bacterial colonization by including antimicrobials in their composition (Table 3). There are two main types of antimicrobial compounds:

1. Silver compounds. Silver has a board spectrum activity, and can kill Gram-positive and Gram-negative bacteria, including Pseudomonas aeruginosa, MRSA, and VRE. The action of silver is due to the silver ions released from the material, but the wound must have enough moisture to allow the silver molecules to exchange ions and release the positive ions of silver. Therefore, applying a silver patch on a dry wound does not release the silver charge for disinfection[23].

2. Iodine compounds. Iodine has broad spectrum activity against bacteria, fungi, and viruses. However, it has a toxic effect on tissues and is therefore not recommended for long-term direct use. There are two forms of iodine used in dressings, one is povidone-iodine or polyvinylpyrrolidone-iodine complex products, such as Inadine, and the second is Cadexomer iodine products, such as Iodosorb, where Cadexomer iodine absorbs water and then slowly releases the iodine particles (sustained release). Caution should be taken with the use of iodine for long-term chronic wound healing in patients with thyroid disease. Also, because iodine may be absorbed into the bloodstream, its use should be avoided in pregnant or breast-feeding patients, newborns, and patients with a history of allergy to certain foods, such as sea food, or iodine[24].

Table 3 Antimicrobial dressings with formulation compositions of the coatings

Antimicrobial dressing	Formation compositions of the coating
Urgotul SSD	Silver sulfadiazine 3.75%
Bactrigras	Chlorhexidine acetate BP 0.5%
Acticoat	Nanocrystaline silver 105 mg/100 cm^2
Aqualcell Ag	Silver 141 mg/100 cm^2
Askina calgitol Ag	Silver 8.3 mg/100 cm^2
Iodosorb	Cardexomer containing 0.9% iodine
Inadine	10% povidone iodine (1.0% iodine)

SSD=silver sulphadiazine; BP=British Pharmacopoeia

Specific management in chronic wounds

Diabetic foot ulcers (DFUs)

Diabetic ulcers are the most common chronic ulcers, with 15–25% of diabetic patients having chronic ulcer due to diabetes[26], which can be divided into neuropathic causes (50%), ischemic causes (20%), and neuroischemic causes (30%)[27].

In 2007, prompers and colleagues collected data from 1,229 chronic diabetic foot ulcer patients in 14 European hospitals, and found that 52% of diabetic ulcer patients had non-plantar ulcers. The most frequent ulcers were the dorsal or interdigital area of the toes (32%), while 58% of diabetic chronic ulcer patients had sepsis at the first diagnosis[28].

In diagnosing diabetic ulcers, the first thing to do is to rule out arterial disease because these often occur together. In the treatment of diabetic ulcers in patients with chronic arterial insufficiency, the wound may not heal or its progress may worsen. Arterial disease can be screened for by differentiation using ABI index >0.9, which would indicate that arterial insufficiency is unlikely to be present. However, care must be taken for elderly patients with atherosclerosis, which makes the ABI index higher than reality and can lead to misinterpretation.

The European Wound Management Association (EWMA) has established principles for the care of diabetic foot ulcers as follows:

1. Restoration/maintenance of pulsatile blood flow (local wound care)

The gold standard is regular sharp debridement to remove unhealthy components. Each debridement progresses from chronic wounds to acute wounds[29] and enhances the wound-healing process.

2. Infection control and bacterial management

The use of normal sterile saline (NSS) is recommended for cleaning wounds. In case of infection, the use of three antimicrobials types of dressings is recommended:

- Iodine: effective in killing a wide spectrum of organisms without affecting the healing process[4].
- Silver compounds: silver sulfadiazine kills Staphylococcus aureus, MRSA, and pseudomonas species.
- Mupirocin: Gram-positive infections and MRSA should be used for no more than 10 days.

However, a 2017 Cochrane review by Dumville et al. reported that, in 2,310 patients with diabetic ulcers, there was no conclusive evidence that antimicrobial types were the most suitable for chronic diabetic ulcers[30].

In terms of negative wound pressure therapy, vacuum-assisted wound closure (VAC) is also recommended for the wound dressing of diabetic wounds using a polyurethane foam sponge with a pore size of 400–600 microns in combination with an evacuation tube placed into the body of the sponge to create an equal vacuum throughout the wound. This is a method for transitioning from an open wound to a temporary closed environment. The suction force generates a negative pressure of 50–175 mmHg. The mode of negative pressure wound therapy can use either continuous or intermittent suction.

A 2012 systematic review conducted by Dumville et al. included several studies comparing the efficacy of different materials in the treatment of diabetic wounds, and found that The use of a hydrocolloid-matrix has a healing rate of 70% higher than other wound dressing materials, followed by foams and hydrogels, with healing rates of 52% and 40%, respectively[31].

A systematic review was also performed by Huang et al. in 2015, referring to the use of hyperbaric oxygen therapy (HBO2) in patients with chronic diabetic ulcers. In summary, hyperbaric oxygen therapy was recommended in chronic diabetic ulcers patient with a Wagner Grade >3, and was recommended as a post-operative hyperbaric oxygen therapy in patients with a DFU Wagner Grade >3 undergoing surgical debridement of an infected foot (partial toe or ray amputation; debridement of an ulcer with underlying bursa, cicatrix, or bone; foot amputation; incision and drainage [I&D] of a deep space abscess; or necrotizing soft tissue infection), which can reduce the risk of major amputation and incomplete healing (moderate level evidence, conditional recommendation)[32].

3. Pressure control

Off loading and weight redistribution can be performed to change the load-bearing point of the foot to prevent ulcers and to keep a previous wound from getting worse[33].

4. Metabolic control and blood glucose control

In patients who have HbA1C levels ≥8% and fasting glucose levels ≥126 mg/dl, the rate of limb amputation is high[34].

Pressure injuries

Pressure ulcers are the most common chronic ulcers after diabetic ulcers, and refer to a wound that occurs on the skin and/or subcutaneous tissue, especially above a prominent bone. The wound is caused by repeated pressure and skin loads over a long period of time (Figure 5)[35]. Pressure ulcer grades are classified to reflect the level of tissue damage, referring to the NPIAP Classification (National Pressure Injury Advisory Panel) 2016, divided into four levels and two special levels as shown in Figure 6[36].

For the treatment of pressure ulcers, the same principles apply as for other types of chronic wounds:

- Local treatment is local debridement with the aim of promoting blood flow to the wound bed and reducing inflammation, or flap coverage if indicated[36].

- Nutrition support: NPIAP recommends protein intake of 1.25–1.5 gm/kg/day, Calories 30–35 kCal/kg/day[36].
- Spasticity management in pressure injury patients.
- Psychological factors: 47.4% of patients with pressure injury have major depression and so psychological care can play a significant role in predicting pressure injury recurrence[36].
- Specific treatment is to avoid the pressure position. This is usually the area of bony prominence[36].
- Prevention: risk assessment, skin care, and control of incontinence[36].

Venous leg ulcers

Chronic venous disease is the most important risk factor for a venous leg ulcer. The classification system for chronic venous disorder is CEAP, which refers to clinical, etiological, anatomical, and pathophysiological[37,38]. Chronic venous disease can lead to increased intravenous pressure in the deep, superficial, and perforator system, venous valve insufficiency, or muscle pump deficiency, reducing the venous return to the heart and leading to blood pooling in the lower limbs, The pooling of blood stimulates chronic inflammation, which damages skin to form a venous leg ulcer (VLU). In venous leg ulcers, a wound is considered hard to heal, when it has a reduction rate of <40% over four weeks[7].

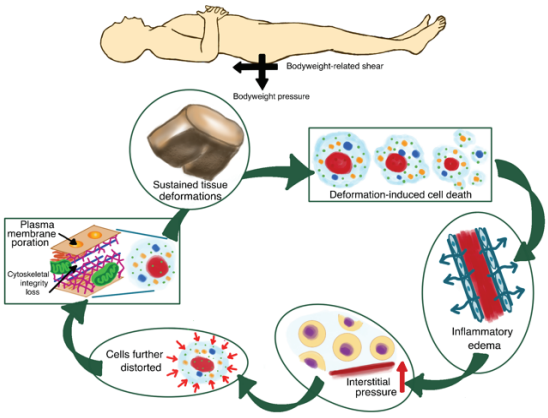


Figure 5 Mechanism of pressure injury[35]

The effective management of VLU includes external compression and venous intervention[7] (Table 4). In addition, a study on medical treatment for VLUs stated that simvastatin can be vasoactive and reduces inflammation. A 2014 study by Evangelista et al. found that the use of simvastatin 40 mg daily for 10 weeks had a significantly higher effect on wound healing than in the placebo group[38,39].

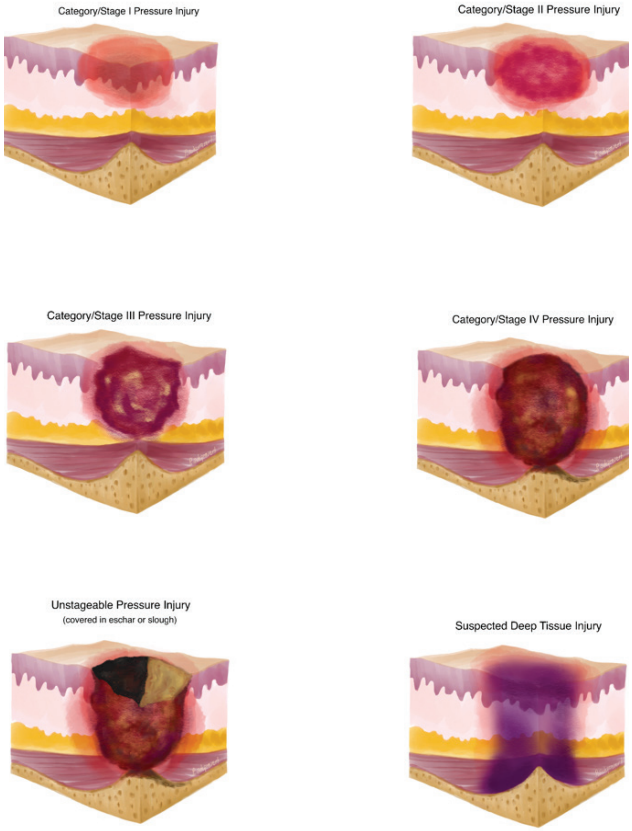


Figure 6 NPIAP 2016 classification of pressure injuries[36]

Table 4 Management of venous leg ulcers

Treatment	Comments
Compression	After vascular evaluation, compression 30–40 mmHg (Contraindication id ABI <0.6)
Elevation	Elevation above the level of the heart at rest
Exercise	Walking activates calf muscle pump
Wound care	TIMERS principles

ABI=ankle brachial blood pressure index

CONCLUSION

Chronic wounds are a common condition. It is important to perform wound dressing to promote the wound-healing process. At present, new wound dressings are being developed and are becoming more diversified. Each type has different properties. A good wound dressing must be able to maintain an appropriate level of moisture for the wound, while at the same time absorbing excessive lymph and serum from the wound. Also, it must also not cause injury to the wound during wound healing.

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