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GUIDELINE

Wound, pressure ulcer and burn guidelines – 1: Guidelines for wounds in general, second edition

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ABSTRACT

The Japanese Dermatological Association prepared the clinical guidelines for the "Wound, pressure ulcer and burn guidelines", second edition, focusing on treatments. Among them, "Guidelines for wounds in general" is intended to provide the knowledge necessary to heal wounds, without focusing on particular disorders. It informs the basic principles of wound treatment, before explanations are provided in individual chapters of the guidelines. We updated all sections by collecting references published since the publication of the first edition. In particular, we included new wound dressings and topical medications. Additionally, we added "Question 6: How should wound-related pain be considered, and what should be done to control it?" as a new section addressing wound pain, which was not included in the first edition.

Key words: **burn, guideline, pressure ulcer, therapy, wound.**

1) BACKGROUND TO THE DRAFTING OF THE "GUIDELINES FOR WOUNDS IN GENERAL"

Guidelines are documents systematically prepared to help medical experts and patients make appropriate judgments in specific clinical situations. The Japanese Dermatological Association decided to draft the "Wound, pressure ulcer and burn guidelines" focusing on treatments, catering to needs for clinical practice. Among them, "Guidelines for wounds in general" is intended to provide the knowledge necessary to heal wounds, without focusing on particular disorders. It informs the basic principles of wound treatment, before explanations are provided in individual chapters of "Wound, pressure ulcer and burn guidelines". In doing so, the guideline aims to improve the general quality of treatment of wounds. Its contents cover the entire course of wound healing, from the initial stages to recovery. As most of the wounds treated in dermatological clinics are intractable chronic skin wounds, the present guidelines deal with chronic skin wounds (except in the chapter on burns). When treating chronic skin wounds, the therapeutic principles differ for shallow wounds and for deep wounds with necrotic tissue or infected granulation tissue attached. Therefore, in "Guidelines for wounds in general", skin wound treatments are discussed by categorizing chronic skin wounds into shallow ones restricted to the upper dermal layers and deep ones that extend further.

2) STATUS OF "GUIDELINES FOR WOUNDS IN GENERAL"

The Wound/Burn Guideline Drafting Committee (Table 1) is composed of members delegated by the Board of Directors of the Japanese Dermatological Association. The Committee has met and issued written deliberations several times since October 2008, and it has now drafted a commentary on wounds in general and five treatment guidelines by taking into consideration the opinions of the Scientific Committee, the Guidelines Committee and the Board of Directors of the Japanese Dermatological Association. The discussion of wounds in general offered in this chapter reflects the current standards of diagnosis and treatment in Japan. However, patients have varied backgrounds, including different underlying diseases, severity of symptoms and complications. Therefore, physicians who perform diagnoses and treatments should determine an approach to prevention, care and treatment together with their patients, and their decisions are not required to be in complete agreement with the present guidelines. Moreover, these guidelines cannot be cited as references in lawsuits or other disputes.

3) MAIN CHANGES TO THE SECOND EDITION

We updated all sections by collecting references published since the publication of the first edition. In particular, we included new wound dressings and topical medications that have been introduced to the market since then. Furthermore, we added "Question 6: How should wound-related pain be considered, and what should be done to control it?" as a new section addressing wound pain, which was not included in the 1st edition.

4) SPONSORS AND CONFLICTS OF INTEREST

All expenses involved in drafting the "Wound, pressure ulcer and burn guidelines" were borne by the Japanese Dermatological Association. No aid was provided by specific organizations, enterprises or pharmaceutical companies. In the event that a Committee member (Table 1) participating in the drafting of these guidelines was involved in the development of a specific, relevant drug, that member abstained from determining to what degree the item in question was recommended. Aside from that, no Committee member has any conflict of interest relevant to the drafting of these guidelines to disclose.

5) REVIEW BEFORE PUBLICATION

Prior to the publication of these guidelines, the Annual Meetings of the Japanese Dermatological Association from 2012 to 2015 were used to present the Committee's annual drafting progress, to solicit opinions from association members and to make necessary revisions.

Table 1. Wound/Burn Guideline Drafting Committee (the head of each section is bold)

Chairperson: Hironobu IHN	
Vice-chairperson: Takao TACHIBANA	
Wounds in General	**Yuji INOUE**
	Sakae KANEKO
	Hiroyuki KANOH
	Yoichi SHINTANI
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6) PLANS FOR UPDATES

The present guidelines are scheduled to be updated in 3–5 years. If a partial update becomes necessary, it will be presented on the website of the Japanese Dermatological Association, as appropriate.

7) DEFINITIONS OF TERMS

The terms used in the present guidelines are defined as indicated below, based on descriptions from Japanese reviews and textbooks. Additionally, portions are quoted from the terminology list of the Terminology Committee of the Japanese Society of Pressure Ulcers (Committee Chairman, Takao Tachibana), and internal consistency of these guidelines was taken into consideration.

"Wound bed preparation": Management of the wound surface environment to promote wound healing. Specifically, this consists of removing necrotic tissue, reducing the bacterial load, preventing wound drying, controlling excessive exudates, and treating and undermining wound margins.

"TIME": Practical principles for wound bed preparation based on an evaluation of the factors preventing wound healing from the viewpoints of tissue (T), infection/inflammation (I), moisture (M) and wound edge (E); and use of the results for treatment and care.

"Granulation tissue": Tissue newly formed by the repair/inflammation response to tissue damage. Grossly, it is a reddish, soft tissue consisting of newly formed blood vessels, connective tissue, fibroblasts and inflammatory cells.

"Epithelialization": When areas of lost skin or mucosa are once again covered by epithelium, namely by epidermis or mucosal epithelium, during the healing process. In the skin, the epidermis regenerates from the epidermis or from the appendages of the skin around the defect (healing by regeneration). However, when there is a deep loss of skin with no residual appendages, the epidermis extends from the peripheries once the wound surface has been replaced by granulation tissue (cicatricial healing).

"Moist wound healing": A method to maintain the wound surface in a moist environment. Such an environment retains polynuclear leukocytes, macrophages, enzymes and cell growth factors from the exudates on the wound surface. It also promotes autolysis, contributes to debridement and does not interfere with cell migration.

"Cytokines": Small soluble proteins or glycoproteins with a molecular weight of 30 kD or lower that are produced and released by cells. Humoral factors that regulate physiological functions of the body such as inflammation, the immune response and cell proliferation by binding to receptors on the surface of target cells and controlling their differentiation, proliferation and activation are collectively called cytokines.

"Growth factors": Factors that promote cell proliferation and differentiation are collectively called growth factors. Most are peptides, and they usually act at the site of their production through a paracrine (acting on neighboring cells) or autocrine (acting on the cells that produced them) mechanism. Fibroblast growth factor (FGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF)-α/-β and hepatocyte growth factor are typical growth factors.

"Lavage": The removal of chemical stimulants, sources of infection and foreign bodies from the skin or wound surface

using the hydraulic pressure or lysing effect of a liquid. Lavage may be performed using physiological saline, tap water, or a mixture of saline or tap water and a surfactant such as soap or detergent, a method that can be referred to as "lavage with soap". The lavage effect may derive from the flow volume or from the hydraulic pressure.

"Debridement": The therapeutic action of cleaning a wound by removing necrotic tissue and aged cells that have ceased to respond to stimulation by promoters of wound healing such as growth factors, as well as foreign bodies and foci of bacterial infections, which are frequently associated with necrotic tissue. Debridement methods include: (i) autolytic debridement induced by occlusive dressing; (ii) mechanical debridement (e.g. wet-to-dry dressing, high-pressure lavage, hydrotherapy, ultrasonic lavage); (iii) debridement using proteases; (iv) surgical debridement; and (v) biological debridement using maggots.

"Wet-to-wet dressing (wet gauze dressing with saline)": The dressing method of applying gauze moistened with physiological saline onto a wound to maintain a moist environment.

"Exudates": The interstitial fluid that seeps out from wounds where the epithelium has been lost. It is rich in protein and contains various inflammatory cells, cytokines and growth factors involved in wound healing.

"Topical agents": Drugs used for localized treatment through the skin or by direct application to a skin lesion, prepared by compounding various active agents with a base.

"Dressing materials": Modern wound dressing materials used to create a moist environment for wounds. Conventional sterilized gauze is excluded.

"Wound dressing materials": Wound dressing materials can be classified into dressing materials (modern dressing materials) and medical materials such as gauze (classic dressing materials). The former are medical materials designed to provide an optimal environment for wound healing by maintaining a moist environment. They must be used selectively according to the state of the wound and the volume of exudates. The latter (classic dressing materials) allow the wound to dry, and they cannot maintain a moist environment if the volume of exudates is low. Other medical materials (aside from conventional gauze) that provide an optimal environment for wound healing by covering the wound and maintaining a moist environment may also be called wound dressing materials or dressing materials.

"Occlusive dressing": All covering methods that aim to achieve moist wound healing by preventing wound drying are classified as occlusive dressing. This is a collective term for dressings that use modern wound dressing materials other than conventional gauze.

"Surgical therapy": Surgical treatments, surgical debridement and open treatments of subcutaneous pockets.

"Negative-pressure occlusive wound therapy": A variation of physical therapy. The wound is maintained in a closed environment, and suction is applied to result in negative pressure by 125–150 mmHg, in principle. This procedure directly eliminates bacteria and the exotoxins released by them, promotes angiogenesis in granulation tissue and eliminates edema.

"Pocket wound": Cavities larger than a skin defect are called pocket wounds. The wall covering an undermined area is called the cover wall or lid.

"Lavage pressure": The pressure applied to remove exudates or residual matter from a wound surface. It is expressed in psi.

"Contamination": A state in which bacteria that do not divide or proliferate are present at the surface of an ulcer.

"Colonization": A state in which bacteria that divide and proliferate are present at the surface of an ulcer. The host's immune capacity and the proliferative capacity of the bacteria are balanced.

"Infection": A state in which bacteria that divide and proliferate at the surface of an ulcer have further increased, and they interfere with the wound healing as their proliferative capacity exceeds the host's immune capacity.

"Critical colonization": Conventionally, the microbial environment of a wound has been classified into infected and aseptic. However, the current trend is to regard the two conditions as continuous (a concept called "bacterial balance"). In other words, wound infection is understood as continuous stages of contamination, colonization and infection. Infection is considered to depend on the balance between the bacterial burden on the wound and the host's resistance. Critical colonization is the stage between colonization and infection; at that stage, the bacteria count has increased beyond the balanced state during colonization, and has started to shift towards infection.

"Ulcer": A loss of cutaneous or mucosal tissue extending beyond the basement membrane (dermoepidermal junction, mucosa). Usually heals leaving a scar.

"Erosion": A loss of cutaneous or mucosal tissue not extending beyond the basement membrane (dermoepidermal junction, mucosa). Usually heals without leaving a scar.

"Pressure ulcer": The application of external force to the body reduces or blocks the blood flow in the soft tissues between the bone and the surface layer of the skin. If this condition persists for a certain amount of time, the tissue sustains irreversible ischemic damage, and a pressure ulcer is formed.

"Maceration": A state in which tissue, particularly the stratum corneum, has absorbed a large amount of water, and has become whitish and swollen. This reduces the barrier function of the skin, and erosion and infection are likely to occur. This is frequently observed at the margins of pressure ulcers.

"Crust": A hard structure formed by the drying of serum, pus and necrotic tissue. Dried and hardened blood is called "blood crust". Crusts are often formed by the drying of the wound surface in skin defects.

8) QUESTIONS AND ANSWERS

Question 1: How should an environment appropriate for the healing of chronic skin wounds be prepared?

Answer: It is important to perform wound bed preparation by removing the factors that inhibit wound healing, and to

apply moist wound healing, which maintains a moist environment at the wound surface, to promote wound healing. Initially, effort should be put into wound bed preparation by eliminating necrotic material, to control excessive exudates and to prevent wound drying by maintaining a moist environment. The TIME concept[1] is advocated as a method to evaluate this. However, the maintenance of a moist environment may delay the healing of contaminated wounds complicated by bacterial or fungal infections. Therefore, it is important to perform tests, including wound observation and the bacterial culture of samples from the wound. Ideally, moist wound healing should be applied throughout the course of the healing process.

Commentary

1. Acute and chronic skin wounds

Before the discovery of antibiotics, bacterial infection of wounds often induced sepsis and resulted in severe outcomes. Therefore, long-standing infection control was the most important part of wound healing, and that wounds should therefore be disinfected and dried. As a result, wound dressing with sterilized gauze was widely practiced. In recent years, however, the idea that gauze dressing allows the wound surface to dry and is likely to damage the granulation tissue and the regenerated epithelium during gauze changes, delaying wound healing, has become prevalent in Japan as well. As a result, moist wound healing is increasingly advocated.[2,3]

Skin wounds are classified into acute and chronic wounds. In acute skin wounds, the wound healing mechanism functions normally, just as in fresh trauma and surgical wounds. In chronic skin wounds, however, certain causes are preventing the wound healing mechanism from functioning normally.[4,5] Causes of delayed chronic skin wound healing are broadly divided into systemic factors, such as underlying diseases, and local factors (Fig. 1).

For chronic skin wounds, the healing process is divided into three phases: the inflammation phase, the proliferation phase and the maturation phase (Fig. 2).[6,7] As cells, cytokines and growth factors, which all play primary roles in wound healing, vary by phase,[8] it is important to prepare an appropriate wound healing environment for each phase.[9,10]

In the inflammation phase, the invasion of pathogenic agents is prevented through infiltration by neutrophils and macrophages, and foreign material is removed. If the wound is excessively washed or disinfected in this phase, the cells that have infiltrated are washed off, and the cells themselves are damaged. For smoother inflammatory cell infiltration, a clean and moist environment should be maintained, as animal experiments have suggested that this can suppress cicatrization.[11] However, as excessive inflammation delays the wound healing, a poultice with a cooling effect or a wet-to-wet dressing (saline gauze dressing) may be selected in this phase, depending on the condition of the wound.

In the cell proliferation phase, blood vessels and extracellular matrix are formed, and granulation occurs. As various cytokines are introduced in this phase, a moist environment should be maintained over the wound surface to promote cell proliferation. If necrotic material is attached to the wound at that time, it can become a hotbed of bacterial infection and prevent the maturation of the extracellular matrix. Therefore, aggressive debridement or lavage to remove necrotic tissue may be needed.

The maturation/reconstruction phase is primarily marked by the maturation of the extracellular matrix and the regeneration/migration of epidermal cells. A moist environment should be maintained at the wound surface while controlling for infection. In this phase, gauze or dressing materials should be changed carefully, as frequent changes may damage the regenerated/migrated epidermal cells.

Wounds caused by pressure (pressure ulcers) present tissue damage caused by ischemia–reperfusion in addition to the above-mentioned processes. Ischemia–reperfusion injuries refer to the idea that the reperfusion of blood to the ischemic tissues generates free radicals (which are tissue-damaging factors) as well as an increase in inflammatory cytokines, causing neutrophil and macrophage infiltration and exacerbated inflammation and tissue damage.[12,13]

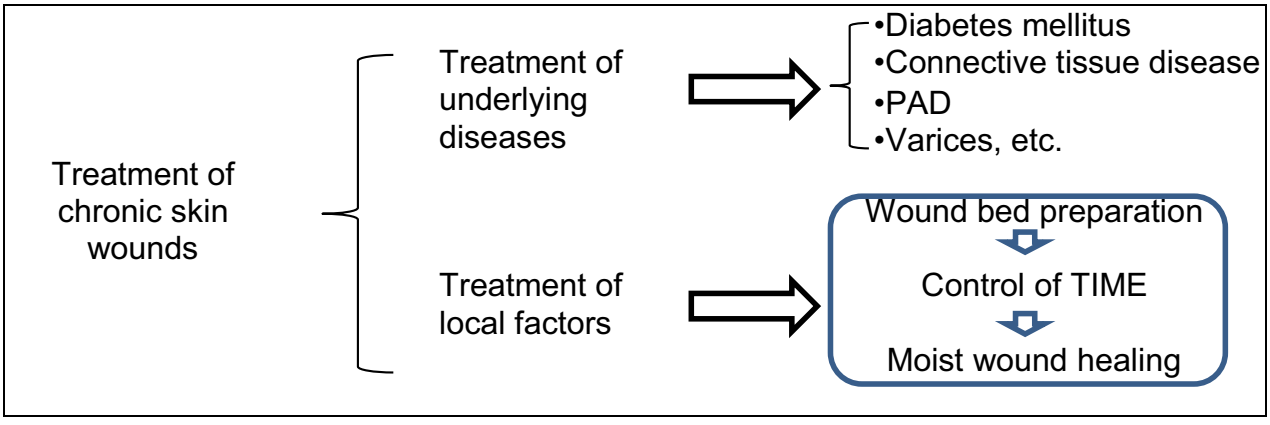
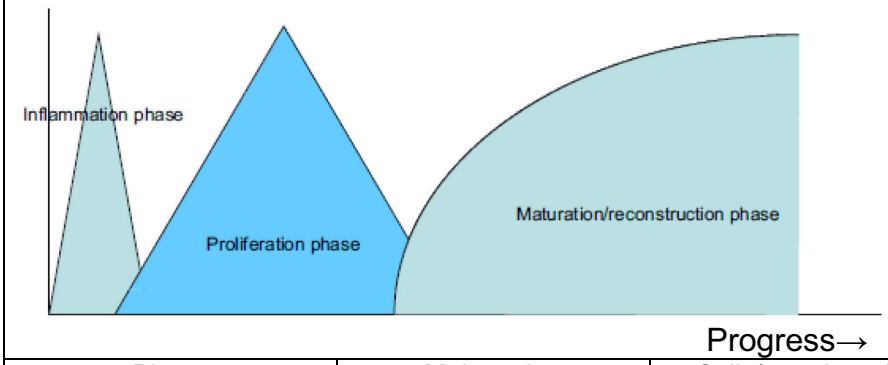


Figure 1. Treatment plan for chronic skin wounds. PAD, peripheral arterial disease.



Phase	Main action	Cells/proteins with primary roles	Cytokines
Inflammation phase	Inflammatory cell infiltration	Platelets, collagen, vascular endothelial cells, neutrophils, macrophages	TGF-α, EGF, PDGF, IL-1, TNF-α, TGF-β, FGF
Proliferation phase	Granulation	Vascular endothelial cells, fibroblasts, keratinocytes	EGF, TGF-β, PDGF, IL-1, TNF-α, IL-2, IL-6, FGF, VEGF
Maturation/reconstruction phase	Wound contraction and epithelialization	Collagen, fibroblasts, keratinocytes	TGF-α, β, PDGF, IL-1, EGF

TGF-α: Transforming growth factor- α, EGF: Epidermal growth factor, PDGF: Platelet-derived growth factor, IL-1: Interleukin-1, TNF-α: Tumor necrosis factor-α, TGF-β: Transforming growth factor-β, FGF: Fibroblast growth factor, IL-2: Interleukin-2, IL-6: Interleukin-6, VEGF: Vascular endothelial growth factor

Figure 2. Parameters associated with the healing process of chronic skin wounds.

2. Treatment of shallow chronic skin wounds

In wound bed preparation for shallow chronic skin wounds with a depth down to the upper dermal layer, it is important to create an environment that promotes the regeneration/migration of epidermal cells. As bacterial infection is controlled and there is no necrotic material attached to the wound, disinfection or excessive lavage should be avoided, and a moist environment should be maintained. This is because in wound healing, a moist environment is more advantageous for epidermal cell growth and angiogenesis,[14–17] and for the control of pain,[18] than a dry environment.

Methods to maintain a moist wound environment include: (i) poultices; (ii) wet-to-wet dressings; (iii) the application of oleaginous ointments; and (iv) occlusive dressings. Among these, (i) and (ii) are useful for controlling wounds in the inflammation phase, as they are effective in cooling the wound and for debridement of necrotic tissues and exudates, as well as to maintain a moist environment. However, they are laborious procedures, and are also impractical for the treatment of large wounds and wounds that require a long healing time. Moreover, while they are effective for wound dressing in the inflammation phase due to their cooling effect, it has been reported that warming promotes wound healing in the proliferation and maturation/reconstruction phases,[19] while cooling may cause a delay. Poultice and wet-to-wet dressing should be used for a limited time on surgical wounds and wounds complicated by infection.

The maintenance of a moist environment with (iii) the application of oleaginous ointments is useful for the treatment of shallow skin wounds, as it keeps the skin moist with periodic mechanical debridement.[20] However, the use of a topical agent is associated with the risk of contact dermatitis and has the negative effect of simultaneously removing cells and exudates useful in wound healing from the wound surface. See Question 4 for information about specific topical medications.

A number of reports[21,22] have confirmed that (iv) occlusive dressing promotes wound healing, and various materials are now in clinical use.[23,24] As long as the appropriate dressing material can be selected for wound bed preparation and moist wound healing, it will promote wound healing. However, a systematic review reported that no clear wound healing promoting effect was confirmed for dressing materials other than hydrocolloids.[25] Among the effects of moist wound healing, the promotion of re-epithelialization of donor sites for split-thickness skin grafts[14] and epithelialization of second-degree burns that do not require surgery has been the subject of attention.[26] However, there have been some recent reports of their effectiveness in promoting epithelization of deep wounds accompanied by bone exposure[27] and after laser irradiation.[28] Occlusive dressings are also recommended from the viewpoint of

medical cost reduction.[29] Covering methods that involve the application of non-medical film materials to wounds have been reported to be both efficacious and economical.[30] However, the use of these materials on wounds is a deviation from their intended purposes. As such, it requires caution.[31]

3. Treatment of deep chronic skin wounds

For the treatment of deep chronic skin wounds with infections or attached necrotic materials, the primary concerns should be the debridement of the necrotic tissues and the control of exudates. The TIME concept (Table 2)[1,5,34] was introduced in 2005 as a proposed method to evaluate this. It is important to be diligent in wound bed preparation while evaluating TIME.

(i) Removal of necrotic tissues. Necrotic material not only interferes with epithelialization, but it is also a cause of increased exudates, and it can even become a hotbed of bacterial infection.[32] Therefore, it is necessary to perform debridement as early as possible. Debridement can be achieved by resecting or scraping off necrotic tissues with a scalpel or scissors (surgical debridement), by lysing necrotic tissues with enzyme preparations (chemical debridement) or through other methods. Surgical or chemical debridement should be selected in consideration of the quantity and quality of the necrotic tissues.

In surgical debridement, emergency treatment may become necessary if the patient's general condition exacerbates. Anesthesia may also be required if necrotic tissues are found over a wide area. However, for small chronic skin wounds, debridement that is limited to an area and does not cause bleeding can most often be performed at the bedside, without anesthesia. In surgical debridement, it is important to pay attention to bleeding diathesis and to a history of oral anticoagulant/antiplatelet administration. Guidelines from the Japanese Circulation Society suggest that it is desirable to perform minor surgery while continuing p.o. administration of warfarin or of an antiplatelet agent if the postoperative bleeding is considered manageable.[33] However, as some patients tolerate the suspension of these medications without risks, the decision to continue or discontinue them should be made in consultation with the attending physician and in consideration of the patient's general condition and wound size.

In chemical debridement, necrotic material is lysed with an enzyme-containing ointment or the like. It takes a longer time than surgical debridement but is advantageous in that it involves a lower risk of hemorrhage and is less painful. Necrotic tissues lyse spontaneously when a moist environment is maintained around the wound and an oleaginous ointment or dressing material is used. However, in such cases, sufficient attention to exacerbation of bacterial infections is necessary, and the latter must be controlled using antibiotics. Moreover, debridement can be performed more smoothly by layering an enzyme preparation and an oleaginous ointment. Specific preparations are described in a separate section (Question 4).

In chronic skin wounds with infected/necrotic tissues, the necrotic material cannot be removed entirely in a single surgical debridement. It can be removed more safely and efficiently by performing surgical debridement in several stages and in combination with chemical debridement, while considering the impact on the patient.

(ii) Control of exudates. In a dry environment, epithelialization is prevented, as necrotic material adheres to the wound surface (thus preventing the migration of epidermal cells) and epidermal cells themselves necrotize from drying. Also, exudates contain large amounts of not only various cells including vascular endothelial cells and blood cells, but also of growth factors and cytokines, and so are useful for wound regeneration.[35]

In a moist environment, on the other hand, granulation occurs in the dermal area. providing conditions favorable for the formation of scaffolds for keratinocyte migration. However, excessive exudates inhibit wound healing by causing edema in the underlying tissues and by promoting bacterial infection.[36,39] Opportunities for bacterial infection are known to be reduced by appropriate treatments,[37,38] and exudates must be controlled to an appropriate level to promote wound healing. In maintaining a moist environment, sufficient attention must be paid to the infection complications.

In addition, caution is needed, as any maceration of the wound periphery caused by excessive moisture delays epithelialization. Negative pressure therapy is an example of a method for controlling exudates. The wound margins are drawn together using negative pressure, which promotes

Table 2. TIME concept

TIME	WBP evaluation item	Treatment	Specific manipulation
Tissue non-viable or deficient	Necrotic tissue/inactive tissue	Debridement	Five kinds of debridement (autolytic, surgical, chemical, mechanical, biological)
Infection or inflammation	Infection or inflammation	Remove sources of infection	Local lavage, local/systemic antibiotic administration
Moisture imbalance	Exudate imbalance	Maintain optimal moist environment	Application of appropriate dressing materials, negative pressure occlusive treatment
Edge of wound: non-advancing or undermined epidermal margin	Delayed healing or undermining at wound margins	Debridement, physical treatment	Surgical debridement, negative pressure occlusive dressing

WBP, wound bed preparation. Adapted from references 5 and 34.

granulation, eliminates exudates, reduces swelling, and even has the effects of not only moist wound healing, but also of wound bed preparation.[40]

(iii) Other treatments. The advantage of the concomitant application of external medications to wounds for reasons other than to promote granulation or epithelialization is not clear. Particularly, the use of ointments containing an antibiotic (antibacterial agent) cannot be recommended, because it may allow bacteria to acquire resistance.[41] Recently, treatment with an occlusive dressing after distribution of autologous blood[42] or bone marrow cells[43] over a wound has recently been reported to promote wound healing to some extent. However, this has only been suggested in case reports, and there has been no further investigation. Although animal studies have reported that the addition of finely minced skin to a wound in a moist environment promotes wound healing,[44] further research in this area is needed.

The moist wound healing of wounds caused by arterial blood flow disturbances from diabetes, peripheral arterial diseases (PAD), connective tissue diseases and the like can result in necrotic tissue lysis as well as an enlargement of the wound. Therefore, in some cases, it is preferable to allow these types of wounds to dry, and at times to develop dry gangrene.[45] Excess granulation refers to when the wound surface is proud of the surrounding healthy skin, and this prolongs epithelialization. Excess granulation commonly involves edematous infected granulation tissue, and it can sometimes be reduced by applying adrenocorticosteroid topical medication. Due to the risk of localized infection, these should not be used casually, and they must be discontinued quickly once the wound surface condition has improved.

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Question 2: Is lavage recommended for promoting healing of chronic skin wounds?

Answer: Lavage is recommended for promoting wound healing. First, it is important to evaluate the condition of the wound. The presence of underlying disorders, the stage of wound healing, the depth of the wound, the presence of undermining, the presence of infection and the presence of necrotic tissue need to be ascertained. In lavaging the wound, the use of cytotoxic disinfectants should be avoided. Rather, a sufficient quantity of physiological saline, distilled water or tap water should be used, and the wound surface is required to be treated gently. Depending on the condition of the wound, debridement, increasing the amount of lavage fluid, regulating lavage pressure and warming the lavage fluid to approximate body temperature are recommended.

Commentary

1) Significance of lavage and points of caution

For chronic skin wounds in which some factors are inhibiting the normal wound healing process, lavage is performed to eliminate local causes. [46,47] The removal of foreign substances, contaminants and microorganisms through lavage, which promotes wound healing, leads to wound bed preparation.[48–50] In recent years, observance of the TIME concept (see Question 1) has been proposed for wound bed preparation.[49,51] Improving each TIME element allows the wound healing mechanism to work normally and the wound bed preparation to be achieved. Although lavage is a procedure used for all wounds, it is considered to be particularly important in approaching the "I" (infection/inflammation) of TIME.

When lavaging wounds, it is important to use a sufficient amount of physiological saline, distilled water or tap water to ensure that substances that cause healing delays are properly removed.[52–58] There is no difference in the rate of infection or recovery by type of lavage fluid. The number of bacteria and contamination level can be reduced more effectively with detergents such as soap.[59–61] It has also been reported that the use of a cleanser on the skin surrounding pressure ulcers during lavage reduces the healing time of the wound itself in comparison with the use of physiological saline.[62] However, no studies have reported what types of lavage fluids or detergents are best for wound healing. Moreover, because damage to the wound surface may delay wound healing, the wound surface needs to be treated gently. Although bacteria and residual materials can be removed by lavaging with pressure,[63–67] caution should be applied, as excessive pressure damages the granulation tissue on the wound surface. Lavage fluids are recommended to be warmed to approximate body temperature.[68] The use of cold lavage fluids need to be avoided: it is not only less effective in removing contaminants, but it may also cause vasoconstriction in diabetic ulcers and in ulcers associated with vasculitis or connective tissue diseases. Conversely, if the lavage fluid is warmed excessively, it may denature the protein on the wound surface. In wounds such as large burns, use of low-temperature lavage fluids has a risk to lower the body temperature. In addition, the use of extremely warm or cold fluids causes discomfort or pain during lavage.

2) Lavage methods

(i) Shallow chronic skin wounds. In erosions and shallow ulcers, the normal wound healing mechanism is expected to operate in the same way as in acute skin wounds. When treating superficial wounds, it is essential not to allow them to be turned into deep wounds by infection or necrosis. Wounds should be kept as clean as possible, using lavage to reduce the number of bacteria and to remove foreign substances and residual materials such as ointments. Moreover, excessive lavage at this stage reduces the amounts of cytokines necessary for wound healing, which may delay healing. Therefore, caution is needed.

(ii) Deep chronic skin wounds with infection or necrotic tissue. Infection and necrotic tissue are the most important local factors that delay wound healing. Lavage is also very significant for the control of critical colonization, which is a phase before overt infection. Along with administration of antibiotics for infection and debridement for necrotic tissue, sufficient lavage is indispensable to wound bed preparation.[47,49,69–72] Disinfectants may be used in the presence of an obvious infection. In such cases, subsequent lavage is expected to minimize unnecessary tissue damage and to prevent sensitization that can lead to contact dermatitis due to disinfectants.

The use of a sufficient amount of lavage fluid is important at this stage. It is difficult to ensure the removal of bacteria and contaminants with a small amount of fluid. Showering and bathing are recommended as simple and sufficient lavage methods. However, caution must be taken because there are exceptional cases. The lavage of patients with extensive burns in a shower or bath using shared equipment was reported to have caused nosocomial infections and to have increased the number of bacteria on normal skin or in uninfected wounds.[73–75] Furthermore, a study of lower limb ulcers caused by diabetes or PAD reported more favorable outcomes in the affected leg from showering than from a foot bath.[76] It was noted that foot baths can cause infections to spread.

The effects of debridement and elimination of bacteria are expected from applying pressure during lavage, but caution is needed to avoid damaging the granulation tissue. At this time, there is no consensus on the appropriate pressure applied for wound lavage. It has been reported that pulsatile lavage enhances pressure ulcer healing.[77]

Although physiological saline, distilled water and tap water are sufficient lavage fluid types, highly acidic electrolyzed water has been reported to reduce the number of bacteria in pressure ulcers to a greater degree than physiological saline.[78] However, it must be used with caution because despite the fact that it has been approved as a disinfectant for medical equipment and as a bactericidal agent for food additives, it has not been approved as a medical product.

(iii) Deep chronic skin wounds in the granulation/epithelialization phase. Once infection has been controlled and the necrotic tissue has been removed, the wound healing mechanism begins to function normally and the granulation/epithelialization progresses. In this period, it is important to perform lavage gently to avoid damaging the wound surface, while successfully removing the ointments or contaminants remaining at the surface. In addition, wounds may be covered with a dressing material for moist wound healing at this stage, but daily lavage is not necessarily required.

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Question 3: How should the surface of chronic skin wounds be disinfected?

Answer: Generally, shallow skin wounds do not require disinfection. In deep skin wounds as well, if infection is not established, lavage is recommended without rigid adherence to the use of disinfection to eliminate bacteria. However, in wounds that are progressing to infection or in which infection has become established, disinfection becomes necessary to control the infection, despite the possibility of some degree of sacrificial tissue damage.

Commentary

Disinfection is an action to exterminate or reduce the numbers of pathogenic microorganisms (such as bacteria) present on the skin or other target areas to eliminate their pathogenicity. Bacteria may also delay wound healing by producing endotoxins, exotoxins and the like. Disinfection is performed to reduce opportunities for latent infection by these microorganisms, usually with disinfectants. The eradication of microorganisms with heat or other physical or chemical means is called sterilization, and it must be distinguished from disinfection.

Disinfectants exert bactericidal effects through protein coagulation or oxidizability. It must be noted that they exert the same effects on the host (the wound surface) as on the microorganisms.[79–81] On the other hand, the histotoxicity of disinfectants is often evaluated in animal models and in the laboratory, and applying the results of such evaluations directly to skin wounds under treatment is questionable. Either way, disinfection should not be continued without a clear objective.

There are various types of disinfectants, but not all have bactericidal activity against all pathogenic microorganisms (Table 3). Specifically, povidone iodine, chlorhexidine gluconate and benzalkonium chloride are appropriate for use on chronic skin wounds.

The different types of disinfectants and methods for their use are described below.

(1) Types of disinfectants

i Povidone iodine: A typical preparation of povidone iodine is 10% Isodine®. This preparation is brown, allowing for clear identification of the disinfected area. Its bactericidal activity is considered to derive from the oxidative power of iodine.[83] The documentation included with Isodine states that most of the bacteria are killed within approximately 30 s of application.[84] As povidone iodine often causes contact dermatitis[85,86] or chemical burns[87] from sweat or exudates when used in wet environments, it must be thoroughly cleaned off after disinfection. If it is allowed to remain on skin tissue in high concentrations, not only will it cause signs of irritation, but it has also been reported to cause localized vascular insufficiency.[88] Therefore, it is important to wash it away sufficiently to prevent residue on the tissue.[89] It must be diluted before use on the face and on mucous membranes, as it is strongly irritating in these areas. Moreover, caution is needed when using it on patients with thyroid dysfunction, as it may affect thyroid hormone-related substances.[90]

ii Chlorhexidine gluconate: Hibitane® and Maskin® are common preparations of chlorhexidine gluconate. They are odorless and colorless, although some products are dyed. As chlorhexidine gluconate is less irritating than povidone iodine, it can be applied to the face and to the external genitalia. Its bactericidal activity is weak, and some strains

Table 3. Disinfectants and effects against various pathogens

	Bacteria	MRSA	*Pseudomonas aeruginosa*	Resistant *Pseudomonas aeruginosa*	Tubercle bacillus	Fungi	Bacteria spores	Hapatitis virus	HIV
Benzalkonium chloride	○	△	○	×	×	△	×	×	×
Benzethonium chloride	○	△	○	×	×	△	×	×	×
Chlorhexidine gluconate	○	△	○	×	×	△	×	×	×
Ethanol for disinfection	○	○	○	○	○	○	×	×	○
Povidone iodine	○	○	○	○	○	○	△	×	○
Mercurochrome	○	○	○	○	×	△	×	×	×
Hydrogen peroxide	○	△	△	△	×	△	×	×	×

MRSA, methicillin-resistant *Staphylococcus aureus*; ○, suitable; △, somewhat suitable; ×, unsuitable. Adapted from reference 82.

survive even after contact for 5 min or longer. It is used in a 0.05% concentration for the disinfection of skin wounds.[91,92] As there have been case reports of anaphylactic shock, its use is contraindicated on the ears and on mucosal surfaces (vaginal, vesical, oral), where absorption is high.[93]

iii Benzalkonium chloride: Osvan® is a preparation of benzalkonium chloride. A related compound, benzethonium chloride, is available as Hyamine® and Bezeton Solution®. It is nearly odorless and non-irritative, and is suitable for disinfection of the skin and mucosa. It is used in a 0.01–0.025% concentration on the mucosa and on skin wounds. For the disinfection of infected skin surfaces, it is used in a 0.01% concentration.[94]

(2) Disinfection methods

These disinfectants exhibit bactericidal effects by denaturing/coagulating the bacterial proteins (often cell membrane proteins), causing bacteriolysis. As they simultaneously exert the same effect on host cells, they are histotoxic. Therefore, disinfection without a clear purpose delays wound healing. If organic materials such as blood, pus, exudates or necrotic tissue are present, disinfectants denature them, which reduces the permeation of the disinfectants into the wound. As a result, their antibacterial effect does not extend to the most important targets. Although they exhibit an effect when used after sufficient lavage to remove necrotic material from the wound, their bactericidal properties are also reduced by the residual soap used in lavage.

After a disinfectant has been applied, it must be allowed to remain for several 10s of seconds to several minutes, as a certain amount of time is required for disinfection. After there has been sufficient contact between the wound and the disinfectant, the adhered disinfectant must be washed off. This helps to keep the damage to host cells caused by the residual disinfectant to a minimum.

(3) Disinfection of skin wounds by type

The effects of bacteria on wounds can be divided into the following stages: (i) contamination (no bacterial proliferation); (ii) colonization (bacteria are proliferating but are harmless to the wound); and (iii) infection (bacteria proliferate and are harmful). It is widely accepted that these stages are continuous, and that infection develops when the balance between the action of the bacteria on the wound (the bacterial burden) and the host resistance is disrupted.[85] Critical colonization is defined as a transitional stage between (ii) and (iii). Infected wounds exhibit characteristic clinical features. NERDS, an acronym for the findings observed when the wound surface is suspected of infection, and STONES, an acronym for the findings observed in deep infections, help to evaluate local infections (Table 4).

If a wound is judged to be colonized, disinfection is not always necessary. Disinfection becomes important when signs of infection are observed in the wound, namely at the stages of critical colonization and infection.[96]

The guidelines of the Wound Healing Society strongly recommend reducing the microbial mass through disinfection when the bacterial count in the local exudates from chronic skin wounds (e.g. diabetic ulcers, venous ulcers, pressure ulcers) reaches at least 1×10^6 colony-forming units/g of sample.[97–99] Given the toxicity of the disinfectants, they also recommend the prompt discontinuation of disinfection once the infection has been controlled. However, the same guidelines include a lower recommendation level for the control of local infection in ischemic ulcers.[100]

Table 4. NERDS and STONES

NERDS: Superficial increased bacterial burden	STONES: Deep component infection
N: Non-healing wound	S: Size is bigger
E: Exudative wound	T: Temperature increases
R: Red and bleeding wound	O: Os (probes to or exposed bone)
D: Debris in the wound	N: New area of breakdown
S: Smell	E: Exudates, erythema, edema
	S: Smell

Adapted from reference 95.

In addition, the International Consensus[101] advocates disinfection with iodine in localized infections complicated by systemic infections, when a patient is at risk of increased susceptibility to infection, and when signs of infection are exacerbated in a wound treated by another method, such as lavage. However, the discontinuation of disinfection is recommended once the wound begins to show signs of improvement.

(1) Shallow chronic skin wounds

In wounds with defects to the epidermis or to the upper layer of the dermis with no clear signs of infection, there is little sense in disinfection.[102] In wounds showing epithelialization, lavage with physiological saline or tap water is sufficient to clean the wound surface. These wounds have various cytokines at the wound surface, and the epidermis being formed is still thin. Therefore, they must be treated gently, and scrubbing during lavage is often unnecessary.

(2) Deep chronic skin wounds

(i) Deep chronic skin wounds with infection or necrosis. Necrotic tissue is usually attached to a wide area of the wound surface. As the presence of necrotic tissue increases the risk of infection, these wounds are considered to be in a permanent state of critical colonization. Indeed, if the balance shifts towards infection, systemic symptoms, including fever, may be observed in addition to local symptoms such as a feeling of warmth, an increase in exudates (such as pus), redness, swelling and pain. Wound healing cannot be expected to occur without control of the infection. Therefore, the removal of necrotic tissue (debridement), lavage and disinfection, and the systemic administration of antibiotics are necessary. As previously stated, the presence of necrotic tissue prevents the

permeation of disinfectants into the wound surface. Therefore, it is vital that they are used after the active removal of that necrotic tissue and cleaning of the wound surface through lavage. In addition, disinfection should be discontinued at an appropriate time, once the infection has been controlled and critical colonization is shifting towards colonization.[103,104] In other words, as long as wound infection is not established, there is no need for rigid adherence to the eradication of bacteria through disinfection. However, if infection is established or is about to be established (the critical colonization stage), disinfection is necessary to control the infection at the cost of some tissue damage.[105] The period over which disinfection is necessary varies with each case, but it is often in the order of several days to 1 week.

(ii) Deep chronic skin wounds in the granulation/epithelialization phase. In the event of a defect of the dermis or of the full thickness of the skin, the risk of infection is higher than in superficial wounds, and a state of colonization is common. In these cases, more time is needed for the epithelialization to progress. This is the granulation phase. Therefore, granulation must not be inhibited by tissue damage caused by unnecessary disinfection. Lavage is necessary and sufficient to maintain the wound's cleanliness, and must be washed with a certain degree of pressure.[81,106]

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Question 4: What topical agents should be used on chronic skin wounds?

Answer: To promote the healing of chronic skin wounds, the wound depth, healing process stage and factors that prevent healing must be understood. To facilitate the healing process, it is then recommended to select and use topical agents that serve a purpose in eliminating the factors that prevent healing by taking into consideration the active agent and the drug base.

Commentary

1) Significance of and precautions for the use of topical agents

As stated above (Question 1), wound healing is delayed by factors such as necrotic tissue, infection, drying, excessive moisture and undermining during the healing process. To eliminate these obstacles or to accelerate the normal healing process, it is necessary to select an appropriate topical agent according to the condition of the wound. Numerous clinical trials of topical agents and reviews written by experts to date have established that topical therapy promotes wound healing.[107–114] On the other hand, the long-term use of inappropriate topical agents can cause drying or excessive moisture at the wound surface. In addition, there is a risk of contact dermatitis or

Table 5. Characteristics of ointment bases

Classification of base			Type of base	Topical agent (representative products)
Hydrophobic base	Oleaginous base	Mineral oil, Animal or vegetable oil	White petrolatum, plastibase	Zinc oxide, dimethyl isopropyl azulene, alprostadil alfadex
Hydrophilic base	Emulsion base	Oil-in-water type (O/W)	Hydrophilic ointment, vanishing cream	Tretinoin tocopheril, silver sulfadiazine
		Water-in-oil type (W/O)	Absorbent ointment, cold cream, hydrophilic petrolatum, lanolin	Lysozyme hydrochloride, solcoseryl
	Water-soluble base		Macrogol ointment	Bucladesine sodium, aluminum chlorhydroxy allantoinate, bromelain
			Macrogol ointment (+ sucrose)	Povidone iodine sugar
			Macrogol 600 (+ beads)	Dextranomer
			Macrogol (+ absorbent polymer)	Iodine-containing ointments
			Macrogol (+ beads)	Cadexomer iodine

Adapted from reference 113.

maceration development on the surrounding skin. Thus, by investigating the effect of topical agents approximately every 2 weeks, depending on circumstances, needless use of ineffective drugs can be prevented . One method for the use of ointment involves spreading it to a uniform thickness (~1–3 mm) over gauze with an ointment spatula or a tongue depressor to prevent the wound surface from drying and the gauze from adhering to it.[110] The applied amount can be increased when the volume of exudates is low, and a polyurethane film may be used to cover the top of the gauze. In addition, if there is undermining, the latter must be filled with a topical agent.

2) Topical agent bases

In topical agents, it is not only the active agent but also the base that plays an important role in the effect of the medication.[107–113] The bases of ointments frequently used to treat wounds are classified into oleaginous, emulsion and water-soluble bases (Table 5).

Oleaginous bases include those derived from minerals such as white petrolatum and plastibase, and those prepared from animal or vegetable oil, such as a simple zinc oxide ointment. These ointments protect the skin, maintain its moisture and cause little irritation. They are suitable for wound surfaces with a low volume of exudates.

Emulsion bases are prepared by emulsifying oleaginous and water-soluble components with a surfactant, and are classified as oil-in-water (O/W) bases, in which oil is dispersed in water, and water-in-oil (W/O) bases, in which water is dispersed in oil. The former have a high moisture level, and they have a hydrating effect on wound surfaces. On the other hand, the latter only have a small amount of contained water, but almost no exudate absorption. Therefore, their moisture-retaining properties are similar to those of oleaginous bases. As an advantage, they can be compounded with both water-soluble and oil-soluble drugs. As they have excellent penetration, they can also be used on wounds with deep ulcers or necrotic tissue, which require strong drug penetration.

Water-soluble bases completely dissolve in water. Macrogol, a condensation polymer of ethylene oxide and water, is a typical example. While drugs compounded with a water-soluble base have a low percutaneous absorbability, they cause little irritation and are highly water absorbent. Therefore, they are useful for wounds with large volumes of exudates. They also have the advantage of being easily washed off with water.

Regarding other bases, those compounded with sucrose or absorbent polymer particles are very highly water absorbent, which makes them suitable for wounds with large volumes of exudates.

In summary, oleaginous ointments that strongly protect wounds and retain their moisture are suitable for shallow wounds and those that produce low volumes of exudates. Meanwhile, water-soluble bases and those that contain sucrose or polymer particles are suitable for deep wounds that produce large volumes of exudates.

3) Selection of topical agents (see Table 6)

a. Shallow chronic skin wounds. The skin plays an important role in the protection of internal organs from the external environment and retention of moisture. Therefore, in the event of a partial loss of skin, the site of loss must be protected and maintained in an appropriately moist environment until it is healed (Table 6). Therefore, shallow wounds (erosions and shallow ulcers within the upper layer of the dermis) are good indications for dressing materials, and topical agents are also effective. Dimethyl isopropylazulene ointment (a moisture-retaining oleaginous base), ointments containing antibiotics (e.g. sodium fusidate and gentamicin sulfate, most of which have oleaginous bases), zinc oxide, white petrolatum and the like are used on these wounds. However, the use of ointments containing antibiotics for 2 weeks or more should be avoided, as it may induce the emergence of resistant bacteria.

b. Deep chronic skin wounds. Those with infection or necrotic tissue— While the migration of inflammatory cells (which produce growth factors and cytokines necessary for granulation)

Table 6. Topical agent selection

Skin wound depth and condition	Representative topical agents indicated	Representative corresponding products	Remarks
Shallow chronic skin wounds	Isopropyl azulene ointment	Azunol® ointment	Wound surface protection and weak anti-inflammatory effect.
	Ointments containing antibiotics	Gentacin® ointment Fucidin Leo® ointment	Antibacterial effects from the presence of antimicrobial agents such as antibiotics. Avoid long-term use to prevent the emergence of resistant bacteria.
	Zinc oxide ointments	Simple zinc oxide ointment	Apply thinly to protect the wound surface (thick application has a desiccant effect).
	White petrolatum	White petrolatum	Use for wound surface protection. Has the advantage of not causing contact dermatitis.
Deep chronic skin wounds (with infection or necrotic tissue)	Cadexomer iodine ointment/external powder preparation	Cadex® ointment Cadex® powder	Released iodine causes strong antimicrobial activity, while polymer particles absorb exudates and eliminate necrotic tissue and bacteria. Not suitable for dried wounds. Powder is more water absorbent, while the macrogol-based ointment is easier to use. When washing, the old polymer particles need to be washed off thoroughly. Contraindicated in patients with iodine hypersensitivity.
	Creams containing silver sulfadiazine	Geben® cream	The contained sulfa drug and silver exert a broad antimicrobial activity on bacteria and fungi. High tissue permeability and moisture content facilitate the softening and autolysis of necrotic tissues. Not suitable for wounds with a high exudate volume. Contraindicated in patients with sulfa drug hypersensitivity, newborn infants, low-birthweight babies (it can cause high bilirubin levels), and mild burn patients (it causes them pain). Pay attention to a possible rise in serum osmolality in patients with extensive burns.
	Sulfadiazine ointments	Theradia Pasta®	Contains sulfadiazine. With a macrogol base, the ability to absorb exudates is high.
	Dextranomer polymer	Debrisan® Debrisan® paste	Polymer particles promote the excellent absorption of exudates and the elimination of bacteria and their degradation products. Preparations containing a macrogol base are easier to use. When washing, the polymer particles need to be washed off thoroughly. Do not apply to ulcers that are difficult to wash due to undermining. Not suitable for dried wounds.
	Bromelain-containing ointment	Bromelain ointment	The protease bromelain acts for the chemical debridement of necrotic tissue. Application to wound margins can cause redness and pain; therefore, pretreat the periphery with an oleaginous ointment. Not suitable for infected wounds.
	Povidone iodine gel	Isodine® gel	Inhibits infection through the strong antimicrobial activity of iodine. Macrogol base. Contraindicated in patients with iodine hypersensitivity.
	Povidone iodine sugar	U-Pasta® Kowa	Strong antimicrobial activity from iodine. Absorbs exudates and reduces edema from the sugar. Not suitable for dried wounds. Stir thoroughly before use. Contraindicated in patients with iodine hypersensitivity.
	Iodine-containing ointments	Iodocoat®	Has similar effects to cadexomer iodine despite the lack of polymer particles. Contraindicated in patients with iodine hypersensitivity.
	Fradiomycin sulfate/ trypsin powder	Francetin® T powder	Has both antibacterial effects from fradiomycin sulfate, and necrotic tissue lysing effects from the protease, trypsin. As a powder, it is not suitable for dried

Table 6. (continued)

Skin wound depth and condition	Representative topical agents indicated	Representative corresponding products	Remarks
			wound surfaces. Contraindicated when the wound surface is bleeding or in patients with severe hepatic/renal damage.
	Iodoform	Iodoform gauze	Dissolves and breaks down the blood and exudates from wounds/ulcers. Exhibits bactericidal effects through iodine release. When used in large quantities, symptoms of iodine poisoning such as delirium, restlessness and somnolence may occur. Therefore, thorough observation is required.
Deep chronic skin wounds (in the granulation/epithelialization period)	Alprostadil alfadex (prostaglandin E1) ointment	Prostandin® ointment	Promotes granulation by increasing the skin blood flow and angiogenesis. Promotes epithelialization by stimulating epidermal cell growth and migration. Suitable for dried wound surfaces due to the oleaginous plastibase base. Contraindicated in pregnant women and patients with heart failure or bleeding.
	Aluminum chlorohydroxy allantoinate	Alkixa® ointment Isalopan® (powder)	This medicine is an aluminum salt derived from allantoin, which promotes granulation and the elimination of necrotic tissue.
	Lysozyme hydrochloride-containing ointment	Reflap® ointment Reflap® sheet	Exhibits tissue-repairing activity such as fibroblast growth promotion, and effective breakdown of purulent discharge. Contraindicated in patients with albumen hypersensitivity.
	Solcoseryl-containing ointments	Solcoseryl® ointment Solcoseryl® jelly	A calf serum extract. Aids granulation by promoting angiogenesis and fibroblast growth. Contraindicated in patients with sensitivity to bovine blood products.
	Trafermin (basic fibroblast growth factor; bFGF) preparations	Fiblast® spray	A recombinant human bFGF preparation that strongly promotes favorable granulation through angiogenesis and fibroblast growth/migration. Dissolve in a dedicated spray bottle before using, and spray onto the wound surface. Due to its effect on cell proliferation, it is contraindicated in patients with a malignant tumor (or a history of it) at the site of administration.
	Tretinoin tocopherol ointment	Olcenon® ointment	Strongly promotes granulation through the growth and migration of vascular endothelial cells and fibroblasts. Suitable for dried wound surfaces due to its emulsion base with a high moisture content. May cause edema in patients with a high volume of exudates. The yellowish wound surface caused by the ointment color can be mistaken for an infection.
	Bucladesine sodium ointment	Actosin® ointment	Promotes granulation and epithelialization through vasodilation, improved blood flow, and the growth and migration of vascular endothelial cells and fibroblasts. Has water absorbability due to the macrogol base. Some patients complain of the unique odor.

Adapted from reference 114.

to wounds is indispensable to their healing, excessive or persistent inflammation prevents granulation and subsequent epithelialization, which delays wound healing. As foreign bodies, infection and necrotic tissue cause inflammation, and they must be removed as much as possible through surgical debridement or sufficient lavage. To promote the autolysis of necrotic tissue, bromelain (which are enzyme preparations),[15] as well as fradiomycin sulfate[116] and cadexomer iodine ointments/external powder preparations,[117–119] are frequently selected. In addition, creams with silver sulfadiazine, which contain a lot of moisture, are believed to promote the softening and lysis of necrotic tissue. They are therefore used to eliminate necrotic issue from wounds with low exudate volumes.[120] Although it is often difficult to remove necrotic tissue completely with chemical debridement alone, the prior softening of necrotic tissue with these agents makes any subsequent surgical debridement safer and easier. For the external treatment of infected wounds, cadexomer iodine ointments/external powder preparations,[117–119,121,122] povidone iodine sugar,[123,124] iodine-containing ointment[125] and iodoform gauze,[126] which contain iodine with strong antibacterial activity, are used. Creams containing silver sulfadiazine[127–129] and sulfadiazine ointments also have strong antibacterial activity, and are therefore often used. If the wound is abnormally rich in exudates due to infection or marked inflammation, granulation may be prevented, or additional infection or inflammation may develop. Moreover, the normal skin surrounding the wound becomes macerated and vulnerable to erosion due to external stimulation. In these cases, the use of topical agents that absorb exudates becomes necessary. Cadexomer iodine ointments/external powder preparations containing polymer particles,[117–120,122] dextranomer polymer[130] and povidone iodine sugar, which contains sucrose,[123,124] are typical options. Ointments containing iodine,[125] which have a bactericidal effect from the continuous release of iodine and an exudate-absorbing effect, and which are easier to handle than polymer-based preparations, are also considered useful.

Those in the granulation/epithelialization phase— Granulation tissue is formed in wounds after the control of infection and the removal of necrotic tissue. However, in deep ulcers and wounds that show a delay in granulation for any reason, topical agents that promote granulation should be used. In addition to trafermin (basic FGF) preparations with a strong granulation-promoting effect,[131–134] alprostadil alfadex (prostaglandin E1) ointments,[135] aluminum chlorohydroxy allantoinate ointments/external powder preparations,[136] lysozyme hydrochloride-containing ointments,[137] solcoseryl-containing ointments,[138] tretinoin tocopherol ointments[139,140] and bucladesine sodium ointments[141,142] are known to promote granulation.

Once the ulcerated area is filled with satisfactory granulation tissue, epithelialization begins. In this period, it is important to protect the wound surface and to maintain a moist environment. Ointments such as those indicated above for the treatment of superficial chronic skin wounds are indicated. To actively induce shrinking of the wound by epithelialization, alprostadil alfadex (prostaglandin E1) ointments[135] and bucladesine sodium ointments[141,142] are considered useful.

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Question 5: How should dressing materials be used?

Answer: Basically, dressing materials have water-retaining properties. However, as their ability to absorb exudates varies with each product, a moist environment appropriate for wound healing can be prepared by selecting them according to the exudate volume. In addition, a sufficient understanding of the materials and of the morphology of each type of dressing is recommended. Caution is needed, as excessive wound moisture leads to maceration of the wound and of the surrounding normal tissue, which delays ulcer healing and can lead to infection.

Commentary

1) Significance of the use of dressing materials and points of caution

When used properly, dressing materials are an effective treatment means for chronic skin wounds, based on the aforementioned TIME and moist wound healing concepts (see Question 1).[143–149] In the present guidelines, dressing materials refer to modern wound dressing materials that promote a moist wound environment. They exclude conventional sterilized gauze.

Among dressing materials, the use of polyurethane film as a secondary dressing to protect the skin is not covered by national health insurance. Therefore, its cost is included in the technical fee. For wounds that reach the dermis or deeper, dressing materials for skin defects that are listed by insurance (i.e. specific insured medical materials) can be used according to the wound depth. They cannot be prescribed because they are not drugs. However, if used by a physician for treatment, health insurance points can be calculated for them. If multiple dressing materials are used at the same site, only the primary material can be included in the calculation. Since the 2012 revision to medical compensation, the use of dressing materials for patients with difficultly commuting to a hospital, who are being treated at home, or for whom an at-home care and guidance management fee is calculated is now covered by national health insurance. This applies even if the patient used the materials him- or herself on a pressure ulcer with a DESIGN-R classification of D3 or D4, including ulcers reaching subcutaneous tissues (including pressure ulcers reaching muscle, bone and the like). Caution is needed, as dressings for surgical suture wounds and wounds with a depth not covered by insurance are no longer covered.

The occlusion of the wound with a dressing material and the creation of a moist environment contribute to wound healing by retaining the cell growth factors and cytokines contained in exudates, by promoting the migration of epidermal cells, and by preventing the spread of, or promoting the autolysis of, necrotic tissue. Moreover, these actions have other effects: they protect

the skin around the wound, prevent contamination, mitigate pain and retain heat. Hutchinson *et al.*[150] reported a significantly lower rate of infection when using a method of treatment involving a moist environment and sealing the wound with a dressing material than when covering the wound with conventional gauze. Most dressing materials are believed to suppress bacterial proliferation, as they are impermeable to bacteria from the outside and accumulated exudates have the ability to resist bacteria.[151] However, in the case of wounds with suspected infection, moisture maintenance can aggravate the infection by fostering a hotbed of bacteria proliferation. This may not only delay the healing of the wound, but it can also worsen it. Therefore, it is important not to use dressing materials that do not allow the observation of the wound.

Recently, various dressing materials containing silver have been introduced. These are not recommended for wounds with an overt infection. However, they have been reported to speed up the shrinking of ulcers when used in cases of suspected critical colonization or on ulcers at risk of infection. Therefore, they may be used in these cases.[149,152] However, evidence is lacking, as some reports have also suggested that the rate of improvement does not differ between the use of dressing materials containing silver and that of dressing materials without silver.[153,154] In addition, as national health insurance only covers the use of dressing materials for a limited period (normally up to 2 weeks, maximum 3 weeks), caution is needed as their selection and use is at the sole discretion of the physician. Dressing materials present an advantage in that they must not necessarily be changed daily. Rather, the appropriate timing of the changes, the number of consecutive days of use (1 week maximum) and so forth must be determined by carrying out daily observations of the wound surface to ensure that there is no infection/sign of infection or peeling off of the dressing material. Moreover, if PAD (conventionally called arteriosclerosis obliterans, or ASO) cause poor blood flow to the wound or if the immune system is compromised, the ability to resist infection is reduced and occlusive dressings should not be applied; if one is applied, thorough care must be taken to change it every day to confirm that no infection has developed underneath the dressing. Although dressing materials can be effective when used appropriately, it must be kept in mind that they may prevent wound healing when used without sufficient knowledge of their properties or without sufficient experience using them.

2) Characteristics of different dressing materials

1. Polyurethane film. Polyurethane film coated with an adhesive on one side is used for the protection or the secondary dressing of shallow wounds with a low exudate production. It is permeable to oxygen and water vapor, but does not let bacteria pass. Its transparency facilitates wound observation.

2. Hydrocolloid. Hydrocolloid comprises a waterproof outer layer and an inner adhesive layer that contains hydrophilic colloid particles. It forms an occluded moist environment that does not interfere with wound healing. As it forms a gel by absorbing water, it is not suitable for wounds that are rich in exudates. Its translucence facilitates wound observation.

3. Hydrogel. Hydrogel has a matrix structure of hydrophilic polymer molecules, within which water is contained. It provides moisture to dried necrotic tissue and promotes its autolysis.

4. Chitin. Non-woven fabric of fibers of the mucopolysaccharide chitin, which is extracted from crustacean shells. After packing the wound lightly, it must be covered with a dressing material. It has a wound cleaning effect from its water absorbent and adsorbent properties, as well as a hemostatic effect. It will break down even if it remains at the wound.

5. Alginate. Sodium calcium alginate extracted from seaweed and prepared into fibers. It is packed into the wound lightly and covered with a dressing material. It has a high capacity to absorb exudates and forms a gel when it absorbs moisture.

6. Hydrofiber. Non-woven fabric of fibers of sodium carboxymethyl cellulose. It is packed into the wound lightly and covered with a dressing material. It has a high capacity to absorb exudates and forms a gel that does not disintegrate after absorbing moisture.

7. Hydropolymer. Absorbent pad made of hydrophilic polyurethane foam that fits into even depressed wounds, as it swells from the absorption of excessive exudates. The periphery is adhesive tape, and the central absorptive pad can be changed easily as it does not gel.

8. Polyurethane foam. Has a three-layer structure: (i) non-adhesive polyurethane on the surface that contacts the wound; (ii) a hydrophilic polyurethane foam at the center; and (iii) polyurethane film on the outer surface. It uses the capillary effect to absorb excessive exudates and stores them in the foam without re-releasing them into the pores (cells). Being non-adhesive, it is less likely to damage the wound surface. It has a certain thickness that protects the affected area, but some skill is needed to apply it. Some products are prepared with an adhesive film and can be applied directly.

9. Dressing materials containing silver. As seen in Table 8, various materials are conferred antibacterial activity by adding silver to them before they are sold.

Table 7. Exudate volume and choice of dressing material

Exudate volume	Suitable dressing materials
Moderate to low	Polyurethane film Hydrocolloid
Low (with dry necrotic tissues) Heavy	Hydrogel Alginate Chitin Hydrofiber® Hydropolymer Polyurethane foam

Table 8. Function and selection of dressing materials

Function	Type	Main product names
Protecting the wound surface	Polyurethane film	Opsite® wound, 3M™ Tegaderm™ Transparent Film Dressing, Perme-aid S
Sealing the wound surface and creating a moist environment	Hydrocolloid	DuoActive®, Comfeel®, Absocure® wound
Moistening dried wounds	Hydrogel	ViewGel®, GranuGEL®, Intrasite Gel System
Absorbing exudates	Polyurethane foam	Hydrosite® plus
	Alginate/CMC	Askina® sorb
	Polyurethane foam/soft silicone	Mepilex® border
	Alginate	Kaltostat®
	Alginate foam	Kurabio® FG
	Chitin	Beschitin® W-A
	Hydrofiber	Aquacel®, Aquacel® Ag
	Hydrofiber/ hydrocolloid	Versiva® XC®
	Hydropolymer	Tielle®
Suppressing infection	Dressing material containing silver	Aquacel® Ag
		Algisite×Ag
		Hydrosite Ag
		Mepilex Ag
Easing pain	Hydrocolloid	DuoActive®
	Polyurethane foam/soft silicone	Hydrosite® AD gentle, Mepilex® border
	Hydrofiber	Aquacel®, Aquacel® Ag
	Hydrofiber/ hydrocolloid	Versiva® XC®
	Chitin	Beschitin® W-A
	Hydrogel	GranuGEL®

Adapted from reference 149.

3) Selection of dressing materials according to the exudate volume and the wound depth

After considering the functions and characteristics of different dressing materials, the volume of exudates can be used as a measure to differentiate them (Table 7). The use of dressing materials with a low absorptive capacity on wound surfaces that produce large volumes of exudates generates excess moisture. Conversely, the use of highly absorptive dressing materials on wounds with little exudate production promotes drying and adhesion to the wound. Therefore, care is needed. The most representative products are listed in Table 8, which is organized by exudate volume and wound depth.

4) Selection of dressing materials according to the chronic skin wound stage

a. Shallow chronic skin wounds. Although it is not covered by national insurance, polyurethane film is often used to protect the wound surface of erosions and blisters. Thin types of hydrocolloid and polyurethane foam are used on non-infected shallow ulcers down to the upper layer of the dermis, as well as to protect wound surfaces and to preserve a moist environment.

b. Deep chronic skin wounds. Those with infection/necrotic tissue— As mentioned above, the management of exudates and the control of infection through the removal of necrotic tissue and the administration of antibiotics are important in the treatment of chronic skin wounds with infection or necrotic tissue. Infection treatment is of particular importance. As occlusion of the wound can exacerbate the infection, occlusive dressing should generally be avoided and primarily topical agents with antibacterial activity should be used for treatment. If dried necrotic tissue is present, a hydrogel can promote its autolysis by increasing the moisture content.

Those in the granulation/epithelialization phase— Bearing in mind the principle of moist wound healing, in the granulation and epithelialization phase (i.e. in the latter half of the healing process of chronic skin wounds) the use of occlusive dressing materials is important to prevent the wound from drying, leading to damage to the healing mechanism, and prevent the granulation tissue or newly formed epidermis from being damaged when changing dressing materials. While many of the external medications used during this period actively promote granulation or epithelialization, dressing materials are used to induce wound healing primarily by maintaining a moist environment and preserving the cytokines at the wound. Hydrocolloids are recommended for a low exudate volume, while alginates, chitin, hydrofibers, hydropolymers and polyurethane foam are recommended for a high exudate volume. If edematous granulation tissue starts to appear and critical colonization is suspected, dressing materials containing silver may be used.

5) Use of dressing materials containing silver

By ionizing into Ag^+, silver has a broad antimicrobial effect against bacteria such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, fungi and viruses. The emergence of resistant strains is quite rare.[155–160] For burns, venous leg ulcers, pressure ulcers and diabetic ulcers, dressing materials with silver have been reported to have a greater wound healing effect than existing treatments. They have also been found to have a significant effect against the bacteria count and signs of infection in wounds after surgical debridement, venous leg ulcers and pressure ulcers.[152,153,161–166] The products sold in Japan frequently have a lower quantity of silver than those marketed abroad. While not all are indicated as-is, this commentary can serve as a reference point. Safety-wise, a study on the use of ACTICOAT® (not yet sold in Japan) reported that Ag ions were absorbed into the blood,

leading to elevated Ag concentrations in the blood and urine and to the development of hepatic dysfunction.[167] Regarding adverse effects from the silver-containing dressing materials sold in Japan, one report indicated that Aquacel® Ag used to treat third-degree burns on legs resulted in progression to anemia.[168] In addition, dressing materials containing silver must be used with caution, as they may locally deposit a black coloring specific to silver preparations.

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Question 6: How should wound-related pain be considered, and what should be done to control it?

Answer: Wound treatment outcomes should not only be evaluated in terms of "healing", as the patient's quality of life (QOL) is also important to consider. Chronic wound pain impacts the QOL, and pain-related stress has been suggested to impede wound healing. Treatment-related pain must be sufficiently heeded, and an appropriate topical agent and dressing material must be selected considering the pain and according to a treatment plan based on the causes of the wound. Negligence to do so can cause neuropathic pain. The chronological evaluation of pain and the effort to identify its aggravating factors can improve the wound treatment itself. In essence, pain is a sensory and emotional experience. It is very important for medical workers to constantly ask their patients questions, to listen closely to their complaints and to watch carefully for non-verbal signs.

Commentary

(1) Pain basics

1) Types of pain. Depending on the pathophysiology, pain can be classified into nociceptive pain, neuropathic pain and psychogenic pain.[169–172] These types of pain are frequently found in tandem. Pain can also be divided into acute pain and chronic pain based on its duration.

(i) Classification by disease condition (Table 9)—

a "Nociceptive pain": Heat, mechanical stimuli or chemical stimuli strong enough to induce pain are stimuli that damage tissue. As such, they are called "noxious stimuli" (conversely, stimuli such as touch, pressure and vibration are known as "non-noxious stimuli"). Nociceptive pain is caused by noxious stimuli. Its degree matches that of the

Table 9. Pain types by disease state

Category	Cause	Characteristics	Subtypes		Pain characteristics
Nociceptive pain	Noxious stimulus	Conforms to the degree of tissue damage, with no damage to the nerve fibers themselves	Somatic pain	Superficial pain (skin and mucous membranes	Sharp pain with clear localization, and reduced sensation in some cases
				Deep pain (e.g. periosteal/ medullary)	
			Visceral pain		Localization is unclear and the pain is a dull tightness without decrease in sensation
Neuropathic pain	Lesion/disease of the somatic sensory nervous system	Pain that continues after the healing of a tissue injury involving nerves	Peripheral nervous system Central nervous system		Decreased sensation during hyperesthesia (spontaneous pain, allodynia, hyperalgesia) Shooting/stabbing pain, burning pain, dull pain, aching pain, throbbing pain
Psychogenic pain	Psychological factors (e.g. depression)	Pain and depression are different manifestations of the same pathology			

tissue damage, without involving any damage to the nerve fibers themselves. It is subdivided into somatic pain, which is carried by the somatic spinal nerves, and visceral pain, which is carried by the splanchnic nerves. Somatic pain is further subdivided into superficial pain at the skin and the mucosa (e.g. pain caused by wounds), and deep pain (e.g. pain of articular origin; periosteal/medullary). Somatic pain is sharp pain with a clear localization. It can be accompanied by reduced sensation in the area innervated by the somatic nerves. On the other hand, visceral pain is not clearly localized at the site of the pain. It is a dull tightening that does not cause reduced sensation at the pain locus (Table 9).

b "Neuropathic pain": The excitement of the nociceptors does not participate in this pain, which is clinically understood to be "severe, intractable pain that continues after an injury to bodily tissue containing peripheral nerves or the central nervous system has healed".[173] Postherpetic neuralgia is a representative example in the field of dermatology. Characteristics include: (i) hyperesthesia (spontaneous pain), allodynia (the sensation of pain from tactile stimuli that do not normally cause pain), concomitant hyperalgesia and occasional reduced sensation; (ii) shooting or stabbing pain, burning pain, dull pain, aching pain, throbbing pain and the like; and (iii) persistent, spontaneous pain, painful attacks or both.

c "Psychogenic pain": Also called "somatoform pain disorder". As pain is an "emotional experience", it is amplified by psychological factors. In particular, pain and depression frequently occur together, and pain can appear as a symptom of depression. On the other hand, pain can also cause depression. Due to this inter-relationship, it has even been suggested that the two may be different expressions of a shared pathology.

(ii) Classification by duration— Acute pain is caused by the transient excitation of the nociceptors by a noxious stimulus. It disappears when the causative trauma or condition heals. A typical condition is acute pain caused by trauma. Chronic pain involves cases in which the pain is found to persist for a long time even after the condition has healed, and cases in which the pain persists for a long time because the condition is difficult to heal. A typical example of the former is postherpetic neuralgia, a neuropathic type of pain, while a representative example of the latter is rheumatoid arthritis, in which the pain is nociceptive. While acute pain is usually nociceptive, chronic pain can be nociceptive, neuropathic or psychogenic.

[2] Pain in chronic wounds and its significance

1. "Nociceptive pain": As chronic wounds break down the skin's barrier function, chronic wound pain is fundamentally nociceptive. It can be induced by changing wound dressings or by lavage, inappropriate medication, the use of dressing materials, debridement and the like. If complicated by prolonged inflammation or infection, the bradykinins derived from damaged tissue or inflammatory mediators, including serotonin, prostaglandins and the like, act as pain-producing substances to generate incessant pain and as amplifying substances that increase the sensitivity of the nociceptors, resulting in hyperalgesia.[171–174]
2. "Neuropathic pain": Wounds that damage the peripheral nerves and chronic wounds that incur repeated noxious stimuli can induce neuropathic pain independent of nociceptor excitation by causing reversible changes to the peripheral or central nervous system.

If neuropathic pain is understood to be "severe, intractable pain that continues after an injury to bodily tissue has healed",

then it either cannot exist in a "chronic wound" or it is in fact caused by the aforementioned mechanism from sustained noxious stimuli caused by improper treatment, insufficient inflammation and infection control, or the like. As a result, wound hyperalgesia, chronic spontaneous pain, hyperesthesia at the wound periphery or allodynia sometimes develop, causing a disproportionately intense pain when peeling away tape that has adhered to the wound's surroundings.

(3) Facts of wound pain management

The facts of wound pain management and the situation in Japan according to the Principles of Best Practice (20086) are summarized below.

1) Identify and treat the cause of the wound. The basis of wound treatment is to first understand its causes. This also helps to ease chronic continuous pain (background pain). For example, elevation and compression therapy must be applied to affected limbs that have venous ulcers, while decompression must be applied to pressure ulcers. Improvement of the blood flow through bypass surgery or catheterization must be applied to ischemic ulcers. These actions may also improve the pain.

2) Evaluate and document the pain frequently. As wound-related pain changes constantly, it should be evaluated frequently. Attention should be paid to treatment-related pain and chronic continuous pain (background pain) that is not associated with the treatment.

Table 10. Comprehensive pain evaluation using NOPQRST

N: Number of painful sites
O: Origin of pain
P: Palliative/provocative factors
Q: Quality of pain
R: Region/radiation of pain
S: Severity of pain
T: Temporal aspect of pain[†]

[†]Intra-day variation, sustained or intermittent. From reference 176.

Table 11. Questionnaire for neuropathic pain screening, Japanese edition

1. I have pain that feels like being pricked by a needle.
2. I have pain that shoots like electricity.
3. I have pain that stings like a burn.
4. I have pain that feels like strong numbness.
5. I experience pain just from the rubbing of my clothes or from a cold breeze.
6. Sensation in the painful area decreases or exacerbates.
7. The skin in the painful area swells up and turns red or purple-red.

Each question is evaluated on the following point scale: 0, absolutely not; 1, a little; 2, yes; 3, yes, quite a lot; and 4, yes, a lot. A total of at least 9 points (sensitivity, 70%; specificity, 76%) indicates a likelihood of neuropathic pain. Source: Working group for the production of a Japanese version of a screening questionnaire for neuropathic pain. From reference 177.

There are the following four objectives for continuous pain evaluation:[175]

1. To assess the temporal pain pattern, and to select and plan treatment methods on the basis of this analysis
2. To determine the efficacy/utility of the treatment
3. To shed light on the factors that improve/worsen the pain
4. To shed light on the barriers (e.g. patient-derived, medical system-related) that affect pain management

Wound-related pain is evaluated by physical examination and medical interview. Besides obtaining physical findings through the traditional visual inspection and palpation, imaging tests and bacterial culture tests can also be performed to evaluate the degree of injury and of infection in bones and soft tissues. NOPQRST can be used as a comprehensive pain evaluation method through medical interview (Table 10).[175] In addition, in order to screen for neuropathic pain, a questionnaire produced by a working group for the production of a Japanese version of a screening questionnaire for neuropathic pain is available (Table 11).[177]

Methods to evaluate pain intensity include: (i) a subjective evaluation method using the subjects' self-reports; (ii) an objective evaluation method based on the physician's observation of the patient (using the activities of daily living); (iii) a psychological evaluation method using an analysis of the psychological state; and (iv) an evaluation based on physiological and imaging tests.[178] As pain is a sensation that depends on individuals' subjective experiences, these methods should be combined to ensure objectivity. However, in the actual clinical setting, subjective evaluation methods are frequently used. Among these, the visual analog scale[179] is often used as it has high sensitivity and reproducibility. In addition, simple methods such as the numeric rating scale (NRS), in which the closest number from 0 to 10 is chosen, and the verbal rating scale (VRS), in which the most applicable statement is selected from a number of options, are used for the elderly, while the Wong-Baker FACES® scale (Fig. 3) is used for children and patients with cognitive disorders. The NRS also includes a method by which the greatest pain that the patient has personally experienced in the past is set as 10, and a method by which the greatest pain experienced prior to treatment is set as 10 (pain relief scale).

Subjective evaluation methods cannot be used in comparison with other individuals. On the other hand, it is important to use the same evaluation method for the same individual throughout the clinical course.

3) Take procedure-related pain into consideration. (i) Wound cleansing: avoid cold cleansing solutions, and lavage wounds gently to avoid causing scraping injuries— To minimize pain, lavage fluid should be warmed to near-body temperature before use.[180] If the wound surface is directly rubbed with gauze or the like, the tissue can become damaged. As this prolongs pain, cleansing should be performed gently at a reasonable water pressure. In chronic wounds, the nerve endings are usually not exposed at the wound surface. Therefore, there

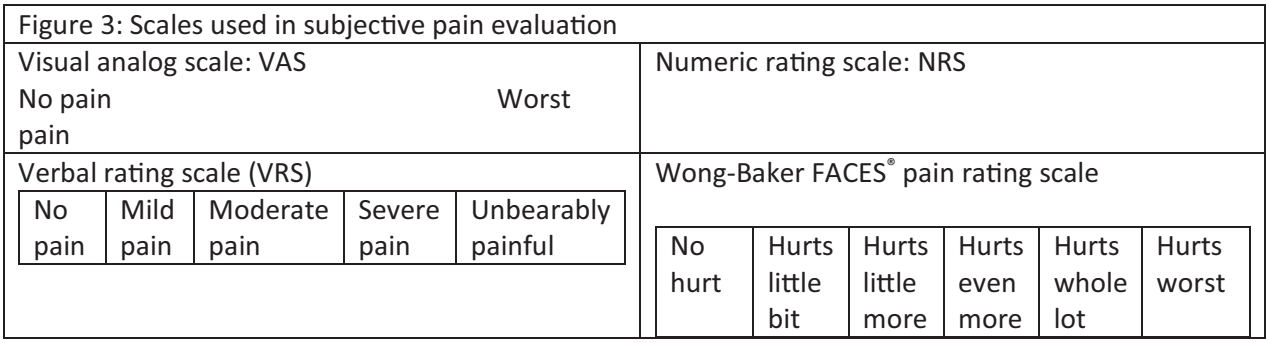

Figure 3. Scales used in subjective pain evaluation.

is no need to consider the osmotic pressure of the cleansing solutions, and distilled water and tap water may be used without issue in addition to physiological saline.[181] Moreover, if disinfection is found to be necessary, ethanol for disinfection, mercurochrome and hydrogen peroxide are strongly damaging to tissue, and 10% povidone iodine is highly irritating. Instead, benzalkonium chloride, benzethonium chloride and chlorhexidine gluconate are considered to be least irritating (see Question 3).

(ii) Debridement: select an appropriate method and include the potential for causing wound-related pain— Debridement methods can be surgical, autolytic, physical, enzymatic or biological (e.g. maggot therapy, which is not covered by national health insurance in Japan). Each method is associated with various levels of pain. Therefore, their respective indications must take into account the degree of urgency, whether blood flow to the tissue has been established and so forth. The operative method is selected according to the underlying condition, the size and depth of the wound and so forth. While surgical debridement for the partial resection of necrotic tissue with clear margins is painless, a local anesthetic is normally required when it is performed until fresh tissue appears. In the case of chronic wounds, pain-control measures are needed for the resection of necrotic tissue mixed with granulation tissue. A topical local anesthetic (Emla® cream) has been reported to relieve pain effectively during the surgical debridement of venous leg ulcers (a procedure not covered by national health insurance in Japan).[182] When applying a topical local anesthetic to an ulcer surface, sufficient care must be taken to avoid local anesthetic toxicity. Wet-to-dry dressing, in which gauze moistened with physiological saline is applied to the wound surface and dry gauze is applied on top, is a physical debridement method that allows the necrotic tissue to adhere to the gauze for removal. However, given the pain and tissue damage involved, its efficacy is limited.[174] Ointments containing the protease bromelain (bromelain ointments) induce chemical debridement. They frequently cause burning or stinging pain, as the water absorbance of the macrogol base can cause wound drying, and the active ingredient is irritating. Silver sulfadiazine cream (Geben® cream) can be used for the debridement of wounds with low volumes of exudates, as the O/W emulsion base has a softening effect and promotes the autolysis of necrotic tissue.[183] The use of dressings such as hydrogels and hydrocolloids should also be considered, as they maintain a moist environment, promote autolysis and cause little pain or tissue damage when dressings are changed. However, as they take time and their effect is limited, their concomitant use with another method is frequently necessary, and they are contraindicated in infected wounds.[184]

(iii) Considerations when changing wound dressings— Pain when changing the dressings is caused by dried dressing materials, exudates that have formed a crust and the strong adhesiveness of dressing materials.[175] The types of adhesives and their characteristics are shown in Table 12. Compared with

Table 12. Characteristics of adhesives used with dressing materials

Adhesive	During application	During removal
Acrylates†	Bonds to skin strongly (strengthens with time) May cause allergic contact dermatitis	May cause pain or tissue damage (skin peeling)‡ May leave adhesive residue on skin
Hydrocolloid	Needs to be molded to the skin surface May curl at the edges May be dissolved by exudates	May leave adhesive residue on skin or wound surface May cause maceration or skin peeling May cause pain or tissue damage
Soft silicone	Reasonable level of adhesion without becoming firmly affixed Adheres rapidly to the skin	Minimal pain when changing dressings Can be reapplied, making it easy to check the condition of the wound

†Adhesive for polyurethane film.
‡As a countermeasure, consider using a release agent or a liquid film to form a protective membrane on the skin surrounding the wound. Quoted from reference 173.

Table 13. Wound pain caused by infection

Bacterial relationship	Pain	Clinical characteristics
Colonization	Not usually present/ related to bacterial damage	Healthy granulation
Localized infection (critical colonization, increased bacterial burden, covert infection)	May be painful	NERDS†
Deep and surrounding skin infection	Increased pains most reliable symptom and may be clinically more useful than any one	STONES†

For details on NERDS and STONES, see Question 3, Table 4. Quoted from reference 175.

Table 14. Wound pain mechanism and treatment options

Type of tissue damage	Pathophysiology of pain	Treatment options
Inflammation	Increase in MMP, tissue damage, immune complex deposition, activation of bradykinins and related substances	Topical and systemic anti-inflammatory
Trauma (including friction and shear)	Activated inflammatory mediators and tissue injury associated with nerve damage	Protect exposed nerve fibers
Pressure	Ischemic injury with tissue damage and nerve fiber irritation, reperfusion injury	Pressure redistribution
Edema	Increase in local interstitial pressure leading to tissue injury	For venous and lymphatic edema: compression, mechanical pumps For cardiac insufficiency and hypoalbuminemia: treatment of the underlying cause

Quoted from reference 174. MMP, matrix metalloproteinase.

conventional dressing materials (or the adhesives used with conventional dressings), use of soft silicone reportedly results in the lowest amount of pain and of stratum corneum exfoliation upon removal.[185–187]

In comparison with dressing materials developed to provide an appropriate moist environment, gauze does a poor job of maintaining a moist environment. It causes wound drying and pain upon removal.[188,189]

However, this evaluation must take into consideration the situation in the West, where topical medications are not normally used for wound treatment. When gauze with a sufficient amount of ointment is in use, the combined use of a secondary dressing such as polyurethane film can prevent the wound from drying, and pain will not necessarily arise (however, care is needed when removing the polyurethane film to avoid irritating the skin at the wound margins). In addition, the use of non-stick gauze and the securing of gauze using tape that causes little irritation upon removal, such as silicone tape, should also be considered.

4) Identify the factors that worsen pain. (i) Localized infection— Wound infection is a cause of pain, and pain is the most common symptom of infected wounds.[190,191] Wound infections are treated by identifying their stage, from colonization, to critical colonization, to infection while referring to the clinical findings indicated by NERDS and STONES (see Question 3 and Table 13).[192] With deep infections particularly, increasing pain is the most useful clinical finding for diagnosis.

(ii) Other factors— Aside from infection, other conditions such as inflammation, trauma, pressure, edema and the like can also cause pain; therefore, these should be considered in the differential diagnosis when pain increases (Table 14).[175] Inflammation can be a major cause of pain depending on the underlying disease. Moreover, the inflammatory cells and the inflammatory mediators in exudates can damage not only the granulation tissue but also the healthy skin surrounding a wound, thereby exacerbating the infection and aggravating the tissue damage.

5) Select an appropriate dressing material and topical agent to minimize the wound-related pain. In wounds in which the nerve endings are exposed at the wound surface, pain arises when the wound is exposed to air or is irritated,[193,194] and drying of the wound surface also causes pain while changing the dressing. Therefore, it is important to maintain an appropriately moist environment at the wound surface. Dressing materials are selected by taking into consideration appropriate adhesion and the balance between the exudate volume and the dressing material's absorptive capacity (see Question 5, Table 7). Even if they are non-sticking, products with a high absorptive capacity require caution, as they may still stick when the wound surface dries. Conversely, the use of an adhesive product with a low absorptive capacity on a wound with a high volume of exudates causes maceration of the wound margins and therefore pain. As soft silicone does not adhere to wound surfaces and seals tightly to the skin at the wound margins, it is rare for the wound margins to become macerated because of exudates. Therefore, the use of soft silicone or of a polyurethane foam product that uses a silicone gel (e.g. Mepilex® border, Mepilex® lite, Hydrosite® AD gentle) is recommended on wound-contacting surfaces.from reference

Although the effects of the active agent are the primary selection criteria for topical agents, the selection of a base suitable for the volume of exudates to maintain the wound surface in an appropriate moist environment is important.

Figure 4: The WHO's three-step pain relief ladder	
Freedom from cancer pain	3
Opioid for moderate to severe pain ±Non-opioid ±Adjuvant	
Pain persisting or increasing	2
Opioid for mild to moderate pain ±Non-opioid ±Adjuvant	
Pain persisting or increasing	1
Non-opioid ±Adjuvant	
Pain	

Figure 4. The World Health Organization's three-step pain relief ladder.

Ointments with a highly absorbent base, such as macrogol, can cause pain due to wound drying. In Japan, iodine-containing ointments (e.g. U-Pasta® Kowa ointment, Cadex® ointment, Iodocoat® ointment) use a macrogol base and are slightly irritating. Caution is also needed when using ointments containing a protease (bromelain ointment), as they also use macrogol as a base and have an active agent that is irritating. Silver sulfadiazine creams (Geben cream) are also contraindicated for minor burns, as they cause pain.

6) Drug therapy for pain. When using drug therapy, the selection of an analgesic must be made on the basis of the estimated contributions of nociceptive pain and neuropathic pain. Nociceptive pain is treated in accordance with the World Health Organization's three-step pain relief ladder (Fig. 4).[195] Mild pain treatment can start with non-opioids (non-steroidal anti-inflammatory drugs or acetaminophen). If the treatment causes strong pain, administration prior to treatment should be considered. If the effect is insufficient, the use of opioids should be considered. The latter is effective in relieving strong pain during the treatment of extensive burns.

At present, the opioids indicated for chronic non-cancer pain include rapid-release morphine preparations (e.g morphine hydrochloride tablets), codeine preparations, fentanyl patches (Durotep® MT patch), tramadol/acetaminophen combinations (Tramcet®), buprenorphine patches (Norspan® tape) and the like. For neuropathic pain, pregabalin and analgesic adjuvants (e.g. antidepressants, antiepileptics, antiarrhythmics, local anesthetics) should be used. Nerve blocks are effective for all types of pain.

7) Building a relationship of trust with the patient. Many chronic pain patients suffer from depression and feel powerless and socially isolated. Complaints about pain differ by individual. It is very important for medical professionals to always ask their patients questions, to listen closely to their complaints and to watch carefully for non-verbal signs. Maintaining favorable communication with patients at the scene of treatment, respecting the wishes of the patient and building a relationship of trust are important. Pain is the most significant factor impacting QOL for chronic wound patients,[196,197] but what such patients desire the most is a brief period of treatment. Thus, treatment must be endeavored based on accurate information.

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