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Research Progress of Chronic Wounds

Lizhen Dai[1], Hongtao Xiong[2,*]

[1]Department of Hand Surgery, Longgang District Orthopedic Hospital, Shenzhen, Guangdong, Shenzhen 518116, Guangdong, China.
[2]Department of Hand and Microvascular Surgery, Shenzhen People's Hospital (The Second Clinical Medical College, Jinan University; The First Affiliated Hospital, Southern University of Science and Technology), Shenzhen 518020, Guangdong, China.

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***Corresponding author:** Hongtao Xiong, Department of Hand and Microvascular Surgery, Shenzhen People's Hospital (The Second Clinical Medical College, Jinan University; The First Affiliated Hospital, Southern University of Science and Technology), Shenzhen 518020, Guangdong, China.
Email: xionghongtaosz@126.com

Abstract

The vast majority of wounds progress unrestrictedly through normal wound healing processes (hemostasis, inflammation, proliferation, remodeling). However, a large proportion of people fail to progress through these steps, resulting in chronic wounds with associated morbidity and costs. How to deal with chronic wounds has become a hot topic in clinical research, and the definition of chronic wounds is still controversial. A retrospective analysis of past clinical cases and literature reviews, the evaluation of the diagnosis and treatment of chronic wounds, and the key points of diagnosis and treatment at the emerging stage. Chronic wounds are commonly divided into: diabetic foot ulcers, pressure ulcers, venous ulcers, and ischemic ulcers. More medical data are still needed to provide more effective options for the diagnosis and treatment of chronic wounds. Currently, treatment is based on the TIME (tissue debridement, infection/inflammation management, water balance, and wound edge) concept. This ensures proper treatment is given. The vast majority of wounds are likely best treated with simple treatment and regular debridement.

Keywords

Chronic wounds, classification, treatment

1. Definition

The term chronic wound first appeared in literature in the 1950s to refer to wounds that are difficult to heal or do not follow the normal healing process [1, 2]. The term's uncertainty about wound duration has been criticized. Various alternative terms have been proposed, such as refractory wounds, non-healing wounds, and complex wounds [3, 4]. "Chronic wounds" are generally defined as "wounds with defective anatomical and functional integrity that have not been repaired in an orderly and timely manner after 3 months" [5]. Leaper and Durani [6] defined it as a wound that did not shrink by 20%-40% in size after 2 months. Recent reviews have also highlighted the lack of consensus on the definition of "chronic wound" and the need for further research in this area [7].

2. Pathogenesis and etiology

The hemostatic phase of wound healing begins immediately after injury, preventing excessive bleeding through vasoconstriction and simultaneous formation of blood clots [8]. Blood clots are composed of fibrin and extracellular matrix proteins (fibronectin, vitronectin, and thrombospondin) that serve as temporary protection of the injured area and a matrix for the migration of leukocytes, keratinocytes, and fibroblasts [9]. Platelets trapped within a blood clot contain growth factors and cytokines that can activate and attract neutrophils, macrophages, endothelial cells, and fibroblasts during the inflammatory and proliferative phases [9]. Once a temporary wound matrix (eg, a blood clot) is in place, vasodilation begins, enabling platelets to release their cytokines and growth factors [10].

At the heart of the inflammatory phase is the process of destroying and removing bacteria and other debris, such as damaged cellular components [11]. Neutrophils are attracted to cytokines and growth factors released during the coagulation phase. They initiate debridement by phagocytosis, which is mediated by the release of antimicrobial reactive oxygen species (ROS) and several proteolytic enzymes (proteases) [10]. In later stages, the inflammatory response is supported by macrophages and lymphocytes [10, 12]. Inflammatory cells are not only important in the defense and clearance of bacteria and debris, they are also an important source of various growth factors and cytokines that initiate the proliferative phase of wound healing [11, 12].

The proliferative stage is characterized by the development of granulation tissue [11]. Fibroblasts migrate to the wound site and synthesize different components (eg, collagen, fibronectin) to form a new extracellular matrix, replacing the temporary wound matrix formed during the coagulation phase [10]. At the end of this stage, fibroblasts differentiate into myofibroblasts. Myofibroblasts are a contractile phenotype of fibroblasts that play a major role in the approach of the wound edge [10]. These processes require an adequate blood supply, which is accomplished by the formation of new blood vessels [11]. Damage to blood vessels during injury and subsequent hypoxia leads to the formation of angiogenesis-promoting factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor and platelet-derived growth factor (PDGF) [8]. These factors bind to endothelial cell receptors of existing blood vessels, which in turn secrete proteolytic enzymes that dissolve extracellular matrix proteins. This enables endothelial cells to proliferate and migrate into the wound [12]. These newly formed blood vessels are responsible for the granular appearance of the granulation tissue. Later, the new blood vessels differentiate into arteries and veins [12].

The wound healing process ends with wound remodeling. During this stage, the extracellular matrix components formed by fibroblasts during the proliferative phase are degraded by matrix metalloproteinases (MMPs) and replaced by stronger collagen I to form scar tissue [11]. To close the wound area, wound contraction by myofibroblasts continues at this stage [8, 9]. Finally, angiogenesis is inhibited, fibroblasts are eliminated, and the wound healing process is ultimately stopped [8, 12]. The result of the final stage is that the strength of scar tissue is comparable to that of undamaged skin [8].

The healing process usually stalls in the inflammatory or proliferative phase. Acute wounds are appropriately progressed to complete wound healing, whereas chronic wounds often exhibit a dysregulated wound healing process [8, 13, 14]. Chronic wounds usually stagnate in the inflammatory phase due to an imbalance between inflammatory cells and their inhibitors [14]. The combination of bacterial contamination and repeated injury due to ischemia (arterial insufficiency), internal (venous insufficiency), and external pressure (immobility, diabetic neuropathy) results in persistent activation of inflammatory cells in the wound [13]. Activated inflammatory cells secrete cytokines, which in turn produce several proteolytic enzymes (eg, MMPs) that actively degrade extracellular matrix components required for proper wound closure [8, 13]. MMPs also degrade growth factors and growth factor receptors, which are important for the progression of subsequent stages of the wound healing process [13].

In addition, chronic wounds often experience an impaired proliferative phase. Fibroblasts, which play a major role in the proliferative phase, have reduced growth factor receptors, reduced endothelial cell mitogenic potential and migratory capacity in chronic wounds. This inhibits the formation of vital granulation tissue, deposition of extracellular matrix, and stimulation of remodeling [8, 14].

3. Common clinical classification

Diabetic Foot Ulcer: Diabetic foot ulcer (DFU) is a common complication of diabetes, accounting for significant morbidity, mortality, and healthcare expenditures. [15] Diabetes can cause peripheral neuropathy and ischemic disease. DFU often appears in the toes and may form callus in stressed areas. Pain is a common feature. When a diabetic foot ulcer is diagnosed, peripheral nerve function and arterial blood flow, structural deformities of the foot, and the presence of clinical infection should be assessed. Active ischemia or infection will significantly affect the treatment plan.

Pressure ulcers: are caused by tissue trauma that occurs due to increased mechanical forces (pressure, shear, or friction). Most commonly, crushing of adjacent tissue is found at bony protrusions, especially on the sacrococcygeal and heel where forces are exerted. Transferring pressure from the affected area is the cornerstone of the treatment of pressure injuries [16].

Venous ulcers: Venous leg ulcers result from chronic venous insufficiency and subsequent edema [17]. It usually occurs in areas with dependent edema, most commonly the medial or lateral ankle or calf. There is usually a large amount of exudate. Pain may occur, but is usually less severe than in ischemic ulcers. To manage venous ulcers, the underlying disease causing leg edema should be investigated and treated, if present. These include venous insuffi-

ciency, heart failure, cirrhosis, chronic kidney disease and deep vein thrombosis, among others. The list of medications should be reviewed, with particular attention to calcium channel blockers, nonsteroidal anti-inflammatory drugs (NSAIDS), and certain oral hypoglycemic agents, all of which can cause edema in the legs.

Ischemic Ulcers: Ischemic ulcers of the legs most commonly occur in the context of peripheral arterial disease (PAD). They are frequently present in patients with cardiovascular risk factors (smoking, diabetes, hypertension, hyperlipidemia, advanced age, family history of atherosclerotic vascular disease) and therefore aggressive modification of these risk factors, especially in It is the bestpreventive strategy in patients with known PAD. The characteristic symptom of PAD is lower extremity leg pain with limited lower extremity mobility (intermittent claudication). Rest pain, especially at night, develops as ischemia worsens. Pain can be severe [18].

4. Diagnostic monitoring methods for chronic wounds

Currently available monitoring methods are: biofilm detection [19, 20]; proteolytic enzyme activity measurement for wound monitoring (infection, non-healing) [21,22]; advanced microbial analysis (sequencing, table type) [23]; computer analysis of digital wound images [24]; imaging techniques for wound monitoring [25]; wearable sensors for wound monitoring [26].

Over the past few years, it has been demonstrated in clinical practice that it is difficult to properly detect factors that complicate the healing of chronic wounds. Therefore, diagnostic tests currently focus on monitoring the wound healing process and timely detection of complications, such as biofilm formation or the onset of infection. This article focuses on two modalities that may have the greatest impact on clinical practice: the monitoring of biofilms and the measurement of proteolytic enzyme activity.

Currently, biofilms are regarded as one of the major challenges in chronic wound healing. As bacteria multiply in a wound, they tend to form groups that wrap themselves in extracellular polymers. The resulting bacterial structures have been described as biofilms. Bacterial grouping within biofilms provides them with protection against endogenous (inflammatory cells) and exogenous (gels, dressings) antimicrobial activity [20]. If these bacteria are pathogenic, biofilm formation can lead to persistent inflammation within chronic wounds, delaying wound healing and complicating wound treatment. Therefore, it is important to effectively remove (pathogenic) biofilms by debridement and subsequent effective antimicrobial therapy. A major challenge in clinical practice is to determine whether biofilms are present in chronic wounds and, in particular, whether such biofilms are pathogenic. Metcalf, Bowler, and Hurlow [20] developed a clinical algorithm for biofilm detection in clinical practice, based on visual indicators, to distinguish biofilms from slough, and to distinguish planktonic bacteria (single cells) from biofilms. indirect indicators. The algorithm enables clinicians to detect biofilms without additional diagnostic tests. [19] demonstrated the ability to visualize biofilms by Gram staining, fluorescence in situ hybridization, and environmental scanning electron microscopy imaging. Although advanced techniques have been employed to detect biofilms, they overlook the importance of distinguishing symbiotic and pathogenic biofilms.

Recent research has specifically focused on measuring proteolytic enzyme activity, believed to be elevated in non-healing and infected wounds. Proteolytic enzymes work primarily during the inflammatory phase to help destroy bacteria and debris. Once the wound progresses to the proliferative stage, the amount and activity of proteolytic enzymes decreases. However, in chronic wounds, the inflammatory and proliferative phases persist, with high proteolytic enzyme activity [21]. Therefore, Serena [21] adopted the idea of measuring proteolytic enzyme activity, is elevated protease activity (EPA), in chronic wound exudate. In a follow-up study, Serena et al. [21] demonstrated a correlation between elevated proteolytic enzyme (MMP and human neutrophil elastase) activity and impaired wound healing. Their method has been commercialized as the WoundChek protease status test. Blokhuis-Arkes et al. [22] demonstrated that elevated proteolytic enzyme activities of human neutrophil elastase, myeloperoxidase and lysozyme are closely related to the infection status of acute and chronic wounds. The researchers are also working on test equipment for clinical practice. Serena et al. and Blokhuis-Arkes et al. encouraged the development of point-of-care diagnostic tools using proteolytic enzyme activity in the treatment of chronic wounds [21, 22].

5. Treatment of chronic wounds

Currently, the routine treatment of chronic wounds is based on the TIME concept [8, 27]. This approach focuses on tissue debridement, infection/inflammation management, water balance, and wound margins to achieve complete epithelialization. The treatment of long-term non-healing wounds needs to be treated according to the specific situation [27]. T (tissue): This involves assessing the presence of nonviable or necrotic tissue, foreign bodies, biofilms. Interventions include debridement, with a variety of techniques available; wound cleaning and negative pressure wound therapy. I (Infection/Inflammation): This involves assessing the etiology of the wound and treating

infection or inflammation not related to infection. Interventions include topical and systemic antibiotics. Localized infection is not advocated for systemic antibiotic therapy due to poor biofilm permeability, altered basal tissue perfusion in chronic wounds, and the risk of antibiotic resistance. Topical infections are treated with topical antimicrobials (silver, iodine, chlorhexidine, methylene blue/crystal violet, surfactants) [28]. M (Moisture Imbalance) involves the assessment and management of wound fluid/exudate. E (Epithelial margin progression) involves assessing and managing the condition of the wound margin and surrounding skin [27].

In general, there are the following processing methods.

1) The wound surface is small, and the reason for non-union is foreign body, necrotic tissue, small sequestrum, or poor drainage. Expansion is needed to scrape out sequestrum, foreign bodies, and necrotic tissue; if the drainage is not smooth, the drainage port needs to be expanded, and a reasonable dressing change should be performed after surgery. If there is no skin defect and acute inflammation of the surrounding soft tissue, after thorough wound expansion, combined with the proper use of local and systemic antibiotics, the wound can be closed directly after surgery to strive for primary wound healing. Compared with dressing change, the course of treatment can be significantly shortened, and the quality of wound healing is also better. After the factors of non-healing of the wound are completely removed, the wound surface can heal quickly.

2) Due to the deep infection and necrotic tissue, and the scope is large, although it is possible to suture the skin directly after debridement, because there may be large or deep cavities after the operation, there may be local accumulation of fluid and blood, which can easily lead to Infections and abscesses form, making surgery a failure. In the face of this kind of situation, thorough expansion should be performed, and correct dressing changes should be done after surgery to promote granulation growth. After the cavity is filled with granulation tissue, depending on the situation, dressing can be continued until the wound heals, or the skin can be sutured directly after secondary expansion, or free skin grafting can be used to close the wound.

3) If the wound does not heal due to the large defect of the skin and the remaining necrotic tissue, the wound expansion should be carried out in time. If the wound conditions permit, a skin graft can be used to eliminate the wound in one stage; if the local base condition is poor, but there is no bone Or other ischemic tissue is exposed, it is estimated that the granulation can grow faster, postoperative physical therapy and wet compress can be used to accelerate the growth of granulation, and free skin grafting can be used in the second stage. If the granulation has aged, the wound can be expanded again to remove the aged granulation tissue. After the fresh granulation grows, further free skin grafting can be performed. In case of granulation edema, local wet compress with 3% sodium chloride solution and pressure bandage can be used. After the granulation edema subsides, free skin grafting can be used to repair the wound.

4) The wound is large and deep. After removing necrotic tissue, foreign bodies, and sequestered bone, it is seen that there is a large range of bone or ischemic tissue exposed in the wound. The wound cannot be sutured directly, and the wound cannot be closed by free skin grafting. If the wound is left open and only treated with dressing change, the exposed tissue will be further infected and necrotic, and it will be difficult for the wound to heal itself. To deal with this kind of situation, it should be possible to perform a one-stage skin flap transplantation to repair the wound on the basis of thorough expansion.

Flap transplantation is performed after debridement of the infected wound. Infection has a great threat to the successful prognosis of the flap. However, clinical practice has proved that the surgical indications and timing of the operation should be strictly controlled. After close observation and timely treatment, the success rate of flap transplantation is guaranteed [29].

6. Conclusion

Chronic wounds are the more common clinical conditions and are those that are difficult to heal or do not follow the normal healing process, and the duration of which is debated. Treatment is based on the TIME concept. This ensures that proper treatment is given and that the reaction of the wound is noticed and acted upon. While many new treatments have emerged over the past 10 years, to date only a few treatments have a clear evidence base on which to practice. Until these data emerge, the vast majority of wounds are likely best treated with simple treatment and regular debridement.

References

[1] Greeley, P. W. (1953). Plastic surgical closure of chronic open wounds of the leg [J]. *Ind Med Surg*, 1953, 22(1): 22-3.

[2] Carleson, R., Garsten, P. (1952). Wound therapy with septofyllin, with special consideration of its effect on chronic leg ulcers [J]. *Nord Med*, 1952, 47(13): 412-6.

[3] Cazander, G., Pritchard, D. I., Nigam, Y., et al. (2013). Multiple actions of Lucilia sericata larvae in hard-to-heal wounds: larval secretions contain molecul es that accelerate wound healing, reduce chronic inflammation and inhibit bacterial infection [J]. *Bioessays*, 2013, 35(12): 1083-92.

[4] Nunan, R., Harding, K. G., Martin, P. (2014). Clinical challenges of chronic wounds: searching for an optimal animal model to recapitulate their co mplexity [J]. *Dis Model Mech*, 2014, 7(11): 1205-13.

[5] Dubhashi, S. P., Sindwani, R. D. (2015). A Comparative Study of Honey and Phenytoin Dressings for Chronic Wounds [J]. *Indian J Surg*, 2015, 77(Suppl 3): 1209-13.

[6] Leaper, D. J., Durani, P. (2008). Topical antimicrobial therapy of chronic wounds healing by secondary intention using iodine products [J]. *Int Wound J*, 2008, 5(2): 361-8.

[7] Kyaw, B. M., JRbrink, K., Martinengo, L., et al. (2018). Need for Improved Definition of "Chronic Wounds" in Clinical Studies [J]. *Acta Derm Venereol*, 2018, 98(1): 157-158.

[8] Demidova-Rice, T. N., Hamblin, M. R., Herman, I. M. (2012). Acute and impaired wound healing: pathophysiology and current methods for drug delivery, part 1: nor mal and chronic wounds: biology, causes, and approaches to care [J]. *Adv Skin Wound Care*, 2012, 25(7): 304-14.

[9] Morton, L. M., Phillips, T. J. (2016). Wound healing and treating wounds: Differential diagnosis and evaluation of chronic wounds [J]. *J Am Acad Dermatol*, 2016, 74(4): 589-605; quiz 605-6.

[10] Velnar, T., Bailey, T., Smrkolj, V. (2009). The wound healing process: an overview of the cellular and molecular mechanisms [J]. *J Int Med Res*, 2009, 37(5): 1528-42.

[11] Tsourdi, E., Barthel, A., Rietzsch, H., et al. (2013). Current aspects in the pathophysiology and treatment of chronic wounds in diabetes mellitus [J]. *Biomed Res Int*, 2013: 385641.

[12] Reinke, J. M., Sorg, H. (2012). Wound repair and regeneration [J]. *Eur Surg Res*, 2012, 49(1): 35-43.

[13] Mast, B. A., Schultz, G. S. (1996). Interactions of cytokines, growth factors, and proteases in acute and chronic wounds [J]. *Wound Repair Regen*, 1996, 4(4): 411-20.

[14] Satish, L. (2015). Chemokines as Therapeutic Targets to Improve Healing Efficiency of Chronic Wounds [J]. *Adv Wound Care (New Rochelle)*, 2015, 4(11): 651-659.

[15] Everett, E., Mathioudakis, N. (2018). Update on management of diabetic foot ulcers [J]. *Ann N Y Acad Sci*, 2018, 1411(1): 153-165.

[16] Dealey, C., Brindle, C. T., Black, J., et al. (2015). Challenges in pressure ulcer prevention [J]. *Int Wound J*, 2015, 12(3): 309-12.

[17] Vivas, A., Lev-Tov, H., Kirsner, R. S. (2016). Venous Leg Ulcers [J]. *Ann Intern Med*, 2016, 165(3): Itc17-itc32.

[18] Hoversten, K. P., Kiemele, L. J., Stolp, A. M., et al. (2020). Prevention, Diagnosis, and Management of Chronic Wounds in Older Adults [J]. *Mayo Clin Proc*, 2020, 95(9): 2021-2034.

[19] Oates, A., Bowling, F. L., Boulton, A. J., et al. (2014). The visualization of biofilms in chronic diabetic foot wounds using routine diagnostic microscopy met hods [J]. *J Diabetes Res*, 2014, 2014: 153586.

[20] Metcalf, D. G., Bowler, P. G., Hurlow, J. (2014). A clinical algorithm for wound biofilm identification [J]. *J Wound Care*, 2014, 23(3): 137-8, 140-2.

[21] Serena, T. E. (2014). Development of a Novel Technique to Collect Proteases from Chronic Wounds [J]. *Adv Wound Care (New Rochelle)*, 2014, 3(12): 729-732.

[22] Blokhuis-Arkes, M. H., Haalboom, M., Van Der Palen, J., et al. (2015). Rapid enzyme analysis as a diagnostic tool for wound infection: Comparison between clinical judgment, microbiological analysis, and enzyme analysis [J]. *Wound Repair Regen*, 2015, 23(3): 345-52.

[23] Becerra, S. C., Roy, D. C., Sanchez, C. J., et al. (2016). An optimized staining technique for the detection of Gram positive and Gram negative bacteria within tissue [J]. *BMC Res Notes*, 2016, 9: 216.

[24] Aldaz, G., Shluzas, L. A., Pickham, D., et al. (2015). Hands-free image capture, data tagging and transfer using Google Glass: a pilot study for improved wo und care management [J]. *PLoS One*, 2015, 10(4): e0121179.

[25] Taverna, D., Pollins, A. C., Sindona, G., et al. (2015). Imaging mass spectrometry for assessing cutaneous wound healing: analysis of pressure ulcers [J]. *J Proteome Res*, 2015, 14(2): 986-96.

[26] Hattori, Y., Falgout, L., Lee, W., et al. (2014). Multifunctional skin-like electronics for quantitative, clinical monitoring of cutaneous wound healin g [J]. *Adv Healthc Mater*, 2014, 3(10): 1597-607.

[27] Harries, R. L., Bosanquet, D. C., Harding, K. G. (2016). Wound bed preparation: TIME for an update [J]. *Int Wound J*, 2016, 13 Suppl 3: 8-14.

[28] Sibbald, R. G., Elliott, J. A., Persaud-Jaimangal, R., et al. (2021). Wound Bed Preparation 2021 [J]. *Adv Skin Wound Care*, 2021, 34(4): 183-195.

[29] Wang Shuhuan. (2011). The third edition of Hand Surgery [M]. Beijing: People's Health Publishing House, 2011: 812.