CONTINUING MEDICAL EDUCATION

WOUND MANAGEMENT

Course Director

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Program Information

Needs assessment

Wound healing is an essential multistep biological process which involves delicate interaction between different cellular and molecular mechanisms and ultimately results in satisfactory healing of the wounds, both surgical and non-surgical wounds. Failure of normal wound healing can predispose to inappropriate pathological wound inflammation, and several complications can ensue. Unrestricted, self-sustaining inflammation is a major underlying cause for failure of chronic wounds to heal. Both local and systemic factors can impair wound healing. Superadded wound infections, in particular, are a strong impediment to wound healing; once appropriately addressed through topical and/or systemic antimicrobials, wound healing and overall patient outcomes can be enhanced. The principles of wound management have been redefined in the past decade. This CME program provides a broad understanding of wound management, and both current and future potential wound healing treatment options for acute and chronic wounds.

Learning objectives

1. To understand concepts related to wound management and identify factors which can affect it
2. To understand the impact of infections on the wound healing process and describe how to circumvent it
3. To describe current and future wound management approaches

Target participants

Dermatologists, surgeons, consultant physicians, and pediatricians

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Dr. Tania Phillips has nothing to disclose with regard to commercial interests.

Method of participation in the program

- Study all parts of the educational activity
- Submit the posttest questions with answers, evaluation and request for certificate of participation forms
- A certificate of participation will be issued by Boston University School of Medicine upon completing the evaluation and the posttest with a score of 60% or better.

Program activity

Release date: August 2020

Expiration date: July 2021

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Contents

CASE

A 57-year-old patient of type 2 diabetes visited medicine OPD in a visibly unwell state, complaining of fatigue, along with an ulcer and pain in his left foot developing since the past 1 month. The pain in his left foot was continuous, leading to difficulty in walking. He walked with a limp. The patient had history of diabetes since last 15 years and was on a combination of metformin 500 gm daily and glimepiride 2 mg daily. There was no other significant medical history, including past history of hypertension, heart disease, peripheral arterial disease or stroke. He had never smoked but used to take alcohol occasionally. On examination, his PR (radial pulse) was 88/minute, regular and good volume, RR was 18/minute and BP was 136/80 mmHg taken in the right arm sitting position. Local examination of the left foot revealed an ulcer 3 cm × 3 cm in the 2nd toe, with inflamed margins and surrounding edema. Left pedal pulse was feeble. Touch sensation in the affected area was also absent. Wound swabs were taken from the ulcer area, wound cleaned and dressed with an antiseptic, and the patient was advised admission which he refused. Samples for blood glucose profile, HbA1c, kidney and liver function tests, complete blood count, CRP, blood culture and urine examination were obtained and sent to the laboratory.

He was empirically started on oral cefuroxime 500 mg twice daily; anti-diabetic medications were continued. Local cleaning of the wound area and application of cadexomer iodine topical preparation over the ulcer site was advised. Additionally, oral serratiopeptidase 10 mg thrice daily was prescribed. His fasting blood glucose was 246 mg/dl, HbA1c was 7.6% and TLC was 16,000 cells/mm^3, with 80% polys. Blood culture and wound swab showed significant growth of MRSA sensitive to linezolid but resistant to cefuroxime. Cefuroxime was discontinued and he was given IV Linezolid 600 mg for 3 days followed by oral linezolid 600 mg twice daily. Dose of metformin was increased to 1 gm/day and glimepiride was continued. In the next visit scheduled after 1 week, his ulcer showed significant improvement with considerable reduction in surrounding edema and cellulitis. Linezolid was prescribed for a total duration of 3 weeks and discontinued with complete healing of ulcer.

SECTION 1

Understanding wound healing and objectives of wound management

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INTRODUCTION

Wound healing is a dynamic process which facilitates recovery after any injury that disrupts continuity of the cutaneous epithelium or subcutaneous tissue. Normal wound healing involves a complex, dynamic interaction between different cellular and acellular components occurring at the site of injury, which results in predictable tissue repair and early restoration of optimal function.[1,2] Any interruption in this physiological process can either delay or completely stall the wound healing cascade, resulting in chronic wounds.[2] Non-healing wounds can be associated with multiple complications, including infections, patient discomfort, prolonged hospital stays, and delayed resumption of normal activities.[1] Over the last few decades, our knowledge regarding the wound healing process has evolved rapidly. Although wound healing is a seemingly continuous process, it progresses through several overlapping stages; an initial stage of coagulation and local inflammation; followed by the proliferative stage; and the final stage of wound remodeling.[3] Several local, regional, and systemic factors can negatively impact wound healing. [2,3] There is growing evidence that psychological and behavioral factors can also affect wound healing outcomes.[1,4]

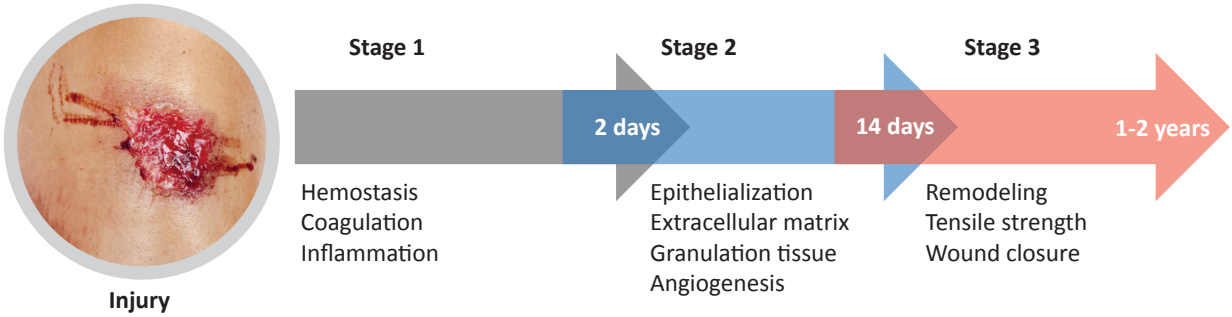
Wound management remains a challenging clinical problem. Effective wound treatment should be the primary objective of all clinicians who attend patients with injuries.[5] The paradigms of wound management have changed with time. While in the past, the practice of keeping the wound dry was considered ideal, there has been a paradigm shift towards provision of a moist environment for achieving optimal wound healing. Several types of dressings are currently available that can optimize the wound environment and accelerate wound healing process.[6] Getting familiar with the challenges posed by poorly healing wounds and identifying appropriate ways of addressing them can optimize wound outcome, reduce pertinent healthcare costs, and improve quality of life of the affected patients.[7]

PHYSIOLOGICAL MECHANISMS INVOLVED IN WOUND HEALING

Wound healing occurs in a continuous manner, although its cellular and biochemical events progress through several overlapping stages. Wound healing process is divided into three broad stages (Figure 1):[3,5]

- **Stage 1** - Coagulation, hemostasis, and inflammation

Figure 1: Stages of wound healing



Based on information from: 1. Hunt TK, Hopf H, Hussain Z. Physiology of wound healing. *Adv Skin Wound Care.* 2000 May-Jun;13(2 Suppl):6-11. **2.** Velnar T, Bailey T, Smrkolj V. The wound healing process: an overview of the cellular and molecular mechanisms. *J Int Med Res.* 2009 Sep-Oct;37(5):1528-42. **3.** Gonzalez AC, Costa TF, Andrade ZA, Medrado AR. Wound healing - A literature review. *An Bras Dermatol.* 2016 Sep-Oct;91(5):614-620.

- **Stage 2** - Proliferation/repair
- **Stage 3** - Remodeling and wound scar formation.

Coagulation, hemostasis, and inflammation

Immediately post injury, both hemostasis and coagulation occur at the wound site, to stem blood loss.[3,5,8] Platelets collect at the site of injury and form a platelet plug, which triggers the coagulation cascade. They release several growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor (TGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF). These growth factors facilitate influx of inflammatory cells, such as leukocytes, neutrophils, and macrophages, to the site of injury.[8,9] These inflammatory cells release several lysosomal enzymes, antibacterial proteases, and reactive oxygen species (ROS), which promote clean-up of bacteria and cellular debris from the wound site.[8] This cellular response is established within the first 24 hours after the injury and can extend for up to two days.[10] The inflammatory phase starts with the influx of neutrophils and macrophages to the wound. The macrophage plays a critical role in phagocytosis and stimulation of angiogenesis and granulation tissue formation through the release of multiple growth factors including TGF beta, PDGF, FGF, interleukins and TNF alpha.[9]

Proliferative stage and deposition of granulation tissue

After the initial stage of hemostasis and inflammation, wound healing enters the proliferative stage. Most wounds enter the proliferative stage within 48 hours of injury.[10] The proliferative stage is characterized by fibroplasia and wound contraction, granulation tissue formation, angiogenesis and epithelialization; fibroblasts which migrate to the site of injury in response to growth factors are important in deposition of collagen, and elastin, as well of secretion of extracellular matrix proteins and proteinases. Type III collagen is predominant early in the healing process. New extracellular matrix containing proteoglycans and glycosaminoglycans is deposited and local epithelialization occurs as keratinocytes migrate over the wound bed from adnexal structures as well as from the wound margins to form a viable epithelial barrier.[9] Triggered by local hypoxia, the release of pro-angiogenic factors, such as PDGF, VEGF, fibroblast growth factor 2 (FGF-2), and progenitor endothelial cells, formation of new blood vessels occur at the wound site.[8,9,11]

Remodeling and wound scar formation

The final stage of wound healing is the remodeling stage, which involves reorganization, degradation, and re-synthesis of the extracellular matrix, to maximize its tensile strength.[8-10] This process is slow but progressive, starting about 2 weeks after the injury and continuing for up to 1 year (or even longer).[10] During this stage, fibroblasts, blood vessels, and inflammatory cells start to disappear from the wound area; type III collagen undergoes degradation and synthesis of stronger type I collagen increases; and the wound gradually closes. These events ultimately culminate in a wound scar.[8,9] However, it is noteworthy that the maximum scar strength never reaches that of unwounded skin.

CLASSIFICATION OF WOUNDS AND FACTORS THAT COMPROMISE WOUND HEALING

Wounds can be grouped into two main categories; acute and chronic wounds. Acute wounds are usually a result of an external injury that disrupts the continuity of the skin and/or subcutaneous tissue. Included in this category are surgical wounds, burns, abrasions, lacerations, and gunshot injuries.[12] Acute wounds heal in a predictable time-frame, usually within 8-12 weeks from the time of injury.[13] Chronic wounds, in contrast, fail to heal in a normal and timely manner. They are usually associated with a predisposing condition that compromises integrity of the skin and connective tissues. This category includes venous leg ulcers, diabetic foot ulcers, and pressure sores.[12] Most wounds enter the chronic phase due to pathological interruption in the normal healing process which prevents their repair in an orderly and timely manner.[13] Chronic wounds are frequently associated with persistent infections, prolonged or excessive inflammation, and drug-resistant microbial biofilms; all factors which contribute to suboptimal response to treatment and poor wound healing. Chronic wounds have emerged as a major challenge for the healthcare professionals worldwide. They can last for months or even years, recur in almost 60-70% patients, and can compromise the daily living activities, and quality of life of affected patients.[7] They incur significant treatment-related costs.[7,14]

Several characteristics differentiate acute wounds from chronic wounds:[9]

- Abnormal function of fibroblasts in chronic wounds is well-documented; this can result from an unfavorable wound environment or defect in the fibroblasts themselves. Fibroblasts from chronic wounds have low proliferative capacity and respond poorly to growth factors.
- High concentration of proteases at the wound site has also been documented in chronic wounds. In addition, there are high levels of inflammatory cytokines and reactive oxygen species. This contributes to a degraded poorly functioning tissue matrix and poor healing.

Factors that compromise wound healing:

Wound healing can be compromised by several local, regional, systemic, and lifestyle factors:

- Local factors which can affect wound healing include edema, ischemia, low oxygen tension, and infections
- Regional factors include arterial and/or venous insufficiency, neuropathy, pressure
- Systemic factors include co-associated disorders such as diabetes, obesity, malnutrition, immunosuppression, cardiac failure, connective tissue disorders, endocrine diseases
- Lifestyle factors such as smoking and alcohol abuse can also variably impact wound healing.[2,3]

Psychological factors, particularly stress, can interrupt wound healing. The underlying mechanism may be related to activation of both the hypothalamic-pituitary-adrenal axis and sympathetic-adrenal-medullary axis, thereby increasing levels of glucocorticoids and catecholamines; both these hormones can interfere in the wound healing cascade at several stages.[1,4]

Table 1: Objectives of wound management

• Heal wound in a timely manner
• Strive for best possible functional and cosmetic scar
• Identify and treat factors which interrupt wound healing
• Treat underlying metabolic and/or systemic abnormalities
• Minimize risk of complications

Based on information from: 1. Sarabahi S. Recent advances in topical wound care. *Indian J Plast Surg*. 2012 May-Aug; 45(2): 379–387. **2.** Frykberg RG, Banks J. Challenges in the Treatment of Chronic Wounds. *Adv Wound Care (New Rochelle)*. 2015 Sep 1; 4(9): 560–582. **3.** Moreira ME, Markovchick VJ. Wound management. *Emerg Med Clin North Am*. 2007 Aug;25(3):873-99, xi.

OBJECTIVES OF WOUND MANAGEMENT

The primary objectives of wound management should be to attempt to heal the wound in a timely manner, with best possible functional and cosmetically appealing scar. Factors which can interfere with the normal wound healing process should be identified and appropriately addressed. Underlying metabolic and/or systemic abnormalities, if present, should also be managed. Additionally, every effort should be made to minimize risk of any wound-related complications (Table 1).[6,7,15]

A thorough patient assessment, particularly focusing on the wound characteristics, is necessary. A full history and physical exam should be performed to detect any systemic cause of poor wound healing.[16] Etiological cause(s) of chronic wounds should be identified and treated. In addition, good wound bed preparation practices are necessary to provide an ideal local environment allowing wounds to heal. All wounds that do not heal sufficiently even after 4 weeks of standard wound care require re-assessment, and possibly advanced wound care therapy.[7]

KEY HIGHLIGHTS

- Any interruption in the wound healing process can either delay or completely stall the wound healing cascade, resulting in chronic wounds.
- Non-healed wounds are associated with several complications, including infections, patient discomfort, prolonged hospital stays, and delayed resumption of normal activities.
- Immediately post injury, hemostasis and coagulation occurs at the wound site. Platelets release several growth factors which contribute to the wound healing process.
- Chronic wounds fail to heal in a normal and timely manner. Common type of chronic wounds include venous leg ulcers, diabetic foot ulcers and pressure sores.
- The primary objectives of wound management should be to attempt to heal the wound in a timely manner, with best possible functional and cosmetically appealing scar.

CONCLUSION

Several factors can affect the normal wound healing process. Clinicians entrusted with wound management should strive for predictable and timely repair of the wound, with best possible functional and cosmetically appealing scar, early detection and management of deterrents to normal wound healing process, and minimize complications.

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SECTION 2

Current concepts related to wound management

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PRINCIPLES OF SPECIFIC WOUND CARE

Wound management that includes basic principles of wound care is critical for optimizing post-injury outcomes. In fact, wound care should be an important component of holistic patient care. All chronic wounds require an organized, systematic management approach which enhances the healing process, thereby allowing the wounds to heal normally in a timely manner.[1] Dr Vincent Falanga[2] first introduced the concept of wound bed preparation, noting that "even the most advanced and sophisticated products require proper wound care and wound preparation". Over the past few decades, standard practices of wound care have changed. Wound bed preparation represents a new direction in wound care thinking. It is a holistic approach involving detailed wound evaluation using evidence-based techniques to prepare the wound bed for healing, as well as removing any barriers to healing. The acronym "*TIME*" has often been used to describe the systematic approach to wound assessment and management. Its four steps are:[1]

- **T**issue management (wound debridement)
- **I**nfection control
- **M**oisture balance
- **E**pithelial (**E**dge) advancement.

Underlying etiopathogenic cause and comorbidities should be addressed in wound management

When initiating wound management, emphasis should be laid on identification and appropriate treatment of the underlying etiopathogenic cause and simultaneous treatment of associated medical comorbidities, if present. Nutrition and blood supply to the wound site should also be optimized, if compromised.

Source: Sood A, Granick MS, Tomaselli NL. Wound Dressings and Comparative Effectiveness Data. *Adv Wound Care (New Rochelle)*. 2014 Aug 1; 3(8): 511–529.

STEP 1

Tissue management – Wound debridement

Necrotic tissue, debris, and slough in the wound are major impediments to its optimal healing; they interfere with wound assessment and can also increase risk of infection. Debridement usually occurs as a natural process during the inflammatory stage of wound healing, and involves removal of devitalized tissue and debris from the wound by neutrophils and macrophages. However, when the physiologic debridement process is impaired by high concentrations of endotoxins in the wound tissue, as

Table 1: Different types of debridement techniques: Their benefits and limitations			
Type	**Selective/Non-selective**	**Benefits**	**Limitations**
Surgical	Selective; but not highly selective	Highly selective; for most types of wounds	Requires surgical expertise; complications of surgical excision and/or anesthesia
Mechanical	Non-selective	Easy to perform; non-skilled	Removes healthy tissues as well; painful
Enzymatic	Selective	Easy to perform; non-skilled	Hypersensitivity reactions to some enzymes possible; some enzymes can cause irritation
Autolytic	Selective	Easy to perform; non-skilled	Can macerate surrounding tissues; only minimal debridement possible
Biological	Selective	Debridement of the deeper tissues of the wound; disinfects the wound; additionally promotes wound healing	Reluctance to use by some patients/ clinicians

Based on information from: 1. McCallon SK, Weir D, Lantis JC. Optimizing Wound Bed Preparation With Collagenase Enzymatic Debridement. *J Am Coll Clin Wound Spec.* 2014 Apr; 6(1-2): 14–23. **2.** Cornell RS, Meyr AJ, Steinberg JS, Attinger CE. Débridement of the noninfected wound. *J Vasc Surg.* 2010 Sep;52(3 Suppl):31S-36S. **3.** Nishijima A, Yamamoto N, Yoshida R, Hozawa K, Yanagibayashi S, Takikawa M, Hayasaka R, Nishijima J, Okada T, Sekido M. Maggot debridement therapy for a patient with critical limb ischaemia and severe cardiac dysfunction: possibility of limb salvage. *Case Reports Plast Surg Hand Surg.* 2017 May 16;4(1):42-47.

seen in chronic wounds, healing is arrested.[3] Wound debridement, therefore, is an essential tool of wound management and involves removal of dead tissue from the wound, facilitating the healing process. There are several debridement methods; surgical, mechanical, enzymatic, autolytic, and biological.[4] Each method has its own benefits and limitations (Table 1).

Different methods of wound debridement

The most direct form of debridement is surgical excision of necrotic tissue from the wound.[4] Surgical debridement requires expertise. During this form of debridement, surgeons specifically remove the necrotic grey and black tissue attached to the wound, leaving the red (muscle), white (tendon, bone, fascia), and/or yellow (subcutaneous fat) tissues intact.[4,5] However, not all wounds require excision in the operating room; moreover, some patients have contraindications to surgical excision. Alternative non-surgical debridement methods usually do not require expertise and can be conveniently performed by non-specialist nurses.[5]

Mechanical debridement involves application of a dressing that adheres to the wound. A wet-to-dry dressing, such as a gauze, is applied over the wound surface and when dry, it is removed along with the attached necrotic tissue. This debridement method is non-selective in nature and removes both the necrotic and healthy wound tissue; moreover, it is often very painful for the patient. Enzymatic debridement is another non-surgical debridement technique which is used for treating non-healing wounds that cannot undergo surgical excision. It involves topical application of enzymes, such as collagenase, that can digest the necrotic tissue from the wound. It is a selective debridement procedure, and is used extensively for wound healing.[5] A recently performed meta-analysis[6] of 22 studies which reported outcome of collagenase therapy for wound debridement showed it to be an effective treatment option for chronic wounds, such as pressure ulcers and diabetic foot ulcers. For healing of burn wounds, it was shown to be effective when used along with topical antimicrobials. Nevertheless, investigators suspected outcome bias in many studies included in this meta-analysis, and called for more randomized clinical trials of this treatment. Additionally, there was statistically significant increase in the risk of adverse events with collagenase therapy compared to alternative treatment options.[6] However, another separate study[7] reported its effectiveness for non-healing wounds in adults, as well as its safety and efficacy in infants and children with necrotic wounds.

Biological debridement or maggot debridement therapy is a time-tested method for wound healing. Recently, this procedure has been modified for debridement of wounds in patients who cannot undergo surgical excision. Since maggots liquefy only the necrotic tissues, leaving the viable tissues intact, it is a selective form of tissue debridement. Maggots usually migrate to the deeper portions of the wound; they can therefore effectively remove necrotic tissue from the depth of the wound where surgical debridement is often difficult. Maggots also have

antibacterial effects, and are therefore suitable for infected wounds. Maggots secrete powerful salivary enzymes which can liquefy necrotic tissue and can also activate several cellular processes, such as fibroblast migration, angiogenesis, and enhanced production of growth factors, which can accelerate the wound healing process. Maggot debridement has been proposed as an adjuvant therapy for ischemic skin ulcers with critical limb ischemia, and may even contribute to limb salvage in these patients.[8] Some patients and caregivers are reluctant to use this therapy, and the treatment can be painful. Autolytic debridement is another form of non-surgical debridement which utilizes the body's own enzymatic mechanisms to remove devitalized tissue, and enhance wound healing. A semi-occlusive or occlusive moisture-retentive dressing, such as hydrogel or hydrocolloid, is applied over the wound surface to provide a moist environment, allowing endogenous enzymes or phagocytic cells to liquefy the necrotic tissue or slough. These dressings are easy to apply and painless. In fact, keeping the wound moist with these dressings will often help to relieve pain.[1]

New and promising debridement techniques for the future

Low-frequency ultrasound therapy has recently been used for debridement and healing of chronic ulcers.[5] Hydrocision or high pressure water irrigation is another technique for performing selective tissue debridement and wound cleaning. The recently introduced Versajet system uses hydro-debridement technique and selectively removes necrotic tissue from the wound site. It has emerged as a fast, selective, and safe method of soft tissue debridement.[9] Negative pressure wound therapy (NPWT) or vacuum-assisted wound therapy, has become established as an effective treatment option for both acute and chronic wounds, particularly diabetic foot amputation stumps.[10,11] In this technique, negative pressure is delivered to wound bed through sealed foam or gauze dressing, which approximates the wound edges, reduces wound edema, facilitates tissue perfusion, and enhances granulation tissue formation. It is not recommended for the treatment of infected wounds.[11]

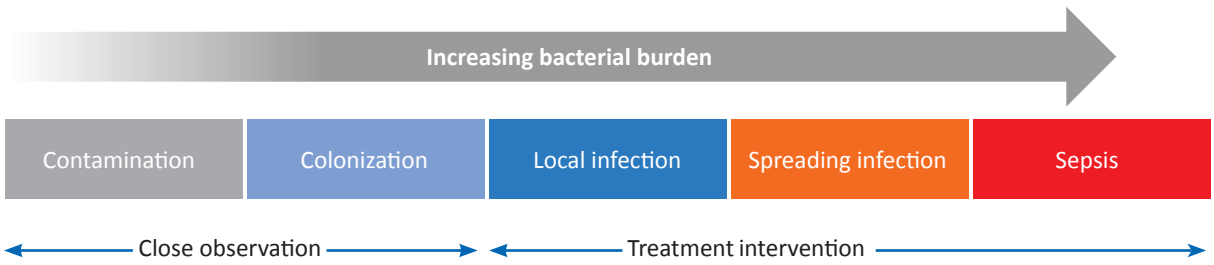
STEP 2

Infections: Another impediment to wound healing

Wounds are rarely sterile, and isolation of bacteria from the wound surface does not necessarily imply infection.[12,13] However, as bacterial multiplication in the wound continues and increases beyond a "critical threshold", the healing process can stall. Aerobic bacteria, primarily Staphylococci and Streptococci species, as well as anaerobic bacteria can co-infect wounds. Most wound infections have a polymicrobial etiology, making it difficult to identify the precise etiological cause.[12] Bacterial bioburden and the body's response to it has been described as a continuum, ranging from "contamination" on one end of the spectrum to "infection" on the other.[1,13] The wound infection continuum (Figure 1) includes:[13]

- **Contamination** indicates presence, but not multiplication of bacteria in the wound
- **Colonization** indicates both the presence and multiplication of bacteria, but no local tissue damage
- **Infection** indicates multiplication of bacteria, resulting in delay in wound healing, and tissue damage
  - » **Local infection or "critical colonization"** indicates wound infection causing local tissue damage

Figure 1: The wound infection continuum



Adapted from: International Wound Infection Insitute (IWII) Wound Infection in Clinical Practice. Wounds International 2016.

» **Spreading infection** indicates spread of infection to the adjoining tissues

» **Systemic infection or sepsis** indicates presence of wound infection with systemic manifestations.

Bacteria in wounds primarily exist in two phenotypic states; either planktonic (free-living) or biofilms. Biofilms form when bacteria are well-established in the wound, and consist of bacterial colonies embedded in a sticky, antibiotic resistant extracellular matrix composed of extracellular polymeric substances (EPS). Pathogenic biofilms often form in chronic wounds and are an important cause of interruption of the wound healing process. They have currently emerged as a major therapeutic challenge due to their resistance to both the host immune response and commonly used antimicrobials. Since biofilms can only be detected in tissue biopsies, pertinent data from human studies is still scarce. Nevertheless, our knowledge on biofilms and their negative effects on wound healing is growing; several potential therapies are being evaluated for their effectiveness in treating biofilm-containing chronic wounds in the future.[14]

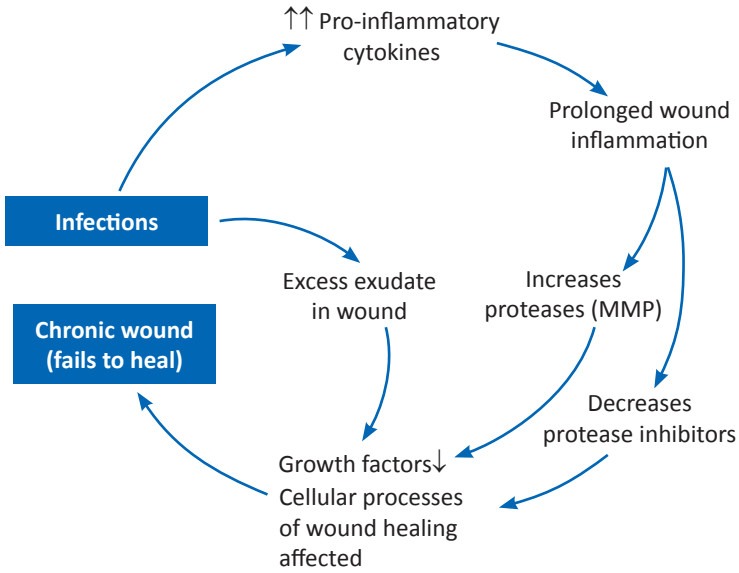
Early detection of wound infection

Infections of acute wounds are easier to detect. Localized wound infection presents with redness, warmth, and swelling around the wound, along with varying degree of exudate. A localized abscess can also form. If redness spreads to the adjoining tissues, with features of lymphangitis, crepitus in the soft tissues, and/or evidence of wound breakdown, possibility of spreading infection should be considered. Systemic signs of infection (or sepsis) include fever or hypothermia, tachypnea, and tachycardia. In severe cases, multi-organ dysfunction or even death can occur. In contrast, infections of chronic wounds are more difficult to detect as they are non-specific. Edema around the wound, worsening pain intensity, malodorous discharge, bleeding from the wound site, change in the color of the wound, bridging, and pocketing can indicate localized infection of chronic wounds. Manifestations of spreading infection and sepsis in acute and chronic wounds are similar.[13]

How do infections arrest the wound healing process?

Because infection and inflammation are intricately linked, infections frequently interrupt the wound healing process. Early detection and timely initiation of management of infection is critical. During wound infections, high bacterial burden and their endotoxins increase the levels of pro-inflammatory cytokines, thereby prolonging

Figure 2: Mechanisms by which infections affect wound healing



MMP: Matrix Metalloproteinases

Adapted from: Guo S, DiPietro LA. Factors Affecting Wound Healing. *J Dent Res*. 2010 Mar; 89(3): 219–229.

the inflammatory stage of wound healing. Prolonged inflammation at the wound site increases concentration of proteases and decreases protease inhibitors, thereby adversely affecting the cellular processes involved in wound healing. Wound exudate can increase. Growth factors, which are important players in the wound healing process, are also rapidly degraded. Wounds, therefore, enter the chronic phase and fail to heal (Figure 2).[15]

Treatment of local wound infections

Confirming wound infection requires microbial evaluation of a deep wound swab or a tissue biopsy taken from the wound site.[1] Cleaning the wound with a low toxicity topical antiseptic solution (such as normal saline or dilute vinegar 0.5% acetic acid) should be the first step in wound management. Concentrated povidone-iodine, detergents and hydrogen peroxide being cytotoxic, should not be used. Wound cleansing removes contaminants, debris, and superficial slough from the wound site, after which topical antiseptics with dressings can be applied.[1,16,17] Biofilm-associated wound infections are often difficult to treat as majority of antimicrobials cannot penetrate the mature biofilm. Surgical debridement of the wound, which can disrupt the biofilm, followed by irrigation with antiseptics is necessary.[1,14] Some antiseptics can disrupt biofilm of common bacteria that infect the wound surface, including octenidine dihydrochloride, povidone and cadexomer iodine, polyhexanide, and nanocrystal silver.[18]

Potential treatment options for wound biofilm disruption

Several novel dressings and therapeutic agents that can specifically target wound biofilms are currently being researched. A surfactant-based wound dressing has recently been developed that can be applied on the wound surface and disrupt existing biofilm, thereby allowing the antimicrobials to act.[19] The novel high-osmolarity surfactant solution technology should be used immediately after wound debridement and can disrupt EPS, biosynthetic polymers that establish the functional and structural integrity of biofilms, thereby facilitating easy removal of the biofilm.[20]

A wide range of antiseptic wound dressings (such as silver- and low dose slow release iodine-based dressings), topical and systemic antimicrobials are currently available for effectively treating wound infections.[1] For colonized/critically colonized wounds, topical antimicrobials are effective. Systemic antimicrobials should be used for clinically infected wounds, systemic or spreading infections. Topical antimicrobials have several advantages over systemic antimicrobials, including:[21]

- Achievement of higher and more sustained concentration of antimicrobial at the site of infection
- Reduced antimicrobial requirement
- Reduced potential of systemic absorption and toxicity
- Reduced need for systemic antimicrobials – thereby, reducing risk of antimicrobial resistance
- Guaranteed treatment adherence, particularly in children.

Currently, topical antimicrobials have emerged as a major asset for the treatment and/or prevention of infections in burn wounds, as well as for treating infections of many other types of non-healing chronic wounds, such as diabetic ulcers, vascular ulcers, and pressure ulcers.[22] They should also be considered for reducing odor associated with non-healing necrotic wounds; and for the treatment of wound infections due to multidrug-resistant organisms that are otherwise not treatable with systemic antimicrobials. Some clinicians also prefer adding topical antimicrobials to systemic antimicrobial therapy for treating infected ischemic wounds in patients who cannot undergo revascularization (Table 2).[21]

The first topical antimicrobials were sulfonamide, penicillin, bacitracin, and tetracycline. Many of these are no longer used by dermatologists because of high risk of contact dermatitis, and rarely anaphylaxis. Over the last

Table 2: Some indications for topical antimicrobials in wound management

• Infections in burn wounds
• Infections in other non-healing chronic wounds (diabetic ulcers, vascular ulcers, and pressure ulcers)
• Reducing odor in non-healing necrotic wounds
• Treating multidrug-resistant wound infections that are otherwise not treatable with systemic antimicrobials
• Can be added to systemic antimicrobials for treating infected ischemic wounds in patients who cannot undergo revascularization

Adapted from: 1. Lipsky BA, Hoey C. Topical antimicrobial therapy for treating chronic wounds. *Clin Infect Dis.* 2009 Nov 15;49(10):1541-9. **2.** Dai T, Huang Y, Sharma SK, Hashmi JT, Kurup DB, Hamblin MR. Topical Antimicrobials for Burn Wound Infections. *Recent Pat Antiinfect Drug Discov.* 2010 Jun 1; 5(2): 124–151.

few years, many newer effective topical antimicrobials, such as fusidic acid, mupirocin, and retapamulin, have been introduced.[21] Clinical use of topical mupirocin, in particular, has increased over the last few years for treating skin and soft tissue infections. It has a broad spectrum of antimicrobial efficacy, and covers methicillin resistant *Staphylococcus aureus* (MRSA) strains.[21,23-25] Similar antimicrobial benefits have been seen with topical retapamulin. It has established *in-vitro* efficacy against a broad spectrum of bacteria; it also has a unique mechanism of action whereby it selectively inhibits bacterial protein synthesis, and has low potential for cross-resistance with other established antibacterial agents.[26]

New treatment techniques for wound infection

Several new techniques are being developed to further improve the treatment of wound infections. Development of next-generation hydrogels which allow controlled antimicrobial release at the wound site is a step in this direction. These antimicrobial hydrogels are being used as wound dressing materials and fillers. They can deliver both antimicrobials and other bioactive materials at a controlled rate into the wound.[27] Chitosan has intrinsic antimicrobial properties and can also act as a delivery system for antimicrobial agents at the wound sites.[28] Recently, biosensors have been developed that are being used in dressings and have the potential to detect changes in the wound environment. They can alert clinicians by either changing color of the dressing or sending an alert on the smart phone to notify the same.[29]

STEP 3

Moisture balance: A major shift in treatment paradigm of wound healing

Maintaining a moist wound environment improves healing.[30-36] Traditionally, the practice of drying the wound bed was the standard of care.[35] In the early 1960s, Winter[30,31] introduced the revolutionary concept of moist wound healing, noting that wounds in a moist microenvironment showed faster re-epithelialization compared to those which were left open to air. Benefits of moist wound healing were confirmed in a porcine study.[33] A porcine model to compare wound healing in wet, moist, and dry wound environments showed that both the wet and moist wounds were associated with faster and better quality of healing compared to dry wounds. Moist wound healing is now a well-accepted treatment concept for acute and chronic wounds. Several mechanisms have been proposed to explain how a moist wound environment facilitates healing (Figure 3). A moist microenvironment prevents dehydration and desiccation of the wound, augments breakdown of devitalized tissue and dead cells, enhances epithelialization, promotes epithelial cell migration, and potentiates growth factor activity. Concerns about possible increase in wound infections in a moist environment have been shown to be unfounded.[31,32]

Wound exudate contributes to a moist healing environment. Both insufficient and excessive exudate can negatively impact wound health; insufficient exudate can dry the wound and promote eschar formation, while excess exudate can damage the surrounding skin (maceration). Therefore, a delicate moisture balance needs to be maintained for optimal wound healing.[1] A multitude of wound dressings are currently available to optimize a moist environment for promoting wound healing.

The choice of dressing depends on the wound characteristics and the moisture status of the wound. An ideal wound dressing should:[34]

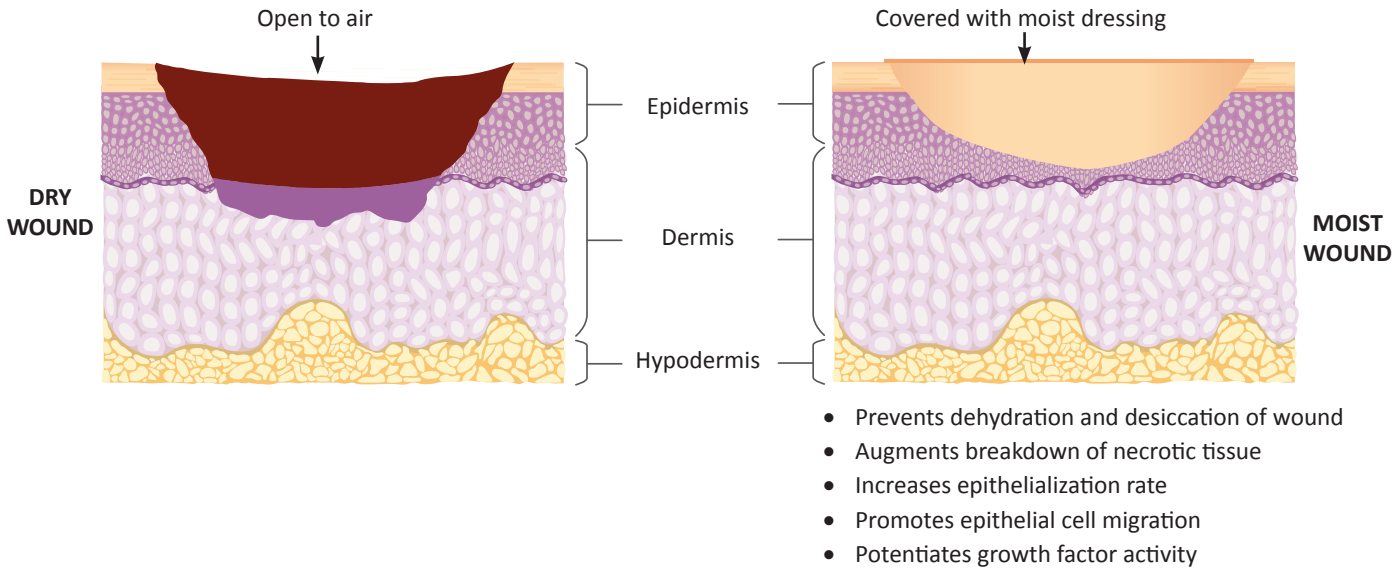
- Maintain and provide a moist wound environment
- Protect against infections
- Allow gas exchange between the wound and surrounding environment
- Promote angiogenesis and connective tissue synthesis
- Provide optimal temperature for maintaining blood flow to the wound site and enhance epidermal migration
- Be non-adherent to the surrounding wound surface
- Be sterile, non-toxic and non-allergic.

Wound dressings are primarily classified into two main categories; passive and interactive dressings. A passive dressing is a simple product, such as a gauze, which only protects the wound but does not interact with it. Interactive dressings, on the other hand, interact with the wound bed and provide an optimal environment at the wound dressing interface to promote healing.[35]

Choice of dressing based on wound characteristics

A wide range of dressings are currently available for promoting moist wound healing, including films, hydrocolloids, foams, alginates, and hydrogels.[1,36,37]

Figure 3: Mechanisms underlying faster and better wound healing in a moist compared to dry wound environment



Adapted from: 1. Junker JP, Kamel RA, Caterson EJ, Eriksson E. Clinical Impact Upon Wound Healing and Inflammation in Moist, Wet, and Dry Environments. *Adv Wound Care (New Rochelle)*. 2013 Sep; 2(7): 348–356. **2.** Field FK, Kerstein MD. Overview of wound healing in a moist environment. *Am J Surg.* 1994 Jan;167(1A):2S-6S.

- **Films** - Dressings composed of transparent adherent polyurethane films are ideal for superficial wounds, such as shallow burns or split thickness skin graft donor sites.
- **Hydrocolloids** - These are soft, moderately absorptive adhesive dressings. Hydrocolloid dressings are composed of two layers, an inner colloidal layer and outer water-impermeable layer. They provide a moist wound environment for healing of wounds with mild amount of exudate, such as abrasions, superficial ulcers, and burns. Because they are waterproof and adherent, they can be worn while bathing or swimming, and can be left on the wound for several days at a time.
- **Hydrogels** – They are composed of hydrophilic materials made from synthetic polymers; as they have high water content, hydrogel dressings are predominantly used for healing of dry wounds with eschar; they are also cooling and soothing for painful wounds.
- **Alginates/hydrofibers –** Wounds with excess exudate require dressings with good absorptive capacity for maintaining optimal moisture balance; these include foams, hydrofibers, and polymeric membrane dressings (PMD). Hydrofibers and PMD are also preferred for packing deep wounds due to their ability to absorb drainage from the wound site and moisten the wound cavity.
- **Foams** - Foams are composed of polyurethane with a waterproof backing. These are moderately absorptive and ideal to use over trauma-prone sites, such as bony prominences.
- **Biological dressings** – These dressings, such as a skin allograft, can be used for treating chronic wounds as they prevent fluid and electrolyte losses, thereby preventing tissue desiccation; they also provide barrier against microbial invasion.

STEP 4

Epithelial (Edge) advancement

Epithelialization is one of the final steps of wound healing. Assessment of the edge of the wound can indicate if epithelialization and closure of the wound margins is progressing normally (indicating normal wound healing), or if healing has stalled and the wound requires re-evaluation. Epithelialization or epithelial edge advancement is therefore a reliable indicator of wound healing and closure. It is frequently impaired in chronic wounds.[38] Non-advancing or undermined wound edges indicate either non-migratory or non-responsive

keratinocytes, abnormality in extracellular matrix, or abnormal protease activity. Factors interrupting wound healing need to be identified and satisfactorily treated. Furthermore, potential therapies that can influence the "edge effect" and can be considered in the management, include skin grafts, biological agents, and adjunctive therapies.[39]

CURRENT ADVANCES IN WOUND MANAGEMENT

Acellular and cellular therapies

Cell-based therapy is an upcoming treatment option for wound healing; it involves therapeutically using cells with excellent wound healing capacity, such as fibroblasts, keratinocytes, bone marrow-derived stem cells, and platelets for difficult-to-treat wounds in clinical practice.[40]

Bioengineered dressings are now used as advanced therapy for non-healing wounds in the USA. Cultured epidermal autografts, generated from autologous cultured keratinocytes, is approved by the FDA as an adjunct to split thickness skin grafting in burn patients.[41] Dermal constructs containing porcine or bovine collagen are used as temporary dressings for burn wounds (Biobrane, integra). Human fibroblasts on an absorbable mesh scaffold have been approved for the treatment of diabetic foot ulcers (Dermagraft). Bilayered skin constructs composed of a bovine collagen gel seeded with neonatal fibroblasts covered with a layer of keratinocytes (Apligraf) has been FDA approved for the treatment of diabetic foot ulcers and venous leg ulcers.[42]

Over the last few years, acellular dermal matrices have been obtained after de-epithelialization to remove cellular contents, and are being used along with other advanced therapies to treat non-healing wounds. They can replace the damaged extracellular matrix at the wound site, optimize wound environment, and provide scaffold for wound repair.[43] Many amniotic membrane products are also being explored in the management of chronic wounds and show promise.[44]

Growth factor therapies

In the past two decades, several clinical trials have evaluated the healing effects of individual human growth factors and cytokines in chronic wounds; such as VEGF, PDGF, basic fibroblast growth factor (bFGF), and granulocyte-macrophage colony stimulating factor (GM-CSF).[45] Becaplermin, a topical human recombinant platelet derived growth factor, has been approved by the FDA for the treatment of diabetic foot ulcers. Randomized clinical trials showed that treatment with this growth factor improved healing by 43% compared to placebo.[46] Unfortunately, majority of other growth factor studies are small in size, with inconsistent results, preventing a definite conclusion to be drawn on the current role of growth factors in chronic wound management.[45]

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) is administration of 100% oxygen at pressures higher than the atmospheric pressure inside an enclosed hyperbaric oxygen chamber. This technique is now being offered as a treatment option for chronic wounds. HBOT is recommended as an adjunctive treatment option for some non-healing wounds, such as diabetic ulcers; infected wounds such as necrotizing soft tissue infections and Fournier's gangrene; thermal burns; traumatic wounds, and crush injuries.[47] One Cochrane review[48] found improved healing in diabetic foot ulcer patients treated with HBOT. However, there was insufficient data for acute and post-surgical wounds.

Electrical stimulation for wound healing

Injuries that disrupt the skin are known to generate electrical fields at wound site which direct cellular responses and facilitate the healing process.[49] In complicated wounds, this electrical field is either weakened or is entirely absent, rendering wounds non-responsive to standard treatment. Electrical stimulation is a unique treatment option which has recently been introduced for management of difficult-to-treat wounds that otherwise do not respond to standard treatment. It is usually combined with standard wound care to improve tissue perfusion and accelerate the healing process in chronic wounds. Devices that are currently being used to electrically stimulate wound healing generate either direct current or mono- and biphasic pulsed current waveforms.[50,51] A recently performed analysis[51] of 16 randomized trials that applied electrical stimulation for wound

KEY HIGHLIGHTS

- Surgical debridement requires expertise. During this form of debridement, surgeons specifically remove the necrotic grey and black tissue attached to the wound, leaving the red (muscle), white (tendon, bone, fascia), and/or yellow (subcutaneous fat) tissues intact.
- Maggots debridement has been proposed as an adjuvant therapy for ischemic skin ulcers with critical limb ischemia, and may even contribute to limb salvage in these patients.
- Adequate moisture balance is a cornerstone of good wound care. A dressing should be chosen which will keep the wound moist but not too wet or too dry.
- Negative pressure wound therapy delivers negative pressure to the wound bed through sealed foam or gauze dressing, which helps to oppose wound edges, reduces wound edema, facilitates tissue perfusion, and enhances granulation tissue formation. It is particularly helpful in post-surgical wounds.
- Systemic antimicrobials should be used for clinically infected wounds.
- Topical antimicrobials and wound cleansers are important in preventing infection and controlling bioburden.

healing, showed either faster reduction in wound area or healing of higher proportion of wounds in 14 out of the 16 randomized clinical trials, attesting the merits of this procedure. This advanced wound care treatment is currently undergoing further evaluation.

CONCLUSION

Chronic wounds are often difficult to treat as they are non-responsive to standard treatment options. Over the past few decades, wound bed preparation has emerged as an important concept in wound care. It is a systematic treatment approach using the TIME principles; primarily involving removal of barriers to healing, tissue debridement, reduction of wound microbial burden, moisture balance and exudate management; and edge of the wound assessment and management. Several novel treatment options have been recently introduced for the management of difficult-to-heal wounds, and have shown varying success.

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