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HIGHLIGHTS

- The distinction between chronic uninfected from infected wounds is challenging.
- Culturing all chronic wounds is inappropriate.
- Debridement is an important step to facilitate the wound healing process.
- Patients with chronic wound infections need a multidisciplinary approach.
- Systemic antibiotics should not be limited to infected cases.

Challenges in the management of chronic wound infections

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Abbreviations

FDA Food and Drug Administration

MBC minimum bactericidal concentration

MIC minimum inhibitory concentrations

MRSA methicillin-resistant *Staphylococcus aureus*

WAR Wounds at Risk

TIME Tissue, Infection/Inflammation, Moisture imbalance, Epithelial edge advancement

ABSTRACT

Objective Chronic wound infections may delay the healing process and are responsible for a significant burden for the healthcare system. Since inappropriate management may commonly occur in the management of these patients, this review aims to provide a practical guide underlining actions to avoid in the management of chronic wound infections.

Methods We performed a systematic review of the literature available on PubMed in the last 10 years, identifying studies about the management of patients with chronic wound infections. A panel of experts discussed about the potential malpractices in this area. A list of Don'ts including the main actions to be avoided was drawn up through the Choosing Wisely methodology.

Results In this review we proposed a list of actions to avoid for an optimal management of these patients. The adequate wound bed preparation and the wound antisepsis should be combined, because the absence of one of them lead to delayed healing and higher risk of wound complications. Moreover, avoiding inappropriate use of systemic antibiotics is an important point because of the risk of selection of multidrug resistant organisms and antibiotic-related adverse events.

Conclusions A multidisciplinary team of experts in different fields (surgeon, infectious disease expert, microbiologist, pharmacologist, geriatrician) is required for an optimal management of chronic wound infections. The implementation of this approach may be useful to improve the management of patients with chronic wound infections.

1. INTRODUCTION

It has been estimated that about 8 millions of people are affected by wounds with or without infections worldwide (1). In the United States, 2% of the entire population is affected by chronic wounds (2). Similar data have been reported in European countries (3). The prevalence of chronic wounds increases with age, and the risk of developing a chronic wound is higher in diabetic and obese patients, because of multiple mechanisms including hyperglycemia, impaired vascular status, neuropathy.

Remarkably, chronic wound infections may delay the healing process with clinical implications (increased pain, reduced quality of life) and a significant burden for the healthcare system. The management of chronic wound infections is complex and requires a multidisciplinary approach. Distinguishing a chronic uninfected wound from an infected wound may be challenging. As a matter of fact, non-traditional signs may characterize chronic wound infections, including increased pain, friable granulation tissue, delayed wound healing beyond expectations, wound breakdown, while foul odor may be not easy to be identified by non-expert personnel (4). Inappropriate management may frequently occur in the management of chronic wound and should be avoided to avert the risk of infection and poor outcomes.

The aim of this review is to provide a practical guide describing actions to be avoided in the clinical practice, while managing chronic wound infections.

2. METHODS

This document has been drafted by a team of specialists of different areas of expertise (microbiology, infectious disease and antibiotic therapy, general surgery, plastic surgery, diabetic foot surgery, expert in wound management, pharmacologist, geriatrician). It focuses on the

management of chronic wound infections. The purpose of this manuscript is to identify common inappropriate actions in chronic wound infections and to provide a list of actions that should be avoided in daily clinical practice. The "Choosing Wisely" methodology is used to identify and summarize these actions, that are named in this manuscript as a list of "Don'ts".

Chronic wound infection refers to a wound that has a slow progression through the healing phases, or shows delayed, interrupted or stalled healing due to intrinsic and extrinsic factors that impact on the individual and their wound (5). Non-healing wounds are defined as those that fail to progress through an orderly sequence of repair in a timely fashion (6, 7). Although there is no clear consensus in the duration of a wound that defines chronicity, a range of 4 weeks to 3 months has been used to define chronic wounds in the literature (8). The Wound Healing Society classifies chronic wounds into 4 major categories: pressure ulcers, diabetic foot ulcers, venous ulcers, and arterial insufficiency ulcers.

This manuscript has been drafted in several steps. First, a literature search was performed to identify specific steps of the management of chronic wound infections commonly considered to be inappropriate. A PubMed/MEDLINE (National Library of Medicine, Bethesda, MD) search was conducted. Search terms used for literature search are reported in **Supplementary Table 1**. Articles pertaining to the topic published in the last 10 years were identified. English language restriction was applied. The expert panel identified the most common inappropriate practices in the management of chronic wound infections during interdisciplinary meetings and a decalogue of 10 "Don't" items was finally identified. Total agreement among the experts was needed to include each item in the decalogue.

3. THE "DON'TS"

The list of "Don't" items and relative references is reported in the **Table 1** and **Table 2**, respectively.

3.1 Don't forget the management of underlying comorbidities and concomitant factors

The optimal management of chronic wound infections requires the control of concomitant disorders: it is imperative to look at the "whole" patient rather than just the "hole" in the patient (9-10).

Thus, all concomitant factors should be considered and adequately treated (11):

- arterial ulcers need revascularization and adequate control of cardiovascular risk factors (12);
- pressure ulcers need an optimization in the patient's mobility, pressure redistribution to reduce pressure, friction, and shear forces and incontinence management (13);
- venous ulcers require compression and improvement of blood flow (14);
- diabetic foot ulcers need adequate vascular supply (through revascularization), infection treatment, plantar pressure redistribution, management of diabetic neuropathy, improvement in glycemic control (15) and in other cardiovascular risk factors (16-17).

3.2 Don't use a single-based expert approach: role of multi-faceted experts in wound care

Concomitant disorders, local pathophysiological mechanisms, such as impaired vascular status, unusual local pressure of the wound site, neuropathy, sustained inflammation, lack of angiogenesis, and altered cell proliferation are mechanisms contributing to the complexity of chronic wounds. A multidisciplinary approach is crucial to manage patients with chronic wound infections (18, 19, 20, 21, 22, 23). Unfortunately, the wound care is generally fragmented. Centers of excellence that orchestrate a multidisciplinary networking approach that includes surgeons, internal medicine,

infectious disease, diabetologists, specialty nursing, and basic scientists is usually lacking or poor represented (24). The promotion of these structures may be useful to overcome some issues in the management of patients with chronic wound care. Moreover, implementing specialized structures may favor the development of standardized protocols in reporting the wound healing success, randomized clinical trials, measurement of quality of life outcomes (25).

3.3 Diagnosis of chronic wound infections: Don't perform routine swabs in all chronic wounds

Culture methodology of wound infections are prone to controversy. The first challenge in this setting is the indication to perform a wound swab. Clinical diagnosis of infection is essential before culturing because 100% of wounds are contaminated at the time of wounding. However, the mere presence of bacteria does not delay wound healing and is not equivalent to wound infection. The excessive and indiscriminate tendency to culture wounds under the false hope that this will identify underlying infection may be misleading and promote unjustified antibiotic use.

Of importance, it is inappropriate to culture all wounds (26). This statement is based on IDSA guidelines about the management of skin and soft tissue infections, that discourages routine cultures of blood or cutaneous aspirates, biopsies, or swabs (27). The identification of infection requires a high degree of suspicion (28). The indiscriminate or routine culturing in the absence of clinical indicators is not advised because it may lead to misdiagnosis and antibiotic overtreatment. **Figure 1** summarizes criteria that should be considered before culturing a chronic wound (4, 29, 30, 31). Several considerations should be performed before a culture swab: first, the physician should clinically differentiate whether the microbiology workup is done in the context of multi-resistant pathogen screening, or whether there are clinical signs of a wound infection requiring systemic antibiotic therapy; swab preparation and technique for wound swabbing should be adequately chosen (32).

Quantitative biopsy (removal of a piece of tissue via a scalpel or punch biopsy) has been promulgated as the gold standard in the diagnosis of wound infection (33). Traditionally,

quantitative culture of wound biopsies was considered to be the reference standard with wound infection being defined as a load of $>10^5$ bacteria per gram of tissue (34). However, this reference standard is rarely used in routine clinical practice and its value for the detection of wound infection remains debated (35). On one hand, quantitative cultures may assist clinicians in determining the threshold above which the bacterial burden of a culture has clinical significance. On the other side, relationship between bacterial counts and clinical signs of sepsis is not linear and methods of specimen collection vary greatly.

A recent study showed that assessment of wound infection by different clinicians does not differ when culture results from wound biopsy versus wound swab are available (36). The high variability in the assessment of wound infection among experts indicates that the timely detection or exclusion of a wound infection is not easy.

In conclusion, diagnosis of wound infection should be based on a combination of clinical judgement and microbiological culture. The wide use of routine swabs may lead to over-diagnosis and over-treatment of these patients. Efforts to identify reference standards for the detection of wound infection are needed.

3.4 Diagnosis of chronic wound infections: Don't perform a biopsy with inappropriate method

Wound biopsies are an essential diagnostic component in the management of chronic wounds. Several practice guidelines recommend wound biopsy when there is no response after 2–6 weeks of appropriate treatment (5). The Food and Drug Administration (FDA) recommends performing biopsies of the wound not only to exclude neoplastic, immune-mediated or primary infectious diseases, but also to diagnose wound infections and to guide treatment (37). Standardized technique for wound biopsy is important to guarantee safety and accurate diagnosis. Biopsy should be obtained from the center of the wound and should include epidermis, dermis, and subcutaneous tissue (38).

3.5 Treatment of chronic wound infections: Don't underestimate the role of biofilm and forget wound debridement

Since there is no specific clinical manifestation for the diagnosis of biofilm, this aspect may be underestimated. Biofilm is present in 90% of chronic wounds and plays a pivotal role in chronic wound infections (39). As a matter of fact, the presence of biofilm in chronic wound infections has important clinical implications:

1) wound debridement is the first key step in the removal of biofilm. Debridement creates a therapeutic 'window' for the action of antiseptics and antibiotics in a 72-hour period, which enables removal of the biofilm and active destruction of the sessile and planktonic bacteria (25);

2) antiseptic able to degrade the extracellular polymeric substances should be preferred; not all antiseptics have efficacy against biofilms. Hydrogen peroxide and sodium hypochlorite products are effective against *S. aureus* and *P. aeruginosa* biofilms (40);

3) if systemic antibiotics are needed, agents active against biofilm should be used.

Biofilm represents a great challenge for clinicians that face with chronic wound infections. Biofilm-related infections are notoriously hard to eradicate (41, 42). Determining the efficacy of antibiotics and the ability to prevent, reduce or eradicate biofilm is important. Although biofilm is a typical characteristic of chronic wounds, no tests to detect and quantify biofilm in chronic wounds are available in clinical practice. Unfortunately, standard wound testing does not allow to detect biofilm infection nor to determine susceptibility of biofilm to various agents (43). Specific methods, such as Tissue Culture Plate method (TCP), Tube Method (TM) and Congo Red Agar (CRA) method, have been recently studied. TCP seems to be the best and most reliable for screening of biofilm formation in comparison to TM and CRA (43). However, these tests are not widely used and their implementation may be useful for clinicians.

Moreover, a major challenge in the management of biofilm-associated infections is the development of adequate, standardized biofilm susceptibility testing assays that are clinically meaningful. New

pharmacodynamic parameters, including minimal biofilm inhibitory concentration, minimal biofilm-eradication concentration, biofilm bactericidal concentration, and biofilm-prevention concentration, have been defined in recent years to quantify antibiotic activity in biofilms (44). Using these parameters, several studies have shown very significant quantitative and qualitative differences for the effects of most antibiotics on planktonic or biofilm bacteria (45, 46). However, several unmet needs still remain open: standardized procedures and breakpoints are needed before they can be implemented in clinical microbiology laboratories for routine susceptibility testing (47). Wound debridement represents a crucial step in wound management (48). Debriding a wound is defined as removing necrotic tissue, foreign material, senescent cells, and bacteria. The removal of debridement can allow wounds to progress beyond the inflammatory stage toward healing. Removing biofilm is one of the difficult practices, because it is adherent to surrounding tissue, is resistant to and poorly penetrated by antibiotics, is resistant to biocides, and evades the body's local immune response (49). A single treatment may cause some bacteria to drop out of a wound biofilm, but following debridement biofilm structures may be pushed into deeper tissue and is likely to reconstitute over time. Clinicians should evaluate indications and contraindications and adopt the best technique for wound debridement. **Figure 2** summarizes indications for and types of the debridement (50): 1) autolytic debridement is the most conservative type of debridement. This type of debridement is a natural process by which endogenous phagocytic cells and proteolytic enzymes break down necrotic tissue. It is indicated for noninfected wounds and may take some days; thus, if a significant decrease in necrotic tissue is not seen, a different method of debridement should be considered; 2) biological debridement, also known as larval therapy, uses sterile larvae of the *Lucilia sericata* species, that release proteolytic enzymes; 3) enzymatic debridement is a selective method for debridement of necrotic tissue using an exogenous proteolytic enzyme, collagenase; 4) surgical debridement is used to remove necrotic tissue using sharp instruments, allowing collection of wound cultures and a complete removal of infected materials; 5) mechanical debridement is a nonselective type of debridement, used to remove both devitalized tissue and debris as well as

viable tissue. It is usually carried using mechanical force: wet-to-dry, pulsatile lavage, or wound irrigation. All of these type of debridement have pros and cons (**Table 3**): the choice of the best type of debridement depends on the objective to obtain, the patient and the type of wound (infected or not) (51).

3.6 Treatment of chronic wound infections: Don't forget the wound bed preparation

Wound bed preparation is a key aspect to accelerate endogenous healing and facilitate the effectiveness of other therapeutic measures. A critical point is the differentiation of wound bed preparation from wound debridement alone. Chronic wounds may require a more difficult bed preparation, which requires expertise and time. Wound abnormalities may be various and for each of them specific corrective measures should be applied. Debridement, removal of infected foci, dressing should not be forbidden in any procedure (52). The TIME concept (Tissue, Infection/Inflammation, Moisture imbalance, Epithelial edge advancement) has been proposed to summarize wound bed preparation and may be considered part of a comprehensive approach to patient with chronic wound infection (53). Each component of the bed wound preparation should be always addressed and optimized to improve the chances of successful wound cure.

3.7 Treatment of chronic wound infections: Don't use topical antibiotics indiscriminately

Various agents are applied topically to treat infected wounds, but their proper role remains unclear. Clinically infected wounds usually require systemic antibiotic therapy, whereas clinically uninfected wounds that are healing as expected do not require antimicrobials (54, 55, 56). There is controversy about the use of topical antibiotic agents to treat poorly healing wounds with signs of infection (57, 58). In some cases, topical antibiotics may be considered for treating infected wounds: mupirocin, active against aerobic gram-positive cocci (except enterococci), is sometimes used for treating or decolonizing chronic wounds (59). A recent randomized clinical trial evaluated

the use of topical gentamicin-collagen sponge in combination with systemic antibiotic therapy in diabetic patients with a moderate or severe foot ulcer infection (60): no differences in clinical cure or pathogen eradication have been found between patients who received topical antibiotic therapy and those who did not. One major problem with topical use of antibiotics is the lack of standardized and approved tests to evaluate their concentrations in wound site and their efficacy.

The use of specific topical antibiotics may be associated with adverse events (61, 62): agents such as neomycin, bacitracin, and lanolin-containing preparations can increase the inflammatory response and are potential sensitizers; topical aminoglycosides, such as gentamicin, can increase the risk of microbial resistance. The indiscriminate use of topical antibiotics is a urgent problem, because some of them can be administered even without a medical prescription, contributing to the spread of multidrug-resistant bacteria. Thus, topical antibiotics should be generally avoided (63).

Antimicrobial peptides (AMPs) represent an emerging category of therapeutic agents. AMPs are oligopeptides composed of amino acid residues that possess antimicrobial activity (64). AMPs interact with the microbial cell membrane anionic phospholipids and possess great potential in effectively killing the bacteria with minimal risk of resistance development. There are a lot of AMPs that accelerate in vivo wound healing via promoting re-epithelization and granulation tissue. Several studies were performed to develop different AMPs formulations which include but are not limited to nanoparticles, hydrogels, nanoparticles+hydrogels, creams, ointments, and wafers. However, no marketed formulations for topical application of AMPs are available, because of difficulties in AMP solubility, stability, release/availability following topical application. AMPs offer promising alternatives to topical antibiotics with mechanisms of action less prone to resistance induction (65).

3.8 Treatment of chronic wound infections: Don’t use systemic antibiotic therapy indiscriminately

The use of systemic antibiotics in patients with chronic wounds is a challenging clinical choice. As a matter of fact, infected wounds may require systemic antibiotic therapy, but the indiscriminate use of systemic antibiotics may increase antibiotic resistance and side effects (66, 67, 68).

Determining if a nonhealing wound is infected can be one of the most challenging steps in the management of chronic wounds. When systemic signs of infection occur, blood cultures should be obtained and systemic antibiotics in combination with topic antiseptics become necessary (69). Deep invasion of bacteria from a chronic wound can lead to regional infections such as cellulitis, myositis, fasciitis, abscess formation, and osteomyelitis (70). These situations should be promptly diagnosed and adequately treated. The excessive and improper use of systemic antibiotics can contribute to adverse drug events and the rise of multidrug-resistant organisms. Some scores have been developed to select patients with chronic wound infections who need systemic antibiotic therapy. The Wounds at Risk (WAR) score incorporates the patient's immune status, immunosuppressive therapies (glucocorticoids, chemotherapy), systemic hematological diseases, occupational and social conditions, wound location and likelihood of contamination, patient's age, and type of the wound (71). Implementing these tools may be useful in clinical practice and can potentially reduce the use of systemic antibiotics in this patient population.

3.9 Treatment of chronic wound infections: Don't underestimate the role of methicillin-resistant *S. aureus*

Chronic wounds may be colonized or infected by healthcare-associated pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) (72). The spread of MRSA in both hospital and community setting represent a great challenge for clinicians (73-74). The significance of *S. aureus* in a patient's wound needs to be assessed for each patient., *S. aureus* may colonize the wound or may cause infection. The discrimination between colonization and infections needs a clinical evaluation by expert physicians. The presence of MRSA in an infected wound poses significant problems because of both topical and systemic antibiotics may be insufficient to achieve

MRSA eradication. The clearance of MRSA in a chronic wound is generally difficult, even if appropriate antibiotics are used. A recent pilot study investigated the possibility of eradication of MRSA in chronic wounds of outpatients (75). All outpatients received topical therapy of the wound with silver-containing wound dressing and were instructed with specific recommendations for wound care: use of antiseptic wound solution within change of dressings, body-washing (hair 1x/day with antiseptic shower foam), daily cleaning of spectacles, hearing aids or other personal objects with antiseptic solution, daily changing of bed-linen, underwear, handkerchiefs, disinfection of all contact surfaces with surface disinfectant. Only in the 42% of patients the MRSA was successfully eradicated. Antiseptic body washes were associated with increased eradication rate. Thus, MRSA-eradication in chronic wounds requires a comprehensive approach and should not be limited to antibiotic therapy (75). Alternative and innovative approaches to manage patients with MRSA infected ulcers are under investigation: nanoparticles, such as cefazolin-loaded noisome, may be a promising candidate for the treatment of biofilm-mediated infections of MRSA (76).

3.10 Treatment of chronic wound infections: Don't forget the role of antisepsis

Antisepsis is an important component of the current therapeutic armamentarium for chronic wound care. A recent WHO guideline advocates the use of good antisepsis perioperatively while reducing the use of systemic antibiotics (77). Antiseptic agents have both a prophylactic and therapeutic role in wound treatment (78). Moreover, antisepsis may support wound healing by causing positive effects on cell proliferation and regeneration. Finally, wound cleansing with antiseptic agents is useful for the preparation for debridement. Thus, antiseptic agents at dressing changes together with wound cleaning, irrigation and debridement should be implemented because their use reduces bacterial burden and suppresses biofilm formation and reformation (30-31).

Several antiseptic agents are available (61). Commonly used antiseptics include iodine in various forms, chlorhexidine, silver and polyhexamethylene biguanide in solutions for lavage, gels, and surgical and chronic wound dressings. The choice of one antiseptic over another one is not easy and

few robust evidences exist. Characteristics of antiseptic agents are important. Ideally, an antiseptic agent should possess all these features: possess a broad antimicrobial spectrum and activity against biofilm (79), being associated with a low risk of pathogens' resistance, demonstrate persistence within the wound bed, be non-injurious to eukaryotic cells and possess minimal allergenicity, favor the wound healing, do not alter wound coloration, have a high tolerability (13, 80) . All these characteristics together with the patient's comfort should be taken into account in the chronic wound care. Antiseptics, including hypochlorous acid, iodine carriers with polyvinylpyrrolidone (PVP or povidone) iodine, silver, chlorhexidine, benzalkonium chloride, triclosan, octenidine, and polihexanide and selected dyes such as Eosine, remain good options in wound care.

Antiseptics applied during wound care may affect the viability of skin cells. Some studies analyzed the impact of antiseptics in cultured fibroblast or keratinocytes. It has been demonstrated that clinically used concentration of chlorhexidine gluconate (2%) permanently halts cell migration and significantly reduces survival of in vitro fibroblasts, myoblasts, and osteoblasts (81, 82). Several in vitro studies on hypochlorous acid reported favorable microbicidal effects against a variety of microbes, while exerting a low cytotoxicity (83). The effect of hypochlorous acid on keratinocytes and fibroblasts depends on concentrations (84). The effect of 0.1 and 0.5% buffered sodium hypochlorite solutions was studied on the viability of basal cells of guinea pig skin: basal cells of the skin exposed to the 0.5% solution showed no reduction in viability after 1 week; cells exposed to the 0.1% solution showed no loss in viability after 2 weeks (85). Cooper and colleagues examined the in vitro effects of three topical antiseptics on fibroblasts and keratinocytes: the cells were exposed to various dilutions of the antiseptic solutions. Sodium hypochlorite was toxic only at the highest concentration and was the least toxic to fibroblasts and keratinocytes of the three tested antiseptic solutions (86).

A key knowledge gap inn wound antisepsis is the determination of categorical breakpoints associated with minimum inhibitory concentration (MIC) or minimum bactericidal concentration (MBC) of topical antiseptics. The development of resistance and tolerance to topical antiseptic

represent an unmet clinical need because it may lead to important implications. The development of biocide nonsusceptibility may result in decreased clinical efficacy of biocides. However, the high concentrations of antiseptic in the wound site may overcome the MIC values of resident microorganisms (87). In support of this hypothesis, nonsusceptibility to biocides have been observed in laboratory studies, but did not emerge in clinical circumstances. Not surprisingly, the mechanism leading to biocide nonsusceptibility appears to be biofilm formation. This observation demonstrates the importance of a combined approach (antisepsis + debridement) in the management of chronic wound infections.

Antiseptic agents play a key role in the management of chronic wound infections if used at appropriate concentrations and for appropriate periods of time (88). A long exposure time facilitates the achievement of the antiseptic effect and allows anti-biofilm activity. In vitro studies showed that hypochlorous acid and some super oxidation solutions are effective in preventing biofilm formation within a 24-hourstime period (89). Conversely, short durations of exposure are ineffective against microbial biofilms. The performance of antiseptic solutions against biofilm is poor using short exposure times that mimic real clinical use (i.e. 15 min application) (90). Thus, prolonged and repeated applications should be promoted.

3. SUMMARY

In this manuscript, an expert panel identified some major issues in the management of patients with chronic wound infections, highlighting which actions should be avoided in the clinical practice.

The multifaceted approach is the milestone of the chronic wound care: comorbidities, concomitant systemic and local factors contributing to the delayed healing process should be adequately treated.

Expert figures should be involved in the management of chronic wound infections: as a matter of facts, each step (from diagnosis to treatment) needs a specialized approach. The milestones of an optimal chronic wound care are represented by the adequate wound bed preparation and the

antisepsis. These procedures should be combined, because the absence of one of them lead to delayed healing and higher risk of wound complications. Since biofilm is a common finding of chronic wounds, repeated debridement is usually required. Antiseptic agents may both prevent and treat local infection. An important aspect that should be considered is the appropriate use of systemic antibiotic therapy: local antisepsis may reduce the use of systemic antibiotics preventing the selection of resistant micro-organisms. Chronic wounds may be colonized or infected by healthcare-associated pathogens, including methicillin-resistant *Staphylococcus aureus*. The presence of subtherapeutic antimicrobial activity, promoted by inappropriate antibiotic use, inadequate bed preparation or lack of treatment of concomitant factors, rapidly promotes the emergence of resistant organisms.

Avoiding inappropriate management of chronic wound is important to achieve better clinical outcome and reduce healthcare costs. Thus, we proposed a list of "Don'ts" that may be useful in clinical practice.

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Table 1. List of "Don'ts" for the optimal management of acute wound infections using the Choosing Wisely methodology.

MULTIFACETED APPROACH	**1**	**Don't forget the management of underlying comorbidities and concomitant factors**
		A holistic approach is the first step to achieve the clinical cure in the management of patients with chronic wound infections. Clinicians should not cure the wound, but the patient and all clinical aspects, without forgetting pain control and psychological involvement to live with a chronic wound.
	2	**Don't use a single-based expert approach**
		A multifaceted approach is needed in this setting. Surgeon, infectious disease expert, geriatrician, nutritionist, microbiologist, nurse should be involved.
DIAGNOSIS	**3**	**Don't perform routine wound swabs**
		All chronic swabs are colonized by bacteria. Wound swabs may be useful if contextualized in a complete clinical evaluation. Routine wound swabs may lead to over-treatment and inappropriate antibiotic use.
	4	**Don't perform a biopsy with inappropriate method**
		Wound biopsy may provide several useful information. However, an appropriate technique should be applied.
TREATMENT	**5**	**Don't underestimate the role of biofilm**
		Biofilm should not be forbidden, because it is part of 90% of chronic wound infections. Combined approach that includes use of antiseptic agents and debridement is required to destroy biofilm.
	6	**Don't forget the wound bed preparation**
		Wound bed preparation may require time and expertise but is a crucial procedure to achieve the wound cure.
	7	**Don't use topical antibiotics indiscriminately**
		There is no evidence about the use of topical antibiotics in chronic wound care.
	8	**Don't use systemic antibiotic therapy indiscriminately**
		Systemic antibiotic therapy should be administered only in case of systemic signs of infections. The wide use of systemic antibiotics increases the risk of selection of multidrug resistant organisms and may lead to adverse events and treatment failure.

	9	**Don't underestimate the role of methicillin-resistant *S. aureus***
		Methicillin-resistant *S. aureus* (MRSA) may be difficult to eradicate in chronic wounds. To achieve the eradication of MRSA in chronic wounds a multifaceted approach including both antibiotic therapy, cleansing and antisepsis should be adopted.
	10	**Don't forget the role of antisepsis**
		Antiseptic agents have several role in the management of chronic wounds: they are useful to prevent and to treat local infections. Moreover, antiseptics are part of wound bed preparation and may reduce the use of systemic antibiotic therapy.
		Antiseptic agents should be used for an appropriate exposure time to guarantee their efficacy. Optimal time of exposure is longer than 15 minutes and may require patients/nurse education.

Table 2. Literature supporting the "Don'ts" for the optimal management of chronic wound infections.

MULTIFACETED APPROACH	**1**	**Don't forget the management of underlying comorbidities and concomitant factors**
		• Jaul E, et al. An overview of co-morbidities and the development of pressure ulcers among older adults. BMC Geriatr. 2018;18:305 • Gilmartin M. A holistic approach to wound care. Nurs Times. 2003;99:64-66. • Tayeb KA. Managing infection: a holistic approach. J Wound Care. 2015;24:20-30 • Appil R, et al. Effect of Family Empowerment on HbA1c Levels and Healing of Diabetic Foot Ulcers. Int J Low Extrem Wounds. 2020, epub of print
	2	**Don't use a single-based expert approach**
		• Mustoe TA, et al. Chronic wound pathogenesis and current treatment strategies: a unifying hypothesis. Plast Reconstr Surg. 2006;117:35S–41S. • Bergendahl L, et al. Development and evaluation of an interprofessional teaching concept for modern wound management. J Dtsch Dermatol Ges 2020. epub of print • Mahmoudi M, et al. Opportunities and Challenges of the Management of Chronic Wounds: A Multidisciplinary Viewpoint. Chronic Wound Care Management and Research. 2020;7:27-36
DIAGNOSIS	**3**	**Don't perform routine wound swabs**
		• Bowler PG. The 10(5) bacterial growth guideline: reassessing its clinical relevance in wound healing. Ostomy Wound Manag 2003;49:44e53 • Kallstrom G. Are quantitative bacterial wound cultures useful? J Clin Microbiol. 2014;52:2753-6 • Haalboom M, et al. Culture results from wound biopsy versus wound swab: does it matter for the assessment of wound infection? Clin

		Microbiol Infect. 2019;25:629.e7-629.e12
	4	**Don't perform a biopsy with inappropriate method**
		• U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry Chronic Cutaneous Ulcer and Burn WoundsDeveloping Products for Treatment. Jun. 2006 • Alavi A, et al.When and how to perform a biopsy on a chronic wound. Adv Skin Wound Care. 2010;23:132-40
TREATMENT	**5**	**Don't underestimate the role of biofilm**
		• Lineback CB, et al. Hydrogen peroxide and sodium hypochlorite disinfectants are more effective against *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms than quaternary ammonium compounds. Antimicrob Resist Infect Control. 2018;7:154 • Omar A, et al. Microbial Biofilms and Chronic Wounds. Microorganisms. 2017;5:9
	6	**Don't forget the wound bed preparation**
		• Schultz GS, et al. Wound bed preparation: a systematic approach to wound management. Wound Repair Regen. 2003;11 Suppl 1:S1-28 • Harries RL, et al. Wound bed preparation: TIME for an update. Int Wound J. 2016 Sep;13 Suppl 3:8-14
	7	**Don't use topical antibiotics indiscriminately**
		• Lipsky BA, et al.Topical antimicrobial therapy for treating chronic wounds. Clin Infect Dis. 2009;49:1541-9. • Uçkay I, et al. A randomized, controlled study to investigate the efficacy and safety of a topical gentamicin-collagen sponge in combination with systemic antibiotic therapy in diabetic patients with a moderate or severe foot ulcer infection. BMC Infect Dis. 2018;18:361. • Kramer A, et al. Consensus on Wound Antisepsis: Update 2018. Skin Pharmacol Physiol. 2018;31:28-58.
	8	**Don't use systemic antibiotic therapy indiscriminately**
		• Jockenhöfer F, et al. W.A.R. scores in patients with chronic leg ulcers: results of a multicentre study. J Wound Care. 2014;23:5–12. • Edwards-Jones V. Antimicrobial stewardship in wound care. Br J Nurs. 2020;29:S10-S16.
	9	**Don't underestimate the role of methicillin-resistant *S. aureus***
		• Reich-Schupke S, Warneke K, Altmeyer P, Stücker M. Eradication of MRSA in chronic wounds of outpatients with leg ulcers is accelerated by antiseptic washes--results of a pilot study. Int J Hyg Environ Health. 2010;213:88-92 • Zafari M, Adibi M, Chiani M, et al. Effects of cefazolin-containing niosome nanoparticles against methicillin-resistant *Staphylococcus aureus* biofilm formed on chronic wounds. Biomed Mater. 2021;16:035001. • Kramer A, Dissemond J, Kim S, et al. Consensus on wound antisepsis: Update 2018. Skin Pharmacol Physiol. 2018;31:28-58. • Adkins CL. Wound care dressings and choices for care of wounds in the home. Home Healthc Nurse. 2013;31:259-67; quiz 268-9. • Mangoni ML, McDermott AM, Zasloff M. Antimicrobial peptides and wound healing: biological and therapeutic considerations. Exp Dermatol. 2016;25:167-73.

	10	**Don’t forget the role of antisepsis**
		• Roth B, et al: Effect of antiseptic irrigation on infection rates of traumatic soft tissue wounds: a longitudinal cohort study. J Wound Care 2017;26:1–6. • Sheldon AT Jr. Antiseptic "resistance": real or perceived threat? Clin Infect Dis. 2005 Jun 1;40:1650-6. • Roberts CD, et al. The Role of Topical Antiseptic Agents Within Antimicrobial Stewardship Strategies for Prevention and Treatment of Surgical Site and Chronic Open Wound Infection. Adv Wound Care (New Rochelle). 2017;6:63-71 • Ortega-Peña S, et al. In vitro microbicidal, anti-biofilm and cytotoxic effects of different commercial antiseptics. Int Wound J. 2017;14:470-479 • Johani K, et al. Evaluation of short exposure times of antimicrobial wound solutions against microbial biofilms: from in vitro to in vivo. J Antimicrob Chemother. 2018;73:494-502

Table 3. Pro and cons of different debridement techniques.

Type of debridement	PRO	CONS	CONSIDER IT WHEN…
Autolytic debridement	Painless	Time-consuming Potential destruction of adjacent tissue	In presence of non-infected wounds As adjunctive therapy in infected wounds (plus mechanical debridement)
Biological debridement	Selective and rapid	Negative psychological reaction of patients Controindicated in: abdominal wound, pyoderma gangrenosum and immunosuppression therapy, areas afflicted by septic arthritis.	Wounds involving the extremities
Enzymatic debridement	Safe and easy to use	Time-consuming Expensive Not recommended for an advanced process, or in patients with known sensitivity to the product's ingredients.	In conjunction with routine surgical debridement When other techniques are not feasible during the initial management of a chronic wound
Surgical debridement	Complete removal of infected tissue Collection of deep material for culture	Need of skilled, qualified and licensed personnel Need of anesthesia or nerve block Painful (postoperative pain) Not selective	Current gold standard for chronic wound infections
Mechanical debridement	Can be performed by nurses in any facility on any size wound Mechanical scrubbing of wounds is inexpensive	Painful Time-consuming Not selective (superficial only and does not remove dead	Chronic wounds with moderate to large amounts of necrotic tissue, regardless of the presence of an active infection

		tissue down to bleeding healthy tissue) Controindicated in patients with poor perfusion or eschar	

FIGURE 1 (Legend). Criteria to consider before culturing a chronic wound.

Cutting KF, White R. Defined and refined: criteria for identifying wound infection revisited. Br J Community Nurs. 2004;9:S6-15

FIGURE 2 (legend). Indications and type of wound debridement.

References

1. Sen CK. Human Wounds and Its Burden: An Updated Compendium of Estimates. Adv Wound Care (New Rochelle). 2019;8:39-48

2. Järbrink K, Ni G, Sönnergren H, et al. The humanistic and economic burden of chronic wounds: a protocol for a systematic review. Syst Rev 2017;6:15–15

3. Phillips CJ, Humphreys I, Fletcher J, Harding K, Chamberlain G, Macey S. Estimating the costs associated with the management of patients with chronic wounds using linked routine data. Int Wound J 2016;13:1193–1197

4. Gardner SE, Frantz RA, Doebbeling BN. The validity of the clinical signs and symptoms used to identify localized chronic wound infection. Wound Repair Regen. 2001;9:178-86.

5. Wound infection in clinical practice. An international consensus. Int Wound J. 2008 Jun;5 Suppl 3:iii-11.

6. Grey JE, Enoch S, Harding KG. Wound assessment. BMJ. 2006;332:285-8.

7. Falcone M, Meier JJ, Marini MG, et al. Diabetes and acute bacterial skin and skin structure infections. Diabetes Res Clin Pract. 2021;174:108732

8. ACS/ASE Medical Student Core Curriculum Non-Healing Wounds. Available at: https://www.facs.org/-/media/files/education/core-curriculum/nonhealing_wounds.ashx. Last access: 26 of March 2021

9. Gilmartin M. A holistic approach to wound care. Nurs Times. 2003;99:64-66.

10. Tayeb KA. Managing infection: a holistic approach. J Wound Care. 2015;24:20-30

11. Karahan A, AAbbasoğlu A, Işık SA, et al. Factors affecting wound healing in individuals with pressure ulcers: a retrospective Study. Ostomy Wound Manage. 2018;64:32-39.

12. Olin JW, Sealove BA. Peripheral artery disease: current insight into the disease and its diagnosis and management. Mayo Clin Proc. 2010;85:678-92

13. Jiang M, Ma Y, Guo S, et al. Using Machine learning technologies in pressure injury management: systematic Review. JMIR Med Inform. 2021;9:e25704.

14. Ren SY, Liu YS, Zhu GJ, et al. Strategies and challenges in the treatment of chronic venous leg ulcers. World J Clin Cases. 2020;8:5070-5085

15. Appil R, Sjattar EL, Yusuf S, Kadir K. Effect of Family Empowerment on HbA1c levels and healing of diabetic foot ulcers. Int J Low Extrem Wounds. 2020 Jun

16. Dixon D, Edmonds M. Managing Diabetic Foot Ulcers: Pharmacotherapy for Wound Healing. Drugs. 2021;81:29-56

17. Nickinson ATO, Houghton JSM, Bridgwood B, et al. The utilisation of vascular limb salvage services in the assessment and management of chronic limb-threatening ischaemia and diabetic foot ulceration: A systematic review. Diabetes Metab Res Rev. 2020:e3326.

18. Mustoe TA, O'Shaughnessy K, Kloeters O. Chronic wound pathogenesis and current treatment strategies: a unifying hypothesis. Plast Reconstr Surg. 2006;117:35S–41S.

19. Businaro R, Corsi M, Di Raimo T, Marasco S, Laskin DL, Salvati B, Capoano R, Ricci S, Siciliano C, Frati G, De Falco E. Multidisciplinary approaches to stimulate wound healing. Ann N Y Acad Sci. 2016;1378:137-142.

20. Brown-Maher T. Multidisciplinary approach to chronic wound care: our 2-year Newfoundland and Labrador experience. J Cutan Med Surg. 2009 May-Jun;13 Suppl 1:S26-8.

21. Werdin F, Tennenhaus M, Schaller HE, Rennekampff HO. Evidence-based management strategies for treatment of chronic wounds. Eplasty. 2009 Jun 4;9:e19.

22. Gottrup F, Holstein P, Jørgensen B, Lohmann M, Karlsmar T. A new concept of a multidisciplinary wound healing center and a national expert function of wound healing. Arch Surg. 2001;136:765-72.

23. Mustoe TA, O'Shaughnessy K, Kloeters O. Chronic wound pathogenesis and current treatment strategies: a unifying hypothesis. Plast Reconstr Surg. 2006;117:35S-41S.

24. Bergendahl L, Werner F, Schmidt A, Ronicke M, Renner R, Erfurt-Berge C. Development and evaluation of an interprofessional teaching concept for modern wound management J Dtsch Dermatol Ges. 2020 published online ahead of print

25. Mahmoudi M, Gould LJ. Opportunities and challenges of the management of chronic wounds: a multidisciplinary viewpoint. Chronic Wound Care Management and Research. 2020;7:27-36

26. Bonham PA. Swab cultures for diagnosing wound infections: a literature review and clinical guideline. J Wound Ostomy Continence Nurs. 2009;36:389-95.

27. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. Clin Infect Dis. 2014;59:147-59.

28. Healy B, Freedman A. ABC of wound healing: infections. BMJ. 2006;332:838-841.

29. Bowler PG. The 105 bacterial growth guideline: reassessing its clinical relevance in wound healing. Ostomy Wound Manage. 2003;49:44-53

30. Dow G. Bacterial swabs and the chronic wound: when, how, and what do they mean. Ostomy Wound Manage. 2003;49:8-13,34-36

31. Cutting KF, White R. Defined and refined: criteria for identifying wound infection revisited. Br J Community Nurs. 2004;9:S6-15

32. Schwarzkopf A, Dissemond J. Indications and practical implementation of microbiologic diagnostics in patients with chronic wounds. J Dtsch Dermatol Ges. 2015;13:203-9.

33. Stotts NA. Determination of bacterial burden in wounds. Adv Wound Care. 1995;8:28-52

34. Bowler PG. The 10(5) bacterial growth guideline: reassessing its clinical relevance in wound healing. Ostomy Wound Manag 2003;49:44e53

35. Kallstrom G. Are quantitative bacterial wound cultures useful? J Clin Microbiol. 2014;52:2753-6

36. Haalboom M, Blokhuis-Arkes MHE, Beuk RJ, et al. Culture results from wound biopsy versus wound swab: does it matter for the assessment of wound infection? Clin Microbiol Infect. 2019;25:629.e7-629.e12

37. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry Chronic Cutaneous Ulcer and Burn WoundsDeveloping Products for Treatment. Jun. 2006 Available at: http://www.fda.gov/cber/gdlns/ulcburn.htm

38. Alavi A, Niakosari F, Sibbald RG. When and how to perform a biopsy on a chronic wound. Adv Skin Wound Care. 2010;23:132-40; quiz 141-2.

39. Omar A, Wright JB, Schultz G, Burrell R, Nadworny P. Microbial biofilms and chronic wounds. Microorganisms. 2017;5:9.

40. Lineback CB, Nkemngong CA, Wu ST et al. Hydrogen peroxide and sodium hypochlorite disinfectants are more effective against *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms than quaternary ammonium compounds. Antimicrob Resist Infect Control. 2018 Dec 17;7:154

41. Evelhoch SR. Biofilm and chronic nonhealing wound infections. Surg Clin North Am. 2020;100:727-732.

42. Ng SF, Leow HL. Development of biofilm-targeted antimicrobial wound dressing for the treatment of chronic wound infections. Drug Dev Ind Pharm. 2015;41:1902-9

43. Harika K, Shenoy VP, Narasimhaswamy N, Chawla K. Detection of Biofilm Production and Its Impact on Antibiotic Resistance Profile of Bacterial Isolates from Chronic Wound Infections. J Glob Infect Dis. 2020;12:129-134.

44. Thieme L, Hartung A, Tramm K, et al. MBEC Versus MBIC: the lack of differentiation between biofilm reducing and inhibitory effects as a current problem in biofilm methodology. Biol Proced Online. 2019;21:18

45. Frank KL, Reichert EJ, Piper KE, Patel R. In vitro effects of antimicrobial agents on planktonic and biofilm forms of *Staphylococcus lugdunensis* clinical isolates. Antimicrob Agents Chemother. 2007;51:888-95

46. Macià MD, Rojo-Molinero E, Oliver A. Antimicrobial susceptibility testing in biofilm-growing bacteria. Clin Microbiol Infect. 2014;20:981-90.

47. Macià MD, Rojo-Molinero E, Oliver A. Antimicrobial susceptibility testing in biofilm-growing bacteria. Clin Microbiol Infect. 2014;20:981-90.

48. Bianchi T, Wolcott RD, Peghetti A, et al. Recommendations for the management of biofilm: a consensus document. J Wound Care. 2016;25:305-17.

49. Attinger C, Wolcott R. Clinically addressing biofilm in chronic wounds. Adv Wound Care (New Rochelle). 2012;1:127-132.

50. Manna B, Nahirniak P, Morrison CA. Wound Debridement. 2021 Feb 20. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan

51. Bekara F, Vitse J, Fluieraru S, et al. New techniques for wound management: A systematic review of their role in the management of chronic wounds. Arch Plast Surg. 2018;45:102-110

52. Schultz GS, Sibbald RG, Falanga V, et al. Wound bed preparation: a systematic approach to wound management. Wound Repair Regen. 2003 Mar;11 Suppl 1:S1-28

53. Harries RL, Bosanquet DC, Harding KG. Wound bed preparation: TIME for an update. Int Wound J. 2016 Sep;13 Suppl 3:8-14

54. Cowling T, Jones S. Topical Antibiotics for Infected Wounds: A Review of the Clinical Effectiveness and Guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017 Mar 20.

55. Caldwell MD. Bacteria and Antibiotics in Wound Healing. Surg Clin North Am. 2020;100:757-776

56. Bowler PG. Antibiotic resistance and biofilm tolerance: a combined threat in the treatment of chronic infections. J Wound Care. 2018 May 2;27(5):273-277.

57. Lipsky BA, Hoey C. Topical antimicrobial therapy for treating chronic wounds. Clin Infect Dis. 2009;49:1541-9.

58. Chrisman CA. Care of chronic wounds in palliative care and end-of-life patients. Int Wound J. 2010;7:214-35.

59. Frank C, Bayoumi I, Westendorp C. Approach to infected skin ulcers. Can Fam Physician. 2005;51:1352-9.

60. Uçkay I, Kressmann B, Malacarne S, et al. A randomized, controlled study to investigate the efficacy and safety of a topical gentamicin-collagen sponge in combination with systemic antibiotic therapy in diabetic patients with a moderate or severe foot ulcer infection. BMC Infect Dis. 2018;18:361.

61. Kramer A, Dissemond J, Kim S, et al. Consensus on wound antisepsis: Update 2018. Skin Pharmacol Physiol. 2018;31:28-58.

62. Adkins CL. Wound care dressings and choices for care of wounds in the home. Home Healthc Nurse. 2013;31:259-67; quiz 268-9.

63. Mangoni ML, McDermott AM, Zasloff M. Antimicrobial peptides and wound healing: biological and therapeutic considerations. Exp Dermatol. 2016;25:167-73.

64. Thapa RK, Diep DB, Tønnesen HH. Topical antimicrobial peptide formulations for wound healing: Current developments and future prospects. Acta Biomater. 2020;103:52-67.

65. Kawano Y, Jordan O, Hanawa T, Borchard G, Patrulea V. Are Antimicrobial Peptide Dendrimers an Escape from ESKAPE? Adv Wound Care (New Rochelle). 2020;9:378–95.

66. Hernandez R. The use of systemic antibiotics in the treatment of chronic wounds. Dermatol Ther. 2006;19:326-37

67. Robson MC, Edstrom LE, Krizek TJ, Groskin MG. The efficacy of systemic antibiotics in the treatment of granulating wounds. J Surg Res. 1974;16:299-306

68. Leaper D, Assadian O, Edmiston CE. Approach to chronic wound infections. Br J Dermatol. 2015;173:351-8.

69. Tiseo G, Mazzone A, Falcone M. Identifying patients with acute bacterial skin and skin structure infection who need blood cultures. Intern Emerg Med. 2019;14:203-206

70. Goh T, Goh LG, Ang CH, Wong CH. Early diagnosis of necrotizing fasciitis. Br J Surg. 2014;101:e119-25

71. Jockenhöfer F, Gollnick H, Herberger K, et al. W.A.R. scores in patients with chronic leg ulcers: results of a multicentre study. J Wound Care. 2014;23:5–12.

72. Campanile F, Bongiorno D, Falcone M, et al. Changing Italian nosocomial-community trends and heteroresistance in *Staphylococcus aureus* from bacteremia and endocarditis. Eur J Clin Microbiol Infect Dis. 2012;31:739-45.

73. Falcone M, Serra P, Venditti M. Serious infections due to methicillin-resistant *Staphylococcus aureus*: an evolving challenge for physicians. Eur J Intern Med. 2009;20:343-7.

74. Venditti M, Falcone M, Micozzi A, et al. *Staphylococcus aureus* bacteremia in patients with hematologic malignancies: a retrospective case-control study. Haematologica. 2003;88:923-30.

75. Reich-Schupke S, Warneke K, Altmeyer P, Stücker M. Eradication of MRSA in chronic wounds of outpatients with leg ulcers is accelerated by antiseptic washes--results of a pilot study. Int J Hyg Environ Health. 2010;213:88-92

76. Zafari M, Adibi M, Chiani M, et al. Effects of cefazolin-containing niosome nanoparticles against methicillin-resistant Staphylococcus aureus biofilm formed on chronic wounds. Biomed Mater. 2021;16:035001.

77. Allegranzi B, Zayed B, Bischoff P, et al. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective

Lancet Infect. Dis 2016; 16:e288-e303

78. Roth B, Neuenschwander R, Brill F, et al. Effect of antiseptic irrigation on infection rates of traumatic soft tissue wounds: a longitudinal cohort study. J Wound Care 2017;26:1–6.

79. Leaper DJ, Schultz G, Carville K, Fletcher J, Swanson T, Drake R. Extending the TIME concept: what have we learned in the past 10 years?(*). Int Wound J. 2012;9 Suppl 2:1-19.

80. Capriotti K, Capriotti JA. Topical iodophor preparations: chemistry, microbiology, and clinical utility. Dermatol Online J. 2012;18:1

81. Liu JX, Werner J, Kirsch T, Zuckerman JD, Virk MS. Cytotoxicity evaluation of chlorhexidine gluconate on human fibroblasts, myoblasts, and osteoblasts. J Bone Jt Infect. 2018;3:165-172.

82. Hidalgo, E.; Dominguez, C. Mechanisms underlying chlorhexidine-induced cytotoxicity. Toxicol. Vitr. 2001; 15: 271–276.

83. Gonzalez-Espinosa D, Perez-Romano L, Guzman-Soriano B et al. Effects of pH-neutral, super-oxidised solution on human dermal fibroblasts in vitro. Int Wound J 2007; 4: 241–50.

84. Severing AL, Rembe JD, Koester V, Stuermer EK. Safety and efficacy profiles of different commercial sodium hypochlorite/hypochlorous acid solutions (NaClO/HClO): antimicrobial efficacy, cytotoxic impact and physicochemical parameters in vitro. J Antimicrob Chemother. 2019;74:365-372.

85. Cotter JL, et al: Chemical parameters, antimicrobial activities, and tissue toxicity of 0.1 and 0.5% sodium hypochlorite solution. Antimicrob Agents Chemother 1985;28:118.

86. Cooper ML, et al: The cytotoxic effects of commonly used topical antimicrobial agents on human fibroblasts and keratinocytes. J Trauma 1991;31:775

87. Sheldon AT Jr. Antiseptic "resistance": real or perceived threat? Clin Infect Dis. 2005;40:1650-6.

88. Roberts CD, Leaper DJ, Assadian O. The role of topical antiseptic agents within antimicrobial stewardship strategies for prevention and treatment of surgical site and chronic open wound infection. Adv Wound Care (New Rochelle). 2017;6:63-71

89. Ortega-Peña S, Hidalgo-González C, Robson MC, Krötzsch E. In vitro microbicidal, anti-biofilm and cytotoxic effects of different commercial antiseptics. Int Wound J. 2017;14:470-479

90. Johani K, Malone M, Jensen SO, et al. Evaluation of short exposure times of antimicrobial wound solutions against microbial biofilms: from in vitro to in vivo. J Antimicrob Chemother. 2018;73:494-502

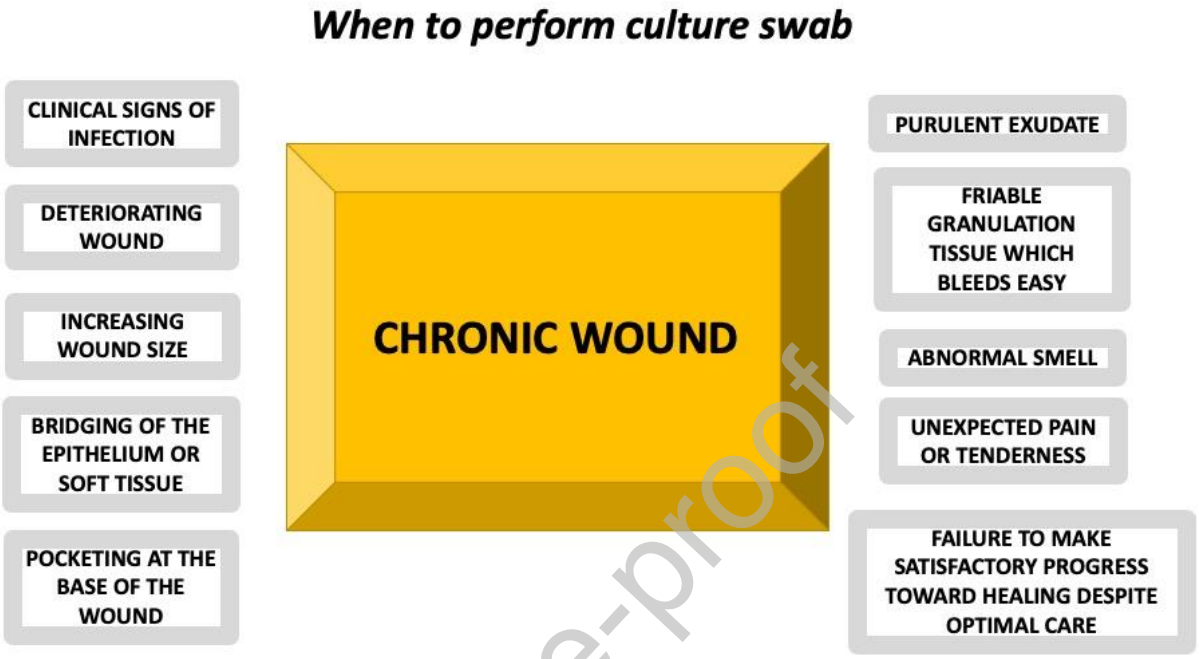
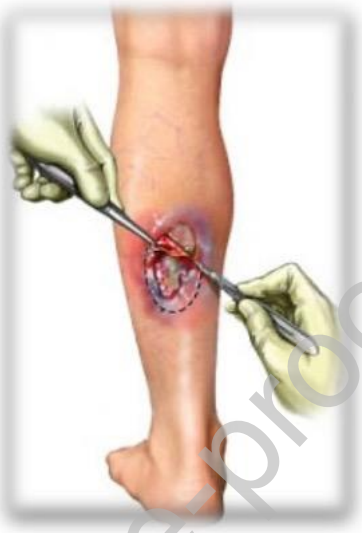


Fig. 1

Fig. 2

INDICATIONS

- Removal of the source of sepsis (necrotic tissue)
- Removal of local infection to decrease bacterial burden, to reduce the probability of resistance from antibiotic treatment
- Collection of deep cultures
- Stimulation of the wound bed to support healing and to prepare for a skin graft or flap



TYPE OF DEBRIDMENT

- Autolytic
- Biological
- Enzymatic
- Surgical
- Mechanical