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Challenges in the management of chronic wound infections

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ABSTRACT

Objectives: Chronic wound infections may delay the healing process and are responsible for a significant burden on healthcare systems. Since inappropriate management may commonly occur in the care 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 in PubMed in the last 10 years, identifying studies regarding the management of patients with chronic wound infections. A panel of experts discussed the potential malpractices in this area. A list of 'Don'ts', including the main actions to be avoided, was drawn up using the 'Choosing Wisely' methodology.

Results: In this review, we proposed a list of actions to avoid for optimal management of patients with chronic wound infections. Adequate wound bed preparation and wound antisepsis should be combined, as the absence of one of them leads to delayed healing and a 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 as well as antibiotic-related adverse events.

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

1. Introduction

It has been estimated that approximately 8 million people worldwide are affected by wounds, with or without infections [1]. In the USA, 2% of the entire population is affected by chronic wounds [2], and 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 hyperglycaemia, impaired vascular status and neuropathy.

Chronic wound infections may delay the healing process, with clinical implications (increased pain, reduced quality of life) and a significant burden on healthcare systems. 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. In fact, non-traditional signs may characterise chronic wound infections, including increased pain, friable granulation tissue, delayed wound healing beyond expectation, wound breakdown and foul odour that may be not easy identified by non-expert personnel [4]. Inappropriate

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management may frequently occur in the management of chronic wounds and should be avoided in order to avert the risk of infection and poor outcomes.

The aim of this review was to provide a practical guide describing actions to be avoided in clinical practice when managing chronic wound infections.

2. Methods

This document focused on the management of chronic wound infections has been drafted by a team of specialists with different areas of expertise (microbiology, infectious disease and antibiotic therapy, general surgery, plastic surgery, diabetic foot surgery, wound management, pharmacologist and geriatrician). 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 was used to identify and summarise these actions, which 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 owing 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 on the duration of a wound that defines chronicity, a range of 4 weeks to 3 months has been used in the literature to define chronic wounds [8]. The Wound Healing Society classifies chronic wounds into four major categories, namely 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 in the management of chronic wound infections commonly considered to be inappropriate. A PubMed/MEDLINE search was conducted. Search terms used for the literature search are given in Supplementary Table S1. 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 the relative references are reported in Table 1.

3.1. Don't forget the management of underlying co-morbidities and concomitant factors

Optimal management of both acute and 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 [11,12][92]

Thus, all concomitant factors should be considered and adequately treated [13]:

- arterial ulcers require revascularisation and adequate control of cardiovascular risk factors [14];
- pressure ulcers require optimisation of the patient's mobility, pressure redistribution to reduce pressure, friction and shear forces, and incontinence management [15];
- venous ulcers require compression and improvement of blood flow [16]; and

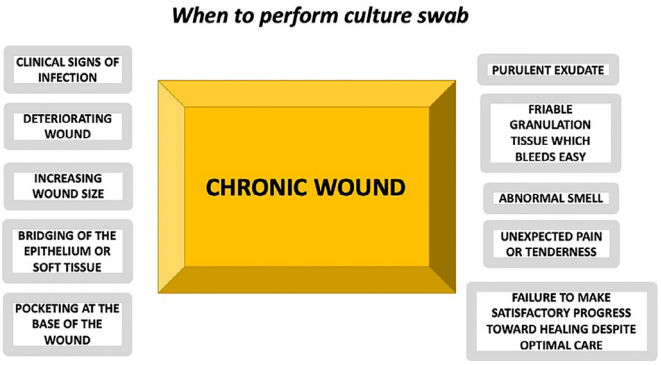

Fig. 1. Criteria to consider before culturing a chronic wound. Adapted from Cutting KF, White R. Defined and refined: criteria for identifying wound infection revisited. Br J Community Nurs 2004;9:S6–15.

- diabetic foot ulcers require adequate vascular supply (through revascularisation), infection treatment, plantar pressure redistribution, management of diabetic neuropathy, and improvement in glycaemic control [17] and other cardiovascular risk factors [18,19].

3.2. Don't use a single expert-based approach: role of multifaceted 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 [20–24]. Unfortunately, wound care is generally fragmented. Centres of excellence that orchestrate a multidisciplinary networking approach including surgeons, internal medicine, infectious diseases, diabetologists, specialty nursing and basic scientists are usually lacking or poorly represented [25]. Promotion of these structures may be useful to overcome some issues in the management of patients with chronic wound infections. Moreover, implementing specialised structures may favour the development of standardised protocols in reporting wound healing success, randomised clinical trials and measurement of quality-of-life outcomes [26].

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

Culture methodology of wound infections is 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 [27]. This statement is based on Infectious Disease Society of America (IDSA) guidelines regarding the management of skin and soft-tissue infections that discourages routine culture of blood, cutaneous aspirates, biopsies or swabs [28]. Identification of infection requires a high degree of suspicion [29]. Indiscriminate or routine culturing in the absence of clinical indicators is not advised because it may lead to misdiagnosis and antibiotic overtreatment. Fig. 1 summarises the criteria that should be considered before culturing a chronic wound [4,30–32]. Several considerations should

Table 1
List of 'Don'ts' for the optimal management of acute wound infections using the 'Choosing Wisely' methodology and supporting literature

		'Don't'	Reference(s)
MULTIFACETED APPROACH	1	**Don't forget the management of underlying co-morbidities and concomitant factors** A holistic approach is the first step to achieve 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.	[9, 10,12,17]
	2	**Don't use a single expert-based approach** A multifaceted approach is needed in this setting. A surgeon, infectious diseases expert, geriatrician, nutritionist, microbiologist and nurse should be involved.	[20,25,26]
DIAGNOSIS	3	**Don't perform routine swabs for all chronic wounds** All chronic swabs are colonised by bacteria. Wound swabs may be useful if contextualised in a complete clinical evaluation. Routine wound swabs may lead to overtreatment and inappropriate antibiotic use.	[30,35,36]
	4	**Don't perform a biopsy with an inappropriate method** Wound biopsy may provide various useful information. However, an appropriate technique should be applied.	[37,38]
TREATMENT	5	**Don't underestimate the role of biofilm** Biofilm should not be forgotten because it is present in 90% of chronic wound infections. A combined approach that includes use of antiseptic agents and debridement is required to destroy biofilm.	[40,41]
	6	**Don't forget wound bed preparation** Wound bed preparation may require time and expertise but is a crucial procedure to achieve wound cure.	[51,52]
	7	**Don't use topical antibiotics indiscriminately** There is no evidence about the topical use of antibiotics in chronic wound care.	[56,59,60]
	8	**Don't use systemic antibiotic therapy indiscriminately** Systemic antibiotic therapy should be administered only in case of systemic signs of infections. Wide use of systemic antibiotics increases the risk of selection of multidrug-resistant organisms and may lead to adverse events and treatment failure.	[11,70]
	9	**Don't underestimate the role of methicillin-resistant *Staphylococcus aureus* (MRSA)** MRSA may be difficult to eradicate in chronic wounds. To achieve eradication of MRSA in chronic wounds, a multifaceted approach including antibiotic therapy, cleansing and antisepsis should be adopted.	[60–62,74,75]
	10	**Don't forget the role of antisepsis** Antiseptic agents have several roles in the management of chronic wounds: they are useful to prevent and 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 min and may require patient/nurse education.	[77,86–89]

be performed before a culture swab: first, the physician should clinically differentiate whether the microbiology workup is done in the context of multiresistant pathogen screening or whether there are clinical signs of a wound infection requiring systemic antibiotic therapy; and swab preparation and technique for wound swabbing should be adequately chosen [33].

Quantitative biopsy (removal of a piece of tissue using a scalpel or punch biopsy) has been promulgated as the gold standard in the diagnosis of wound infection [34]. 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 [30]. 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, the relationship between bacterial counts and clinical signs of sepsis is not linear and methods of specimen collection vary greatly.

i. 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 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. Wide use of routine swabs may lead to overdiagnosis and overtreatment 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 an 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 US 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]. A standardised technique for wound biopsy is important to guarantee safety and accurate diagnosis. Biopsy should be obtained from the centre of the wound and should include the 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, as detailed below.

i. 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-h period, which enables removal of the biofilm and active destruction of sessile and planktonic bacteria [26];
ii. antiseptics able to degrade extracellular polymeric substances should be preferred; not all antiseptics have efficacy against biofilms. Hydrogen peroxide and sodium hypochlorite products are effective against *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms [40];

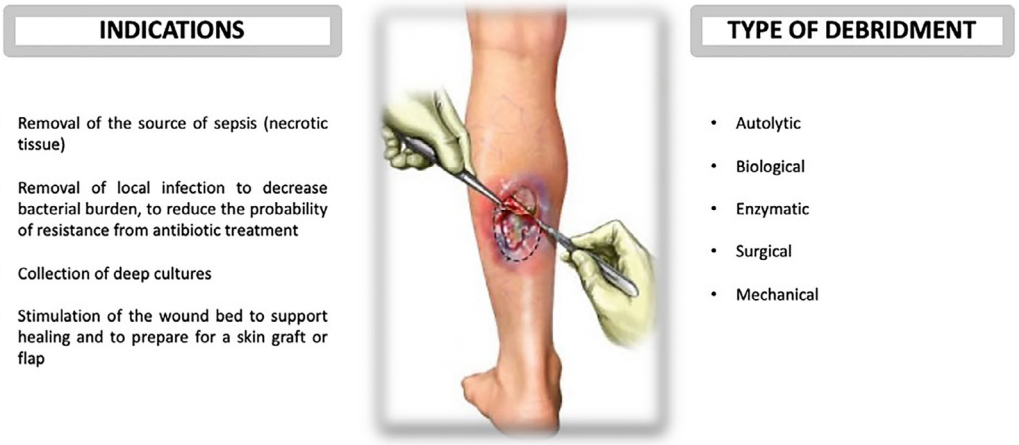

Fig. 2. Indications for and types of wound debridement.

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

Biofilm represents a great challenge for clinicians faced with chronic wound infections as 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 or to determine the susceptibility of biofilm to various agents [43]. Specific methods, such as the tissue culture plate method, tube method and Congo red agar method, have recently been studied. The tissue culture plate method appears to be the best and most reliable for screening of biofilm formation in comparison with the tube method and Congo red agar method [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, standardised biofilm susceptibility testing assays that are clinically meaningful. New pharmacodynamic parameters, including minimum biofilm inhibitory concentration (MBIC), minimal biofilm eradication concentration (MBEC), 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 in the effects of most antibiotics on planktonic and biofilm bacteria [45,46]. However, several unmet needs still remain: standardised procedures and breakpoints are needed before they can be implemented in clinical microbiology laboratories for routine susceptibility testing [46].

Wound debridement represents a crucial step in wound management [47]. Debriding a wound is defined as removing necrotic tissue, foreign material, senescent cells and bacteria. Debridement can allow wounds to progress beyond the inflammatory stage towards healing. Removing biofilm is one of the most difficult practices because it is adherent to surrounding tissue, is poorly penetrated by antibiotics, is resistant to biocides, and evades the body's local immune response [48]. 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 are likely to reconstitute over time. Clinicians should evaluate indications and contraindications and adopt the best technique for wound debridement. Fig. 2 summarises the indications for and types of debridement [49]: (i) 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 non-infected 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; (ii) biological debridement, also known as larval therapy, uses sterile larvae of *Lucilia sericata* (common green bottle fly) that release proteolytic enzymes; (iii) enzymatic debridement is a selective method for debridement of necrotic tissue using an exogenous proteolytic enzyme (collagenase); (iv) surgical debridement is used to remove necrotic tissue using sharp instruments, allowing collection of wound cultures and complete removal of infected materials; and (v) mechanical debridement is a non-selective type of debridement used to remove both devitalised tissue and debris as well as viable tissue. It is usually carried out using mechanical force (wet-to-dry, pulsatile lavage or wound irrigation). All of these type of debridement have pros and cons (Table 2): the choice of the best type of debridement depends on the objective, the patient and the type of wound (infected or not) [50].

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

Wound bed preparation is a key aspect to accelerate endogenous healing and to 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 and dressing should not be forgotten in any procedure [51]. The TIME concept (Tissue, Infection/Inflammation, Moisture imbalance, Epithelial edge advancement) has been proposed to summarise wound bed preparation and may be considered part of a comprehensive approach to patients with chronic wound infections [52]. Each component of bed wound preparation should always be addressed and optimised 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

Table 2
Pro and cons of different debridement techniques

Type of debridement	Pros	Cons	Consider it when...
Autolytic	Painless	Time consuming Potential destruction of adjacent tissue	In presence of non-infected wounds As adjunctive therapy in infected wounds (plus mechanical debridement)
Biological	Selective and rapid	Negative psychological reaction of patients Contraindicated in: abdominal wound, pyoderma gangrenosum, immunosuppressive therapy and areas afflicted by septic arthritis	Wounds involving the extremities
Enzymatic	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	Complete removal of infected tissue Collection of deep material for culture	Need of skilled, qualified and licensed personnel Need of anaesthesia or nerve block Painful (postoperative pain) Not selective	Current gold standard for chronic wound infections
Mechanical	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 tissue down to bleeding healthy tissue) Contraindicated in patients with poor perfusion or eschar	Chronic wounds with moderate to large amounts of necrotic tissue, regardless of the presence of an active infection

usually require systemic antibiotic therapy, whereas clinically uninfected wounds that are healing as expected do not require antimicrobials [53–55]. There is controversy about the use of topical antibiotic agents to treat poorly healing wounds with signs of infection [56,57]. 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 decolonising chronic wounds [58]. A recent randomised clinical trial evaluated the use of topical gentamicin–collagen sponge in combination with systemic antibiotic therapy in diabetic patients with moderate or severe foot ulcer infection: no differences in clinical cure or pathogen eradication were found between patients who received topical antibiotic therapy and those who did not [59]. One major problem with topical use of antibiotics is the lack of standardised and approved tests to evaluate their concentrations at the wound site and their efficacy.

Use of specific topical antibiotics may be associated with adverse events [60,61]: agents such as neomycin, bacitracin and lanolin-containing preparations can increase the inflammatory response and are potential sensitisers; and topical aminoglycosides such as gentamicin can increase the risk of microbial resistance. Indiscriminate use of topical antibiotics is an 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 generally be avoided [62].

Antimicrobial peptides (AMPs) represent an emerging category of therapeutic agents. AMPs are oligopeptides composed of amino acid residues that possess antimicrobial activity [63]. AMPs interact with anionic phospholipids in the microbial cell membrane and possess great potential to effectively kill bacteria with minimal risk of resistance development. There are many AMPs that accelerate in vivo wound healing via promoting re-epithelisation and granulation tissue. Several studies have been performed to develop different AMP formulations, including but 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 and release/availability following topical application. AMPs offer promising alternatives to topical antibiotics with mechanisms of action less prone to resistance induction [64].

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

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 indiscriminate use of systemic antibiotics may increase antibiotic resistance and side effects [65–67].

Determining whether a non-healing 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 [68]. Deep invasion of bacteria from a chronic wound can lead to regional infections such as cellulitis, myositis, fasciitis, abscess formation and osteomyelitis [69]. These situations should be promptly diagnosed and adequately treated. 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 require systemic antibiotic therapy. The Wounds at Risk (WAR) score incorporates the patient's immune status, immunosuppressive therapies (glucocorticoids, chemotherapy), systemic haematological diseases, occupational and social conditions, wound location and likelihood of contamination, patient's age and type of wound [70]. 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 Staphylococcus aureus (MRSA)

Chronic wounds may be colonised or infected by healthcare-associated pathogens, including MRSA [71]. The spread of MRSA both in hospital and community settings represents a great challenge for clinicians [72,73]. The significance of *S. aureus* in a patient's wound needs to be assessed for each patient. *Staphylococcus aureus* may colonise the wound or may cause infection. Discrimination between colonisation and infection requires clinical evaluation by expert physicians. The presence of MRSA in an infected wound poses significant problems because both topical and sys-

temic antibiotics may be insufficient to achieve MRSA eradication. 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 [74]. 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 (including hair 1 × /day with antiseptic shower foam); daily cleaning of spectacles, hearing aids or other personal objects with antiseptic solution; daily changing of bed linen, underwear and handkerchiefs; and disinfection of all contact surfaces with surface disinfectant. MRSA was successfully eradicated in only 42% of patients. Antiseptic body washes were associated with an increased eradication rate. Thus, MRSA eradication in chronic wounds requires a comprehensive approach and should not be limited to antibiotic therapy [74]. 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 MRSA infections [75].

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 World Health Organization (WHO) guideline advocates the use of good antisepsis perioperatively while reducing the use of systemic antibiotics [76]. Antiseptic agents have both a prophylactic and therapeutic role in wound treatment [77]. Moreover, antisepsis may support wound healing by causing positive effects on cell proliferation and regeneration. Finally, wound cleansing with antiseptic agents is useful in the preparation for debridement. Thus, antiseptic agents at dressing changes together with wound cleaning, irrigation and debridement should be implemented because their use reduces the bacterial burden and suppresses biofilm formation and reformation [31,32].

Several antiseptic agents are available [60]. Commonly used antiseptics include iodine in various forms, chlorhexidine, silver and polyhexamethylene biguanide in solution for lavage, gels, and surgical and chronic wound dressings. The choice of one antiseptic over another is not easy and little robust evidence exist. Characteristics of antiseptic agents are important. Ideally, an antiseptic agent should possess all of the following features: a broad antimicrobial spectrum and activity against biofilm [78], being associated with a low risk of pathogen resistance, demonstrate persistence within the wound bed, be non-injurious to eukaryotic cells and possess minimal allergenicity, favour wound healing, not alter wound coloration, and have a high tolerability [15,79]. All of these characteristics together with the patient's comfort should be taken into account in chronic wound care. Antiseptics, including hypochlorous acid, iodine carriers with polyvinylpyrrolidone (PVP or povidone) iodine, silver, chlorhexidine, benzalkonium chloride, triclosan, octenidine and polyhexanide, as well as selected dyes such as eosin remain good options in wound care.

Antiseptics applied during wound care may affect the viability of skin cells. Some studies analysed the impact of antiseptics on cultured fibroblasts or keratinocytes. It has been demonstrated that the clinically used concentration of chlorhexidine gluconate (2%) permanently halts cell migration and significantly reduces survival of in vitro fibroblasts, myoblasts and osteoblasts [80,81]. Several in vitro studies on hypochlorous acid reported favourable microbicidal effects against a variety of microbes while exerting low cytotoxicity [82]. The effect of hypochlorous acid on keratinocytes and fibroblasts depends on the concentration [83]. The effect of 0.1% and 0.5% buffered sodium hypochlorite solutions on the viability of basal cells of guinea pig skin was studied: basal cells of skin exposed to the 0.5% solution showed no reduction in viability after 1 week, whereas cells exposed to the 0.1% solution showed no loss in viability after 2 weeks [84]. Cooper et al. examined the in vitro effects of three topical antiseptics on fibroblasts and keratinocytes: 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 [85].

A key knowledge gap in wound antisepsis is the determination of categorical breakpoints associated with the minimum inhibitory concentration (MIC) or minimum bactericidal concentration (MBC) of topical antiseptics. Development of resistance and tolerance to topical antiseptics represent an unmet clinical need because they may have important implications. The development of biocide non-susceptibility may result in decreased clinical efficacy of biocides. However, the high concentrations of antiseptic in the wound site may overcome the MICs of resident micro-organisms [86]. In support of this hypothesis, non-susceptibility to biocides has been observed in laboratory studies but did not emerge in clinical circumstances. Not surprisingly, the mechanism leading to biocide non-susceptibility 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 [87]. A long exposure time facilitates achievement of the antiseptic effect and allows antibiofilm activity. In vitro studies showed that hypochlorous acid and some superoxidised solutions are effective in preventing biofilm formation within a 24-h time period [88]. Conversely, short durations of exposure are ineffective against microbial biofilms. The performance of antiseptic solutions against biofilms is poor using short exposure times that mimic real clinical use (i.e. 15 min application) [89]. Thus, prolonged and repeated applications should be promoted.

4. Summary

In this manuscript, a panel of experts identified some major issues in the management of patients with chronic wound infections, highlighting actions that should be avoided in clinical practice. Malpractices in the management of chronic wound infections became more and more frequent during the COVID-19 pandemic. As a matter of fact, COVID-19 pandemic caused collateral damage in healthcare in terms of reduced hospitalization and postponed treatment of patients with chronic illness [90][91]

A multifaceted approach is the milestone of chronic wound care: co-morbidities as well as 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 fact, each step (from diagnosis to treatment) needs a specialised approach. The milestones of optimal chronic wound care are represented by adequate wound bed preparation and antisepsis. These procedures should be combined because the absence of one of them leads 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 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 colonised or infected by healthcare-associated pathogens, including MRSA. The presence of subtherapeutic antimicrobial activity, promoted by in-

appropriate antibiotic use, inadequate bed preparation or lack of treatment of concomitant factors, rapidly promotes the emergence of resistant organisms.

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

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Competing interests: MF has received grants and/or speaker honoraria from MSD, Angelini, Shionogi and Nordic Pharma; FP has received personal fees from Angelini, Basilea Pharmaceutica, Correvio, Gilead, Hikma, Merck Sharp & Dohme, Nordic Pharma, Pfizer, Sanofi Aventis and Thermo Fisher; SS has received grants from Shionogi, Biosynth, Biotest and Nordic Pharma and has participated as a speaker for Pfizer, Angelini, bioMérieux, MSD and Nordic Pharma. All of these potential competing interests are outside the submitted paper. All other authors declare no competing interests.

Ethical approval: Not required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jgar.2021.05.010.

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