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What COVID-19 taught us: New opportunities and pathways from telemedicine and novel antiseptics in wound healing

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Abstract

The COVID-19 pandemic deeply impacted the capacity of the health systems to maintain preventive and curative services, especially for the most vulnerable populations. During the pandemic, the wound healing centres in Italy assisted a significant reduction of the frequency of their hospital admission, since only urgencies, such as severe infections or wound haemorrhagic complications, were allowed to the hospital. The aim of this multidisciplinary work is to highlight the importance of a new pathway of wound care with patient-based therapeutic approach, tailored treatments based on the characteristics of the wound and fast tracks focused on the outpatient management, reserving hospital assessment only for patients with complicated or complex wounds. This analysis highlights the point that patients with chronic wounds need to be critically evaluated in order to find the best and most appropriate care pathway, which should vary according to the patient and, especially, to the characteristics of the wound. Moreover, the most adequate topic antiseptic should be started as soon as possible. An appropriate and correct management of the wound care will allow to link the knowledge based on years of clinical practice with the new challenges and the need to visit patients remotely, when possible.

KEYWORDS

antiseptics, COVID-19, fast track, telemedicine, wound healing

Key Messages

- the COVID-19 pandemic deeply impacted the health systems worldwide
- during the pandemic, the wound healing centres in Italy assisted a significant reduction of the frequency of their hospital admission
- patients with chronic wounds need to be critically evaluated in order to find the best and most appropriate care pathway

- an appropriate and correct management of the wound care will allow to link the knowledge based on years of clinical practice with the new challenges and the need to visit patients remotely, when possible

1 | INTRODUCTION

The COVID-19 pandemic deeply impacted the capacity of the health systems to maintain preventive and curative services, especially for the most vulnerable populations. A major challenge has been reserved to the wound care management, which needed to be significantly reorganised to evolve and to allocate energies and resources in a new model of care.

During the pandemic, the wound healing centres in Italy assisted a significant reduction of the frequency of their hospital admission because only urgencies, such as severe infections or wound haemorrhagic complications, were allowed to the hospital.[1] On the other hand, home care organisations have not always been able to meet all care needs with serious harm to patients and increased health care costs.

For this reason, it is crucial to tailor the management of wound care according to patient-related risk factors and based on wound microenvironment characteristics and on the most appropriate multidisciplinary care pathways for each wound type.

According to the time of healing, wounds can be classified into acute and chronic wounds[2]; wound repair depends on numerous factors,[3] and chronic wounds do not follow the normal steps of the wound healing process, which usually takes less than 3 months.[4,5]

It has been known that some patient's related risk factors can contribute to the establishment of complex and chronic wounds. Among these factors, sex,[6] gender[7] and nutrition[8] might play an important role. Impaired mobility represents an important variable in the development of chronic wounds, and it can represent a risk factor, especially for pressure ulcers.[9] Concomitant diseases can impact the healing, as well as the related therapies. Firstly, some particular diseases, such as vasculitis,[10] autoimmune diseases,[10] immunological disorders and diabetes can exacerbate the complexity of the wound.[11,12] Moreover, catheter- or valve-bearing patients and patients treated with particular medications (such as corticosteroids or other immunosuppressive agents or hydroxyurea) are more prone to develop complex wounds. All the variables mentioned above, together with a high microbial load, the presence of foreign bodies or other environmental factors,[11] can deeply delay (or make impossible) the wound healing. An appropriate clinical risk assessment is mandatory, as reported in Table 1.

The aim of this multidisciplinary work is to highlight the importance of a new pathway of wound care with patient-based therapeutic approach, tailored treatments based on the characteristics of the wound and fast tracks focused on the outpatient management, reserving hospital assessment only for patients with complicated or complex wounds.

The plastic surgeon plays a central role in the management of chronic and complex wounds, through an accurate theoretical knowledge of the tegumentary system, the wound healing process and the practical knowledge of the different available treatments and instruments of skin wounds.

In this view, it is necessary to merge the well-established clinical practice in wound care with technological innovations driven by the pandemic in both modern dressings, and telemedicine and Artificial intelligence (AI) for the multidisciplinary assessment of non-healing wounds.

1.1 | Microenvironment

The reasons for healing failure can be various, but the microenvironment plays a crucial role.The microenvironment is defined as the extracellular compartment and can be classified as dry, moist or wet, depending on the level of hydration.[13]

Between the components of the microenvironment, the presence of vascular endothelial dysfunction results in a reduced activity of the endothelial nitric oxide synthetase (eNOS) and an overproduction of the reactive oxygen species (ROS).[14] The function of ROS in wound healing varies, including the recruitment of different immune cells to the wound site (which are involved in the repair process) and the regulation of angiogenesis. Also, ROS are produced by macrophages to kill pathogens. For these reasons, ROS manipulation is a promising element, which can be considered when treating the wound.[15] New therapeutic strategies aimed to improve also the MMPs regulation for a better treatment of the wound healing.[16] **Matrix metalloproteinases** (MMPs**)** are a group of calcium-dependent zinc proteins, which are involved in the degradation of the extracellular matrix. These proteins can be classified based on their substrate affinity in collagenases, gelatinases, stromelysins, matrilysins, metalloelastanes, membrane-type MMPs and

TABLE 1 Clinical risk assessment

Endogenous	Exogenous
Immunosuppression	Prosthesis
Diabetes	Systemic therapies
Malnutrition	
MRSA	
Surgical wounds	

other MMPs.[17] Their activity depends on different cell types, such as fibroblasts, endothelial cells and keratinocytes, in response to numerous cytokines, hormones and growth factors.[18] A dysregulation in MMPs can prolong the inflammatory state and increase the timing of the healing.[19]

The pH of the microenvironment influences both MMPs and bacterial growth and might be considered a healing parameter and a possible target to prevent a wound from becoming a non-healing wound. The intact skin is characterised by a pH range between 4 and 6, depending on the body location and age. On the contrary, the wound microenvironment is characterised by a pH above 7, which leads to the growth of the most common bacteria.[20] At the moment, pH value is the only variable related to the microenvironment, which can be assessed, even at home, by the patient or his caregiver, using paper strips[21] or a near-infrared fluorescent pH sensing film.[22]

The bacterial load is another factor involved in the healing delay.[23] In fact, the colonisation of the wound by bacteria may really facilitate the establishment of the chronic wound, which is mostly characterised by the presence of *Pseudomonas* spp, *Staphylococcus* spp, *Enterobacter* and even some nosocomial pathogens, such as *Stenotrophomonas* spp.[24] These bacteria can be free or can create a biofilm, a complex structure consisting of bacterial cells, extracellular matrix and extra polymeric substance (EPS).[25] Biofilm is characterised by slow-growing bacteria, which develop multidrug tolerance, and the extracellular matrix[5] prevents the action of orally administered antibiotic therapy, resulting in the establishment of antibiotic resistance,[26] often associated with the indiscriminate abuse of systemic therapy.[27]

Factors that might be involved in the establishment of wound healing are reported in Figure 1.

The British Society for Antimicrobial Chemotherapy (BSAC) and the European Wound Management Association (EWMA) recommended the preferential use of antimicrobials not containing antibiotics for the treatment of infected wounds.[28] Antibiotics-free antimicrobials are administered through the cutaneous route, which may guarantee a high concentration and is characterised by a lower risk to develop resistance.[29] On the other hand, this route is characterised by some limitations, such as the depth of penetration, possible side effects, the potential cellular damage and the patient compliance.[27]

1.2 | Role of the antisepsis in the wound care

Complex wounds include different types of lesions, which can be classified, according to their aetiology, as arterial, venous, diabetic and pressure ulcers.[30] All these wounds are characterised by excessive levels of inflammation, persistent infections, drug-resistant bacteria and a lack in response to healing.[31] Moreover, all of them can deeply impact patients' quality of life.[4,32,33,34] The dressing of the complex wounds should always follow the TIME principles (tissue debridement, infection or inflammation, moisture balance and edge effect),[35] which include the tissue debridement, the infection control, the moisture balance and edges the wound.[36]

A precise assessment of the infection needs to be performed. Nowadays, two groups of criteria are used to identify chronic wounds with infectious processes, called NERDS and STONEES. NERDS criteria are adopted when a biofilm or a critical colonisation is present. NERDS wounds are non-healing, exudative wounds, which bleeds, smells and debris.[37,38] On the other hand, STONES criteria are adopted to assess the infection. STONEES wounds are characterised by increased temperature, exudative, erythema or oedema and smell.[37,38]

A critically infected or colonised wound must be treated with systemic antibiotics in order to treat the infection, restore the microenvironment and to facilitate healing.[27] On the other hand, the risk of sepsis is null, wounds must be dressed with antiseptics, defined as chemical/based agents, which are able to reduce the bacterial load.[39] Because the aim of the wound care consists in removing the non-vital tissue, to prevent the infections, to promote the healing and to control the pain,[40] an antiseptic must be aggressive on biofilm and non-viable tissues, but also it should ideally show a similar tolerability than physiological saline solution, Ringer solution or inert hydrogels. In fact, during the wound care, the adjacent tissues result exposed to the antiseptic, highlighting the need to carefully evaluate its tolerability.[41]

Although antiseptics are widely used on the intact skin, to prevent critical colonisation, their use in the dressing of open wounds (such as lacerations, abrasions, burns and chronic ulcers) is still debated.[40] In fact, antiseptics showed a concentration-dependent cytotoxic activity in vitro against fibroblasts, keratinocytes and leucocytes, involved in the healing process.[40] *According*

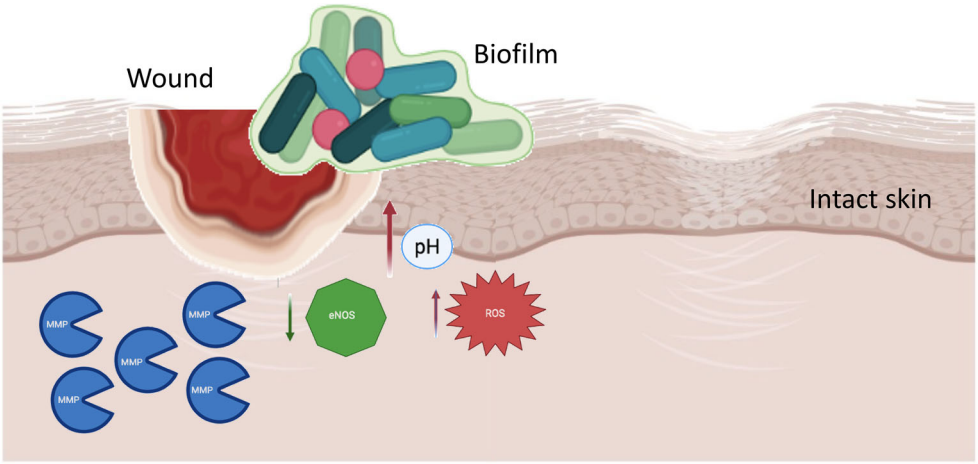

FIGURE 1 Factors that can influence the microenvironment. eNOS, endothelial nitric oxide synthetase; MMP, matrix metalloproteinases; ROS, reactive oxygen species

to Italian law, antiseptics and disinfectants aimed to treat the skin and mucosal tissue are defined as pharmacological drugs and are managed according to the Italian medicine agency.[42] On the contrary, if the mechanism of action mostly consists in a mechanical effect (as in case of solutions or gauze), the product is defined as a medical device.[41]

According to the CDC, the efficacy of antiseptics depends on numerous factors related to the microorganism (such as their number and location, their resistance), to the product (such as the concentration and the power) or to the environment (physical and chemical factors, organic and inorganic matter, duration of exposure).[43]

The right antiseptic approach should be created by deeply analysing the efficacy and tolerability of the different products and the patient's conditions, in order to prevent systemic infections and to allow the treatment in an outpatient setting. Finally, the **cost-effectiveness** should be taken into account to choose the ideal antiseptic approach,[41] avoiding the use of ineffective products or conversely abuse of aggressive products. The treatment-related costs based on bioburden are reported in Table 2.

The use of antiseptic treatment should be carefully evaluated according to the patient's conditions and comorbidities (immunocompromised patients, diabetic patients or patients who underwent surgery) and the complexity of the lesion, as well as the antiseptic persistence and the time of action and the tolerability. The most used disinfectants and antiseptics are reported in Table 3.

In the light of recent wound care management reorganisation (due to the COVID 19 pandemic), the need of all-inclusive and technologic materials became increasingly strong, and the use of sterile, single-dose packaging is strongly encouraged.

1.3 | How to treat complex wounds

Topical antiseptics should be the first-line treatment to remove bacteria from the wound site in order to allow a proper healing. Unfortunately, sometimes the administration of systemic antibiotics is necessary, especially when an early and adequate antisepsis is not provided.[44] The antimicrobial treatment approach should always consider patient's conditions, possible drug-drug interactions and adverse events,[45,46] but the main objective is to restrict the use of systemic antibiotics just to cases with confirmed clinically significant infections and/or with systemic signs of infection. The abuse of antibiotics for chronic skin lesions is one of the major drivers for antimicrobial resistance.[47] The ideal topical antimicrobial agent should be characterised by a broad spectrum, long duration, low toxicity and the ability to reach the wound without any systemic implication.[40] In case of complex wounds and severe clinical picture (such as surgical wounds and nosocomial pathogens, immunodeficient patients or patients with diabetic foot), topical treatments need to be excluded or coupled with systemic antibiotics. Acute bacterial skin and skin-structure infections (ABSSSIs) are one of the most common reasons to reach out to a health care facility. In these cases, current guidelines focus the attention on the need of antibiotics with a broad spectrum for the Gram-positive bacteria, especially MRSA. FDA recently approved the use of dalbavancin, oritavancin, tedizolid and delafloxacin in the treatment of ABSSSIs.[48,49]

Recently, the use of long-acting antibiotics became a new therapeutic approach, which allows to treat systemic infections in an outpatient setting.[50]

TABLE 2 Treatment-related costs based on bioburden

Bioburden	Setting	Treatment	Costs
Contamination	Domiciliary care	The treatment aims to control the bioburden	Low
Colonisation	Domiciliary care	Local treatment	Low
Local infection	Domiciliary care/medical office	Local treatment/antibiotics	Medium
Infection	Medical office/Hospital	Antibiotics	High
Sepsis	Hospital/ICU	Antibiotics	Very High

TABLE 3 Most used disinfectants and antiseptics

Category	Active compound	Activity
Disinfectants		
Low level	quaternary ammonium	Gram positive (++), Gram negative (+), Mycobacterium spp (−), Fungi (+−), Viruses (−), Spores (−)
Intermediate level	70–90% isopropyl and ethylic alcohol	Gram positive (+++), Gram negative (+++), Mycobacterium spp (+−), Fungi (++), Viruses (envelope: ++; no envelope +−; HIV +++), Spores (−)
High level	6% hydrogen peroxide	Gram positive (++), Gram negative (+++), Mycobacterium spp (++), Fungi (+), Viruses (+), Spores (−)
	1.1-0.05% sodium hypochlorite electrolytic solution	Gram positive (+++), Gram negative (+++), Mycobacterium spp (++), Fungi (++), Viruses (++), Spores (++)
Antiseptics		
Low level	Chlorhexidine	Gram positive (+++), Gram negative (++), Mycobacterium spp (+−), Fungi (+), Viruses (envelope:+; no envelope:−), Spores (−)
Intermediate level	0.05% sodium hypochlorite electrolytic solution	Gram positive +++, Gram negative +++, Mycobacterium spp: ++, Fungi: ++, Viruses (envelope:++; no envelope:++), Spores: ++.
	iodophors with more than 40/50 mg of free iodine	Gram positive (+++), Gram negative (+++), Mycobacterium spp (++), Fungi (++), Viruses (++), Spores (+)
	70-90% isopropyl and ethylic alcohol	Gram positive (+++), Gram negative (+++), Mycobacterium spp (+−), Fungi (++), Viruses (envelope: ++; no envelope +−; HIV +++), Spores (−)

1.4 | Multidisciplinary approach and fast track: through a new conception of the wound care

As reported above, chronic wounds involve different patients (most of the time affected by chronic diseases) in different care facilities. These lesions require a multidisciplinary approach, able to involve different health care professionals, which can contribute to the resolution of the wound.[51,52,53,54] The ideal multidisciplinary team should include general and vascular surgeons, a wound care nurse, an infectious disease specialist, a physical therapist, a dietitian and an internist,[55] with clearly structured interactions and well-defined care pathways and algorithms.[56]

A new and innovative approach is the "fast track model", which consists of a multimodal care pathway with the aim to promote an early recovering and reduce hospitalisation.[57]

The recent COVID-19 pandemic challenged the health care system all over the world, deeply affecting numerous medical practices. In fact, numerous patients with chronic diseases assisted to a reduction of the medical care. Among all the fields, the wound care management resulted in a necessary modification of the assisted care pathways.[58] In this period, because the access to the hospital facility was strictly limited to emergency care and COVID-19 patients, a new strategy needed to be applied in order to facilitate the wound care management in high-risk patients.[59] In fact, without a regular dressing,

the chances to develop infections are high and often might increase the risk for the loss of limbs.[60] During this challenging era, facilities needed to reorganise their care pathways, in order to protect the patients and also the personnel.[32] Rogers and colleagues developed a triage system in order to better classify the wounds based on their characteristics. The aim was to better manage each patient in the adequate context (hospital or outpatient setting) and to avoid hospital overcrowding, as well as treating each patient according to his conditions.[60]

Investigators created four levels of priority based on the infection. The first level of priority included moderate infections and sepsis, gas gangrene and acute limb-threatening ischaemia; the second level of priority included patients with mild and moderate infections, dry gangrene, osteomyelitis, chronic limb ischaemia, worsening foot ulcers and active Charcot foot; the third level of priority included improving foot ulcers and inactive Charcot foot. Finally, the four levels included the majority of the diabetic patients with stable disease with foot wounds. According to these criteria, level one patients should be treated in the hospital setting, level two patients should be treated in an outpatient clinic, office-based laboratory, surgery centre or podiatry office, while level three and four patients can be treated at home, taking the advantages of the telemedicine.[60]

1.5 | Telemedicine and artificial intelligence

Data showed in the studies highlighted the efficacy and safety of telemedicine in wound care, as well as a non-inferiority compared with standard care.[61] According to Cannavale et al, the use of telemedicine during the COVID-19 pandemic in Italy aided the management of the chronic wound even in critical patients, highlighting the chance to apply this new care pathway in the day-by-day wound management.[59]

The assessment of the patients through telemedicine needs to be conducted according to some outcome indicators, such as the time of healing and colorimetric evaluations.[62]

According to Scalise and colleagues, a normal telemedicine consultation usually consists of 25 minutes visit and allows to clearly evaluate both preventive and therapeutic devices, as well as the type of dressing.[1] Telemedicine really improved access to medical consultations during the COVID-19 pandemic, as reported in Figure 2.[1]

AI, based on algorithms, which can self-learn and refine overtime, could be the solution for a better wound care practice. In fact, through the use of this technology, each clinician could share his experience with other colleagues all over the world, being part of a large volume of data collection. This could help to standardise the practice and to improve the level of specialisation. Moreover, AI could help patients and caregivers to perform the wound dressing in the outpatient setting.[63]

Bacterial fluorescence imaging is a new method, which consent to visualise and monitor the bacterial load in the wound in real time, using a 405 nm violet light. This light is able to excite bacteria and tissue within the wound, causing the emission of a fluorescent light. The outputs consist of a green, fluorescent emission in case of non-contamination, and a red or cyan fluorescence when bacteria are present.[64] Moreover, it has been demonstrated that a red light might be predictive of a moderate/heavy bacterial load.[65] Recently, this system has been adapted and used to implement the role of telemedicine in wound care. This system includes a device, which is able to send the images of the wound to the clinician in real time, allowing to assess the wound, to measure it, to evaluate the bacterial load and to provide wound care advice via telemedicine.[66]

Wound Viewer is a new AI medical device, which has been recently tested. This device is able to collect different clinical data, such as three-dimensional wound measurement, tissue composition and wound classification according to the WBP protocol. Data are collected and shared through a protected data system. In order to evaluate the precision and the usefulness of the device in the remote wound evaluation, a clinical trial has been conducted among 150 patients. The results showed that AI would really help the clinician to conduct an effective remote wound assessment, reaching 97% of accuracy in the WBP classification and tissue segmentation analysis compared with that performed by clinicians.[67]

2 | CONCLUSIONS

COVID-19 pandemic has really challenged the worldwide health care system, underlying critical issues and improvement needs. Mostly chronic and critical patients suffer for this difficult situation, and a modification and a reorganisation of the standard of care was needed.

In this scenario, patients with chronic wounds need to be critically evaluated in order to find the best and most appropriate care pathway, which should vary according to the patient and, especially, to the characteristics of the wound. The most

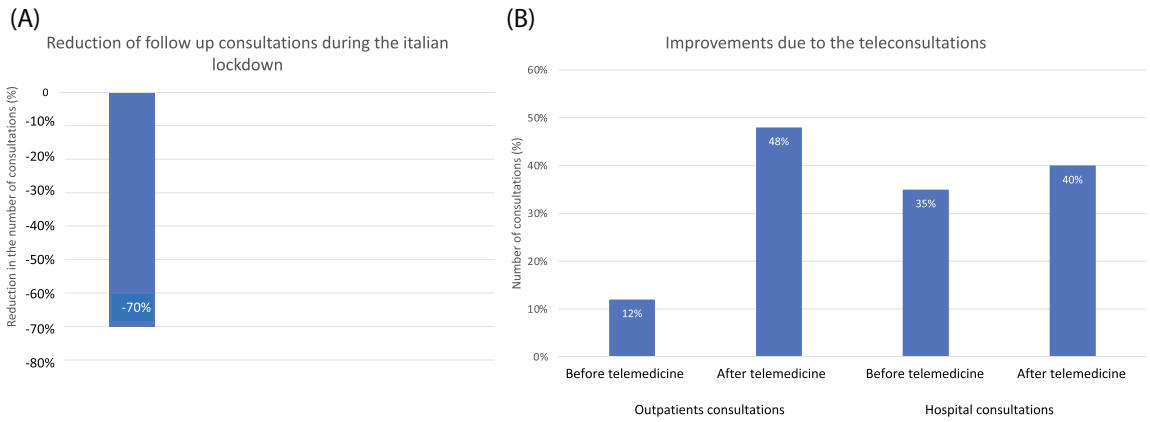

FIGURE 2 Improvements in the access to medical consultations due to telemedicine. A, Reduction in the follow-up visits due to the COVID-19 pandemic. B, Number of outpatients and hospital consultations before and after the telemedicine. All values are expressed as percentage. Graphical elaboration from Scalise, 2020[1]

adequate topic antiseptic should be started as soon as possible, in order to restore the homeostasis in the microenvironment and to avoid, in the absence of systemic infections, the indiscriminate administration of antibiotics, which could lead to dangerous mechanism of resistance.

An evaluation of the lesion should be performed in order to avoid, if possible, to visit the patient and treat the wound in a hospital setting, preferring a home care management. Patients and caregivers should be educated and trained, and telemedicine should be preferred if possible.

An appropriate and correct management of the wound care will allow to link the knowledge based on years of clinical practice with the new challenges and the need to visit patients remotely, when possible. These components will lead to the creation of a hybrid system, which will place together a traditional management with the most innovative technologies in telemedicine and AI.

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All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study

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