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REVIEW ARTICLE

Antimicrobial and antiseptic strategies in wound management

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Abstract

Wounds, especially chronic wounds, represent a global problem costing millions of dollars per year in developed countries and are characterised by microbial complications including local or overt infection, delayed healing and spread of multiresistant germs. Therefore, antimicrobial wound management is a major challenge that continues to require new solutions against microbes and their biofilms. As systemic antibiotics can barely penetrate into wound biofilms and topically applied ones can easily lead to sensitisation, antisepsis is the method of choice to treat germs in wounds. This brief review discusses the role of antiseptics in reducing bioburden in chronic wounds. Balancing antimicrobial potency and tolerability of antiseptic procedures is critical in wound therapy. However, antiseptics alone may not be able to achieve wound healing without addressing other factors regarding the patient's general health or the wound's physical environment. Although the precise role of bioburden in chronic wounds remains to be evaluated, planktonic as well as biofilm-bound microbes are indications for antiseptic intervention. Octenidine dihydrochloride and polyhexanide are the most effective, as well as best tolerated, antiseptics in wound management today, and new strategies to reduce bacterial wound burden and support the body's immune response are being developed.

Antisepsis

Antimicrobial activity versus tissue tolerance

While there are many types of antiseptics, all of them must balance antimicrobial activity against the tolerance limits of living tissue. Teot has described antisepsis as 'a procedure aiming to achieve a temporary result making it possible at the level of living tissue within the limit of their tolerance to eliminate or kill microorganisms' (L. Teot, personal communication, 2010). Antisepsis can be achieved by biological, electrical and chemical procedures. Biological antisepsis can be performed by sterilised maggots of the *Lucilia sericata* fly, electrical antisepsis by electrostimulation and chemical antisepsis by using different solutions. Biological and electrical antisepsis cause only weak log reductions, whereas chemical antisepsis is able to eliminate far more than three log steps of germs (1). Consequently, chemical antisepsis plays the primary role in antimicrobial wound management with bioantisepsis and electroantisepsis playing minor but concomitant roles.

Key Messages

- the primary intention for using antiseptics is to prevent infection, reinfection and potential disturbance of wound healing; however, balancing antimicrobial potency and tolerability of antiseptic procedures is critical in wound therapy
- in chronic ulcer wounds, a significantly greater bacterial diversity can be expected than can be obtained by conventional culture techniques, and in recent years, biofilms have also been focussed on as key players in non-healing wounds and chronic infections
- antimicrobial strategies consist of removing or killing bacteria, supporting concurrent flora, host defence and general health of the patient, supplying energy and stimulating healthy inflammation
- methods to decrease bioburden include irrigation, negative pressure wound therapy (NPWT), NPWT with

instillation of topical wound solutions and various methods of debridement
- experimental methods to reduce wound bioburden include laser therapy, photodynamic therapy, cold plasma therapy and support of pathogen competition

Antiseptics for clinical wound management – general considerations

Antiseptics have to meet the following specifications. The main goal of antisepsis is the irreversible inactivation of bacteria, viruses and fungi (biocidal activity). If total elimination cannot be achieved, a substantial reduction of germs and biofilms is also within the scope of wound antisepsis. The primary intention of using antiseptics is to prevent infection, reinfection and potential disturbance of wound healing.

Further and secondary goals of antiseptic therapy are to support wound healing by causing positive effects on cell proliferation and regeneration. These effects, apart from pure microbicidal activity, have been demonstrated for polyhexamethylene biguanide (polyhexanide) (2). Further positive effects by antiseptics include wound cleansing, which can support debridement.

The ideal antiseptic combines broad-spectrum activity (bacteria, spores, viruses and fungi), immediate onset of activity, long-lasting activity (over hours), potency in the presence of blood and other proteins (organic compounds), activity against biofilms, safe activity on healthy as well as injured skin (on 'naked' cells), good solubility in water and organic liquids, good stability, good tolerance without adverse effects, lack of allergenicity and double efficacy combining germicidal with cleansing effects. Kramer *et al.* have introduced the biocompatibility index (BI), which measures the therapeutic safety of an antiseptic and thus allows comparison of different substances not only by antimicrobial efficacy per se but also in relation to biological (side) effects (3–6). Finally, low cost, safe handling and storage are recommended. In my experience, octenidine dihydrochloride and polyhexanide are the most effective, as well as best tolerated, antiseptics currently in wound management.

Antibiotics and antiseptics

Conventionally, bacteria and fungi are killed using antibiotics and antiseptics, which are available in combination with wound dressings. In general, antibiotics for local wound therapy are not recommended because of minimal effectiveness (not reaching bactericidal concentrations in situ), potential contribution to formation of resistant strains and possible sensitisation. However, in some indications with a small fraction of antibiotic classes, local wound therapy still plays a major role in clinical treatment of specific infections (e.g. keratitis, conjunctivitis and otitis). In the case of wound infection, systemic antibiotic use is generally recommended (with the exception of bagatel wound infections such as noncomplicated scrapes and punctures). Together with systemic antibiotic use, local antisepsis is the anti-infective treatment of choice. In the case of spreading pathogens, only local antisepsis is needed to immediately stop microbial replication and therewith the relevant spread in the wound environment. This is of particular importance in treating infections by multidrug-resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* and organisms producing extended spectrum beta-lactamase. Extensive experience with effective antisepsis of local wounds has been documented in Europe since the introduction of the antiseptics, polyhexanide and octenidine dihydrochloride. Whenever contact with deeper structures involving cartilaginous tissue is expected, alternatives to these formulations must be considered. Also, in the case of fistulas with weak oxygen supply, the use of octenidine dihydrochloride is generally obsolete.

Wound bioburden

Wound bacteria – from contamination to colonisation

The progression from contamination to colonisation involves different types of microbes that enter and populate a wound over a period of time. Typically, gram-positive bacteria enter the wound space first; coagulase-negative staphylococci (CoNS) are the predominant group derived as commensals from the physiological environment of intact skin in the vicinity of the wound. This bacterial group can be regarded as the main reservoir of the autochthonous antimicrobial self-defence of the skin.

Days to weeks later, depending on the individual immunological habitat control of the patient, gram-negative bacteria, mainly rods, invade the field and compete with residing species. The origin of this contamination and later colonisation is the urogenital space of the patient, which harbours many different species, including enterobacteriaceae such as *Escherichia coli*, *Klebsiella pneumoniae spp. pneumoniae* and *Enterobacter spp*., or the near environment of the patient, that is, often Pseudomonadaceae, *Acinetobacter* or yeasts. These environmental germs typically originate from hygienic barrier defaults in daily hospital hygiene and contaminate or colonise even areas with poor nutritional supply such as saline solutions, nebulisers and drinking water.

In 'maturing' wounds, new changes of the wound flora appear with anaerobes as new colonisers benefitting from the altered redox potential in the wound milieu, which is pioneered by aerobe flora (*E. coli*) reducing the oxygen content in the microenvironment. Anaerobes are frequent in chronic wounds. In patients with chronic venous insufficiency (CVI), Hansson *et al.* (6) reported up to 30% of chronic ulcer wounds harbouring peptostreptococci. As accurate diagnostics of these germs are difficult and expensive, this family typically is underestimated in clinical diagnostics. However, albeit frequent positivity as shown in scientific work and despite demonstrating a significant pathogenic potential of some species, their exact clinical role in wound healing remains to be determined.

Effects of bacterial wound burden

Despite some knowledge about bacterial interaction with the epithelium and the role of bacteria in wound homeostasis, final conclusions regarding this relationship are still not closer. Accordingly, the precise effect of bacterial colonisation on wound healing remains to be elucidated. For some pathogens like *S. aureus* and group A streptococci, it is far beyond doubt that this flora can easily provoke more or less severe infections with consequent healing disturbance depending on host immunity, inoculum size and virulence of the strains (7).

As mentioned above, the basic question regarding the potential of bacteria to negatively influence wound homeostasis (disturbing wound healing without infection) beside or in parallel with their classic infective potency (ability to cause infections) is yet unanswered. In the light of well-documented partial effects of some species, however, we can also assume negative *in vivo* effects of bacterial wound burden on healing homeostasis. These may be due to the release of tissue-destroying (lytic) enzymes, exotoxins and endotoxins and antiphagocytic effects, all of which potentially lead to deterioration of wound healing. As no chronic wound is colonised by a single species but most often — and growing with 'wound age' — by a multitude of aerobe and anaerobe species, the biological effects exerted by microbes must also be considered as the net result of microbial 'networking' and cannot be predicted from the well-described effects of one specific species (8).

In chronic ulcer wounds, a significantly greater bacterial diversity can be expected than can be obtained by conventional culture techniques, and $\geq$100 species can be found by modern molecular diagnostics (i.e. arrays). This difference is owing to the difficulty in isolating small amounts of bacterial growth and also the presence of 'unculturable species', detected only by molecular techniques. However, the added value of these results on clinical decisions appears questionable because fundamental answers cannot yet be given regarding the qualitative impact of different species per se as well as in the networking scenario.

Other important microbial players in acute wounds are *Pseudomonas aeruginosa* and *E. coli*. In most cases, these germs do not cause critical infections in chronic wounds, as long as no further distress impedes healing (e.g. foreign bodies or immune alterations including polytrauma and malnutrition). During regular wound healing, these pathogens may be isolated in smaller amounts in the wound and disappear before wound closure as a result of natural defence mechanisms.

In recent years, biofilms have been focused on as key players in the scenario of non-healing wounds and chronic infections (9). Biofilms often dominate in chronic wounds, foreign-body (suture) infections, endocarditis, cystic fibrosis (chronic bronchopneumonia), persistent otitis media, chronic rhinosinusitis, chronic osteomyelitis and infected prosthetic joints, intravenous catheters and stents. The microbes in biofilms are welded together by a self-produced biopolymer matrix of polysaccharides, proteins and DNA from the initiating microbes. Biofilm formation is initiated by planktonic bacteria reversibly attached to a surface and still susceptible to antibiotics (phase 1). The minimal inhibitory concentration and minimal bactericidal concentration of antibiotics needed with biofilm-growing bacteria may be up to 100- to 1000-fold higher than those needed with planktonic bacteria. In phase 2, biofilm-growing bacteria irreversibly bind to the surface and multiply to produce a slimy polymer matrix around the microcolonies. During the next days, the biofilm grows in thickness and exhibits maximum resistance to antibiotics. In phase 3, focal areas of the biofilm dissolve and form metastatic daughter films in the surrounding area. Once a biofilm is formed, it usually requires removal and antibiotic flanking treatment. To prevent establishment of a biofilm, interventions must be made before phase 2 and include physical measures (e.g. compression of the leg and early removal of any kind of wound debris like necrotic tissue), antibiotics and antiseptics. Octenidine and polyhexanide are two biofilm-active modern antiseptics with different clinical features. The most frequently encountered species in chronic wound biofilms are gram-negative rods (enterobacteriaceae) and *P. aeruginosa*, faecal streptococci (*Enterococcus faecalis* and *Enterococcus faecium*) and *S. aureus*.

Determinants of clinical infection

Currently, the progression from sterile wound surface to bacterial contamination, colonisation, critical colonisation and infection is described as a dynamic continuum without clear demarcations where infections appear, critical colonisation is reversible and relevant disturbance takes place (wound continuum model) (10).

Heavily colonised wounds can heal in the presence of adequate energy or oxygen supply. Biofilm or planktonic colonisation is not necessarily the pathophysiological-inciting mechanism of deteriorated wound healing. Neither the pure qualitative aspect of microbial bioburden in a wound (i.e. the presence of pathogens *S. aureus* or *P. aeruginosa*) nor the quantitative aspect of detecting a significant (i.e. 10^5 colony-forming units/g tissue) (11) amount of wound bioburden per se determines whether infection is present or not. Moreover, it must be kept in mind that infection does not represent the worst scenario in the lifetime of a wound. Microbial bioburden per se may act as a significant player in disturbing wound healing, without the necessity of deep invasion of tissue by germs. The exact role of this disturbance as well as its mechanism are as yet poorly understood and critical points such as the exact beginning or progression kinetics of the local infection cannot be determined, even by bioptic intervention.

Impact of a wound's physical environment on wound healing

It is important to bear in mind that a wound's physical environment (i.e. foreign bodies, bacteria and cell debris) is as crucial to proper healing as its physiological environment (i.e. pH, temperature, electrical field, cellular interactions and quorum sensing). A wound may fail to heal if issues affecting the overall health of the patient – especially the respiratory and circulatory systems – are not addressed.

Treatment of underlying diseases not only includes direct therapeutic interventions (i.e. treating neoplasms or metabolic diseases like diabetes mellitus) but also comprises support of general health. For example, respiratory hygiene must be supported (i.e. the maintenance of adequate gaseous exchange, which is compromised by smoking, asthma and pollinosis).

Haemodynamic health, including macrocirculation and microcirculation, is basically critical for adequate wound healing (12). In this concept, amongst others, the control of fibrinogen levels, body mass and haemoglobin plays a substantial role. In chronic ulcer wounds, supporting haemodynamic health may denote recanalisation, stent implantation, bioprosthesis implantation, dilatation or pharmacological intervention with vasoactive components in arterial insufficiencies. Venous haemodynamic failure most often is caused by CVI, thrombotic syndrome, peripheral arterial oxygen disease or traumatic injuries and is treated by venous stripping or intraluminal ablative intervention (laser and steam). This therapy is most often effective in preventing the development of new wounds, or trigger healing of manifest, chronic ulcer wounds, when the vessels are not irretrievably compromised by disease. If tissue oxygenation can be achieved and sustained, even heavily colonised and infected wounds can heal without further antimicrobial intervention. Conversely, antimicrobial intervention and debridement (removing necrotic tissue as a foreign body) are of no permanent value, if the underlying cause of disease (the deficient energy or oxygen supply in the tissue caused by haemodynamic insufficiency) is not addressed.

Additional factors in a wound's physical environment include foreign bodies in the wound and other physical factors (e.g. the influence of lower temperatures), which can make healing impossible. Most wounds will heal if the pathophysiological-inciting mechanism is addressed; however, wound infections in the presence of a foreign body will most often fail to heal unless the foreign body is removed (13). Pathogens by far do not have the same impact on wound distress as foreign bodies in the wound. Consequently, an infected wound with a foreign body can heal on its own when the foreign body is removed, but will never do so, if only bacteria are eliminated and/or an energy supply is provided.

In general, it may be concluded that wound healing as a reflector of a patient's general health always benefits from ameliorating the individual's health care and vice versa. A wound embedded in an unhealthy body situation or containing a foreign body cannot heal, with or without microbes at its site. However, once underlying disease states and respiratory or haemodynamic issues have been addressed, the pathophysiological role of microbial wound bioburden (including biofilms as inciting mechanisms of infection and healing disturbance) stresses the primary need for specific or non-specific antimicrobial treatment.

Ways to defeat bioburden in wounds: removing bacteria

Antimicrobial strategies consist of removing or killing bacteria; supporting concurrent flora, host defence and general health of the patient; supplying energy; and stimulating healthy inflammation. As noted by Warriner *et al.*, 'while immune response is the governing factor in development of wound infection, reduction of bioburden if achieved to a sufficient degree and sufficient duration can enable host defence to regain control (14)'.

Removing bacteria from wounds can be achieved in different ways. The simplest method is wound irrigation by rinsing, whereas a more complicated technique is mechanically assisted lavage (e.g. jet lavage and hydrodynamic debridement). Negative pressure wound therapy (NPWT; V.A.C.® Therapy, KCI USA, Inc., San Antonio, TX) is a widely used method that removes exudate and infectious materials by applying continuous or intermittent subatmospheric pressure via tubes connected to a reticulated open-cell foam dressing placed in the wound bed. Simple surgical debridement is the most efficient, cost-effective, and practiced treatment for wounds that are suspected of any kind of 'contamination' (e.g. bacteria, foreign bodies and soil) or infection. Debridement can also be accomplished by electrophysical means (i.e. ultrasonification), high-pressure application of sterile water or saline and cold or low-temperature plasma (15), ablative laser or biodebridement with live maggot antisepsis (16). The application of sterilised maggots of the blowfly *L. sericata* can be described as mixed debridement combining physical removal (by ingestion and metabolism of necrotic material and germs) and bioantiseptic killing of bacteria in the wound. Wound dressings with special physical properties allowing a gradient from the wound bed to the dressing material can achieve pure physical removal of significant amounts of bacteria from the wound without any adverse effects.

Negative pressure wound therapy

The effects by which NPWT achieves excellent results in an increasingly wide spectrum of wound types (e.g. highly infected and/or complicated wounds involving osseous structures, like traumatic infections or ankle fracture infections) are not fully understood but are related to intermittent or continuous negative pressure directly transmitted to the cellular substructures of the vital wound bed. Despite some observations showing no bacterial reduction and even growth acceleration during NPWT (17), in most cases conspicuous wound healing has resulted after NPWT (17–19). These results again raise questions regarding the role of specific microbiology during wound healing. One message to be drawn from these facts is that primary antibiosis is apparently not a dominant wound healing concern in non-infected but strongly colonised venous ulcer wounds, arguing against a leading role of bacteria in wounds 'stuck in healing' (20). A second message is the recommendation of routine antisepsis in the treatment of chronic venous ulcer wounds for reasons other than hygienic ones. In heavily contaminated, colonised or infected wounds, NPWT can be combined with antiseptic instillation (NPWTi; V.A.C.® Instill Wound Therapy and V.A.C. VeraFlo™ Therapy, KCI, San Antonio, TX, USA). NPWTi can introduce a topical antiseptic solution into the wound bed (e.g. polyhexanide, which is the most frequently used), allow the solution to rest in the wound bed for a planned period of time and then remove it during a cycle of NPWT (21). In infected (traumatic) wounds,

especially, a clinical benefit can be deduced from longstanding clinical experience with antiseptics, but evidence must be drawn from appropriate clinical studies before recommendations can be made.

Experimental methods to reduce wound bioburden

Further techniques to eliminate bacterial burden in wounds include laser therapy, photodynamic therapy and cold plasma therapy. These techniques are still experimental. Modern advances in development are the reinforcement of physiological flora by autotransplantation of living colonies and application of microbicidal peptides derived in vitro from skin bacteria or genetically synthesised. Basic aspects reinforcing self-defence, such as living (staphylococcal flora) and physical (skin) barriers, include hygienic measures to ensure distance of the wound area from other body sites with relevant pathogen colonisation (e.g. oral, perianal and urethral space) or other colonised wounds. This is generally realised by implementation of a functioning multibarrier system. This complex, skin protection by application of continued skin care is of utmost importance (e.g. choice of a suitable wound dressing that avoids self-recontamination due to dressing contamination and failure of accurate wound management with adequate dressing changes).

Supporting pathogen competition

Another strategy is supporting germs that are known to protect the skin, as part of the physiological skin flora. CoNS are the predominant flora fulfilling these criteria and work by two mechanisms: first by occupying the first line of defence zone of the wound (wounded naked cells) and second by secreting antimicrobial enzymes. Supporting concurrent flora as a therapeutic method is currently in the experimental stage. As described above, treating underlying diseases is crucial to wound healing and effectively supports healing via restoring the physiological defence flora. In this concept, only pure antimicrobial local treatment is recommended for hygienic purpose (MRSA sanitation) or infection intervention (flanking antibiotic therapy).

Conclusion

Although the precise role of bioburden in chronic wounds remains to be evaluated, planktonic as well as biofilm-bound microbes are indications for antiseptic intervention. Octenidine dihydrochloride and polyhexanide are the most effective, as well as best tolerated, antiseptics in wound management today. With increased understanding of the complex interplay between the physical and physiological environments of a wound and the need to address treatment-resistant bacteria and biofilms, better strategies for use of antiseptics and other techniques will continue to be developed.

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