Role of topical antimicrobials in wound management

All wounds contain microorganisms, and the host response to this is based on various factors, including the number of bacterial species present and their virulence. Antimicrobial agents, including antiseptics, can be used to prevent the growth of microbial pathogens in critically colonised and locally infected wounds. This article explains the theory behind the bioburden continuum and gives recommendations on the best use of topical antimicrobials.

Keywords: wound bioburden; topical antimicrobials; clinical signs of infection

Wound healing is a complex, multi-stage process that is influenced by many intrinsic and extrinsic factors. The development of a wound infection negatively impacts on this process, delaying healing. In some cases, the effects are life-threatening. The increasing prevalence of chronic illness and thus of chronic wounds, together with the emergence of antibiotic-resistant bacteria, warrants further efforts to improve wound management practices and prevent wound infection. This is an intricate field, primarily because of the issues associated with nosocomial infections, wound colonisation and biofilms, which are influenced by the health of the host and the characteristics of the microbes.

Bacteria in wounds

Microorganisms are present in all chronic wounds and are acquired from the indigenous flora of the human host or from the external environment. Human infection is caused by four types of microorganisms: bacteria, fungi, viruses and protozoa. While a minor, acute healing wound may allow time for only a relatively small number of skin contaminants to take residence, the continued exposure of devitalised tissue in a slowly healing chronic wound is likely to facilitate the colonisation and establishment of a wide variety of endogenous microorganisms, and increase the likelihood of infection.

However, the presence of microorganisms such as bacteria does not necessarily indicate that an infection has occurred or that it will lead to impaired wound healing. This is supported by studies that have reported the presence of one or more bacterial species in up to 95% of chronic wounds. However, more bacterial species have been noted in larger wounds with a long duration, and there is a significantly greater chance that an ulcer will fail to heal if four or more bacterial groups are present. Of note in many studies is that *Staphylococcus aureus* and *Pseudomonas aeruginosa* were the most common wound isolates and were present in both healing and non-healing wounds.

Polymicrobial wounds thus contain several potential pathogens, any one of which can cause infection. This delays healing, and the ensuing morbidity and risk of mortality causes patients great distress.

The level of bacterial burden is defined by the presence of replicating microorganisms within a wound, the bacterial load, the virulence of the microorganism and the host reaction. Schultz et al. argued that the pathogenic species may be much more important than the number of organisms within the chronic wound, while host susceptibility is probably the most important pre-determinant of the risk of infection.

Wound bioburden

The concept of wound bioburden has been introduced to describe the increased metabolic load imposed by multiplying bacteria in the wound bed, which are often present as multiple strains, and their ability to spread in tissues and produce toxins. This bioburden continuum represents a broad range of bacterial states, from that of wound contamination through to infection. The terms used to described the various stages in the continuum are defined below:
**Contamination** — defined as the presence of non-replicating microorganisms in the wound.4

**Colonisation** — defined as the presence of replicating organisms that are adhering to the wound but not causing injury to the host.4 Colonised wounds are characterised as those that are progressing normally with no necrotic tissue and with limited slough that is usually thin and mobile in depth and character.13 While the wound may be progressing normally, there is no consensus on the impact of bacterial colonisation on wound healing.16

**Critical colonisation** — there is no universally agreed definition of this. It is proposed that a wound is critically colonised when bacteria causes a delay in healing.4 Kingsley and Jones further defined this term as a wound that is indolent (not healing) despite seemingly appropriate therapy.15 Non-healing can first be detected when the wound margins fail to change. Such wounds are characterised as having increased exudate, often with over 50% slough at the base. There may be malodour but no cellulitis. Bright friable granulation tissue that bleeds easily, especially at dressing removal, may be present.4,17,18 Additionally, an unpleasant or putrid malodour may be accompanied by new areas of necrosis or breakdown in the wound base.4

**Infection** — this signifies microbial growth and the presence of replicating microorganisms within the wound, resulting in injury to the host and the interruption of wound healing.5,19 This occurs when virulence factors expressed by one or more microorganism in a wound outcompete the host’s natural immune system and the subsequent invasion and dissemination of microorganisms in viable tissue provokes a series of local and systemic host responses.3 Host susceptibility is probably the most important determinant of wound infection and is influenced by various local and systemic factors.4,19 This is illustrated in the following equation:

\[
\text{Bacterial load} \times \text{virulence} \over \text{Host resistance}
\]

**Biofilm** — created when a single-cell planktonic bacterium adheres to the surface of the wound by attaching to the exposed extracellular matrix proteins.20 Wound biofilms are polymicrobial communities and do not comprise a particular type or species of bacterial cell. They are held together by extracellular polymeric substrates associated with a surface, and are resistant to environmental stresses that can overwhelm a lone bacterium.21 Biopsies of 16 acute and 50 chronic wounds showed that 60% of chronic wound beds demonstrated definite biofilms compared with 6% of acute wounds.22 This study concluded that chronic wounds showed evidence of biofilms significantly more often than acute wounds.

### Antimicrobials

These are agents that either kill or inhibit the growth and division of microorganisms.23 They include antibiotics (which act on specific target sites), antiseptics, disinfectants and other agents (which act on multiple cellular target sites).23 Antibiotics and antiseptics are defined below:

- **Antibiotics** — a chemical substance produced by a microorganism that has the capacity, in dilute solutions, to selectively inhibit the growth (static) of, or to kill (cidal), other microorganisms.23
- **Antiseptics** — agents that destroy or inhibit the growth of microorganisms in or on living tissue.24 They have a broad spectrum of activity that includes bacteria, fungi, viruses, protozoa and prions. Several categories exist, including alcohols (ethanol), anilides (triclocarban), biguanides (chlorhexidine), bisphenols (triclosan), chlorine compounds, iodine compounds, silver compounds, peroxygens and quaternary ammonium compounds.25 Commonly used products in clinical practice today include povidine-iodine, chlorhexidine, alcohol, acetate, hydrogen peroxide, boric acid, silver nitrate, silver sulfadiazine and sodium hypochlorite.24

### Identifying infection

The precise pathways to overt or ‘frank’ infection of a wound are complex and involve a number of defined stages: following colonisation of a wound, immunocompetent individuals react immediately with an acute, innate, inflammatory response that leads to the ingress of phagocytic cells and blood proteins.26 When this response occurs in the early stages of wound healing, it serves to remove tissue debris and detrimental microorganisms.26 In contrast, inflammation associated with wound infection involves the development of erythema, pain, raised local temperature and swelling.19 Microbiological factors, such as the quantity, type and interaction of pathogens, act together with host factors, such as immune responses and
tissue conditions, to predispose an individual to infection. Importantly, infection is identified clinically based on signs and symptoms, thereby supporting the need for ongoing, purposeful wound assessment.

Cutting and Harding proposed that, in chronic wounds, additional signs and symptoms of infection beyond the well-established ones of pain, erythema and swelling, may be present and should be observed for. These additional signs and symptoms include:

- Friable granulation tissue
- Delayed healing
- Abnormal smell
- Discolouration
- Unexpected pain or tenderness
- Pocketing at the wound base
- Bridging of epithelium
- Wound breakdown.

Gardner et al. assessed the validity of the classic signs of infection and formulated a list of 12 criteria specific to chronic wounds based on the work of Cutting and Harding. Their study identified that the 12 criteria indicated wound infection more accurately than the classic signs alone. Increasing pain and wound breakdown had a positive predictive value of 1.00 — in other words, all of the wounds with increasing pain or wound breakdown were infected, as confirmed by wound biopsy culture.

A study aiming to identify the clinical criteria for wound infection, using a Delphi technique, involved 54 wound-care experts. It identified that cellulitis, malodour, delayed healing or deterioration were the clinical criteria for wound infection common to all wound types. Pain was an important indicator of infection, and was described as increased pain, unexpected pain or change in nature of pain. Other criteria that may assist with the early recognition of infection included: oedema, increased exudate and the sudden appearance or increase in the amount of slough.

### Topical antimicrobials

The topical application of antimicrobials to a chronic wound will never affect the systemic factors that contribute to its failure to heal. However, topical antimicrobials may be used to prevent wound infection in patients at high risk. Topical antimicrobials present advantages over topical antibiotics as they do not cause the emergence of drug-resistant bacteria and have a broader antimicrobial spectrum and lower sensitisation rates.

### When to use

While the immune response is the governing factor in the development of infection, the reduction of bioburden, if achieved to a sufficient degree and for a sufficient duration, can enable the host defences to regain control. The careful selection of topical antimicrobials agents and their application at a correct dosage can help achieve these goals. These agents are intended to prevent ingress of microbes into the wound, provide a barrier to cross-infection and prevent the progression from localised to overt infection.

Infection interrupts healing and extends the time to wound closure. Thus, preventing infection prevents delayed healing. At worse, infection can result in sepsis and even death. Indeed, patients who acquire nosocomial wound infections have significantly higher mortality rates than those who do not.

Vowden and Cooper suggested that use of topical antimicrobials should be considered when it is suspected that a wound is progressing towards overt infection or an interruption in the healing process is observed. According to Bowler, this occurs before infection when a wound is failing to heal but the clinical signs of infection are not apparent, such as when the wound is critically colonised. Application of topical antimicrobial agents at this stage is recommended to redress the host-bacterial imbalance in favour of the host.

Fig 1 shows the stages at which topical antimicrobial agents may be recommended; it considers the bacterial load and virulence, and takes account of the local and systemic resistance to the development of infection. Antibiotics should be reserved for acute infections and their choice based on both assessment and laboratory sensitivity analysis.

The selection of antimicrobial agents must be influenced by the specificity and efficacy of the agent, its cytotoxicity to human cells, its potential to select resistant strains and its allergenicity. Further consideration should be given to the condition of the wound bed, the size and shape of the wound, level of exudate and severity of bacterial load.

Evidence of the clinical efficacy of topical antimicrobial agents is limited because of the wide range of wound types, the diversity of products and differences in study outcomes. However, evidence from controlled trials is emerging that demonstrates lower rates of infection in venous leg ulcers when topical antimicrobials are used in conjunction with compression therapy.
Early studies supported the use of topical antimicrobials in critically colonised wounds. The use of antimicrobial dressing on these wounds, which did not have clinical signs of infection, accelerated healing with decreased exudate in many patients and resulted in an improvement in surface semiquantitative bacterial swab results. A further case series of 126 patients with chronic wounds demonstrated a reduction in clinical signs of infection and a statistically significant reduction in exudate levels when antimicrobial dressings were used (p<0.001).

Systematic reviews provide the most powerful evidence on antimicrobials. A systematic review of antibiotics and antiseptics in venous leg ulcers reported that when cadexomer iodine was compared with standard care the pooled estimate from two trials for frequency of complete healing at 4–6 weeks indicated significantly higher healing rates for cadexomer iodine (RR 6.72, 95% CI 1.56 to 28.95).

When to stop
There is no definitive guidance on when to stop using topical antimicrobial agents. However, ongoing wound assessment should identify if the factors that promoted their initial use are still persisting within the wound bed. Once the infection or critical colonisation is reduced and the wound is showing signs of healing, it is advisable to change the choice of dressing to reflect the needs of the wound. However, host systemic factors that lower resistance to infection, such as poor tissue perfusion due to ischaemia, drug therapies or diabetes, may be ongoing. In such cases, continued use of topical antimicrobial agents may be justified.

Assessing the wound bed
Ongoing assessment and documentation will help to identify the early signs of infection. Based on previous studies and the European Wound Management Association position documents, there are two key elements that should be routinely monitored in wound assessment: pain and wound size. Validated pain assessment tools that are easy to use and suitable for both adults and children are available. A variety of wound measurement tools are also available, and a review by Flanagan supported by further studies on venous and diabetic ulcers, have found that failure of chronic wounds to reduce in size by 30% over four weeks is an indicator of poor healing.

Conclusion
The prevention and treatment of infection is still a major concern, both in wound care and health care in general. The use of topical antimicrobial agents in wound management can contribute to
this, and their choice should be based on comprehensive assessment of the patient and wound. When the host’s ability to resist infection is reduced and the bacterial load is increasing, topical agents can help prevent the progression from colonisation to infection.

Key points

1. Regular wound assessment should identify early signs of wound infection. This includes measurement of wound size and assessment of pain, signs of delayed healing, increasing exudate, malodour and erythema.

2. Topical antimicrobials may be used when early signs of infection are identified or in wounds with high bacterial load.

3. The choice of antimicrobial should be based on wound characteristics, size, exudate, evidence of efficacy, cost-benefit and patient acceptability.

4. Follow manufacturers’ instructions in the application of topical antimicrobials.

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