ANTIMICROBIALS AND NON-HEALING WOUNDS: AN UPDATE

INCLUDING A CONCISE APPROACH TO TREATING POTENTIALLY INFECTED WOUNDS

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Antimicrobials and Non-healing Wounds: An Update

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1. Introduction and aim

The global prevalence of non-healing wounds (also referred to as chronic wounds, hard-to-heal wounds or complex wounds) with mixed aetiologies has been estimated at 2.21 per 1000 population (1). The number of individuals developing non-healing wounds is increasing due to changing lifestyles (2) and an ageing population (3). These wounds therefore present a major social and financial burden, not only for the affected individuals and their families, but also for healthcare systems around the world (4).

This document is aimed at two major audiences: healthcare providers of all types, who are tasked with providing hands-on care to patients with wounds, and researchers, who may derive ideas for future investigations from our suggestions and support when applying to funding agencies for research projects. The purpose of the document is to provide an update on existing knowledge on antimicrobials, including a general clinical approach to prescribing antimicrobials. It is not a guideline document and does not deal with particular topical products with antimicrobial agents.

Wound infections are common in clinical practice and, while the most common etiologic agents are bacteria, fungi and occasionally other microorganisms cause some wound infections (5). Because infection is one of the most frequent factors associated with stalled wound healing, prevention of infection and the proper use of antimicrobial agents is key in wound management. We recognise that many types of microorganisms can infect wounds, but bacterial species dominate as etiologic agents. Thus, nearly all antimicrobials used for treating wounds are aimed at bacteria, and these agents are what we discuss in this document.

The growing problem of antimicrobial resistance (AMR) is an urgent issue requiring an immediate, global, coordinated action plan (6,7). The word 'antimicrobial' is an umbrella term referring to disinfectants, antiseptics, antivirals, antifungals, antiparasitics and antibiotics used to inhibit the growth of or kill various microorganisms (8,9). AMR refers to the phenomenon of microorganisms developing mechanisms by which they are no longer susceptible to various agents, rendering them ineffective for treatment. Effective antimicrobial agents (including antiseptics and antibiotics) are essential for protecting patients against infection in many settings and situations, including post-operative wound infection and the management of various types of non-healing wounds. Worldwide evidence has shown that common wound pathogens are increasingly becoming resistant to antibiotics (10). It is therefore necessary that all wound care specialists employing systemic or topical antimicrobials should be aware of, and adhere to, the principles of appropriate use. To support the clinical decision-making process in this setting, the European Wound Management Association (EWMA) has undertaken this update of a document reviewing an approach to Antimicrobials and Non-healing Wounds, initially published in 2013 (11).

The aims of this update document are to:

- Highlight current knowledge regarding the use of antimicrobial agents, particularly in non-healing wounds
- Discuss new information and progress in this field since 2013
- Offer recommendations for future actions

- Provide practical guidance for clinical practice concerning the appropriate use of antibiotics and antiseptics in wound management

This update is structured according to the 2013 Antimicrobials and Non-healing Wounds document (11) with the following headings: the principal role of bioburden in wounds, treatment, the patient perspective and economics and organisation of care. Under these headings, the paper provides an update on the knowledge achieved in each field and updated answers to the questions raised in the 2013 publication. In addition, this document includes a new section on future perspectives and antimicrobial stewardship, to highlight the strategies that have generally been adopted within this field since 2013 and outline their impact on the use of antimicrobial agents in wound management. Finally, this document includes a revised algorithm on how to treat with antimicrobials in wound management (12).

2. The principal role of bioburden in wounds

Thomas Bjarnsholt

The Antimicrobials and Non-healing Wounds document from 2013 (11) posed several questions regarding the role of microorganisms in wounds and how they may potentially delay healing. Issues discussed included those related to the balance between infecting bacteria and immune defences, and the possible consequences of this interaction on wound healing.

We argued that the factors that determine the outcome of host–pathogen interactions are incompletely understood (13,14). The impact of microbial cells and their products on healing have still not been fully elucidated; furthermore, the factors leading to the transition of an acute wound into a chronic wound are only partially explained at present.

2.1 Biofilms

Bacteria exist either as planktonic organisms or in aggregates called biofilms (15). In past decades, the presence of planktonic bacteria has been correlated with acute infections and biofilms to chronic infections (16–18). Yet recent publications challenge this paradigm. For example, the distribution of single cells and aggregates does not seem to be different in cases of acute, compared to chronic, pneumonia. However, there seems to be a difference in the metabolism of the infecting bacteria, with acute infections being dominated by more metabolically active bacteria compared to chronic infection (19). Non-healing wounds have also been shown to harbour vast numbers of single cells (manuscript in preparation), but we do not know what role they play in relation to aggregated bacteria.

Most of our knowledge about biofilms is derived from in vitro studies, where tolerant bacteria are dormant and closely resemble the stationary growth of planktonic bacteria. This dormancy is thought to be established by increasing gradients of nutrients and oxygen as the layers of bacteria increase (20). The matrix of the biofilm also plays a role. While it is not a 'bullet-proof' physical shell surrounding the bacteria, the matrix components chelate and/or neutralise certain antimicrobial agents, but allow some to penetrate more freely (21).

Reduced susceptibility of bacteria in biofilms to antiseptics, antibiotics and most host defence mechanisms is correlated to the development of bacterial aggregation, which is referred to as 'tolerance'. Tolerance is distinct from resistance, which is usually caused by the acquisition by the microorganisms of determinants that regulate active mechanisms that directly diminish the action of antimicrobial agents and allow cell division and microbial growth. Tolerance enables the cells in biofilms to withstand long-term exposure to antimicrobial agents without a loss of viability. Many antibiotics show high levels of antimicrobial activity only on metabolically active bacteria.

Despite the publication of numerous papers on bioburden and biofilms in acute and chronic wounds over the past decade, this scientific field has not moved much beyond what we knew in 2013.

2.2 Questions covered in 2013 & updated statements

The following section includes the key questions concerning the role of bioburden in wounds from the 2013 document (11), for which there are new findings, leading to adjustments of the statements provided in the original document.

Q1: Do bacteria impair wound healing in a non-infected, non-healing wound?

The precise role of bacteria in wounds and their implications for wound healing is still not understood. However, the question, as it was posed in 2013 regarding the presence of bacteria without infection, but still causing delayed wound healing, is probably no longer valid. It was stated that bacteria could delay wound healing even in the absence of clinical signs of infection. However, it now appears that, if wound healing is delayed, an inflammatory response is on-going, even if it is not obvious macroscopically. New diagnostic approaches are encouraged, as bacteria without an inflammatory response would not delay wound healing.

Q2: Is the number of a specific bacterium per gram (or cm3) of tissue an adequate indicator of infection in all types of wounds?

The term critical colonisation has been abandoned in the recent clinical guidelines (22), and we know that bacteria are very heterogeneously distributed. Therefore, a cut-off number of bacteria in a sample is not representative of the entire wound (22) and is not an adequate definition of the presence of infection.

Q3: Should microbial cells always be eliminated from a wound, and do we know enough to set an indication for topical antimicrobial intervention from a microbiological perspective?

The conclusion from 2013 is still valid; that is, we do not yet understand the role of the presence of different bacterial or fungal species on wound healing. However, we believe that the presence in tissue of microorganisms considered to be classical pathogens (e.g., Staphylococcus aureus) generally indicates infection and should be treated with antimicrobials.

Q4: Is the type or virulence of bacteria important?

The role of various bacterial or fungal species in impairing wound healing has not yet been clarified.

Q5: What is critical colonisation?

The term critical colonisation has now been abandoned (see Question 2). However, as suggested in 2013, further investigation into the relationship between bioburden, inflammatory response, clinical manifestations and outcomes is still needed.

Q6: Is the removal of microorganisms from wounds a sufficient endpoint to assess the efficacy of the use of antimicrobials in wounds?

Reducing the microbial load is theoretically an appropriate endpoint, but it faces difficulties in practice. Using quantitative bacteriology as an endpoint for the efficacy of an antimicrobial agent is hampered by the heterogeneous distribution of bacteria, and by the practical difficulties of conducting this measurement in clinical microbiology laboratories. It is extremely difficult to monitor the reduction of bacteria during treatment using wound swabs, or even tissue biopsies. Thus, quantitively monitoring microorganism counts has not been shown to be useful in determining the efficacy of antimicrobials for treating wounds.

Q7: Does the presence of a biofilm itself influence wound healing?

The role of biofilms in impairing the healing of wounds is still controversial, but data suggest that bacteria generating an inflammatory response probably do impair wound healing. Non-healing

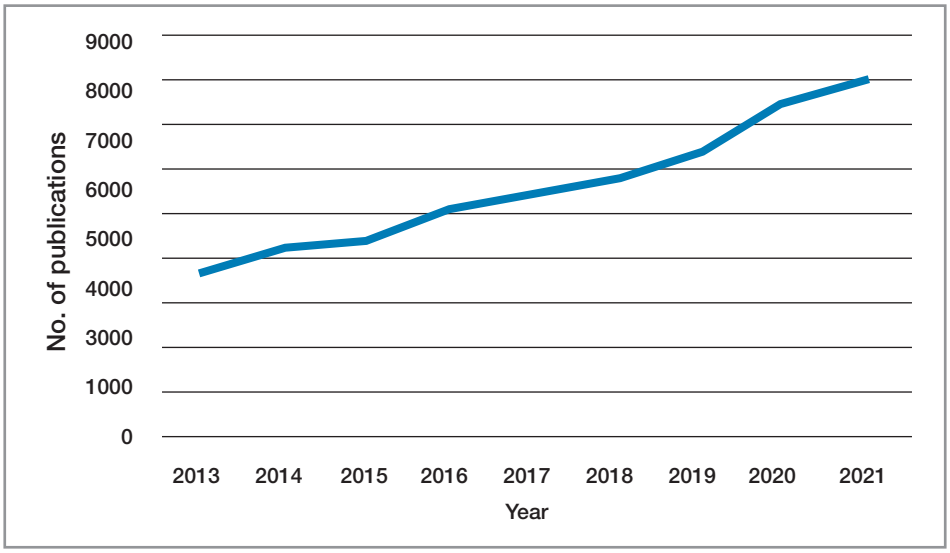

Figure 1: Number of PubMed-indexed publications using the word biofilm* 2013–2021. Source: PubMed.gov, generated by the author.

wounds contain bacteria both in biofilms and as single cells, but why they are not eradicated and what role they play remain open questions.

Q8: Is the presence of a biofilm in a wound always undesirable?

This is still an emerging area of research, and we may have to rethink how we investigate the role of biofilms in non-healing wounds and chronic infections in general.

Q9: How can bacteria in biofilms be removed from wounds?

It might not be the aggregation of bacteria per se that is the issue, but rather the physiology of the bacteria and the microenvironment of the wound bed that leads slow-growing or dormant bacteria not to be eradicated by antimicrobial agents (23).
Q10: Is there any antimicrobial agent that is not expected to select for resistance or tolerance in bacteria in the wound?

Eventually, it is likely that resistance will develop against any topical antimicrobial. Continuous and pro-active monitoring for resistance is therefore a must. In experiments, bacteria treated with honey, povidone iodine, octenidine, polyhexanide and chlorhexidine in vitro have not been shown to develop resistance, but more research is needed (11).

2.3 Overall conclusions

Despite an ever-increasing number of publications (see Figure 1) related to the presence and possible treatment of biofilms in wounds, there has not been any significant progress in the field.

The reasons for this lack of progress are not fully understood, but we suspect that the way we envision bacteria in the wound bed could be at least partly to blame. There seems to be too great a focus on extrapolating data from studies of laboratory-grown biofilms and their behaviour to bacteria in the wound bed. The in vitro biofilms and experimental systems are not wrong, but they do not fully encompass the wound microenvironment (24,25,26). We also encounter problems with the treatment of non-healing wounds because the antibiotic standard minimal inhibitory concentration (MIC) is not transferable to wounds and in vitro biofilm susceptibility only reveals that the bacteria are more tolerant (27).

In conclusion, some major challenges that remain are:

- Our experimental models do not adequately assess the biogeography and dynamics of a wound bed (23). It is easy to identify the mismatch between experimental models and a real infection, but it is extremely difficult and complicated to dissect the biology of infections.

- The field needs to initiate new approaches to avoid repeating errors made in the 2013 conclusions in future updates. To support this goal, we suggest:
  - Focusing more on the infectious microenvironment (i.e., the physiology of the infecting bacteria)
  - Realising that we must design our experiments to simulate actual infection, instead of basing these only on the experimental models available

2.4 Implications for clinical practice

Clinical practice is often influenced by a lack of knowledge regarding the role of biofilms in non-healing wounds. This means that most clinicians still treat the patient on the basis of wound culture results. At the same time, at least one recent survey indicates that healthcare professionals have adopted an in vitro-based mental model for how bacteria grow in non-healing wounds (26). In addition, industry and basic researchers seem dedicated to an in vitro-influenced approach to developing strategies for wound healing.

3. Treatment

Edgar Peters

3.1 Introduction

This chapter covers existing controversies from the perspective of the providers of antimicrobial treatment and other aspects of wound care.

Signs and symptoms of inflammation caused by tissue invasion of micro-organisms define the presence of wound infection. High-level evidence for topical antiseptics and topical antibiotics derived from meta-analyses and randomised clinical trials is limited. An analysis of 149 Cochrane systematic reviews assessed the strength of evidence presented in 44 of these reviews and demonstrated that only for some local and systematic wound care interventions could strong conclusions about effectiveness be drawn (28). Similar conclusions were drawn in more recent systematic reviews of the use of topical antimicrobial agents in diabetic foot ulcers (DFUs) and burns (29); there are only few available studies, usually of low quality, on the efficacy of topical antimicrobial agents in diabetic foot wounds and burns. Antimicrobial efficacy is currently almost exclusively evaluated in vitro in bacteria in planktonic phenotypes (30). Standardised methods for evaluating antimicrobials and antiseptics in wound biofilms have been developed, but are not being used in patient care. Below, we discuss the topical use of antibiotics (i.e., antimicrobial compounds that can be used both topically and systemically) and antiseptics (i.e., antimicrobial compounds that can only be used topically).

Topical antibiotics

Guidelines for using antibiotics both therapeutically and prophylactically have been developed (31–33), but the quality of the evidence used to formulate these guidelines is of low quality (34).

Topical antibiotics are prescribed more often than suggested in the guidelines (35). This leads to higher consumption of antibiotics, and the high consumption of antibiotics is associated with a high degree of antibiotic resistance (36). The continued emergence of antibiotic-resistant strains and limited investment by pharmaceutical companies in new antibiotics has curtailed the clinical efficacy of available antibiotics (37,38). The risk of developing side effects, such as allergy or antibiotic resistance, has resulted in recommendations stating that it is contraindicated to use topical antibiotics for the treatment of non-healing wounds (39).

Antiseptics

The emergence of microbes with reduced susceptibility to antiseptics is a continuing problem (40–42).

Both antibiotic and antiseptic resistance mechanisms can be caused by a reduction of cellular influx and the higher activity of efflux pumps, blocking entrance and increasing drug excretion, respectively (42–46). The prevalence of organisms with cross-resistance to antibiotics and antiseptics has also been recognised (47–50). Bacteria have an innate defence against toxic compounds via the up-regulation of multidrug efflux pumps. These include qacA in S. aureus and mexAB-oprM in P. aeruginosa. Once expressed, these efflux pumps are fairly indiscriminate and will not only excrete antiseptics, but also antibiotics and heavy metals. Expression of the efflux pumps can therefore result in multidrug resistance (51). It therefore seems important not only to optimise antibiotic use, but also to monitor and even restrict the use of antiseptics in the healthcare environment (42,52–54).

3.2 Indications for treatment

To prevent infection

Guidelines on diabetic foot infection published by the International Working Group on the Diabetic Foot (IWGDF) suggest how and when to treat diabetic foot infections and how to manage wounds (55–57). Other features (or secondary) signs suggestive of infection include the presence of necrosis, abnormal coloration, friable granulation tissue, non-purulent secretions and fetid odour. Such secondary signs might be helpful when inflammation is absent (e.g., in some cases of neuropathy or ischemia). The limited available evidence does not support the use of systemic antibiotics for treating clinically uninfected wounds in the diabetic foot, to either enhance healing or prevent clinical infection (56,58). There is no compelling evidence to support that the presence of many bacteria hampers wound healing (59,60).

A Cochrane review of honey-based dressings in all wound types was published in 2015 (61) and concluded, as did the 2020 IWGDF guidelines (56,58), that relative to its comparators, honey had an unclear effect on healing. It suggested that health services should avoid the routine use of honey dressings until sufficient evidence of effect is available (56,58).

In summary, there is little new evidence to support the use of antibiotic or antiseptic topical treatments to prevent wound infection, or to promote the healing of chronic ulcers (55,56,58–62).

Resolution of infection

There is a limited number of comparative studies of resolution of infection as an endpoint, and these are predominantly in the diabetic foot. In the previously mentioned 2020 systematic review, there were 25 controlled studies of (systemic) diabetic foot infections (56). One publication on the use of a topical antibacterial peptide, compared with oral antibiotics in mildly infected DFUs, showed it resulted in comparable outcomes with fewer side effects (55). Unfortunately, antibacterial peptides like these are not currently available in clinical practice. The systematic review also identified studies of topical antimicrobial treatment of diabetic foot infections (including one Cochrane systematic review)(29). Three small randomised controlled trials (RCTs) compared topical treatments of superoxidised water with other topical antiseptics or systemic antibiotics in (post-surgical) diabetic foot wounds (63–65), one of topical iodophor application compared with either acrinol or a control group. Although there were some differences in outcomes, it was not possible to draw conclusions from these studies because of potential bias; incomplete reporting; underpowered study designs; or a lack of reported outcomes on wound healing, infection occurrence or the resolution of infection. The previously mentioned 2017 Cochrane review of antimicrobial dressings in DFUs pooled several studies of antimicrobial dressings (29). These antimicrobials included products with various forms of silver (silver sulfadiazine, silver ion dressing/ionic silver, silver nitrate, silver oxide, silver collagen), various forms of iodides (cadexomer, povidone and compound/tincture), superoxidised water, zinc, silver sulphadiazine, tretoinin, pexiganan cream and chloramine. The authors concluded that the quality of the studies was low, which made it hard to draw conclusions. There was low-certainty evidence that the use of an antimicrobial dressing instead of a non-antimicrobial dressing might increase the number of DFUs healed over a medium-term follow-up period. Also, there is moderate-certainty evidence that there is little difference in the risk of adverse events related to treatment between systemic antibiotics and topical antimicrobial treatments (29).

Another Cochrane review of the topical treatment of facial burns identified only two studies using topical antimicrobial dressings with silver sulphadiazine or sodium carboxymethylcellulose silver (66). The application of silver in a dressing was found to make little or no difference in the proportion of healed wounds (with low certainty evidence), or in the resolution of wound infection (with very low certainty evidence).

Strengths and limitations of the current evidence base

Much can be gained from reporting study results in a standardised fashion, such as those offered by the IWGDF and CONSORT standards (67,68). The development of tests and techniques to improve tissue sampling and analysis, imaging technology and scientific progress in cellular and molecular biology has enabled the development of more 'objective' wound outcome parameters for assessing both the wound condition and the treatment intervention. However, tests that use physiological changes and molecular biology to assess wound healing are still not widely used outside pre-clinical research settings. The challenge, especially with regard to non-healing wounds, is still that objective endpoints (preferably assessed by an independent observer) are difficult to achieve. Some controversy concerning how to measure infection remains: should it be by the examination of clinical signs and symptoms, by microbiological methods, by laboratory parameters indicating inflammation or by a combination of these parameters (68)? Different wound classification systems have been suggested for assessing clinical infections, primarily relating to acute skin infection, acute surgical infection and chronic diabetic foot infections. The updated IWGDF classification (55) and the closely related WIfI classification (69) are more widely used to assess the severity of DFU infection, the LRINEC score for necrotising soft tissue infection (70), the USC (71), the DUSS and MAID and the DFI for other wounds (72–75).

3.3 Questions covered in 2013 & updated statements

In this section, we have included key questions concerning the treatment of wound infections from the 2013 document (11) for which there are new findings leading to adjustments of the statements provided in the original document.

Q1: Do we have clinical data which demonstrates that the use of topical antimicrobial treatments prevents reinfection in non-healing wounds?

There are limited clinical data to support that the use of topical antibiotic or antiseptic treatments can prevent the recurrence of infection. To our knowledge, there are no new clinical data to support that the use of antiseptic treatments can prevent recurrence of infection.

What type of evidence should we be looking for?

Q2: Should wound dressings and antimicrobial agents be tested only against planktonic bacteria?

We believe that, if biofilms inhibit wound healing, antiseptic and topical (and systemic) antibiotic treatments should be tested against them in future clinical studies (see Section 2.1).

It could be argued that the reason why so many dressings and antimicrobial agents fail to eradicate bacteria from non-healing wounds and other chronic infections is that they were designed only for planktonic bacteria. Susceptibility testing of sessile bacteria in biofilms is not widely available in clinical microbiology laboratories – only in research settings. In the future, however, it will be important to assess the efficacy of antimicrobials in bacteria in biofilm, as new drugs and devices are developed to fight bacteria in biofilms.

Q3: What endpoints do we need to justify the use of topical and local antimicrobial treatments in non-healing wounds?

To justify the use of topical and local antimicrobial treatments in non-healing wounds, we propose that studies primarily use the endpoints of either prevention or the resolution of infection. The use of increased healing rates or shorter healing times as primary endpoints is also valid, but the study must then be adequately designed so the correlation between the antimicrobial intervention and outcome can be validated. As infection should be

defined clinically, and the number of bacteria in wounds has no clear relation with infection, the use of bacterial quantification (e.g., 'reduction of bioburden') or the achievement of sterility to define resolution of infection is not useful. Other factors that can play a role in wound healing should be controlled for if wound healing parameters are used as endpoints (e.g., limb ischemia, biomechanical pressure, venostasis and local necrosis).

Infection as endpoint

Q4: Can resolution of infection be used as an endpoint in wound healing studies?

We think that resolution of wound infection is a valid endpoint in a wound healing study and that clinical parameters should be used for the definition of wound infection.

Resolution of infection is a clinically important factor for healing and could be a valuable endpoint in an RCT. As mentioned, the commonly used endpoints of wound closure, healing rate, time to complete, epithelialisation, quality of life and wound environment are all only, to some extent, dependent on the presence of infection.

The critical point is how infection should be evaluated. It is most often defined by the presence of clinical signs and symptoms. It is, unfortunately, not always possible to rely entirely on clinical signs and symptoms of infection, due to the lack of visible responses of the innate immune system (e.g., in case of ischemia, neurological dysfunction or an immunocompromised state, see Section 3.2). Several updated infection classifications based on the presence of clinical signs and symptoms, sometimes combined with laboratory parameters, are currently available to assist in assessing the presence of wound infection. There is no evidence that one classification or wound score is better than another. Decisions on a local or systemic treatment, or a combination of these treatments, must follow the diagnosis of infection.

Strengths and limitations of the current evidence base

Q5: What are the controversies regarding the methodology of studies providing evidence for topical antimicrobial treatment?

There is a lack of agreement among clinicians regarding the conduct of research in wound management. Generating a strong evidence base is fraught with methodological challenges.

RCTs are still considered the reference standard in evidence-based healthcare for conducting clinical trials (76); however, because clinicians need to know how the products will work on their cohort of patients, other types of (non-controlled) study designs may also be relevant. Clinical studies in wound care are often hampered by inadequate sample sizes and cohort variability, non-blinded outcome assessments and inadequate follow-up, and a lack of clear descriptions of interventions is often present in wound care research (67,68). Although guidelines have been published in an attempt to standardise research conduct and reporting, there seems to be lack of agreement in research on wound management (77). For researchers, this makes funding for clinical research challenging, and for clinicians it diminishes the availability of the different treatment options due to conflicting results. It is important, however, to highlight that a lack of evidence of efficacy is not the same as evidence of inefficacy.

3.4 Overall conclusions & implications for clinical practice

Based on the findings in this section, we conclude that:

- Little clinical data supports that the use of topical antibiotic or antiseptic treatments can prevent the occurrence or recurrence of infection

- Already available tests should be adopted clinically for antimicrobial effects on micro-organisms in a biofilm (sessile) phenotype and for those in the planktonic phenotype

- Studies on the value of topical antimicrobial treatment for wounds should have either prevention of clinical infection or clinical resolution of infection as the primary endpoint

- The use of wound healing as one type of primary endpoint is acceptable, but the study must be adequately designed so the correlation between the antimicrobial intervention and outcome can be validated

- Resolution of a wound infection is a valid primary endpoint

- Wound infection should be defined by the presence of clinical signs and symptoms of inflammation and may be supported by various laboratory parameters

- Researchers should adhere to standard research guidelines to support improved uniformity and comparability of clinical studies

4. The patient perspective

Sebastian Probst

4.1 Introduction

Currently there is a growing interest in understanding an individual's perspectives on their own treatment and care. The 'patient perspective' is defined as the individual's experience of living with a non-healing wound and its impact on him/her, including the physical, psychosocial and goal-oriented dimensions of the disease and its treatment. Asking not only what an individual wants or needs, but also what they value, results in more meaningful decision-making for both preventive and responsive wound care. This chapter summarises the main points from the 2013 document on the patient perspective, provides an overview of where we are now and discusses how clinical practice and research could proceed.

4.2 The clinical needs of individuals with non-healing wounds

Every individual with a non-healing wound should expect to have access to treatment that is timely, appropriate, person-centred and of the highest quality. A lack of appropriate attention to the clinical needs of the patient can lead to an increased risk of bioburden. Evidence demonstrates that patients expect that healthcare professionals inform them not only about the most accurate, but also about non-standard, treatment options (78). In dealing with wounds with a problematic bioburden, accurate and on-going assessment should be done to ensure correct identification of the patient's clinical needs, to employ the most appropriate interventions. Nevertheless, with the rising threat of antibiotic resistance, antibiotics should only be used when necessary. To positively influence clinical outcomes, the patient should be included in all decisions when possible.

Safety of patients with wounds

Patient safety aims to ensure the prevention of errors and adverse effects to healthcare patients. Often, the relationship between wound infection and patient safety is not clearly appreciated. Nevertheless, the link between the quality of healthcare services and the prevalence of nosocomial infections and care-induced lesions in patients with wounds is clearly demonstrated (79). Nosocomial infections contribute to increasing morbidity, mortality and excessive healthcare costs. Patients' confidence in the capacity of health services is consequently reduced. Correct patient and wound assessment might sometimes be challenging, making the choice of treatment difficult. In an attempt to manage bioburden, clinicians may often overuse antimicrobials (80). This tendency is exacerbated by a perceived demand from patients on physicians to prescribe antimicrobials, particularly antibiotics (81). On the other hand, insufficient treatment of infected wounds might compromise the health and well-being of the individual (82).

Patient involvement

Patients with non-healing wounds need a plan of care that often continues over months, years or even a lifetime. Patients and their families should receive information on how to manage a wound, be involved in decision-making and be satisfied with the care they receive (83). However, patients and their families often receive too little support, information and advice from health professionals, and are not well integrated into the planning of wound care interventions (84). Thus, nurses and physicians need skills to empower patients and their families. Patients often believe that antibi-

otics are needed and can persuade the physician to prescribe them. If a reduction in the use of antimicrobials is to be achieved, it demands the involvement of patients and their families as equal partners in the decision-making and care process, as well as access to ongoing education and self-management support according to their capabilities.

4.3 Questions covered in 2013 & updated statements

In this section, we cover the key questions concerning the patient perspective on antimicrobial treatment of wound infection from the 2013 document (11) for which there are new findings leading to adjustments of the statements provided in the original document.

Q1: Is the link between inappropriate management of individuals with wounds and patient safety clearly appreciated?

Judicious use of antiseptic products and antibiotic therapy is key to delivering safe and effective patient care, and to limiting the emergence of drug-resistant organisms. Education and training for both patients and clinicians, implementing integrated standards of care, ensuring good communication and teamwork are all essential to ensure the appropriate use of antimicrobials. This, in turn, will aid in achieving a robust patient safety culture within healthcare services that will drive enhanced clinical outcomes.

Q2: Does the insufficient application of agreed-upon standards of care for infection in non-healing wounds impact patient outcomes?

Symptoms and signs caused by wound infection, such as pain, odour and purulent exudate, have a great impact on the quality of life of both patients and their relatives. These symptoms are associated with anxiety, reduced social interactions and increased dependence on others, which in turn may interfere with healing. While drainage from wounds may be managed by frequent dressing changes, wound odour is difficult to hide. For managing wound odour, professionals generally rank treatment with antiseptics as most efficacious (85); however, there is sparse data on which antimicrobials, given by which route and for how long are most appropriate. Furthermore, there is little published information on the safety of using various antimicrobials in managing wound odour, so they are often not used (86).

Q3: Are patients considered equal partners in planning wound care interventions?

We believe that achieving a reduction of the inappropriate use of antimicrobials for the management of wounds requires the involvement of not only healthcare personnel, but also the empowerment of affected patients and their families. This may be achieved through the efforts of a properly constructed interdisciplinary wound care team. Nurses, physicians, pharmacists and other members of the team need skills to care for and teach patients, as well sufficient designated time to assess and manage these complex patients.

4.4 Overall conclusions & implications for clinical practice

Evidence demonstrates that including patients in the decision-making process about their care can enhance their motivation and knowledge (87). The need for patient involvement may change over the trajectory of their illness, being influenced by factors such as the patient's age, the duration of their wound, their underlying diseases, their level of education and literacy. Healthcare professionals must therefore explore each patient's perspective to gain insights on the complex issues that impact their individual patient's life. Providing proactive wound management while including the patient perspective may improve the wound outcomes and encourage the patient to engage as an active partner in his/her management. More research is needed concerning these various aspects of involving patients and their families in the care of their wounds.

For clinical practice, these conclusions point to the following recommendations:

- Healthcare providers should strive to involve patients and their families in wound care.
- Correctly assessing the presence, type, severity, and microbial cause of infection in a wound is key to identifying the appropriate and judicious use of antimicrobial products in their management.
- Educating and empowering patients and their families about managing the wound will likely lead to better clinical outcomes and patient satisfaction.

5. Economics & organisation of care

Jan Apelqvist

5.1 Introduction: the burden of non-healing wounds

In 2013 (11), we described how non-healing wounds are associated with long recovery duration and a high incidence of complications, most frequently infection, resulting in a considerable financial burden both from a societal perspective and from the perspective of the healthcare providers. These costs are estimated to account for up to 2–4% of the healthcare budget, with an expected substantial underestimation due to a lack of adequate data from many countries and an increasing elderly and diabetic population.

Recent data are provided in a retrospective cohort analysis of the electronic records of patients with wounds managed by the UK's National Health Service (NHS) in 2017/2018 (88). In this analysis, the resource use and costs of primary and secondary care sectors in the UK were evaluated. According to this study, there were an estimated 3.8 million patients with a wound managed by the NHS in 2017/2018. Annual levels of resource use attributable to wound management included 54.4 million district/community nurse visits, 53.6 million healthcare assistant visits and 28.1 million practice nurse visits. The annual NHS cost of wound management was £8.3 billion; 81% of the total annual NHS costs were incurred in the community; and 78% of patients with DFUs and 41% of individuals with venous leg ulcers (VLU) had a recorded infection. The annual prevalence of wounds increased by 71% between 2012/2013 and 2017/2018. There was a substantial increase in resource use over this period, and patient management costs increased by 48% in real terms. Corresponding data have been presented in various countries/regions in the Western world and been related to an increasing elderly population, increased prevalence of diabetes and individuals with multiple organ diseases (89–97). For wound type-specific costs and considerations, please see the 2013 EWMA Document (11).

The high prevalence of infection in DFU and the accompanying economic burden was also described in the 2013 document (11). Since then, several studies and reviews have been presented concerning the need for effective DFU interventions, but few have been subject to a full economic evaluation (89,91,92,94–114). All interventions examined in these evaluations were cost-effective or cost-saving in a clinical situation involving DFU infection. Collectively, they suggested that the short- and long-term implementation of such interventions could reduce the burden of DFU infections on healthcare systems while still providing optimal patient management. Although the evaluations captured the standard care for DFUs and associated costs, other concerns arose related to the issue. These included assessments of antibiotic efficacy, the route and setting of administration and the overall strategies embodied. However, as illustrated in a systematic review of diabetes-related foot infections, most studies included in the final analysis were too heterogeneous to allow comparison. This conclusion is in agreement with a 2018 EWMA document about advanced therapies in wound management (115), which pointed to the scarcity and limited robustness of the available economic studies on advanced therapies in wound management. A corresponding conclusion was made in a systematic review regarding VLU

(116). Based on these publications, we conclude that there is an increased economic focus on wound management, particularly with regards to infection, but there is a substantial need for more robust studies (117).

However, these data remain difficult to obtain in many countries and in the various relevant healthcare organisations for several reasons (95,118,119):

- Lack of adequate population-based data
- Patients are treated by different healthcare professionals/disciplines and at varying levels of care (e.g., inpatient/outpatient, primary care, home care, or patient self-care/private care)
- Patients who are not followed to a specific endpoint
- Differences in resources used or available
- Different treatment strategies
- The influence of different reimbursement systems
- The economic cost/price of the product or procedure used varies across countries, regions and depending on whether it is reimbursed or not and who is the payer

It can still be concluded that non-healing wounds often result in a considerable financial burden, associated with long healing times and a high incidence of complications. When evaluating the consequences of a wound infection, it is therefore essential to view the consequences as an integrated part of the total management and resource utilisation of an individual with a non-healing wound (11).

5.2 Questions covered in 2013 & updated statements

It is important to be aware of costs associated with the non-optimal management of complex wounds, particularly in cases with cross-sectional care. The economic impact of the organisation of care and the danger of fragmented care due to the lack of coordination between various disciplines and levels of care, has been illustrated in reports with regard to the management of complex wounds, particularly DFUs (120–122)(123–126). A substantial number of studies indicate the importance of organisation in wound care, as well as the interdisciplinary coordination of treatment strategies to achieve optimal care with regard to both outcome and cost (127).

The following questions were answered in the 2013 document Antimicrobials and Non-Healing Wounds (11).

- What is the cost effectiveness of antiseptic versus antibiotic treatment (not just prices of products, but also societal costs)?
- Is it cheaper to amputate limbs of an individual with an infected wound than to treat (conservatively) with antibiotics?
- Do restrictions on the use of products due to their price have consequences, and what are these consequences?

As no new conclusions have been presented since 2013, these questions are not repeated in this update, but can be found in the document published in 2013 (11).

In this updated paper, we do, however, find it important to highlight the importance of recognising the perspective of each of the relevant decision-makers when an economic analysis is performed. In wound care, decision-makers include clinicians, hospitals or other healthcare provider organisations and third-party payers. For example, from a hospital-management perspective, the cost of intravenous antibiotics or revascularisation could be considered high, particularly because it might

prolong the length of the in-hospital stay. However, from a societal perspective, the use of antibiotics and revascularisation in this case is only a fraction of the total cost spent to achieve complete wound healing.

5.3 Overall conclusions & impliations for clinical practice

Concerning the economics and organisation of care, in relation to the management of wound infections, we conclude the following:

- If cost and resource-use studies are lacking, clinicians lack the robust economic arguments and strong outcome data that they must present to fundholders in order to support the implementation of the most cost-effective treatments and care strategies for infected wounds.
- Infection is the most frequently occurring complication in non-healing wounds. When evaluating the consequences of a wound infection, it is essential to see its management and outcome as an integrated part of the total management and resource utilization of an individual with a non-healing wound. It is important to identify interventions and strategies early, to avoid complications and facilitate healing, and in terms of cost implications.
- It is essential to be able to understand and use health economics as a valuable tool in clinical practice for developing efficient treatment strategies for the prevention and treatment of individuals with wounds.

6. Future perspectives & antimicrobial stewardship

Karen Ousey and Benjamin A. Lipsky

6.1 Introduction

Much discussion and many papers have addressed the continued increasing global threat of AMR (128–130). Increasing resistance of microorganisms to antimicrobials is predicted to be associated with up to 10 million deaths annually by 2050, exceeding deaths associated with cancer (131). The increasing use of antibiotics in recent decades has led to selection pressure that encourages antibiotic-resistant strains to emerge and increase in prevalence (131). Judicious use of all antimicrobial agents is urgently needed to retain effective methods for treating and preventing infections, thus avoiding a return to the constraints (e.g., in surgical procedures or immunocompromising therapy) that characterised the pre-antibiotic era (12).

All open wounds are contaminated or colonised with microorganisms, but not all contaminated wounds become infected. As wound infections are associated with considerable morbidity, occasional mortality and substantial financial expense, it is incumbent upon all healthcare providers to make efforts to prevent them. As noted by the International Wound Infection Institute's (IWII) 2022 guideline Wound infection in clinical practice (132), the likelihood of a wound becoming infected is related to characteristics of the individual (systemic and multifactorial host factors), their wound and the environment. Prevention of wound infection is focused on implementing strategies to reduce the patient's individual risk factors (8,9,133).

A key approach to reducing the problems of AMR and wound infection is following the principles of antimicrobial stewardship (AMS). AMS refers to the supervised and organised use of antimicrobial agents (132). In healthcare, this refers to a coordinated programme designed to decrease the spread of infections caused by multidrug-resistant organisms and improve clinical outcomes by encouraging appropriate and optimised use of all antimicrobials (134). In brief, these include: avoiding prescribing antimicrobials unless they are necessary, prescribing as narrow a spectrum of antimicrobial therapy as required, choosing the most appropriate route of therapy and limiting the duration of treatment to the shortest time necessary (135). Several authoritative organisations have emphasised the need for implementing AMS principles (12). The 2013 EWMA document identified ensuring prudent use of antimicrobial agents as an area requiring urgent action. The continuing increase in the prevalence and costs of wound infections (93,136,137), and the persistent problems in developing new antibiotics (138), necessitate novel approaches to optimising and conserving current interventions aimed at preventing infection (139). A recent paper in The Lancet using predictive statistical modelling approximated that, in 2019, there were 4.95 million global deaths associated with, and 1.27 million deaths directly attributable to, bacterial AMR (6).

While much of the focus of AMS is on systemic antibiotic agents, judicious use of topical antiseptics also plays a role in preventing and managing wound infection (22). This begins with only using these agents to treat clinically infected wounds and moves to limiting the duration of treatment based on the findings of regular wound assessments (22,29,132,140,141). Selection of topical

antimicrobial treatment should also consider the following (132,140):

- Antimicrobial action of known efficacy for likely or confirmed pathogens
- Broad-spectrum agents only when likely polymicrobial pathogens or unpredictable sensitivities
- Known or likely efficacy in achieving clinical goals of care of the individual
- Minimal cytotoxicity, irritancy and allergenicity to wound tissue and peri-wound skin
- Fast acting (when severe infection); long acting (when patient adherence is a problem)
- Low propensity to select for AMR
- Local availability of agents and guidance for their use

Topical antimicrobials play a role in treating the wound when it is likely to be clinically infected or confirmed as containing biofilm. There is no clear evidence that treatment with topical antimicrobials can prevent wounds from becoming infected, but in those at high risk (e.g. occurring in immunocompromised or post-high risk surgery patients), prudent use may be appropriate (29,141).

In wound care, early identification of infection is an integral part of AMS programmes, as its eradication helps avoid non-healing. Key AMS strategies include (12,142): promoting known effective infection control methods such as hand hygiene practises; creating and a continually updating a local, evidence-based AMS knowledge base; ensuring educational opportunities for clinicians about the appropriate use of antimicrobials; auditing actual antimicrobial treatments to identify and correct inappropriate practices related to decisions to treat; the selection of empirical and definitive regimens, route and dose of therapy; and the duration of therapy. The main goals are to only treat clinically infected (not uninfected) wounds, using the narrowest spectrum antimicrobial regimen at the lowest required doses, for the shortest required duration. This effort should be supported through the development and incorporation of infrastructure that allows clinicians to diagnose infection accurately, and to rapidly institute appropriate antimicrobial treatment (135,143).

Numerous global initiatives have been created to measure the effects of programmes developed to tackle AMR, including:

- 2014 Transatlantic Taskforce on Antimicrobial Resistance (TATFAR)(144)
- Global Antibiotic Resistance Partnership (GARP)(145)
- Global Health Security Agenda (GHSA)(146)
- Global Action Plan on Antimicrobial Resistance (130)
- The UK's five-year national action plan (129)
- The Tripartite Partnership among the Food and Agriculture Organization of the United Nations (FAO), the World Health Organization (WHO) and the World Organisation for Animal Health (OIE)(147)
- World Antimicrobial Awareness Week, coordinated annual by the WHO (148)

Many factors contribute to the misuse of antimicrobials. Key issues identified by the WHO include: clinicians' fears related to diagnostic uncertainty; limited clinical skills and knowledge; litigation anxiety associated with withholding or constraining antibiotic therapy; and failure to properly follow available clinical guidelines (149). Furthermore, healthcare workers with heavy workloads often lack time both to fully evaluate the cause and appropriate management of an infection, and to take advantage of opportunities to update their knowledge. Management strategies for wound in-

fection must be properly targeted and provided in a timely, efficient, evidence-based manner, preferably by a multi-professional team. Adopting such a systematic approach should help reduce the adverse outcomes that so often occur with wound infections (12). Indeed, a study in Sweden (149) demonstrated the potential for improved wound management using a national quality registry for structured ulcer care. The project data revealed an immediate effect of their Registry of Ulcer Treatment within wound management in significantly reducing healing time from 146 days (21 weeks) in 2009 to 63 days (9 weeks) in 2012. They also noted a reduction of antibiotic treatment from 71% before registration to 29% between registration and ulcer healing (149).

While antimicrobial therapy is a key component of treating infected wounds, optimal management also involves cleansing and debriding the wound and selecting appropriate dressings, devices (e.g., for pressure offloading), vascular assessment and optimised nutrition. Other broader and pragmatic issues to consider include various administrative, psychological and social factors that may interfere with the wound healing process.

6.2 Questions & statements

As antimicrobial stewardship was not specifically discussed in the original version of this document (11), we have added the following questions to this update to highlight the aims of this approach and provide guidance on the appropriate use of antimicrobials in wound management.

Q1. Which types of antimicrobial agents should clinicians choose to treat wound infections, while minimising the risk of AMR?

Before deciding which antimicrobial to use, it is essential to assess whether to use any, as these agents are generally reserved for managing clinically infected wounds. Infection of a wound is defined by the presence of at least two of the classical (inflammatory), or possibly secondary, signs or symptoms of inflammation. For infected wounds, there are a range of topical and systemic antimicrobial products available. Clinicians should consider the most appropriate class of agent, route of therapy, spectrum of activity required and duration of therapy. For optimal definitive therapy, clinicians should obtain appropriate material (tissue, rather than swabs) for culture and sensitivity testing and then seek guidance from local and national policies and guidelines. When in doubt, clinicians should seek input from experts, including (when available) an interdisciplinary team. For additional information relating to the identification of wound infection, we refer to the IWII 2022 Wound Infection in Clinical Practice document (132).

Q2. Should antimicrobials be used to prevent an infection?

Uninfected wounds generally do not require antimicrobial therapy; no high-quality data demonstrate that administering antimicrobials either prevents wound infection or accelerates wound healing. Numerous studies have documented there is an excessive use of antibiotics to treat patients with uninfected but non-healing wounds.

An essential practice for both treating and preventing wound infection is wound bed preparation. Any tissue that is suspected of being devitalised or colonised by biofilm requires vigorous therapeutic cleansing of microorganisms and detritus from the wound bed. Rigorous therapeutic cleansing of chronic or hard-to-heal wounds and is performed: to remove excessive wound exudate or debris from the wound bed to optimise visualisation and assessment; prior to collection of a wound sample (swab or biopsy) to reduce contamination; and to assist in hydrating a desiccated wound bed (150).

Antimicrobials (most often antiseptics) may be indicated for selected patients or types of wounds that are at high risk of infection. This might be treating in conjunction with extensive surgical debridement as a component of biofilm-based wound care (151), to help prevent infection in high risk (e.g. contaminated) surgery, or when the consequences of infection are serious (e.g.

An antimicrobial strategy for non-healing wounds should include:

- *Routinely determining if the wound is infected*
- *Surveillance programmes for wound infection*
- *Clear and achievable metrics*
- *Local policies to review the appropriateness of antimicrobial use*
- *Accessible multi-professional educational programmes*
- *Antimicrobial guardianship programmes*
- *Patient awareness campaigns*

Table 1: Antimicrobial strategy for non-healing wounds

cardiac valve surgery)(152). IWII 2022 also states there is a role for judicious wound irrigation with an antiseptic solution in selected circumstances. Both healthcare professionals and their patients should be educated on the clinical and financial benefits of not using the precious and limited resource that antibiotics represent for uninfected wounds. A strong infection control programme, in collaboration with AMS guardians, can provide useful advice and education.

6.3 Overall conclusions

This section is aimed at briefly exploring the value of antimicrobial stewardship programmes and highlight actions needed from various key stakeholders to help achieve the goals for the appropriate use of antimicrobials in wound management. AMR is undoubtedly among the gravest global threats to clinical medicine, but we now have methods to reduce its occurrence and improve outcomes in treating wounds. We hope that readers will be both chastened by the crisis and heartened by the role they can play in reducing the risk and improving outcomes in patients with wounds.

Setting/field	Action	Difficulties
Research community & industry	Areas of active research include those related to: management of biofilm and the use of new techniques (e.g. infrared and digital imaging) in the early diagnosis of wound infection; standardisation of methods to evaluate the effectiveness of antimicrobial dressings against both planktonic and biofilm bacteria and microbial communities associated with wounds	Collecting comparable data from different sites Limited available research in various aspects of biofilms Lack of equity and global guidance for the use of new technologies Limited prospective, cohort and comparative (especially randomised controlled) studies of these issues, as well as of the role of antimicrobial treatments for clinically uninfected non-healing wounds
Clinical practice/ healthcare organisations/ payers	Develop wound-specific AMR education programmes Ensure all healthcare professionals are aware of AMS principles Implement established AMS pathways Implement available AMS guardian programmes	Lack of data on the appropriate use of antimicrobials in wound care Lack of data to support specific recommendations Variations in costs for, and organisation of, wound care across settings/ countries Frequent unrestricted use of antibiotics, and a lack of national pharmaceutical policies to coordinate surveillance, regulation and education
Payers	Motivate reimbursement systems to implement effective wound care strategies in both in- and out-patient settings to promote the appropriate use of antimicrobials	Variations in funding and recording methods impair identifying reasons for, and duration of, prescribed antimicrobial therapies

Table 2: Future perspectives for research, clinical practice and payers

7. A concise approach to treating potentially infected wounds

This updated algorithm (11), with recommendations on routes of treatment with antimicrobials in accordance with stewardship principles, is aimed at providing concise guidance for clinical practitioners in implementing our key messages.

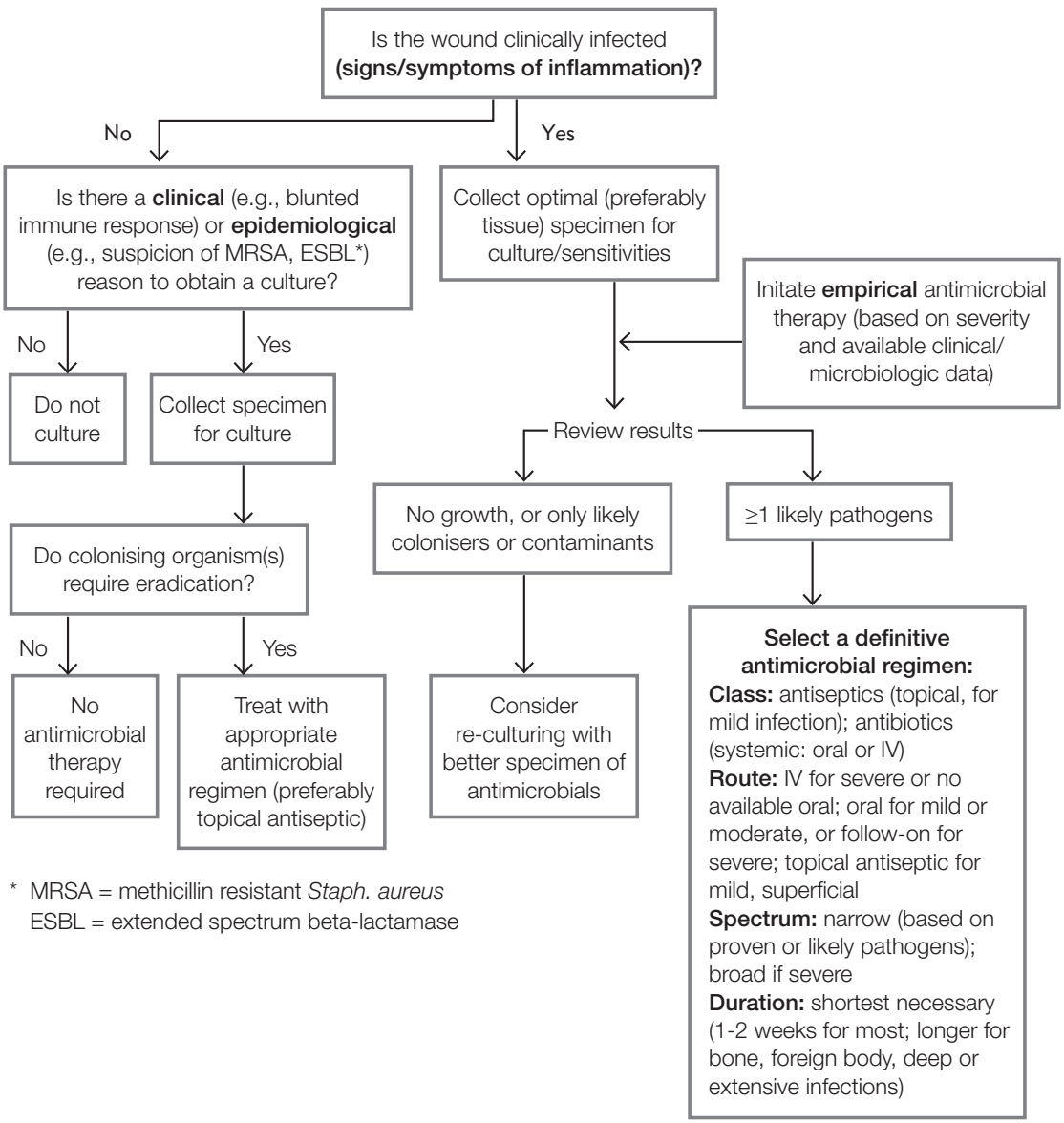

Figure 2: Algorithm on when to treat/not to treat with antibiotics and antiseptics

8. Conclusion

This update document on Antimicrobials and Non-healing Wounds provides support for clinical decision-making using the latest evidence for an appropriate use of antibiotics and antiseptics in wound management. AMR is a global problem in clinical practice, even though methods to reduce the occurrence of antimicrobials and improve outcomes when caring for wound patients exist. Wound infection is one of the most frequently occurring complications in non-healing wounds. The presence of infection can be established via clinical signs and symptoms of inflammation that may be supported by various laboratory parameters. Towards this end, healthcare professionals must have the knowledge and skills to evaluate wound infection and knowing the consequences of different routes of treatment. Antimicrobial stewardship must be seen as an integrated part of the total management and resource utilization of an individual with a non-healing wound. While it is important to identify interventions and strategies early to avoid complications and facilitate healing, these also often have cost implications. Preventing, managing and treating wound infection in clinical practice ideally involves not only antibiotics and antimicrobials, but also an understanding of the individual patient's perspective on how an infection impacts their life. Providing proactive wound management while including the patient perspective is necessary to improve the wound outcomes and encourage the patient to engage as an active partner in his/her treatment.

Clinical practice, however, shows that there is still a lack of knowledge, especially about the role of biofilms in non-healing wounds, with a tendency to adopt an in vitro-based model for how bacteria grow in non-healing wounds. Taking into consideration the latest evidence on the value of topical antimicrobial treatment for wound care, the primary endpoint should be defined either as the prevention of clinical infection, clinical resolution of infection or resolution of a wound infection. It is therefore recommended that researchers adhere to standard research guidelines to support improved uniformity and comparability of clinical studies.

9. Glossary

Term	Definition
Antibiotic	A chemical substance that either kills or inhibits the growth of a microorganism, such as bacteria, fungi or protozoa, and which can be used both topically and systemically. Antibiotics have three major sources of origin: (i) naturally isolated, (ii) chemically synthesised or (iii) semi-synthetically derived. They can be classified according to their effect on bacteria—those that kill bacteria are bactericidal, while those that inhibit the growth of bacteria are bacteriostatic. Antibiotics are defined according to their mechanism for targeting and identifying microorganisms—broad-spectrum antibiotics are active against a wide range of microorganisms; narrow-spectrum antibiotics target a specific group of microorganisms by interfering with a metabolic process specific to those particular organisms (153).
Antimicrobial	The term 'antimicrobial' is an umbrella term and refers to disinfectants, antiseptics (sometimes referred to as skin disinfectants), antivirals, antifungals, antiparasitics and antibiotics (132).
Antimicrobial resistance	The ability of a microorganism to survive and even replicate during a course of treatment with a specific antibiotic or antiseptic. It can arise from gene acquisition and/or mutation. Failure to resolve an infection with the first course of an antibiotic or antiseptic treatment may mean that the infection spreads or becomes more severe. Intrinsic resistance: Bacteria have never been shown to be susceptible. Acquired resistance: Previously susceptible bacteria have become resistant as a result of adaptation through genetic change. Multidrug resistance: Corresponds to resistance of a bacterium to multiple antibiotics (153).
Antimicrobial tolerance	Tolerance is distinct from resistance, since resistance is caused by the acquisition of determinants that regulate active mechanisms, which directly diminish the action of the antimicrobial agent and allow cell division and microbial growth, whereas tolerance enables the cells in biofilms to sustain longterm exposure to the antimicrobial agents without loss of viability or genetic change. Antimicrobial tolerance is not due to a permanent genetic change (18).

Term	Definition
Antiseptic	An antiseptic is a topical agent with broad spectrum activity that inhibits the multiplication of, or sometimes kills, microorganisms. Depending upon its concentration, an antiseptic may have a toxic effect on human cells (132).
Bacteria	Prokaryotes can be divided into categories, according to several criteria. One means of classifying bacteria uses staining to divide most bacteria into two groups (Gram-positive, Gram-negative), according to the properties of their cell walls (153).
Bioburden	Bioburden is the population of viable microorganisms on/in a product, or on a surface (154).
Biofilm	A coherent cluster of bacterial cells imbedded in a biopolymer matrix, which, compared with planktonic cells, shows increased tolerance to antimicrobials and resists the antimicrobial properties of host defence (18).
Host defence	The capacity of an organism or a tissue to withstand the effects of a harmful environmental agent (18).
Non-healing wounds	Wounds that fail to progress through an orderly and timely sequence of repair. Also referred to as chronic, complex and hard to heal wounds (11).
Reduction of bioburden	Reduction of the size and diversity of a microbial population (154).
Wound infection	When the quantity of microorganisms in a wound becomes imbalanced such that the host response is overwhelmed and wound healing becomes impaired. Transition from non-infected to infected is a gradual process determined by the quantity and virulence of microbial burden and the individual's immune response (132). Signs and symptoms of inflammation caused by tissue invasion of micro-organisms define the presence of wound infection.

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