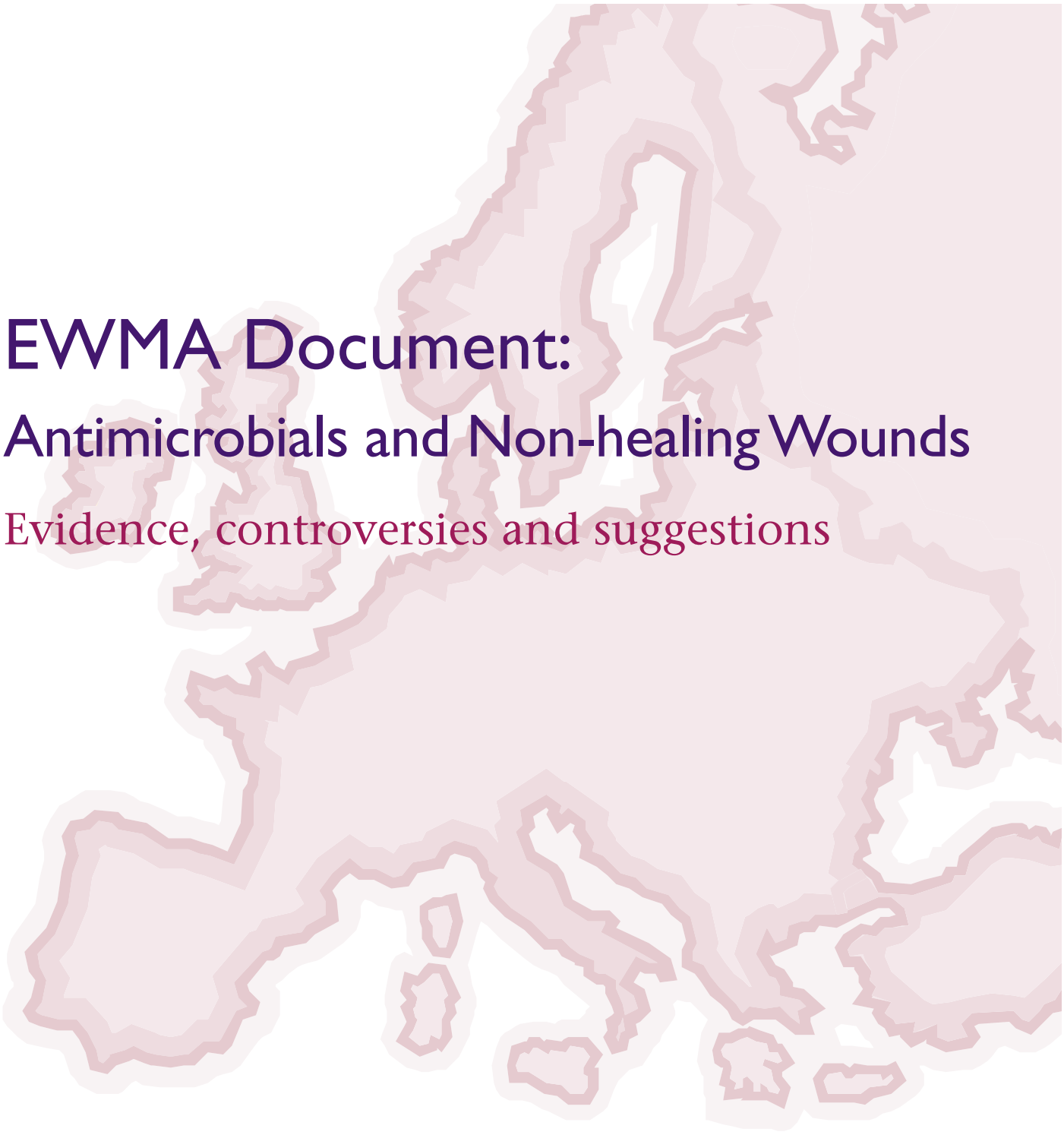
EWMA Document:

Antimicrobials and Non-healing Wounds

Evidence, controversies and suggestions



A EWMA Document

JWC journal of wound care

EUROPEAN · WOUND · MANAGEMENT · ASSOCIATION EWMA

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The document is supported by an unrestricted grant from B. Braun Medical, BSN Medical, ConvaTec, PolyMem, Flen Pharma, Lohmann & Rauscher, Mölnlycke Health Care, Schülke & Mayr, Smith & Nephew and sorbion.
Eucomed Advanced Wound Care Sector Group provided initial funding for the document.

This article has not undergone double-blind peer review.
This article should be referenced as: *Gottrup, F., Apelqvist, J., Bjansholt, T. et al. EWMA Document: Antimicrobials and Non-healing Wounds—Evidence, Controversies and Suggestions. J Wound Care. 2013; 22 (5 Suppl.): S1–S92.*

Published on behalf of EWMA by MA Healthcare Ltd.
Publisher: Anthony Kerr
Editor: Daniel Shanahan
Designer: Alison Cutler
Published by: MA Healthcare Ltd, St Jude's Church, Dulwich Road, London, SE24 0PB, UK
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Contents

Introduction

Non-healing wounds are a significant problem for health-care systems worldwide. In the industrialised world, almost 1–1.5% of the population will have a problem wound at any one time. Furthermore, wound management is expensive; in Europe, the average cost per episode is €6650 for leg ulcers and €10000 for foot ulcers, and wound management accounts for 2–4% of health-care budgets. These figures are expected to rise along with an increased elderly and diabetic population.[1–4]

Infection is one of the most frequent complications of non-healing wounds. It can jeopardise the progression towards healing, result in longer treatment times and increase the resource use. In the worst cases, it can result in a major amputation or a life-threatening condition. Wounds are disposed to infection, as the exposure of subcutaneous tissue following a loss of skin integrity provides a moist, warm, and nutrient-rich environment, which is conducive to microbial colonisation and proliferation. Consequently, use of antimicrobial agents is important in wound management.

Inappropriate use of antimicrobials (especially antibiotics) creates an environment for the selection of resistance against the currently available antimicrobial products, with the potential consequence of significantly jeopardising patients' health status. The development of so called 'superbugs' is foreseeable and is the background for increased political involvement.[5–7]

In 2009, the EU member states adopted council conclusions concerning innovative incentives for effective antibiotics. This is one of the single most powerful, concerted political stances on antibiotic resistance ever. Here it is recognised that the spread of antibiotic resistance is a major threat to public health security worldwide and requires action at all levels. Hence, they call upon the member states to develop and implement strategies to ensure awareness among the public and health professionals of the threat of antibiotic resistance and of the measures available to counter the problem.

This has been followed by several pan-European initiatives, such as the conference 'Combating Antimicrobial resistance—Time for Joint Action' in March 2012,[7] in which the European Wound Management Organisation (EWMA) participated. The conference conclusions were that there was a substantial gap in the knowledge in this area.

Furthermore, the European Commission has followed this by a report on implementation of the council recommendations on patient safety, in which they conclude that 'even if many member states have taken a variety of actions, there is still considerable room for improvement'.[8,9]

Resistance to antibiotics results in a considerable decrease in the possibility of effectively treating infections, and increases the risk of complications and death.[10] In the European Union (EU) alone, it is estimated that 2 million patients acquire nosocomial (hospital-acquired) infections each

year,[11] of which more than half are drug-resistant.[12] Infections based on resistant bacteria are associated with up to two-fold increase in mortality compared with infection with susceptible microbes.[13]

Coupled with insufficient investment in the development of new antibiotic treatments, the issue of drug-resistant bacteria is becoming a pressing public-health concern. In 2007, the European Antimicrobial Resistance Surveillance System (EARSS) reported that *Staphylococcus aureus* had become resistant to the antibiotic meticillin (MRSA), indicating that beta-lactam antibiotics are not suitable for empiric treatment of wound infections in Europe.[14] To date, there is no collection of data for bacterial resistance in wounds.

Despite a tremendous amount of literature covering the effects and use of antimicrobials, and the development of resistance in the wound area, there is a lack of a consistent and reproducible approach to defining, evaluating and measuring the appropriate and adequate use of antimicrobials locally/topically in wound management, from a clinical and industry perspective.

This lack of information can best be illustrated by the fact that, despite the extensive use of antimicrobials in wounds, their use remains controversial for wound management. These controversies have never been discussed and evaluated in detail, which is a major reason for wound infection persisting as one of the most serious influencing factors for the existence of non-healing wounds.

> This document describes the controversies surrounding use of antimicrobials in wound management, and hopes to raise interest in how to solve these problems for the future use of antimicrobials

This document describes these controversies and hopes to raise interest in how to solve these problems for the future use of antimicrobials. For this reason, EWMA established the group, which produced this document.

By discussion and clarification, we hope to contribute to a reduction in the burden of care, in an efficient and cost-effective way.

Statement

There are a large number of antimicrobial wound care products available, but we need to be better prepared for selecting the right product for the right patient, for the right wound, at the right time. There is confusion among policy makers, patients, clinicians and researchers as to the controversies for the use of antimicrobials in wounds. Most discussions and recommendations do not differentiate between different types of antimicrobials, especially with regard to antibiotics and antiseptics.[5]

Aim

The intention of this document is to focus on the responsible design and use of antimicrobial strategies in wounds that fail to progress through an orderly and timely sequence of repair. In this document, these types of wounds are defined as 'non-healing'.[15] The focus is not on a specific type of non-healing wound, but to provide more general recommendations for these types of wounds.

Animal and cellular models, acute wound (surgical/trauma wounds) and burns are excluded from this document. Systemic infections, debridement as a bioburden control and other types of wound management strategies will not be covered in detail.

The document structure is inspired from the different elements that are normally included in the health technology assessment (HTA) approach.

> The intention of this document is to focus on the responsible design and use of antimicrobial strategies in wounds that fail to progress through an orderly and timely sequence of repair

It is not a traditional position document that discusses different treatment strategies, when to use which product, or an assessment of one product over another.

The overall aim of this document is to highlight current knowledge regarding use of antimicrobials, particularly in non-healing wounds, to discuss what still is controversial and give suggestions for future actions.

Objectives

These goals will be achieved by the following:

1. Producing an update of each topic mentioned, including statements on which items have been shown to be based on evidence at the highest level.
2. Uncovering controversies and issues related to use of antimicrobials in wound management; describe possible solutions and the pros and cons of each
3. Summarising the information presented and offer perspectives for further work.

The intentions of the document are to present a platform of viewpoints from which we can build messages for the different stakeholders, including patients, health professionals, policy makers, politicians, industry and hospital administrators.

Structure and content of the document

The document includes the different aspects of health-care perspectives surrounding the central theme of antimicrobials in wounds. Each chapter begins with an introduction to the current knowledge and status of the specific topic; we have called this 'where are we today.' This section also covers an assessment of the current literature and what evidence there is for the existing consensus.

The method for the evidence assessment builds upon EWMAs previous work with outcomes[15] and

is the foundation for the recommendations made in this document.

The second section of each chapter will address the relevant controversies. Each controversy has its own subtitle, which is stated below the the author group's statement. Following the statement, the controversy is discussed and a short conclusion is given.

The present document tries to uncover the controversies with regard to the use of antimicrobials in wound care, with a focus on non-healing wounds. Most research with regard to infection and wound healing is related to acute wounds and a minor part is related to non-healing wounds; however, some evidence from acute wounds will be presented when applicable.

The document will focus on local (topical) treatment with antimicrobials, such as antibiotics and antiseptics. Treatment with systemic antibiotics is not within the scope of the present document, but results may be used in case of lacking evidence for local treatment. The document will consider infection rate as a continuum (for the document's definition of infection please refer to Table 2-1). We will present overall treatment strategies, but not judge whether one treatment is better than another or compare treatment strategies (or products). Therefore, there will be no discussion of practical treatments or descriptions of clinical guidelines; however, the organisational aspects of treatment will be explored. Since the authors are residents of Europe and EWMA is a European association, the document will only take European patients and health-care systems into consideration.

The opinions stated in this document have been reached by a consensus of the authors involved, weighing their professional opinions based on their individual research and that of their peers as well as their own clinical experience.

Method and terminology

Search history and development of the document

Each chapter of the document has been divided between the authors and the editor, and the co-editor has provided feedback in an edited draft. This process has been repeated several times; the group edited the final document and all authors agreed on all controversies, statements and discussions. The final draft was sent to a review process during which resource persons, EWMA Council members and supporters were asked to comment on the draft in an internal validation process.

Besides an initial literature search, a specific literature search was made with regard to the study design, endpoints and outcomes in comparative/randomised controlled trials (RCTs) on the antimicrobial treatment of wounds. This systematic review was made to supplement an earlier literature search conducted in 2009.

Definitions

For the full list of definitions used in the document, please refer to Table 2-1.

Table 2-1. Definitions used in the document

Term	Definition
Antibiotics	A chemical substance that either kills or inhibits the growth of a microorganism, such as bacteria, fungi or protozoa. 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.[6]
Antimicrobial agents	Any substance with the ability to inhibit a microorganism, which means that the definition inludes both antibiotics and antiseptics, irrespective of being in the form of a dressing, solution, gel or drug.
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.[6]
Antimicrobial tolerance	The ability of a microorganism to survive and even replicate during a course of treatment with a specific antibiotic or antiseptic. 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 long-term exposure to the antimicrobial agents without loss of viability or genetic change. Antimicrobial tolerance is not due to a permanent genetic change.[16]

Table 2-1. Definitions used in the document continued

Term	Definition
Antiseptic	Agents inhibiting the growth and development of microorganisms. An antiseptic is a non-specific chemical possessing antimicrobial properties that can be used on skin, wounds and mucous membranes.[17]
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.[6]
Bioburden	Bioburden is the population of viable microorganisms on/in a product, or on a surface.[17]
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.[16]
Colonisation	Microbial multiplication in or on the wound without an overt immunological host reaction.[16]
Contamination	Microbial ingress into the wound without growth and division.[17]
Empirical antibiotic therapy	Antibiotic therapy covering at the most probable or important micro organism with the most probable resistance pattern.[17]
Endpoints	The occurrence of a disease, symptom, sign, or laboratory abnormality that constitutes one of the target outcomes of a clinical trial.[18]
Host defence	The capacity of an organism or a tissue to withstand the effects of a harmful environmental agent.[16]
Infection	Invasion and multiplication of microorganisms in body tissues, evoking an inflammatory response (systemic and/or local) and causing local signs of inflammation, tissue destruction, and fever.6 It is perhaps worth noting that definitions of wound infection vary,[19] but that diagnosis is based on clinical signs and symptoms.[16]
Outcome	Documentation of the effectiveness of health care services and the end results of patient care.[15]
Recurrence of infection	A reoccurrence of the same illness from which an individual has previously recovered.[17]
Reduction of bioburden	Reduction of the size and diversity of a microbial population.[17]
Resource utilisation	The total amount of resources actually consumed, compared against the amount of resources planned for a specific process.[6]
Wound cleansing	Removing harmful substances (for example, microorganisms, cell debris and soiling) from the wound, so that the healing process is not delayed/hindered, or to reduce the risk of infection.[17]

The principal role of bioburden in wounds

This chapter will describe the controversies surrounding the significance of bioburden in wounds from a scientific point of view:

Host-pathogen interactions and outcomes in wound healing

- Does infection impair wound healing?
- Do bacteria impair wound healing in a non-infected, non-healing wound?

Microbiology

- Is the number of a specific bacterium per gramme/cm^3 of tissue an adequate indicator of infection in all types of wounds?
- Should microbial organisms always be eliminated from a wound?
- Do we know enough to set an indication for topical antimicrobial intervention from a microbiological perspective?
- Is the type or virulence of bacteria important?
- What is critical colonisation?
- Is removal of microorganisms from wounds a sufficient endpoint for the efficacy of the use of antimicrobials in wounds?

Biofilm

- Does the presence of a biofilm itself influence wound healing?
- Is the presence of a biofilm in a wound always undesirable?
- How can bacteria in biofilms be removed from wounds?

Resistance and tolerance to antimicrobial interventions

- Is there any antimicrobial agent that is not expected to select for resistance or tolerance in bacteria in the wound?

Where are we today?

Historical background

The formulation of the germ theory of disease by Koch in 1876 established the role of infectious agents in the causation of infection; from this, the relevance of antimicrobial agents in treating and preventing infections became evident. The use of antimicrobial interventions in treating wounds has a long history and even ancient civilisations are known to have devised crude antimicrobial topical wound remedies from local materials, such as wine, vinegar, honey, plant extracts and minerals. With the development of

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the chemical industry during the 19th century, antiseptics became available for treating wounds. Surgical procedures were feared as they often resulted in life-threatening infections, known as hospital gangrene, and mortality rates were 70–80%.[20] The need for handwashing was first recognised by Ignaz Semmelweis and, in the late 19th century, Joseph Lister developed a concept of aseptic surgery in which carbolic acid was used to reduce the microbial contamination of surgical instruments, the operating theatre environment, incision sites and the surroundings.

The systemic use of chemical agents as 'magic bullets' to treat infection was pioneered by Paul Ehrlich at the beginning of the 20th century. Later, the discovery of antibiotics (Alexander Fleming) provided a variety of natural and semi-synthetic antimicrobial agents that were able to limit the growth of specific infectious agents, by targeting a precise intracellular site or pathway. Clinicians began to rely on antibiotics instead of antiseptics for preventing and treating systemic and localised wound infections, due to their rapid mode of action and effectiveness. Additionally, reports of cytotoxicity obtained from animal models[21,22] discouraged use of antiseptics in wound care.

Antibiotics have been used extensively in medicine and agriculture. During the 1950s, antibiotic-resistant bacteria were first reported; more recently, antiseptic-resistant bacteria have been detected. Continual microbial evolution and the spread of resistant strains have led to increased prevalence and emergence of multidrug-resistant strains. This has reduced the efficacy of antimicrobial agents in contemporary practice and the dilemma of managing wound infection effectively in the future must be carefully considered. Although a wide range of antimicrobial products are available for treating wounds, few are without limitations (Table 3-1 and Table 3-2).

Host-pathogen interactions and outcomes in wound healing

Loss of integrity of the skin provides an opportunity for the ingress of microbial cells, and the presence of microorganisms in wounds is not uncommon. The outcome of complex interactions between the

human host and wound bioburden is not readily predictable, but three conditions are recognisable:

1. When conditions within a wound do not favour the multiplication of any of the contaminating microbes present, their persistence is short-term and wound healing may not be affected (contamination)[17]

2. Colonisation occurs when a stable equilibrium is reached by microbes that successfully evade host defences and grow without eliciting a systemic immune responses or overt clinical symptoms.[23] There is evidence that colonisation does not impair wound healing in venous leg ulcers[24]

3. When an imbalance arises because host immunological competence is compromised and/or microbes manifest virulence factors, overt wound infection results and microbial invasion into host tissues leads to cellular damage, immunological responses, and the development of clinical signs and symptoms.[25]

The factors that determine the outcome of host-pathogen interactions are not completely understood,[26,27] and the impact of microbial cells and their products on healing are also not yet fully elucidated. Furthermore, the reasons for the transition of an acute wound to a chronic wound are, at present, only partially explained.

Microbiology

The bacterial diversity in non-healing wounds is high.[28,29] In investigating the bacterial flora by conventional culturing, it was observed that chronic venous leg ulcers harbour *S. aureus* (in 93.5% of the ulcers examined), *Enterococcus faecalis* (71.7%), *Pseudomonas aeruginosa* (52.2%), coagulase-negative staphylococci (45.7%), *Proteus* spp. (41.3%) and anaerobic bacteria (39.1%).[30] Another study of chronic venous leg ulcers found the most common bacteria to be *S. aureus* (65%), *Enterococcus* (62%) and *Pseudomonas* (35%).[31] All of the studies characterising the microbial flora of non-healing wounds agree on the nearly universal presence of *S. aureus*.[31–34] In addition, most studies recovered *P. aeruginosa* in approximately half of the investigated venous leg ulcers and showed that the deep dermal tissues of all non-healing wounds harbour multiple bacterial species.[30,33,35] The organisation and distribution of two bacterial species in the chronic wound bed has been explored in two studies.[35,36] Two specific peptide nucleic acid (PNA) probes for fluorescent *in situ* hybridisation (FISH) analysis, one for *S. aureus* and one for *P. aeruginosa*, in combination with a universal bacterial probe were used in both studies. The observations revealed that both bacteria might be present in the same wound but at distinct locations, and that very few bacteria of different species were observed in close proximity to each other.[31]

In diabetic foot wounds, Gram-positive aerobic cocci were found in 59% of cultures (of which 24% were *S. aureus*), and Gram-negative aerobes were found in 35% of cultures (23% *Enterobacteriaceae*, of which 29% were *Escherichia coli* and 28% were *Proteus mirabilis*). *P. aeruginosa* was present in 8% of all isolates and anaerobes accounted for fewer than 5% of all isolates.[37] Other groups have used molecular techniques, such as 16S sequencing and denaturing gradient gel electrophoresis (DGGE), to elucidate the microbiota of non-healing wounds,[23,38–40] and found more diverse microbial communities, including anaerobic bacteria, in many wounds. In diabetic foot ulcers, De Sotto and coworkers[37] found that taking deep tissue cultures, as opposed to superficial wound swabs, led to a substantial reduction in the number of cultured species, and a reduction in the prevalence of multidrug-resistant organisms and the number of organisms considered mere colonisers. Therefore, it can be concluded that there is substantial evidence for the presence of considerable amounts of bacteria in all types of non-healing wounds.

Traditional culturing techniques are normally used to provide qualitative information on the presence of potential pathogens and their antibiotic sensitivities. However, antimicrobial interventions will be chosen on empirical criteria when patients present with spreading wound infections. Rapid molecular characterisation of wound microbial flora is not routinely available and does not yet provide adequate information on antimicrobial susceptibility.

Biofilms

Until 40 years ago, medical scientists thought bacteria to exist solely as free-living organisms and, as such, were studied in laboratory experiments in shaken cultures. This form is now described as the planktonic phenotype. In the late 1970s, it was realised that bacteria may occur in aggregates in nature and in chronic infections.[41,42] This aggregating process was later termed the biofilm growth phenotype.[43] The planktonic and biofilm growth phenotypes are distinct not only because bacteria in biofilms are sessile, but because they exhibit extreme resistance/tolerance to antibiotics and many other conventional antimicrobial agents, as well as an extreme capacity to evade host defences.[33,34,44–46]

Biofilm in wounds

Biofilm were first associated with healed wounds when they were detected on sutures and staples that had been removed from surgical incision sites.[47] Murine models were used to investigate the ability of staphylococci to form biofilm in acute wounds[48–50] and to delay healing.[51] The first direct evidence of the presence of biofilm in non-healing wounds was based on the microscopic observation of bacterial aggregates.[52–54] The biofilm growth phenotype protects the bacteria from antibiotics and other antimicrobial agents, such as silver, and host defence mechanisms (such as the immune system). The phenotype has been defined as:

> *'A coherent cluster of bacterial cells imbedded in a matrix, which are more tolerant to most antimicrobials and the host defence, than planktonic bacterial cells'.*[55]

This suggests that if the bacteria succeed in forming a biofilm within the wound bed, they will be extremely difficult to eradicate, other than by surgical or mechanical wound debridement. Essentially, biofilm consist of aggregated bacteria in multiple layers. It is not know how many bacterial layers it takes for the aggregate to reach the biofilm-tolerant phenotype. Most of our knowledge 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.[56]

The matrix of the biofilm also plays a role. It is not a bullet-proof physical shell surrounding the bacteria; instead, the matrix components chelate and/or neutralise different antimicrobial agents, whereas others freely penetrate. A secondary effect of many bacterial aggregates is the initiation of cell-to-cell signalling, also termed quorum sensing, which initiates virulence factors and increased antimicrobial and host tolerance.

Resistance and tolerance to antimicrobial interventions

Resistance to an antimicrobial agent can arise by mutation and/or gene acquisition.

Reduced susceptibility of biofilm to antimicrobial agents and host defence mechanisms is correlated to the development of bacterial aggregation and is referred to as 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. Conversely, tolerance enables the cells in biofilm to sustain long-term exposure to the antimicrobial agents without loss of viability.

Biofilm disruption and dispersal experiments suggest that tolerance is readily reversible, whereas resistance due to mutational events is not.[57] The many cell layers in biofilm cause metabolic activity gradients that mediate slower growth rate of the inner part of the biofilm and decrease access to nutrients and oxygen. The matrix of the biofilm also contributes to tolerance, as some of the matrix components, such as extracellular DNA and alginate, are known to chelate antibiotics.[58] Many antibiotics show high levels of antimicrobial activity only on metabolically active bacteria.

Controversies

Host-pathogen interactions and outcomes in wounds

Q Does infection impair wound healing?

Statement

Wound infection may interrupt the wound healing process.

Discussion

Wound healing is normally expected to proceed according to expected timeframes,[59] but can be prolonged by various intrinsic and/or extrinsic factors. At present, there is insufficient information on the way in which either acute or chronic infection impacts the events of healing.

Conclusion

More research into the effects of microbial cells and their products on the cells and components involved in wound repair is indicated.

(For further discussion, look at the influence of bacteria on wound healing below).

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

Statement

Some bacteria have the potential to impair wound healing in the absence of infection, but there is insufficient evidence from a clinical perspective. However, there are *in vitro* data that have shown that some bacteria can impair wound healing.

Discussion

Even though no definite conclusions can be drawn at the moment, a study by James et al.[54] established an elevated presence of microbial aggregates in non-healing wounds compared with acute wounds, using scanning electron microscopy (SEM). In addition, it has been reported that *P. aeruginosa*-infected wounds appear significantly larger in size than wounds that do not contain *P. aeruginosa*.[60–62]

Both cellular and humoral responses take part in the inflammatory process of non-healing wounds.

> Some bacteria have the potential to impair wound healing in the absence of infection, but there is insufficient clinical evidence

Similar to any other infection, polymorphonuclear leucocytes (PMNs; the majority of white blood cells) are detected in high amounts in non-healing wounds, especially when infected with *P. aeruginosa*.[63] But what role does *P. aeruginosa* possibly play? It was demonstrated by Jensen et al.[64] that *P. aeruginosa* biofilms are capable of eliminating human neutrophils by excreted rhamnolipids. Bjarnsholt et al.[52] proposed that this elimination also occurs in infected wounds. The consequences are a chronic inflammatory condition, a continuous influx of neutrophils and an efflux of intracellular degradation enzymes from dead neutrophils, such as reactive oxygen species (ROS) and matrix metalloproteinases (MMPs). *P. aeruginosa* also seems to play a role in the success rate of split-thickness skin grafting, substantiating the negative role of bacteria in wound healing.[65]

In a recent study,[66] the bioburden of 52 non-healing, neuropathic, non-ischaemic, diabetic foot ulcers, without clinical evidence of infection, was investigated. It was found that microbial load, diversity and the presence of potential pathogens was grossly underrepresented by swabs processed by conventional bacterial culture compared with those whose DNA was characterised by sequencing bacterial ribosomal genes. Ulcer depth was positively correlated with abundance of anaerobes and negatively correlated with abundance of *Staphylococcus*. Ulcer duration was positively correlated with bacterial diversity and higher levels of Gram-negative bacteria, but not *Staphylococcus*. Ulcers in patients with poor glycaemic control had higher levels of *Staphylococcus* and *Streptococcus*.

Conclusion

In laboratory studies, it has been shown that some bacteria have the potential to impair wound healing in the absence of infection, but there is insufficient clinical evidence to draw definitive conclusions. Further studies elucidating the precise role of bacteria are urgently needed.

Microbiology

Q Is the number of a specific bacterium per gramme/cm^3 tissue an adequate indicator of infection in all types of wounds?

Statement

We believe that the definition of infection for acute wounds ($\geq 10^5$ bacteria/cm^3 tissue[67]) may not be appropriate for non-healing wounds.

Discussion

A relationship between skin graft survival in animal wounds and the presence of bacteria was demonstrated by Liedburg, Reiss and Artz,[68] and confirmed in humans by Krizek, Robson and Kho.[67] Krizek et al.[67] showed that, on average, 94% of grafts survived when $\leq 10^5$ cfu/g bacteria were present in biopsies and only 19% survived when the count exceeded 10^5 cfu/g. Quantitative bacteriology was performed on wounds undergoing delayed closure and those with $\leq 10^5$ cfu/g bacteria at closure healed successfully, but those with $> 10^5$ cfu/g bacteria did not.[69] Similarly, bacterial numbers were shown to influence infection[70] and the successful closure of pedicled flaps.[71]

In 1969, a rapid means of estimating bacterial numbers using a stained slide prepared immediately from biopsy material was developed.[72] Hence, the 10^5 cfu/g threshold became the generally accepted definition of infection.[73,74] However, multiple sampling of seven decubitus ulcers and two postoperative samples showed the limited value of a single tissue sample;[75] also, estimating bacterial numbers in tissue collected from burn patients failed to distinguish between colonised and infected patients.[76] Therefore, relevance of determining bioburden size in non-healing wounds and the 10^5 guideline has been challenged.[77]

Laboratory protocols for the routine processing of wound swabs usually aim to isolate and identify potentially pathogenic organisms. They do not

normally include the quantitative assessment of bacterial cells, whereas those for biopsies may. However, biopsies are not often employed in the diagnosis of infection. In enumerating bacterial numbers, methods are generally designed to estimate the total viable number of aerobic bacteria, even though no single method can provide suitable laboratory conditions to support the cultivation of all aerobic bacteria. Numbers of a specific bacterium could be reasonably and accurately estimated, but this would not necessarily reflect the total viable count of all bacteria. Moreover, compared with a quantitative molecular technique, conventional bacterial counting gave an underestimate on average of 2.34 log and a maximum difference of more than 6 log.[66] It is important to note that swabs are used to recover bacteria from the wound surface, whereas biopsies sample deeper tissue. Since varying protocols may have been used in different laboratories, comparison of bacterial numbers in different studies is unwise. Furthermore, methods to detect biofilm during the routine processing of clinical specimens derived from wounds are not yet available.

Many different bacterial and fungal species have been identified in non-healing wounds. The quantity of each species may vary and whether small amounts of one bacterium might boost one of the major inhabitants of a wound is not known. From microscopic investigations, we know that the bacteria in non-healing wounds are primarily found in small, local and very heterogeneously distributed biofilm aggregates;[78–80] however, some of these small aggregates elicit a massive neutrophil infiltration and a delay in healing, whereas others do not. This indicates that the number of bacteria per cm^3 tissue may not be relevant, while which species are present may.

Conclusion

There is a need to investigate the relationship between microbial population sizes in non-healing wounds and clinical indicators of infection.

Q-i Should microbial organisms always be eliminated from a wound?

Statement

The causal relationship between the presence of microorganisms in a wound and the progress of wound healing is not entirely understood, but we believe that not all microbial organisms must be eliminated from the wound.

Q-ii Do we know enough to agree on an indication for use of topical antimicrobial intervention from a microbiological perspective?

Statement

Unlike indications for initiating systemic antibiotic therapy for wound infections, indications for initiating topical antimicrobial agents are less well-defined. We believe that it is likely that both indications for systemic and topical antimicrobial agents are equal.

Discussion

The human body is not germ free, but supports a diverse natural flora of microbial species without detriment. Some evidence demonstrates that healing in a sterile wound proceeds at slower rates than in non-sterile wounds. Animal models have been used to explore the effects of bacteria on healing rates. Faster healing in wounds that had been inoculated with staphylococci compared with similar wounds protected from environmental contamination by dressings was reported by Carrel in 1921,[81] and wounds inoculated with either *S. aureus* or *Bacillus subtilis* showed a rapid gain in tensile strength.[82]

Accelerated healing has also been reported in wounds infected with Gram-negative bacteria where the presence of *Proteus* or *E. coli*, or both evoked a greater inflammatory response and increased wound strength due to increased collagen content.[83] Some evidence suggests that this effect was related to inoculum size. Wounds

that received 10^7 cfu or more *E. coli* exhibited signs of infection by gross appearance and higher tensile strength, those with 10^3–10^6 cfu *E. coli* had a high tensile strength but variable signs of infection, and those with 10^2 cfu *E. coli* were weaker than control wounds and without infection.[84]

The involvement of different microbial species in delayed healing has been extensively investigated; however, conflicting evidence linking bioburden to healing progress exists. Although *S. aureus* is commonly isolated from wounds, it has not always been linked to infection.[85] *P. aeruginosa* was associated with enlarged ulcers[61] and enlarged pressure sores,[86] but was not thought to cause delayed healing. This pathogen produces a range of virulence determinants, of which expression is influenced by bacterial numbers via chemical signalling or quorum sensing. For example, rhamnolipids from *P. aeruginosa* impair neutrophil function and impact healing.[52] Incidence of anaerobes and chronic wound infection has been linked,[85] and synergistic relationships between anaerobes and coliforms facilitate infections at low population densities.[87] Hence, determining the number of specific bacteria may be more informative than determining total bacterial numbers in the future.

Longitudinal studies have indicated that the presence of a diverse flora, rather than any particular species, is linked to recalcitrant wounds.[88,89] Since the impact of microbial flora on wounds does not yet seem to be adequately explained, it is difficult to predict how antimicrobial interventions will affect rates of healing. However, it should be cautioned against dismissing the presence of certain combinations of bacteria detected in wounds, such as coliforms and anaerobes, since they can act synergistically to facilitate infection.

A correlation between decreasing bacterial load and the rate of wound healing was demonstrated by Lyman et al. in 1970,[45] and the need to reduce microbial populations to less than 10^6 cfu/ml wound exudate to abolish delayed healing in pressure ulcers was demonstrated.[46]

In a recent retrospective cohort study,[90] it was demonstrated that individualised topical treatment regimens, including topical antibiotic therapy aimed at specific bacterial species identified with molecular diagnostics, resulted in significantly improved healing outcomes compared with either the use of systemic antibiotics indicated by molecular diagnostics or to standard care.

Molecular characterisation of strains of *S. aureus* isolated from diabetic foot ulcers suggested that strains isolated from uninfected ulcers that healed or had a favourable outcome differed from those derived from infected ulcers.[91]

Conclusion

At present, the evidence to show that controlling wound bioburden improves healing outcomes is limited. There is a need to determine the effects of each individual species as well as the effects of combinations of species on healing outcomes.

Q Is the type or virulence of bacteria important?

Statement

Some bacteria are more aggressive than others in causing infection in a wound.

Discussion

Identification of serious pathogens, such as beta-haemolytic (Group A and G) *Streptococcus*, is always of clinical significance in a non-healing wound. However, studies correlating specific bacterial species to wound healing indicate that the presence of *P. aeruginosa* plays an important role in wound healing and the success rate of skin grafting.[65] Additionally, it has been reported that *P. aeruginosa*-infected wounds appear significantly larger in terms of area than wounds that do not contain *P. aeruginosa*.[60–62]

The expression of virulence determinants in bacteria is often influenced by the numbers of individuals present in the population of a species. This is known as quorum sensing and explains why bacteria present in high numbers may be virulent, but the same organism at low numbers is not. It also indicates that enumerating specific bacteria rather than whole communities may be more informative for initiating antimicrobial interventions.

Conclusion

Group A and G beta-haemolytic streptococci are clinically significant in wounds. In some studies and in certain wounds, *P. aeruginosa* seems to play an important role.

Q What is critical colonisation?

Statement

Critical colonisation is a term used to describe wounds that fail to heal due to microbial multiplication, without tissue invasion or an overt host immunological response.

Discussion

The term critical colonisation was first used in 1996 to explain delayed wound healing that was ameliorated by topical antimicrobial treatment.[92,93] It was used to modify the conventional model of wound infection (where contamination, colonisation and infection were distinct outcomes), to explain the wide spectrum of conditions between wound sterility and infection. This model later became known as the wound infection continuum, where increasing bioburden was related to clinical circumstances and critical colonisation was intermediate to colonisation and infection.[94] Hence critical colonisation might be considered to be synonymous with local infection, or covert infection.

Traditionally, indicators of wound infection were considered to be swelling, erythema, pain, increased temperature and loss of function. Additional indicators have been identified,[95,96] but their importance depends on wound type. Sometimes, critical colonisation is defined as $\geq 10^5$ or $\geq 10^6$ organisms per gramme of tissue.[97–99] Mnemonic terms have been suggested to evaluate clinical signs and symptoms that distinguish between critical colonisation and infection;[100] indicators of critical colonisation were a non-healing wound, increased exudation, red friable tissue, the presence of debris and malodour. Indicators of infection were defined as increasing wound size and temperature, ability to probe to bone, new breakdown, oedema, erythema, increased exudation and malodour. In a study to evaluate the ability of these clinical indicators to discriminate between critical colonisation and infection, with respect to bacterial burden according to semi-quantitative swab culture, combining any three signs gave sensitivity and specificity of 73.3% and 80.5% for critical colonisation, and 90% and 69.4% for infection, respectively.[101] While wounds containing debris, friable tissue and exhibiting increased exudate (critically colonised) were found to be five times more likely to yield scant or light bacterial growth, those with elevated temperature (infected) were eight times more likely to give moderate or heavy growth. Thus some indicators had greater weight than others.[101]

In a clinical study, inclusion criteria for patients with chronic venous leg ulcers with signs of critical colonisation stipulated that only one of four clinical signs was required,[102] suggesting that different ways of defining critical colonisation exist. Recently, the extent of critical colonisation in combat wounds was thought to be associated with inflammatory response.[103] One of the important arguments against using the term critical colonisation and against its importance in wound healing is that evidence does not support using systemic antibiotic therapy for

treating clinically uninfected wounds, either to enhance healing or as prophylaxis against clinically overt infection.[34,36] As mentioned earlier, the relationship between high bacterial load and clinical outcome is uncertain.

With this in mind, it does not seem appropriate to use bacterial load, critical colonisation or bioburden as outcomes for studies on topical antimicrobial agents, until further studies clarify how these outcomes should be defined.

Conclusion

At present, a consensus on how to define and identify critical colonisation has not been reached. We believe the term is confusing and needs a stricter definition before it can be used in clinical practice or as an endpoint in research. Further investigation into the relationship between bioburden, inflammatory response and clinical outcome is needed. It does not seem appropriate to use bacterial load, critical colonisation or bioburden as outcomes in studies of topical antimicrobial agents.

Q Is removal of microorganisms from wounds a sufficient endpoint for demonstrating the efficacy of the use of a topical antimicrobial agent in wounds?

Statement

Removal of microorganisms is not a sufficient endpoint for the efficacy of a topical antimicrobial agent. It is not a very good surrogate parameter to demonstrate the clinical significant effect of an antimicrobial product.

Discussion

The efficacy of systemic antimicrobial agents, as well as topical antimicrobial agents, has traditionally been evaluated using a combination of *in vitro* tests, *in vivo* models and clinical studies. Few clinical studies have monitored wounds for the eradication of microorganisms. Clinical studies designed to evaluate topical antimicrobial agents often use infection or time to healing as endpoints, rather than the eradication of microbial species from wounds. As mentioned earlier, many different microbial species have been identified in non-healing wounds. The quantity of each species may vary and whether small amounts of one bacterium might boost one of the major inhabitants of a wound is not known. Microscopic investigations showed that the bacteria in non-healing wounds are primarily found in small biofilm aggregates;[78–80] however, while some of these small aggregates elicit a massive neutrophil infiltration and delay in healing, others do not.[65,104] This might indicate that the number of bacteria may be less relevant than which species are present.

> Removal of microorganisms is not a sufficient endpoint for the efficacy of a topical antimicrobial agent

Conclusion

If an antimicrobial agent is intended to eradicate a specific organism from a wound, then monitoring its persistence during a clinical trial is justified. Otherwise, until the impact of a given species or mixed community on wound healing is understood, monitoring bioburden may not yield meaningful information.

Biofilm

Q Does the presence of a biofilm itself influence wound healing?

Statement

Biofilm may be present in non-healing wounds, but their influence on wound healing in the clinical setting is uncertain. The major issue is the lack of a clinical definition.

Discussion

The first direct evidence of biofilm involvement in non-healing wounds was based on the detection of bacterial aggregates.[52–54] These three publications were preceded by a number of reports suggesting the presence of biofilms in wounds and were followed by articles elaborating on and expanding the observations of biofilm in non-healing wounds.[105,106]

In a previous study,[80] Kirketerp-Møller et al. collected and examined chronic wound samples obtained from 22 different patients, all clinically suspected to be infected by *P. aeruginosa*. Using classic culturing methods, *S. aureus* was detected in the majority of the wounds, whereas *P. aeruginosa* was observed less frequently. In contrast, using PNA FISH, the authors found that a large fraction of the wounds that harboured *P. aeruginosa* aggregated as microcolonies imbedded in a biofilm. These microcolonies were detected inside the wound bed, whereas *S. aureus*, when present, was detected on the surface of the wounds. This finding is supported by other observations,[53] demonstrating that *S. aureus* forms microcolonies encased in an extracellular matrix on the surface of the wound bed.

In one study,[54] a statistically significant association between the presence of microbial aggregates in non-healing wounds compared with acute wounds was established by SEM. However, not all non-healing wounds contain biofilms; thus, the presence of biofilms in non-healing wounds does not by itself account for failure to heal.

Conclusion

Biofilm have been demonstrated to be present in non-healing wounds and seem to interact with the wound bed. However, the clinical influence of biofilm on wound healing is not yet fully elucidated. Evidence that biofilm contribute to chronic inflammation in a wound exists, but how that influences wound healing remains unclear.

Q Is the presence of biofilm in a wound always undesirable?

Statement

The presence of a biofilm in a wound does not always lead to treatment failure and/or delayed healing.

Discussion

Although wound chronicity was associated with the presence of biofilm,[54] not all non-healing wounds can be assumed to contain biofilm. The discovery of biofilm on the intradermal surfaces of closures in healed wounds,[47] for example, demonstrates that the presence of biofilm does not always result in adverse effects in surgical wounds.

Conclusion

It is presently not known whether the effects of biofilm in any wound always lead to problems. No specific indications for treatment of biofilms have been established for non-healing wounds and may have differing outcomes in differing circumstances. This is an emerging area of research.

Q How can bacteria in biofilms be removed from wounds?

Statement

Bacteria in biofilms will be difficult to remove, other than by mechanical or surgical means.

Discussion

It is well established from *in vitro*, *in vivo* and patient

studies that bacteria growing in biofilms are almost impossible to eradicate with antibiotics.[107] On the other hand, bacteria in acute infections that are not in the biofilm mode of growth are still susceptible to appropriate antibiotics. One approach to managing biofilm in non-healing wounds has been suggested, whereby physical removal of the biofilm by sharp debridement is immediately followed by antimicrobial strategies targeted at planktonic bacteria to prevent the re-establishment of the biofilm.[54,108]

Treating non-healing wounds containing biofilm with antibiotics alone is unlikely to lead to bacterial eradication, but could select antibiotic-resistant bacteria. Evasion of immune defence is supported by observations that *P. aeruginosa* biofilms are surrounded by neutrophils, but are not penetrated.[52,63] This is very similar to what has been observed with *in vitro* biofilms overlaid with freshly-isolated human PMNs.[56] There seem to be similarities between patients with cystic fibrosis (CF) and those with a chronic wound. Both patient groups suffer from defects in the primary line of defence. CF patients experience a build-up of thickened mucus that hampers the mechanical process of clearing bacteria. Non-healing wounds consist primarily of granulation tissue composed of a network of collagen fibres, new capillaries, and extracellular matrix together with PMNs, macrophages, and fibroblasts. Embedded in this environment are biofilm, but these are not eradicated by PMNs. The biofilm seem to suppress the activity of the cellular defence system, which might explain the lack of wound healing with the presence of biofilm or vice versa.

Several antimicrobial agents have been shown to inhibit biofilms *in vitro* (Table 3-1). In one model,[109] iodine was shown to be more effective at disrupting mixed biofilms of *Pseudomonas* and *Staphylococcus* than either antibiotics or silver-containing dressings.

The resistance or tolerance to antibiotics and antiseptics, and the evasion of the host's immune system would imply that if bacteria succeed in forming a biofilm in the wound bed, they would be extremely difficult to eradicate other than by surgical or mechanical wound debridement. The re-establishment of a biofilm relies initially on planktonic cells, which may be susceptible to antimicrobial agents; thus, biofilm removal coupled with methods to prevent new biofilm formation may offer a future management strategy.

Conclusion

Bacteria in biofilm are tolerant to antibiotics, some antiseptics and the host immune defence mechanisms; they seem to be most effectively removed by mechanical or surgical means. The re-establishment of a biofilm relies initially on planktonic cells, which may be susceptible to antimicrobial agents, so biofilm removal coupled with methods to prevent new biofilm formation may offer a future management strategy. Additional innovative anti-biofilm agents also need to be found.

Resistance and tolerance to antimicrobial interventions

Q Is there any antimicrobial agent that is not expected to select for resistance or tolerance in bacteria in the wound?

Statement

Eventually, it is likely that resistance will develop against any topical antimicrobial. In experiments, bacteria treated with honey, povidone iodine, octenidine, polyhexanide and chlorhexidine *in vitro* have not been shown to develop resistance. Resistance against silver has been described; however, its consequences and clinical impact is controversial or not known.

Discussion

The more frequently an agent is utilised, the greater the opportunity to select for resistant mutants

and for transmission to susceptible individuals. Resistance to an antimicrobial agent can arise by spontaneous mutation, by chemically or physically induced mutation, and by gene acquisition.

Gene transfer between bacterial species is achieved by three distinct processes: transformation, transduction and conjugation. Resistance determinants are transferred between strains on plasmids, transposons and integrons. Possession of a resistance determinant may go undetected until selection pressure is applied. In the presence of an inhibitor, such as an antibiotic or antiseptic, susceptible microbial cells will be inhibited, leaving resistant strains unaffected and able to flourish without competition.

Antibiotic resistance is well documented.[110] Resistance to some topical agents used in wound care has also been reported (Table 3-1 and Table 3-2) and instances of resistance to both antibiotics and antiseptics are known.[111] At present, most information is obtained from *in vitro* data, which is out of the scope of the present document. However, resistance to bacteria can only be tested *in vitro*.

The interval between the introduction of an antimicrobial agent and the emergence of resistant strains is unpredictable. The likelihood that resistant strains will arise can be estimated in training experiments where cultures are repeatedly subcultured in low concentrations of an inhibitor. To date honey, povidone iodine, octenidine and polyhexaninde (PHMB) failed to select for resistant organisms using this approach (Table 3-3). A caveat to this remark is that these mentioned substances have not been as thoroughly studied as other products, such as chlorhexidine and silver. Resistance against silver has been described; however, its consequences and clinical impact are controversial, or not known. More studies performed to resistance increase the chance that resistance against the substance will be found.

Biofilm disruption and dispersal experiments suggest that tolerance is readily reversible, but resistance due to mutational events is not.[57] Tolerance is correlated to the aggregation of bacteria. The many cell layers in the aggregates cause metabolic activity gradients. This mediates a slower growth rate of the inner part of the biofilm and decreases access to nutrients and oxygen. Many antibiotics show only high levels of antimicrobial properties on bacteria with metabolic activity or bacteria that multiply. The matrix of the biofilms also contributes to tolerance, as some of the matrix components are known to chelate antibiotics such as extracellular DNA and alginate.[49]

Since chronic infections, by definition, last for long periods, the development of genetic and induced resistance also plays a major role in treatment failure. Exposure of microbial cultures to antimicrobial agents increases the selection pressure for resistant variants to grow and multiply.

Conclusion

Resistance to antimicrobial agents seems to be possible with most antimicrobials, even though bacteria treated with honey, povidone iodine, octenidine and polyhexanide in *in vitro* experiments thus far did not develop resistance. The more frequently an agent is used, the greater is the opportunity to select for resistant mutants and for transmission to susceptible individuals. We have to recognise that resistance of wound pathogens against the wide range of antimicrobial agents used in wound care is not routinely measured, either due to lack of available technology or resources. There may come a time when this is necessary and suitable methods will have to be introduced.

Table 3-1. Active bioburden control: Properties of topical antibiotics utilised in wound care

— Not detected + Weak effects ++ Significant effects +++ Severe effects

Clinical use	Antibiotic	Target site/ mode of action	Resistant bacteria isolated and citation	Antibiofilm activity	Local cytotoxicity	Systemic toxic effects	Allergenicity
1948	Bacitracin	Interferes with bacterial cell-wall synthesis	*S. aureus*[112] Beta-haemolytic streptococci (2)[113]	N/A	—	+	+++
1948	Mafenide	Inhibits folic acid biosynthesis	N/A	+	+	++	++
1950s	Polymyxin E (colistin)	Disrupts bacterial cell membranes by binding to phospholipids	*P. aeruginosa*[114] *Acinetobacter baumannii* *Klebsiella* spp.	+	+	++	+
1960s	Neomycin	Inhibits bacterial protein synthesis	*S. aureus*[115] *E. coli*[116] *P. aeruginosa*[117]	N/A	++	++	+++
1967	Silver sulphadiazine	Prevents folic acid biosynthesis	Gram-negative bacilli[118]	N/A	++	+	+++
1971	Gentamicin	Interrupts bacterial protein synthesis by binding to 30s ribosomal subunit	Gram-negative bacilli[119] *S. aureus*[118] High level resistance in enterococci[119]	+	+	+++	+
1985	Mupirocin	Inhibits bacterial protein synthesis and RNA synthesis	*S. aureus*[119]	+	+	—	+
1987	Amphotericin	Disrupts cell membranes	*Candida albicans*[120]	N/A	++	+++	+

Table 3-2. Active bioburden control: Properties of antiseptic agents used in antimicrobial wound dressing

Clinical use	Topical antimicrobial agent	Target site/ mode of action	Resistant bacteria first isolated	Examples of antibiofilm activity	Examples of cytotoxicity (*in vitro* tests)	Examples of systemic toxicity and allergenicity
Antiquity	Silver	Interacts with thiol groups in membrane-bound enzymes and binds to DNA to cause strand breakage	*E. coli*[123] *Enterobacter cloacae*[122] *P. aeruginosa*[123] *A. baumannii*[124]	*P. aeruginosa*[125] 10 multidrug resistant bacteria[126] *P. aeruginosa* and *S. aureus*[109]	Human keratinocytes[127] Monolayers, explants and murine model[128] Human diabetic fibroblasts[129] Murine fibroblasts[130]	Argyria and argyrosis[131]
Antiquity	Honey	Prevents cell division in staphylococci and disrupts outer membranes of *Pseudomonas*	—	*P. aeruginosa*, *S. aureus*[132] MRSA[133]	—	—
1827	Hypochlorite (also known as Eau de Javel, EUSOL, Dakin's solution and bleach)	Superoxidising agent—inhibition of glucose oxidation and DNA replication, depletion of adenine nucleotides, protein denaturation	—	*E. coli*, *S. aureus*[134] MRSA[135] *P. aeruginosa*, *S. aureus*[136] *P. aeruginosa*, *S. aureus*[137]	Rabbit ear chamber[21] Human fibroblasts[22]	Corrosive to skin, depending on concentration (HPA)
1839	Iodine	Oxidation of thiol groups, amino groups, binding to DNA and reduction of fatty acids in membranes	—	—	—	Renal and thyroid dysfunction[138]
1887	Hydrogen peroxide	Forms free radicals, which oxidise thiols groups in proteins and cause breaks in DNA strands	—	*S. epidermidis*[139] *P. aeruginosa*, *S. aureus*[136] *P. aeruginosa*, *S. aureus*[137]	Human fibroblasts[22]	Cardiac arrest due to embolism[140]
1933	Quaternary ammonium compounds (cetrimide, benzalkonium chloride)	Disruption of the bacterial inner membrane	*E. coli*[141] *Serratias marcescens*[142] *P. aeruginosa*[143]	*E. coli*, *S. aureus*[134]	Murine fibroblasts[144] Murine fibroblasts[130]	Possible hypersentitivity[145]

Table 3-2. Active bioburden control: Properties of antiseptic agents used in antimicrobial wound dressing continued

Clinical use	Topical antimicrobial agent	Target site/ mode of action	Resistant bacteria first isolated	Examples of antibiofilm activity	Examples of cytotoxicity (*in vitro* tests)	Examples of systemic toxicity and allergenicity
1954	Chlorhexidine	Disruption of the bacterial inner membrane and coagulation of cytoplasmic components	*Proteus mirabilis*[146] *Pseudomonas* sp.[147] *S. aureus*[148,149]	*E. coli*, *S. aureus*[134] *P. aeruginosa*[150] *P. aeruginosa*, *S. aureus*[137]	Murine fibroblasts[144] Murine fibroblasts[130]	Risk of anaphylactic reaction to chlorhexidine allergy[151]
1956	Povidone iodine	Oxidation of thiol groups, binding to DNA and reduction of fatty acids in membranes	—	*P. aeruginosa*, *S. aureus*[109] *S. epidermidis*[139]	Human fibroblasts[22] Murine fibroblasts[130]	Renal and thyroid dysfunction[138] Allergic reactions[152]
1981	Cadexomer iodine	Oxidation of thiol groups, binding to DNA and reduction of fatty acids in membranes	—	*S. aureus*[153]	Human fibroblasts[154]	Renal and thyroid dysfunction[138]
1984	Octenidine	Disruption of bacterial membranes	—	*P. aeruginosa*, *S. aureus*[155]	Murine fibroblasts[144] Murine fibroblasts[130] Chronic venous leg ulcers[156]	—
1994	Polyhexanide (polyhexamethylene biguanide [PHMB])	Disruption of bacterial membranes by binding to phospholipids	—	*E. coli*, *S. aureus*[134] *P. aeruginosa*[150]	Murine fibroblasts[144] Murine fibroblasts[130]	Hypersensitivity rare, but possible[157]
2005	Slow-release hydrogen peroxide products (based on glucose oxidase and lactoperoxidase)	Forms free radicals, which oxidise thiols groups in proteins and cause breaks in DNA strands	—	*P. aeruginosa*, MRSA[158]	—	—

Table 3-3. Active bioburden control: Antimicrobial agents demonstrated not to select for resistant mutants (listed alphabetically)

Antimicrobial agent	Organisms tested	No. of passages
Chlorhexidine	*S. aureus*[159]	100
Manuka (Leptospermum) honey	*S. aureus, P. aeruginosa*[160] *E. coli, P. aeruginosa, S. aureus*, MRSA[161]	Not stated 28
Octenidine	MRSA[162] *S. aureus*[159]	>13 100
Polyhexanide (polyhexamethylene biguanide [PHMB])	*S. aureus*[159]	100
Povidone iodine	*E. coli, Klebsiella aerogenes, P. aeruginosa, Serratia marcescens*[163] *S. aureus*[159]	20 100
Silver	*S. aureus*[164]	42

Treatment

The purpose of this chapter is to cover the controversies, as they are seen from the perspective of care providers:

Recurrence of infection

- Do we have clinical data that prove that the use of topical antimicrobial treatment prevents/ resolves infection in wounds and non-healing wounds, and/or decreases/increases wound healing rate?
- Does the use of topical antimicrobial treatment in wounds reduce the recurrence of infection?

What type of evidence should we be looking for?

- Should wound dressings and antimicrobial agents be tested only against planktonic bacteria?
- What endpoints do we need to justify the use of topical and local antimicrobial treatments in non-healing wounds?

Infection as endpoint

- Can infection be used as an endpoint in wound healing studies?

Strengths and limitations of the current evidence base

- What are the controversies?
- What are we looking for from these products and are RCTs an adequate way to evaluate them?

Where are we today?

Decisions relating to the antimicrobial treatment of wounds are influenced by clinical evidence, the availability of appropriate antimicrobial interventions, patient need and practitioner expertise. The choice between systemic or local treatment depends on the perception of signs and symptoms of infection, and previous management regimes. In cases of spreading infection, systemic antibiotics are normally selected on an empirical basis. Otherwise, local wound care strategies are chosen and/or prophylactic measures are initiated.

Expert opinion and personal preferences are factors in selecting treatments, but decisions are primarily informed by available evidence. The quantity of published evidence relating to wound care is substantial but conflicting, and high-level evidence derived from meta-analyses and RCTs is limited. A recent analysis of 149 Cochrane systematic reviews assessed the strength of the evidence presented in 44 reviews and demonstrated that few interventions for local and systematic wound care demonstrated strong conclusions regarding effectiveness.[165]

Active/passive control

Strategies to manage the bioburden of wounds can be divided into active and passive processes. Those

antimicrobial interventions that inhibit the growth and division of microbial cells associated with wound tissue exert active control, whereas those that facilitate the removal of material from wounds without necessarily inhibiting the microbial flora can be regarded as passive control.

Active control of bioburden can be achieved by topical antibiotics and antiseptics (Table 3-1 and Table 3-2). Many are employed in the decontamination of wounds colonised by antibiotic-resistant strains. Antiseptics used for skin disinfection or wound cleansing are included in Table 3-2. Inhibitors formulated into antimicrobial agents include cadexomer and povidone iodine, honey, hydrogen peroxide-generating systems, hypochlorite, PHMB, octenidine and silver. Antimicrobial dressings normally act as a barrier either to prevent microbes from gaining access to the wound, or to prevent them from escaping from the wound and contributing to cross-infection. In some dressings, the active antibacterial component migrates into the wound bed, whereas in others it is confined to the dressing. Evidence that effective concentrations of the active components are achieved within the wound is limited.

Passive control of bioburden occurs when microbial cells bind to dressings and are removed from the wound environment when the dressing is changed. This can happen with dressings that incorporate antimicrobial components, as well as dressings without active inhibitors. In the latter case, a device may exploit the net negative charge associated with the surface of the microbial cells or hydrophobic/hydrophilic interactions to establish irreversible binding between the bioburden and the dressing. Examples of these bacteria-removing agents are limited at present. Hydration Response Technology or Dialkylcarbamoylchloride (DACC) has been able to bind and inhibit the growth of bacteria and resistance has not been described.[166]

Features of different categories of antimicrobial agents

The antimicrobial agents used in wound care can generally be divided in antibiotics, antiseptics and disinfectants. As disinfectants are not used on living tissue, and therefore not applied to humans, we will only discuss antibiotics and antiseptics below. The definitions of antibiotics and antiseptics are provided in Table 2-1. While antibiotics are enterally or parenterally administered to patients, and can be transported through the blood or lymphatic system to other parts of the body, antiseptics (and a few antibiotics when applied locally) are confined to topical use locally. In this document, systemic application of antibiotics will not be covered.

Ideally, antimicrobial preparations destined for wound care should possess a broad spectrum of antimicrobial activity, be fast acting and stable, without selecting for resistant strains. Furthermore, these agents should not be cytotoxic to host tissue, induce adverse effects, possess mutagencity, be carcinogenic or prolong wound healing, or be expensive. Mutagenic and carcinogenic agents have no place in wound care, but balancing antimicrobial effectiveness against cytotoxicity is difficult.

Antimicrobial efficacy is evaluated *in vitro*. Although standardised tests to determine minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) by suspension tests have been used for antiseptic solutions,[167] and challenge tests are available for ointments, standardised methods for evaluating wound dressings or biofilms have not yet been established. However, a biocompatibility index was developed to evaluate antiseptic efficacy of planktonic antibacterial activity in relation to cytotoxicity, which divides the concentration at which a 50% solution of murine fibroblasts are damaged by the concentration required to achieve a 3-log reduction of test bacterium within 30 minutes at 37°C. The ideal topical antimicrobial agent

would be one that inhibits a wide range of potential pathogens without exhibiting cytotoxicity.[130]

Topical antibiotics

Guidelines for using antibiotics both therapeutically and prophylactically have been developed,[168–170] but it is apparent that compliance has been less than satisfactory,[171] and the quality of the evidence used to formulate these guidelines may appear weak.[172] In a British hospital, a varied choice of treatment regimens was selected for treating wound infections,[173] demonstrating the difficulties in compliance with the guidelines. Furthermore, it is thought that more than 50% of all medicines are inappropriately prescribed, dispensed or sold, and that half of all patients fail to take them correctly.[174]

It is thought that more than 50% of all medicines are inappropriately prescribed, dispensed or sold, and that half of all patients fail to take them correctly

Resistance to an antimicrobial agent may be an inherent feature of an organism; otherwise, it can be acquired by mutation or gene acquisition. Since antibiotic-producing organisms are widely distributed in nature, it is not surprising that antibiotic resistance determinants have been identified in DNA extracted from 30000-year-old samples of permafrost recovered from the Yukon (Canada).[175] The use of antimicrobial agents removes sensitive strains and allows resistant strains to increase prevalence. A suitable example is mupirocin. In 100 different countries where mupirocin was available, mupirocin-resistant strains were detectable; however, in Norway, where mupirocin was not licensed, mupirocin-resistant *S. aureus* has not been detected.[176] In Brazil, the incidence of mupirocin-resistant MRSA was found to increase over a 5-year period, but was reduced during the next 5 years when the use of mupirocin was restricted.[159,176,177]

Genetic analysis of antibiotic resistance determinants suggests widely differing origins for drug-resistant organisms (MDROs), such as MRSA,[178] and extended spectrum beta-lactamase-producing organisms (ESBLs).[179] Recently, antibiotic-resistant strains with antiseptic-resistance have also been reported,[180,181] and the selection of MDROs by biocides, such as antiseptics, has been recognised.[182,183]

The continued emergence of antibiotic-resistant strains and limited investment by pharmaceutical companies in new antibiotics has curtailed the clinical efficacy of antibiotics.[184,185] Despite increasing awareness of antibiotic resistance, it has been shown that the possibility of contributing to the problem of antibiotic resistance does not influence physicians' attitudes with regard to prescribing patterns,[186] as patient needs are prioritised over broader public-health issues. Although this study investigated the treatment of a hypothetical patient with community-acquired pneumonia, such a conflict will exist in treating many other infections.

The risk of developing side effects, such as allergy and antibiotic resistance, has in some countries, such as Denmark, resulted in recommendations stating that it is contraindicated to use topical antibiotics for treatment of non-healing wounds.[187]

Antiseptics

Antiseptics are used extensively in health care on human tissue, while disinfectants are restricted for the decontamination of environmental surfaces and medical equipment. However, their benefits have not been unchallenged. Concerns about their effects on wound tissue were raised in 1915,[188] and have continued until present. Over the years, cytotoxicity tests have relied on either animal models or the culture of keratinocytes, fibroblasts, lymphocytes, and neutrophils *in vitro*. Two notable preclinical studies discouraged the use of antiseptics in wound care.[21,22] Cytotoxicity has been reported for some of the agents used topically in wounds (Table 3-1 and Table 3-2). Another limitation for some antiseptics and antibiotics is the sensitisation of patients (Table 3-1 and Table 3-2). Sensitisation or allergic reactions could be found with every ingredient and can lead to anaphylactic reactions in extreme cases.[189,190]

The emergence of microbes with reduced susceptibility to antiseptics was first recognised in the 1950s,[191] and is a continuing problem.[149,192,193] While the microbial adaptations that confer antibiotic resistance are well characterised,[194] they are less well understood for antiseptics and generally depend on either restricting access of agents into the cell or actively pumping them out.[193,195–197] The prevalence of organisms with cross-resistance to antibiotics and antiseptics is currently low; however, in order to minimise the risk of prevalence, it is important to monitor the use of antiseptics in the health-care environment.[193,198,199]

Indications for treatment

Prevent Infection

Guidelines on diabetic foot infection rececently published by the International Working Group on the Diabetic Foot (IWGDF) and the Infectious Diseases Society of America (IDSA) discuss how and when to treat diabetic foot infections.[200–204] The limited available evidence does not support use of systemic antibiotics for treating clinically uninfected wounds in the diabetic foot, to either enhance healing or prevent clinical infection.[36,205]

Currently, there is little evidence to support the beliefs of some wound specialists that diabetic foot wounds that lack clinical signs of infection may be 'subclinically' infected. In such subclinical infections, wounds contain a high bioburden of bacteria (usually defined as $\geq 10^5$ organisms per gramme of tissue) that would result in non-healing wounds[34,35] (see Chapter 3). In some cases, when it is difficult to decide whether a chronic wound is clinically infected (such as in case of ischaemia), it may be appropriate to seek secondary signs of infection, such as abnormal colouration, malodour, friable granulation tissue, undermining of the wound edges, unexpected wound pain or tenderness, or failure to show healing progress despite proper treatment.[206] In these unusual cases, a brief, culture-directed course of systemic antibiotic therapy may be appropriate. However, in the strictest sense antibiotic treatment of such wounds should be called treatment of acute infection, not prophylactic treatment or prevention of infection. Additionally, in a systematic review, most patients were on systemic antibiotics.[204]

In another systematic review of wound-care management in diabetic foot wound healing, the use of aminoglycoside-loaded beads as a topical antibiotic on the wound at the time of forefoot amputation was described.[205] In a non-randomised cohort study, the treatment seemed to have a weak but significant effect on the need for later surgical revision. However, little can be drawn from this study, as the apparent effect could have resulted from confounding influences.[207]

To date, there have been several studies of antiseptics, dressing products and wound care management. The above-mentioned systematic review on the use of these products in diabetic foot ulcers was published in early 2012.[208] In it, a large,

good-quality, observer-blinded RCT was identified, which reported no differences between three products with or without topical antiseptic effects in terms of healing by 24 weeks, as well as between a variety of secondary outcome measures, including the incidence of secondary infection.[209] Another large, non-blinded RCT reported no differences between an alginate- and a silver-impregnated dressing in the incidence and velocity of healing, with no significant differences in occurrences of infection between the groups.[210] The results of these large, well-designed trials contradicted the results of a small, earlier study that suggested some benefit of the silver dressing. In a Cochrane database systemic review regarding topical silver for preventing wound infection, it was concluded that there is insufficient evidence to establish whether silver-containing dressings or topical agents promote wound healing or prevent wound infection.[211]

However, a small study on the use of oak bark extract compared with silver sulphadiazine for 6 weeks showed a significant benefit in terms of healing for oak bark extract. Although, the effect on bacteria in the wound and the quality of the study were difficult to assess due to missing details.[212]

Only one controlled clinical study was performed to assess the effects of honey on diabetic foot ulcers.[213] This study, a small, non-blinded study of poor design, reported no differences in healing time between the use of honey and of povidone iodine; antimicrobial features of honey were not specifically assessed in this study.[213]

In summary, there is little evidence to support the use of antibiotic or antiseptic topical treatments to prevent wound infection, particularly in diabetic foot ulcers. In addition, there was little evidence to support the choice of any one dressing or wound application in preference to any other in attempts to promote healing of chronic ulcers of the foot in diabetic patients in this systematic review.[208]

Another systematic review of wound-care management included antimicrobial agents used for non-healing wounds.[214] Thirty studies were evaluated, of which nine concerned the use of systemic antibiotics and 21 topical agents. No evidence to support systemic antibiotics in venous leg ulcers, mixed aetiology wounds, pressure ulcers, pilonidal sinuses or diabetic foot ulcers was found. Conflicting evidence for silver-based products in venous leg ulcers was reported, none of the topical agents examined were effective in preventing infection in pressure sores and the evidence for other topical agents was equivocal. This has been confirmed by Cochrane database systemic reviews.[211,215,216]

In an RCT comparing manuka honey with hydrogel, manuka honey was shown to eradicate MRSA from 70% of chronic venous leg ulcers at 4 weeks compared with 16% in those treated with hydrogel.[217] The potential to prevent infection was thought to be increased by removing MRSA.

The clinical evidence to support the use of topical antimicrobial interventions to prevent infection in pressure leg ulcers is also sparse. One systematic review concerning topical silver[211] identified 26 RCTs (2066 patients) in which silver-containing dressings and topical agents containing silver, compared with non-silver-containing comparators, were evaluated in uninfected wounds. The authors concluded that there was insufficient evidence to demonstrate that either silver-containing dressings or topical agents prevented wound infection or enhanced wound healing. Some weak evidence suggested sustained silver-releasing dressings showed a tendency to reduce the risk of infection in chronic pressure ulcers was reported, but sample sizes were too small for either statistical analysis or formulating conclusions.[218]

The use of honey- and silver-coated bandages improved the outcomes of malignant wounds.[219]

No differences were found between the two regimens, and both types of dressings are recommended for use by patients with malignant wounds containing tumour debris and necrosis.[219]

Resolution of infection

There are a limited number of comparative studies with resolution of infection as an endpoint, predominantly in the diabetic foot. (Please see Table 4-1 for more details, please refer to Appendix 1 for further overview). In the previously mentioned systematic review, 33 studies were identified with controlled studies of (systemic) diabetic foot infections;[203] one publication on the use of a topical antibacterial peptide in combination with oral antibiotics in mildly infected diabetic foot ulcers showed comparable outcomes with fewer side effects.[220] Two small, single-centre RCTs compared topical treatments of superoxidised water with other topical antiseptics in diabetic foot ulcers. Odour reduction, cellulitis and extent of granulation tissue were significantly better in the group of patients treated with superoxidised water than in controls treated with another topical disinfectant.[221] There was an 81% reduction in periwound cellulitis in the intervention group versus 44% reduction in the controls. In patients with post-surgically infected diabetic foot wounds, patients treated with superoxidised water seemed to do better than those treated with iodine, although details of interventions and outcomes were suboptimal and were not in chronic ulcers but in surgical wounds.[222] In another study of topical disinfectants, iodophor application significantly reduced the amount of bacteria in a wound compared with either acrinol or a control group. No outcomes were reported on wound healing, infection occurrence or resolution.[223]

> There is little evidence to support the use of antibiotic or antiseptic topical treatments to prevent wound infection, particularly in diabetic foot ulcers

In 2007, a Cochrane review of the clinical evidence for the efficacy of silver in treating contaminated and infected wounds identified three RCTs (877 patients).[224] No improvement in healing was observed and insufficient evidence to support the use of silver-containing dressings or topical agents in treating contaminated and infected wounds was found. Another systematic review of literature included RCTs and non-randomised studies, identifying 14 pertinent studies (1285 patients).[225] Here, some evidence that silver-releasing dressings had positive effects on infected wounds was found, but the need for further well-designed studies was emphasised. A PHMB-containing dressing was recently shown to reduce bacterial bioburden in infected wounds at 4 weeks compared with the control group treated with a foam comparator.[226]

Strengths and limitations of the current evidence base

The cornerstone of evidence-based practice is the integration of high-quality research evidence into clinical decision making. This evidence is used in combination with clinical judgement and experience to plan the most appropriate patient treatment.[227] Poorly-conducted research will only

yield poor results, which have no place within the clinical arena.[228,229] Laboratory tests—unless for microbial resistance—can only strive to simulate clinical conditions and may not be confirmed by clinical performance. Hence, clinical evidence has greater importance than *in vitro* data. Nevertheless the *in vitro* data are a part of the scientific puzzle to understand the disease and to develop strategies for their therapy.

The chosen outcomes should be clinically relevant and, where possible, measured in an objective fashion. If objectivity is not possible, some control over a subjective assessment is desirable. Blinding assessors to the treatment allocation, for instance, is a powerful tool for reducing measurement bias. Intervention studies of cutaneous non-healing wounds rely heavily on observational data and use outcomes with varying degrees of reproducibility that usually focus on the condition of the wound.

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 (surrogate outcome parameters) that relate to both the wound condition and the treatment intervention being assessed (for example, exudation rate, pain, granulation rate, resolution of necrosis or infection).

However, tests that use physiological changes and molecular biology to assess wound healing are still not widely used in the clinical setting.

The challenge, especially with regard to non-healing wounds, is that subjective endpoints are difficult to achieve and maintain. If the only gold standard were total wound closure, no therapy would ever be considered efficacious. Conversely, if a non-specific endpoint is chosen, any positive findings may not translate into a clear clinical benefit at the bedside. Therefore, the primary outcome measure selected for any wound study should be appropriate to the intended purpose of the intervention. For this reason, it is important that the study protocol clearly defines the primary intention of wound treatment/intervention and provide a rationale for the outcome measures selected to assess this aim.

To assess how outcome parameters with regard to antimicrobial treatment and wounds are used, defined and evaluated, a literature search on chronic/problem wounds/ulcers was performed, with the objective of examining and registering their use of endpoints, the quality of their endpoint definitions and the robustness of their methodologies from perspective of the EWMA Patient Outcomes Group (POG) document. The search criteria were limited further and included comparative studies and RCTs published from 2003 to September 2009. The primary objective of the analysis was to identify outcome parameters used as primary and secondary endpoints, and to examine how these were defined.

The search was then completed with an additional search for studies published 2009–2011. Additional articles were also identified from Cochrane and systematic reviews published 2008–2012 with regard to RCTs of wounds treated with antimicrobials or with an aim to prevent infection in wounds with a focus on non-healing ulcers. After evaluation of abstracts, these articles were selected for analysis.

All articles were reviewed with the primary objective of examining which outcomes were used as the primary or secondary endpoint(s) of the study.

The analysis identified 66 studies (24 in leg ulcers, 18 in diabetic foot ulcers, four in pressure ulcers, four in burns, and the remaining in mixed ulcers and other wounds), of which five included systemic antibiotic treatment and four focused on prevention of infection as endpoints.

The remaining studies were RCTs with topical antimicrobial agents (n=47) with a total of 89 presented endpoints. In 17 of these studies, a primary endpoint was predefined.

The endpoints were divided into categories and number of studies. As shown in Table 4-1, the most commonly-used endpoints were changes in wound condition, reduction rate and wound closure. A substantial number of endpoints were either not predefined or insufficiently defined. Seventeen studies had either 'resolution of infection' (n=11) or 'prevention of infection' (n=6) as the given endpoint, without giving further operational definitions of infection. In studies, involving antimicrobial agents, in which the endpoint could be considered as predefined, only four of these were studies involving infection, or resolution or control of infection.

A major problem with regard to the clinical evaluation of the use of antimicrobials in the treatment of wounds is the lack of consensus on the classification of infection, the definition of a wound with an infection and the resolution of infection. The most frequent definition with regard to resolution of infection in studies was 'at the discretion of the physician.'

Different classification systems have been suggested for clinical infections, primarily relating to acute

Table 4-1. Endpoints in comparative clinical studies of antimicrobial agents in non-healing wounds (for more details, please refer to Appendix 1)

Endpoints	Total no. of studies	Leg ulcers	Diabetic foot ulcers	Malignant fungating wounds	Pressure ulcers	Burns	Mixed ulcers	Other
Rate of reduction	15	5	2	1	1	—	4	2
Signs of infection	15	2	8	—	2	—	3	—
Healing time	11	4	4	—	1	2	—	—
Biomarkers and bacteriology	9	3	1	—	—	1	4	—
Dressing performance	4	3	—	—	—	1	—	—
Wound closure	4	3	1	—	—	—	—	—
Symptoms, signs	3	2	1	—	—	—	—	—
Change in wound condition	2	1	—	—	—	—	1	—
Costs and resources used	2	1	1	—	—	—	—	—

skin infection, acute surgical infection and chronic diabetic foot infections. Until recently, there was no widely accepted method for classifying the severity of infection; however, two classifications have now been designed to assess the severity of diabetic foot ulcer infections. They were developed by the IWGDF and the IDSA, and have been evaluated and suggested to be useful tools for grading foot infections and predicting clinical outcomes.

There is much controversy concerning how infection should be measured—should it be by examination of clinical signs, by microbiology, by laboratory parameters indicating inflammation, or by a combination of these parameters? Infection in wound management can be evaluated in different ways, focusing on the possibility of prevention, its resolution and/or the time to resolution. Some composite measures have been suggested to overcome the variability that occurs when different clinicians are involved. In the present analysis, infection (resolution of infection or infection episodes) was an endpoint in 19% (n=17) of the endpoints in the comparative studies. Five of these studies were in subjects with acute superficial skin infections treated with systemic antibiotics, four studies were in subjects with burns and a substantial number were performed on patients with so-called mixed ulcers. It must be recognised that most of the available data on infection relate to acute skin infections; the use of systemic antibiotics and outcomes are frequently not predefined. A major conclusion is that there are a limited number of comparative studies with regard to antimicrobials in non-healing wounds and that these studies frequently lack adequately predefined or evaluated endpoints, also with regard to infection.

The limitations of adequately predefined endpoints in these studies are a major barrier for evaluating the importance of various strategies, such as antimicrobials. The most important endpoints should be prevention of infection, resolution of infection, wound healing, wound healing time or time for resolution of an infection. To be able to properly evaluate the value of antimicrobials in wounds, we need a new set of tools and endpoints for these studies, which are clearly illustrated by the enclosed evaluation of endpoints in the presented studies. Better infection measurement could have significant impact on study participants in terms of being exposed to more invasive procedures and wounding, such as biopsies. The benefits/risks need to be carefully weighted.

Controversies

Recurrence of infection

Q Do we have clinical data that prove that the use of topical antimicrobial treatments prevents reinfection in non-healing wounds?

Statement

There are no clinical data to support that the use of topical antibiotic or antiseptic treatments can prevent recurrence of infection.

Discussion

To our knowledge, there are no clinical data to support that the use of antiseptic treatments can prevent recurrence of infection. The few studies on the prevention of recurrence that have been performed investigated systemic antibiotics. Possible endpoints that can be used in studies of prevention of recurrence are identical to the ones used for prevention.

Conclusion

There are no clinical data to support that the use of topical antibiotic or antiseptic treatments can prevent recurrence of infection.

What type of evidence should we be looking for?

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

Statement

We think that if biofilms impact wound healing, antimicrobial treatments should be tested against biofilms.

Discussion

It could be argued that the reason 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.

With the knowledge that bacteria may be present in biofilm in non-healing wounds, dressings and antimicrobial agents should be tested for their efficacy against biofilm using appropriate test models. Most important is to culture the bacteria in the biofilm. Several *in vitro* model systems have been developed during the last decades, both for high-throughput screening and in-depth investigations. For high-throughput screening, static microtitre plate assays,[230] or the Calgary Biofilm Device,[231] in which 96 (or more) pegs fit into microtitre plates, are the most common. These assays can be used to test for biomass accumulation by staining the biomass using crystal violet. Crystal violet staining on the other hand does not discriminate between live and dead bacteria. To test whether the bacteria are being killed in these assays, the bacteria must be cultivated to determine the number of viable cells.

For more in-depth investigations, a continuous flow-cell system,[232] colony biofilms,[233] drip flow reactors,[234] or the rotating disk reactors[235] can be used. Regrettably, these models are only used in experimental laboratories. No methods for susceptibility testing of biofilms are currently available for clinical microbiology. Few antibiotics are efficient in killing bacteria in biofilms, making susceptibility testing not a valid option at the moment. However, in the future it will be important as new drugs are developed.

For all the methods, it must be emphasised that the bacteria need to adapt to the biofilm phenotype. For aerobic bacteria, approximately 12 hours are required for a young semi-tolerant biofilm to develop, but 24–36 hours are needed for a fully mature and tolerant biofilm to develop

As for any drugs, further testing in appropriate animal biofilm models are needed.[236]

Conclusion

It is logical to test for antimicrobial effects on cells in a biofilm, as well as cells in the planktonic phase. Several methods exist to test for susceptibility of biofilm phenotypic bacteria. However, few antibiotics and disinfectants efficiently kill bacteria in mature biofilms at present and biofilm susceptibility testing is not yet available for clinical purposes.

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

Statement

We think that, to justify the use of topical and local antimicrobial treatments in non-healing wounds, the endpoints should primarily be either prevention of infection or 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.

Discussion

To justify the use of topical antimicrobial treatments in non-healing wounds, the endpoints should primarily be either prevention of infection or resolution of infection. As infection should be defined clinically and the number of bacteria in wounds has no clear relation with infection (Chapter 3), the use of bacterial quantification (such as 'reduction of bioburden') or sterility to

> There are no clinical data to support that the use of topical antibiotic or antiseptic treatments can prevent recurrence of infection

define resolution of infection is not desirable. The use of increased healing rate or shorter healing time as a primary endpoint is also valid, but the study must then be adequately designed so the correlation between the antimicrobial intervention and outcome can be validated.

Many writers discuss what is termed the hierarchy (or pyramid) of evidence.[237] Systematic reviews and meta-analyses are at the top of the hierarchy because pooling of good-quality studies, using similar methodologies, on similar cohorts of patients, gives greater weight of evidence either for or against an intervention, compared with the interpretation of the outcomes of one study alone. However, where few studies pertaining to a particular aspect of clinical care exist, RCTs with definitive results are next on the pyramid,[237] followed by RCTs with non-definitive results, cohort studies and case reports.[237] In order to place trial evidence on the correct rung of the hierarchy ladder, it must be appraised for the relative merits of results achieved. Fundamentally, individuals conducting critical appraisal ask whether the study findings can be believed.[228]

Level 1A evidence is preferred, but if not available, we will use other evidence levels.

Conclusion

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

Infection as endpoint

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

Statement

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

Discussion

Clinical infection of a wound leads to non-healing wounds, increased treatment times, higher expenses, increased suffering, and risk of severe complications. For this reason, 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, epithelialisation, quality of life, and wound environment are all to some extent dependent on the presence of infection.

The critical point is how infection should be evaluated. Should clinical signs, bacterial load or laboratory parameters (for example, leukocytosis, C-reactive protein [CRP] or erythrocyte sedimentation rate) define presence of infection?

There have been few published papers on infection as an endpoint. Resolution of infection has been used as an endpoint in comparative studies at the

discretion of the physician and sometimes supported by a scoring system. Those studies where infection has been used as an endpoint may not have defined it adequately (if at all) and it has frequently been defined as 'at the discretion of the physician.'

A few studies have used a scoring system. Since infection is a clinical diagnosis, it would make sense to use a clinical scoring system to define infection. Several scoring systems have been used in the past. Examples of classifications are the Meggit-Wagner, PEDIS and IDSA, SAD/SAD and SINBAD, and UT systems. All were originally diabetic foot ulcer classifications and therefore include typical diabetic foot ulcer outcome indicators, such as neuropathy and arterial disease. Other schemes were specifically developed as wound scores. Examples of these are the USC,[238] the DUSS and MAID, and the DFI.[239–242] The IDSA and the IWGDF classification system might be most suitable to describe infection and can also be used to guide therapy. The Meggit-Wagner and SINBAD classifications are not useful to describe infection, as they provide a dichotomous description of infection without further definitions of infection. The UT classification uses a dichotomous description for infection, but infection is better defined in stages and there is evidence that the system adequately predicts outcome. The PEDIS, IDSA, and S(AD)/SAD provide a semi-quantitative, four-point scale to describe infection and may better predict outcomes of diabetic foot infections. The Ulcer Severity Index is complex and there are no data available on the predictive qualities for infection. The DUSS and DFI are less complex and provide wounds scores that have been successfully tested in large clinical trials. 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. In clinical trials, an externally blinded evaluation of the wound is preferable to eliminate investigator bias.

Conclusion

Wound infection is a valid primary, but most often secondary, endpoint. It should be recognised by clinical signs and may be supported by laboratory parameters. Decisions on a local or systemic treatment, or a combination of these, must follow the diagnosis of infection. In clinical trials, an externally blinded evaluation of the wound is preferable to eliminate investigator bias.

Strengths and limitations of the current evidence base

Q What are the controversies with regard to the methodology of studies providing evidence for topical antimicrobial treatment?

Statement

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

Discussion

There is much debate within the published literature and media alike pertaining to the use of antimicrobial agents in wound management. At the essence of these arguments are issues of efficacy, efficiency and value for money.[243] In other words, do the products do what they are supposed to do and, in doing so, are they safe and cost effective? Practicing clinicians are continuously challenged to provide high-quality care with limited resources. However, the ability to manage increasing demands on the health service is greatly influenced by the available resources.[244] It is unlikely that there will ever be sufficient revenue to meet all health-care challenges; therefore, prevention of unnecessary health-related complications is more important than ever.[245] Inherent in this aspiration is the need for clinicians to adopt the concept of evidence-based practice into daily care delivery.[246]

The generation of new evidence in the wound healing and tissue repair field is fraught with

challenges. RCTs are considered the gold standard for conducting clinical trials and are one of the most powerful tools in research today.[247] The argument prevails that the way in which evidence is generated in wound care remains challenging because of difficulties in achieving all of the quality markers of the RCT.[248] As a result of issues such as inadequate sample sizes, non-blinded outcome assessment, inadequate follow up and lack of clear descriptions of interventions, wound-care research often falls short of expectations.[249] Therefore, Gottrup[248] argues that the foundation of the problem lies in the lack of agreement regarding the conduct of research in wound management. Furthermore, Gottrup[248] argues that the time has arrived for the development of consensus on what parameters/outcomes are the most important to explore in order to have acceptable evidence.

The increasing prevalence of chronic, non-healing wounds, combined with the fears regarding antibiotic resistance,[29] has meant that clinicians are continuously seeking alternate methods of treating these wounds.[243,250] However, in doing this, there is the uncertainty regarding the evidence base to support or refute use of antimicrobial agents for the management of infection and bacterial burden.[215,224,251–253] For clinicians, this makes funding and subsequent availability of the different treatment options, challenging.[254] The Cochrane Collaboration is explicit in the type of evidence eligible for inclusion in their reviews of interventions.[255] RCTs are the main studies, although controlled clinical trials and cluster trials are commonly included.[255] As such, the Cochrane reviewers do not propose that they are summarising all of the evidence available, rather are focussing on a particular type of evidence.[255] The choice of the type of evidence to include relates to the desire to reduce the margin for bias, thereby increasing the believability of the results.[255] As discussed previously, a major limitation is the lack of evidence of efficacy, as there are limited trials available.[256] It is important to highlight that lack of evidence of efficacy is not the same as evidence of inefficacy and those who interpret the findings as such, are very much misguided.

Conclusion

Practitioners are challenged by the lack of clear evidence to support the use of many topical antimicrobial products used in clinical practice. Lack of evidence of efficacy is not the same as evidence of inefficacy, and often the foundation of the problem lies in the lack of agreement regarding the conduct of research in wound management. The time has arrived for the development of consensus on what parameters are the most important to explore, in order to have an acceptable evidence base for practice.

Q What are we looking for from these products and are RCTs an adequate way to evaluate?

Statement

We believe that, for certain approval processes, an RCT is the appropriate way to compare between products. However, because clinicians need to know how the products will work on their cohort of patients, other types of study designs may also be relevant. Due to the healthy selection bias in all RCTs, there is an additional need for larger cohort or data collection studies to understand how a product acts or work in an unselected population. Therefore, there is an urgent need for larger cohort studies from which natural outcomes, as well as criteria for future endpoint parameters, could be defined and evaluated.

Discussion

It is in recognising the limitations of the evidence base that Jadad and Haynes[257] highlighted the importance of considering the wider context of evidence-based practice. They argue that much of the advances in health care knowledge of the past decades has not arisen due to intervention studies

with large outcomes, but rather has arisen from the accumulation of many smaller scale studies.[257] This is very much in keeping with the arguments of EWMA, where they have always stressed the important role of controlled trials, cohort studies and case reviews in contributing to our understanding of how interventions impact on clinical outcomes.[15]

Clearly, for the practicing clinicians, all of this information is relevant as it reflects more accurately the cohort of patients they encounter on a daily basis.[258] The external validity of the studies therefore becomes increasingly important.[259] Thus, Gottrup et al.[15] argue that the essential issue is to develop a consistent and reproducible approach to define, evaluate and measure appropriate and adequate outcomes in RCTs, as well as other clinical studies, such as cohort studies, comparison studies of treatment regimens with registry data and real-life studies. Furthermore, the recommendation is that the particular properties (such as substance, total content of substance release kinetics etc, and how that matters for the wound bioburden) of a wound dressing and its reasons for use should guide the outcome measure of choice for evaluation purposes, as well as the development and certification/reimbursement process.[15] It is clear from these recommendations that this is the direction needed for the further development of our understanding of the role of antimicrobial agents in wound management.

> The time has arrived for the development of consensus on what parameters are the most important to explore, in order to have an acceptable evidence base for practice

Conclusion

In generating an evidence base pertaining to antimicrobial products, it is important to consider both the internal and external validity of the study design. The essential issue is to develop a consistent and reproducible approach to define, evaluate and measure appropriate and adequate outcomes, which are clinically relevant. It is in this way that the drive for an evidence-based practice can be enhanced.

Patients' perspective

This chapter will cover the controversies as they are seen from the patients' perspective. Below are listed the controversies discussed in this chapter.

Meeting the clinical needs of patients

- Q Does the lack of appropriate attention to the clinical needs of the patient lead to an increased risk of bioburden?

Patient safety as it applies to wounds

- Q Is the link between inappropriate management of individuals with wounds and patient safety clearly appreciated?
- Q How do we secure patient safety?

Patient involvement

- Q How is the patient integrated in the treatment?

Where are we today?

Meeting the clinical needs of patients

The UN Committee on Economic, Social, and Cultural Rights argues that the right to health contains four elements: availability, accessibility, acceptability, and quality.[260] For individuals with non-healing wounds, the right to health means that they should expect to have access to treatments that are timely, appropriate, patient centred and of the highest quality. The EU report on the rising threat of antibiotic resistance stresses that, in order to maintain efficiency, they should only be used when strictly necessary; thus, in wound management, the availability of alternate therapies is seen as being increasingly important.[7,261] Thus, in dealing with wounds with a problematic bio-burden, accurate and on-going assessment is central in ensuring that the clinical needs of the patient are identified, and appropriate interventions are employed. Furthermore, the planning of care should be cognisant of the ethical and cultural principles of care and, as such, including the patient, where possible, in all decision making is central to success.

Patient safety

The concept of patient safety as it applies to wounds

Over the past years, changes in the traditional role of the heath professional, increased patient empowerment, greater demand for safety in the delivery of high-quality health care and an increased awareness of the incidence of adverse clinical events, have stimulated a growing interest in patient safety.[262] Therefore, the concept of patient safety has become a key issue in the provision of health care today.[263] At its essence, patient safety aims to ensure prevention of errors and adverse effects to patients associated with health care.[264] Further, WHO[265] argues that

challenges to achieving safe patient care do not necessarily relate to individual practitioners, but rather are associated with failing processes and weak systems. Thus, they emphasise the important role of education and training, integrated standards of care, communication and team work in achieving a robust patient safety culture within health-care services.[265]

The increasing prevalence and incidence of nosocomial wounds is closely linked with quality of care and, as such, these rising figures reduce society's confidence in the health service's ability to deliver care that is timely, appropriate and effective.[266] The OECD Health Care Quality Indicators (HCQI) Project[267] includes hospital-acquired pressure ulcers and surgical site infection rates as a key quality measures for international benchmarking of medical care at the health-system level. From a health care delivery perspective, 25–50% of acute hospital beds are occupied by patients with a wound, with up to 60% of these representing non-healing wounds (infected surgical wounds, pressure ulcers, leg/foot ulcers).[4] It is argued that surgical site infections (SSIs) account for 17% of all nosocomial infections.[268] Furthermore, European figures suggest that the mean length of extended hospital stay attributable to SSIs is 9.8 days, at an average cost per day of €325.[269]

Over treatment

With the emergence of antibiotic-resistant strains of bacteria, the need for topical antimicrobial agents that effectively manage wound infection becomes increasingly more clinically relevant. In keeping with the patient safety agenda, use of antimicrobial products should be underpinned by a clear understanding of how these products work, including their relative indications and contraindications. In the absence of such an understanding, the safety of the patient may be compromised. Systematic patient and wound assessment are central to providing the information needed to plan effective management strategies; however, therein is the challenge. While the recognition of overt wound infection is often relatively easy, some wounds do not necessarily display very distinctive characteristics, making assessment challenging. This in itself poses a problem for the practicing clinician in balancing the desire to make the right choice of topical wound treatment with the risk of unnecessary use of an antimicrobial product. Fletcher[270] argues that clinicians may overuse antimicrobials in an attempt to manage bioburden; however, in doing so, they may not actually be clear whether the wound had a problematic bioburden or not. Other authors have also suggested that clinicians should currently use topical antiseptics only selectively for a short duration, since there is little information on systemic absorption of antiseptic agents, evidence of clinical efficacy is meagre and we need information on development on resistance.[243]

The impact of wound infection on quality of life

It is accepted that wound infection causes pain,[271] odour[272–274] and production of exudate.[275] These wound-related symptoms have a big impact on patients and families. For most, the wound becomes the centre of their lives. They must adjust and dispense their activities of daily living to the needs of the wound. Due to wound infection, some patients report a lack of movement and an increased dependence.

The effect of pain on lifestyle is devastating and, as it is a complex phenomenon, has a serious impact on the quality of life of patients.[276] In the literature it is widely understood that wound infection causes pain. Furthermore, it is recognised that there is an association between pain and stress. This stress may intrude with healing. Through a Delphi study of 21 wound experts, Cutting and colleagues investigated whether there was a causal relationship between wound infection and the onset of, or a change in, the nature of pain.[277] The authors claim that patients with a wound infection generally experience more pain than those with non-infected wounds.[277]

Wound exudate due to an infection is another symptom that has an impact on the quality of life of patients and their families. It is reported that patients express that they are distressed about the leaking from the wound and that they are concerned that this might be obvious to others, especially if the exudate is extruding through the clothes.[275] Most patients express concerns that there is uncertainty whether the dressing is applied correctly, due to the constant leaking.

This means that there is a stressful demand of frequent clothes washing, which could lead to patients cutting themselves off socially. Management of a leaking wound necessitates frequent dressing changes, and there is an increasing risk of maceration and malodour that may not be eliminated in an effective way.[272,278,279]

Wound odour is identified in most research as one of the symptoms that causes the most distress to patients, families and health professionals. Wound infection related odour is one of the most difficult symptoms to treat.[208] It has been recorded in the literature that odour is a very distressing factor in wound management, as most patients with a wound experience mental anguish.[281] It is a subjective issue that depends on many variables, such as the patient's ability to perceive odour.[274] The problem with wound odour is that it is difficult to hide, as the management possibilities are limited.[275]

Gethin et al.[217] demonstrated in their study that antimicrobials were not the most frequently-used dressings in managing malodour in wounds. However, the results demonstrate that professionals ranked antimicrobials highest in terms of levels of efficacy for odour management. The results demonstrate that in clinical practice, there is an interesting disparity between what is used and what is considered effective. One reason for this might be that there is little literature that addresses patient safety and antimicrobials. The

> In clinical practice, there is an disparity between what is used and what is considered effective

available literature is mostly of qualitative nature and deals with the experiences of patients or the perspectives of clinicians.

In conclusion, evidence in this area is not strong and more research is needed to support clinicians' decision making when and how to use antimicrobials in the context of patient safety.

Controversies

Patient safety

The concept of patient safety as it applies to wounds

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

Statement

Often, the relationship between wound infection and patient safety is not clearly appreciated; however, from an EU perspective, the effective prevention and management of infected wounds is closely linked to patient safety.

Discussion

The increasing prevalence and incidence of health care-acquired wounds are closely linked with quality of care and, as such, these rising

figures reduce society's confidence in the health service's ability to deliver care that is timely, appropriate and effective.[266] These infections are associated with substantial morbidity, mortality and excessive health-care costs.[282] In response, the OECD HCQI Project[267] includes hospital-acquired infection and, more specifically, SSI rates as key quality measures for the international benchmarking of medical care at the health-system level. Thus, the effective prevention and management of infected wounds are closely linked to quality of care, with the rational use of antibiotics and focused use of antimicrobial agents having an important capacity to positively influence clinical outcomes.

Avoidance of unnecessary side effects of treatments employed, such as anaphylaxis or cytotoxicity, is also a central concern.[283] Overall, the lack of focused attention on the judicious use of antimicrobial treatments is accelerating the emergence of drug-resistant organisms, primarily through the improper use of antimicrobials, all of which have a significant impact on the potential for delivery of safe, effective patient care.[261]

Conclusion

Prevention and management of infected wounds is closely linked to quality of care and patient safety. Focused use of antimicrobial agents is an important consideration in the drive for enhanced clinical outcomes.

Insufficient treatment

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

Statement

Lack of adherence to agreed standards of care for the prevention and management of infection impacts negatively on clinical outcomes and the achievement of patient safety initiatives.

Discussion

The decision to use a topical antimicrobial agent should be based on the clinical needs of the patient.[284] It is here that the concepts of health and social gain importance, as fundamentally all clinical decision making has an effect on the individual, the health service and, in the long term, society as a whole.[282] However, it is important to note that failure to address the specific symptoms experienced by the individual with an infected wound can cause them to become non-concordant with treatment strategies, thereby worsening clinical outcomes and increasing the risk of further complications associated with infection.[286]

It is evident from the literature that the incidence of infection in both surgical wounds and wounds in general is closely linked to quality of care and patient safety.[287] More worrisome, however, is the impact of SSI on the individual. Indeed, those with SSI display significantly lower scores on the Medical Outcomes Study 12-Item Short-Form Health Survey (SF-12) post-surgery ($p=0.004$).[268] They also have far greater opportunity costs in terms of requirements for outpatient visits, emergency room visits, readmissions and home-care services than their matched counterparts.[268] Although this data relates to acute wounds, and the current document is focussing mainly on non-healing wounds, it is important to mention SSI because any infected wound could potentially become a chronic wound, if the infection is not managed appropriately.

Therefore, central to the achievement of standards that potentiate clinical outcomes matched with patient safety initiatives is the correct assessment and management of wounds and their associated problems.[288] Inherent in this goal are the appropriate use of antimicrobial products and the judicious use of antibiotic therapy.[283] Insufficient treatment of wound infection compromises the health and well-being of the individual, increasing morbidity and

mortality. Furthermore, poor treatment strategies can compromise the effective use of the increasingly limited number of existing antimicrobials.[261]

Conclusion

Accurate and on-going assessment of infected wounds is the key to identifying the correct treatment pathway. Failure to provide appropriate care pathways for those with infected wounds compounds the burden on the individual and society as a whole.

Over treatment

Q Is the risk of over treatment and its potential contribution to the development of resistance clearly appreciated?

Statement

Overuse of antimicrobials has a negative impact on health and social gain, and on the availability of effective treatments in the future.

Discussion

At the essence of choosing an antimicrobial product is the knowledge that the patient can benefit from such a treatment plan; if the decision to use antimicrobials is based on guesswork rather than on objective criteria, the balance between effectiveness and efficiency can never be achieved.[289] Not only is this clinically unhelpful, it also contributes to increasing the economic burden of wound care, which, in the long term, has an impact on product availability.[290] Indeed, today more than ever before, a fine balance between revenue and expenditure must be achieved.[291]

Despite the increasing awareness of the importance of judicious use of antibiotic therapy, Gurgen[292] identified that in one primary care setting, 57% of all patients with wounds received antibiotics and 13% received more than one course of treatment. Worryingly, Gurgen argues that such interventions do not appear to be related to the wound presentation and thus concluded that there is an overuse of antibiotic therapy within certain clinical settings. Such findings are not unique; indeed, the Committee on the Environment, Public Health and Food Safety clearly articulated how inappropriate prescription of antimicrobial agents by physicians is a major source of overuse and this, in turn, contributes to the rising prevalence of resistance.[261] Also of importance is the pressure placed by patients on physicians to prescribe antimicrobials, particularly antibiotics. This is a confounding factor that also must be addressed.[261] Thus, the importance of education for both patients and clinicians alike on the appropriate use of antimicrobials is seen as being fundamental in combating the overuse of these therapies. Such strategies are clearly of importance to drive home the link between overuse and the risk of resistance, which is a real, increasing public-health threat.[93,261]

Conclusion

Inappropriate prescription of antimicrobials (particularly antibiotics) by physicians is a major source of overuse, which contributes to the rising prevalence of resistance. Education of both patients and health professionals is essential in driving forward the agenda for change where appropriate use of antimicrobial agents is the key to successful outcomes.

Patient involvement

Q Are patients considered equal partners in planning wound care interventions?

Statement

The patient stays are at the centre of all clinical decision making. This is two-sided; it is best for the patient and relies on knowledge.

Discussion

Patient needs in chronic wound care often continue over months, years or even a lifetime. Therefore, planning wound care requires

empowering patients and their families by involving them in decision making and ensuring that they are happy with the care they receive. Probst and colleagues[275] demonstrated how patients and their families receive little support and practical information from health professionals. Other literature demonstrated that health professionals need to include patients and their families in their care by providing information and advising them on how to manage a wound, where to source dressings and how to choose the appropriate dressing, and how to cope with wound-related symptoms.[275]

In some countries, antibiotics are bought over the counter, which puts the patient in control of their own treatment. Some patients can persuade the physician to prescribe antibiotics; therefore, if physicians are handing out more antibiotics, it shows how power and authority has drifted away from the physician. Once the patient would simply ask the doctor's advice and then follow it obediently, now the consultation might be seen as a roughly equal exchange. This means that the physician is no longer the only 'expert' in the consulting room, since the patient may very well come armed with detailed, even if half-digested, information gleaned from the internet.

> Overuse of antimicrobials has a negative impact on health and social gain, and on the availability of effective treatments in the future

The patients usually believe that antibiotics are needed if impaired or sick, even if they have a viral illness. Empowerment, in the form of involvement and education of patients and their families as partners in the care process, eases, among other things, proactive health care-seeking behaviours.[293] Empowerment means different things to different people. It assumes that health professionals treat patients and their families as equals, listen to their concerns, and invite and encourage them to be involved in decision-making processes, according to their own capabilities. In addition, patients and their families should show confidence in their ability to take co-responsibility for their daily management. It also demands that health professionals ensure access for patients to ongoing education and self-management support from all relevant disciplines.[294] This can be done through demonstrating the purpose of using antibiotics or antimicrobials.

Conclusion

If a reduction in use of antibiotics/antimicrobials is to be achieved, it demands the involvement of patients and their families. Patients and their families must be empowered. This can be achieved through a multidisciplinary wound care team. Nurses and physicians need the skills to empower patients, as well as to plan sufficient time to assess the situation of the patient.

Organisation

This chapter will cover the controversies as they are seen from the point of view of health administrators.

General organisation in wound management

- Q Does organisation have any influence on the treatment of patients with non-healing wounds?
- Q Does organisation of the use of antimicrobials have any influence on the development of antimicrobial resistance in wound management?

Access to treatment

- Q Do patients have equal access to treatment (such as infection treatment)?

Competencies

- Q Should wound care of infection be provided by all staff, or only by those trained in the assessment and management of individuals with infected wounds?
- Q Does education have any influence?

Other influences

- Q Should the use of antimicrobial agents in non-therapeutic situations be monitored?
- Q Would it help to monitor agriculture production and the consumption of antimicrobial products in the primary and secondary sectors?

Specialised antimicrobial treatment is an important part of the present health care. A need for a formal education and organisation is of pivotal importance. The organised wound area should be an integrated and accepted part of the health-care system. In this section, suggestions for models will be described and evaluated.[2,295–297]

Where are we today?

Organisation

The ideal concept seems to be a wound-healing centre consisting of multidisciplinary, well-educated personnel working full time with wound problems and able to care for patients with all types of wound problems throughout the entire course of treatment.[2,295]

The employees of the centre should be recruited from relevant specialties and form a multidisciplinary team of staff.

In primary care, these teams should organise the plans for treatment in the primary sector and local hospitals, and should coordinate teaching and education of local health professionals.[298] The team should also be the central referral organisation for wound patients in the local region and, in the case of healing problems, it should also serve as a referral to specialised wound healing centres.

Access to treatment

Fortinsky et al.[299] identified that the odds of being hospitalised as being much higher for a home-care patient with a wound compared with

one without. This suggests that the appropriate management of infected wounds has a central role to play in patient-safety initiatives, as infection contributes to increasing morbidity and mortality, and decreases overall health and social gain.[269] Management of non-healing, infected wounds requires a multidisciplinary team approach.[269] For example, in the diabetic foot, infection has devastating consequences; therefore, rapid diagnosis and initiation of appropriate local and systemic therapies are essential to avoid loss of limb and threats to life.[300]

Education

A number of Cochrane reviews have explored the impact of different educational strategies on clinical outcomes and concluded that inter-professional education, printed education materials and educational meetings can all positively affect the process and patient outcomes.[301–303] The evidence suggests that it is valuable to invest in educational strategies, focusing on mixed approaches with inter-professional attendance because these interventions have a positive impact on clinical outcomes. It is also known that the care delivered to patients with wounds is influenced by the knowledge and experience of the individual clinician; therefore, education and training are fundamental to ensuring enhanced clinical outcomes.[304]

Which model to use when organising and educating about antimicrobials?

The first question to answer is—what is the role of the microbiology laboratory in guiding antibiotic treatment in wound management?[28]

1. Microbiological data are important in confirming that the chosen regimen is appropriate
2. The microbiologist can play an important role in advising on whether to treat a wound and, if so, on the antibiotic treatment choice
3. Most clinicians prescribe broad-spectrum antibiotic agents before reviewing a microbiology report and, in many cases, the treatment may be inappropriate or may not be necessary; this can have a serious impact on hospital budgets. Furthermore, broad-spectrum antibiotics can adversely affect the normal gastrointestinal microflora, potentially predisposing patients to *Clostridium difficile* colitis and selecting for resistance in some bacterial strains (e.g., vancomycin-resistant *Enterococcus*)[305]
4. The role of the microbiology laboratory is to determine the clinically-significant isolates, perform antimicrobial susceptibility testing and provide subsequent guidance on the most appropriate treatment[306]
5. Use of microbiologists will facilitate successful wound management and assist in the control of antibiotic usage, thus stemming the spread of antibiotic-resistant bacteria.

The second question, therefore, is which organisational and educational model is best-suited for wound treatment, particularly relating to prophylaxis and treatment of wound patients with antimicrobials, and how the microbiologist can be optimally placed in this organisational/educational model to provide the best-possible continuous dialog between the microbiology department and the wound care practitioner.

To achieve these goals, it is essential to ensure that:

1. Only wounds that are likely to benefit from a microbiological investigation are sampled (wounds with clinical signs of infection or those that are failing to heal because of infection)
2. The microbiologist has an understanding of the clinical presentation of the wound

3 The microbiologist has an understanding of the method of wound sampling, and the microbiologist is aware of the requirements of the practitioner and the urgency of the results

4 The practitioner understands the rationale for the advice given by the microbiologist (for example, that mixed anaerobic-aerobic culture may not merely indicate a 'dirty' wound but may emphasise the significance of microbial synergy).[28] By adopting the microbiological approach to the multidisciplinary organisational/educational model, significant cost and time savings may be achieved, resulting in prompt and appropriate treatment for the patient.

> The first question to answer is—what is the role of the microbiology laboratory in guiding antibiotic treatment in wound management?

Presently-used models

General wound management

When focusing on organisational and educational models for antimicrobial use in the wound area, very few functional clinical models have been described. However, this model has been used in a multidisciplinary/multi-professional organisation, and is an integrated and accepted part of the health care system.[2,295,297,307] In these centres, a special model for collaboration has been developed between the centre staff and the microbiology department of the hospital.[2,307] In addition to the close teamwork in diagnosing bacterial infections and treating particularly infected wounds, a weekly visit with a senior microbiologist (consultant/professor) has been established in the wound centre. During this visit, all patients being treated with antimicrobials, particularly antibiotics, are discussed and a strict treatment plan for each patient is created. The microbiologist also participates in clinical rounds to better understand what the wounds look like when swabbed. From the microbiologist's point of view, this provides a better background for evaluating, discussing and recommending the use of antimicrobials in the treatment of wounds.

Is there any prior evidence for similar organisational types in general, or related to collaborations with microbiologist? Not at the highest level, but the general multidisciplinary centre structures has been shown to provide more continuity and standardisation over the treatment course, resulting in 83% satisfactory treatment courses, 80% satisfactory wound diagnosis, and 90% and 73% satisfactory conservative and surgical treatments, respectively.[308] Furthermore, multidisciplinary approaches to wound care in both the primary health-care sector and in hospitals have demonstrated a reduction in home visits and the range of products used.[309,310] By standardising treatment plans, the healing of certain non-healing wounds is improved.[307,311]

One of the fundamental parts of the organisational model described here is a standardised education programme for all involved personal.[312] Education is one of the fundamentals of such an organisation, and the goal for the future should be to achieve a general consensus on the minimal education programme needed.[313]

Diabetic foot ulcer patients

Diabetic foot ulcer patients with an infection may begin as a minor problem but often progress if not managed appropriately.[93,200] Depending on where the patient presents for care, primary-care providers, emergency-department clinicians, internists or hospitalists are often primarily responsible for initially managing a diabetic foot infection. Initial management includes deciding when and with whom to consult for issues beyond the scope of practice or comfort level of the primary clinician. Providing optimal patient care usually requires involving clinicians from a variety of specialties, which may include endocrinology, dermatology, podiatry, general surgery, vascular surgery, orthopaedic surgery, plastic surgery, wound care, and sometimes psychology or social work.

Specialists in infectious diseases or clinical microbiology often make a valuable contribution, particularly when the diabetic foot infection is severe, complex, previously treated or caused by antibiotic-resistant pathogens. In light of the wide variety of causative organisms and the absence of widely accepted, evidence-based antibiotic treatment algorithms, such consultation would be especially valuable for clinicians who are relatively unfamiliar with complex antibiotic therapy.

Care provided by a well-coordinated, multidisciplinary team has been repeatedly shown to improve outcomes.[298,307,314–319] Two retrospective studies have shown decreased amputation rates following the establishment of multidisciplinary teams for the treatment of diabetic foot infections.[320,321] A prospective observational study also found reduced rates of recurrent foot ulceration by using a multidisciplinary team approach.[322]

A variant on the multidisciplinary team approach is the diabetic foot care rapid-response team, which can be comprised of an *ad hoc* group of clinicians, who have mastered at least some of the essential skills for managing diabetic foot infections.[323] Moderate and severe diabetic foot infections frequently require surgical procedures. Severe infections may be pose an immediate life- or limb-threatening risk, and require urgent surgical consultation. The surgeon's area of specialty training is less important than his or her experience and interest in diabetic foot infection and knowledge of the anatomy of the foot. Following surgery, the wound must be properly dressed and protected.

Clinically, the advantages of introducing an organisational model in wound management seem clear-cut, but evidence at the highest level in the Cochrane system has not yet been produced. Nevertheless, the multidisciplinary model mentioned offers a unique opportunity for recruiting a sufficient number of patients for clinical and basic research and providing evidence for the materials and procedures used for treatment of infected wounds.

Controversies

Organisation in wound management

Q Does organisation have any influence in the treatment of patients with non-healing wounds?

Statement

The management of non-healing wounds with complications such as infection cannot be considered isolated from the whole patient. Therefore, a multidisciplinary approach is required to enhance clinical outcomes.

Discussion

Lack of organisation is demonstrated by a study of the primary health care sector in the central part of Copenhagen.[324] A number of general problems were documented for patients with all types of non-healing wounds. Of all patients with wound problems, only 51% had a significant

diagnostic examination; 40% of patients with expected venous leg ulcers were not treated with compression; 34% of patients with foot ulcers were not investigated for diabetes mellitus, and only 50% of patients with a pressure ulcer had offloading treatment. A lack of organisation seems to be the primary problem and care delivery by individuals, rather than by a team, is not always in the best interest of the patient.[325]

A team approach with collaboration between all health professionals is required to facilitate quality holistic care[326] and increase the chance of success, particularly when the talent and creativity of all employees are recognised.[327] Establishment of multidisciplinary teams has been shown to be beneficial for treatment of patients suffering from complicated wound conditions, including infection. The main objectives for such organisation are to improve prophylaxis and treatment of patients with all types of wound problems. This has essentially been achieved during the establishment of a multidisciplinary/multi-professional organisation in the primary and secondary health-care sectors.[2,295,297,307] This system consists of hospital centres and smaller units within the primary health-care sector.

Organisation systems such as this have resulted in a number of improvements. The referral policy has been simplified and centralised. Treatment plans, including diagnostics, treatment and prevention, have been optimised. Different types of educational services, basic and clinical research, and prevention programs have been established. Collaboration models for the relationship between the hospital and community sectors must also be organised.

Conclusion

The clinical outcomes of non-healing wounds with complications such as infection will improve in several ways if the treatment strategy is organised using a multidisciplinary team function.

Q Does organisation of the use of antimicrobials have any influence on the development of bacterial resistance in wound management?

Statement

In spite of high-level evidence in the Cochrane system regarding strategies to guide appropriate antibiotic usage, evidence for this has not yet been established in organisational models.

Discussion

To our knowledge, this type of organisation has only been described in a multidisciplinary/multi-professional centre model.[2,307] Here, clinical evidence shows that time for obtaining a microbiological diagnosis, beginning of treatment and controlling the length of antimicrobial treatment can be decreased using this model. Doing this, treatment outcomes were improved and the risk for development of bacterial resistance could be decreased.

Strategies to guide appropriate antibiotic selection in order to reduce the development of antimicrobial resistance have been addressed by national and international organisations. Resistance typically varies regionally, and even between local administrative zones, creating a need to establish both national and local organisation systems.[6] ABS (antibiotic stewardship) programmes can encompass a number of different interventions, some of which include education and guidelines; formularies and restricted prescribing; review and feedback for providers; information technology to assist in decisions; and antibiotic cycling.[328–330] Proper ABS results in the selection of an appropriate drug, optimisation of the dose and duration, and minimisation of toxicity and conditions for the selection of resistant pathogens.[330]

Policies that guide appropriate antibiotic use are most commonly based on interventions creating non-financial incentives and are generally

categorised as persuasive (facilitating change in prescribing behaviour) or restrictive (forced change) initiatives.[6] These initiatives can be subdivided into the following categories:

1. Simple persuasive interventions, such as the use of low-cost interventions (audit, feedback, printed educational material and educational outreach visits by academic detailers). Also, educational outreach visits by academic detailers (university or non-commercial-based educational outreach) and the use of best-practice or consensus-driven guidelines can be a successful intervention to improve antibiotic prescribing[331]

2. Simple restrictive interventions have demonstrated a more statistically significant reduction in inappropriate antibiotic prescribing[332]

3. Complex, multifaceted interventions appear to be the most effective mechanism for addressing antibiotic resistance and inappropriate antibiotic use.[333,334] The literature documenting the cost-effectiveness of such interventions is small, but growing.

> Access to treatment is a function of the availability of appropriate interventions, the knowledge and skill of clinical staff, and financial issues

Conclusion

Ultimately, there is no evidence on the highest level in the Cochrane system to address this controversy. However, there is some evidence that patient outcomes, health-care organisation and society will improve when wound management is organised, both for wound management in general, and more specifically related to use of antimicrobials. Different models are available and both teams focusing on a single wound type and larger specialised wound-healing centres covering different types of wounds and treatment modalities have been shown to improve outcomes. However, a multidisciplinary/multi-professional centre model appears to be the optimal treatment approach in wound management, but the cost-effectiveness of this approach has not yet been determined.

Access to Treatment

Q Do patients have equal access to treatment of infection?

Statement

Patients do not always have equal access to treatment; yet access to appropriate wound-management services is intrinsically linked to the potential for good clinical outcomes

Discussion

For individuals with infected wounds, it remains important that their clinical needs are met in an appropriate and timely manner. One of the most important lessons we have learned over the lifetime of the EWMA is the distinct difference between the pathophysiological processes in healing and non-healing wounds. The key message is that the lack of attention to the clinical manifestations of the infected wound seriously hampers the

ability to make a correct diagnosis and plan for subsequent treatment.[312] Clearly, diagnosis should be made at the earliest opportunity, as failure to do so will place the individual at risk of systemic infection and even death.[300] Therefore, it is evident that access to appropriate treatment for infected wounds is intrinsically linked to the potential for good clinical outcomes. Interestingly, a study by McCluskey and McCarthy[335] noted that, of a sample of 150 nurses in the acute care setting, the majority felt that they were only moderately competent in wound assessment. This suggests that there is some confusion in practice and, as such, patients with infected wounds may not always have their clinical needs met in an appropriate manner.

Conclusion

Access to treatment is a function of the availability of appropriate interventions, the knowledge and skill of clinical staff, and financial issues, among others. It is important that those with infected wounds have their clinical needs met in a timely manner. Failure to do so will negatively impact the ability to achieve good clinical outcomes.

Competencies

Q Should wound care of infection be provided by all staff, or by those trained in the assessment and management of individuals with infected wounds?

Statement

Individuals with infected wounds should only be cared for by those trained and competent in the provision of wound-management services.

Discussion

Health professionals are accountable for the provision of safe, evidence based, clinical care to individuals with infected wounds. Competence, the ability to practice safely and effectively, is central to ensuring the safety of those cared for by health professionals.[336] This concept is in keeping with patient safety initiatives,[263] and the drive for accountability and quality in health-service delivery.[245] Furthermore, it is clearly aligned with the WHO patient safety programme.[264]

The impact of wound infection on the individual is profound, increasing the risk of significant morbidity and mortality.[269] Wound infection prolongs hospital stay, increases health-care costs and impacts negatively on health and social gain.[269] Early recognition of infection and rapid intervention with appropriate treatment is essential to enhance clinical outcomes.[300] In order to achieve this, competence in wound management is essential.[335] Continuing professional development is a lifelong process, ultimately enabling health professionals to develop and maintain the knowledge, skills, attitudes and competence needed to practice appropriate wound management.[336] Indeed, the importance of knowledge in facilitating effective clinical decision-making in wound management is well alluded to.[337–341]

Conclusion

For those with infected wounds, timely provision of appropriate care is closely linked with a patient safety agenda. Thus, it is important that those caring for individuals with infected wounds are competent to do so.

Q Does education have any influence at all?

Statement

Education is important to the development of competence in the management of wounds; however, the ability to put into practice what one has been taught is also important.

Discussion

A national cross-sectional investigation showed that almost all general practitioners (98%) believed that wound healing significantly affects their patients; whereas, few (16%) understood basic

wound healing physiology.[342] It has also been recommended that it is time to integrate knowledge about wound healing, tissue repair, wound care, long-term scarring and rehabilitation.[343]

Perceived control, the belief that one can directly influence outcomes (such as wound infection), is an important variable in the prediction of behavioural intention of an individual.[344] Perceived control is influenced by factors such as knowledge, skill, time, opportunity, autonomy and resources—all of which warrant consideration in planning services.[344] Individual characteristics of each clinician influence their ability to problem solve when dealing with individuals with infected wounds. Of these characteristics, the content of the education received is a central determinant of effective decision making. Therefore, the quality of knowledge gained is a key consideration in ensuring that clinicians are delivering care that is appropriate for those with infected wounds.[337]

Internal and external influences over behaviour also have wide-reaching implications for wound management. Of importance is opportunity, which in this instance is taken to mean the working environment in which the clinician is practising, and which influences the clinician's decision-making. In reality, there are many organisational and environmental factors in the clinical setting that impact one's ability to practice in a particular manner.[345]

Conclusion

To achieve a reduction in infected wounds it is not simply a matter of providing education and training, but rather it is also important to provide the necessary resources to ensure that there is ample opportunity to practice what has been learned. The organisational culture where care is provided plays a key role and, as such, management needs to understand this and foster an environment in which best practice in wound management becomes a reality in the clinical setting. Knowledge comes over time and requires a feedback loop of metrics.

Other influences

Q Should the use of antimicrobial agents in non-therapeutic situations be monitored?

Statement

Yes.

Discussion

Antimicrobial agents are used in many non-therapeutic situations, particularly to maintain hygienic conditions in hospitals, clinics, schools, nurseries, care homes, toilets, leisure centres, offices, kitchens, restaurants, hotels, food processing plants, abattoirs and farms. Appropriate use of antimicrobial agents is needed to reduce and prevent the spread of resistance. Use should be restricted to essential circumstances and follow best-practice guidelines, as inappropriate use promotes the emergence and spread of resistant strains. Injudicious use must be controlled, but the extent of the problem is largely unknown. Surveillance systems to monitor antimicrobial resistance in medical and veterinary practice exist in Europe, but they are not comprehensive. More research into where and how antimicrobial strains evolve and spread is needed.

Conclusion

Wider antimicrobial surveillance schemes would provide more information on the origin and spread of antimicrobial resistance.

Economics

Below are listed the controversies discussed in this chapter:

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

Where are we today?

Risk to patients and increased burden on health-care provision

Non-healing wounds are associated with long recovery duration, with or without delayed healing, and a high incidence of complications, often resulting in a considerable financial burden both from a societal perspective and from the perspective of the health-care providers.[4,346,347] Chronic leg ulcers affect approximately 1% of the adult population in developed countries.[348,349] It is generally accepted that, where appropriate research-based treatment protocols are in place, about 50% of ulcers will heal within 4 months, 20% will heal within 4 months to 1 year, 20% do not heal within 2 years, and approximately 8% fail to heal, even after 5 years.[349,350] In many countries and in various health-care systems, these data are difficult to obtain for several reasons:

1. Lack of adequate population-based data
2. Patients who are treated by many disciplines and at different levels of care (inpatient/outpatient, primary care, home care, or patients/relatives)
3. Patients who are not followed to a specific endpoint
4. Differences in resources used or available
5. Different treatment strategies
6. The influence of different reimbursement systems
7. The economic cost/price for the product or procedure used.[4,346,347]

The economic cost of non-healing ulcers are a staggering 2–4% of the health-care budget, but still with a substantial underestimation due to lack of adequate data from many countries and an increasing elderly and diabetic population.[4] At the moment there is limited information regarding the cost of wound infection in non-healing wounds, as resources spent are either focused on the total cost of treating individuals with various wounds, or on costs for specific interventions or length of stay in hospital. Corresponding challenges are related to patients with other kinds of wounds, such as acute wounds, post-surgical wounds, hospital-acquired infections and wounds of other aetiologies. There is an urgent need for evaluation of strategies and treatments for this patient group to reduce the burden of care, not only with regard to clinical outcome, but also in an efficient and cost-effective way.

Diabetic foot ulcers

The International Diabetes Federation[347] estimates that the number of people living with diabetes is expected to rise from 366 million in 2011 to 552 million by 2030. Furthermore, almost 183 million people with diabetes are unaware that they have the condition.[347] People with diabetes are 50 times more likely to develop a foot ulcer than their non-diabetic counterparts;[351] the prevalence of foot ulceration in diabetic patients ranges 3–10%.[351] Every 20 seconds, a lower limb is lost as a consequence of diabetes. Globally, approximately 4 million people develop a diabetic foot ulcer, each year.[346,347] Up to 85% of diabetes-related amputations are preceded by a foot ulcer.[346,347] Furthermore, diabetes is the leading cause of non-traumatic limb amputation and re-amputation in the world.[352,353] Up to 25% of the estimated 20 million people with diabetes in the USA will develop a diabetic foot ulcer during their lifetime.[354,355] Roughly 50% of diabetic foot ulcers become infected and approximately 20% of these will undergo a lower-extremity amputation (LEA).[356] Foot ulcers also cause a loss of mobility for the individual patient, thereby decreasing social functioning.[357]

The indicative annual cost for EU has been estimated at €4-6 billion; however, from a diabetic foot ulcer perspective, the costs associated with infection management are intrinsically linked to the severity of the disease, the incidence of infection and peripheral arterial disease.[314] As such, estimates for Europe are placed as high as €10 billion, annually.[314] The direct cost for healing without amputation is estimated at €2157–7169 compared with healing with an amputation, which is estimated to be €14 409–58 700 in various studies (without correction for changes in currency rate, inflation).[346,358] Diabetes consumes 12–20% of health-care resources, of which 20–40% are related to diabetic foot morbidities.[204,346,347] These consequences are especially challenging because the prevalence of diabetes is expected to increase to more than 7% of the adult population by 2025.[347]

The estimated direct cost of treating a diabetic foot ulcer in the USA is up to US$20 000 and a major limb amputation costs approximately US$70 000.[346,359,360] Recent estimates suggest that diabetic foot ulcers and amputations alone cost the USA health-care system approximately US$30 billion annually.[359,360] In most health-care systems, lower extremity complications account for 20–40% of the total cost of diabetes.[346]

Pressure ulcers

Pressure ulcers are a largely preventable problem, yet despite the advances in technology, preventive aids and increased financial expenditure, they remain a common and debilitating concern.[361] Internationally, prevalence rates range 8.8–53.2%,[361–363] and annual incidence rates vary 7–71.6%.[364–367] The presence of a pressure ulcer has, for some time, been considered an indicator of the quality of care,[368] and incidence figures reduce society's confidence in the health service's ability to deliver care that is timely, appropriate and effective.[266]

The proportion of the total health-care budget spent on pressure-ulcer care is about 1% in the Netherlands[369] and up to 4% in the United Kingdom (UK).[370] However, cost-specific figures for non-healing pressure ulcers are hard to obtain, as most reports do not provide grading. A multiplicity of factors influence the total cost of care for pressure ulcers,[4,370–372] and reliable data related specifically to the costs of non-healing pressure ulcers are limited.[4] A study by Bennett[370] estimated the cost of healing a category IV pressure ulcer to be about 10 times that of healing a category I ulcer. They also estimated that, in 2000, the cost to heal a category IV non-healing (in this case infected) pressure ulcer was £9670 versus £7750 for a category IV ulcer that healed without complication within the expected time frame.

From a health-care delivery perspective, 25–50% of acute hospital beds are occupied by patients with a wound, with up to 60% of these representing non-

healing wounds (infected surgical wounds, pressure ulcers, leg/foot ulcers).[4] In the UK, costs for pressure-ulcer management have been estimated at 4% of the annual health care budget,[370] with nurse or health-care assistant time accounting for up to 90% of the overall costs.[373] Furthermore, having a pressure ulcer increases length of stay by a median of 4.31 days,[374] and is associated with higher mean unadjusted hospital costs (US$37 288 versus US$13 924; p=0.0001)[375] and increased risk of mortality (relative risk [RR]=1.92; 95% confidence interval [CI]=1.52; 2.43).[376]

Leg ulcers

In Europe, the direct cost of treating a leg ulcer varies between € 2500 and €10 800 (averaging €6650), indicating an annual cost in the EU of €6.5 billion for venous ulcers only.[4,248,371,377]

In 1991, the cost of leg ulcer treatment in the USA was estimated to be between US$775 million and US$1 billion.[378]

In the UK, the total cost of treating venous leg ulcers for 2005/2006 was estimated to be £168–198 million.[379] The factors positively correlated with increasing cost were duration of active therapy, ulcer size and the presence of at least one comorbidity.[377,380] However, the epidemiological data suggest an increasing presentation of ulcers that are not of pure venous origin, but are a result of various degrees of arterial disease and other confounding factors. To date, there are limited data available on the natural outcome, resource utilisation, and cost of arterial and mixed leg ulcers.[15]

Studies have explored the prevalence of chronic venous disease, suggesting that it to be 0.18–1.9%. In 2008, the adult population in the EU was 414 million, with 84 million of those over 65 years. The prevalence in the adult population is 0.12–0.32%, meaning that 490 000–1.3 million adults in the EU have leg ulcers. The prevalence of leg ulcers increased in the older population (103 in every 10 000 aged ≥70 years),[381] with an incidence of venous leg ulcers in the population over the age of 65 of 1.16%, meaning that 980 000 people in the EU develop leg ulcers each year. Herber et al.[382] identified that the presence of a leg ulcer not only affected the individual from a physical perspective, but also from both a social and psychological perspective. In a cost-of-illness study from Hamburg (Germany), the annual total cost for lower leg ulcer summed up to a mean of €9060/patient/year (€8288 direct, €772 indirect costs). Exploratory predictor analyses suggest that early, inter-professional disease management could lower treatment costs.[383]

> Pressure ulcers are a largely preventable problem, yet despite the advances in technology, preventive aids and increased financial expenditure, they remain a common and debilitating concern

The use of health economics to improve the management of non-healing ulcers

During recent years, positive examples have illustrated the possibility to reduce both resource

utilisation and costs with simultaneously important improvements in health-related quality of life (HRQoL) for affected patients. Successful projects are often associated with a broader perspective, including not only the costs of dressings and other material, but also costs of staff, frequency of dressing changes, total time to healing and quality of life.[358]

Health economics and organisation of care

It is less common to study and evaluate organisation of wound care or management systems, but these studies can provide important and useful information to improve outcomes. It is also important to be aware of the costs associated with non-optimal management of ulcers.

The most important factor disclosed in most health economic studies, particularly in the field of diabetic foot infections, is the organisation of care and the lack of coordination between various disciplines and levels of care.[354–356,384–392] Studies of the economic cost of diabetic foot ulcers, in which patients were followed until healing was achieved, irrespective of the level of care, were a breakthrough for the recognition of the diabetic foot and the need for coordination of knowledge and disciplines to avoid amputation and heal ulcers.[346] These findings have been confirmed in various health-care systems globally, indicating the danger with regard to fragmented care and too many caregivers treating too few patients to get experience and, therefore, not recognising high-risk patients in time.[354–356,384–392] Management and prevention of diabetic foot infections, according to guideline-based care, are cost-effective and even cost saving, compared with so called 'standard care'.[356,388,389,391] For example, optimal foot care as described by IWGDF[204] for diabetic ulcers alone, is cost-effective if at least a 25–40% reduction in the incidence of ulcers or amputation is achieved.[356,388,389,391]

In the USA, it is estimated that if the above measures were adopted, they could prevent 48–73% of diabetic foot ulcers and LEAs, saving the health-care system up to US$21.8 billion annually. The conclusions from these studies are that the management of diabetic foot infections according to present guidelines would result in improved survival and a reduction in the number of diabetic foot complications.[200]

Additionally, it is essential to follow resource utilisation until a final end point (healing) to achieve a recognition of the total resources and cost.[346] Many health-economic studies of non-healing ulcers have focused on reducing hospital stay and treatment at hospital-based specialist clinics. However, a substantial number of resources are used in outpatient facilities in primary care and home care. When analysed by care setting, home health-care accounted for the largest proportion (48%) of the total cost for treatment of venous leg ulcers in the USA. A study in the UK calculated that, in 2000, the mean annual cost per patient for treatment at a leg ulcer clinic was €1205 and €2135 for treatment by community nurses.[379] The finding that home health care accounts for a significant proportion of the total medical costs, suggests that promoting high-quality care in outpatient clinics is likely to improve cost efficiency. This is illustrated by a Swedish study in primary care in which a system for early diagnosis of lower-leg ulcers and introducing a strategy to reduce the frequency of dressing changes resulted in a substantial reduction in resources used and economic cost.

All of these studies indicate the importance of organisation in wound care and coordination of treatment strategies to achieve an optimal care, with regard to both outcomes and cost.

Health economics and factors related to healing of non-healing wounds

When evaluating wound infection, it is essential to consider the consequences of a wound infection as an integrated part of the total management and

resource utilisation, particularly with regard to the treatment of an individual with an infection, through resolution and healing of the infection being achieved. Frequently, the cost to treat the infection has been related to cost for antibiotics and hospital stay. At present, there are few high-quality studies regarding wound management and health economics, and there is confusion regarding how these studies should be performed, particularly with regard to endpoints and resource utilisations.[248]

In patients with non-healing diabetic foot ulcers, especially those with deep foot infections, primary healing costs on average €15 416 compared with €27 966 for healing with amputation. The dominating factors related to the high cost have been identified as the number of surgical procedures, length of in hospital stay and time to healing.[387] In a prospective study following diabetic patients with foot ulcers until healing, with or without amputation,[346,384,385] the highest costs were associated with inpatient care and topical treatment of wounds (including staff, transportation and materials). The costs for systemic antibiotics, outpatient clinic visits and orthopaedic appliances were low in relation to the total costs of patients, both with and without amputation.[385] In the same study, the total cost for healing a foot ulcer was strongly correlated to the severity of the lesion and comorbidities.[385]

A number of reports have suggested the cost-effectiveness of different new technologies and dressings for the treatment of non-healing wounds. Although many of these products are more expensive than standard-of-care treatment, their use may be cost-effective if they result in faster healing or reduce the resources used.[384] However, it is important to be aware that a treatment could be cost-effective in one group of patients, or for one type of wound, but not in another. An intervention could also be cost-effective when used in one setting, or country but not in another.[314,393 394]

When assessing use of resources, it is important not to focus on individual items, such as dressings or procedures, but to adopt a broader view of total resource use.[314,394] Few studies in wound care provide a full cost-effectiveness analysis. Comparisons of results from various health-economic studies are further complicated by differences in study design. This includes whether the study is prospective or retrospective, the patient inclusion criteria, the type of wound, the health-care setting studied (primary care or secondary care), treatment practices, period of investigation, the reimbursement system and the countries included.[15] Most studies focus on clinical outcomes only and include analysis of the estimated direct medical costs for wound treatment, but not indirect costs relating to the loss of productivity, individual costs for patients and families, and reduced quality of life.

Health economics to compare treatment interventions

Many of the design parameters of a study are dependent on the perspective of the analysis (on the perspective of the relevant decision-maker). In wound care, decision makers include clinicians, hospitals or other health-care provider organisations and third-party payers, and the perspective of any analysis determines which costs and outcomes are relevant. Ideally, the prices used to value resources would reflect their opportunity cost—their value in their best alternative use. In practice, opportunity costs are usually approximated by market prices. When cost is used as an outcome parameter in wound management, it is essential to measure all the quantities of resources used and then add the value of those resources, according to a predefined protocol. It is recommended to show resource use and costs separately. Reporting resources separately also allows testing whether differences between programme costs are sensitive to changes in unit prices.

Table 7-1. Suggested items in resource utilisation in non-healing wounds* from which direct cost can be estimated (The items are listed according to category)

*Adapted from Ragnarson-Tennvall & Apelqvist (1997)[385]

1 Evaluation	2 Medical treatment	3 Surgical treatment	4 Topical treatment	5 Orthotic appliances	6 Hospital stay
Clinical examination (generalised/localised)	Cardiovascular agents	Vascular:	Time required for applying and changing dressings or any topical treatment.	Shoes/insoles	Hospital bed days
Laboratory:	Anticoagulants	— percutaneous transluminal angioplastry	Resources for transportation (patient or staff)	Special orthotic appliances	Resources used in hospital
— metabolic control of diabetes mellitus	Antibacterial agents (oral/parenteral)	— reconstructive surgery	Available category of staff	Total contact cast	Category of clinic
— haemorheology	Steroids	Orthopaedic:	Frequency of changes	Prosthesis/wheelchair	
Vascular:	Immunosuppressive agents	— incision/drainage	Primary dressing materials, drugs or other type of device		
— noninvasive vascular testing	Insulin—hypoglycaemic agents	— revision/resection	Accessory material:		
— angiography	Analgesic agents	— minor/major amputation	— cleansing agents — fixation (e.g. tape to adapt the dressing to the skin) — gloves, etc.		
Infection: — X-ray, bone scan, CT, MRI — bacterial culture — biopsy					
Socioeconomic: — living conditions — Attempted Daily Learning (ADL) — compliance, knowledge					
Biomechanical (walking pattern, foot dynamics)					

Health economics in non-healing ulcers and reimbursement

In a study comparing resource use associated with diabetic foot infections in three European foot centres in different countries, substantial differences were identified in inpatient stay, use of antibiotics and vascular surgery.[390] The authors concluded that these differences could largely be explained by variations in access to inpatient and outpatient facilities, the patient selection bias, patients' characteristics, reimbursement systems and health-care systems, and these results were confirmed in the EURODIALE study.[314,394]

In a comparison of diabetes-related foot lesions in patients in the Netherlands and California,[395] the duration of hospital stay was substantially longer in the Netherlands, but the incidence of lower extremity major amputation was higher in the USA. This has important implications in the drive to cut costs through early discharge. The authors suggested that these differences might be explained by differences in access to health care, health-care financing and reimbursement systems. Although hospitalisation is obviously more expensive than home care, the long-term cost effectiveness of these options must be examined. For some patients, wound care strategies (such as offloading) can be successfully implemented in an inpatient setting, thereby avoiding expensive adverse events, such as amputation. Ultimately, this may be less expensive overall than a prolonged period of home care in which these expensive adverse events are more likely to occur. Reimbursement in some countries favours amputation because of shorter hospital stays and reduced length of time healing.[314,394,395]

Summary

Non-healing wounds often result in a considerable financial burden, which is associated with a long healing time and a high incidence of complications. When evaluating the consequences of a wound infection, it is essential to view the consequences as an integrated part of the total management and resource utilisation 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 often have cost implications. Clinicians need to be able to present robust economic arguments and strong outcome data to fund holders. A major problem in the analysis of the cost of disease states is that comparisons of cost analyses are compounded by variations in care protocols and the different economic statuses of different countries (such as variations in rates of pay to health professionals and in reimbursements). Substantial efforts will be required to identify a series of standardised criteria for cost analyses that can be used to further identify the most economically effective ways to treat non-healing wounds.

Controversies

Q What are the economic consequences of not making the correct diagnosis in due time?

Statement

The consequence of not making the correct diagnosis and corresponding treatment strategy will be a delay in adequate treatment and intervention, a delay in healing and, ultimately, increased cost.

Discussion

The most important factors related to high resource utilisation in treating non-healing ulcers is the need for surgery, in-hospital stays, and wound healing time (duration of ulcer). The consequence of inadequate diagnosis will be a delay in adequate treatment and a subsequent delay in healing, ultimately leading to increased cost. It has to be recognised that health-economic data are essential to describe resources spent with regard to any condition, but especially non-healing ulcers. Treatment of patients with this condition frequently involves many disciplines and incurs large costs. A

description of how these resources could be spent more effectively, both from the patient and the health-care perspective, is essential when evaluating the consequences of a wound infection. Cure of wound infections should be seen as an integrated part of the total management and resource utilisation of an individual with non-healing wound.

Conclusion

The most important factors related to the high resource utilisation in treating non-healing ulcers is the need for surgery, length of inpatient stay and wound healing time (duration of ulcer). Therefore, the consequence of inadequate diagnosis will be a delay in adequate treatment and a subsequent delay in healing, ultimately leading to an increased overall cost.

Q What is the cost effectiveness of antiseptic versus antibiotic treatment (not just prices of products, but also societal costs)?

Statement

To our knowledge there are no studies available differentiating the cost effectiveness of antiseptic compared with local antibiotic treatment.

Discussion

As part of wound healing, both antiseptics and local antibiotics are used to treat wound infection. When investigating the different outcomes between antiseptics and antibiotic treatments, the outcomes need to be considered as an integrated part of total management and resource utilisation. The total resource utilisation not only involves the direct costs to cure the infection, but also the cost incurred until healing is achieved. Also, the societal costs of healing should be taken into consideration, not just the price of a specific item.

There are very limited data comparing cost effectiveness among various treatment strategies in non-healing ulcers. Most studies evaluating economic cost, or resources used, have been based on clinical trials, which limits their external validity. Frequently, the cost to cure the infection has been related to the cost of antibiotics and/or in-hospital stay. At present, there are few high-quality studies examining wound management and health economics, and to our knowledge there are no studies regarding the difference in cost effectiveness of antiseptic versus local antibiotic treatments.

Most studies evaluating economic cost, or resources used, have been based on clinical trials, which limits their external validity

Conclusion

There are very limited data comparing cost effectiveness between various treatment strategies in non-healing ulcers. When analysing resources spent in treating complex ulcers, it is important to consider all resources spent to achieve healing, not just the price (or cost) of one specific item. To our knowledge, there are no studies available analysing the cost effectiveness of antiseptic compared with local antibiotic treatment.

Q Is it cheaper to amputate limbs of an individual with an infected wound than to treat (conservatively) with antibiotics?

Statement

The direct cost associated with performing an amputation in diabetic patients with infected wounds (Table 7-1) is higher than when treating without performing an amputation, if diabetic patients are followed to healing.

Discussion

It is essential to consider the total resources spent to heal a patient with a non-healing infected ulcer. In some countries, the elevated cost for conservative treatment with antibiotics and in-hospital stay may lead to an early amputation. This is a common assumption in countries with health-care systems in which antibiotics have a higher reimbursement price and patients are not followed until healing is achieved.[300,346,384,395,396] However, in the few studies that have analysed the total direct cost to achieve healing of an infected foot ulcer, the price for antibiotics comprised 15% of the total cost. Lower-leg amputation is frequently related to high resource utilisation, due to resources spent following amputation. It is essential to analyse and understand that the costs are different due to the different perspective. It is important to evaluate the cost from the societal perspective and not only from the perspective of the hospital. In patients with diabetes and deep foot infection, the total direct cost was twice as high in patients treated with an amputation compared with those treated conservatively. The most important cost-driving factors were wound duration and the number of surgical procedures. The price of antibiotics cannot be used as the only determinant to evaluate treatment cost.[387]

Conclusion

The limited data available on patients with infected diabetic foot ulcers suggest that the direct costs are higher for healing with an amputation than without.

Q Do recommendations to restrict the use of products due to their price per item have consequences, and what are these consequences?

Statement

The price of a single item in treating individuals with non-healing ulcers should never be the key factor for decision making.

Discussion

It is very important to recognise the perspective of each of the relevant decision-makers. In wound care, decision makers include clinicians, hospitals or other health-care 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.

The price of a single item in treating individuals with non-healing ulcers should, therefore, never be the key factor for decision making. Each intervention must be evaluated in light of the total resources spent to achieve a specific goal, such as wound healing or resolution of an infection. When cost is used as an outcome parameter in wound management, it is essential to measure all resources used and then add the value of those resources, according to a predefined protocol, to a specific endpoint (outcome). It is recommended to show resource use and cost separately, as the prices of product/drug/device are set differently in various countries or regions.

Conclusion

The price of a single item in treating individuals with non-healing ulcers should never be the key factor for decision making. Each intervention should be evaluated from the perspective of the total resources spent to achieve a specific goal, such as wound healing or resolution of an infection.

Future perspectives

Potential consequences if we do nothing

Judicious use of all antimicrobial agents is becoming an urgent necessity, in order to retain effective treatments for infection and avoid a return to the conditions that existed before the antibiotic era. Overuse of antibiotics has provided a selection pressure that has allowed antibiotic-resistant strains to emerge and increase in prevalence (see Chapters 3 and 4). Antibiotic resistance increases patient morbidity, extends hospital stay, and increases treatment costs and mortality rates.[397,398] These outcomes have a social and economic impact;[397] incorrect use of antibiotics wastes time and resources, erodes patient confidence and reduces staff morale. Many surgical procedures and cancer therapies rely on antibiotics to prevent and/or treat ensuing infections, and these treatments will become impossible without effective antibiotics.[398] Moreover, the potential threat of failure to treat wound infections will have an immediate impact in conflict areas or episodes of natural disasters.

Factors that contribute to the misuse of antibiotics are diverse, the WHO has identified the key issues as diagnostic uncertainty, lack of skills and knowledge, fear of litigation, and failure to properly utilise clinical guidelines.[398] The unrestricted use of antibiotics in many non-European countries promotes antibiotic abuse. Additionally, national pharmaceutical policies may be absent; therefore, coordinated opportunities to improve surveillance, regulation and education are lost. The unethical promotion of antimicrobial interventions by commercial organisations additionally contributes to misuse. Health professionals with heavy workloads may find that time constraints lead to limited opportunities to update knowledge and a reliance on incomplete diagnoses.

Several programmes have been initiated to address the problems emanating from antibiotic resistance, yet few tangible effects have been realised (Table 8-1).

As mentioned in the introduction, infection is one of the most frequently occurring complications of non-healing wounds. There is a concern regarding the use of antimicrobials in the society and, as a consequence, antimicrobial treatment strategies in non-healing wounds have been challenged. The consequences of these controversies have an impact with regard to both overuse or underuse of antimicrobials in wound management.

Therefore, it is essential that management strategies are targeted effectively, to ensure timely and efficient wound-management services. Indeed, adopting a systematic approach to patient and wound assessment will lead to early detection of infection and other complications, and the initiation of appropriate treatment plans.[399] However, importantly, the process of wound management involves not only the application of an appropriate dressing, drug or device, but also consideration of broader factors that may impede the wound healing process.[400]

Therefore, as wounds remain a significant health-care problem, effective prevention and

Table 8-1. The debate and initiatives to control antimicrobial resistance

Year	Country/Origin	Organisation	Report
1998	UK	Select Committee on Science and Technology of the House of Lords	Resistance to antibiotics and other antimicrobial agents
2001	Switzerland	World Health Organization (WHO)	Global strategy for containment of antimicrobial resistance
2004	USA	Infectious Diseases Society of America (IDSA)	Bad bugs, no drugs
2009	USA	IDSA	Bad bugs, no drugs: no ESCAPE!
2009	Sweden	European Centre for Disease Prevention and Control	The bacterial challenge: time to react
2011	Belgium	European Commission	Communication from the European Commission to the European Parliament and the Council: Action Plan against the rising threats from antimicrobial resistance
2011	USA/EU	Transatlantic taskforce on antibiotic resistance (TATFAR)	Recommendations for future collaborations between the US and EU
2012	Switzerland	WHO	The evolving threat of antimicrobial resistance

management strategies should be core components of the strategic planning of health-care services.[288]

With regard to the bioburden in non-healing wounds, there are three major issues

1 The microbiological definition of a wound infection:

Many different bacterial and fungal species have been identified in non-healing wounds. The quantity of each species may vary, and it is not know whether small amounts of one bacterium might boost one of the major inhabitants of a wound. This suggests the number of bacteria/cm^3 tissue may not be relevant, but rather which species are present may. We need research that focus on these issues, since most of the information available today are obtained from acute wounds, animal or other experimental models.

There is a need to investigate the relationship between microbial population sizes in non-healing wounds and clinical indicators of infection.

In the future, a stricter definition of the terms 'problematic bacterial load' or 'critical colonisation' will be needed before they can be used in clinical practice or as endpoints in research.

2 Antimicrobial resistance:

There remains a great deal of uncertainty about resistance to topical antimicrobials. The bacterial resistance described in the literature is primarily in relation to the use of antibiotics. Clearly, further systematic reviews of evidence may be warranted and there is a need to monitor indicators for emergence of resistance to antimicrobials in practice settings.

Due to increasing antibiotic resistance, there is an urgent need for adjuvant or alternative treatments, better controls on the use of antimicrobials in human and veterinarian medicine, and consistent restrictions and guidelines in all European countries. Use of excipients may in the future improve the outcome results of antimicrobial treatment.

3 Presence and importance of biofilms:

From a clinical perspective, we lack a clear understanding of the presence, importance, and proper intervention for biofilm in non-healing wounds.

With regard to treatment of non-healing wounds, there are several major issues

1 Lack of awareness of antibiotic resistance and of the value of antimicrobial treatment influences physicians' attitudes to prescribing patterns:

Physicians need guidance and education with regard to a structured management of antimicrobial treatment for non-healing wounds. They need to understand that, in order to be effective, antimicrobial treatment should be targeted both to the right wound and to the right patient. There is no proof that routine administration of antibiotics is effective for prophylaxis or treatment in non-infected non-healing wounds.

Due to the increasing resistance towards antibiotics and the need for an effective antimicrobial strategy for non-healing wounds, there is an urgent need for the use of an antimicrobial treatment regime that does not include antibiotics. There needs to be greater clarity about when and where to use each treatment modality.

2 An abundance of products are available, but there is no consensus regarding the value of topical antimicrobials in non-healing wounds.

Most research is conducted by industry rather than government agencies. It is not surprising that the available evidence is mostly brand-specific. Companies have little incentive to conduct broad-based research. In combination with a lack of willingness of governments to fund the necessary clinical research, this has created a gap in the present evidence with regard to outcomes and

Due to the increasing resistance towards antibiotics, there is an urgent need for the use of an antimicrobial treatment regime that does not include antibiotics

results of interventions in the general population. A more widespread description covering all aspects of the health care is desirable, and the main problems, such as the availability of evidence, controversies or myths, should be discussed.

3 There is a need for cohort studies, comparative studies, or RCTs with regard to antimicrobial treatments in non-healing wounds with a design and end-points that focus on resolution or prevention of infection:

The majority of comparative studies with regard to the use of antimicrobial agents in wound treatment has been focused on either acute wounds or non-infected wounds. A need for further, well-designed studies has been emphasised; however, the limitations of predefined adequate endpoints in studies are a major barrier for evaluating the importance of various treatment strategies, such as antimicrobials. The most important endpoints with regards to antimicrobial treatment should be the prevention of infection, resolution of infection,

wound healing, time to wound healing or time for resolution of an infection. Any recommendation needs to acknowledge that, while RCT evidence is ideally required to support proof of efficacy, other non-RCT methods may also be useful in determining the impact of antimicrobials in practice settings.

Wound infection is a valid endpoint in a wound healing study and clinical parameters should be used for the definition of wound infection. To properly evaluate the value of antimicrobial agents in wound treatment, we need a new set of tools and endpoints for these studies. The commonly-used endpoints of wound closure, healing rate, epithelialisation, quality of life and wound environment are all, to some extent, dependent on the presence of infection. Resolution of infection has been used as an endpoint in some comparative studies, either at the discretion of the physician and sometimes supported by clinical signs and bacterial load, or laboratory parameters. Since infection is a clinical diagnosis, it would make sense to use a clinical scoring system to define infection, as well as resolution of infection.

From the patient perspective—a holistic approach is mandatory

- Physicians and caregivers are unaware of the importance of patients' and their families' attitudes towards management.

In the management of a patient, attitude and expectations of treatment have to be considered, especially in health-care systems where management of wounds is relying on relatives and family as a resource. Ultimately, we have to treat not only a wound, but an individual with a wound, also considering the patients' social environment. Furthermore, patient safety strategies consider ignoring health-care needs or failing to provide adequate health care for appropriate wound management as a form of neglect. Patient safety groups place the onus of adequate wound management firmly in the hands of care providers. Therefore, it is of utmost importance that emphasis is placed on a systematic assessment of the patient, the wound and the environment in which care is provided. This will enhance the likelihood that adverse changes in the patient's condition are readily recognised and appropriate treatment plans are initiated. For this reason, the patient and the family should to be an integral part of the future management of non-healing wounds.

From the organisation perspective, this is the major issue

- Individuals with infected wounds should only be cared for by those trained and competent in the provision of wound management services.

In most health-care systems, policy makers and caregivers are frequently unaware that in most patients with a non-healing wound, with or without infection, the condition is related to comorbidity and concurrent disease, necessitating a multifactorial treatment, in which antimicrobial treatment is a part. More than a decade ago, it was identified that limited availability of adequately-trained personnel and diagnostic equipment compounds the suffering of patients. Furthermore, it increases the costs to an already over-stretched health budget. Especially regarding diabetic services, it has been concluded that structured multi-professional interventions, such as interdisciplinary collaboration and professional and patient education, result in improved patient outcomes and service delivery. To achieve this, all the members of the multidisciplinary team must work together, as no single profession has all the required skills.

The multidisciplinary model offers a unique opportunity for recruiting a sufficient number of patients for clinical and basic research, thereby producing evidence for the materials and procedures used for treatment of infected wounds.

For this reason, the organisational perspective need to be elaborated and further developed.

From the economic perspective, this is the major issue

- Treatment with antimicrobial agents for non-healing wounds is frequently described in terms of the price of various devices or drugs.

Non-healing wounds often result in a considerable financial burden, which is associated with the length of time to heal and the high incidence of complications. The price of a single item in treating individuals with non-healing ulcers should never be the key factor for decision making; each intervention has to be evaluated from the perspective of the total resources spent to achieve a specific goal, such as wound healing or resolution of an infection.

While it is important to identify interventions and strategies early to avoid complications and facilitate healing, these often have cost implications.

Treatment with antimicrobial agents for non-healing wounds is frequently described in terms of the price of various devices or drugs

For the future we need standardised criteria for cost analyses, which can be used to further identify the most economically effective ways to treat non-healing wounds. ■

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Appendices

Appendix 1. Primary endpoints of antimicrobial randomized controlled trials (RCTs)

Diabetic foot ulcer (DFU) | Leg ulcer (LU) | Mixed | Pressure ulcer (PU)
Malignant fungating wound (MFW) | Burn | Other

First author et al.	Title	Journal and publication year	Endpoint	Type of ulcer	Pre-definition of endpoint	Measurement technique
Biomarkers & Bacteriology						
Dumville, J.C. et al.	Larval therapy for leg ulcers (VenUS II): randomised controlled trial	BMJ. 2009; 338: b773	Bacterial load	LU (mixed)	—	Lab analyses; Clinical observation; Visual analog scale
Dumville, J.C. et al.	Larval therapy for leg ulcers (VenUS II): randomised controlled trial	BMJ. 2009; 338: b773	MRSA	LU (mixed)	—	Lab analyses; Clinical observation; Visual analog scale
Sipponen, A. et al.	Beneficial effect of resin salve in treatment of severe pressure ulcers: a prospective, randomised and controlled multicentre trial.	Br J Dermatol. 2008; 158: 5, 1055–1062	Eradication of bacterial strains	PU (category II– IV EPUAP) n=37	Not defined	Bacterial cultures
Verdú Soriano, J. et al.		J Wound Care. 2004; 13: 10, 419–423	Quantitative decrease of bacteria level/ or no. of germs	Mixed: chronic wounds (not further defined)	% reduction in wound volume at week 24	Bacterial quantitative and qualitative
Motta, G.J. et al.	Impact of antimicrobial gauze on bacterial colonies in wounds that require packing.	Ostomy Wound Manage. 2004; 50: 8, 48–62	Bacterial count before and after treatment	Mixed: different types of wounds (lacking tables in the article!!)	Bacterial count before and after treatment	Cultures

First author et al.	Title	Journal and publication year	Endpoint	Type of ulcer	Pre-definition of endpoint	Measurement technique
Biomarkers & Bacteriology						
Tredget, E.E. et al.	A matched-pair, randomized study evaluating the efficacy and safety of Acticoat silver-coated dressing for the treatment of burn wounds	J Burn Care Rehabil. 1998; 19: 6, 531–537	Level of antimicrobial effectiveness; patient comfort ease of use for the wound care provider Wound pain	Burn	No definition	Antimicrobial effectiveness: by quantitative burn wound biopsies performed before and at the end of treatment Wound pain VAS during dressing removal application, and 2 hours after application
Beele, H. et al.	A prospective randomised open label study to evaluate the potential of a new silver alginate/ carboxymethylcellulose antimicrobial wound dressing to promote wound healing	Int Wound J. 2010; 7: 262–270	Progress of wounds towards or away from infection Wound deterioration and progress of wounds towards or away from healing Wound healing/ deterioration	LU	Not defined	Infection: based on the signs and symptoms of 'critically colonised' or at risk of an infection wound deterioration and progress of wounds towards or away from healing: assessed by semi-quantitative evaluation and by change in wound area from baseline. Wound healing was evaluated semi-quantitatively by assigning weights to each non-healing or healing component. Deterioration=−1, stagnation=0, improvement=1 and healed=2.
Trial, C. et al.	Assessment of the antimicrobial effectiveness of a new silver alginate wound dressing: a RCT.	J Wound Care. 2010; 19: 1, 20–26	Reduction of local infection, local tolerance, acceptability and usefulness	Mixed (infected chronic ulcers)	No definition	Local signs of infection using a clinical score ranging from 0 to 18, and the evolution of the bacteriological status for each wound
Verdú Soriano, J. et al.	Effects of an activated charcoal silver dressing on chronic wounds with no clinical signs of infection.	J Wound Care. 2004; 13: 10, 419–423	Reduction in the number of bacteria	Mixed (infected chronic wounds)	No definition	Samples for bacterial status and cultivation were obtained by surface smear (spatula) and percutaneous aspiration first at baseline and then after 15 days of treatment

First author et al.	Title	Journal and publication year	Endpoint	Type of ulcer	Pre-definition of endpoint	Measurement technique
Biomarkers & Bacteriology						
Della Paola, L. et al.	Super-oxidised solution (SOS) therapy for infected diabetic foot ulcers	Wounds. 2006; 18: 9, 262–270.	Reduction in bacterial load, healing time, incidence of skin reactions	DFU	Probe to bone test, plain radiograph and debridement	Microbiological sample
Change in Wound Condition						
Carneiro, P.M. and Nyawawa, E.T.	Topical phenytoin versus EUSOL in the treatment of non-malignant chronic leg ulcers	East Afr Med J. 2003; 80: 3, 124–129	Presence of discharge (purulent, serous, absent), Healthy granulation tissue	LU (various aetiologies)	Presence of discharge (purulent, serous, absent)	Clinical evaluation
Gray, M. and Jones, D.P.	The effect of different formulations of equivalent active ingredients on the performance of two topical wound treatment products	Ostomy Wound Manage. 2004; 50: 3, 34–44	Erythema	Mixed: Experimental laser induced partial thickness wounds	Not defined Erythema,oedema, scabbing and reepithelialisation	10-point scales for each endpoint
Costs & Resources Used						
Clay, P.G. et al.	Clinical efficacy, tolerability, and cost savings associated with the use of open-label metronidazole plus ceftriaxone once daily compared with ticarcillin/clavulanate every 6 hours as empiric treatment for diabetic lower-extremity infections in older males	Am J Geriat Pharmaco. 2004; 2: 3, 181–189	Institutional cost	DFU (Wagner 1–3, infection)	Cost for antibiotics and treatment days —contract prices	Generalised per patient group not individualised
Jull, A. et al.	Randomized clinical trial of honey-impregnated dressings for venous leg ulcers	Br J Surg. 2008; 95: 2, 175–182	Cost	LU (VLU)	No definition (infection, adverse effects QoL, cost/effect)	—
Dressing Performance						
Dumville, J.C. et al.	Larval therapy for leg ulcers (VenUS II): randomised controlled trial.	BMJ. 2009; 338: b773	Adverse effects	LU (mixed)	No definition	Lab analyses Clinical observation Visual analog scale
Jull, A. et al.	Randomized clinical trial of honey-impregnated dressings for venous leg ulcers	Br J Surg. 2008; 95: 2, 175–182	Adverse effects	LU (VLU)	Infections, adverse effects QoL, cost/effect	Clinical sign of infection

First author et al.	Title	Journal and publication year	Endpoint	Type of ulcer	Pre-definition of endpoint	Measurement technique
Dressing Performance						
Tumino, G. et al.	Topical treatment of chronic venous ulcers with sucralfate: A placebo controlled randomized study	Int J Molecular Med. 2008; 22: 1, 17–23	Safety	LU (VLU; n=100)	Therapy tolerance	Haematological and haematochemical analysis: 4-point scale of tolerance based on lab results
Chen, J. et al.	Effect of silver nanoparticle dressing on second degree burn wound [in Chinese]	Zhonghua Wai Ke Za Zhi. 2006; 44: 1, 50–52	Effect	Burn (2nd degree)	No definition	Reduction in bacterial colonisation of the wounds
Healing Time						
Jude, E.B. et al.	Prospective randomized controlled study of Hydrofiber dressing containing ionic silver or calcium alginate dressings in non-ischaemic diabetic foot ulcers	Diabetic Med. 2007; 24: 3, 280–288	Speed of healing, time to heal	DFU	Percent wound area reduction or cm^2/week	Tracing photograph
Kucharzewski, M. et al.	Treatment of venous leg ulcers with sulodexide	Phlebologie. 2003; 32: 5, 115–120	Numbers healed	LU (VLU; n=44)	No definition	Computerised planimetry Swab
Jull, A. et al.	Randomized clinical trial of honey-impregnated dressings for venous leg ulcers	Br J Surg. 2008; 95: 2, 175–182	Time to healing Change in ulcer size	LU (VLU)	No definition	Photograph
Tumino, G. et al.	Topical treatment of chronic venous ulcers with sucralfate: A placebo-controlled randomized study	Int J Molecular Med. 2008; 22: 1, 17–23	Healing rate	LU (VLU; n=100)	Healing rate in days Overall efficacy rated on 4-point scale	Lesion size (cm^2) Days to healing Evolution of granulation tissue Clinical signs of inflammation, exudate and swelling, symptoms of pain/burning Healing rate (3/4-point scales used)
Opasanon, S. et al.	Clinical effectiveness of alginate silver dressing in outpatient management of partial-thickness burns.	Int Wound J. 2010; 7: 6, 467–471	Healing time Pain	Burn	Demographics (age, gender, type of burn injury, location of burn and TBSA burn%) Wound characteristics	Healing progression was assessed in terms of time to healing. Visual analog pain scale 1–10;
Muangman, P. et al.	A prospective, randomized trial of silver containing Hydrofiber dressing versus 1% silver sulfadiazine for the treatment of partial thickness burns.	Int Wound J. 2010; 7: 4, 271–276	Time to healing Pain during dressing changes, Cost-effectiveness.	Burn	Not defined	Day of wound closure Pain scores at each dressing change Hospital charges, patient's transportation cost, time of dressing change Burn wound infection

First author et al.	Title	Journal and publication year	Endpoint	Type of ulcer	Pre-definition of endpoint	Measurement technique
Healing time						
Chuangsuwanich, A. et al.	The efficacy of silver mesh dressing compared with silver sulfadiazine cream for the treatment of pressure ulcers	J Med Assoc Thai. 2011; 94: 5, 559–565	Healing rate and percentage reduction	PU (category III/IV)	No definition	PUSH score
Dimakakos, E. et al.	Infected venous leg ulcers: management with silver-releasing foam dressing	Wounds. 2009; 21: 1, 4–8	Ulcer healing after 9 weeks	LU	Not defined	Initial wound diameter, depth, degree of exudation
Michaels, J.A. et al.	Randomized controlled trial and cost-effectiveness analysis of silver-donating antimicrobial dressings for venous leg ulcers (VULCAN trial)	Br J Surg. 2009; 96: 1147–1156	Complete ulcer healing at 12 weeks	LU	—	Complete epithelialisation of the ulcer with no scab, and 12 weeks was chosen on the basis of national guidelines related to the care of venous ulcer
Jude, E.B. et al.	Prospective randomized controlled study of Hydrofiber dressing containing ionic silver or calcium alginate dressings in non-ischaemic diabetic foot ulcers	Diabetic Med. 2007; 24: 280–288	Time to healing	DFU	No definition	Time in days to 100% healing was estimated by Kaplan-Meier survival analysis applying intent-to-treat analysis on all 67 subjects in each primary dressing group
Miller, C.N. et al.	A randomized-controlled trial comparing cadexomer iodine and nanocrystalline silver on the healing of leg ulcers	Wound Repair Regen. 2010; 18; 359–367	Wound healing rate (% change in wound size) and the number of healed wounds (100% closure) over a 12-week period. Wound size was measured using the Advanced Medical Wound Imaging System V2.2 (AMWISt) software	LU	No definition	Wound healing rate (% change in wound size) No. of healed wounds (100% closure) over a 12-week period. Wound size: the Advanced Medical Wound Imaging System V2.2 (AMWISt) software
Piaggesi, A. et al.	A randomized controlled trial to examine the efficacy and safety of a new super-oxidized solution for the management of wide postsurgical lesions of the diabetic foot	Int J Lower Extrem Wounds. 2010; 9: 10; 10–15	Healing rate at 6 months	DFU	In percentages	In percentages, measuring, photograph Sampled for qualitative microbiology

First author et al.	Title	Journal and publication year	Endpoint	Type of ulcer	Pre-definition of endpoint	Measurement technique
Healing Time						
Hadi, S.F. et al.	Treating infected diabetic wounds with superoxidated water as anti-septic agent: a preliminary experience	J Coll Physicians Surg Pak. 2007; 17: 12, 740–743	Wound healing time, duration of hospital stay, downgrading of the wound category and need for additional interventions	DFU	Not defined	Not defined
Signs of Infection						
Martínez-De Jesús, F.R. et al.	Efficacy and safety of neutral pH superoxidised solution in severe diabetic foot infections	Int Wound J. 2007; 4: 4, 353–362	Infection control	DFU	Resolution of cellulitis >50% of erythema	Clinical observation Photographs
Lipsky, B.A. and Stoutenburgh, U.	Daptomycin for treating infected diabetic foot ulcers: Evidence from a randomized, controlled trial comparing daptomycin with vancomycin or semi-synthetic penicillins for complicated skin and skin-structure infections	J Antimicrob Chemother. 2005; 55: 2, 240–245	Resolution of infection	DFU (infection)	Cured improved failure	Independent observer
Kästenbauer, T. et al.	Evaluation of granulocyte-colony stimulating factor (Filgrastim) in infected diabetic foot ulcers	Diabetologia. 2003; 46: 1, 27–30	Resolution of cellulitis	DFU (infection)	Clinically defined, Infection score	Scoring system ('Total Wound Score')
Lipsky, B.A. et al.	Topical versus systemic antimicrobial therapy for treating mildly infected diabetic foot ulcers: a randomized, controlled, double-blinded, multicenter trial of pexiganan cream	Clin Infect Dis. 2008; 47: 12, 1537–1545	Clinical cure or improvement of infection	DFU (mild infection)	'Total Wound Score'	Scoring system ('Total Wound Score')
Clay, P.G. et al.	Clinical efficacy, tolerability, and cost savings associated with the use of open-label metronidazole plus ceftriaxone once daily compared with ticarcillin/clavulanate every 6 hours as empiric treatment for diabetic lower-extremity infections in older males	Am J Geriatr Pharmacother. 2004; 2: 3, 181–189	Resolution of infection	DFU (Wagner 1–3 infection)	One out of: Temperature < 38.3°C Cap-glucose monitoring Wound staging, WBC < 10 000	Per protocol summarised parameter

First author et al.	Title	Journal and publication year	Endpoint	Type of ulcer	Pre-definition of endpoint	Measurement technique
Signs of Infection						
Lipsky, B.A. et al.	Ertapenem versus piperacillin/tazobactam for diabetic foot infections (SIDESTEP): prospective, randomised, controlled, double-blinded, multicentre trial	Lancet. 2005; 366: 9498, 1695–1703	Resolution of infection	DFU (infection)	Favourable clinical response/cure	At the discretion of the physican
Lipsky, B.A. et al.	Treating diabetic foot infections with sequential intravenous to oral moxifloxacin compared with piperacillin-tazobactam/ amoxicillin-clavulanate	J Antimicrob Chemother. 2007; 60: 2, 370–376	Resolution of infection	DFU (infection)	Clinically defined	At the discretion of the physician
Lipsky, B.A. et al.	Treating foot infections in diabetic patients: a randomized, multicenter, open-label trial of linezolid versus ampicillin-sulbactam/amoxicillin-clavulanate	Clin Infect Dis. 2004; 38: 1, 17–24	Resolution of infection	DFU (infection)	Cured, improved or failure	At the discretion of the physician
Jull, A. et al.	Randomized clinical trial of honey-impregnated dressings for venous leg ulcers	Br J Surg. 2008; 95: 2, 175–182	Infection	LU (VLU)	No definition	Clinical sign of infection
Krishnamoorthy, L. et al.	The clinical and histological effects of Dermagraft in the healing of chronic venous leg ulcers	Phlebology. 2003; 18: 1, 12–22	Wound infection	LU (VLU)	No definition	Clinical sign
Meaume, S. et al.	A study to compare a new self-adherent soft silicone dressing with a self-adherent polymer dressing in stage II pressure ulcers.	Ostomy Wound Manage. 2003; 49: 9, 44–51	Signs of inflammation	PU (category II; n=38)	No defintion	Size by tracing: other variables as present or absent Exudate: low, moderate or high Granulation tissue as covering 0–25%, 26–50%, 51–75%, 76–100% Surrounding skin damage was described as redness, blisters or other Dressing removal was rated as very easy, easy, minor difficulties or difficult

First author et al.	Title	Journal and publication year	Endpoint	Type of ulcer	Pre-definition of endpoint	Measurement technique
Signs of Infections						
Cereda, E. et al.	Disease-specific, versus standard, nutritional support for the treatment of pressure ulcers in institutionalized older adults: a randomized controlled trial	J Am Geriatr Soc. 2009; 57: 8, 1395–1402	Infection occurrence and hospitalisation (days of antibiotic therapy; days in hospital)	PU (category II–IV)	No definition	Data records
Kordestani, S. et al.	A randomised controlled trial on the effectiveness of an advanced wound dressing used in Iran	J Wound Care. 2008; 17: 7, 323–327	Presence of infection	Mixed: chronic wounds (28 PU [NPUAP], 20 LUs, 12 DFU [Wagner])	Clear definition of infection	Swabs Planimetry
Meaume, S. et al.	Evaluation of a silver-releasing hydroalginate dressing in chronic wounds with signs of local infection	J Wound Care. 2005; 14: 9, 411–419	Wound severity, infection	Mixed: LU, PU	Definition by index score	Score system (ASEPSIS Index Score)
Meaume, S. et al.	Evaluation of a silver-releasing hydroalginate dressing in chronic wounds with signs of local infection	J Wound Care 2005; 14; 9, 411–419	Wound infection	Mixed (chronic infected wounds)	No definition	Wounds were assessed daily over 14 days to complete a modified ASEPSIS index to evaluate risk of infection
Reduction Rate						
Purandare, H. and Supe, A.	Immunomodulatory role of Tinospora cordifolia as an adjuvant in surgical treatment of diabetic foot ulcers: a prospective randomized controlled study	Indian J Med Sci. 2007; 61: 6, 347–355	Change in wound area	DFU	No definition	Peccoraro Wound severity score Manual measurement of ulcer
Martínez-Sánchez, G. et al.	Therapeutic efficacy of ozone in patients with diabetic foot	Eur J Pharmacol. 2005; 523: 1–3, 151–161	Wound area reduction	DFU	No definition	Tracing, computer
Tumino, G. et al.	Topical treatment of chronic venous ulcers with sucralfate: a placebo-controlled randomized study	Int J Molecular Med. 2008; 22: 1, 17–23	Ulcer size	LU (VLU; n=100)	Healing rate in days Overall efficacy rated on 4-point scale	Lesion size (cm^2) Days to healing Evolution of granulation tissue Clinical signs of inflammation, exudate and swelling: symptoms of pain and burning: healing rate (3/4–point scales used)

First author et al.	Title	Journal and publication year	Endpoint	Type of ulcer	Pre-definition of endpoint	Measurement technique
Reduction Rate						
Yapucu Günes, U. and Eser, I.	Effectiveness of a honey dressing for healing pressure ulcers	J Wound Ostomy Continence Nurs. 2007; 34: 2, 184–190	Healing	PU (category II/III; n=26	Change in PUSH score	Acetate tracing PUSH tool
Meaume, S. et al.	Evaluation of a silver-releasing hydroalginate dressing in chronic wounds with signs of local infection	J Wound Care. 2005; 14: 9, 411–419	Closure rate	Mixed: LU, PU	No definition	Percentage area reduction Tracing
Harding, K. et al.	A prospective, multi-centre, randomised, open label, parallel, comparative study to evaluate effects of AQUACEL Ag and Urgotul Silver dressing on healing of chronic venous leg ulcers	Int Wound J. 2011; doi: 10.1111/j. 1742-481X.2011. 00881.x	Size reduction	LU (VLU)	No definition	Photograph Wound status, perilesional skin appearance and condition of the wound were recorded
Lazareth, I. et al.	The role of a silver releasing lipido-colloid contact layer in venous leg ulcers presenting inflammatory signs suggesting heavy bacterial colonization: results of a randomized controlled study	Wounds. 2008; 20: 6, 158–166	Reduction of surface area	LU (VLU)	No definition	No definition
Wunderlich, U. and Orfanos, O.E.	Treatment of venous ulcera cruris with dry wound dressings. Phase overlapping use of silver impregnated activated charcoal xerodressing [in German]	Hautarzt. 1991; 42: 7, 446–450	Epithelialisation Reduction of ulcer size	LU	No definition	The parameters of wound healing were documented
Jørgensen, B. et al.	The silver-releasing foam dressing, Contreet Foam, promotes faster healing of critically colonised venous leg ulcers: a randomised controlled trial	Int Wound J. 2005; 2: 1, 64–73	Reduction rate	LU (VLU)	No definition	Wound size was traced using transparent wound tracing sheets and measured using Image Pro Plus S.O software
Münter, K.C. et al.	Effect of a sustained silver-releasing dressing on ulcers with delayed healing: the CONTOP study	J Wound Care. 2006; 15: 5, 199–206	Reduction in wound size	Mixed (chronic wounds)	No definition	No definition

First author et al.	Title	Journal and publication year	Endpoint	Type of ulcer	Pre-definition of endpoint	Measurement technique
Reduction Rate						
Russell, L.	The CONTOP multinational study: preliminary data from the UK arm	Wounds UK. 2005; 1: 44–54	Relative reduction in wound area	Mixed (chronic wounds)	No definition	No definition
Lund-Nielsen, B. et al.	Qualitative bacteriology in malignant wounds—a prospective, randomized, clinical study to compare the effect of honey and silver dressings	Ostomy Wound Manage. 2011; 57: 7, 28–36.	Reduction of wound size Dressings influenced the presence of potential wound pathogens that may increase the risk of wound infection	MFW	Swab cultures	Digital photographs Swab
Robson, V. et al.	Standardized antibacterial honey (Medihoney) with standard therapy in wound care: randomized clinical trail	J Adv Nurs. 2008; 65: 3, 565–575	Healing time Time to 50% reduction in wound area	Mixed (chronic wounds)	Assessment with report forms	Wound photographs and measurements
Gethin, G. et al.	Manuka honey vs. hydrogel—a prospective, open label, multicentre, randomised controlled trail to compare desloughing efficacy and healing outcomes in venous ulcers	J Clin Nurs. 2009; 18: 3, 466–474	Wound healing Slough reduction	LU (VLU)	No definition	Measurement using Visitrak digital planimetry
Marshall, C. et al.	Honey vs povidone iodine following toenail surgery	Wounds UK. 2005; 5: 10–18	Time for complete re-epitelisation	Other	Assessment for toenail surgery	Assessment
Robson, V. et al.	Randomised controlled feasibility trail on the use of medical grade honey following microvascular free tissue transfer to reduce the incidence of wound infection	Br J Oral Maxillofac Surg. 2012; 50: 4, 321–527	Reduction of incidence of wound infection	Other	Swab	Swab
Nagl, M. et al.	Tolerability and efficacy of N-chlorotaurine in comparison with chloramine T for the treatment of chronic leg ulcers with a purulent coating: a randomized phase II study	Br J Dermatol/ 2003; 149: 3, 590–597	Intensity of pain	LU (not defined)	Intensity of pain	VAS scale

First author et al.	Title	Journal and publication year	Endpoint	Type of ulcer	Pre-definition of endpoint	Measurement technique
Symptoms, Signs						
Varas, R.P. et al.	A prospective, randomized trial of Acticoat versus silver sulfadiazine in the treatment of partial-thickness burns: which method Is less painful?	J Burn Care Rehabil. 2005; 26: 4, 344–347	Pain	Burn	No definition	VAS
Romanelli, M. and Price, P.	Health-related quality of life aspects after treatment with a foam dressing and a silver-containing foam dressing in chronic leg ulcers	J Am Acad Dermatol. 2005; 52: 21	Reduction of odour Pain	LU	No definition	No definition
Della Paola, L. et al.	Super-oxidized solution (SOS) therapy for infected diabetic foot ulcers	Wounds. 2006; 18: 9, 262–270	Reduction of bacterial load	DFU	No definition	Measuring the number of strains quantified at enrollement and at the time of operative closure
Wound Closure						
Jude, E.B. et al.	Prospective randomized controlled study of Hydrofiber dressing containing ionic silver or calcium alginate dressings in non-ischaemic diabetic foot ulcers	Diabetic Med. 2007; 24: 3, 280–288	Wound closure	DFU	Not defined	Days to closure
Lazareth, I. et al.	The role of a silver releasing lipido-colloid contact layer in venous leg ulcers presenting inflammatory signs suggesting heavy bacterial colonization: results of a randomized controlled study	Wounds, 2008; 20: 6, 158–166	Wound closure	LU	Yes	Clinical evaluation
Jull, A. et al.	Randomized clinical trial of honey-impregnated dressings for venous leg ulcers	Br J Surg. 2008; 95: 2, 175–182	Complete healing	LU (VLU)	Complete epithelialisation, no scab	Complete epithelialisation, no scab
Daróczy, J.	Quality control in chronic wound management: the role of local povidone-iodine (Betadine) therapy	Dermatology. 2006; 212: (Suppl. 1), 82–87	Percentage healed Relapse rate of superficial bacterial skin infections (bacterial culture)	LU (VLU; n=63)	Percentage healed Relapse rate of superficial bacterial skin infections (bacterial culture)	No definition

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