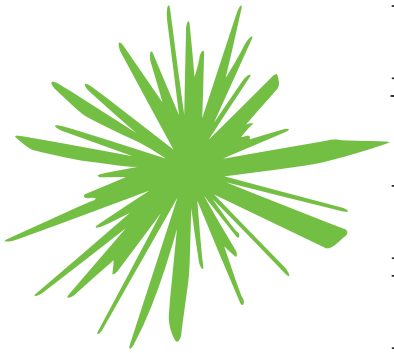
INTERNATIONAL CONSENSUS UPDATE **2016**



INTERNATIONAL WOUND INFECTION INSTITUTE

WOUND INFECTION IN CLINICAL PRACTICE

Principles of best practice

2016

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Foreword

The International Wound Infection Institute (IWII) is an organisation of volunteer interdisciplinary health professionals dedicated to advancing and improving practice relating to prevention and control of wound infection. This includes acute wounds (surgical, traumatic and burns) and chronic wounds of all types, although principally chronic wounds of venous, arterial, diabetic and pressure aetiologies.

Wound infection is a common complication of wounds. It leads to delays in wound healing and increases the risk of loss of limb and life. Implementation of effective strategies to prevent, diagnose and manage, is important in reducing mortality and morbidity rates associated with wound infection.

This second edition of *Wound Infection in Clinical Practice* is an update of the first edition published in 2008 by the World Union of Wound Healing Societies (WUWHS). The original document was authored by leading experts in wound management and endorsed by the WUWHS. The intent of this edition is to provide a practical, updated resource that is easy-to-use and understand.

For this edition, the IWII collaborative team has undertaken a comprehensive review of contemporary literature, including systematic reviews and meta-analyses when available. In addition, the team conducted a formal Delphi process to reach consensus on wound infection issues for which scientific research is minimal or lacking. This rigorous process provides an update on the science and expert opinion regarding prevention, diagnosis and control of wound infection. This edition outlines new definitions relevant to wound infection, presents new paradigms and advancements in the management and diagnosis of a wound infection, and highlights controversial areas of discussion.

We hope this updated resource will guide your clinical practice and will serve as an informative resource for the education of other health professionals, as well as individuals with, or at risk of, wound infection.

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Principles of best practice

This update provides an opportunity to explore contemporary advances in wound infection knowledge and practice. Since 2008, scientific and clinical understanding of chronic wound infection has developed significantly.[1-3] In particular, awareness of the presence and impact of wound biofilm has advanced enormously; however, understanding of its pathogenesis is yet to be clarified fully[4-8]. A holistic approach to individuals with, or at risk of, active wound infection remains essential to best practice in prevention, identification and management of wound infection. This is of particular importance in the context of increasing antibiotic resistance.

This update is the result of a comprehensive literature review that identified relevant contemporary evidence, together with a formal Delphi process to establish expert consensus on topics where scientific evidence is lacking. The full methodology is outlined in Appendix 1. Key updates appraised in this edition include:

- The wound infection continuum
- Definitions related to wound chronicity
- Identification and diagnosis of wound infection
- Topical and systemic management of wound infection using a holistic approach.

The primary determinants of the pathological process through which presence of bacteria and other microorganisms results in wound infection and harmful effects on an individual with, or at risk of, a wound remains the same. These primary factors can be briefly outlined as:

- The ability of the immune system to combat potential pathogens (host defence)[9-11]
- The number of microbes in the wound. A greater number of microbes can overwhelm host defences[11]
- The species of bacteria or microbe present. Some microbes have greater capacity to produce a detrimental effect in low numbers (virulence) and some are able to form and reform biofilm more rapidly.[12, 13]

PRACTICE POINT

The effectiveness of the host's defence system, together with the quantity and virulence of microbes, influences the development of wound infection

"A holistic approach to individuals with, or at risk of, active wound infection remains essential to best practice in prevention, identification and management of wound infection. This is of particular importance in the context of increasing antibiotic resistance."

DEFINITIONS

International debate regarding the wound infection continuum and definitions associated with wound infection is ongoing. A persistent area of contention has been identification of the point at which management of wound infection should commence, particularly for wounds that do not exhibit the classic signs and symptoms associated with wound infection.

Through three rounds of Delphi voting, the IWII expert authors agreed on the following:

- Critical colonisation should be removed from the wound infection continuum due to the lack of a specific definition or unanimous understanding of the term
- The term 'microbes' should replace 'bacteria' in the wound infection continuum, given the understanding that organisms other than bacteria (e.g. fungi) are common causatives of wound infection
- Presence of biofilm should be added to the wound infection continuum
- Definitions for acute and chronic wounds.

The IWII experts reached agreement on the following definitions:

Acute wound: a wound with an aetiology that occurs suddenly, either with or without intention, but then heals in a timely manner.

Chronic wound: a wound that has a slow progression through the healing phases, or shows delayed, interrupted or stalled healing due to intrinsic and extrinsic factors that impact on the individual and their wound. A chronic, non-healing wound could be suggestive of a biofilm, providing holistic evaluation has excluded or corrected underlying pathologies such as ischaemia.

Biofilm: a structured community of microbes with genetic diversity and variable gene expression (phenotype) that creates behaviours and defences used to produce unique infections (chronic infection). Biofilms are characterised by significant tolerance to antibiotics and biocides while remaining protected from host immunity.

The wound infection continuum

PRACTICE POINT

Wound infection is the presence of microbes in sufficient numbers or virulence to cause a host response locally and or systemically

Box 1: Advances in terminology

The term 'critical colonisation' has been a topic of debate since it was first proposed in 1998 as a concept describing the identification of wound infection through clinical observation rather than microbial confirmation.[1] Several terms are synonymous with critical colonisation, including local infection, topical infection and covert infection. Regardless of the term used, it is now generally accepted that a wound with microbial imbalance exhibits subtle signs and symptoms that can be observed by experienced clinicians.[2, 3] These covert signs of local infection are often apparent before the wound exhibits classic (overt) signs and symptoms.

Wound infection is the invasion of a wound by proliferating microorganisms to a level that invokes a local and/or systemic response in the host. The presence of microorganisms within the wound causes local tissue damage and impedes wound healing.[3, 11] Intervention is generally required to assist host defences in destroying the invading microorganisms.[3] The wound infection continuum provides a framework through which the impact microbes have on a wound and wound healing can be conceptualised (Figure 1).

STAGES IN THE WOUND INFECTION CONTINUUM

The relationship between the host, the wound and microorganisms in the development of wound infection has been well described in the literature. However, the concept of wound microbial balance and the progression from a state of wound contamination to systemic infection is yet to be established fully.

It is well acknowledged that it is more than the presence of bacteria that leads to adverse events in wounds. The wound infection continuum has been updated to reflect that microbes other than bacteria are associated with wound infection, and microbial virulence (as well as numbers) contributes to the development of wound infection.[2, 3, 11, 14-16] The stages in the wound infection continuum describe the gradual increase in the number and virulence of microorganisms, together with the response they invoke within the host (Figure 1).[3]

Contamination

Wound contamination is the presence of non-proliferating microbes within a wound at a level that does not evoke a host response.[2, 3] Virtually from the time of wounding, all open wounds are contaminated with microbes. Chronic wounds become contaminated from endogenous secretions (i.e. natural flora) and exogenous microbial sources, including poor hand hygiene practised by healthcare clinicians and environmental exposure.[17] Unless compromised, the host defences respond swiftly to destroy bacteria through a process called phagocytosis.[18]

Colonisation

Colonisation refers to the presence within the wound of microbial organisms that undergo limited proliferation without evoking a host reaction.[3, 11] Microbial growth occurs at a non-critical level, and wound healing is not impeded or delayed.[18, 19] Sources for microorganisms may be natural flora, exogenous sources or as a result of environmental exposure.

Local infection

Wound infection occurs when bacteria or other microbes move deeper into the wound tissue and proliferate at a rate that invokes a response in the host.[2, 11] Local infection is contained in one location, system or structure. Especially in chronic wounds, local wound infection often presents as subtle signs that can be considered covert signs of infection[20, 21] that may develop into the classic, overt signs of infection. This is discussed in more detail opposite and in Table 1.

Spreading infection

Spreading infection describes the invasion of the surrounding tissue by infective organisms that have spread from a wound. Microorganisms proliferate and spread, to a degree that signs and symptoms extend beyond the wound border.[22, 23] Spreading infection may involve deep tissue, muscle, fascia, organs or body cavities.

Systemic infection

Systemic infection from a wound affects the body as a whole,[22] with microorganisms spreading throughout the body via the vascular or lymphatic systems. Systemic inflammatory response, sepsis and organ dysfunction are signs of systemic infection.[23]

In the development of this update, the IWII experts agreed that the display of covert signs of infection is an early stage of local infection, and does not represent a distinctly different phase in the wound infection continuum. Thus, the term 'critical colonisation', which has previously been poorly defined, has been removed from the continuum in this update (Box 1).

Table 1 provides detailed information regarding the signs and symptoms commonly exhibited by the individual and the wound as infection emerges and proliferates. This includes the distinction between covert and overt local infection.

Figure 1 | IWII wound infection continuum[22, 24, 25]

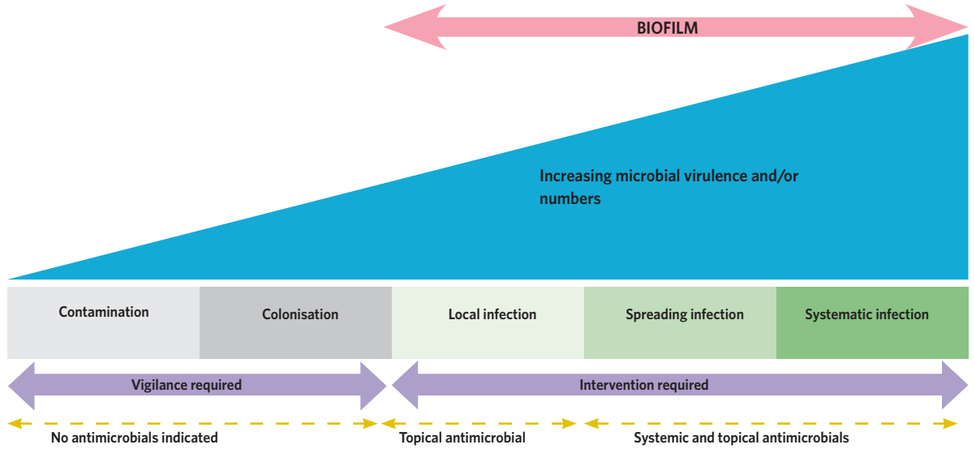

Table 1: Signs and symptoms associated with stages of the wound infection continuum

Contamination[26]	Colonisation[26]	Local infection		Spreading infection[22, 23]	Systemic infection[22, 23]
All wounds may acquire micro-organisms. If suitable nutritive and physical conditions are not available for each microbial species, or they are not able to successfully evade host defences, they will not multiply or persist; their presence is therefore only transient and wound healing is not delayed	Microbial species successfully grow and divide, but do not cause damage to the host or initiate wound infection	Covert (subtle) signs of local infection:[2, 27-36] ■ Hypergranulation (excessive 'vascular' tissue) ■ Bleeding, friable granulation ■ Epithelial bridging and pocketing in granulation tissue ■ Wound breakdown and enlargement ■ Delayed wound healing beyond expectations ■ New or increasing pain ■ Increasing malodour	Overt (classic) signs of local infection:[2, 27, 28, 35, 36] ■ Erythema ■ Local warmth ■ Swelling ■ Purulent discharge ■ Delayed wound healing beyond expectations ■ New or increasing pain ■ Increasing malodour	■ Extending in duration +/- erythema ■ Lymphangitis ■ Crepitus ■ Wound breakdown/ dehiscence with or without satellite lesions ■ Malaise/ lethargy or non-specific general deterioration ■ Loss of appetite ■ Inflammation, swelling of lymph glands	■ Severe sepsis ■ Septic shock ■ Organ failure ■ Death

Biofilm in the wound

The wound infection continuum has been updated to include biofilm. Early research has provided evidence regarding biofilms and the disease concept.[37, 38] The seminal work of three studies published in 2008 confirmed that biofilms develop in wounds.[4, 6, 14] Using scanning electron microscopy, in 2008 James et al, via a prospective study, established that 60% of chronic wounds contained biofilm, compared to 6% of acute wounds.[4] Since then, a rapidly expanding body of scientific literature has described the impact of biofilm on a wound. The growing understanding and acceptance of the role of biofilm in wound infection has led to evolution in clinical management of the chronic, non-healing wound that seeks to address potential presence of biofilm.[39, 40] Revision of the wound infection continuum highlights the significant progression of both scientific knowledge and clinical practice with respect to understanding and managing wound biofilm.

BIOFILM CYCLE

Despite significant advances, emerging science from the laboratory has yet to provide us with a full understanding of wound biofilm in the clinical context. However, biofilm-associated complications that increase the risk of morbidity and mortality warrant emphasis on wound bed preparation[41] that incorporates the principles of biofilm-based wound care (BBWC).[23, 42-44] Treatment strategies should be based on the cycle of biofilm[38, 45] (Figure 2), and aim to prevent attachment, interrupt quorum sensing and planktonic phenotypic changes, and to prevent or delay re-formation of biofilm.

Figure 2 illustrates the cycle of biofilm formation, maturation and dispersal. Based on *in vitro* research the stages in the biofilm cycle are briefly described:

Planktonic
In the planktonic phase, free-floating, non-attached single microbes attach to a surface or each other. In this early phase, the attachment is weak and reversible. The attachment is mediated by pili, flagella or other surface appendages or specific receptors.[46, 47] Most antimicrobial treatments are based on disrupting or killing microbes during the planktonic phase.

Irreversible attachment
If single microbes that are anchored together or to a surface are not separated, the attachments made via pili, flagella and other appendages become stronger and irreversible. Attachment of microbes is mediated by the secretions of the extracellular polymeric substance (EPS). The EPS surrounds the growing colony and acts as a protective barrier against the host immune response.[47]

Cell proliferation
After attachments become strong and irreversible, microbe cells begin proliferating via a mechanism called quorum sensing (a process by which bacteria can regulate and respond to fluctuations in cell population density).[48] When quorum-sensing molecules are secreted, other microbes become attracted to, and join, the biofilm colony.[47] This process results in formation of micro-colonies.

Growth and maturation
The biofilm grows and differentiates, culminating in a mature biofilm community with structural features such as water channels and towering clusters of cells. The host's defences are inadequate to eradicate the biofilm, but recognise its presence with inappropriate over-recruitment of neutrophils, pro-inflammatory cytokines and excessive host-derived proteases. This leads to tissue destruction and increased capillary permeability which, in turn, provides nutrition for the biofilm.[47] Once biofilm is in the mature state, it is postulated that normal wound management strategies are less effective.

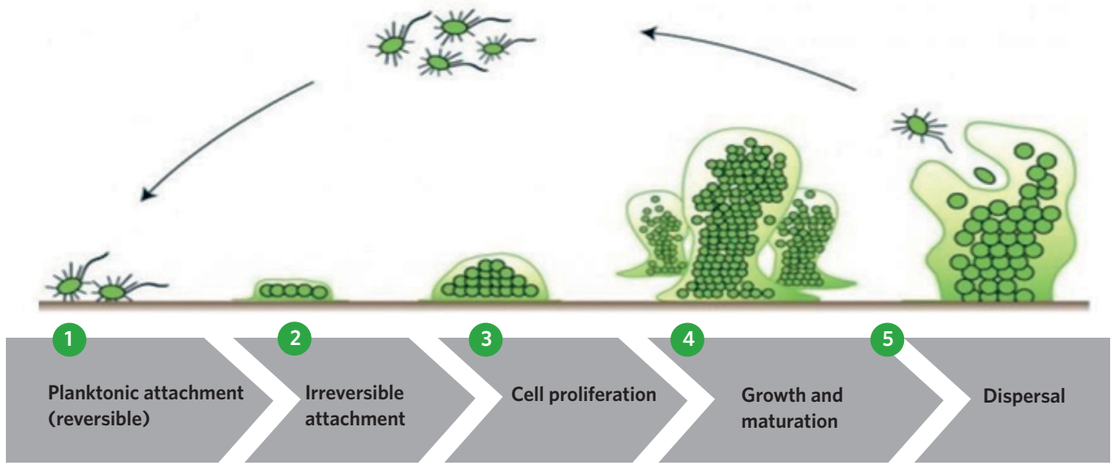

Figure 2 | Biofilm cycle

(Adapted from Stoodley et al, 2002[38] and Clinton and Carter, 2015.[45] *Reprinted with permission*)

Dispersal
Mature biofilm begins reseeding the wound surface with planktonic microbes as either a passive or active dispersal process. Abundant nutrition is suggested as one trigger for passive dispersal.[47, 49]

PRACTICE POINT

Biofilm cannot be directly visualised in a wound. The experienced clinician may suspect biofilm is present through observation of indicative wound characteristics

IDENTIFYING BIOFILM IN A WOUND

The identification of biofilm in a wound via visual indicators has been a recent area of debate.[23] Some commentary has suggested that 'foreign' material (e.g. fibrin, necrosis, slimy surface substance) on a wound surface represents biofilm.[50, 51] However, research on wound samples indicates that, while biofilm may account for the visible appearance of some wounds, it is not a conclusive indicator.

Further, many wounds that appear to be healthy to the naked eye are shown via laboratory investigation to have biofilm present that contributes to stalled healing.[52] Biofilm can form deep in wound tissue where it is impossible to identify visually.[5, 53] Further research is required for this particular aspect of biofilm identification, and research on identification of signs and symptoms of biofilm continues in laboratory and clinical fields.[51] Box 2 outlines the criteria indicative of a potential biofilm.

Box 1: Criteria indicative of potential biofilm

- Failure of appropriate antibiotic treatment
- Recalcitrance to appropriate antimicrobial treatment
- Recurrence of delayed healing on cessation of antibiotic treatment
- Delayed healing despite optimal wound management and health support
- Increased exudate/moisture
- Low-level chronic inflammation
- Low-level erythema
- Poor granulation/friable hypergranulation
- Secondary signs of infection

Diagnosis of wound infection

Understanding the risk factors, and the signs and symptoms of wound infection is imperative for health professionals. The presumptive diagnosis of wound infection is principally based on the clinician's assessment of the individual (host), the wound and periwound tissue, and host responses such as systemic inflammatory response or sepsis. Comprehensive assessment for wound infection aids early detection and timely treatment.

RISK OF INFECTION

Characteristics of both the individual, their wound and the wound environment can contribute to the development of infection in a wound. The type of wound (i.e. acute or chronic) contributes to infection risk, and a variety of additional factors associated with the operative procedure increase the risk for infection in surgical wounds.[54, 55]

In most cases, development of wound infection is multifactorial and occurs when cumulative risk factors overwhelm the host's defence system.[55] Table 2 outlines factors that are associated with an increased risk of wound infection.

Table 2: Factors associated with increased risk of wound infection

Characteristics of the individual[21, 40, 41, 56-60 21, 40, 41, 54, 55, 58, 61-66]

- Poorly controlled diabetes
- Prior surgery
- Radiation therapy or chemotherapy
- Conditions associated with hypoxia and/or poor tissue perfusion (e.g. anaemia, cardiac or respiratory disease, arterial or vascular disease, renal impairment, rheumatoid arthritis, shock)
- Immune system disorders (e.g. acquired immune deficiency syndrome, malignancy)
- Inappropriate antibiotic prophylaxis, particularly in acute wounding
- Protein-energy malnutrition
- Alcohol, smoking and drug abuse

Characteristics of the wound[21, 40, 54, 55]

Acute wounds	Chronic wounds	Both wound types
■ Contaminated or dirty wounds	■ Degree of chronicity/duration of wound	■ Foreign body (e.g. drains, sutures)
■ Trauma with delayed treatment	■ Large wound area	■ Haematoma
■ Pre-existing infection or sepsis	■ Deep wound	■ Necrotic wound tissue
■ Spillage from gastro-intestinal tract	■ Anatomically located near a site of potential contamination (e.g. perineum or sacrum)	■ Impaired tissue perfusion
■ Penetrating wounds over 4 hours		■ Increased exudate or moisture
■ Inappropriate hair removal		
■ Operative factors (e.g. long surgical procedure, hypothermia, blood transfusion)		

Characteristics of the environment[21, 40, 66]

- Hospitalisation (due to increased risk of exposure to antibiotic resistant organisms)
- Poor hand hygiene and aseptic technique
- Unhygienic environment (e.g. dust, unclean surfaces, mould/mildew in bathrooms)
- Inadequate management of moisture, exudate and oedema
- Inadequate pressure off-loading
- Repeated trauma (e.g. inappropriate dressing removal technique)

SIGNS AND SYMPTOMS OF WOUND INFECTION

Characteristics of both the individual, their wound and the wound environment can contribute to the development of infection in a wound. The type of wound (i.e. acute or chronic) contributes to infection risk, and a variety of additional factors associated with the operative procedure increase the risk for infection in surgical wounds.[54, 55] In most cases, development of wound infection is multifactorial and occurs when cumulative risk factors overwhelm the host's defence system.[55] Table 2 (page 10) outlines factors that are associated with an increased risk of wound infection.

Infection in acute wounds (including surgical/traumatic wounds and burns) in otherwise healthy individuals is usually obvious to an experienced clinician. Individuals present with classic (overt) signs and symptoms of wound infection (Table 1, page 8).[23] However, in immunocompromised individuals and those with chronic wounds, early detection of infection relies on identification of subtle or covert signs of infection. Covert signs of wound infection include:[2, 27-36]

- Friable, bright red granulation tissue
- Increasing malodour
- New or increased pain or change in sensation
- Epithelial bridging and pocketing in granulation tissue
- Delayed wound healing beyond expectations
- Wound breakdown and enlargement or new ulcerations of the peri-wound (satellite lesions).

Clinicians need to act promptly if an individual with a wound demonstrates signs of potentially fatal infection, including systemic inflammatory response, sepsis, extensive tissue necrosis, gas gangrene or necrotising fasciitis.

Scoring systems and diagnostic criteria have been developed to assist in the identification of infection in specific types of acute wounds. For example, the ASEPSIS[67] scoring system is validated for assessing surgical site infection in sternal wounds.[68] The Centers for Disease Control and Prevention have developed definitions for wound infection; however, they are limited to types of surgical site infection.[69] Validated scoring systems to aid diagnosis of wound infection in chronic wounds have not yet been developed. If a wound infection scoring system is used to aid diagnosis, it should be reliable and valid for the type of wound being assessed.[68]

PRACTICE POINT

Do not undertake microbiological analysis of wound specimens in the absence of an appropriate indication

INVESTIGATIONS TO DIAGNOSE WOUND INFECTION

Clinical assessment can be supplemented with microbiological investigation, blood tests and/or imaging to:

- Establish specific pathogen strains in the wound
- Confirm the microbes are sensitive to the type of antibiotics commenced or to be prescribed
- Identify any possible complications
- Guide management strategies.

Microbiology

Microbiological investigations depend on the availability of local services. Microbiology should not be undertaken routinely or without substantial cause.[70-72] Indications for undertaking microbiological analysis are provided in Box 3.

Box 2: Indications for wound specimen collection for standard microbiological analysis[22, 72]

- Acute wounds with classic signs and symptoms of infection
- Chronic wounds with signs of spreading or systemic* infection‡
- Infected wounds that have failed to respond to antimicrobial intervention, or are deteriorating despite appropriate antimicrobial treatment
- In compliance with local protocols for the surveillance of drug-resistant microbial species
- Wounds where the presence of certain species would negate a surgical procedure (e.g. beta haemolytic streptococci in wounds prior to skin grafting)

* In individuals showing signs of sepsis, blood cultures are also indicated, and other likely sites of infection should be considered for sampling

‡ In patients with compromised immune competency (e.g. those taking immunosuppressants or corticosteroids, or with diabetes mellitus or arterial peripheral disease), consider sampling chronic wounds with signs of local wound infection and/or delayed healing

PRACTICE POINT

It is important to recover species at and below the wound surface, therefore wound cleansing and debridement (if necessary) without antimicrobials should be completed before sampling when using the Levine technique

Sampling techniques to obtain a specimen for microbiological analysis include wound culture or swabbing the wound bed, needle aspiration and tissue biopsy. Where pus is present it should be collected directly by syringe or swab.

Despite being the most widely used technique for microbial monitoring, wound culture may not distinguish between colonisation and wound infection.[73] Unequal distribution of pathogens in wounds has been demonstrated,[5] and this can influence the effectiveness of a wound swab in attaining a microbial specimen. Although definitive studies on the optimum method of sample collection have not yet been performed, several studies suggest that the Levine technique (Table 3) is more effective than the Z-swab technique.[73-75]

Table 3: Levine technique

Step	Action	Further information
1	Cleanse and debride wound prior to wound culture	■ Inform and seek permission from patient to obtain specimen ■ Cleanse wound using warm normal saline ■ Debride non-viable tissue as required ■ Cleanse wound again
2	Moisten culture tip	■ Moisten culture tip with sterile normal saline, especially with dry wounds
3	Where to obtain specimen	■ Obtain specimen from cleanest area in the wound ■ Where possible, do not obtain from slough or necrotic tissue
4	Technique	■ Inform the patient that procedure may cause discomfort ■ Place wound culture into wound ■ Firmly press swab into wound and rotate ■ Using a sterile technique, place swab into culture container
5	Label appropriately	■ Patient label on culture container and pathology slip ■ Provide site, time and initials of who obtained specimen (e.g. left medial distal malleolus wound) ■ Provide as much relevant history as appropriate: ■ Current antibiotic or medication (steroid) ■ Comorbidity (DM) ■ Specific microbe suspected (*Pseudomonas aeruginosa*) ■ Provisional diagnosis of wound ■ Duration of wound
6	Apply dressing as appropriate	■ Medicated dressings may be appropriate ■ Moisture management and wound bed preparation principles should be adhered to

The literature suggests that wound biopsies are recommended for wounds with antibiotic-resistant species and to determine the effect of antimicrobial intervention. In clinical practice, wound biopsies are rarely performed on a routine basis[73] due to cost, access to services and discomfort to the individual.[76]

All wound samples should be transported to the microbiology laboratory for processing within 4 hours, accompanied by full clinical details to ensure that appropriate testing is performed. Documentation accompanying the wound sample should include:[77]

- Details about the wound (e.g. anatomical location, duration and aetiology)
- Details about the individual (e.g. demographics and significant contributing comorbidities)
- Clinical indication for the wound sample (e.g. signs and symptoms and suspected microbes)
- Current or recent antibiotic use.

Quantitative analysis is not routinely available. Characterisation of microbial flora takes at least 24 hours (longer for anaerobes, mycobacteria and fungi). When rapid investigation is required (e.g. in cases of sepsis) a blood culture may yield results within 4 hours, or microscopic examination of specimens by more specialised laboratory staff may guide antimicrobial therapy faster.

EMERGING DIAGNOSTIC TECHNIQUES

Standard clinical microbiology laboratory results only provide information about a small percentage of the total bacterial species that are present, particularly in chronic wounds.[77] Testing for fungi and anaerobic bacteria requires additional investigations and processing.

If sensitivities are provided, less experienced clinicians may feel the need to commence antibiotics without considering the clinical indications. Clinicians should be wary of interpreting a microbiology report in isolation. Consider the report in the context of the individual, their wound and your clinical judgement. If appropriate, consult a microbiologist or an infectious disease expert.

Since many microorganisms are difficult to culture by standard techniques, strategies to characterise genetic markers of microbial species using molecular techniques have been developed in specialist facilities.[78-80] These molecular techniques, some of which are used to identify biofilm in a wound,[81-83] are summarised in Table 4.

Table 4: Types of microscopy[81-83]

Type of microscopy	Mechanism	Limit of resolution (maximum magnification)	Advantages	Disadvantages
Light microscopy	Visible light	0.2 μm (1500x)	■ Mostly used on isolated cultures or sections of tissue ■ Gram stain used to establish presumptive identification of species ■ Low-cost and readily available	■ Impossible to obtain definitive identification of microbial species ■ Cannot identify biofilm
Fluorescence microscopy (FISH)	Ultraviolet light	0.1 μm (2000x)	■ With fluorescent dyes/labels, species can be identified and their relative locations mapped ■ Can identify biofilm	■ Use limited to microbial cell suspensions and thin tissue sections ■ Cost of specific dyes and probes ■ Only fluorescent structures observed
Confocal laser scanning microscopy (CLSM)	A laser beam coupled to a light microscope	0.1 μm (2000x)	■ With fluorescent dyes/labels, species can be identified and their relative locations mapped ■ Tissue blocks can be examined and images obtained at regular depths can be reconstructed to generate 2D or 3D structure of the whole specimen ■ Can identify biofilm	■ Cost of equipment and technical support ■ Cost of specific dyes and probes ■ Fluorescence decays relatively quickly ■ Only fluorescent structures are observed
Scanning electron microscopy (SEM)	Electrons are beamed onto the specimen from an angle and deflected electrons are collected	10 μm (500,000x)	■ Minimal sample preparation time ■ Images of the surface layers of specimens provide insight into 3D structure ■ Can identify biofilm	■ Cannot examine living material ■ Dehydration of samples may cause changes ■ Cost of equipment and technical support
Transmission electron microscopy (TEM)	Electrons are beamed through a thin section of the specimen	0.2 μm (5,000,000x)	■ Images provide detailed information on internal cellular structures ■ Can identify biofilm[84]	■ Cannot examine living material ■ Specimen preparation is lengthy, and may introduce artefacts ■ Cost of equipment and technical support

In addition, use of DNA sequencing techniques that can more precisely identify species of microbes in a wound specimen is rapidly advancing, including microbes not identified by culture-based techniques. Samples of genetic material from a biofilm are obtained and a universal barcode marker is amplified using polymerase chain reaction, a technique that creates multiple copies of the organism's DNA sequence.[85] These DNA samples are analysed and compared with a database of existing DNA sequences to identify all of the microbial species involved in wound infection[85] and to inform the selection of strategies to manage biofilm.[86] In the future, DNA sequencing will likely have a greater role in diagnostics.[87, 88]

Holistic management

PRACTICE POINT

Implement local infection control policies and procedures

Characteristics of both the individual, their wound and the wound environment can contribute to the development of infection in a wound. The type of wound (i.e. acute or chronic) contributes to infection risk, and a variety of additional factors associated with the operative procedure increase the risk for infection in surgical wounds.[54, 55]

In most cases, development of wound infection is multifactorial and occurs when cumulative risk factors overwhelm the host's defence system.[55] Table 2 (page 10) outlines factors that are associated with an increased risk of wound infection.

A holistic approach is essential to diagnose and treat wound infection accurately. Effective management of a wound infection in the light of co-morbidities and subsequent wound healing requires an interdisciplinary team approach.[89] The goal of patient-centred care is to readjust the interaction between the individual and the infecting pathogen in favour of the individual by:

- Optimising the host response
- Reducing the number or virulence of microorganisms in the wound
- Optimising the wound healing environment.

OPTIMISING HOST RESPONSE

Measures to optimise the host response attempt to maximise healing potential by enhancing the ability of the individual to resist infection. This includes addressing systemic and/or intrinsic factors that may have contributed to the development of the wound infection (e.g. optimisation of glycaemic control and the use of disease-modifying drugs in rheumatoid arthritis).[90-92]

Factors that contribute to wound infection are often the same factors that contributed to the development of the initial wound. Local moisture management, pressure offloading and oedema control are recognised as important interventions for maximising the wound healing environment and decreasing biofilm nutrition.[93]

INFECTION CONTROL IN WOUND CARE

To prevent further contamination and cross infection, it is important to maintain an aseptic non-touch technique when managing the wound. Performing the aseptic technique during relevant clinical procedures (e.g. changing the wound dressing) protects the individual by reducing exposure to pathogenic microorganisms. Aseptic technique also reduces the risk of cross infection.

A risk assessment should be conducted prior to performing wound management procedures. If it is necessary to touch any area of the wound directly, sterile gloves and equipment are required. Asepsis is supported by standard precautions, including:[94]

- Practising regular and effective hand hygiene
- Appropriate use of sterile and non-sterile gloves
- Use of personal protective equipment (e.g. mask and gown)
- Conducting wound care in a clean environment
- Strategic sequencing of care
- Sharps management
- Environmental controls.

PRACTICE POINT

Individuals with severe sepsis require immediate, high-level resuscitation with fluids, oxygen and systemic antibiotic therapy

EFFECTIVE MANAGEMENT OF WOUND INFECTION

Effective wound management requires holistic assessment of the individual, their wound and the wound care environment to promote host defence and response to infection. For individuals with significant and life-threatening infection (e.g. sepsis), admission to a higher level of monitoring/care and with immediate resuscitation with fluids, oxygen and antibiotics is imperative. Management strategies for individuals with, or at risk of, wound infection is summarised in Figure 3.

EFFECTIVE WOUND INFECTION MANAGEMENT

Optimise individual host response

- Optimise management of comorbidities (e.g. diabetes, tissue perfusion/oxygenation)
- Minimise or eliminate risk factors that increase infection risk where feasible
- Optimise nutritional status and hydration
- Assess and manage other anatomical sites of infection (e.g. urinary tract, chest)
- Treat systemic symptoms (e.g. pain, pyrexia)
- Promote psychosocial support
- Provide appropriate systemic antimicrobial therapy
- Ensure the individual is engaged in development of an personalised management plan
- Promote education by the interdisciplinary wound management team to the individual and their caregivers

Reduce wound microbial load

- Prevent cross infection by implementing universal precautions and aseptic technique
- Facilitate wound drainage
- Ensure peri-wound hygiene and protection
- Manage wound exudate
- Optimise the wound bed:
  - Remove necrotic tissue, debris, foreign bodies, wound dressing remnants and slough
  - Disrupt biofilm by debriding
  - Cleanse the wound with each dressing change
- Use appropriate dressings to manage exudate – a dressing containing an antimicrobial may be considered
- If deemed necessary, consider an appropriate topical antiseptic for a short period for time (e.g. 2 weeks)

Promote environmental and general measures

- Perform wound care in a clean environment
- Determine that the appropriate aseptic technique required is based on risk assessment of the patient, the wound and the environment
- Store equipment and supplies appropriately
- Provide education for the individual and their caregivers
- Regularly review local policies and procedures

Regular reassessment

- Diagnostic interpretation requires holistic knowledge of the individual and their wound
- Evaluate interventions based on efficacy in resolving signs and symptoms of wound infection and the overall condition of the individual. Consider the following:
  - Has the individual's pain decreased?
  - Has exudate decreased?
  - Has malodour resolved?
  - Has erythema and oedema decreased?
  - Is there a reduction in non-viable tissue?
  - Is the wound reducing in size and/or depth?
- Monitor condition of the peri-wound, particularly in heavily exuding wounds
- If there is limited or no improvement in signs and symptoms of wound infection, reassess the individual and their wound and adjust the management plan
- Consider if further investigations are required
- Consider referring the individual to specialised services (e.g. a wound clinic)
- Document wound assessments (e.g. serial digital photography)

Figure 3 | Effective management of wound infection[95]

Wound bed preparation

Necrotic, non-viable tissue provides a focus for infection, exacerbates the inflammatory response and impedes wound healing.[12] This includes foreign material (wound dressing remnants, multiple organism-related biofilm or slough, exudate and debris) on the wound bed. The principles of wound bed preparation are the entrenched concepts, which also include the acronyms TIME (Tissue; Infection/Inflammation; Moisture; Edge)[23, 96] and Biofilm-based Wound Care (BBWC).[97] These principles promote maintenance of a healthy wound bed through therapeutic wound cleansing, disruption of biofilm and removal of necrotic, non-viable tissue through wound debridement.

DEBRIDEMENT

To stimulate wound healing and manage bioburden there are a number of methods of debridement (see Table 5). It has been demonstrated that debridement provides a window of opportunity in which the biofilm defences are temporarily interrupted, allowing increased efficacy of topical and systemic management strategies.[13] Further research is required to establish the optimal frequency of debridement; however, expert opinion suggests that debridement should be performed at least weekly. To disrupt biofilm attachment and prevent dispersal, use a combination of debridement strategies together with therapeutic cleansing with topical antiseptics and application of antimicrobial wound therapy dressings.[12, 98] New, effective biofilm disruptors that do not contain antiseptic may offer an alternative to antiseptic-containing therapies.

Table 5: Types of debridement

Type of debridement	Method	Effect on biofilm
Surgical	Performed in the operating room using scalpel and scissors[91, 99]	■ Disrupts biofilm and removes foci of infection[99] ■ If all tissue is removed, deeper biofilm can be disrupted[99]
Conservative/sharp	Performed using aseptic technique with sterile curette, scalpel and scissors[91, 99]	Removes and disrupts superficial biofilm[99]
Autolytic	Selective, slow debridement that occurs naturally and can be aided by using topical agents and contemporary wound dressings, including:[91, 99] ■ Cadexomer iodine ■ Honey ■ Fibre gelling wound dressings ■ Polyhexamethylene biguanide (PHMB)	Varying efficacy on biofilm depending on the product and the phase of the biofilm cycle in which it is applied[99]
Mechanical	Non-selective debridement performed using:[99] ■ Therapeutic irrigation (4 to 15 psi) ■ Monofilament fibre pads ■ Low-frequency ultrasound ■ Hydrosurgery	Some levels of disruption and removal of biofilm[99]
Enzymatic/ chemical/surfactant	Application of exogenous enzymes or chemicals to the wound surface, including:[99] ■ Alginogel ■ Enzymatic debriders ■ Wound cleaners and gels with high or low concentrations of surfactant	Some levels of disruption and removal of biofilm[99, 106]
Biosurgical/ larval therapy	Sterile fly larvae that produce a mixture of proteolytic enzymes[91, 100, 101]	Good evidence of removal of biofilm *in vitro*[100, 101]

The impact of the different types of debridement on biofilm is dependent upon its stage in the life cycle. Clinicians should be aware of the efficacy of different debridement strategies and therapeutic topical agents on biofilm prevention, maturation and dispersal. When performing wound debridement, they should always work within the scope of practice, and local policy and procedures.

CLEANSING INFECTED WOUNDS

Infected wounds should be cleansed thoroughly at each wound dressing change. There is a difference between rinsing a wound and cleansing a wound. Therapeutic wound cleansing exhibits the following characteristics:[23]

- Application of a cleansing solution that has potential to disrupt biofilm and kill planktonic bacteria and other organisms (Table 6 outlines the efficacy of various cleansing solutions)
- Promotion of safety of the wound and the individual
- Availability in a variety of settings (hospital, clinic and home environment)
- Irrigation that is performed at an appropriate pound per square inch pressure
- The periwound being maintained and protected from maceration.

PRACTICE POINT

Stop anointing wounds and start cleansing wounds

The ideal cleansing agent and the optimal method of wound cleansing has not been established conclusively. There may be a role for judicious irrigation with an antiseptic solution (see Topical Antimicrobial Therapy).

Surfactants lower the surface tension between the wound bed and the liquid (or between two liquids), thereby promoting spread of the liquid across the wound bed and facilitating separation of loose, non-viable tissue. This characteristic has been capitalised on in the development of several surfactants that are combined with antimicrobials (e.g. polyhexamethylene biguanide [PMHB] and undecylenamidopropyl betaine; octenidine dihydrochloride and phenoxyethanol; and octenidine and ethylhethylglycerin).[23] The use of these surfactant-containing antimicrobial cleansers or antimicrobial preservative-containing cleansers is useful for disrupting biofilm in the wound.[102, 106]

There are also newer cleansing agents that are super-oxidised and/or have lower concentrations of hypochlorous acid and sodium hypochlorite compared with traditional highly toxic preparations that are no longer recommended. These newer solutions are purported to disrupt biofilm and kill planktonic bacteria and other organisms while being safe for the wound and the individual.[103, 104]

APPLICATION TO PRACTICE

Prompt diagnosis and treatment of infection promotes wound healing and minimises the impact on the individual, their carer and healthcare systems. Treatment of an infected wound should follow a clear and decisive treatment plan.

Management of comorbidities requires a multidisciplinary team approach. Thorough wound hygiene technique and wound debridement will facilitate eradication of microbes, either planktonic or biofilm. In the absence of systemic signs of wound infection, local treatment with antiseptics, surfactants (in gel or solution form) and antimicrobial dressings may be sufficient.

Post-debridement, topical antimicrobials have been recommended in order to prevent (or at least delay) attachment of planktonic microbes and to kill any disrupted or dispersed biofilm. Table 7 provides a summary of topical options for wound infection.

PRACTICE POINT

Regular reassessment of the individual, their wounds and the management plan is essential

Table 6: Cleansing solutions and gels

Solution	Type	Cytotoxicity	Effect on biofilm	Comments
Sterile normal saline	Isotonic[105]	None	None	■ Sterile, non-antiseptic solution[103]
Sterile water	Hypotonic	None	None	■ Sterile, non-antiseptic solution[103]
Potable tap water	Varies in content	Unknown/variable	None	■ Not sterile[103]
Polyhexa-methylene biguanide (PHMB)	Surfactant antimicrobial	Low to none[23]	Surfactant qualities disrupt biofilm attachments[23, 106]	■ Available in gel and irrigation preparations that can be used together or separately ■ Lowers liquid surface tension, allowing greater spread and facilitating separation of non-viable tissue[23] ■ Does not promote bacterial resistance[23]
Octenidine dihydrochloride (OCT)	Surfactant antimicrobial	■ *In vitro* tests show high toxicity[107] ■ Lack of absorption suggests no systemic effects[107] ■ Not shown to disrupt healing	■ Prevents formation of new biofilm for at least 3 hours[108] ■ Inhibits planktonic and bacterial biofilm growth for up to 72 hours[108]	■ Available in gel and irrigation preparations that can be used together or separately[107] ■ Lowers liquid surface tension allowing greater spread and facilitating separation of non-viable tissue[108]
Super-oxidised with hypochlorous acid (HOCL) and sodium hypochlorite (NaOCL)	Antiseptic	May vary depending on concentrations	■ Penetrates biofilm rapidly, killing formations from within[103] ■ Does not promote resistant bacteria strains[103]	■ Purported to provide desloughing and antimicrobial activity ■ Available in gel and irrigation preparations that can be used together or separately
Povidone iodine	Antiseptic	Varies depending on concetrations[108]	■ Inhibits development of new biofilm[110] ■ Eradicates young biofilm colonies[110] ■ Significantly reduces mature biofilm colonies[110]	■ Modulates redox potentials and enhances angiogenesis, thereby promoting healing[111] ■ May inhibit excess protease levels in chronic wounds[111]

Table 7: Topical wound infection therapies

Antimicrobial agent	Type	Biofilm efficacy	Guidance for use
Enzyme alginogel	Alginate gel with two enzymes: ■ Lactoperoxidase ■ Glucose oxidase	■ Prevents formation of biofilms at concentration M0.5% (w/v)[112,113] ■ Inhibits growth of established biofilms at higher concentrations ■ Does not disrupt biofilm biomass[112,113]	■ Concentrations of alginate of 3% and 5% depending on level of exudate[112,113]
Iodine (povidone and cadexomer)	■ Solution ■ Impregnated wound dressings ■ Powder and paste	■ Inhibits development of new biofilm[110, 114] ■ Eradicates young biofilm colonies[110, 115] ■ Significantly reduces mature biofilm colonies[110, 114]	■ Contraindicated in individuals sensitive to iodine or with thyroid or renal disorders[110] ■ Contraindicated in those with extensive burns[110]
Honey	■ Medical grade ■ Honey impregnated dressings	■ Inhibits biofilm growth[116-118] ■ Reduces biofilm colony formation[119] ■ Inhibits quorum sensing of biofilm, thereby reducing ability to proliferate[120]	■ Select products that have been gamma irradiated[119] ■ Leptospermum species is more effective than other types[119]
Silver	■ Salts (e.g. silver sulphadiazine, silver nitrate, silver, sulphate, silver CMC) ■ Metallic, e.g. nanocrystalline, silver-coated nylon fibres ■ Impregnated wound dressings	■ Denatures existing bacterial biofilm in concentrations over 5 μg/ml120	■ Change more frequently in wounds with heavy exudate ■ Avoid in individuals with silver sensitivities[121]
Ionic silver combined ethylenediamine-tetraacetate (EDTA) and benzethonium chloride (BEC) (antibiofilm agents)	■ Carboxymethylcellulose gelling dressing impregnated with ionic silver enhanced with EDTA and BEC	■ Combines antibiofilm and antimicrobial components that work in synergy to disrupt biofilm and expose associated microorganisms to the broad-spectrum antimicrobial action of ionic silver[122] ■ Eradicates mature biofilm within 5 days[124] ■ Prevents biofilm formation[124] ■ Associated improvement in healing rates[125]	■ Change more frequently in wounds with heavy exudate ■ Avoid in individuals with sensitivities to silver, EDTA or BEC[123]
Surfactant	■ Concentrated surfactant gels with antimicrobial preservatives	■ Prevents biofilm formation[126] ■ Increases antibiotic efficacy ■ Eradicates mature biofilm	■ Can be used between and post-debridement to prevent re-establishment of biofilm ■ May require daily application for the first few days

Topical antimicrobial therapy

PRACTICE POINT

Use antiseptics at the lowest effective concentration to minimise harm to skin and tissue cells involved in wound healing

The term 'antimicrobial' refers to disinfectants, antiseptics and antibiotics.[11] Disinfectants are substances recommended by the manufacturer for application to an inanimate object to kill microorganisms and are not suitable for internal use. Some disinfectants in lower concentrations are used as antiseptics (e.g. sodium hypochlorite).

TOPICAL ANTISEPTIC THERAPY

Antiseptics, also known as skin disinfectants, have a disruptive or biocidal effect on bacteria, fungi and/or viruses, depending on the type and concentration of the preparation. Antiseptics have multiple sites of antimicrobial action on target cells and therefore have a low risk of bacterial resistance. Thus, antiseptics have the potential to play an important role in controlling bioburden in wounds while limiting exposure to antibiotics and reducing the risk of further antibiotic resistance.[127] In the context of increasing resistance to antibiotics and the dramatic fall in the number of antibiotics in development, restriction on the use of potentially useful antiseptic treatments (e.g. silver) is particularly unfortunate.

Topical antiseptics are non-selective and may be cytotoxic if not delivered to the wound in a sustained manner. This means they may kill skin and tissue cells involved in healing (e.g. neutrophils, macrophages, keratinocytes, and fibroblasts), thereby impairing the healing process. Cytotoxicity may be concentration-dependent,[11, 23] as some antiseptics in low concentrations are not cytotoxic. Newer-generation antiseptics such as PMHB[23] and octenidine dihydrochloride[107] are non-cytotoxic. It is essential to use products with a sustained release of antimicrobial agent at concentrations low enough to minimise toxicity but still able to destroy or inhibit bacterial and fungal growth.

Many older antiseptics, including hydrogen peroxide and sodium hypochlorite (e.g. EUSOL), are no longer recommended due to the high risk of tissue damage associated with their use.[128, 129] The exception is use for wound management in low-resource settings, where alternative, contemporary antiseptics are not always available.

PRACTICE POINT

Use a topical antiseptic for 2 weeks before reaching conclusions regarding its effectiveness in managing infection in a wound

In general, most healing wounds do not require the use of antimicrobial therapy. Topical antiseptic therapies are recommended for the following:[23]

- Prevention of infection in individuals who are considered to be at an increased risk
- Treatment of localised wound infection
- Local treatment of wound infection in cases of local spreading or systemic wound infection using antiseptics, in conjunction with systemic antibiotics.

Duration of use should be individualised and based on regular wound assessment. Many clinicians recommend the use of a 2-week challenge with a topical antiseptic, as this allows sufficient time for the topical agent to exert a beneficial activity. Usage should be reviewed after 2 weeks and the management plan adjusted accordingly.[23, 103]

The practice of alternating or rotating topical wound therapies has gained popularity.[130] The premise for this strategy is that suppression of a range of microbials is attained through the application of different topical antiseptics in a 2- or 4-week rotation. In conjunction with therapeutic cleansing and debridement, alternating the type of antiseptic applied to the wound may assist in restoration of microbial balance; however, further research is required to support this emerging clinical practice.[130]

PRACTICE POINT

Topical antibiotics are not recommended for general management of wound infection

TOPICAL ANTIBIOTICS

The use of topical antibiotics, which contain a low-dose form of antibiotic, may induce resistance. Controversy surrounds the use topical anitbiotics and the debate is compounded by extensive work on the microbiota of the individual wound. Given the global concern regarding antibiotic resistance, use of topical antibiotics for wound management should only be considered in infected wounds under very specific circumstances by experienced clinicians.[131] Examples include the use of:

- Topical metronidazole gel for the treatment of malodour in fungating wounds[132]
- Silver sulphadiazine for the treatment of burns and wounds[130]
- Mupirocin, a specific topical antibiotic, with no similar compounds used systemically or orally.[133]

The overall evidence on the efficacy of topical antimicrobials in the management of wounds is confusing. Most use is based on laboratory studies rather than clinical research. Of concern is the topical use of chloramphenicol ophthalmic ointment used widely by plastic surgeons as a post-operative topical surgical prophylaxis.[134]

Application of a single dose of topical chloramphenicol to high-risk sutured wounds after minor surgery produces a moderate absolute reduction in infection rate that is statistically, but not clinically, significant.[134] A theoretical, but as yet inconclusively proven, risk of chloramphenicol-induced idiosyncratic aplastic anaemia exists with topical ophthalmic therapy. A small number of non-fatal cases of suspected topical chloramphenicol-induced blood dyscrasia have been reported.[135, 136]

TOPICAL ANTIFUNGAL THERAPY

Topical antifungal therapy can be used in conjunction with good wound care practice (e.g. management of wound exudate and other sources of moisture in which fungi proliferate). Accurate identification of fungi, although rare, is imperative in selecting appropriate topical and systemic treatment.[137] The association of fungal infection with a high mortality rate in individuals with burns suggests more aggressive management with systemic treatment is appropriate.[138, 139]

Wound sampling and molecular analysis suggest that chronic wounds with fungal-associated biofilm have unique microbial profiles that require an individualised approach. Antifungal therapies (e.g. topical miconazole) may be appropriate; however, poor penetration throughout biofilm that contributes to selection of resistant phenotypes is a risk.[15, 140]

Antibiotic therapy

PRACTICE POINT

Systemic antibiotics should be reserved for use only when the degree of infection is not able to be controlled with local intervention (i.e. topical antiseptic and debridement at every dressing change) alone

Antibiotics should not be used routinely for the promotion of wound healing alone. Judicious use of antibiotics is reserved for wound infections confirmed by clinical signs and symptoms and/or confirmation by microbiological inquiry. Antibiotics must be used in combination with prudent wound management strategies such as wound bed preparation (i.e. debridement and therapeutic cleansing).[11, 141, 142]

Overuse of antibiotics in humans and livestock, combined with inappropriate antibiotic prescribing and patterns of use, has resulted in an increase in antibiotic resistance around the world.[142, 143] Over time, strains of bacteria that do not succumb to the bactericidal effect of antibiotics proliferate and spread throughout communities. As a result, untreatable, multi-resistant bacteria are becoming more common and leading to increased mortality rates.[143, 144]

Standard wound culturing and advanced technologies (see Investigations to diagnose wound infection) do not necessarily provide conclusive information regarding the identity of causative bacteria in an infected wound or treatments to which the causative microbe will be sensitive.[141] Using the wrong antibiotic therapy therefore contributes to development of multi-resistant bacteria.[144]

Even when an appropriate antibiotic is chosen to manage a wound infection, there are treatment challenges. Antibiotics must be able to reach the anatomical site of infection in adequate concentrations in order to be effective in destroying infective agents. The bioavailability of different antibiotics is variable and dependent on their ability to cross tissue barriers and penetrate into bone (e.g. to treat osteomyelitis). The penetration of an antibiotic is influenced by absorption, circulation, profusion and plasma protein binding.[11, 145] If uncertain, contact a pharmacist or medical microbiologist for advice.

ANTIBIOTIC PROPHYLAXIS

Prophylaxis is the use of one or more measures to prevent the development of disease in individuals who are at high risk of infection. While prophylactic interventions may be chemical, biological or mechanical, in the case of surgical wounds, prophylaxis usually refers to systemic antibiotic therapy.[146]

Antibiotic prophylaxis is most often used to prevent infection in surgical incision sites and traumatic wounds where the level of microbial contamination is expected to be significant.[54]

Future developments

With the ever-increasing resistance of pathogens to antibiotics, there is an urgent need to develop new and novel treatments for wound infection. At present, a variety of research projects are being undertaken to evaluate the role of several methods for treating infection. Some of this promising work is outlined below.

New dressing technologies such as a combination silver dressings incorporating EDTA and surfactant BeCL have demonstrated *in vitro* biofilm disruption with safe topical application.[125] As previously stated the evidence that surfactant has effectiveness for anti-biofilm activity is growing. A new concentrated surfactant gel without an antiseptic but containing an antimicrobial preservative system has demonstrated biofilm disruption efficacy in an explant model.[106]

Multicellular organisms have evolved an arsenal of host-defence molecules,[106] including antimicrobial peptides (AMPs), aimed at controlling microbial proliferation and at modulating the host's immune response to a variety of biological insults. Antimicrobial peptides may have therapeutic potential for the treatment of non-life-threatening skin and other epithelial injuries.[147] Two examples include talactoferrin, which has been shown to stimulate wound healing, and pexiganan, which was developed for the topical treatment of diabetic foot ulcers.

Bacteriophages and lysins are interventions that use bacterial viruses as antibacterial agents, ultimately causing lysis and death of host bacterial cells. These interventions were in popular use many years ago, but the development of antibiotics in Western countries rendered their use obsolete. However, they were still being developed in countries such as Russia, and are now being reinvestigated in the Western world.[103]

Therapeutic monoclonal antibodies are available to treat cancer and other diseases. Thus far, none have been approved for the treatment of bacterial infection; however, there is considerable ongoing research in this field. Antibodies that bind directly to the bacteria usually work by opsonising the bacteria for phagocytosis.

Potentiators of currently used antibiotics, including antibody–antibiotic conjugates, could function either by reversing resistance mechanisms in naturally sensitive pathogens or by sensitising naturally resistant strains. Much of this work is still *in vitro*; however, there is much potential for future use of these methods.[148, 150]

Research is also in progress to explore the use of nanoparticles to deliver target therapeutic agents to the wound bed. This may prove useful in managing bacteria and fungi.

Photodynamic therapy uses photosensitising drug agents, which are selectively absorbed by bacteria. These molecules, when exposed to visible light, produce reactive oxygen species lysing the bacteria. Research is ongoing into the use of this therapy in inhibiting wound infection.

Other areas of research involve developments in detection and management of biofilm, including:[151]

- Diagnostic tests to detect biofilm at the bedside
- A clearer understanding of strategies for debridement to disrupt biofilm
- Treatments that block biofilm formation through disruption of quorum sensing.

Point-of-care bedside detection of bacteria is also progressing with electronic devices, nanoparticles and photodynamic therapy. A device (Moleculight) now exists that illuminates the wound with a narrow band of violet light, causing fluorophores in the bacteria to fluoresce, enabling capture of an electronic image. Approximately 10 species of bacteria common to chronic wounds are detected to a depth of 1.5mm. Initial clinical testing of the devices has proven useful in guiding wound debridement. Studies are required to elucidate the clinical significance of findings.

Glossary of terms

Aerobe: An organism that requires the presence of oxygen in its environment in order to survive and multiply.[152]

Anaerobe: An organism that can survive and multiply in the absence of oxygen in its environment. Some bacteria are classified as facultative anaerobes as they can sense concentration of oxygen in their environment and adjust their metabolism accordingly.[152]

Antimicrobial: A substance that acts directly on a microbe in a way that will either kill the organism or significantly hinder development of new colonies. The term incorporates disinfectants, antiseptics and antibiotics.[91] Antimicrobial therapy may be required when other methods of eradication of wound infection are insufficient to manage localised wound infection, or when the infection is systemic/spreading.

Antibiotics: A small natural or synthetic molecules that have the capacity to destroy or inhibit bacterial growth.[153, 154] Antibiotics target specific sites within bacterial cells while having no influence on human cells, thus they have a low toxicity. They may be administered systemically or in topical preparations. Antibiotic resistance is a major global health concern.[143, 144]

Antifungals: Pertaining to a substance that kills fungi or inhibits their growth or reproduction. Can be systemic or topical agents.

Antisepsis: The removal of bioburden from living tissue.

Antiseptics: Non-selective agents that are applied topically in order to inhibit multiplication of or kill microorganisms. They may have a toxic effect on human cells. Development of resistance to antiseptics is uncommon.

Aseptic technique: A wound management technique that minimises introduction of new pathogenic microorganisms into the wound and protects the individual and health professional from cross infection.[40, 155]

Bacteria: A prokaryotic unicellular organism that may range from benign to an invasive pathogen. They may be aerobic, anaerobic, motile or immotile. They typically have a cell wall and membrane, which become the targets of many antibacterial compounds.

Bactericidal: Agents that kill bacteria through single or multiple cellular processes.

Bacteriostatic: Refers to bacterial multiplication/growth that has been prevented or inhibited, but may resume if the inhibitory agent is removed.

Bioburden: Degree or load of microorganisms (e.g. bacteria, virus, fungi) that create contamination in a wound.[91] The degree of bioburden is influenced by the quantity and virulence of microbes.

Cellulitis (also known as spreading infection): Occurs when bacteria and/or their products have invaded surrounding tissues causing diffuse, acute inflammation and infection of skin or subcutaneous tissues.[153, 156]

Crepitus: A crackling feeling or sound detected on palpation of tissues that is due to gas within the tissues being released by anaerobic microorganisms.[91] Crepitus may be associated with presence of Clostridium perfringens.

Debridement: The removal of devitalised (non-viable) tissue from or adjacent to a wound.[154] Debridement also removes exudate and bacterial colonies (e.g. biofilm) from the wound bed and promotes a stimulatory environment. Methods of debridement include autolytic debridement (promotion of naturally occurring autolysis), biological debridement (e.g. larval therapy), conservative sharp debridement, enzymatic debridement, mechanical debridement, low-frequency ultrasonic debridement and surgical sharp debridement.[157]

Delayed wound healing: Wound healing that progresses at a slower rate than expected for the individual and the wound. In open surgical wounds, the epithelial margin can be expected to advance approximately 5mm per week.[33] Clean pressure injuries can be expected to show signs of healing within 2 weeks.[91]

Disinfectant: Substances recommended by the manufacturer for application to a non-living object to kill microorganisms.

EDTA: Ethylenediaminetetra-acetic acid

Eschar: A thick, coagulated crust or slough produced by a corrosive application, thermal burn or by gangrene.[91]

Foreign body: Presence in the wound of non-natural bodies that may be a result of the wounding process (e.g. gravel, dirt or glass) or arise from wound repair (e.g. sutures, staples, orthopaedic implants or drains).

Friable: Tissue that bleeds easily, usually due to a high bioburden.[91]

Fungi: Eukaryotic, filamentous (multicellular fungal hyphae) or budding (single cellular yeast) or dimorphic organism that is a member of the kingdom Fungi. This includes a large number of ubiquitous organisms, some of which are potential pathogens.

Granulation tissue: The pink/red, moist, shiny tissue that glistens and is composed of new blood vessels, connective tissue, fibroblasts, and inflammatory cells that fills an open wound when it begins to heal. It typically appears deep pink or red with an irregular, granular surface.[153]

Induration: Hardening of the skin and subcutaneous tissues around a wound[91] due to inflammation, which may be secondary to infection.

Lymphangitis: Inflammation of lymph vessels, seen as red skin streaks running proximally from a site of infection.

Necrotic tissue/necrosis: Dead (devitalised) tissue that is dark in colour and comprised of dehydrated, dead tissue cells. Necrotic tissue acts as a barrier to healing by preventing complete tissue repair and promoting microbial colonisation.[158]

Periwound: The area immediately adjacent to the wound edge and extending out as far as the tissue colour and consistency changes extend.

Persister cells: A cell that resists a generally toxic level of a drug (e.g. an antibiotic) or intervention although the organism is generally not genetically resistant to the treatment.[159]

Phenotype: Observable characteristics or traits of a living organism that arise from its genetic make-up.

pH: A measure on a scale from 0 to 14 of acidity or alkalinity, with 7 being neutral, greater than 7 being more alkaline and less than 7 being more acidic.[91]

Phagocytosis: The process by which certain living cells (phagocytes) engulf or ingest other cells or particles.

Planktonic bacteria: Planktonic cells are bacteria growing in a free-floating environment, meaning they are not part of a structured community or biofilm.[47]

Pocketing: This occurs when granulation tissue does not grow in a uniform manner across the entire wound or when healing does not progress from the bottom up to the top of the wound. Pockets can harbour bacteria.[91]

Potable water: Water that is fit for consumption by humans and animals.[91]

Prophylaxis: The use of one or more measures to prevent the development of disease in susceptible hosts with high risk of infection. Prophylactic interventions can be chemical, biological or mechanical, but in the case of surgical wounds are usually systemic antibiotics.[146]

Pyrexia: Abnormal elevation of the body temperature, or a febrile condition.[160]

Quorum sensing: A density-dependent cell-to-cell communication system through small molecules that regulates the gene expressions and behaviour of bacteria within the community.[47, 161]

Resistance/tolerance: Antimicrobial resistance refers to a specific mechanism of drug resistance; for example, production of a beta-lactamase enzyme that confers resistance to beta-lactam antibiotics (i.e. penicillin). Tolerance refers to the decreased susceptibility and enhanced tolerance to antimicrobials in a non-specific manner.[143] Biofilms have enhanced tolerance to antimicrobials because of reduced penetration and metabolism within the biofilm.

Sepsis: Sepsis is a life-threatening complication, characterised by a range of signs and symptoms, arising from an overwhelming host response to infection. Signs and symptoms of sepsis include excessive pain; confusion or disorientation; shortness of breath; shivering, fever or very cold temperature; high heart rate; and clamminess. It may also include more localised signs of infection (e.g. diarrhoea, sore throat, respiratory symptoms).[162]

Sequester: To detach or separate abnormally a small portion from the whole.[160]

Slough: Soft avascular or non-viable tissue. The colour and thickness varies depending on hydration of the tissue and may be obscuring underlying structures or tunnelling.

Surfactant: Surfactant is a complex naturally occurring substance made of six lipids (fats) and four proteins that is produced in the lungs. It can also be manufactured synthetically. Surfactant reduces the surface tension of fluid in the lungs and helps make the small air sacs in the lungs (alveoli) more stable.

Wound culture: A sample of tissue or fluid taken from the wound bed and placed in a sterile container for transportation to the laboratory. In the laboratory, the sample is placed in a substance that promotes growth of organisms and the type and quantity of organisms that grow are assessed by microscopy. Wound cultures are used to determine the type and quantity of microorganisms in a wound.[163]

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Appendix 1: Methodology

Literature search

This edition of *Wound Infection in Clinical Practice* is underpinned by a targeted literature search to identify relevant research published since the previous edition in 2008. Searches were conducted in four major medical databases: Medline, Embase, CINAHL and the Cochrane Library. Searches were made for research in nine broad fields related to wound infection: diagnosis, systematic/holistic management, topical management, antibiotic therapy, emerging research, terminology, biofilm management, wound cleansing and terminology. Search terms related to wound infection were combined with terms specific to each broad field. The search was limited to articles published in database-listed journals since 2008 in English language.

After identification, references were screened for their relevance to the project and grouped according to the wound infection-related topics for which they provided evidence. References considered to provide high-quality research and/or unique information were reviewed more thoroughly by the IWII experts. Approximately 300 references were identified and reviewed as part of the literature search. Additional references known to the experts were added to those identified in the literature search, including seminal papers from pre-2008.

Delphi process

In order to make updates to clinical topics for which there is limited or no scientific evidence, the IWII expert group engaged in a Delphi process. The process was designed to elicit consensus from the expert panel through an iterative process involving a number of voting rounds. A sub-group of experts developed the specific statements that were posed to the expert panel for discussion and agreement. These statements emerged from the literature review and early development of this document. The broad areas covered by the statements for consensus voting related to:

- Definitions and terminology
- Clinical indicators of a chronic wound
- Clinical indicators of the presence of biofilm in a wound
- Update and presentation of the wound infection continuum
- Signs and symptoms of wound infection.

The Delphi process was iterative, with three rounds of voting required to reach agreement on the statements on which the expert panel voted. The statements were presented to the expert panel with a brief discussion presenting the background of each issue. This provided every member of the panel with sufficient baseline knowledge to form an opinion. As with a typical Delphi process,[164-166] the expert panellists voted their level of agreement with each presented statement, based on the background discussion and their extensive expertise in the field. A nine-point Likert scale, labelled from 'strongly agree' through to 'strongly disagree', was used for responses. After each voting round, the level of agreement of the entire voting panel was calculated to determine the level of consensus.

For each statement, the expert panel members were required to provide qualitative comments as a rationale for their level of agreement. As with a typical Delphi process,[164-166] these comments were moderated and fed back to the group in subsequent voting rounds. Panel member comments accumulated over the three voting rounds, building up a reasoning summary that presented the opinion in agreement and/or disagreement of each statement.

Votes were cast using a custom designed web interface[167] and the level of consensus was calculated automatically by a computer script[167] based on previously reported methodology[167] that has been validated in the wound care context.[169, 170] Due to the nature of the project, participant anonymity was not possible. However, individual votes and comments provided in feedback remained anonymous to both the moderator and other participants.

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