# Acute and chronic wound infections: microbiological, immunological, clinical and therapeutic distinctions

**Abstract:** Wound infection is a complex pathology that may manifest either as a rapid onset acute condition, or as a prolonged chronic condition. Although systemic antibiotic therapy is often appropriate and necessary for acute wound infections, it is often used inappropriately, excessively and unsuccessfully in chronic wound infections. Overuse of antibiotics in chronic (hard-to-heal) wound management contributes to antibiotic resistance. This literature review confirms that acute and chronic wound infections are significantly differentiated by their cause (microbial phenotype), the subsequent host immune response and by the resulting clinical manifestations. Consequently, recognition of the type of wound infection followed by appropriate and timely therapy is required to improve wound healing outcomes while encouraging more judicious and responsible use of antibiotics.

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**acute • antibiotics • antimicrobial stewardship • biofilm • chronic • hard-to-heal • infection • wound • wound care • wound infection • wound healing • wound hygiene • wounds**

Wound infection prevents healing and without timely diagnosis and appropriate action, it may lead to a prolonged clinical condition that has significant health and economic consequences. Diagnosis of wound infection by a healthcare practitioner (HCP) is most frequently based on clinical signs and symptoms, but an accurate diagnosis requires a multifactorial approach and is often more difficult than it is commonly considered to be.

The classic signs of inflammation, including calor (warmth), dolor (pain), tumor (swelling) and rubor (redness), typically drive clinical suspicion of acute wound infection, yet infection is only one trigger of the host inflammatory response. Therefore, total reliance on the classical signs of inflammation can be misleading. Furthermore, clinical signs of inflammation can vary based on host characteristics and microbial pathogenicity. Microbial phenotype (planktonic and/or biofilm), as well as species and load, can play a key role in virulence expression and host inflammatory response. With increasing knowledge of the complexities of wound infection, there is greater understanding of the tactics that microorganisms use to defend themselves and launch assault on the host, hence supporting a greater awareness of the clinical tactics that are required to combat wound infection most effectively. By examining the subtleties of infection and inflammation in acute and chronic (hard-to-heal) wounds, treatment strategies for both wound types can be reconsidered to promote more judicious antibiotic therapy and foster better antimicrobial stewardship in wound care.

Based on literature evidence collated from PubMed/Medline searches, with no time limit on references included, the aim of this review is to address the microbiological, immunological and clinical characteristics of acute and chronic wound infections, with a view to guiding the most appropriate and effective wound management, and improving outcomes in an often devastating, yet underappreciated clinical condition.

## Wound infection

Wound infection is a host inflammatory response to interfering microorganisms that either directly or indirectly damage viable host tissue, hence preventing wound healing. This differs from previous definitions in that it considers the critical distinctions between acute and chronic wound infections, which will be discussed further in this paper.

### Wound infection and inflammation

Wound infection causes inflammation, but since it is only one of many potential causes of inflammation, accurate diagnosis of the cause is essential to ensure appropriate therapy.

Inflammation is a non-specific defensive response to tissue injury,[1] the goal of which is to eliminate or limit the damage caused by an injurious agent. Inflammation is the body's natural vascular response to harmful physical, biological or chemical stimuli. Such stimuli may include cell damage, chemical irritants or the presence of microbial pathogens. Inflammation associated with microbial pathogens is the body's

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**Fig 1.** Left axilla periulcer dermatitis of this dehisced but currently granular healing site of remote surgical removal of hidradenitis suppurativa tissue. Irritation resolved with improved moisture management and topical zinc oxide for tissue protection (patient consent was obtained for the use of this photograph)

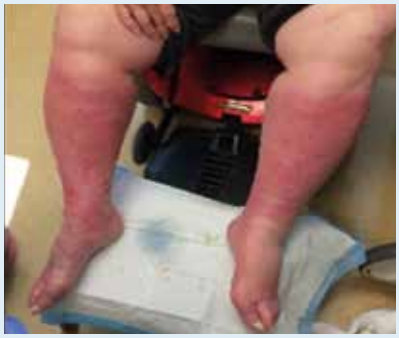
attempt to protect the host from wound infection. Unfortunately, as will be discussed later, several factors can compromise the adequacy of this inflammatory response, allowing infection to develop. However, although infection causes inflammation, it is important to acknowledge that infection is not the only cause of inflammation[2] and, consequently, antibiotics are not always the appropriate treatment for inflammation. An example of this is contact dermatitis (CD) which can be caused by either a toxic irritant or a contact allergen. Clinical signs of CD can include erythema, swelling, warmth and blistering as a result of the inflammatory immune response to the irritant (Fig 1).[3] It can be difficult to rule out an infection in such cases, but treatment of CD will not be resolved by antibiotics; in fact, antibiotics have been found to possibly complicate this skin condition.[4] CD is typically managed by removal of the allergen or irritant, and administration of topical or systemic steroids to calm the host's immune response.

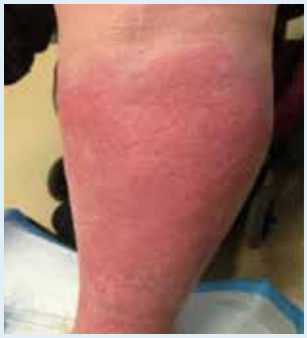
Another example is venous stasis dermatitis. This condition may look like cellulitis (Fig 2) and is often treated with hospitalisation and intravenous (IV) antibiotics.[5] However, venous stasis dermatitis is not an infection; it is an inflammatory response to cell damage resulting from venous hypertension.[6] Therefore, it is quite likely that when such a condition is treated with hospitalisation and IV antibiotics, it is the bed rest that resolves the inflammation.

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disorder that involves skin barrier dysfunction, cutaneous and systemic immune dysregulation, skin microbiota dysbiosis, a strong genetic influence, a characteristic clinical symptom of pruritus or itching, and is a condition still without a safe, targeted treatment.[7] Current management for AD involves the use of topical emollients to enhance skin barrier function and symptom management with steroids, but this strategy is not curative. Interestingly, a recent study suggested that staphylococcus biofilms may play an important role in the pathogenesis of AD and numerous other dermatologic diseases.[8] Bleach baths have been considered for AD treatment, but use is limited due to concerns about keratinocyte toxicity, just as toxicity has also been a concern in wound care.

With increasing understanding of wound pathophysiology, particularly with respect to the influence of microbial biofilm on wound healing, it may be more likely that dermatology can benefit from some of the treatment paradigms being studied in wound care. Perhaps a strategy known to impact biofilm tolerance would benefit some dermatologic conditions more effectively than a treatment designed to subdue the inflammatory response. Conversely, wound care strategies may benefit from the depth of understanding in dermatology regarding clinical and pathophysiological variations in skin inflammation, and how this may be distinguished from infection.

**Fig 2.** Bilateral leg venous dermatitis on minimally ambulatory, obese patient with venous insufficiency complicated by general nonadherence to compression recommendations. This inflammation may be mistaken for cellulitis (patient consent was obtained for the use of these photographs)





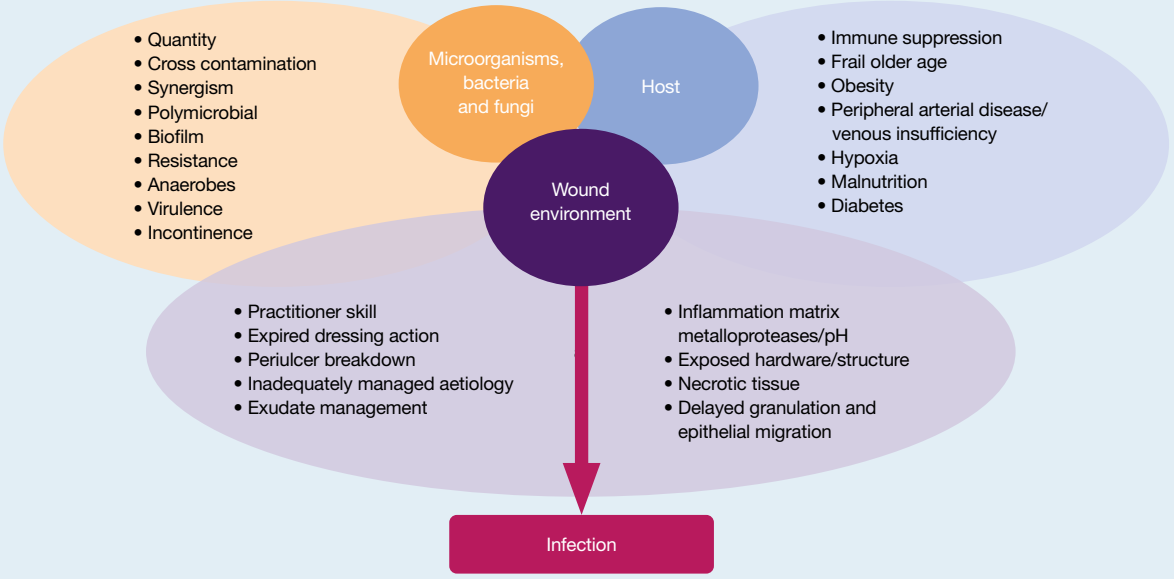
### Wound infection risk factors

Wound infection risk is influenced by interactions between three key elements:

1. The host resilience to microbial interference
2. The local wound environment
3. The microbial bioburden (numbers, virulence and phenotype) (Fig 3).

**Host resilience:** the risk of developing a chronic (hard-to-heal) wound increases with age[9] due to deceleration of the healing response, and increased incidence of cardiovascular disease and diabetes in the older population.[10] Poorly controlled diabetes will impact host resistance to wound infection because elevated blood sugar, even in the short-term, will significantly impact the innate immune response.[11,12] Also, wounds that involve arterial insufficiency have limited access to the host's systemic immunity (i.e., neutrophils), which

**Fig 3.** Factors influencing wound infection risk




will also impact infection risk.[13] In somewhat the same way, wounds related to venous hypertension will be at greater risk of infection if compression is not applied to redirect venous congestion away from the wound and improve local tissue perfusion.

**Local wound environment:** an inadequately managed wound environment may further exacerbate the risk of wound infection. An effective wound healing plan must involve an informed assessment of all factors involved in the wound's aetiology, timely and effective removal of all unwanted substances (for example, biofilm and devitalised host tissue), as well as optimal exudate and microbial management. The wound appearance and healing trajectory provide key clues to the response to current wound management and the health of the wound environment. Meticulous wound bed preparation and treatment adjustments based on barriers can improve the wound environment. However, inappropriate wound treatments guided by inadequately skilled HCPs, a poorly managed wound aetiology, insufficient wound bed preparation,[14] overlooking important subtle changes in a wound's appearance, and failure to engage the patient can increase risk for acute wound infection. Progression to acute wound infection has been reported to increase the cost of care by up to 70%.[15] Unlike disease states, such as diabetes and obesity, wound care is not yet a recognised specialty, so wounds are often managed as a comorbidity of other conditions by a non-specialist.[16] This limits the impact of efforts to overcome the growing challenge that wounds present. Physicians, who drive much of the wound care in the US, have been reported to receive only about 4.5 hours of wound healing physiology in their four years of medical training.[17] The same is true for many general nursing education programmes. The unregulated requirement for clinical expertise adds an innate infection risk to wound care.

**Microbial bioburden:** the microbial load, species and phenotype will also impact wound infection risk. It is generally acknowledged that risk of wound infection increases as the microbial load increases.[18] As early as 1964, Bendy reported that wound exudate with a microbial load of $\geq 10^6$ viable cells per ml was associated with increased risk of infection,[19] and in 1967 Krizek et al. reported a low success rate in grafting of wounds when tissue microbial load was $>10^5$ viable cells per gram.[20] However, quantitative microbiology alone cannot determine infection status of wounds, and it is generally acknowledged that qualitative microbiology (diversity of species, microbial interactions, synergy etc.) is equally, if not more, important than microbial load.[21] As an example, Bowler reported co-synergy between *Staphylococcus aureus* and *Prevotella loescheii* (an anaerobe) in an infected leg ulcer.[22] In this particular case, although both organisms are potential pathogens, the anaerobe would only grow in the presence of *Staphylococcus aureus*, indicating that *Staphylococcus aureus* provided a growth factor for virulence expression in the anaerobe.

Over the last two decades, awareness of a third microbial component that has a significant impact on wound healing has become evident, namely the biofilm phenotype. Biofilm is a natural and predominant form of bacterial existence, involving the aggregation and attachment of bacterial cells to a surface, followed by the formation of a self-produced extracellular polymeric

substance (EPS) that provides protection against external hostilities. It is now widely acknowledged that biofilm is invariably associated with delayed wound healing and chronicity.[23–25] Microorganisms in biofilm form are notably more tolerant to external threats, including host defences, systemic antibiotics and topical antimicrobial agents.[26] The tolerance associated with the biofilm phenotype significantly reduces the effectiveness of antibiotics and antiseptics in controlling wound microbial bioburden. Since microbial load, species and phenotype impact wound infection risk, all should be considered when determining best treatment strategy.

## Host inflammatory response to acute and chronic wound infections

Although the key processes involved in a host inflammatory response to acute and chronic wound infections are similar, a key differentiator is that acute wound infections involve host-controlled inflammation whereas chronic wound infections involve microbe-controlled inflammation, which ultimately have very different clinical outcomes for the patient. This was exemplified in a study by Gurjala et al. who compared acute and chronic (biofilm) infections in a rabbit ear wound model.[24] In this in vivo model, a chronic biofilm infection was shown to be associated with a sustained and lower-grade host inflammatory response (measured by interleukin (IL)-1β and tumour necrosis factor (TNF)-α expression) when compared with wounds that were actively (acutely) infected, indicating a true phenotypic difference in the bacteria–host interaction between the two types of infection.[24] Whereas acute wound infections provoke a host inflammatory response due to the direct action of invading planktonic pathogens on viable tissue, inflammation associated with chronic wound infections is provoked indirectly by persistent biofilm.

The association between both acute and chronic wound infections and the host inflammatory response are described in more detail in the following sections.

## Acute wound infection

An acute wound infection involves invasion of viable wound tissue by metabolically active planktonic microorganisms that trigger a host inflammatory response,[27] i.e., a direct host response to virulence expression (for example, enzymes and toxins) and tissue invasion by the pathogens involved. Acute infection typically manifests clinically as a clear and obvious (overt) condition. Diagnosis is most frequently made by HCPs based on classic signs of inflammation (i.e., calor (warmth), dolor (pain), tumor (swelling) and rubor (redness)). Neutrophils are an essential part of the innate human immune response that serves to prevent infections and facilitate tissue repair, and they are actively involved in both acute and hard-to-heal wound inflammation.[28] In acute infections, neutrophils phagocytose invading planktonic cells, which are subsequently killed by intracellular oxidative and non-oxidative mechanisms. In addition to intracellular killing, neutrophils also release neutrophil extracellular traps (NETs) via a process called NETosis. NETs are weblike structures of DNA coated with enzymes (for example, myeloperoxidase, elastase, cathepsin G), that trap and inactivate bacteria extracellularly, thereby minimising damage to host cells.[28] Microorganisms in biofilm form are not considered to be responsible for acute wound infections; instead, the planktonic microorganisms dispersing from a mature biofilm are the major drivers of subsequent acute infections.[29]

## Chronic wound infection

Chronic wound infection typically manifests as an unclear and prolonged (covert) condition, in which biofilm is the root of the problem.[30] Whereas planktonic bacteria associated with acute, invasive infections are generally cleared by an innate host immune response and antibiotics, chronic wounds are commonly hard to heal. Sessile biofilm communities associated with chronic infections remain tolerant to antimicrobial onslaught. As a foreign body on the surface of a wound, biofilm triggers the accumulation of neutrophils that are unable to phagocytose associated bacterial cells but continue to release enzymes and oxygen metabolites that damage surrounding host tissue while the biofilm community persists.[30] In chronic infections, a vicious cycle exists whereby sustained inflammation caused by persistent biofilm leads to continued and excessive production of NETS which results in tissue damage,[28] and amplifies biofilm formation.[31] Planktonic cells disseminating from mature wound biofilm act as 'bait' for continued neutrophil recruitment and persistent inflammation,[32] which may ultimately, as stated previously, lead to acute infection in neighbouring tissue.[30] Wolcott et al. described 'biofilm-hijacked host inflammation', whereby wound biofilm controls and benefits from the host inflammatory response by upregulating pro-inflammatory cytokines and inducing a persistent and tissue-destructive immune response.[32] Resulting exudate production and accumulation of devitalised tissue provides a continued nutrient source for the biofilm, thereby enhancing its own fitness at the expense of the host.[32] This series of events is in marked contrast to virulence expression and tissue invasion by active planktonic bacteria in acute wound infections.

More recently, Moser et al. reported that the host immune response is unable to eliminate biofilm, and instead accelerates collateral host tissue damage via persistent inflammation, continuous oxidative damage, fibroblast senescence and a lack of beneficial growth factors needed for wound healing.[33] Moser et al. also proposed a wound biofilm (chronic infection) continuum, involving an initial phase in which a microbial load stimulates neutrophil recruitment, but as the biofilm matures, pro-inflammatory cytokines are produced (for example, interleukins and TNF-α) when the host response becomes overwhelmed and

**Table 1. Inflammation and infection in acute and hard-to-heal wounds**

| | Acute wound infection | Chronic wound infection |
|---|---|---|
| **Causative agent** | • Metabolically active planktonic microbial cells | • Metabolically passive and sessile biofilm microbial cells |
| **Infectious process** | • Invasion of host viable tissue via virulence expression (e.g., microbial enzymes, toxins) | • Biofilm (parasitic) persistence on host tissue[32]<br>• Persistent inflammation, continuous oxidative damage, fibroblast senescence, degradation of growth factors, sustained NET release[28,33] |
| **Inflammatory response** | • Host-controlled response<br>• Neutrophil recruitment to tissue site<br>• Increase in intracellular oxidative burst and microbial killing<br>• NET activation and release (NETosis)[28] | • Microbe-controlled response<br>• Low-grade inflammatory response (IL-1ß and TNF-α expression) compared with acute wounds[24]<br>• Neutrophil aggregation around biofilm, ineffective action leading to host cell senescence and oxidative damage[33]<br>• Persistent NETosis[28] |
| **Clinical manifestation** | • Erythema<br>• Heat<br>• Pain/tenderness<br>• Oedema | • Delayed wound healing[17, 33–36]<br>• Wound breakdown[35]<br>• Dull/dark red granular or discoloured tissue[34,35]<br>• Increased exudate[32,34,35]<br>• Friable, unhealthy granulation tissue/bleeding[35,36]<br>• Increased exudate/purulence[32,34,35]<br>• Increased pain[34–36]<br>• Increased malodour[35,36]<br>• Hypergranulation[36]<br>• Epithelial bridging and pocketing in granulation tissue[36] |

NET—neutrophil extracellular trap; IL-1ß—interleukin 1ß; TNF-α—tumour necrosis factor-α

attenuated, leading to continuous oxidative stress, degradation of growth factors, inability to control infection, and ultimately to prevent tissue resolution.[33]

Aside from its impact on the host inflammatory response, biofilm has been shown to prevent wound re-epithelialisation and granulation tissue formation,[24] confirming its ability to stop wound healing.

## Comparing and contrasting acute and chronic wound infections

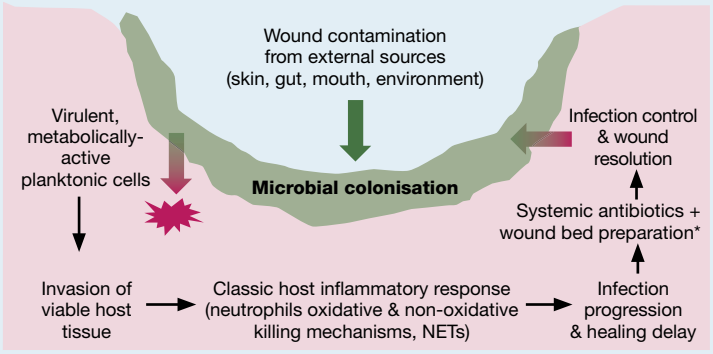
Table 1 highlights key differences between acute and chronic wound infections, from causative agents to host inflammatory response and clinical manifestations, which may assist HCPs in distinguishing a chronically infected wound from an acutely infected wound. Interestingly, Davis,[34] Gardner et al.,[35] Wolcott et al.,[32] and Haesler et al.[36] all observed similar clinical manifestations of stalled wounds that did not appear to be acutely infected (Table 1). Davis considered these clinical observations to be related to a phase in the wound infection continuum referred to as 'critical colonisation'. Historically, the term 'critical colonisation' has been used to describe a phase of a wound infection continuum during which the microbial load caused a noticeable change in wound bed appearance along with obvious healing delay.[34] However, evolving scientific understanding has led to the consensus that these clinical changes more accurately result from the presence of a maturing biofilm (Table 1).[27] The clinical signs previously considered to be due to critical colonisation,[34] also noted by Gardner et al. as a sign of secondary infection[35] and now agreed to be related to biofilm maturation,[36] reflect the harm caused to wound bed tissues by the host's sustained low-grade inflammatory effort to clear the wound of a parasitic biofilm. Upon resolution of host-related risk factors for wound recalcitrance, any ongoing wound chronicity is directly related to a biofilm-induced chronic infection.[37,38]

## Diagnosing acute and chronic wound infections

**Acute wound infections:** diagnosis of a local acute wound infection can generally be based on overt clinical signs and symptoms, namely redness, swelling, pain and heat. On occasion, acute wound infections may persist due to biofilm contamination of surgical hardware, for example, wires or prostheses. Elgharably et al. reported that infected postoperative sternotomy wounds, unresponsive to IV antibiotic therapy, were caused by mature biofilm present on stainless steel wires removed from the surgical site.[39]

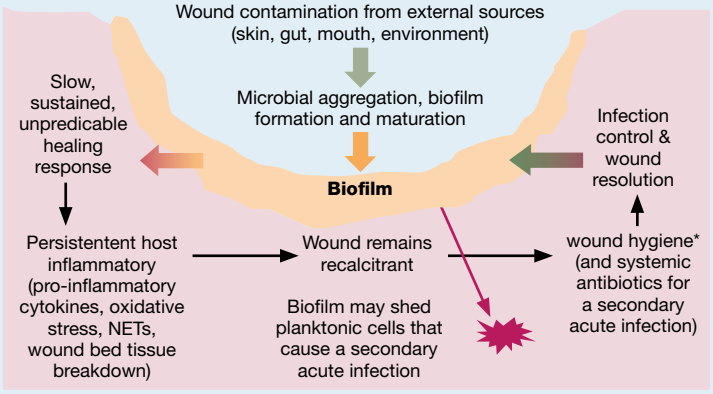
**Chronic wound infections:** a noticeable delay in healing, along with persistent inflammation and recurrent infections that respond poorly to systemic or topical antimicrobial agents, are indicators of chronic biofilm infection.[40] However, clinical signs and symptoms in chronic wound infections tend to be less obvious (covert) than in acute wound infections (Table 1) and, consequently, HCPs often rely on familiar but inconsistently informative methods for determining infection status, particularly wound microbiology.[41] Wound microbiological analysis typically involves a qualitative assessment (i.e., types of microorganisms) and a semi-quantitative assessment of microbial load (i.e., an approximation of the microbial load indicated as light, medium or heavy growth). However,

**Fig 4.** Acute wound infection progression and resolution




*Sharp or mechanical debridement, cleaning, topical antimicrobials; NET—neutrophil extracellular traps

**Fig 5.** Chronic wound infection progression and resolution




*Repetitive sharp or mechanical debridement, noncytotoxic antiseptic cleanser, topical antimicrobials; NET—neutrophil extracellular traps

semi-quantitative analysis has been shown to be particularly unreliable.[42] In a clinical study comparing semi-quantitative and quantitative analysis of 428 tissue biopsies collected from 350 hard-to-heal wounds, almost half (44.3%) of the semi-quantitative cultures showing 'light growth' had quantitative bacterial loads of $>10^5$ colony forming units (CFU)/g.[42] In a study conducted on 180 patients in which six clinicians determined infection status based on wound biopsy, swab and reported clinical signs and symptoms, significant variability in reporting infection status existed between the experts, emphasising the current challenges in using clinical signs and symptoms and microbiology data to diagnose infection in complex wounds.[43] Additionally, a review of related literature reported that, since 1980, most of the data have shown little to no benefit of quantitative tissue biopsy analysis, with several studies reporting poor correlation between wound microbiology and clinical signs and symptoms (between 25% and 39%).[44] Based on this review, Kallstrom concluded that laboratory data should not replace clinical analysis.[44]

Because clinical signs and symptoms of chronic wound infection can be subtle, with inconsistent interpretation among HCPs, together with the questionable value of assessing microbial load, total dependence on either of these methods is not a reliable indicator of wound infection. Fortunately, emerging point-of-care technologies are now beginning to provide additional means of determining wound microbial load and infection status. Fluorescence imaging can now be used to visually locate wound tissue with elevated bacterial loads ($>10^4$ CFU/g),[45,46] and has also been shown to detect biofilm in vitro.[47]

Also, since the host inflammatory response plays such an important role in both acute and chronic wound infections, technologies to detect host inflammatory markers that are triggered by the presence of interfering microorganisms offer a new approach to determining wound infection status. In a clinical study involving 81 patients with hard-to-heal and acute wounds, elevated neutrophil enzymes (myeloperoxidase, elastase and lysozyme) were shown to determine wound infection status more accurately than clinical signs and symptoms when compared with wound swab microbiological analysis.[48] These data indicate that detecting neutrophil enzymes in wound fluid may be a more accurate method of determining wound infection status than clinical signs and symptoms and wound microbiology data, and hence help to guide optimal wound management.

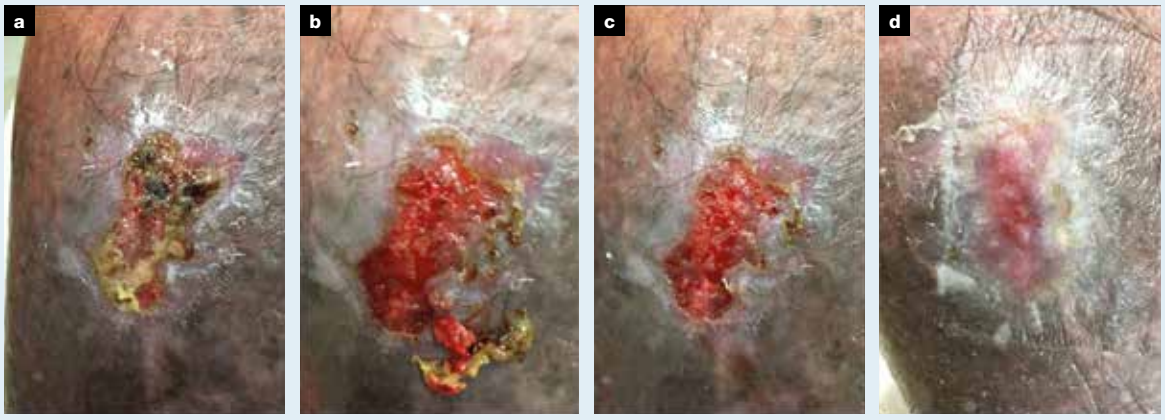
## Treatment approaches for acute and chronic wound infections

Since chronic wound infections are microbiologically, immunologically and clinically distinct from acute wound infections, they require different treatment strategies.

**Acute wound infection:** acute wound infection (Fig 4) results from invasion of pathogens into viable host tissue, triggering a host inflammatory response that is unable to resist assault under pre-existing clinical circumstances. Guided systemic antibiotics will help the host immune system to regain control over microbial invasion. In diagnosing acute wound infection, all potential risk factors must be considered to ensure that healing potential is maximised. Since microbial load is directly related to infection risk,[18] the most effective control will likely be achieved by a combination strategy involving systemic antibiotics and appropriate local wound bed preparation involving removal of any unwanted materials (e.g., devitalised host tissue), and maintenance of an optimally moist wound healing environment.[49–51]

**Chronic wound infection:** since biofilm is the principal cause of chronic wound infection (Fig 5) and promotes

**Fig 6.** Traumatic ulcer, referred to wound centre following failure of systemic antibiotic therapy over a period of three months (**a**). Following wound hygiene involving sharp debridement, an antimicrobial cleanser and an antibiofilm dressing, the wound fully re-epithelialised after seven days (**b**, **c**, **d**) (patient consent was obtained for the use of these photographs)




a tissue-destructive host inflammatory response that prevents wound progression,[32,52] treatments aimed at disarming, disrupting and removing biofilm are essential for resolution. In biofilm form, bacteria are sessile and metabolically quiescent; they are not invading viable host tissue, although there is risk that planktonic cells may be shed from the biofilm to initiate a subsequent acute infection. So, after confirming that healing potential is maximised, biofilm removal is necessary to revert from a biofilm-controlled to a host-controlled inflammatory response. The goal is to minimise the risk for subsequent acute infections and to create an environment conducive to healing. The resilience and persistence of biofilm requires more than standard wound bed preparation, instead requiring a multi-modal topical wound treatment strategy to achieve successful biofilm submission.[53,54] Wolcott et al. reported that wound debridement was essential for disruption of biofilm but provided only a therapeutic window of up to 48 hours when the microbial load was more susceptible to antibiotics and antiseptics.[55,56] Therefore, successful treatment of a chronic infection must involve a focus on both maintaining biofilm disruption and preventing its reformation by more effectively addressing microbial load. Such an antibiofilm wound hygiene strategy has been proposed by an expert advisory group,[54] and a subsequent survey among 1478 HCPs showed strong agreement for implementation of the wound hygiene strategy as a successful approach to biofilm management in hard-to-heal wounds.[57] A chronic wound infection requires a repetitive, multi-modal topical treatment strategy, but does not require systemic antibiotics unless clinical signs and symptoms of acute infection are present (Fig 6).

While local wound management is essential to resolve chronic wound infections and facilitate healing, it is also important to recognise that wounds of all aetiologies can insidiously become biofilm-impeded hard-to-heal wounds. Infection can evolve in a periprosthetic surgical site many months or years after implant surgery. The surface of a prosthetic implant offers a ready interface for bacterial attachment and biofilm formation.[58] An implant is relatively inaccessible to immune response due to lack of blood flow in the hardware which restricts the ability of the immune cells to reach the foreign surface to clear the infection. This can result in a chronic, subacute infection resulting from biofilm contaminated hardware. The difficulty in treating any such chronic infection is further compounded by the innate antimicrobial tolerance of the biofilm phenotype and can often only be resolved with removal of the contaminated implant, therefore making prevention a critical focus.[59]

## Antimicrobial resistance and hard-to-heal wounds

Antimicrobial resistance (AMR) is one of the biggest public health challenges of our time, claiming at least 700,000 lives per year worldwide, and will be responsible for an estimated 10 million deaths by the year 2050, at an estimated cost of US$100 trillion to the global economy.[60] The US Centers for Disease Control and Prevention (CDC) reported that up to 50% of antibiotic prescriptions in the US are inappropriate or ineffective,[61] and a survey in Norway revealed that 53% of patients with hard-to-heal wounds were treated with systemic antibiotics prior to referral to a specialist wound care facility.[62] In his 1945 Nobel Prize acceptance speech, Alexander Fleming warned, 'It is not difficult to make microbes resistant to penicillin by exposing them to concentrations not sufficient to kill them.' Stewart et al. confirmed that when compared with free-floating, planktonic microorganisms, mechanisms involved in the biofilm phenotype strengthen microorganism tolerance to antimicrobial treatments, resulting in either extended

or ineffective treatment regimens,[26] making antibiotics an unreliable treatment for biofilm-impeded hard-to-heal wounds.

Biofilm formation is a crucial step in the pathogenesis of chronic infections, including foreign body-related infections.[38] Wolcott stressed the importance of acknowledging that hard-to-heal wounds are chronic infections,[37] and that therapy must be directed at local biofilm control (wound hygiene), with systemic antibiotics being reserved for cases where there is evidence of bacterial invasion of viable host tissue. Serena et al. recently reported that a post hoc analysis of multicentre antibiotic prescribing patterns did not correlate with clinical signs and symptoms of wound infection or with wound bacterial load, leading to haphazard use of systemic antibiotics and topical antimicrobials for wound treatment.[63]

## Summary

Acute and chronic wound infections are two distinct types of infection that are differentiated by bacterial physiological states (planktonic and biofilm), by the subsequent host inflammatory response that they trigger, and by the resulting clinical manifestations. Whereas the host inflammatory response in acute wound infections is triggered by actively invading planktonic bacteria, chronic wound infections are characterised by a tissue-destructive inflammatory response triggered by the persistence of a tolerant biofilm. Acknowledging the pathogenic nature of wound biofilm is therefore critical to diagnosing the type of infection, and ultimately determining optimal therapy.

Whereas acute wound infections are treated primarily with systemic antibiotics and appropriate local wound care, treatment of chronic wound infections must focus on a repetitive, multimodal wound hygiene strategy (biofilm disruption and inhibition of rematuration) until the obstructive action of biofilm is neutralised and a wound shifts towards healing. In most cases, antibiotics are inappropriate and ineffective in chronic wound infections and associated overuse exacerbates antibiotic resistance on a global scale. Multimodal wound hygiene is the most effective approach to combatting biofilm in chronic wound infections, thereby facilitating wound healing, and reducing the current overuse and misuse of antibiotics in wound care. **JWC**

**Reflective questions**

- What differentiates acute and chronic wound infections?
- Do classic signs of inflammation (dolor, rubor, calor, tumor) always indicate an infection? Why?
- What is biofilm-hijacked host inflammation?
- Should antibiotics be a first line of treatment for a chronic, hard-to-heal wound? Why?

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