

Wound infection-associated pain

Not only does wound infection and the release of pro-inflammatory modulators result in pain and delayed healing, but pain-related stress reduces the immune response to infection. Treatment of pain and infection should be equal priorities

infection; pain; healing rates; delayed healing; stress and anxiety; venous leg ulceration

Wound infection can cause pain and psychological stress, and often results in delayed healing.¹⁻⁶ Diagnosing and managing such infection presents many challenges to the practitioner.^{2,3,7,8} This review outlines our current knowledge of wound infection and wound-related pain, particularly pain known to be related to infection.

Pain as an indicator of infection

Wound infection results from the dynamic interactions that take place between the host and pathogens. It occurs when microorganisms grow, multiply and invade host tissue, leading to cellular injury and host immunological reactions which overwhelm defence strategies.⁹

The precise pathways to overt or 'frank' infection of a wound are complex and involve a number of defined stages: from colonisation of a wound, immunocompetent individuals react immediately with an acute, innate, inflammatory response which leads to the ingress of phagocytic cells and blood proteins. This response, in the early stages of wound healing, serves to remove tissue debris and detrimental microorganisms. In contrast, the inflammation associated with wound infection involves development of erythema, pain, raised local temperature and swelling.⁹ Indeed, pain has been the most frequent sign heralding the onset of infection.⁸

Individuals at increased risk of contracting a wound infection are those with suboptimal immune responses.¹⁰ Neonates and the elderly are thus at particular risk of infection.

Distribution patterns of microorganisms determine outcome in terms of the accepted definition of infection. Wounds are classified as 'infected' when the bioburden exceeds a threshold limit where the host response becomes overwhelmed. Wounds sustaining a bacterial population are described as firstly 'contaminated', secondly 'colonised', thirdly 'critically colonised' and, finally, infected or overtly infected.¹¹ In infected wounds, microbial growth, multiplication and invasion into host tissue lead to

cellular injury and overt host immunological reactions.⁹ Wound healing is delayed as a result.¹ Other clinical signs include sensations of pain, which in turn have been implicated in delayed wound healing due in part to raised levels of stress.²⁻⁶

Delayed healing and increasing pain are suggestive of a possible progression from critical colonisation to overt infection.¹² Infection interrupts the normal healing process, so early diagnosis and appropriate treatment are essential. Signs and symptoms of infection such as raised levels of or change in the nature of pain, spreading redness and increased exudate should prompt the clinician to consider infection. Thereafter, a wound swab or biopsy, and measures to treat the infected wound with antibiotics or other antimicrobial agents are indicated. Early diagnosis of infection reduces the risk of complications (morbidity), so leading to improved patient outcomes and reduced treatment costs.

The most frequent pathogens associated with wound infections in the UK are *Staphylococcus aureus*, *Streptococcus* species, *Pseudomonas aeruginosa* and anaerobes.⁹ These organisms often form biofilms, making antimicrobial therapy of critical colonisation and infection clinically challenging.^{1,13,14} Although the presence of such pathogens can be detected with wound swabs, the use of microbial assessment alone for the diagnosis of wound infections is less reliable than undertaking a holistic assessment using clinical signs such as the presence of cellulitis, delayed healing and unexpected pain. Microbial assessment alone is hampered by the incompletely understood nature of microbial interactions (eg, synergy) and the complicated variety of host-pathogen interactions that may occur.^{1,9}

The classical signs and symptoms of wound infection are recognised as pain, redness (erythema), heat, oedema and purulence. However, these are not always apparent, especially in the early stages when diagnosis is important for prompt treatment.¹⁵ In 1994, Cutting and Harding¹⁶ identified several more 'subtle' signs heralding the onset of infection in acute and chronic wounds. In validating these criteria, Cutting¹⁷ established that 97.5% of deci-

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sions on the infection status of the wound, made with reference to the Cutting and Harding¹⁶ checklist, were corroborated by wound-swab culture.

Gardner et al.⁸ assessed the validity of the classic signs of infection and 12 signs specific to secondary wounds. They found that the latter indicated infection more accurately than the classic signs. Specifically, the validation study involved 36 patients with chronic wounds, of which 11 (31%) were infected, as assessed by quantitative cultures of wound tissue. Patients were assessed for the presence of 12 signs and symptoms of infection without the assessor knowing the infection status of the wound. The presence or absence of the clinical signs and symptoms was then compared with the 'true' infection status of the wounds, as determined by culture.⁸

Based on the four parameters of sensitivity, specificity, discriminatory power and positive predictive value, clinical signs demonstrating validity were:

- Increasing wound pain
- Friable granulation tissue
- Foul odour
- Wound breakdown.

Increasing pain and wound breakdown had a positive predictive value of 1.00 — that is, 100% of the wounds with increasing pain or wound breakdown were infected. Other than these, only friable granulation tissue and foul odour had positive predictive values greater than 0.50. By inference, this finding suggests that infected wounds are associated with higher levels of pain than non-infected wounds.

A Delphi study⁷ was conducted to obtain consensus expert opinion on wound-infection criteria in six wound types: acute wounds, arterial ulcers, burns (partial and full-thickness), diabetic foot ulcers (DFUs), venous leg ulcers (VLUs) and pressure ulcers. It concluded that the following signs and symptoms were common to all of the wound types:

- Pain
- Delayed healing
- Cellulitis
- Malodour
- Wound breakdown.

For all wound types, cellulitis was consistently ranked highly as a criterion for infection. Delayed healing was cited as a criterion in acute wounds (primary and secondary), DFUs and VLUs. However, unexpected pain/tenderness, increased levels of pain or change in the nature of pain were cited for all wound types. Furthermore, in both partial- and full-thickness burns, the onset of pain where previously pain-free was recognised as a sign of infection.⁷

If PUs, which can cause localised pain, become infected, the pain often increases and it is likely that the nature of the pain will change according to the immunological response.^{18,19}

Prevalence

Wound infection is a common surgical complication leading to significant mortality and morbidity.²⁰ Surgical site infections (SSIs) are the most common type of hospital-acquired infection for surgical patients in the UK²¹ and the US,²² occurring in about 10%²³ and 38%²² of patients respectively. SSIs impair wound healing, prolong the hospital stay, cause unnecessary pain²⁴ and may increase the use of medical resources and care costs.²⁵

Virtually all chronic wounds have high levels of bacterial counts. For example, the bacterial profile of patients with chronic VLU was shown to be:

- *S. aureus* (93.5% of the investigated ulcers)
- *Enterococcus faecalis* (71.7%)
- *P. aeruginosa* (52.2%)
- Coagulase-negative staphylococci (45.7%)
- *Proteus* species (41.3%)
- Anaerobic bacteria (39.1%).²⁶

Data from the Eurodiale study showed a high prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease;¹⁵ specifically, of 1,229 patients evaluated, 58% had a clinically infected wound.²⁷

There is a paucity of information on the incidence and prevalence of chronic wound infection. Nevertheless, it is clear that chronic wounds are colonised by a variety of pathogens that can very quickly infect a wound should circumstances permit.

Infection and wound pain

Inflammatory responses following tissue damage sensitise peripheral pain receptors (nociceptors) in the skin. In chronic wounds, this inflammatory response is prolonged, which is partly attributable to uncontrolled matrix metalloprotease (MMP) activity. Repeated stress and/or pain may attenuate the hypothalamic-pituitary-adrenal (HPA) axis feedback mechanism, resulting in excess inflammatory responses that suspend wound healing in the inflammatory phase.²⁸ Stress modulation of MMP expression has been reported, which may influence wound healing.²⁹

In acute wounds, pain subsides when healing progresses through the uninterrupted phases of inflammation, proliferation and remodelling. Persistent inflammation, and the tissue damage associated with it, may activate peripheral and central nociceptors. These prolonged inflammatory responses result in spontaneous pain, an increase in wound sensitivity (primary hyperalgesia) and increased sensitivity to the uninjured peri-wound or surrounding skin (secondary hyperalgesia).^{30,31} If stimuli such as repeated dressing change or interventions that evoke iatrogenic pain, as opposed to background pain due to underlying wound aetiology,²⁷ are in place, patients become locked in a cycle where the pain threshold is reduced and any sensory stimulus registers as pain (allodynia).^{30,32}

Wound-healing complications resulting from infection further contribute to the pain levels experienced.⁸ Sibbald et al.³³ claimed that, while pain is uncommon in diabetic foot disorders, it can be indicative of limb-threatening complications such as deep infection, Charcot changes or critical ischaemia. Pain is a major consideration for patients with burn injuries,^{34,35} particularly if infection is present. In a retrospective study, 60 out of 165 patients with burn injuries were diagnosed with infection with a significant increase in pain intensity.³⁵ Wasiak et al.³⁶ noted that if superficial and partial-thickness wounds become infected, they can progress to a deeper burn.

Infection stimulates inflammatory responses which lead to a constant influx of neutrophils that compete for nutrients and oxygen while at the same time releasing enzymes, free oxygen radicals and inflammatory mediators.³¹ These agents damage tissue and lead to a cycle of bacterial proliferation and continued tissue destruction.³⁷ Sibbald et al.³⁸ propose that enzymes and pro-inflammatory mediators irritate nerve endings, thereby increasing pain. Additionally, unexpected pain or tenderness is an indicator of infection in granulating wounds.¹⁸

Infection and delayed healing

From a microbiological perspective, successful wound healing is dependent on maintaining a host-manageable bioburden.³⁹ Several studies have confirmed that a certain, undefined, bioburden can delay healing.³⁷⁻⁴⁵ Bacteria in chronic wounds produce MMPs, a cause of the tissue damage observed in critical colonisation and infection.⁴⁶ Due to their destructive effect on growth factors and extracellular matrix proteins, these proteolytic enzymes contribute to 'uncontrolled' inflammation and thus wound chronicity. Bjarnsholt et al. proposed that delayed wound healing is, in part, caused by inefficient eradication of infecting, opportunistic pathogens.¹

Doughty et al.⁴⁷ suggested that infection delays VLU healing. Between 80% and 100% of leg ulcers become colonised with bacteria, the most common isolates of which are *S. aureus* and *P. aeruginosa*.⁴² *S. aureus* is the most common isolate in DFUs.⁴⁸ Both species, along with haemolytic streptococci, have been associated with delayed wound healing.^{42,49} Madsen et al.⁴⁹ evaluated possible influences of selected bacterial species on the healing of VLUs. Complete healing within the observation period of 180 days was noted in:

- 10.5% of patients with and 35% of those without *P. aeruginosa* (p=0.0631)
- 21.6% of patients with and 62.5% of those without *S. aureus* (p=0.0278)
- 10.5% of patients with and 35% of those without haemolytic streptococci (p=0.0631).

In a study involving 70 patients with VLUs,

Davies et al.⁵⁰ indicated that bacterial density was associated with non-healing. Wound flora was quantified after sampling by swabbing and biopsy, and a significant association between healing and bacterial diversity in the wound (as assessed by swab) (p=0.023) was demonstrated. Furthermore, the bacterial density of a wound surface area identified by swabbing (p=0.018) or biopsy (p=0.038) was shown to be an independent predictor of non-healing.

These results support previous findings on the influence of bacterial diversity, and the interactions between different species of bacteria, on wound healing.^{39,42} Chronic infections are often polymicrobial.⁴⁸ Trengove et al.⁴³ demonstrated that the presence of any one specific bacterial group did not delay wound healing, but that the presence of four or more bacterial groups was associated with delayed healing.

In patients with diabetes, wound infection presents as a common complication. Kirsch et al. have demonstrated that, in animal studies, experimental excision wounds inoculated with *S. aureus* showed a significant delay in epidermal healing compared with non-inoculated diabetic wounds (59% versus 84%; p<0.05).⁵⁰

Pain and delayed healing

Evidence suggests that psychological stress results in the dysregulation of immune function. In patients with chronic wounds, pain is a common cause of such stress, which may indirectly impair the normal wound healing process by way of local detrimental effects on the biological processes required for wound repair.² Freedman et al.⁵¹ and Reddy et al.⁵² recognised that failure to manage pain in patients with chronic wounds significantly impairs healing.

Stress and anxiety resulting from wound pain are activate the HPA axis which stimulates cortisol production.²⁸ Stress can also be induced by the anticipation of pain and associated anxiety²⁸ — for instance, while waiting for a dressing change.² Such anticipatory-induced anxiety has been shown to activate cholecystokinin, which plays a crucial role in pain transmission.^{28,53}

Several studies have demonstrated the association between stress and impaired healing. These were not necessarily studies associated with pain-induced stress, but they all demonstrated a relation between stress and delayed wound healing.³⁻⁶ Glaser et al. studied levels of pro-inflammatory cytokines in experimentally-induced skin blisters in women reporting high levels of stress, revealing significantly lower levels of interleukin-1 alpha (IL-1 α) (p<0.03) and IL-8 (p<0.04) compared with the controls.⁶ This is indicative of a deficient inflammatory response which will reduce the body's defences against invading organisms.²⁵ Although a variety of human and animal laboratory studies have

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shown that stress delays healing of standardised punch biopsy wounds, there is only limited direct evidence that chronic wound pain is associated with psychological stress and delayed wound healing.² Two studies in patients with chronic VLU indicate that experiences of anxiety and depression in patients with these types of wounds are associated with wound pain and delayed healing.^{54,55} The studies do not give direct evidence for a link between poor pain control and prolonged wound healing, but lend support to the hypothesis that, by reducing wound pain and associated stress, wound healing rates can be improved.² However, in a recent study⁵⁶ post-surgical pain intensity in women who had undergone elective gastric bypass surgery was significantly associated with the delayed healing of a 2mm punch biopsy wound. The authors concluded that their findings extend previous laboratory models of wound healing to a surgical population, so providing the first evidence

that pain has an important influence in post-surgery wound healing.

The need to treat both pain and infection

In view of the evidence that infected wounds have higher levels of pain and higher sensitivity to pain, along with the implications that prolonged pain delays healing and reduces patients' quality of life, the need to control both pain and infection to expedite wound healing is clear. Recent products, such as soft silicone dressings, hydrogels, Hydrofiber and alginates are less likely to cause the pain levels associated with changing traditional, dry dressings.²⁹ The combination of silver with such dressings to address infection and associated impaired healing, and the use of atraumatic adhesives, may have benefits in terms of reducing stress-induced pain and combating infection in chronic wounds.

Conclusion

Wound infection and the release of pro-inflammatory modulators result in both local pain and delayed healing. Evidence suggests that pain-related stress or anticipation of such pain reduces the immune response to infection. By implication, the treatment of pain is as important as the treatment of infection itself.

With this in mind, the development of advanced dressing technologies aimed at minimising trauma through the use of an atraumatic adhesive technology and the incorporation of broad-spectrum antimicrobial agents such as silver may be a means of controlling both pain and infection in chronic wounds, with a consequent positive impact on healing rates.

That infected wounds are more painful than uninfected wounds makes it all the more important that wound infection is treated at the earliest opportunity and that the agents used to achieve this have a rapid and sustainable effect. ■



Fig 1. An infected, sloughy sternotomy wound that has begun to dehisce. The wounds made for the insertion of chest drains are also showing signs of infection. Note the peri-wound erythema and evidence of exudate. Pain was a major factor for this patient



Fig 2. Pressure area damage to the buttocks has become infected. Clear signs of spreading erythema, exudate, undermining and necrotic tissue

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