Title:

The impact of infection on the four stages of acute wound healing: An overview.

Abstract:

The impact of infection on acute wound healing is multifaceted resulting in disruption to every stage of wound healing. At present there are significant challenges associated with the diagnosis and treatment of wound infection with the inappropriate use of antimicrobial dressings potentially resulting in poorer wound healing. The relative risks of contamination of high quantities of bacteria and of virulent species is yet to be fully elucidated, however the important symbiotic relationship between bacteria and host immunity is well recognised and has inspired the development of novel smart dressings that help maintain this symbiosis by selectively destroying pathogenic bacteria. The consequences of acute wound infection for patients may include surgical wound dehiscence, pain, prolonged hospital stays and psychological stress which may in themselves become inimical to wound healing. This article presents an overview of the impact of infection on acute wound healing considering each of the four stages of healing.

Key Words:

Acute wound; Infection; four stages; healing; impact

Introduction:

Wound healing depends on a complex interplay of physiological processes and is reliant on prerequisites including adequate nutrition, tissue normoxia and immunocompetency as well as the absence of foreign material, pathogenic microbes and implementation of appropriate treatment regimens (Guo and DiPietro 2010). Amongst the numerous intrinsic and extrinsic factors affecting wound healing, infection is arguably the most common and potentially preventable obstacle to healing (Ceilley and Han 2017).

Acute wounds are typically expected to follow a normal healing trajectory following the four stages of healing (see table 1) (Demidova-Rice 2012). Most acute wounds are caused by surgery and early definitions of wound infection were developed based on the planktonic bacteria present in acute wounds (Ayello and Baranoski 2016). According to the International Wound Infection Institute (IWII 2016) wound infection is characterised by the presence of proliferating bacteria in viable tissue that cause damage to tissues and prevent healing. Significantly, this differs from wound colonisation characterised by the presence of replicating bacteria in a wound without causing damage to tissues (Partlet et al 2019). Currently, wound infection present challenges to clinicians and patients with wounds and diagnosis of infection remaining heavily reliant on subjective clinical judgement (IWII 2016). With growing antibiotic resistance (World Health Organisation 2018) more evidence is needed to support novel treatments that combat infection and restore wounds to normal healing trajectories without encouraging resistance in bacteria or the development of biofilm leading to wound chronicity. For example, the development of novel smart dressings that help maintain this symbiosis by selectively destroying pathogenic bacteria (Zhou et al 2018).

This article will explore the pathophysiology of bacterial infections and the impact of infection on acute wound healing considering the impacts on each of the four key phases of wound healing.

Mechanism of infection

Acute wound infections typically start by contamination of local flora, this contamination may lead to colonisation followed by local infection and eventually systemic infection if left untreated (Bowler 2002). Despite the variations in flora at acute wound sites, *Staphylococcus aureus* is consistently found to be the most prevalent causative organism associated with infected acute wounds (Russo et al 2016). Although, other than the high prevalence of *Staphylococcus aureus* on skin, it remains unclear exactly why this bacterium is so commonly the cause of wound infection Parlet et al (2019). Previously it was suggested that quorum sensing (chemical signalling) between bacterial species present on the epidermis allowed regulation of virulent characteristics between bacterial flora which in unbroken skin, supports a diversity of bacterial species and prevents foreign species from disturbing natural flora (MacLeod and Mansbridge 2016). In wounds however, this cell-cell communication is disrupted potentially leading to up-regulation of *Staphylococcus aureus* virulent behaviour causing the release of exotoxins and subsequent destruction of competing bacteria and wound tissues (Partlet et al 2019). Adding to the protective function of quorum sensing in normal flora, symbiosis exists between bacteria in the biome and host immune agents. This symbiotic relationship between bacterial flora and host immune peptides was demonstrated in a study by Cogen et al (2010) in which *Staphylococcus epidermidis* antimicrobial δ-Toxin was found to cooperate with host antimicrobial peptides to destroy the virulent group A *Streptococcus* bacteria. Controversially, the use of probiotics has been suggested as a potential therapy to regulate bacteria in infected wounds by maintaining host-biome symbiosis, however studies investigating this remain in their infancy (Lukic et al 2017).

The relative impacts of virulence and levels of contamination in the genesis of infection

The progression of an acute wound from contaminated to infected remains the subject of debate, with a continuing lack of clarity as to the influence that various intrinsic and extrinsic factors have on the development of infection however, many risk factors have been identified (IWII 2016). Specifically, the impact of host immune function is considered a major factor in the progression of wound infection (Hansis 1996). However, it remains unclear whether the virulence or quantity of the contaminating organisms is more important in the development of infection in immunocompetent patients (Cooper 2013). In a study by Spencer et al (2010) investigating the impact of methicillin-resistant

Staphylococcus aureus (MRSA) decolonisation preoperatively showed significant reductions in surgical site infections following decolonisation (p=0.0093). Prior to the investigation MRSA was demonstrably associated with significantly more infections than *Staphylococcus aureus* in a population of surgical patients (p=0.0162) (Spencer et al 2010). This study lends credence to the theory that virulence is potentially a greater influence on the probability of developing infection and suggests healing may be prolonged in acute wounds infected by virulent microbes that could have been identified by wound culture prior to their proliferation and subsequent manifestation as infection.

However, virulent contamination does not always lead to infection and the use of prophylactic decontamination could ultimately delay healing in acute wounds (Storm-Versloot et al 2010). Indeed, not all heavily colonised wounds are considered to be infected and the development of infection in a wound appears to be dependent on both the toxins released by the bacteria and the intensity of the host response, with host immune enzymes considered to enhance tissue destruction (Lazareth et al 2012). Despite this, areas of anatomy densely populated with bacterial flora, such as the bowel, continue to be considered a high risk for infection following injury (Chida et al 2019). A review of the utility of quantitative cultures by Doern (2014) determined that higher bacterial density in tissues is not associated with bacteraemia or sepsis, indicative of more severe infection, and concluded that screening for pathogenic organisms yields greater use in clinical practice.

Physiology of bacterial activity in wound tissue in the four phases of healing

Normal wound healing is widely accepted to consist of four concurrent processes, including, haemostasis, inflammation, proliferation and maturation (Demidova-Rice 2012). In infected acute wounds these processes are disrupted, resulting in poor healing and the potential development of wound chronicity (Malone 2017).

Haemostasis

The main function of haemostasis is protection of the vascular system preventing excessive blood loss and subsequent loss of organ function (Velnar et al 2009). However, following the release of toxins by bacteria vascular injury can occur in the wound tissue leading to a neuronal reflex response causing contraction of vascular smooth muscle to reduce extravasation into the wound bed (Strecker-McGraw et al 2007). According to Velnar et al (2009) this response is only effective in transversally interrupted arterioles with

a diameter <0.5cm. Notably, in longitudinally interrupted vessels this response may exacerbate bleeding (Lawrence 1998). In either case, following sufficient blood loss from the affected vessel, hypoxia and acidosis cause the reversal of the neuronal response and a resumption of bleeding (Velnar et al 2009).The action of anaerobic bacteria has also been demonstrated to inhibit endothelial tubule formation (Stephens et al 2003). This manifests clinically in the appearance of a dark red friable wound bed (Ayello and Baranoski 2016).

Klinger and Jelkmann (2002) proposed that the role of platelets may extend beyond those associated with haemostasis. Specifically, platelets have been demonstrated to bind to bacterial pathogens and release biocidal peptides including cc-chemokines and cxc-chemokines ultimately assisting dedicated immune cells during the inflammatory response (Klinger and Jelkman 2002). However, the increase in platelet concentration associated with bacterial infection is reportedly linked to unhelpful local thrombosis, establishing a hypoxic wound environment conducive to further anaerobic bacterial proliferation (Dow 2001).

A review of primary clinical studies on the impact of novel haemostatic agents in wound infection suggested that they may accelerate healing, (Lacci and Dardik 2010) however common methodological issues including a lack of homogeneity between treatment groups, small sample sizes and inadequate study lengths provided weak evidence for the relative impact that intervention focussed on this phase of healing has on clinical outcomes. The review by Demidova-Rice et al (2012) focussed on chronic wounds which may limit its applicability to acute wounds, it is also challenging to determine the impact that interventions focussed on one healing phase may have on overall healing as other phases of healing occur concurrently and therefore must be considered when evaluating treatments.

Inflammation

The inflammatory phase is intended to establish an immune barrier to bacterial contamination and destroy bacteria introduced into the wound during injury (Velnar et al 2009). The inflammatory response is broadly categorised into two phases, early and late (Hart 2002). The early phase involves an initial haemostatic response followed by the arrival of leukocytes to the site of injury following stimulation by haemostatic agents (DiPietro et al 2001). The late phase includes the action of a host of immune cells; these cells orchestrate a synergistic effort to eliminate bacteria through processes such as

phagocytosis, the release of reactive oxygen species and proteinases to remove devitalised tissue (Hart 2002).

In the presence of infection, the immune response is initially heightened causing the release of greater quantities of reactive oxygen species and proteinases which indiscriminately damage biological tissues (Hart 2002). This paradoxically stimulates a subsequent down-regulation of the host immune response to protect viable tissues damaged by the action of host immune cells combined with endotoxins released by bacterial lysis (Lazareth et al 2012). Endotoxins are associated with the release of pro-inflammatory cytokines interleukin 1-β and tissue necrosis factor-α counteracting the downregulation by host immunity (Jones et al 2004). This conflict in inflammatory regulation in the late inflammatory stage is typical of wound infection and ultimately prevents progression into the proliferative stage (MacLeod and Mansbridge 2016).

Endotoxin concentrations can be augmented using topical antiseptics such as ionic silver dressings which cause the release of bacterial cell contents, as indicated in a review by Storm-Versloot et al (2010). These authors concluded that topical silver did not aid wound healing and, in some cases, slowed healing in non-infected wounds. This demonstrates the relative impacts of exotoxin release in colonised wounds compared with the endotoxins released during bacterial destruction and proliferation. Ultimately this highlights the need for careful consideration of clinical intervention with regards to the use of antiseptics due to potentially adverse effects on the inflammatory phase of healing in wounds.

It is thought that the plasticity of macrophages is primarily responsible for the transition of wounds from the inflammatory to the proliferative stage following successful bacterial decontamination (Mosser and Edwards 2008). Notably, macrophages in their regulatory and reparative phenotypes stimulate keratinocytes, fibroblasts and endothelial cells to promote tissue regeneration (Mosser and Edwards 2008). In acute wound infection this transition is delayed due to the increased burden on the immune cells to destroy invading bacteria, creating a risk of planktonic bacteria forming biofilms potentially leading to wound chronicity (MacLeod and Mansbridge 2016). From the patients' perspective the inflammatory reactions created by acute wound infection may elicit pain, foul smelling exudate and an increased length of hospital stay (Ayello and Baranoski 2016). This may ultimately contribute to psychological stress which is associated with poorer wound healing and potentially poorer concordance with treatment plans (Walburn et al 2009).

Proliferation

The proliferative phase aims to re-establish an epithelial barrier by contraction of the wound via processes including angiogenesis, fibroplasia and epithelialisation (Gonzalez et al 2016).

Bacterial infection results in extensive disruption of proliferative processes and may result in tissue necrosis as bacteria secrete cytotoxic enzymes and oxygen radicals (Jones et al 2004). Endotoxins released during bacterial proliferation have been associated with disorganised collagen deposition resulting in reduced tensile strength and surgical wound dehiscence (Ovington 2003). The action of both fibroblasts and keratinocytes are inhibited in wound infection due to the release of cytokines such as interleukin 1-β and tissue necrosis factor-α (Stephens et al 2003). These cytokines lead to an increase in matrix-metalloproteinases (MMPs) which decrease production of growth factors (Landen et al 2016).

Contrary to the destructive characteristics of bacteria, a review by Osherov and Ben-Ami (2016) found angiogenesis to be dependent on the presence of bacteria. Further demonstrating the symbiosis between bacterial and human cells (MacLeod and Mansbridge 2016). In infected wounds, poorly regulated angiogenesis due to bacteria can result in hypergranulation which is associated with higher levels of exudate and maceration of periwound tissue (Hampton 2007). However, controversy exists surrounding the pathogenesis of hypergranulation with malignancy and inflammation due to foreign bodies such as occlusive dressings also considered causative factors (Vuolo 2010). Notably, hypergranulation is reported to occur in non-infected wounds creating a risk for secondary infection, this generates challenges to clinicians determining whether the infection was the cause or the result of hypergranulation which may ultimately influence treatment decisions (Vuolo 2010). A recent study investigating the impact of antimicrobial dressings on surgical wound hypergranulation following gastrostomy placement, found that despite hypergranulation occurring in 69.5% of patients wounds only 8.9% were considered to be infected and; antimicrobial dressings did not prevent hypergranulation (Leon et al 2018). Gastronomy tubes are thought to stimulate hypergranulation by inducing an increased inflammatory response as a reaction to the foreign body (Borkowski 2005). The weak association of hypergranulation with infection is reflected in the IWII (2016) consensus suggesting that hypergranulation is a covert sign of infection, it is clear

that more research is needed to determine the impact of infection on this essential process and for clinicians to be aware that hypergranulation is a potentially poor indicator of infection (Vuolo 2010). Specifically, the inappropriate use of antimicrobial dressings to counteract hypergranulation may worsen healing outcomes by causing a local increase in endotoxin concentration re-stimulating an inflammatory response (Jones et al 2004).

Clinically the impact of infection on the proliferative phase of healing may manifest in slow or absent signs of wound healing, further wound breakdown or the phenomena of hypergranulation (Ayello and Baranoski 2016, Hampton 2007).

Maturation

Following the re-establishment of functional microvasculature and the elimination of damaging bacteria, dermal and epidermal cell regeneration can occur leading to wound closure and scar formation, this process can take several months (Demidova-Rice et al 2012). According to Xue and Jackson (2015) the maturation phase and particularly the formation of scar tissue is heavily dependent on the inflammatory stage; the lack of scarring in foetal tissues has been attributed to the absence of an inflammatory response in foetal tissue. This observation led to debate around whether inflammation is necessary for healing or an evolutionary development to hasten healing in dirty environments helping to reduce mortality (Eming et al 2007). Although infection is known to extend inflammation it is unclear what impact this may have on the maturation of the wound, notably acute wounds in elderly patients show increased inflammation but heal with less scarring (Eming et al 2007).

A study by Singer and McClain (2002) on acute burn wounds in swine found that infected wounds were associated with statistically significant slower epidermal maturation ($p<0.001$) and deeper scarring ($p<0.001$). It is thought that the destruction of matrices by MMPs, loss of fibronectin and mucopolysaccharide create deeper tissue damage than in non-infected wounds which contributes to the deeper level of scarring (Singer and McClain 2002). However, results of clinical trials using animal models do not reliably produce similar results in human subjects (Elliot et al 2018). Studies on human wound maturation have shown that significant variation in both time to scarring as well as aesthetic appearance of scars are present even in non-infected acute wounds (Bond et al 2008). Ultimately it remains unclear what the impact of acute wound infection has on this phase of healing, although it appears to be dependent on factors including age, host

immunity and the success of other healing processes such as the formation of healthy granulation tissue (Eming et al 2007, Vuolo 2010).

Conclusion:

Overall, the impact of infection on acute wound healing is multifaceted resulting in disruption to every stage of wound healing (Ayello and Baranoski 2016). At present there are significant challenges associated with the diagnosis and treatment of wound infection (IWII 2016) with the inappropriate use of antimicrobial dressings potentially resulting in poorer wound healing (Storm-Versloot et al 2010). The relative risks of contamination of high quantities of bacteria and of virulent species is yet to be fully elucidated, however the important symbiotic relationship between bacteria and host immunity is well recognised and has inspired the development of novel smart dressings that help maintain this symbiosis by selectively destroying pathogenic bacteria (Zhou et al 2018). The consequences of acute wound infection for patients may include surgical wound dehiscence, pain, prolonged hospital stays and psychological stress which may in themselves become inimical to wound healing (Ovington 2003, Walburn et al 2009). Finally, the overall aesthetic appearance of a previously infected healed wounds may be poorer with deeper levels of scarring although the influence of infection on scarring is yet to be fully described (Bond et al 2008).

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Table 1. Four stages of wound healing and the impact of infection

Stage of healing	**I: Haemostasis**	**II: Inflammation**	**III: Proliferation**	**IV: Maturation**
Key processes	• Release of inflammatory mediators • Fibrin formation • Growth factor release	• Increased vascular permeability • Infiltration of immune cells	• Angiogenesis • Formation of extra-cellular matrix	• Epithelialisation • Scarring
Impact of infection	• Inhibition of endothelial tubule formation, appearing as dark red friable granulation tissue. (Stephens et al 2003) • Thrombosis caused by aggregation of platelets involved in immune response, creates hypoxic wound tissues (Klinger and Jelkmann 2002)	• Greater concentration of reactive oxygen species (ROS) in wound tissues, causing indiscriminate tissue damage (Hart 2002). • Bacterial toxins cause destruction of healthy cells (Lazareth et al 2012) • Dysregulated inflammation and tissue destruction manifests as pain, swelling and foul odour (Ayello and Baranoski 2016).	• Disorganised collagen deposition leading to wound dehiscence (Ovington 2003). • Inflammatory cytokines cause increase in matrix metalloproteinases (MMP) decreasing growth factor production. (Landen et al 2016). • Hypergranulation may occur (Hampton 2007).	• Damage to matrices by MMPs and loss of fibronectin and mucopolysaccharide may lead to slower and deeper scarring (Bond et al 2008).