Role of infection in wound healing

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Abstract:
Chronic wounds, particularly infected wounds are clinically very important due to their significant impact on health budgets as well as patients’ health worldwide. Patients with diabetes mellitus, vascular diseases especially peripheral vascular disease and pressure ulcers are major categories of patients presenting with chronic wounds. It is known that there are multiple factors determining chronic wound prognosis. The presence of multiple types of pathogenic bacteria, with specific virulence and adherent (biofilm) properties, contribute a significant role to the development of chronic wounds. This review article is based on the research project entitled “An investigation of the impact of bacterial diversity, pathogenic determinants and biofilms on chronic wounds”. The research findings have been published in form of research papers as well as conference posters. The aim of this article is to highlight various important aspects of bacterial impact on wound healing.

Keywords: Chronic wounds; wound healing; wound infections.

Introduction:
Chronic infections are clinically very important and huge amount of health budgets worldwide are consumed on managing them along with economic burden of diabetes mellitus. These infections usually result after damage or defects in the primary defence mechanisms. One of the major clinical challenges is non-healing wounds like diabetic foot, vascular and pressure ulcers. Approximately 17 million people develop chronic wound infections and 550,000 die from these infections worldwide every year. Chronic wounds are estimated to develop in 1–2% of the population of developed countries during their lifetime. Along with local causes various systemic diseases such as hypertension are linked with chronic wounds.

When superficial skin layer (epidermis) is lost along with dermis or deeper layers, we call this a wound or an ulcer. A wound has been described as “a physical break in epithelium integrity and the subsequent host response to repair this break”. A wound lasting for 6 weeks or over is a chronic wound. Chronic wounds are of three categories; healable, non-healable and maintenance. The first type heals with proper treatment. Similarly, maintenance wounds could heal and are actually healable wounds. They stay for a long time due to limited resources and care. Once treated properly they progress to healing. Non-healable wounds have extensive tissue damage or damage to blood supply such that it cannot be treated/corrected.

Bioburden:
The actual bacterial load or bioburden, defined as the “metabolic load imposed by bacteria in the wound bed” plays an important role in chronic wounds. The bioburden not only includes total bacterial numbers in the wound but also their metabolic activities, nutrient consumption and production of toxic substances.

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Using a scanning microscopy, observations have been made that reveal that the bioburden is higher in cases of chronic wounds compared to acute wounds. Bioburden, specific organisms and immune response are the main factors contributing to the development of chronic wounds. Researchers claim that the presence of a bacterial load of $>10^5$CFU as a cut off value to determine whether a wound will become infected or not. There is another view which claims that the presence of more virulent organisms can result in infections even if bacterial load is less than $10^4$ Colony Forming Units (CFU). A recent study has reported that only higher bacterial load ($>10^4$CFUs/g) is associated with poor healing of wounds, even in absence of infection signs.

**Bacterial growth and wound healing:**
Skin acts as a barrier against infections. So, if this protection is lost as in case of wounds bacteria can colonize and cause damage mainly by interfering with normal protective mechanisms like antibacterial secretions. Bacteria grow over all chronic wounds. For this we never consider a wound surface sterile. Gontcharova and co-workers found a notable difference in the number of opportunistic pathogens between normal skin (1.54%) and wounds (20%), indicating that the skin harbours the majority of bacteria which are usually harmless.

Colonization of a wound bed is characterized by surface growth of bacteria, however, there is no noticeable immune response while critical colonization or infection occurs when bacterial number increases and interferes with the healing process. This difference between colonization and infection should be understood by health care professionals. This is because treatment for infection is recommended while colonization does not need to be treated. It is not clinically possible to assess difference amongst these three (colonization, contamination, infection).

Bacterial infection plays a major role in delaying wound healing by enhancing inflammatory response and tissue damage and wound healing is enhanced if surface dead tissue is removed as such scabs which act as a reservoir for the majority of microorganisms.

Factors affecting the wound microbiome determines the fate of a wound as both acute and chronic wounds are colonized with bacteria; however, the outcomes are different for both types of wounds. Infection control is regarded as an important component of wound bed preparation (WBP). Wound healing is a highly complex and organized process involving many cellular components. These phases are haemostasis, inflammation, proliferation and remodelling. Proposed mechanisms responsible for improper healing include a prolonged inflammatory response, the presence of biofilms, failures of skin to re-epithelialise, and an imbalance of micro-molecules.

The inflammatory response of chronic wound infections is different which results in less prominent symptoms compared to acute infections. This response mainly involves Immunoglobulin G (IgG) antibodies and polymorphic nuclear neutrophils (PMNs) which continuously, but in a controlled manner, keep migrating to the infection site. Keratinocytes play an active part in interactions of the innate immune system. The presence of neutrophils has been reported to slow migration of keratinocytes. Microbial growth, such as *S. Aureus* biofilms, activates apoptosis in keratinocytes.

Similarly, bacterial biofilm is now being considered as one of the main factors influencing wound healing. It affects healing processing by various mechanisms particularly by providing a safe environment for bacterial growth. Bacteria growing in form of biofilm have been reported to have ten times higher survival rate compared to their planktonic growth. In a wound bed, there is abundance of nutrients as well as protection against antimicrobials and immune system. Similarly, low blood flow and lack of oxygen provides extra protection for these bacteria. It is also being investigated whether the presence of biofilms can reduce surface penetration of oxygen.

**Prevention, problems and future directions:**
There are many unanswered questions related to bacterial involvement in wound healing. For example, what exactly determines whether a wound will become chronic? What is the exact source of bacteria in various wounds? Why and how do multiple bacterial species survive together? Which species are more pathogenic? Similarly, it is still unclear which treatment strategy is the best. More specifically, it is yet to be determined how the biofilm load interferes with the healing process. It is still unclear why and how exactly microorganisms adapt their growth form biofilms. Although it is claimed that biofilm interferes with re-epithelialisation, no model system has proved it yet.

Controlling wound care infection is very important as these infection can not only result in systemic infections but can also affect systemic disease. Clinically there are several challenges in avoiding infections and infection transfer. Microbes can...
colonize patients and health care workers\textsuperscript{48}. They can also grow in substances such as normal saline or some disinfectants\textsuperscript{23}. These could act as reservoir for infection spread or cross contaminations. This means it is necessary for health care workers to understand that there is a difference amongst clean, sterile and dirty objects\textsuperscript{49}. There is no agreed criterion to determine and differentiate deep infection and critical colonization. If we can diagnose wound infection based on clinical examination, this would be a desirable clinical goal but no single clinical sign has been reported to be able to tell us the difference between superficial colonization or deeper invasion and infection\textsuperscript{20}. Sibbald et al (2006) have presented NERDS (indicating superficial growth) and STONEES (indicating deeper moderate or heavy infection) categories of combination of signs and symptom to differentiate between superficial bacterial colonization and deeper invasion and infection\textsuperscript{50}. We need to verify and further develop such criteria. Currently, there is no ‘gold standard’ for determining the correlation between bacterial load/bioburden and wound chronicity. It is therefore very important to develop more robust and accurate methods, such as molecular methods, to quantify bacterial load and diversity of chronic wounds. Once this has been developed and validated, we can definitely improve wound treatment plans and healing outcomes\textsuperscript{51}. Similarly, sample collection from wound surface can affect the results. The samples collecting surface materials for bacterial growth do not represent bacterial population invading deep in the wound tissue\textsuperscript{52}. The role of the skin microbiome or normal microbial flora in the healing process is still not very well known, though advanced techniques are providing a large amount of data indicating their beneficial role in maintaining normal skin health. It is important to increase our knowledge of the skin microbiome to understand the microbial composition of normal skin as well as the wound microbial composition. This will allow us to set criteria, develop methods to prevent, diagnose and effectively treat such infections\textsuperscript{19}. The exact role of microbes in acute and chronic infections requires further research and understanding. It is not fully known which bacterial species specifically contributes to chronic wound and biofilm formation. Acute bacterial infections must be diagnosed and treated quickly as they involve planktonic bacteria but if left untreated, could result in chronic infection\textsuperscript{8}. Wound management and treatment will improve by revealing details regarding wound microbial flora\textsuperscript{53}. Culture based techniques are not very useful for diagnosis of infection involving biofilm. This also holds true for the identification of many microbes which require special laboratory culture requirements, for example, anaerobes. Culture based methods have limitations, therefore, molecular methods should be developed \textsuperscript{16,54}. Diagnosis and confirmation of biofilm presence in chronic wounds is very important and requires further investigation\textsuperscript{38,55}. To our understanding, the determination of bacterial types, their virulence and biofilm markers could increase our understanding of the wound environment and this information could be used to propose more effective diagnostic, prophylactic and treatment options.

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