Wound Healing, Bacteria and Topical Therapies

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Interruptions to wound healing occur for both intrinsic (arising from the patient) and extrinsic (arising from environment or procedures) reasons. One of the important extrinsic factors that may impinge on speedy resolution of a wound is the presence of bacteria. The mere presence of bacteria should not be construed as infection, as colonisation is considered a "normal" event with acute and chronic wounds being colonised by different populations of bacteria[1,2]. The survival and proliferation of these micro-organisms depends on the efficiency of the host's immune system and the availability of the necessary chemical and physical factors required [3]. In order that the immune system functions as efficiently as possible an adequate local blood supply is required so that oxygen, nutrients and inflammatory cells are delivered to the wound as part of the wound bed preparation activity[4].

Bacteria are the most abundant form of life on this planet and in order to guarantee maintenance of this position they have developed a number of adaptive systems. These include bacterial synergy, quorum sensing and biofilm formation.

Bacterial synergy (collective bacterial activity) can have a more potent effect on tissue (pathogenicity) than the sum of the behaviour of individual bacterial species. Current thought suggests that synergistic activity in multi-species populations leads to infection where individual species may not be pathogenic. Trengove et al found that there was a greater likelihood of poor healing if four or more species of bacteria were identified in a wound[5].

Bacteria are capable of communicating with each other using signaling molecules that are released when a certain population density (quorum) is achieved. Bacterial communication in this way permits co-ordination of activity that includes among others expression of virulence factors such as toxins and enzymes.

Biofilm formation is another example of adaptation and survival[6]. Under certain conditions bacterial populations may protect themselves by producing a protective coat or biofilm. This exopolysaccharide coat affords protection from antibiotics and inflammatory cells. Within the biofilm the bacteria are undetectable using conventional means. While in this "quiescent" state virulence factors are produced which increases bacterial pathogenicity on release from the biofilm. Although biofilms exist, for example in the mouth and vagina, they have yet to be characterised in wounds.

Difficulty arises for the clinician in differentiating between levels of the bioburden; i.e. the continuum of contamination → colonisation → infection[7]. Contamination refers to bacterial presence without multiplication. Colonisation is bacterial multiplication without a host reaction whereas a wound is deemed infected when this multiplication induces a host reaction.

One approach to assist with identifying wound infection relies on the lower limit of 10^5 (100,000) viable organisms per gram of tissue (fewer bacteria = colonisation). Bowler has challenged the value of this laboratory guideline as a definitive diagnostic aid[8]. Nine years ago Cutting & Harding recommended that diagnosis of wound infection should be based primarily on the clinical signs present[9]. A developing concept is that of critical colonisation, a term meaning that the micro-organisms are interfering with wound healing without inducing obvious clinical signs of infection[8]. Critical colonisation refers to the inability of the wound to maintain a balance between the increasing bioburden and an effective immune system – the wound has become compromised, but is not yet demonstrating overt clinical signs of infection other than non-healing. Terminology referring to this state includes, indolent, recalcitrant and the possibly out-moded label 'silent infection'. The

Table 1. Delivery systems for silver in wound management

Arglaes™ (Maersk)	**Actisorb Silver 220™** (Johnson & Johnson)	**Acticoat™** (Smith & Nephew)	**Avance™** (SSL)	**Contreet™** (Coloplast)
a semi-permeable film dressing incorporating a complex of calcium and sodium phosphates from which a continuous release of silver ions is provided[20].	contains metallic silver impregnated into charcoal cloth all of which is enclosed in a sleeve of non-woven nylon[21].	presents as a polyester and rayon sheet sandwiched between a two-layer polyethylene net dressing. The outer dressing is coated with nanocrystalline silver and this provides a steady release of silver ions[20].	is an absorbent hydropolymer dressing with a silver compound bonded into it. It is claimed the silver zirconium phosphate is microbicidal to bacteria as the exudate is taken up into the dressing[21].	provides a slow-release of silver as the wound exudate is absorbed. The carrier dressing in this instance is hydrocolloid but the exact nature of the silver compound has not yet been disclosed

need therefore exists to develop and validate clinical signs of infection in addition to those proposed by Cutting & Harding (1994) that will assist in identifying critical colonisation[9].

It is not intended to discuss here the merits of systemic antibiotic therapy for spreading infection (cellulitis) but to consider the role of topical antiseptics in local infection.

The advantage of topical antiseptics is that they are able to assist in re-establishing the bacterial balance in a wound but may be harmful to healthy cells[10].

According to Lawrence fashion has not, in recent years, encouraged the use of antiseptics when managing wound infection[11]. This trend is changing however and resurgence in their use may be seen with the increasing availability of dressings impregnated with the antibacterial agent silver, e.g. Arglaes™ (Maersk), Actisorb Silver 220™ (Johnson & Johnson), Acticoat™ (Smith & Nephew), Avance™ (SSL) and Contreet™ (Coloplast). Additionally silver possesses a broad-spectrum of activity and as an antiseptic, it has a far lower propensity to induce bacterial resistance than antibiotics.

The medicinal use of silver has been exploited for over 2000 years, but it has been in common use as an antimicrobial since the 19th century. It probably fell out of use in the latter part of the 20th century as silver was used in the form of silver nitrate solution that caused argyria (staining of the skin) and a burning sensation on application. Additionally toxicity is related to the delivery system used e.g. nitrate or sulphadiazine[12]. Today other forms of silver are available which do not have the disadvantages of earlier solutions. Modern dressings are capable of delivering silver through a slow yet sustained release mechanism. This helps to avoid toxicity yet ensures delivery of a therapeutic dose of silver to the wound. A systematic review of antimicrobials in chronic wounds found only three small randomised trials (up to 2000) evaluating the clinical impact of silver-based dressings on venous ulcer healing and these had conflicting results, therefore more clinical trials are required[13].

Silver sulphadiazine is commonly used in burn wound care and leg ulcer management. It is microbicidal against a broad range of antibiotic-resistant organisms[14] including *Pseudomonas aeruginosa* and *Staphylococcus aureus*[15]. Silver sulphadiazine cream should be changed every 24-48 hours depending on the level of exudate produced by the wound. Although relatively inexpensive the need for frequent dressing changes increases management costs with the additional nursing time required.

Topical silver possesses the distinct advantage over systemic antibiotics in that it is delivered directly to the target area. In locally infected wounds where there is an inadequate blood supply (e.g. ischaemia) the likelihood of a therapeutic dose (adequate concentration) of antibiotic being delivered is diminished. The topical route avoids this drawback. Additionally, if biofilm formation is demonstrated in wounds, antibiotic therapy may be ineffective due to the impenetrable exoploysaccharide coat. Silver may however be able to breach this defence. When considering silver loaded dressings applied topically, two possible actions exist in which they may be effective. The silver ions may be donated to the wound and thereby exert their microbicidal effect in situ or the bacteria may be sequestered into the carrier dressing and rendered ineffective there. Whatever mode of action exists, the availability of the silver is critical to the therapeutic effect of the dressing. It is unlikely that topical application of silver has any long-term effects with respect to the wound microflora. Cessation of topical silver in an at-risk wound would probably see a return to an otherwise unmanageable bioburden.

The sample of "new" silver dressings identified above indicates the novel delivery systems so far utilised. (Table 1).

Alternative options include hydrogel and Hydrofiber® carrier systems.

A new addition to the family of silver-containing dressings is the AQUACEL® Ag technology[16]. The manufacturer's claim that silver is delivered in low but effective concentrations and kills a broad spectrum of pathogens including antibiotic resistant bacteria[14]. One potential advantage of the Hydrofiber® delivery system is the high absorptive capacity, and gelling with consequent ease of removal[17]. Hydrofiber® dressings absorb fluid directly into the fibres and the associated bacteria are sequestered and retained within the dressing[18]. The addition of ionic silver to the Hydrofiber® carrier ensures that a wide range of pathogens are killed[16]. Extended wear time, decreased dressing changes and associated reduced nursing time should assist in lowering wound care costs. Additional considerations in dressing selection include; ease of application and removal, effect on ulcer pain and hence patient comfort. It would appear that Hydrofiber® technology is able to fulfil these functions[17].

Infected wounds will often respond to an increased microbial load with a sudden rise in exudate production[19] and it is important that the dressing application is able to cope with this. This biological/bacterial imbalance (critical colonisation) increases the likelihood of infection. The opposite can be said for healing wounds (figure 1).

If a dressing application is to be of benefit in a microbially-challenged wound then it has to demonstrate that it can cope with a deteriorating situation. A combined antimicrobial/absorbent dressing would appear to offer advantageous therapeutic possibilities that will progress the wound towards healing.

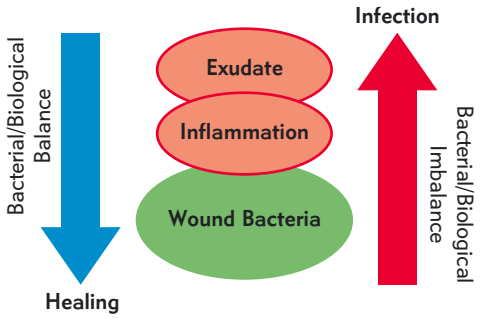

Figure 1:
Relationship between bacterial balance, exudate and healing.

AQUACEL® Ag dressing appears to hold much promise in the management and prophylaxis of local wound infection. It will be interesting to see how it compares with other dressings with regards to bacterial sequestration, antimicrobial activity, and fluid handling, and their impact on wound infection and healing. ■

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Notes:

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