USING ANTIMICROBIALS FOR WOUND INFECTION AND BIOFILMS

Identifying wound infection and implementing an effective treatment plan quickly are vital steps in reducing the health implications for the patient undergoing wound care, as well as lessening the economic burden to the health service. The use of topical antimicrobials offers an effective method of eradicating bacteria from the wound bed, but it requires a holistic assessment of the patient, an understanding of the different types of antimicrobials available and their appropropriate use.

"In a biofilm, planktonic bacteria encase themselves in an extra cellular polymeric substance which adheres to the wound bed."

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Wound infection is a complication that often contributes to a wound that is failing to heal (World Union of Wound Healing Societies [WUWHS], 2008). A wound that is infected presents many challenges to clinicians and may have a significant impact on the patient and on healthcare organisations. This may be due to the increased expense of longer treatment times; unpleasant symptoms affecting the patient's quality of life; and more serious consequences, possibly resulting in the loss of a limb, or even in the loss of life (European Wound Management Association [EWMA], 2005).

The treatment for wound infection is usually aimed at reducing bacterial load with antibiotics and/or topical antimicrobials (WUWHS, 2008). The function of an antimicrobial agent is to either kill or inhibit the growth of microorganisms (EWMA, 2005). The types of antimicrobials that are available and used in wound care include antibiotics and antiseptics (Gottrup et al, 2013). A slow and ineffective reponsive to wound infection may be due to a lack of clinical assessment and poor decision-making.

Antibiotics

Antibiotics are defined according to how they target and identify microorganisms; their action is usually focused on a specific part of the bacterial cell, which may be the cell wall, cell membrane, nucleic acid synthesis or protein synthesis (Maillard, 2002). In general, antibiotics are recommended when clinical infection is clearly evident (WUWHS, 2008). However, indiscriminate use for other systemic infections has led to bacterial resistance (Gottrup et al, 2013), a development that has caused significant concern within healthcare organisations due to the lack of available antibiotics for treating resistant bacterial infections (Department of Health, 2013).

Antiseptics and antimicrobials

The concerns surrounding antibiotic use and the rise of bacterial resistence has driven an interest in the application of topical antiseptics and antimicrobials. These are non-specific agents that target several areas within the cell, inhibiting multiplication and causing cell death (Maillard, 2002). There is also little resistance reported and appropriate use can assist in preparing the wound bed for wound healing by eradicating potentially damaging

bacteria (Atiyeh et al 2009). The use of topical antimicrobials is considered of key importance when treating patients with signs and symptoms of wound infection (EWMA, 2005; WUWHS, 2008; Wounds UK, 2011). There is a growing body of evidence to support the use of these products in clinical practice (Atiyeh et al, 2009). However prolonged use of antimicrobials (typically >2 weeks) is not advised and, because of its non-selectivity, may inhibit wound healing (Bowler, 2001; Zou et al, 2013).

Cooper et al (1991), Burd et al (2007) and Zou et al (2013) demonstrated that antiseptics, such as silver, had a detrimental effect on fibroblasts and keratinocytes. Conversely, a systematic review by Dorosow et al (2003) indicated there was no evidence to support this *in vitro*.

It is extremely important for nurses to be able to justify the use of products such as antimicrobials and to ensure they are used correctly and appropriately. Inappropriate use of antimicrobials has been demonstrated in clinical practice. In an audit of patients' electronic records detailing visits by district nurses, it was demonstrated that antimicrobial dressings were used in 44% of patients without any clinical rationale for use (Mahoney, 2014).

The need to rationalise the use of treatments such as antimicrobials and to establish the size of the problem has come about due to an increased pressure to create cost savings and prevent the unnecessary use of expensive, inappropriate treatments (Ousey and Shorney, 2009).

Gottrup et al (2013) recognised that there are a vast amount of topical antimicrobials available and that it is crucial to enable clinicians to select the "right product for the right patient at the right time". The decision to instigate a topical antimicrobial should follow a holistic assessment to ensure that an optimum environment is obtained to facilitate wound healing and to identify underlying aetiologies that, without treatment, may prevent wound healing (Wounds UK, 2011). It is essential that any clinician using topical antimicrobial products have an adequate understanding of these properties. Because the characteristics of different topical antimicrobials vary, when selecting a product the clinician should consider the following:

- Contraindications
- Ability to kill or inhibit bacteria
- Mode of action
- Potential cell toxicity
- Wear time
- Dressing presentation.

Identifying wound infection

Some areas of controversy regarding the treatment of infected wounds and the use of topical antimicrobials lie in the lack of an agreed definition of infection, and the limited evidence surrounding their correct usage. This may lead to overuse, or inappropriate use, of antimicrobial dressings (Brown, 2006). The knowledge and understanding nurses have of wound infection and the use of antimicrobials has also been identified as an issue in practice (Dowsett, 2009).

Dowsett (2009) used a combination of questionnaire and non-participant observation of 47 community nurses to establish knowledge of wound care. It was found that only 19 nurses were able to identify wound infection correctly. After the instigation of an education programme, the use of antimicrobial dressings reduced from 60% to 43%. This indicates that nurses may not have adequate knowledge to be able to identify wound infection correctly, which possibly contributes to the costly and inappropriate use of antimicrobials.

It is also recognised that different wound types may display different clinical signs and symptoms, or may even appear to be asymptomatic (EWMA, 2005), which may lead to difficulties in identifying the existence of wound infection.

Clinical indicators that have been suggested as classic signs and symptoms for wound infection include:

- Oedema
- Erythema (redness)
- Pain
- Increased temperature and purulent exudate (Gottrup et al 2013).

EWMA (2005) recognised that additional indicators may be present in chronic wounds or may even be absent. These additional signs and symptoms specific to chronic wounds include:

- Serous exudate with inflammation
- Delayed healing
- Friable granulation that bleeds easily
- Discoloured darker granulation
- Pocketing at the wound bed base
- Increased odour
- Wound breakdown.

Wound infection should be diagnosed using observational skills and a wound swab taken to confirm the presence of bacteria, which will facilitate a plan of action following identification (White and Cutting, 2008). The use of wound swabbing in itself remains controversial as it may only reveal surface bacteria and no resident bacteria in deep tissues that may cause infection; conversely, it may also identify organisms that are present, but not problematic (Angel et al, 2011).

The Levine technique

The Levine technique has been suggested as the most appropriate method for carrying out a wound swab sample (World Union of Wound Healing Societies –WUWHS; 2008). The suggested methodology is as follows:

- Cleanse the wound before taking the swab to remove surface bacteria.
- The swab is then rotated over 1 cm^2 area of the wound, applying enough pressure to ensure bacteria deep within the wound tissue is obtained.

What are biofilms?

A further issue in clinical practice is a wound that develops a biofilm colonisation. Chronic wounds have been identified as being poly-microbial. Thomsen et al (2010) isolated an average of 5.4 species of bacteria present on chronic wounds. Most bacteria isolated

are free flowing and planktonic in formation. Chronic wound infection may result in the production over time of a biofilm in which planktonic bacteria encase themselves in an extracellular polymeric substance that adheres to the wound bed; this lets the biofilm colonies grow and communicate with each other by cell-to-cell signalling known as quorum sensing, which increases resistance to antimicrobials. The biofilm colonies are also able protect themselves from the host response so that they are not removed by neutrophils.

Why are biofilms problematic?

Biofilms do not display the recognised signs and symptoms of infection or initiate a host response (White and Cutting, 2006). Their presence has, however, been linked *in vitro* to a detrimental effect on wound healing at a cellular level (Stephens et al, 2003). Biofims are not identified from wound swabbing, as they are attached to the wound bed rather than free-floating (Saur and Camper, 2001) and their identification is usually from advanced microscopy techniques. Due to their complex polymicrobial presentation, the protective matrix and senescence, although cells are unable to replicate, they are able to remain metabolically active. This increases the biofilm's ability to gain resistance to antimicrobials/antibiotics, making them difficult to treat effectively (Gottrup et al 2013).

Recognising wounds with biofilm

The identification of a biofilm within a wound is often based on subjective observational assessment by a clinician. *Pseudomonas* commonly forms biofilms colonies in chronic wounds (Gottrup et al, 2013) and is easily identified by its colour and odour (*Figure 1*).

If a biofilm is not visible and cannot be identified through bacterial swabbing, how do we know it is are there? Phillips et al (2010) suggested that chronic wounds with biofilms may display the following characteristics:

- Excessive exudate
- Poor-quality granulation tissue
- Signs and symptoms of local infection
- Recurring infection after antibiotic cessation
- Negative wound culture
- No healing despite optimal wound and host support
- Infection lasting >30 days
- Gelatinous material that is easily removed form the wound surface
- Surface reforms quickly.

Interventions for removal and reduction of biofilms

The most common antimicrobials that are used in practice are the following:

- Cadexomer and povidone iodine
- Silver
- Honey
- Polyhexamethylene biguanide (PHMB) (Atiyeh et al 2009).

Dressings may kill or inhibit bacteria actively within the wound bed, or some dressings control bacteria passively by removing and binding the bacteria to the dressing. Dressings such as dialkyl carbmoyl chloride (DACC) technology have been shown to bind bacteria irreversibly and to inhibit bacterial growth. Most of the evidence around the efficacy of antimicrobials has been around planktonic bacteria and further research is required into how antimicrobials can penetrate and eradicate biofilms. With the knowledge that biofilms may not respond to treatment with topical antimicrobials, it may be confusing for the clinician to select an appropriate product.

Debridement

It would appear that a combination of strategies may reduce the formation of biofilms (Gottrup et al, 2013). Phillips et al 2010 suggested a "clean and cover approach". It has been demonstrated that frequent debridement should be undertaken to physically remove the biofilm colonies. This might be surgical, jet lavage (hydrosurgery), bio-surgical or mechanical. Surgical debridement requires clinician skill and competence,

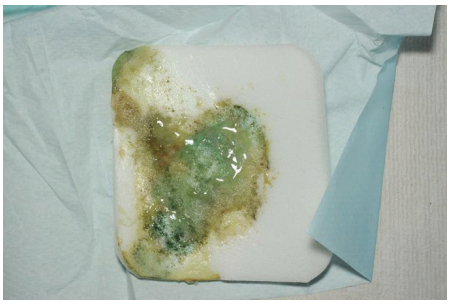

Figure 1. ***Biofilm formed by Pseudomonas aeruginosa bacterium can be identified by the colour and odour of the wound.***

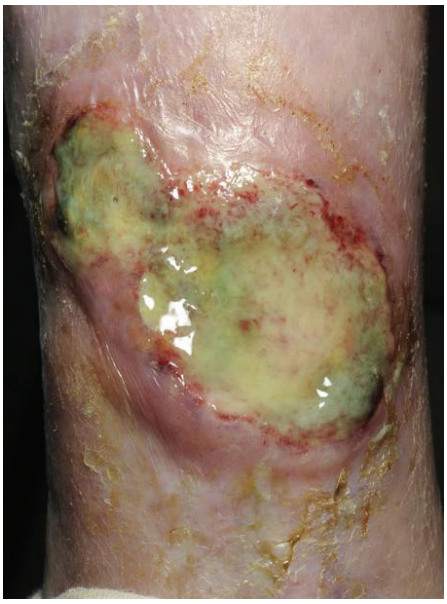

Figure 1. ***Wound with biofilm requiring debridement.***

and may not easily be achieved in all areas of clinical practice. Jet lavage involves the intense pressured irrigation of water on to the wound bed, which physically removes debris and requires a local anaesthesia to be administered. It may be performed only by an appropriately trained clinician and is also considered costly (EWMA, 2013).

Biosurgery, or larval therapy, may be considered as another debridement method. The lavae are known to secrete antimicrobial substances that may reduce the bacterial load of the wound in conjunction with producing proteolytic enzymes that degrade slough and eschar (EWMA, 2013) Various other methods of mechanical debridement have been suggested. Such techniques include using cleansing products

containing a surfactant, which has been shown to disrupt biofilm production (e.g. Prontosan® solution, B. Braun) (Andriessen and Strohal, 2010).

A monofilament cloth (Debrisoft®, Activa Healthcare) may also be an easy-to-use method for mechanical wound debridement and disruption of biofilm colonies (Keast and Lindholm, 2012).

Antimicrobial dressings

After debridement, use of dressings containing antimicrobials should then be considered to kill planktonic bacteria and prevent biofilms from reforming. Phillips et al (2010) suggested that the antimicrobial selected should have a broad spectrum and be able to kill rather than inhibit bacteria. However, more research is required to increase our knowledge and understanding of biofilms and correct treatment. *Figure 2* shows a wound with possible biofim that requires debridement.

Dressing selection should be made according to what is available on local formulary, based on holistic patient assessment. Other considerations should be the condition of wound bed, exudate levels, patient sensitivities and contraindications. Products such as silver dressings have been removed from formularies in some areas due to the belief that they are expensive and do not improve healing (Michaels et al, 2009). However, most clinical experts believe that, used correctly, silver products have a significant role in clinical practice (Wounds international 2012).

The effect of certain dressings on biofilms can be categorised and described as follows:

Silver

- Silver in its metallic form is unable to kill bacteria, however on contact with aqueous fluid such as exudate, silver ions become positively charged, enabling its bactericidal properties (Wounds international, 2012)
- Silver has a broad-spectrum antibacterial action and is effective in eradicating planktonic bacteria (Percival et al, 2005), however, it is needed in high quantities to infiltrate and eradicate biofilms. Bjarnsholt et al (2007) revealed that most silver dressings that may be effective in planktonic bacterial infections did not contain high enough silver content to eradicate biofilms *in vitro*. Silver dressings are helpful in the 'clean and cover' approach where biofilms are debrided and the silver is then used to prevent biofilm reformation.
- The amount and availability of silver within dressings varies considerably. Phillips et al (2010) suggested that products with a high kill rate are preferable to those that inhibit bacterial growth.
- Dressings may be coated in silver (e.g. nano crystalline silver), or the silver may permeate the dressing itself, or a combination of both.
- Available in many different dressings such as:
  - Alginate: e.g. Acticoat absorbent®(Smith & Nephew), Sorbsan Silver® (Aspen Medical)
  - Foam: e.g Biatain Ag® (Coloplast), Mepliex Ag® (Mölnlycke Health Care);
  - Hydrofiber: e.g. Aquacel® Ag (ConvaTec), Durafiber Ag® (Smith & Nephew)
  - Non adherent dressings: e.g Atrauman Ag® (HARTMANN), Acticoat® Flex (Smith & Nephew).

  The decision of which product to use will be made according to wound bed characteristics, such as exudate, wound adherence and frequency of dressing change. For maximum impact, the dressing should be in contact with the wound surface.
- Practice caution in patients with allergy to silver; should be removed before MRI scanning or radiotherapy.
- Some indication that silver may have a detrimental effect on keratinocytes and fibroblasts (Atiyeh et al, 2009)

PHMB

- There is some evidence that cleansing solutions that contain PHMB and a surfactant called betaine (Prontosan) have the ability to disrupt biofilms (Andriessen and Strohal, 2010)
- Has a broad spectrum of antimicrobial action
- PHMB is available in several formulations of dressing foam, e.g Kendall AMD® (Covidien); gel, e.g. Prontosan® Wound Gel (B. Braun); cleansing fluid, e.g. Prontosan® Wound Irrigation Solution (B. Braun)
- Considered non toxic to cells (Wehner, 2009).

Honey

- Honey is a broad-spectrum antimicrobial, there is currently no evidence to indicate that it can eradicate biofilms but has been shown to prevent biofilm formation (Cooper and Jenkins, 2008)
- Available in several formulations such as liquid, alginate, ribbon and tulle. Product selection will depend on wound characteristic and exudate
- Caution in patients with allergies to bee venom or honey
- Some patients report pain due to high osmolarlity of the product
- May reduce odour
- Is considered an effective debridement agent (Coulborn et al, 2009).

Iodine

- Available in many dressing formulations, such as solutions, e.g Betadine® Solution (Purdue Products L.P), ointment, e.g Iodosorb® Ointment (Smith & Nephew). Dressing presentations include povidone iodine and cadexomer odine. Cadexomer iodine contains polysaccharide beads which absorb exudate and allow the slow release of iodine. It also has the ability to debride the wound bed.
- Broad-spectrum antimicrobial.
- Some evidence *in vitro* that povidone

iodine and cadexomer iodine may disrupt biofilms (Presteri et al 2007).

- To be used with caution on large, open wounds and in patients with thyroid problems. Iodine is also contraindicated in breast feeding mothers and pregnancy (Boothman, 2010). No more than four dressings at one time should be used. The absorption of iodine from modern iodine dressings is thought to be minimal, however, it is related to the size of the wound and the duration of treatment (Steen, 1993; Boothman, 2010). Long-term use is, therefore, not recommended.

When to stop using antimicrobials

Gottrup et al (2013) identified that although there was an abundance of literature examining the effects and use of antimicrobials, there is, at present, no reproducible evidence to evaluate and measure the appropriate use of antimicrobials. Similarly, Fife et al (2010) highlighted the issue that guidelines for use of antimicrobials and recommended length of time to be used are based on expert opinion rather than clinical evidence.

To encourage clinicians to stop antimicrobial use within an acceptable time frame a 'Two week challenge' approach has been suggested (Wounds International, 2012). Once antimicrobial treatment has commenced the wound should be reassessed after 2 weeks. If there is no improvement, reconsider treatment; if there is improvement and infection still present, continue and reassess in a further 2 weeks; if the infection has resolved, stop treatment and refer to local wound care guidelines.

Conclusion

Wound infection is often difficult to diagnose and costly to treat. Inappropriate antimicrobial usage is often a result of inadequate clinical assessment. Wounds that contain a biofilm colonisation are particularly difficult to treat and identify. A combination of debridement and antimicrobial dressings has been recommended to eradicate the biofilm colonies; however, more research is required within this field. WE

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