POSITION
DOCUMENT

Management of **wound infection**

An integrated approach to managing wound infection

Demystifying silver

Topical management of infected grade 3 and 4 pressure ulcers

Topical antimicrobials and surgical site infection

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POSITION DOCUMENT

Management of wound infection

CJ Moffatt

The management of wound infection has long tested man's ingenuity. The advent of antibiotics in the 1950s revolutionised the control of bacterial infections, but with the recent escalating prevalence of bacterial resistance there has been renewed interest in the use of topical antimicrobials, particularly silver, iodine, honey and larval therapy. Unfortunately, injudicious application of some of these agents and a paucity of clinical evidence to support their use have led to further controversies.

This position document, on 'Management of wound infection', continues last year's exploration of the criteria for wound infection by tackling the complex clinical challenges healthcare professionals face when making decisions about how to treat wound infection. It pays particular attention to the appropriate use of topical antimicrobials. It must be noted that the antimicrobial agents discussed in this document exclude topical antibiotics.

A recurring theme of all four papers is the lack of robust *in vivo* data for using topical antimicrobials for managing infected wounds. Nonetheless, the authors have critically appraised the evidence that is available and have formulated recommendations to help clinicians make practical decisions.

The first paper by Vowden and Cooper describes the clinical stages of infection using healing rate in association with subtle or overt signs of infection to help make the decision to intervene. The paper stresses the importance of understanding the role that specific bacteria may play in different clinical situations, of establishing therapeutic goals and of ongoing evaluation of the response to therapy. It also emphasises the need for optimal wound management and an understanding of the properties of the dressing carrying the antimicrobial agent in relation to managing the local wound environment.

The second paper by Maillard and Denyer describes the bactericidal mechanisms of action of silver and the differences in effectiveness against bacterial groups. While its role in the control of bacteria such as *Pseudomonas aeruginosa* is well recognised, less is known of its action against anaerobes, which are a common problem in chronic wounds. The authors consider factors that influence the efficacy of silver within the wound and how these relate to clinical practice. Advice is given on using the various products available, including the important potential of combining silver with other antimicrobial agents.

Moore and Romanelli, in the third paper, conclude that topical antimicrobials have a role in the management of grade 3 and 4 pressure ulcers with a high bacterial burden or signs of early localised infection. The authors also recognise the complexity of these wounds and again stress the importance of choosing the correct product to deal with issues such as anatomical position, wound undermining and levels of exudate.

In the final paper, Melling, Gould and Gottrup address the use of topical antimicrobials in surgical wounds that have been closed by primary intention and in which a superficial infection has developed. The authors stress that although antiseptics play a major role in the prevention of infection during surgical procedures, antimicrobials have only a limited role in the management of these wounds. They describe the situations where topical antimicrobials may be a useful adjunct to treatment.

The standard, in terms of the level of wound bed bacterial colonisation that is acceptable, will vary according to the mechanism of treatment proposed. A lower colonisation level, with the elimination of specific bacterial strains, may be required in wounds undergoing surgical closure by skin grafting or free flap and in wounds receiving bio-engineered skin products.

A wound does not have to be sterile to progress towards healing and the use of topical antimicrobial therapy simply to lower microbial load in the healing wound can never be justified. Many problems associated with antibiotic resistance have occurred. While more data are desperately needed to clearly justify when and what agent to use, it is clear that if current topical antimicrobial agents are to remain effective they must be used sensibly and appropriately.

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POSITION DOCUMENT

An integrated approach to managing wound infection

P Vowden[1], RA Cooper[2]

INTRODUCTION

All wounds contain micro-organisms, yet the majority are not infected. The spectrum of interactions between the microbial community and the host may gradually reach a point at which the wound healing process is impaired or localised detrimental host effects are initiated. When this transition occurs, immediate intervention to pre-empt infection is indicated.

Many problems associated with the emergence and increased prevalence of antibiotic resistance have arisen because of the use and misuse of antibiotics. Resistance to topical agents has also been reported[1], and so if current antimicrobial agents are to remain effective they must be used wisely. This article examines the clinical observations and management strategies required to establish the need for appropriate antimicrobial intervention.

MICROBIOLOGY

It must be recognised that the diagnosis of wound infection is a clinical judgment and that information on microbial species provided to practitioners by laboratories may have little value if considered without reference to the patient[2]. Advice is appropriately sought from laboratories when confirmation of an infection is needed, when an antimicrobial intervention has failed, when a patient requires screening for a specific organism or when healing is stalled and all other confounding issues have been addressed.

Samples collected from wounds for laboratory analysis include swabs, pus, biopsies, fine needle aspirates and occasionally wound debris. Issues relating to the collection of samples have been debated elsewhere[3,4]. Bacteria are normally isolated from swabs taken from chronic wounds; yeasts, fungi or protozoa (rarely) might also be recovered. More specialised molecular techniques rely on the analysis of DNA to reveal additional microbial species that may not have been cultivated by routine methods[5,6]. A specimen from every wound should not, however, be sent for laboratory analysis.

Knowing the identity of certain micro-organisms within a wound may clarify management issues because:

- in the presence of systemic infection identification of antibiotic sensitivity patterns may be beneficial
- beta-haemolytic streptococci or *Pseudomonas* species are detrimental to skin grafts and need to be eradicated before surgery
- certain bacterial combinations (eg *Escherichia coli* and *Bacteroides fragilis*) might suggest synergistic relationships where lower numbers potentiate clinical infection[7]
- a colonised antibiotic-resistant strain (eg MRSA) might indicate patient segregation or decontamination before further treatment.

WHEN TO INTERVENE

Microbial involvement in delayed healing must be suspected when other causes have been eliminated. Products of certain microbial species are known to affect wound healing, such as exotoxin A of *Pseudomonas aeruginosa*[8], the endotoxin released from cell walls of dead Gram-negative bacteria and the destructive enzymes of staphylococci, streptococci, pseudomonads and anaerobes. It has also been suggested that the presence of mixed

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KEY POINTS

1. Wound management strategies must aim to provide optimal conditions to promote rapid healing.
2. Topical antimicrobial therapies should be considered when progress towards overt infection is suspected, or when interrupted healing is observed.
3. Long-term use of antimicrobial agents must be avoided.
4. Antibiotic use should be limited to specific clinical situations (eg overt infections) and directed towards susceptible organisms.
5. Wound status must be regularly reviewed, and management strategies changed when progress towards healing is not achieved.

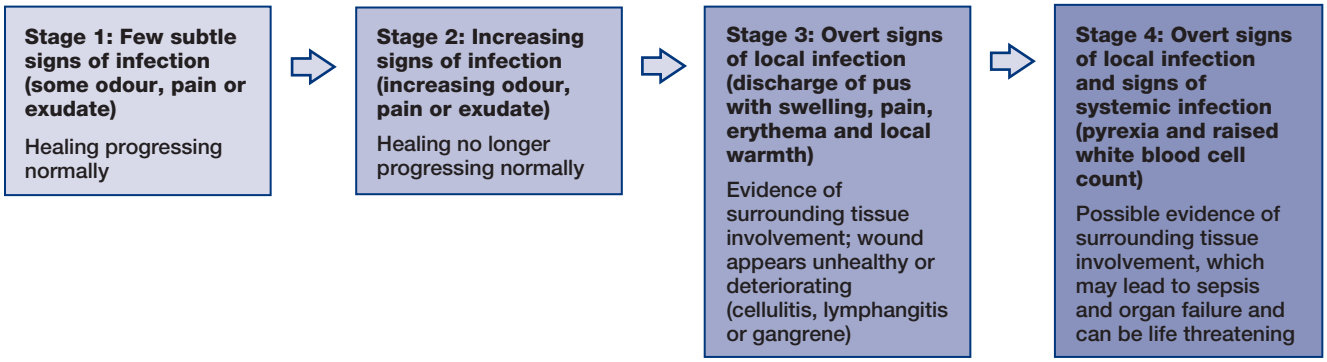

Figure 1 | **Clinical stages for determining a therapeutic strategy**

communities of organisms might indirectly impede wound healing by promoting a chronic inflammatory response[7]. Antimicrobial intervention has been shown to remove the barriers to healing in such wounds[9,10].

The validity of using numbers of microbial cells to define infection has been questioned because large populations can be recovered from wounds without overt infection[11]. Nevertheless, reducing numbers to pre-empt the development of wound infection can be justified[12]. The difficulty is that at present microbial influences on healing cannot be identified by routine tests. Wound deterioration or failure to progress towards wound healing is one of the features of wound infection. Therefore, healing rate in association with subtle or overt signs of infection helps the decision to intervene.

Clinical stages

Criteria for recognising early wound infection were outlined and discussed in the 2005 European Wound Management Association position document[13]. Using these early signs, clinical stages of infection can be defined around which a therapeutic strategy can be built (Figure 1). Each stage requires a different management strategy and can be applied to both infected acute and chronic wounds.

Clearly, in stage 1 specific antimicrobial intervention is not needed. Wound dressing regimens should be designed to follow the principles of moist wound healing using products selected to optimally manage the patients' symptoms while encouraging wound healing. The aim in stage 2 is to rapidly prevent the development of overt infection and then to return the patient to simple dressings designed to support moist wound healing. In these wounds, whether acute or chronic, topical antimicrobials may have a part to play in restoring bacterial balance.

Wounds at stages 3 and 4 require appropriate use of systemic antibiotics, possibly in combination with topical antimicrobial agents if the wound is open and its bed needs therapeutic intervention.

MANAGEMENT

The management algorithm in Figure 2 gives guidance on the protocol for managing potential and overt infection. The principles underpinning this guidance are to:

- provide an optimal environment to promote rapid healing
- minimise the use of antimicrobial agents that may adversely affect human cells
- use antimicrobial agents appropriately to reduce the selection of resistant strains
- restrict the use of systemic agents to occasions when they are specifically indicated
- avoid topical sensitisation or allergic reactions.

Dressing requirements

When a reduction in microbial load is required, the selection of antimicrobial dressings must also take into account the primary and secondary dressing requirements. Decisions need to be based on the ability of the dressing to manage increased exudation, remove

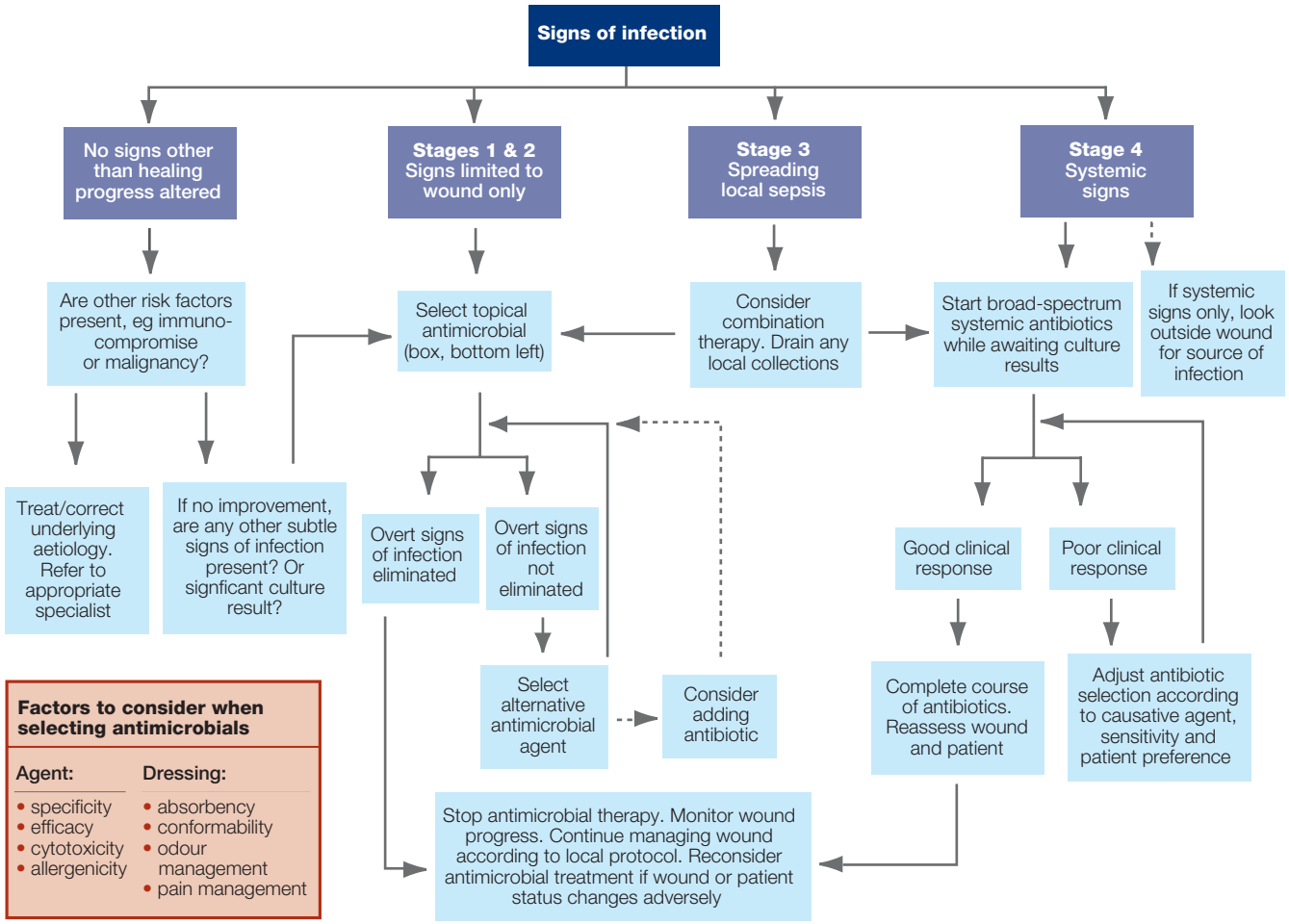

Figure 2 | **Algorithm for managing wound infection**

necrotic tissue, reduce malodour, conform to the site and shape of the wound, perform wound bed preparation functions, satisfy patients' expectations and meet treatment goals.

As with all wounds it is important to frequently reassess the wound bed and surrounding tissues, monitoring for signs of spreading or systemic infection. If the wound improves and signs of infection resolve, therapy should be discontinued and moist wound healing should be managed according to local protocols. If the wound continues to deteriorate or there is no improvement within seven to 10 days the wound and patient should be reassessed, alternative causes of deterioration (such as ischaemia) considered and issues relating to possible immuno-compromised status addressed. If infection is still considered likely alternative antimicrobials and/or antibiotics should be selected in line with micro-organism culture and sensitivity results.

SELECTING TOPICAL ANTIMICROBIALS

The over-riding objective must always be to provide optimum conditions to support rapid healing. In selecting antimicrobial agents to reduce or eradicate micro-organisms, choice must be influenced by the specificity and efficacy of the agent, its cytotoxicity to human cells, its potential to select resistant strains and its allergenicity. The range of topical antimicrobial agents currently used includes chlorhexidine, products containing iodine (cadexomer iodine and povidone iodine) and products containing silver (silver sulfadiazine and silver-impregnated dressings).

Table 1 | **Comparison of commonly used antimicrobials**

	Antimicrobial properties					
	Gram +ve	Gram –ve	Fungi	Endospores	Viruses	Resistance
Chlorhexidine[1,22]	+++	++	+	0	+	+
Honey[22]	+++	+++	+++	0	+	0
Iodine[1,22]	+++	+++	+++	+++	++	0
Maggots[14-16,19,22]	+++	++	ND	ND	ND	0
Silver[1,22]	+++	+++	+	ND	+	+

ND = no data.

Another means of reducing microbial load is the application of maggots. Not only do they remove bacteria[14-16], but they provide both debridement[17] and enhancement of healing[16,18]. Larval removal of Gram-positive bacteria is more efficient than the removal of Gram-negative bacteria[19], so greater numbers of maggots might be required for a wound infected with Gram-negative bacteria. Honey is antimicrobial and acts as a debriding agent. It also helps with odour control[20]. The availability of 'CE'-marked honey-containing wound care products has stimulated increased professional interest. Table 1 provides a comparison of commonly used antimicrobials.

Efficacy

Evidence of the clinical efficacy of topical antimicrobial agents is somewhat limited because of the wide range of different wound types, the diversity of products and the costs of clinical studies. Case reports, cohort studies and randomised controlled trials (RCTs) contribute to knowledge, but systematic review of RCTs provides the most powerful evidence. However, the conclusions of these studies often question the quality of clinical evidence by criticising the design of studies. Meta-analysis has demonstrated the inadequacy of evidence for the efficacy of topical agents other than silver sulfadiazine in the treatment of chronic wounds[21].

Specificity

Many of these agents have a long history of use in treating wounds, but modern formulations aim to make relatively low concentrations of the active agent available in the wound environment to overcome former criticisms of painful, irritant and discolouring treatments. Agents (such as povidone iodine or chlorhexidine) used prophylactically on traumatic wounds, or pre-operatively on intact skin may have relatively short contact times, whereas antimicrobial agents incorporated into dressings can have longer contact times. In laboratory tests all have been demonstrated to inhibit a wide range of bacteria, some fungal species and some viruses, but only iodine is sporicidal[1,22]. All have been shown to inhibit antibiotic-resistant strains of bacteria[1,22].

In comparing the *in vitro* effectiveness of povidone iodine and chlorhexidine against MRSA, iodine inhibited all 33 strains tested, but chlorhexidine inhibited only three strains[23]. Povidone iodine has been reported to inhibit biofilms. One *in vitro* study compared the effectiveness of four antiseptics against biofilms present on Teflon chips; 10% solution of povidone iodine caused significant reduction in viable cells after a 10-minute exposure, but no reductions in bacterial numbers were seen with the other antiseptics (one of which was chlorhexidine) after a 60-minute exposure[24].

The ability of some antimicrobial agents to modulate the secretion of pro-inflammatory cytokines by human cells indicates their potential to influence the activity of cells associated with healing[25,26]. Differential effects of topical antimicrobials on healing rates also demonstrate an influence[9,10,27]. A comparison of honey with povidone iodine showed faster healing times with iodine dressings following total nail avulsion, but no significant difference for partial toenail surgery[28]. Recently, evidence of the effect of silver

ANTIMICROBIALS

Antimicrobials are agents that either kill or inhibit the growth and division of micro-organisms. They include antibiotics (which act on specific cellular target sites), antiseptics, disinfectants and other agents (which act on multiple cellular target sites).

dressings in the treatment of chronic wounds has expanded[29-31], but no studies compared two antimicrobial dressings.

Adverse effects

Another factor that influences the choice of topical antimicrobial agent is the potential to induce adverse effects. Antimicrobial agents have the potential to inhibit human cell growth and might, therefore, affect healing. Hypochlorite is particularly tissue toxic[32]. No agents seem to be devoid of these possibilities, although such events are normally rare. Extensive use of antimicrobials also risks the selection of resistant strains. The development of antiseptic resistance has already been noted with agents such as chlorhexidine[1]. There is also concern over resistance to inorganic ions such as silver[33]; the mechanism of which was first documented in 1998[34]. To date resistance to iodine and honey has not been shown.

CONCLUSION

Unambiguous recommendations for the use of topical antimicrobial agents cannot be readily formulated at present. Antimicrobial agents are inappropriately used if reduction in microbial loads is not intended. Reviewers and researchers seem to agree that more specific endpoints should be used in clinical studies and that larger numbers of patients must be evaluated. Since findings are regularly being published, revisions become necessary and the findings of ongoing Cochrane reviews into the efficacy of dressings and/or topical agents in the treatment of pressure ulcers, venous leg ulcers, burns, fungating wounds and surgical wounds are awaited.

References

1. McDonnell G, Russell AD. Antiseptics and disinfectants: activity, action, and resistance. *Clin Microbiol Rev* 1999; 12(1): 147-79.
2. Schmidt K, Debus ES, St Jessberger, et al. Bacterial population of chronic crural ulcers: is there a difference between the diabetic, the venous, and the arterial ulcer? *Vasa* 2000; 29(1): 62-70.
3. Gilchrist B. Wound infection. 1. Sampling bacterial flora: a review of the literature. *J Wound Care* 1996; 5(8): 386-88.
4. Slater RA, Lazarovitch T, Boldur I, et al. Swab cultures accurately identify bacterial pathogens in diabetic foot wounds not involving bone. *Diabet Med* 2004; 21: 705-09.
5. Redkar R, Kalns J, Butler W, et al. Identification of bacteria from a non-healing diabetic foot wound by 16S rDNA sequencing. *Mol Cell Probes* 2000; 14: 163-69.
6. Davies CE, Hill KE, Wilson MJ, et al. Use of 16S ribosomal DNA PCR and denaturing gradient gel electrophoresis for analysis of the microfloras of healing and nonhealing chronic venous leg ulcers. *J Clin Microbiol* 2004; 42: 3549-57.
7. Percival S, Bowler PG. Understanding the effects of bacterial communities and biofilms on wound healing. *www.worldwidewounds.com/2004/july/Percival/Community-Interactions-Wounds.html* (accessed 2 February 2006).
8. Heggers JP, Haydon S, Ko F, et al. Pseudomonas aeruginosa exotoxin A: its role in retardation of wound healing. *J Burn Care Rehabil* 1992; 13(5): 512-18.
9. Sibbald RG, Browne AC, Coutts P, et al. Screening evaluation of an ionized nanocrystalline silver dressing in chronic wound care. *Ostomy Wound Manage* 2001; 47: 38-43.
10. Fumal I, Braham C, Paquet P, et al. The beneficial toxicity paradox of antimicrobials in leg ulcer healing impaired by a polymicrobial flora: a proof-of-concept study. *Dermatology* 2002; 204(Suppl 1): 70-74.
11. Bowler PG. The 10^5 bacterial growth guideline: reassessing its clinical relevance in wound healing. *Ostomy Wound Manage* 2003; 49: 44-53.
12. Lyman LR, Tenery JH, Basson RP. Correlation between decrease in bacterial load and rate of wound healing. *Surg Gynecol Obstet* 1970; (April): 616-21.
13. European Wound Management Association (EWMA). Position Document: *Identifying criteria for wound infection*. London: MEP Ltd, 2005.
14. Thomas S, Andrews AM, Hay NP, et al. The anti-microbial activity of maggot secretions: results of a preliminary study. *J Tissue Viability* 1999; 9: 127-32.
15. Beasley WD, Hirst G. Making a meal of MRSA - the role of biosurgery in hospital-acquired infection. *J Hosp Infect* 2004; 56: 6-9.
16. Horobin AJ, Shakesheff KM, Woodrow S, et al. Maggots and wound healing: an investigation of the effects of secretions from Lucilia sericata larvae upon interactions between human dermal fibroblasts and extracellular matrix components. *Br J Dermatol* 2003; 148(5): 923-33.
17. Armstrong DG, Salas P, Short B, et al. Maggot therapy in "lower-extremity hospice" wound care: fewer amputations and more antibiotic-free days. *J Am Podiatr Med Assoc* 2005; 95: 254-57.
18. Horobin AJ, Shakesheff KM, Pritchard DI. Maggots and wound healing: an investigation of the effects of secretions from Lucilia sericata larvae upon the migration of human dermal fibroblasts over a fibronectin-coated surface. *Wound Repair Regen* 2005; 13: 422-33.
19. Steenvoorde P, Jukema GN. The antimicrobial activity of maggots: in-vivo results. *J Tissue Viability* 2004; 14(3): 97-101.
20. Molan PC. Re-introducing honey in the treatment of wounds and ulcers - theory and practice. *Ostomy Wound Manage* 2002; 48(11): 28-40.
21. O'Meara SM, Cullum NA, Majid M, et al. Systematic review of antimicrobial agents used for chronic wounds. *Br J Surg* 2001; 88(1): 4-21.
22. Cooper R. A review of the evidence for the use of topical antimicrobial agents in wound care. *www.worldwidewounds.com/2004/february/Cooper/Topical-Antimicrobial-Agents.html (accessed 2 February 2006).*
23. McLure AR, Gordon J. In-vitro evaluation of povidone-iodine and chlorhexidine against methicillin-resistant Staphylococcus aureus. *J Hosp Infect* 1992; 21: 291-99.
24. Kunisada T, Yamada K, Oda S, et al. Investigation on the efficacy of povidone-iodine against antiseptic-resistant species. *Dermatology* 1997; 195(Suppl 2): 14-18.
25. Tonks AJ, Cooper RA, Jones KP, et al. Honey stimulates inflammatory cytokine production from monocytes. *Cytokine* 2003; 21(5): 242-47.
26. Moore K, Thomas A, Harding KG. Iodine released from the wound dressing Iodosorb modulates the secretion of cytokines by human macrophages responding to bacterial lipopolysaccharide. *Int J Biochem Cell Biol* 1997; 29: 163-71.
27. Kjolseth D, Frank JM, Barker JH, et al. Comparison of the effects of commonly used wound agents on epithelialization and neovascularization. *J Am Coll Surg* 1994; 179: 305-12.
28. Marshall C, Quenn J, Manjojoran J. Honey vs povidone iodine following toenail surgery. *Wounds UK* 2005; 1(1): 10-18.
29. Jørgensen B, Price P, Andersen KE, et al. The silver-releasing foam dressing, Contreet foam, promotes faster healing of critically colonised venous leg ulcers: a randomised, controlled trial. *Int Wound J* 2005; 2(1): 64-73.
30. Meaume S, Vallet D, Morere MN, et al. Evaluation of a silver-releasing hydroalginate dressing in chronic wounds with signs of local infection. *J Wound Care* 2005; 14: 411-19.
31. Coutts P, Sibbald RG. The effect of a silver-containing Hydrofiber® dressing on superficial wound bed and bacterial balance of chronic wounds. *Int Wound J* 2005; 2(4): 348-55.
32. Leaper DJ. EUSOL. *BMJ* 1992; 304: 930-31.
33. Silver S, Phung le T. A bacterial view of the periodic table: genes and proteins for toxic inorganic ions. *J Ind Microbiol Biotechnol* 2005; 32: 587-605.
34. Percival SL, Bowler PG, Russell D. Bacterial resistance to silver in wound care. *J Hosp Infect* 2005; 60(1): 1-7.

Demystifying silver

J-Y Maillard[1], SP Denyer[2]

INTRODUCTION

Ionic silver (at a concentration of 10^{-9} to 10^{-6} mol/L) is bactericidal, fungicidal, virucidal and protozoicidal[1,2]. This broad-spectrum activity is beneficial for its use as a topical application. Although silver has been used for many centuries and in wound management for a long time, its bactericidal mechanisms of action are still not fully understood[1]. Silver has now assumed a prominent position in wound care and it is therefore appropriate to examine this agent in more detail and to look at the varied mechanisms of action, rationales for use and potential deficiencies of silver as an example of an antimicrobial product.

Uptake into the cell

To be effective silver must interact with and penetrate into the micro-organism to reach its target sites. It is thought that silver ions may compete with other cations for adsorption (taking up) sites on the cell[3]. Bacterial cells usually possess two types of uptake system for heavy-metal ions[4]: a non-specific system (transports many types of ions across the cell membrane) and a substrate-specific system (transports only one or select ions) that may be switched on or off by the cell under particular conditions. Although not well documented for silver ions, it is possible that the bacterial cell cannot stop the transport of metal ions into the cytoplasm (because non-specific transporters cannot be switched off). This would explain the cytotoxicity of heavy metals against bacteria[4]. The increased efficacy of silver sulfadiazine over silver nitrate may be explained by the apparent higher uptake of silver in the presence of a sulfonamide[3].

Molecular activity

Interference with cell respiration

The molecular activity of silver is explained by its strong affinity for electron donor groups containing sulphur, oxygen and nitrogen. This causes inhibition of bacterial enzymes and interferes with respiration at the cell membrane level[5]. Interaction of ionic silver with thiol groups in particular is demonstrated with the inactivation of silver ions by amino acids such as cysteine and sodium thioglycolate[6].

Interruption of DNA transcription

Ionic silver forms complexes with nucleic acid bases[7], although it does not cause clumping or disrupt the double helix *in vitro*. Whether clumping of silver occurs in the wound *in vivo* needs further research. The main mechanism of action of silver *in vivo* was suggested to be an irreversible reaction with DNA bases, although this is unlikely because silver will interact preferentially with external structures, as evidenced by gross structural changes such as surface and membrane blebs[1,8,9]. The number of target sites involved and the extent of damage contribute to the overall lethal efficacy.

EFFICACY

As for many biocides, the efficacy of silver is influenced by several factors that may be inherent to its nature or to its application.

Type of micro-organism

Ionic silver has a broad spectrum of activity (it is bactericidal, fungicidal, virucidal and protozoicidal), although more resistant micro-organisms, such as spores, cysts and mycobacteria, are less inactivated or not inactivated at all[1]. It is well recognised that silver nitrate shows strong activity against *Pseudomonas aeruginosa* but not necessarily as strongly against other micro-organisms. From early work on silver nitrate compresses, Cason *et al* reported that silver nitrate failed to reduce significantly colonisation with *Staphylococcus aureus* or coliform bacilli when compared with other antiseptic prophylaxis[10].

There is relatively little information on the efficacy of silver and silver-containing products against anaerobes[11], although these organisms are present in chronic wounds[12]. The combination of silver and a sulfonamide has been demonstrated to be synergistic against several vegetative bacteria commonly associated with burn infections[3]. In addition,

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using certain types of dressing (eg silver-containing Hydrofiber®) might enhance removal and inactivation of micro-organisms by sequestration (retention) within the dressing matrix[13].

Cytotoxicity

The use of early silver formulations, such as solutions and creams, for treating open wounds was associated with several unwanted effects (see Box, right). Cytotoxicity has been recognised with the use of silver cream and ointments[14]. *In vitro* keratinocyte toxicity has been described with silver-containing dressings in some studies[18] but not others[19], indicating the choice of keratinocyte cell type and methodology is important. *In vivo* studies and clinical evaluations of such silver dressings showed no tissue toxicity[20].

The cytotoxicity of silver sulfadiazine is associated with release of the sulfonamide rather than silver, and it has been associated with severe blood and skin disorders (burning, itching and rashes). Leucopenia and argyria (skin decolourisation resulting from elemental silver deposition) have also been recognised[21]. A study in 2002 reported an increased production of toxic shock syndrome toxin from *S. aureus* as a result of exposure to low concentrations of silver sulfadiazine[22]. Although this may be cause for concern, the clinical significance is unclear.

Concentration

One of the most important factors affecting the efficacy of a biocide is its concentration[23]. Silver has a low concentration exponent, which means that it will retain its efficacy when diluted. However, silver is poorly soluble in water and as a result misleading levels of activity have been reported[24].

Adsorption, precipitation and organic load

Silver ions are adsorbed rapidly to surfaces, presumably by interacting with negatively charged sites[7], and availability decreases in the presence of chlorides, phosphates, sulphides and hard water. Theoretically the organic load of proteinaceous body fluids (or soiling with pus) could be an important factor affecting the efficacy of silver.

The maximum level of available silver has been reported to be approximately 1μg/ml in a physiological environment *in vitro*[25]. Concentrations in excess of this are likely to serve only as a reserve against depletion in solution. Above this concentration silver ions complex with anions, predominantly chloride, to form an insoluble inactive silver salt[25]; there is no evidence that silver or silver salts are active in the dried state.

The sustained efficacy of a formulation depends on the bioavailability of the silver ions and as such the delivery vehicle is of paramount importance to ensure a slow but sustained release of silver. Most silver-containing dressings possess a high concentration of the agent. The development of silver-containing dressings has, in some cases, allowed for the controlled delivery of silver, ensuring activity while controlling potential toxicity and side effects; the rate of silver release and deposition is controlled through hydration[26].

One should note that dressings, including those containing silver, act as a barrier to wound contamination, but they cannot eliminate micro-organisms already colonising a wound. The high level of silver reactivity might impair its penetration into the wound bed, which might be of concern if bacteria are residing in deeper tissue[27].

Temperature and pH

A rise in temperature increases bactericidal activity. Therefore, testing for *in vitro* activity at room temperature may show a lower efficacy than testing at a higher skin temperature. Activity also increases at alkaline pH, although some combinations (eg silver sulfadiazine) are unstable at alkaline pH. Skin pH is usually acidic, although bacterial contamination and growth may alter this[28]. Factors affecting the activity of silver are listed in Table 1.

SILVER FOR WOUND MANAGEMENT

The application of silver-containing dressings in the management of chronic wounds is gaining momentum. An early study showed the use of silver nitrate resulted in a higher proportion of successful grafts compared with other antiseptic prophylaxis[29]. There is also evidence that silver may have anti-inflammatory properties because it down-regulates

NEGATIVE EFFECTS OF SILVER

- Cytotoxicity[14]
- Staining of skin and fabric
- Methaemoglobinaemia
- Electrolyte disturbance[15]
- Retardation of wound healing[16]
- Longer slough separation time[10]
- Inactivation of enzyme debriding agents[17]

Table 1 | **Factors affecting the activity of silver for application to open wounds**

Micro-organisms	Efficacy depends on the type of micro-organism (see text)
Toxicity	Some cytotoxicity is inevitable due to the non-specific action of silver
Concentration	Activity is not greatly affected by dilution due to its low concentration exponent
Adsorption	Rapid adsorption to some surfaces
Precipitation	Rapid precipitation when combined with chloride, phosphate and sulphide, effectively reducing the concentration of available silver
Organic load	Concentration greatly affected by soiling (eg proteins)
Temperature	Activity increases by a factor of 1.6 per 10°C rise
pH	Increased activity with alkaline pH (some combinations can be unstable at alkaline pH)

metalloproteinase activity, which may be elevated in chronic wounds[30]. However, there is a paucity of good-quality trials despite the extensive use of dressings worldwide[31,32].

Advances in impregnation techniques and polymer technologies have fuelled the latest interest in silver-based dressings. These modern products have developed from our understanding of the properties of silver, particularly the interactions between silver and the dressing and between the dressing and the wound. They aim to improve conditions for wound healing primarily by controlling the wound bioburden.

Measures to improve the efficacy of silver dressings in wounds include:

- development of dressings that incorporate excess silver to encourage sustained release of the agent, although ultimately the wound environment dictates the amount of ionic silver available in solution (see section on adsorption)
- optimising contact of the dressing with the wound will ensure maximum exposure to silver and a potentially better antimicrobial efficacy[33]
- the sequestration property of certain dressings, combined with the activity of silver, can play a part in reducing the bioburden[13].

However, there are wide variations in the structure, formulation and concentration of silver used in these products.

Dressings and preparations containing silver have a better antimicrobial efficacy than do silver nitrate or silver sulfadiazine alone[34,35]. Combining silver sulfadiazine with other antiseptics, such as chlorhexidine or povidone iodine, may enhance bactericidal activity (and reduce the likelihood of bacterial resistance) but could increase cytotoxicity[19]. Combinations are not novel, however: they were investigated in a trial in 1971 after an outbreak of silver-resistant *S. aureus* in Melbourne, Australia[19]. Recently, Garner and Heppell comprehensively reviewed the clinical application of silver sulfadiazine combined with cerium[36].

The use of established silver formulations, such as silver nitrate solution and silver sulfadiazine, has been associated with a longer slough separation time[10], slower wound healing[16] and inactivation of enzyme debriding agents[17]. Silver-containing dressings were developed to palliate these side effects, notably using a slow but sustained release of silver, decreasing local cytotoxicity and staining and enhancing wound healing and fluid handling. In the absence of robust data to direct clinicians, it is important to adopt a common sense approach and select a dressing that essentially provides an appropriate, conformable cover for the wound surface to ensure maximum efficacy[33].

BACTERIAL RESISTANCE

There is evidence for bacterial resistance to silver. Therefore, exposure to silver might select resistant micro-organisms and this could play an important part in the predominance of intrinsically silver-resistant bacteria where silver is used widely[37-39]. Li *et al* reported the development of bacterial resistance to high concentrations of silver (>1024ppm) by repeated exposures to increasing concentrations *in vitro*[40]. The precise mechanism by which these concentrations were achieved is unclear.

CONCLUSION

Silver has many properties making it suitable as a topical antimicrobial in wounds showing signs of infection. The problem lies in the lack of robust data guiding clinicians in decisions about which bacteria it is likely to be effective against and which delivery systems are suitable for which wound types. Combining silver (or silver sulfadiazine) with another broad-spectrum antimicrobial offers an attractive route to greater efficacy, although this combination may be more cytotoxic and may result in higher clinical costs[41]. The future must focus on providing substantial evidence for the use of silver and monitoring for bacterial resistance.

KEY POINTS

1. Silver is a broad-spectrum antimicrobial agent with a low toxicity in wound applications.
2. Silver is active in its ionic form, the concentration of which is influenced by silver salt solubility.
3. Silver can be formulated in a variety of dressing systems offering reservoir capability.
4. Bacteria resistant to silver have been identified.
5. Silver used in dressings must be supported by further scientific and clinical evaluation.

References

1. Russell AD, Hugo WB. Antimicrobial activity and action of silver. *Prog Med Chem* 1994; 31: 351-71.
2. Maillard J-Y. Virus susceptibility to biocides: an understanding. *Rev Med Microbiol* 2001; 12(2): 63-74.
3. Richards ME, Taylor RG, Xing DKL, et al. An evaluation of the antibacterial activities of combinations of sulphonamides, trimethoprim, dibromopropamidine, and silver nitrate compared with uptakes by selected bacteria. *J Pharm Sci* 1991; 80(9): 861-67.
4. Nies DH. Microbial heavy-metal resistance. *Appl Microbiol Biotechnol* 1999; 51(6): 730-50.
5. McDonnell G, Russell AD. Antiseptics and disinfectants: activity, action, and resistance. *Clin Microbiol Rev* 1999; 12: 147-79.
6. Liau SY, Read DC, Pugh WJ, et al. Interaction of silver nitrate with readily identifiable groups: relationship to the antibacterial action of silver. *Lett Appl Microbiol* 1997; 25: 279-83.
7. Richards RM. Antimicrobial action of silver nitrate. *Microbios* 1981; 31: 83-91.
8. Coward JE, Carr HS, Rosenkranz HS. Silver sulphadiazine: effect on the growth and ultrastructure of Staphylococci. *Chemotherapy* 1973; 19: 348-53.
9. Coward JE, Carr HS, Rosenkranz HS. Silver sulphadiazine: effect on the ultrastructure of Pseudomonas aeruginosa. *Antimicrob Agents Chemother* 1973; 3(5): 621-24.
10. Cason JS, Jackson DM, Lowbury EJ, et al. Antiseptic and aseptic prophylaxis for burns: use of silver nitrate and of isolators. *BMJ* 1966; 2: 1288-94.
11. Jones SA, Bowler PG, Walker M, et al. Controlling wound bioburden with a novel silver-containing Hydrofiber® dressing. *Wound Repair Regen* 2004; 12(3); 288-94.
12. Bowler PG. The anaerobic and aerobic microbiology of wounds: a review. *Wounds* 1998; 10(6): 170-78.
13. Newman GR. Visualisation of bacterial sequestration and bactericidal activity within hydrating Hydrofiber® wound dressings. *Biomaterials* 2006 [in press].
14. Mehta DK (Ed). Silver nitrate. In: *British National Formulary*. Issue 50. Oxford: Pharmaceutical Press, 2005.
15. Sweetman S (Ed). Silver nitrate. In: *Martindale: the complete drug reference*. 33rd edition. London: Pharmaceutical Press, 2002.
16. Muller MJ, Hollyoak MA, Moaveni Z, et al. Retardation of wound healing by silver sulphadiazine is reversed by aloe vera and nystacin. *Burns* 2003; 29: 834-36.
17. Sweetman S (Ed). Silver sulfasalazine. In: *Martindale: the complete drug reference*. 33rd edition. London: Pharmaceutical Press, 2002.
18. Lam PK, Chan ES, Ho WS, et al. In vitro cytotoxicity testing of a nanocrystalline silver dressing (Acticoat) on cultured keratinocytes. *Br J Biomed Sci* 2004; 61(3): 125-27.
19. Fraser JF, Cuttle L, Kempf M, et al. Cytotoxicity of topical antimicrobial agents used in burn wounds in Australasia. *ANZ J Surg* 2004; 74: 139-42.
20. Dunn K, Edwards-Jones V. The role of Acticoat with nanocrystalline silver in the management of burns. *Burns* 2004; 30(Suppl 1): S1-S9.
21. Mehta DK (Ed). Silver sulfasalazine. In: *British National Formulary*. Issue 50. Oxford: Pharmaceutical Press, 2005.
22. Edwards-Jones V, Foster HA. Effects of silver sulphadiazine on the production of exoproteins by Staphylococcus aureus. *J Med Microbiol* 2002; 51: 50-55.
23. Russell AD, McDonnell G. Concentration: a major factor in studying biocidal action. *J Hosp Infect* 2000; 44(1): 1-3.
24. Hamilton-Miller JM, Shah S, Smith C. Silver sulphadiazine: a comprehensive *in vitro* reassessment. *Chemotherapy* 1993; 39(6): 405-09.
25. Percival SL, Bowler PG, Russell D, et al. Bacterial resistance to silver in wound care. *J Hosp Infect* 2005; 60(1): 1-7.
26. Walker M, Cochrane CA, Bowler PG. Silver deposition and tissue staining associated with wound dressings containing silver. *Ostomy Wound Manage* 2006; 52(1): 42-50.
27. Burrell RE. A scientific perspective on the use of topical silver preparations. *Ostomy Wound Manage* 2003; 49(5A Suppl): 19-24.
28. Messager S, Hann AC, Goddard PA, et al. Use of the 'ex-vivo' test to study long term bacterial survival on human skin and their sensitivity to antisepsis. *J Appl Microbiol* 2004; 97(6): 1149-60.
29. Klasen HJ. A historical review of the use of silver in the treatment of burns. II. Renewed interest for silver. *Burns* 2000; 26: 131-38.
30. Lansdown AB, Sampson B, Laupattarakasem P, et al. Silver aids healing in the sterile skin wound: experimental studies in the laboratory rat. *Br J Dermatol* 1997; 137(5): 728-35.
31. Vermeulen H, Ubbink DT, Goossens A, et al. Systematic review of dressings and topical agents for surgical wounds healing by secondary intention. *Br J Surg* 2005; 92(6): 665-72.
32. O'Meara SM, Cullum NA, Majid M, et al. Systematic review of antimicrobial agents used for chronic wounds. *Br J Surg* 2001; 88(1): 4-21.
33. Jones S, Bowler PG, Walker M. Antimicrobial activity of silver-containing dressing is influenced by dressing conformability with wound surface. *Wounds* 2005; 17(9): 263-70.
34. Wright JB, Lam K, Hansen D, et al. Efficacy of topical silver against burn wound pathogens. *Am J Infect Control* 1999; 27: 344-50.
35. Yin HQ, Langford R, Burrell RE. Comparative evaluation of the antimicrobial activity of ACTICOAT antimicrobial barrier dressing. *J Burn Care Rehabil* 1999; 20: 195-200.
36. Garner JP, Heppell PS. Cerium nitrate in the management of burns. *Burns* 2005; 31: 539-47.
37. Wenzel RP, Hunting KJ, Osterman CA, et al. Providencia stuartii, a hospital pathogen: potential factors for its emergence and transmission. *Am J Epidemiol* 1976; 104(2): 170-80.
38. Bridges K, Lowbury EJ. Drug resistance in relation to use of silver sulphadiazine cream in a burns unit. *J Clin Pathol* 1977; 30(2): 160-74.
39. Silver S. Bacterial silver resistance: molecular biology and uses and misuse of silver compounds. *FEMS Microbiol Rev* 2003; 27: 341-53.
40. Li XZ, Nikaido H, Williams KE. Silver-resistant mutants of Escherichia coli display active efflux of Ag+ and are deficient in porins. *J Bacteriol* 1997; 179: 6127-32.
41. Fong J, Wood F, Fowler B. A silver coated dressing reduces the incidence of early burn wound cellulitis and associated costs of inpatient treatment: comparative patient care audits. *Burns* 2005; 31: 562-27.

Topical management of infected grade 3 and 4 pressure ulcers

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INTRODUCTION

Recognising early signs of infection in complex wounds such as grade 3 and 4 pressure ulcers demands vigilant and skilled observation. The management involves many different interventions and strategies. These include the use of pressure redistributing surfaces, repositioning, nutrition, pain control, continence care and skin and wound care[1]. Topical interventions such as debridement, maggot therapy and topical negative pressure therapy have an important role to play. However, this article focuses mainly on the use of topical antimicrobials, in particular iodine and silver. Older products such as honey are re-emerging onto the market and there is an increasing interest in research into the use of this product[2].

BACKGROUND

Iodine

A systematic review exploring the use of antimicrobial agents for managing chronic wounds found a number of randomised controlled trials (RCTs) that examined the use of topical antimicrobials in the treatment of pressure ulcers[3].

One RCT compared a povidone iodine dressing with a hydrocolloid dressing in grade 2 and 3 pressure ulcers. The authors reported no statistically significant difference between the groups for complete/partial healing or reduction in ulcer area at 56 days. The second RCT compared a povidone iodine ointment with 0.1% gentian violet as an ointment in elderly women with pressure ulcers. No information was provided on concomitant pressure relief. No statistically significant difference was found between the groups for change in wound healing area at 14 weeks. The third RCT compared the healing rates of an ointment containing the antiseptic oxyquinoline with a standard emollient. Again, no statistically significant differences were noted between the groups. A further trial looked at ulcers of varying aetiologies including pressure ulcers. A povidone iodine dressing was compared with hydrocolloid dressings. At 12 weeks no statistically significant difference in healing rates was found.

It is important to highlight that these studies were underpowered, making it difficult to show a statistical difference between groups, even if one existed. Therefore, more rigorous examination is needed before firm conclusions can be drawn.

Silver

Coutts and Sibbald explored the effect of silver-containing Hydrofiber® dressings on the wound size and bacterial balance of wounds of varying aetiologies[4]. Of the 30 wounds included, four were pressure ulcers with local wound infection. The authors monitored the effect of the dressing on wound size and on signs and symptoms of increased bacterial burden for four weeks or to complete healing. Data are not provided separately for the pressure ulcer wounds, although the authors indicate that 56% of wounds decreased in size. Bacterial balance was measured as a reduction in slough and peri-wound maceration. However, the precise method for assessing slough and maceration is not described. The authors report improvement in maceration in 46% of wounds and a decrease in slough in 50% of wounds. No inferential statistics were conducted. However, the authors conclude that the dressing has a role to play in moisture balance, exudate control and bacterial balance.

KEY POINTS

1. Topical antimicrobials (iodine and silver) have a role in the management of wounds with a high bacterial burden or signs of early localised infection.
2. Considerations when choosing a dressing include wound condition, exudate level and adaptability of the dressing to suit the wound.
3. Be aware of potential contraindications to products; if in doubt refer to manufacturers' guidance.
4. Use silver and iodine dressings only as indicated; overuse may lead to bacterial resistance.
5. Ongoing assessment of the patient and wound are essential to monitor and evaluate outcomes.

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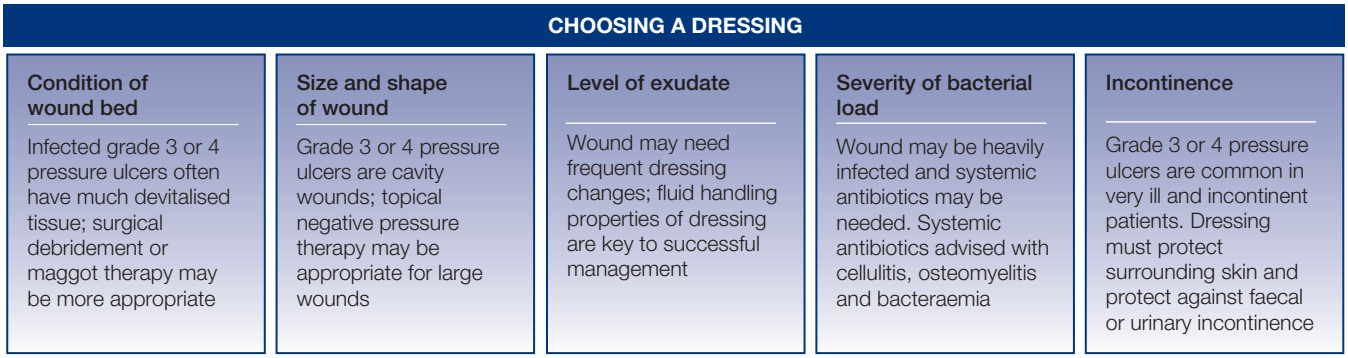

Figure 1 | **Considerations when choosing a dressing**

A comparative study examined silver sulfadiazine, povidone iodine and physiological saline in the treatment of chronic pressure ulcers. It showed that silver plays a key role in maintaining bacterial balance[5].

NEW FORMULATION PRODUCTS

Improved formulation products offer new opportunities with fewer toxicity problems for the topical management of infected pressure ulcers. An *in vitro* study has shown the properties of the dressing carrying the silver in relation to the materials used and the ability of the dressing to handle fluid are more important than the amount of silver in the dressing[6]. Cadexomer iodine is a highly absorbent product that slowly releases iodine into the wound over time. Both povidone iodine and cadexomer iodine may be effective at reducing bacterial loads within the pressure ulcer. However, there is evidence that cadexomer iodine may also be able to accelerate wound healing[7].

Consideration also needs to be given to the efficacy and efficiency of the product against specific bacteria (see pages 2–6). Unfortunately, there is currently a lack of good-quality evidence on which to base clinical decisions[3].

MANAGING INFECTION

Assessment

The maintenance of bacterial balance in pressure ulcers has been shown to be important for wound healing[8]. A careful holistic assessment is necessary to recognise early infection in grade 3 and 4 pressure ulcers. Sanada *et al* have clearly described the subtle changes that may take place in both the patient and the chronically inflamed wound[9].

Increasing pain should warn of deterioration in the condition of the ulcer and may indicate the presence of osteomyelitis. Pain should be regularly assessed using the same pain scoring tool at each assessment[10].

The role of nutrition in the management of infected grade 3 or 4 pressure ulcers is unclear[11]. However, there will be an increased metabolic need during infection, along with increased production of wound fluid. If intake of food and fluids is inadequate, a full nutritional assessment involving the dietitian should be conducted[12].

Cleaning the wound bed

These ulcers are likely to contain substantial devitalised tissue, which exacerbates the bacterial load. Tissue management (debridement of devitalised tissue) will therefore be needed. Because of the presence of infection surgical debridement is usually the method of choice[13], although the risk of bleeding and exacerbation of pain need to be assessed. If surgical debridement is chosen the need for systemic antibiotics should be carefully assessed; for example, they will be needed for heavy debridement with extensive bleeding[13].

A recent systematic review concluded that there is no good trial evidence to support the use of a particular solution or technique for cleansing pressure ulcers[14]. Nonetheless, infected grade 3 or 4 pressure ulcers need to be cleansed principally because of the

USING TOPICAL ANTIMICROBIALS

Conformability	Size of wound	Exudate management	Safe use of product	Other factors
May be cavity wound with irregular shape or in difficult location. Dressing must be in contact with all areas so agent can reach bacteria[16]	May need cutting to size. Wound may be too big for cadexomer iodine product. Rope alginate or Hydrofiber® silver dressing may be more appropriate	Wound may be heavily exudating. If supersaturated dressing will be ineffective and bactericidal efficacy reduced	Consider underlying medical condition and product sensitivity, eg iodine dressings. Effectiveness of dressings should be reviewed regularly to avoid prolonged use	Odour management, maceration protection (the surrounding skin should be protected using an appropriate skin barrier protector), pain on removal

Figure 2 | **Considerations for topical antimicrobials**

production of large volumes of exudate, which is often foul smelling. The consensus opinion on management is to gently irrigate the wound with normal saline at room temperature.

Dressing the wound bed

Dressing choice will be based on the assessment of the patient and the wound (Figure 1). Where there are subtle changes in the patient and/or wound indicating infection it may be worth considering topical antimicrobial therapy (see pages 2–6).

Further points to consider when selecting an antimicrobial are the specific wound management objectives and the ability of the dressing to meet these objectives. The desired frequency of dressing change, the size of the wound and the proposed time frame planned for use of the product will influence dressing choice (Figure 2)[15]. It is important to be familiar with the manufacturers' recommendations for use, for example some products need to be wetted before use.

CONCLUSION

The use of newer formulation topical antimicrobials, particularly silver and iodine products, is increasingly being recommended as one component of the management of wounds with a problematic or increasing bacterial burden[7]. Careful assessment, appropriate care planning, effective selection and regular evaluation of outcomes are central to successful use of these products in clinical practice.

References

1. Bergstrom N, Allman R, Alvarez OM, et al. Ulcer Care. In: *Treatment of pressure ulcers. Clinical Practice Guideline Number 15*. Rockville, MD, USA: US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research,1994; (15): 45-57. Available at: www.ahcpr.gov/clinic/cpgonline.htm (accessed 30 March 2006).
2. Molan PC. Re-introducing honey in the management of wounds and ulcers - theory and practice. *Ostomy Wound Manage* 2002; 48(11): 28-40.
3. O' Meara SM, Cullum NA, Majid M, et al. Systematic review of antimicrobial agents used for chronic wounds. *Br J Surg* 2001; 88: 4-21.
4. Coutts P, Sibbald RG. The effect of a silver containing Hydrofiber® dressing on superficial wound bed and bacterial balance of chronic wounds. *Int Wound J* 2005; 2(4): 348-56.
5. Kucan JO, Robson MC, Heggers JP, et al. Comparison of silver sulfadiazine, povidone-iodine and physiologic saline in the treatment of chronic pressure ulcers. *J Am Geriatr Soc* 1981; 29: 232-35.
6. Parsons D, Bowler PG, Myles V, et al. Silver antimicrobial dressings in wound management: a comparison of antibacterial, physical and chemical characteristics. *Wounds* 2005; 17(8): 222-32.
7. Drousou A, Falabella A, Kirsner RS. Antiseptics on wounds: an area of controversy. *Wounds* 2003; 15(5): 149-66.
8. Robson MC, Mannari RJ, Smith PD, et al. Maintenance of wound bacterial balance. *Am J Surg* 1999; 178(5): 399-402.
9. Sanada H, Nakagami G, Romanelli M. Identifying criteria for pressure ulcer infection. In: European Wound Management Association (EWMA). Position Document: *Identifying criteria for wound infection*. London: MEP Ltd, 2005; 10-13.
10. European Wound Management Association (EWMA). Position Document: *Pain at wound dressing changes*. London: MEP Ltd, 2002.
11. Stratton RJ, Ek AC, Engfer M, et al. Enteral nutritional support in prevention and treatment of pressure ulcers: a systematic review and meta-analysis. *Ageing Res Rev* 2005; 4: 422-50.
12. European Pressure Ulcer Advisory Panel. EPUAP guidelines on the role of nutrition in pressure ulcer prevention and management. *EPUAP Review* 2003; 5(2): 50-63. www.epuap.org/review5_2/page5.html (accessed 2 February 2006).
13. Romanelli M, Flanagan M. Wound bed preparation for pressure ulcers. www.worldwidewounds.com/2005/july/Romanelli/Wound-Bed-Preparation-Pressure-Ulcer.html (accessed 2 February 2006).
14. Moore Z, Cowman S. Wound cleansing for pressure ulcers. *Cochrane Database Syst Rev* 2005; 4: CD004983.
15. Bale S, Jones V. Wound care nursing: a patient centered approach. London: Balliere Tindall, 1997; 3-46.
16. Jones S, Bowler PG, Walker M. Antimicrobial activity of silver-containing dressings is influenced by dressing conformability with a wound surface. *Wounds* 2005; 17(9): 263-70.

POSITION DOCUMENT

Topical antimicrobials and surgical site infection

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INTRODUCTION

Over the past 150 years improvements in aseptic techniques and developments in antimicrobials have reduced infection rates following surgery. It is therefore only a small percentage of surgical wounds healing by primary intention that become infected. However, when such wounds fail to heal the economic burden may be considerable[1]. The patient may need readmission, surgical intervention and intravenous antibiotics. This article examines the management of surgical site infection (SSI) in wound healing with a focus on topical antimicrobials, particularly silver and iodine. SSI was defined in the 2005 European Wound Management Association position document[2].

BACKGROUND

Driven by an increase in antibiotic resistance, topical antimicrobials are being increasingly used in wound treatment and care, especially for infected or open wounds healing by secondary intention. To be effective, in a short contact time, concentrations needed to be adequate, which increased the risk of toxicity to tissues and delay to wound healing[3]. These potential adverse effects gave topical antimicrobials a bad reputation (in some cases justified). However, studies have shown that at lower concentrations some are not cytotoxic and may reduce bacterial counts[4–11].

Human and animal studies examining the effects of topical antimicrobials in acute wounds have focused on their ability to reduce bacterial counts and prevent infection. They have produced conflicting findings, some of which are summarised in Table 1.

TREATMENT OF SSIs

Wound assessment

Holistic patient assessment is often the key to promoting normal wound healing. Risk factors such as diabetes, obesity, poor nutrition and ischaemia need to be identified and addressed, if possible. It is important to note that serum albumin levels may fall with highly exudative wounds and this could adversely affect wound healing.

A thorough wound assessment may identify early signs of infection and allow appropriate treatment to be started before wound breakdown. Tools are available to help clinicians assess the surgical wound and identify infection[2].

Incision and drainage

Opening of infected wounds and allowing purulent material to discharge has been practised for thousands of years, and the benefit of doing so is probably the origin of the term 'laudable pus'. In most cases removing clips or sutures from at least part of the wound is adequate to allow drainage of purulent fluid. Deeper collections of infected fluid can often be drained percutaneously with the insertion of a catheter (attached to a drainage system) under CT or ultrasound guidance. Occasionally the wound needs to be surgically reopened and debrided[28].

Most surgical wounds that are re-opened are left to heal by secondary intention, although some may be closed after treatment and after clinical indications of infection have gone. Delayed primary healing occurs when a wound, re-opened after infection, is re-closed after four to five days of local treatment with systemic antibiotic cover (early

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KEY POINTS

1. The use of topical antimicrobials may be considered for certain types of infected surgical wounds in addition to standard treatment (systemic antibiotics for spreading infection and incision and drainage to release pus).
2. Good-quality randomised controlled trials of new antimicrobial dressings are needed.
3. Current evidence suggests that topical antimicrobials are most beneficial as prophylaxis against the development of infection.
4. Topical antibiotics should be avoided because they may cause hypersensitivity reactions and super-infections and may select resistant bacteria.

Table 1 | **Clinical trials of topical antimicrobials in acute wounds**

Oxidising solutions (hydrogen peroxide, sodium hypochlorite)	Limited research for hydrogen peroxide in acute wounds. Doubts about microbial capacity at non-toxic dilutions. Animal and human studies found no detrimental effect on wound healing, but little impact on bacterial loads[12–14]. One study following appendicectomy identified no toxicity, but ineffective at preventing infection[13]. Lineaweaver *et al* were able to find a bactericidal, non-toxic dilution of sodium hypochlorite[12]. However, Cannavo *et al* found no benefit to acute wound healing when using sodium hypochlorite soaked gauze[15]. Hypochlorites advocated in wound care only when used with caution as debriding agents.
Acetic acid	*In vitro* studies suggest cytotoxic[16,17]. Two uncontrolled studies in humans suggested effective for acute wounds with *Pseudomonas aeruginosa*[18,19].
Chlorhexidine	Effective for patients' skin and for hand washing before surgery. Animal studies suggest may disturb healing[20,21], although other studies indicate not cytotoxic at lower concentrations and may aid wound healing[5,6]. Reduced microbial complications in acute wounds during dental surgery[22], but no effect on wound infection or length of stay after appendicectomy[23].
Silver	Used for burns and skin grafting as a prophylactic to prevent infection[24]. Most animal studies found no adverse effects on healing[9–11]. Many new preparations being introduced[25].
Iodine	Animal studies show reduced bacterial count with povidone iodine and cadexomer iodine[8,9]. One study in humans suggested povidone iodine reduced risk of infection in surgical wound healing[26], although another study suggested ineffective at reducing bacterial load[27]. Research with cadexomer iodine shows reduced bacterial counts and improved healing[8].

reclosure), and in more than 90% of cases healing will occur without any complications[29,30].

Antibiotics

Despite increasing concerns about antibiotic-resistant bacteria, appropriate use of systemic antibiotics is still recommended where there is clear evidence of cellulitis, lymphangitis or systemic-related complications (eg bacteraemia and sepsis)[30]. Antibiotic treatment is indicated in this circumstance irrespective of results from wound cultures. The type and dosage of antibiotics can be adjusted at a later date if culture sensitivities indicate an alternative regimen is more appropriate. If wound cultures indicate infection but there are no clinical signs, antibiotics should usually be withheld until the result has been confirmed. Topical antibiotics should usually be avoided because they may cause hypersensitivity reactions and super-infections and may select resistant bacteria[31]. Superficial SSIs do not necessarily require systemic antibiotics and may heal independently in the absence of systemic infection.

Other agents

It is clear that topical antimicrobial dressings have been used in the past and continue to be used for SSIs. Research into acute wounds has concentrated on illustrating that topical antimicrobials have no cytotoxic effects and may aid prevention of infection. There is little evidence of systemic toxicity from modern antimicrobials[32], and there is some evidence to suggest that the application of topical antimicrobials may prevent infection in acute wounds[19,22,24,26]. However, most of these studies examined the use of antimicrobials for open wounds, which are often heavily contaminated. Most surgical wounds are closed (sutured) and these findings may not be relevant.

Healing by secondary intention

One systematic review examining the role of dressings and topical agents for surgical wounds healing by secondary intention found no evidence to support their use[33]. Of the 13 studies included, six involved patients who had undergone pilonidal sinus excision, five involved patients with postoperative wound breakdown, one included patients who had undergone abdomino-perineal resection and one involved patients who had undergone a below-knee amputation.

Five of the 13 studies examined the role of ribbon gauze soaked with antimicrobials and compared them with alternative dressings (usually foam). There was no identified

INDICATIONS FOR TOPICAL ANTIMICROBIALS			
Wounds with necrotic or poor blood supply	**Wounds continually re-contaminated or infected (eg faecal fistulae)**	**Patients with specific antibiotic allergy or antibiotic-resistant infections**	**Wounds benefiting from delayed primary closure principle**
Systemic antibiotics may not penetrate infected ischaemic tissue at therapeutic doses; local agents may be more successful	High levels of bacterial contamination at wound site delays wound healing. Prolonged systemic antibiotic cover is undesirable. Topical antimicrobials reduce bacterial burden and may prevent further re-infection	Particularly where prolonged systemic antibiotic therapy has failed in an infected open surgical wound	Infected or heavily contaminated wounds may initially be left open. Topical antimicrobials may be a treatment option at this stage. After a few days, the wounds are usually free from infection and can be cleaned and re-closed (delayed primary closure principle) with a single dose of prophylactic antibiotic. This procedure can shorten the healing time and improve cosmetic outcome

Figure 1 | **Indications for topical antimicrobials**

benefit to wound healing with antimicrobial therapy, but gauze dressings caused more discomfort and patients were less satisfied than when their wounds were dressed with foam dressings.

Healing by primary intention

There is a lack of good-quality studies examining the benefits of topical antimicrobials in surgical wounds healing by primary intention, although some recent research has suggested that topical antimicrobials can be used as a 'rescue remedy' for surgical wounds failing to heal due to infection (see Figure 1)[34]. In addition, topical antiseptics (eg ionic silver) are now being used in combination with the best wound care products, such as Hydrofiber® dressings, alginates, foam, hydrogels and even topical negative pressure therapy[25]. However, comparative randomised trials are needed before these treatments can be routinely recommended. Antimicrobials may also be used before closure, as prophylaxis.

It has been suggested that povidone iodine has good tissue penetration compared with silver, which may destroy only surface bacteria[35], so the use of povidone iodine for closed surgical wounds may be more appropriate. One study tested the effects of povidone iodine on closed acute wounds in animals and found no beneficial effect, although the authors did not state the strength of povidone iodine used[36].

Topical antimicrobials may not be as effective against the bacteria that reside in wounds as they are against the same bacteria *in vivo*. This is because the presence of exudates such as serum, blood and pus may reduce the activity of some antiseptics[37].

Selecting an appropriate dressing

Most infected surgical wounds do not completely break down. Therefore, access to the wound site is often limited and may be through a partially opened suture line or superficial tissue separation. Considerations when choosing dressings are given in Table 2.

CONCLUSION

Large, good-quality trials looking at new antimicrobial dressings are needed before they can be recommended for routine use in infected surgical wounds. A cost–benefit analysis is also essential and a balance needs to be found between any negative impact on wound healing and the short-term benefits of reducing bacterial load[31]. The strongest evidence suggests that topical antimicrobials have a role to play in prophylaxis (ie skin preparation before surgery); however, these agents are unlikely to benefit closed surgical wounds because penetration is likely to be poor. There are certain circumstances where topical antimicrobials can be used as a rescue remedy for surgical wounds that are failing to heal.

Table 2 | **Considerations when choosing a dressing**

Frequency of dressing changes	Do not use preparations with slow-release formula for wounds requiring frequent dressing changes. Many preparations release active elements when dressing absorbs fluid and may be inappropriate for dry wounds[38]. Water-based creams (containing antimicrobials) are not appropriate for excessive exudate[3].
Wound size	It has been alleged that some preparations can be absorbed systemically, but there is no clear evidence to support this. Caution should be used in large wounds and clinicians should refer to the manufacturer's advice sheet if necessary for further information.
Wound location	Dressings should be flexible. In orthopaedics most surgical wounds are over the joint and dressings should allow free movement for postoperative mobilisation. Choose appropriate formulations where access to the cavity is limited to a partially opened suture line.
Pain	Dressings providing moist, non-adherent contact are least likely to cause pain when removed. Gauze has been associated with pain at dressing change[39].
Patient preference	Establish any intolerance to antimicrobial dressings in initial stages of treatment. Compliance improved if dressing meets patients' needs (ie manages exudates, comfortable, flexible, not bulky, causes minimal pain on application and removal).

References

1. Leaper DJ, Goor HV, Reilly J, et al. Surgical site infection – a European perspective of incidence and economic burden. *Int Wound J* 2004; 1: 247-73.
2. Melling AC, Hollander DA, Gottrup F. Identifying surgical site infection in wounds healing by primary intention. In: European Wound Management Association (EWMA). Position Document: *Identifying criteria for wound infection*. London: MEP Ltd, 2005; 14-17.
3. Scanlon E. Wound infection and colonisation. *Nurs Standard* 2005; 19: 57-62.
4. Tur E, Bolton L, Constantine BE. Topical hydrogen peroxide treatment of ischemic ulcers in the guinea pig: blood recruitment in multiple skin sites. *J Am Acad Dermatol* 1995; 33(2:1): 217-21.
5. Brennan SS, Foster ME, Leaper DJ. Antiseptic toxicity in wounds healing by secondary intention. *J Hosp Infect* 1986; 8(3): 263-67.
6. Shahan MH, Chuang AH, Brennan WA, et al. The effect of chlorhexidine irrigation on tensile wound strength. *J Periodontol* 1993; 64(8): 719-22.
7. Rodeheaver G, Bellamy W, Kody M, et al. Bactericidal activity and toxicity of iodine-containing solutions in wounds. *Arch Surg* 1982; 117: 181-85.
8. Mertz PM, Oliveira-Gandia MF, Davis SC. The evaluation of cadexomer iodine wound dressing on methicillin resistant Staphylococcus aureus (MRSA) in acute wounds. *Dermatol Surg* 1999; 25: 89-93.
9. Kjolseth D, Frank JM, Barker JH, et al. Comparison of the effects of commonly used wound agents on epithelialization and neovascularization. *J Am Coll Surg* 1994; 179: 305-12.
10. Lansdown AB, Sampson B, Laupattarakasem P, et al. Silver aids healing in the sterile skin wound: experimental studies in the laboratory rat. *Br J Dermatol* 1997; 137(5): 728-35.
11. Geronemus RG, Mertz PM, Eaglstein WH. Wound healing. The effects of topical antimicrobial agents. *Arch Dermatol* 1979; 115: 1311-14.
12. Lineaweaver W, Howard R, Soucy D, et al. Topical antimicrobial toxicity. *Arch Surg* 1985; 120(3): 267-70.
13. Lau WY, Wong SH. Randomized, prospective trial of topical hydrogen peroxide in appendectomy wound infection. High risk factors. *Am J Surg* 1981; 142: 393-97.
14. Leyden JJ, Bartelt NM. Comparison of topical antibiotic ointments, a wound protectant, and antiseptics for the treatment of human blister wounds contaminated with Staphylococcus aureus. *J Fam Pract* 1987; 24(6): 601-04.
15. Cannavo M, Fairbrother G, Owen D, et al. A comparison of dressings in the management of surgical abdominal wounds. *J Wound Care* 1998; 7(2): 57-62.
16. Cooper ML, Laxer JA, Hansbrough JF. The cytotoxic effects of commonly used topical antimicrobial agents on human fibroblasts and keratinocytes. *J Trauma* 1991; 31(6): 775-84.
17. Lineaweaver W, McMorris S, Soucy D, et al. Cellular and bacterial toxicities of topical antimicrobials. *Plast Reconstr Surg* 1985; 75: 394-96.
18. Phillips I, Lobo AZ, Fernandes R, et al. Acetic acid in the treatment of superficial wounds infected by Pseudomonas aeruginosa. *Lancet* 1968; 1: 11-13.
19. Sloss JM, Cumberland N, Milner SM. Acetic acid used for the elimination of Pseudomonas aerguinosa from burn and soft tissue wounds. *J R Army Med Corps* 1993; 139(2): 49-51.
20. Saatman RA, Carlton WW, Hubben K, et al. A wound healing study of chlorhexidine digluconate in guinea pigs. *Fundam Appl Toxicol* 1986; 6(1): 1-6.
21. Niedner R, Schopf E. Inhibition of wound healing by antiseptics. *Br J Dermatol* 1986; 115(Suppl 31): 41-44.
22. Lambert PM, Moris HF, Ochi S. The influence of 0.12% chlorhexidine gluconate rinses on the incidence of infectious complications and implant success. *J Oral Maxillofac Surg* 1997; 55(12): 25-30.
23. Crossfill M, Hall R, London D. The use of chlorhexidine antiseptics in contaminated surgical wounds. *Br J Surg* 1969; 56(12): 906-08.
24. Livingston DH, Cryer HG, Miller FB, et al. A randomized prospective study of topical antimicrobial agents on skin grafts after thermal injury. *Plast Reconstr Surg* 1990; 86(6): 1059-64.
25. Parsons D, Bowler PG, Myles V, et al. Silver antimicrobial dressings in wound management: a comparison of antibacterial, physical and chemical characteristics. *Wounds* 2005; 17(8): 222-32.
26. Viljanto J. Disinfection of surgical wounds without inhibition of wound healing. *Arch Surg* 1980; 115: 253-56.
27. Lammers RL, Fourre M, Callaham ML, et al. Effect of povidone-iodine and saline soaking on bacterial counts in acute, traumatic, contaimated wounds. *Ann Emerg Med* 1990; 19(6): 709-14.
28. Patel CV, Powell L, Wilson SE. Surgical wound infections. *Curr Treat Opinions Infect Dis* 2000; 2: 147-53.
29. Gottrup F, Gjøde P, Lundhus F, et al. Management of severe incisional abscesses following laparotomy. Early reclosure under cover of metronidazole and ampicillin. *Arch Surg* 1989; 124: 702-04.
30. Gottrup F. Wound closure techniques. *J Wound Care* 1999; 8: 397-400.
31. White RJ, Cooper R, Kingsley A. Wound colonization and infection: the role of topical antimicrobials. *Br J Nurs* 2001; 10(9): 563-78.
32. Lansdown AB, Williams A. How safe is silver in wound care? *J Wound Care* 2004; 13(4): 131-36.
33. Vermeulen H, Ubbink D, Goossens A, et al. Dressings and topical agents for surgical wounds healing by secondary intention. *Cochrane Database Syst Rev* 2004; (2): CD003554.
34. Grubbs BC, Statz CL, Johnson EM, et al. Salvage therapy of open, infected surgical wound: a retrospective review using Techni-Care. *Surg Infect* 2000; 1(2): 109-14.
35. Sibbald RG, Browne AC, Coutts P, et al. Screening evaluation of an ionized nanocrystalline silver dressing in chronic wound care. *Ostomy Wound Manage* 2001; 47(10): 38-43.
36. Kashyap A, Beezhold D, Wiseman J, et al. Effect of povidone iodine dermatologic ointment on wound healing. *Am Surg* 1995; 61(6): 486-91.
37. Drosu A, Falabella A, Kirsner RS. Antiseptics on wounds: an area of controversy. *Wounds* 2003; 15(5): 149-66.
38. Thomas S. A structured approach to the selection of dressings. www.worldwidewounds.com/1997/july/Thomas-Guide/Dress-Select.html (accessed 2 February 2006).
39. Moffatt CJ, Franks PK, Hollinworth H. Understanding wound pain and trauma: an international perspective. In: European Wound Management Association (EWMA). Position Document: *Pain at wound dressing changes*. London: MEP Ltd, 2002; 2-7.