

The role of topical metronidazole in the management of infected wounds

KEY WORDS

- ▶ bacterial infection
- ▶ cost efficiencies
- ▶ biofilm
- ▶ chronic wounds

Abstract: With an increasing ageing population, the presentation of chronic wounds, and thus rates of infection, have also risen. Infection can delay wound healing, cause malodour, excess exudate and pain, leading to further morbidity, reducing patient quality of life and increasing the cost of treatment. Topical antimicrobials can be used as part of a wound management plan to tackle infection, enabling chronic wounds to progress to healing, particularly if the wound has a decreased or depleted blood supply. Antibiotic and antiseptic agents have varying antimicrobial activities and can be used in addition to debridement to treat infection. This article focuses on the role of topical metronidazole in treating infected, malodourous wounds and highlights the continued relevance of topical metronidazole in the management of infected wounds.

Chronic wounds represent a significant burden to both patients and the NHS. They are often associated with pain, exudate and odour, and can reduce patients' mobility and lead to social isolation. As chronic wounds predominantly occur in older people, they are increasing in prevalence. The UK population has been steadily getting older and this trend is projected to continue in the future. In 2016, there were 11.8 million UK residents aged 65 years and over, representing 18% of the total population – 25 years earlier, there were 9.1 million, accounting for 15.8% of the population (Office for National Statistics, 2018). The Health Survey for England shows that in 2016, 29% of those aged 60–64 years had two or more chronic conditions; in those aged 75 years and over this figure rises to almost 50% (NHS, 2016).

Due to their longevity, chronic and non-healing wounds – and their associated comorbidities – are associated with high treatment costs (Frykberg and Banks, 2015). The Burden of Wounds study found that the NHS spent an estimated £4.5–5.1bn on wound treatment in 2012–13 (Guest et al, 2017).

Inflammation, infection and the formation of biofilms are common features of chronic wounds (Frykberg and Banks, 2015). It has become widely accepted that most chronic and hard-to-heal wounds contain biofilm, and that biofilm delays

and/or prevents healing (WUWHS, 2016). See Figure 1 for further information on the stages of the Wound Infection Continuum (IWII, 2016).

The presence of infection delays healing and can be associated with complications including cellulitis, gangrene, haemorrhage and lower-extremity amputations (Järbrink et al, 2016).

PREVENTION AND MANAGEMENT OF INFECTION

Infection prevention is an important component of wound management. Implementing best practice will reduce the risk of cross contamination, improve patient outcomes and promote rapid wound healing.

The signs and symptoms of infection are listed in Box 1. Holistic assessment is important, and a careful history should be taken to identify the presence of any factors that increase the risk of infection (see Box 2).

The presence of a deep infection or abscess can be masked in patients with neuropathy; however, they are more likely to present with flu-like symptoms or pain (Wounds UK, 2013). If infection is suspected, clinicians should examine the wound bed and periwound area, and document signs of redness, unexplained pain or malodour (Wounds UK, 2013).

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The TIMES framework, see Box 3, should be applied when developing a chronic wound management plan. Infection causes a rapid increase in the production of exudate, so it needs to be effectively managed to protect the surrounding skin from maceration and excoriation (Wounds UK, 2013). Appropriate debridement of non-viable or devitalised tissue reduces the bioburden and reduces odour (Wounds UK, 2013). Debridement is unlikely to remove all biofilm, therefore the application of topical antimicrobials as a wound-cleansing agent with a surfactant component and/or antimicrobial dressing, should be considered (Wounds UK, 2013). Systemic antibiotics may also be appropriate for patients at high risk of adverse outcomes (Wounds UK, 2013).

ANTIMICROBIALS

Antimicrobials can have broad- or narrow-spectrum activity against gram-positive, gram-negative, aerobic, anaerobic, planktonic and sessile bacteria, fungi and spores commonly found in wounds. Topical formulations are useful in the management of infection as they provide a high and sustained concentration of antimicrobial at the site of infection and have limited or no systemic absorption or toxicity (Wounds UK, 2013). They should be used when wound bioburden appears to be interfering with wound healing or there is an increased risk of adverse outcomes (Wounds UK, 2013). Topical antimicrobials should be selected based on a patient’s needs, as their modes of action, ability to handle exudate, pain or odour vary. Box 4

lists the properties of an ideal topical antimicrobial for the treatment of chronic wounds. The effect of the antimicrobial selected should be monitored at each dressing change and assessed at 2 weeks.

Antiseptic agents, such as povidone iodine, silver nitrate and chlorhexidine, inhibit or kill organisms within a wound or on intact skin. They have a broad spectrum of action but are often toxic to host tissue (Lipsky and Hoey, 2009; IWII, 2016). They can be applied as topical formulations or incorporated into dressings. Interestingly, similar efficacy against common pathogens has been reported between honey, iodine and silver, but significant differences have been found when these agents have been included in dressings (Bradshaw, 2011). Consideration should therefore be given to how the agent is applied.

Antibiotic agents are naturally or synthetically produced chemicals that kill or inhibit microorganisms. Antibiotics usually act on a specific cell target and can be used to target particular pathogens; however, some have broad-spectrum activity (Lipsky and Hoey, 2009). They are relatively non-toxic to host tissue and can be used topically or systemically. The topical antimicrobials available in the UK for the management of skin infections or wounds are listed in Table 1.

Antimicrobial medicines are among the most commonly prescribed medicines in both primary and secondary care. The use, misuse and overuse of antimicrobial medicines is considered to be a major driving force towards increased antimicrobial

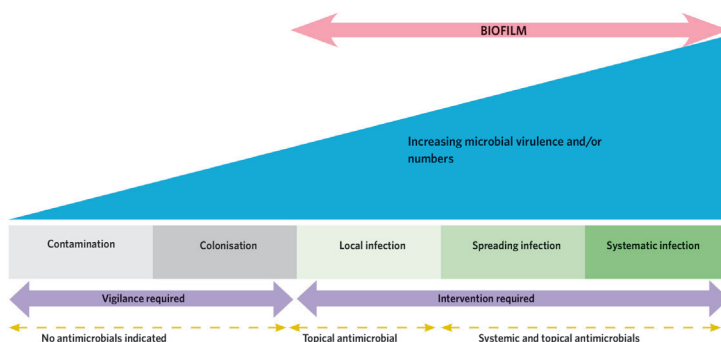


Figure 1: The Wound Infection Continuum (IWII, 2016)

Box 1. Signs and symptoms of infection (adapted from IWII, 2016)

Covert 'subtle' signs of local infection:

- » Hypergranulation
- » Bleeding/friable granulation
- » Epithelial bridging and pocketing in granulation tissue
- » Wound breakdown and enlargement
- » Delayed wound healing
- » New or increasing pain
- » Increasing malodour

Overt 'classic' signs of local infection:

- » Erythema
- » Local warmth
- » Swelling
- » Purulent discharge
- » Delayed wound healing
- » New or increasing pain/tenderness
- » Increasing malodour

Box 2. Risk factors for infection (Wounds UK, 2013)

- » Older age
- » Very young (neonatal)
- » Compromised immune system
- » Presence of certain chronic medical conditions (e.g. diabetes or circulatory disorders)
- » Smoking
- » Excessive alcohol consumption
- » Malnutrition
- » Medications (e.g. antibiotics, chemotherapy, antiplatelet drugs, glucocorticoid steroids, NSAIDs)

Conflict of Interest

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resistance (WHO, 2012). Although there appears to be a causal link between prescribed antibiotics and emerging resistance, there are many other factors that also play a role in the development of this resistance. While a blanket ban on antimicrobial use does not lend itself to practical treatment options, a more thoughtful approach to the choice and use of the available antimicrobial treatments can help stem the emergence of resistance.

TOPICAL METRONIDAZOLE

Metronidazole is an antibiotic that can be used to eliminate both anaerobic and aerobic bacteria. The gel is highly active against gram-positive and -negative bacteria and is the treatment of choice for anaerobic infections (Löfmark et al, 2010). A multicentre study found that the application of metronidazole gel significantly decreased the anaerobic organism colonisation of wounds ($p=0.0006$) (Findlay et al, 1996). It helps maintain a moist wound environment and is effective in tackling odour associated with infection (Kavitha et al, 2014). Many patients find malodour distressing; therefore the management of odour should be taken into consideration when devising a wound management plan.

The efficacy of topical metronidazole has been assessed in the treatment of a wide range of wounds. A literature review including 15 studies deduced that topical metronidazole generally resulted in the reduction or eradication of wound odour as well as a decrease in the volume of exudate, decrease in pain, improvement in wound appearance, decrease in surrounding cellulitis and the halting of tissue necrosis in various types of wound (Paul and Pieper, 2008).

A review by Lyvers and Elliott (2015) concluded that metronidazole – as a cream, gel, lotion or intravenous solution – is useful in the treatment of malodorous pressure ulcers. Of the 59 cases included in the review, 56 reported nearly complete resolution of odour 2–7 days after the initiation of treatment. Kavitha and colleagues (2014) advocate the use of metronidazole in the treatment of diabetic foot ulcers containing necrotic, sloughy or granulating tissue to promote autolysis and odour control. Findlay et al (1996) reported that by day 14 of their multicentre study,

the application of 0.75% metronidazole gel had led to a decrease in odour from 95% of malodorous benign and cancerous cutaneous ulcers. A smaller clinical study of 16 participants described similar results: at 2 weeks, all patients and investigators reported a significant decrease in wound odour following the application of 0.75% metronidazole gel, with 10 participants reporting no odour (Kalinski et al, 2005).

Findlay et al (1996) reported a significant reduction in the volume of discharge produced by wounds after 14 days of treatment with 0.75% metronidazole gel ($p<0.0001$). Kalinski and colleagues (2005) had similar findings, with a noticeable reduction in exudate from a variety of wounds after just two applications (48 hours) of topical metronidazole. This reduction in exudate persisted throughout the 2-week treatment period.

Various studies have shown that the application of topical metronidazole is associated with reduced wound pain and/or does not cause pain on application. For example, the patients in a multicentre trial reported significant reductions in pain after 2 weeks of treatment with 0.75% metronidazole gel (Finlay et al, 1996). Their median pain scores fell from 3.7 on day 1 to 2.0 on day 7 and had dropped to 1.0 on day 14. One study found that the application of topical metronidazole was not associated with any pain (Kalinski et al, 2005).

ANABACT: A BROAD AND COST-EFFECTIVE TREATMENT

Anabact Gel is an aqueous gel that contains 0.75% metronidazole. It is licensed for the treatment of malodorous gravitational ulcers (leg ulcers caused by varicose veins or resulting from deep vein thrombosis) and decubitus ulcers (otherwise known as pressure ulcers) as well as fungating tumours. It can therefore be prescribed for the management of a wide range of infected wounds.

The wound should be thoroughly cleaned before Anabact Gel is applied over all the affected tissue. The area should then be covered with a non-adherent dressing. The gel needs to be applied twice a day and progress reviewed at 2 weeks.

Table 1. Properties of topical antimicrobials (Lipsky and Hoey, 2009; Dumville et al, 2017; BNF, 2018)

Product	Spectrum of action	Advantages	Disadvantages	Indications
Bacitracin	Broad-spectrum activity against many gram-positive organisms	<ul style="list-style-type: none"> - Activity not impaired by blood, pus or necrotic tissue - No cross-resistance with other antibiotics - Minimal absorption 	<ul style="list-style-type: none"> - May cause reactions (allergic, anaphylactic, contact dermatitis) - Inactive against most gram-negative organisms - May lead to overgrowth of drug-resistant organisms including fungi 	Prevention of infection in minor skin wounds
Fusidic acid	Staphylococcus aureus, streptococci, corynebacteria and clostridia	<ul style="list-style-type: none"> - Penetrates intact and damaged skin plus crust and cellular debris 	<ul style="list-style-type: none"> - Requires 3 daily applications - May cause hypersensitivity reactions - Staphylococci resistance emerging 	Staphylococcal skin infection
Metronidazole	Many clinically-important anaerobic and some aerobic bacteria	<ul style="list-style-type: none"> - Reduces odour, exudate and inflammation associated with anaerobic and aerobic infections 	<ul style="list-style-type: none"> - Could drive resistance to systemic formulations - Requires 1–2 daily applications 	Malodorous fungating tumours, gravitational ulcers and decubitus ulcers*
Mupirocin	Gram-positive aerobes, some gram-negative aerobes (not Pseudomonas aeruginosa), corynebacteria, and obligate anaerobes	<ul style="list-style-type: none"> - Minimal potential for allergic reactions 	<ul style="list-style-type: none"> - Rare local burning and irritation - Polyethylene glycol can accumulate with repeat application in large wounds - Long-term use can cause staphylococci resistance, which is increasing 	Bacterial skin infections, particularly those caused by gram-positive organisms (except pseudomonal infection)
Neomycin	Gram-negative organisms (not Pseudomonas aeruginosa), some gram-positive bacteria	<ul style="list-style-type: none"> - Requires 1–3 daily applications - Low cost - May enhance re-epithelialisation 	<ul style="list-style-type: none"> - Caution required in large wounds, especially with azotaemia - Hypersensitivity reactions (1–6%) - Streptococci are generally resistant - Inactive against obligate anaerobes 	Bacterial skin infections
Retapamulin	Staphylococci (not MRSA), streptococci and some anaerobes	<ul style="list-style-type: none"> - May be active against some mupirocin-resistant Streptococcus aureus strains - Broader activity than mupirocin 	<ul style="list-style-type: none"> - May cause local irritation - Not effective against MRSA - Expensive 	Superficial bacterial skin infections caused by Staphylococcus aureus and Streptococcus pyogenes that are resistant to first-line topical antibacterials
Silver sulfadiazine	Many gram-positive and gram-negative organisms including Pseudomonas aeruginosa	<ul style="list-style-type: none"> - Requires 1–2 daily applications - Low rate of hypersensitivity reaction 	<ul style="list-style-type: none"> - Potential cross-reaction with other sulphonamides - Rarely causes skin staining 	Prophylaxis of infection in burn wounds, conservative management of finger-tip injuries, adjunct to short-term treatment of infection in pressure sores and leg ulcers, adjunct to prophylaxis of infection in skin graft donor sites and extensive abrasions

*Depending upon the formulation

There are no published studies supporting the use of topical erythromycin, clindamycin, aminoglycosides other than neomycin, gramicidin, or tetracyclines for treating chronically infected wounds.

Box 3. TIMES Framework (Wounds UK, 2017)

- ▶▶ T – Tissue, non-viable or deficient
- ▶▶ I – Infection/inflammation
- ▶▶ M – Moisture imbalance
- ▶▶ E – Edge of wound non-advancing or undermined
- ▶▶ S – Surrounding skin

Box 4. Ideal antimicrobial properties (Lipsky and Hoey, 2009; IWII, 2016)

- ▶▶ Properly targeted antimicrobial spectrum for the particular type of infected wound
- ▶▶ Rapid bactericidal activity
- ▶▶ Persistent or residual skin activity, allowing more infrequent dosing
- ▶▶ Activity in the presence of body fluids and proteins in wound exudate
- ▶▶ Low likelihood of inducing bacterial resistance
- ▶▶ Some local skin penetration but no systemic absorption
- ▶▶ No associated toxic (to host tissue) or allergic reactions
- ▶▶ Acceptable cosmetic and aesthetic qualities
- ▶▶ Low cost

Anabact Gel is up to 54% cheaper gram-for-gram than the market leader (C&D, 2018) and comes in three sizes (15g, 30g and 40g), which reduces waste. Prescribing this product could therefore lead to cost savings for the NHS and wound care budgets.

CONCLUSION

Topical metronidazole is effective in the reduction of odour, exudate and pain in patients with a wide variety of malodorous wounds. Anabact Gel is the only metronidazole formulation licensed for the treatment of leg and pressure ulcers and is a cost-effective option in the management of wounds with a foul odour. WUK

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