Does modern wound care need topical antimicrobials?

Bacterial influence is one of the most important factors in delayed healing, particularly in wounds that are healing by secondary intention. Best practice for controlling critical colonisation and infection has not been defined but systemic antibiotics are generally accepted as being the preferred choice for treating infection. These are given intravenously when infection spreads beyond the immediate wound margins with the potential for causing bacteraemia, and orally when infection is more localised.

However, the widespread use of antibiotics in all branches of healthcare over the past 60 years has led to increased resistance and now there is a global imperative to restrict their use in order to protect their viability for the care of future generations. Wound care is one health sector where this might be possible with the advent of topical antimicrobials in formulations better designed for application to open wounds than the earlier, sometimes cytotoxic, antiseptic solutions.

The recent inaugural meeting of the Wound Infection Institute in Budapest was an attempt to create a worldwide multidisciplinary forum to debate, educate, research and reach consensus on the understanding and treatment of wound infection. One of the hot topics from the workshops of that meeting was the use of topical antimicrobials and this debate continues this discussion. Both authors' area of expertise is in diabetic foot ulcers. AK

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Which topical microbials should be used in modern wound care for diabetic foot ulcers and why?

WJ: I have taken the word antimicrobial to refer to specific antibacterial agents, and have not considered antiseptics, or agents active against yeasts and fungi. The answers to these questions are all interlinked and, in particular, they are linked by the important fact that there is little scientific evidence to substantiate the use of topical antimicrobials in clinical practice. Topical agents may be effective and may be preferable to systemic therapy in some circumstances but we simply do not know. Evidence from randomised trials is urgently needed.

The key word in the question above is 'should'. It implies that there are right and wrong options, but there are none.

ME: Iodine, silver and mupirocin are potentially useful as antimicrobials in the diabetic foot ulcer. In vitro, iodine is effective against a wide spectrum of organisms. It comes in a variety of formulations including cadexomer iodine. Apelqvist and Tennvall (1996) compared its effectiveness using Iodosorb (Smith & Nephew, Hull) with standard dressings in diabetic patients with cavity ulcers of the foot. More ulcers healed completely in the cadexomer group by 12 weeks, but the difference was not significant (O'Meara et al, 2000).

Silver compounds have broad-spectrum antimicrobial actions against Gram-negative and Gram-positive organisms and they may be useful in the diabetic foot. However, a recent review of silver-based wound dressings and topical agents for treating diabetic foot ulcers found no suitable randomised or controlled clinical trials to evaluate their clinical effectiveness (Bergin et al, 2006). Mupirocin is active against Gram-positive infections including MRSA. To avoid the development of resistance, mupirocin should not be used for more than 10 days and should not be regarded as a prophylactic.

At the diabetic foot clinic at King's College Hospital, topical fusidic acid is not used because of concern of developing antibiotic resistance. We do not use neomycin because of the risk of sensitisation or topical metronidazole because if a wound in a diabetic patient has an odour suggestive of anaerobes, an oral or parenteral metronidazole is used. If it cannot be tolerated systemically, metronidazole gel could be used.

When should topical antimicrobials be used?

WJ: The simple answer is that, in the absence of scientific evidence, they could be used at any time that the clinician believes they may be beneficial. If the question was rephrased to read, When do *you* use topical antimicrobials? my answer would be:

- When a wound smells badly, suggesting significant colonisation or infection of more superficial layers by anaerobic bacteria, metronidazole gel can effectively eliminate the smell.
- When there is superficial colonisation by *Pseudomonas aeruginosa*. While I may rely simply on antiseptics such as iodine, I will also sometimes use silver sulphadiazine (Flamazine®) — more for the sulphadiazine than the silver.

WJ: *Topical agents may be effective and may be preferable to systemic therapy in some circumstances but we simply do not know. Evidence from randomised trials is urgently needed.*

ME: *Topical antimicrobials may be used in the neuropathic foot, but if any signs of infection are noted in the neuroischaemic foot, systemic therapy is probably indicated.*

I have used topical fusidic acid once on the recommendation of a plastic surgeon following forefoot amputation. I never use bacitracin or mupirocin on wounds, but would be interested to see evidence to suggest that I should.

ME: Many ulcers are colonised with a stable bacterial population. If the bacterial burden increases there will be bacterial imbalance and so-called critical colonisation may develop. This may show itself as increased exudate and the ulcer base may change from healthy pink granulations to yellowish or grey tissue. The ulcer may stop healing, and there may be an indication for the use of antimicrobials in these circumstances.

It is essential to differentiate between the neuropathic and the neuroischaemic foot as their overall prognosis is different. Infection in the neuroischaemic foot is often more serious than in the neuropathic foot which has a good arterial blood supply. Topical antimicrobials may thus be used in the neuropathic foot, but less readily in the neuroischaemic foot. If any signs of infection are noted in the neuroischaemic foot, systemic therapy is probably indicated.

Topical antibiotic preparation use is common in the USA but not in the UK — is either country right or wrong?

WJ: No, but the difference between the two cultures indicates that factors other than clinical science are involved.

ME: Some clinicians have considerable reservation for using topical antibiotics for foot ulcers. The presence of infection in a diabetic ulcer is a highly significant staging post on the road to amputation. Although amputation may result from severe ischaemia or gross deformity of Charcot's osteoarthropathy, this is rare and infection is usually the final stage before amputation. Thus infection should be treated aggressively and there is some doubt regarding the efficacy of topical antimicrobials.

Also, there are concerns about the effect of antimicrobials on the ulcer itself. They may be toxic to healing tissue and they may encourage development of resistance if used in low concentrations for a prolonged duration. They are also thought to predispose to sensitisation particularly to the associated preservatives. Furthermore, because of the risk of infection in diabetes, it may be preferable to keep the wound dry in the diabetic foot and avoid topical preparations that would moisten it.

It is common 'doctrine' not to use topical antibiotics for fear of inducing resistance but there is no clear evidence that this can be worse when using topical antimicrobials than systemic antimicrobials. Would it be reasonable to reconsider using multi-antibiotic gels/ointments for open wound environments and what are the issues and concerns involved?

WJ: I always understood that the main drawback of topical application (especially of penicillins) was adverse reaction rather than that of inducing resistance, but in the absence of firm evidence to incriminate modern products, I agree that it is reasonable to re-evaluate their use – as single agents in the first instance. If there is a logical reason for combining different agents of proven efficacy, then the clinical benefit of such combinations could also be explored. The issues are:

- Availability of different agents. It is worth noting that pexiganan, one of the few products of proven efficacy (Ge et al, 1999), is not in production.
- Investment by industry to enable the required studies to be undertaken
- Evidence of effectiveness
- Acceptability and adverse events
- Cost.

ME: It would be reasonable to consider their use in the diabetic foot ulcer. However, the indications for their use would need to be clearly defined. Questions to consider would include:

- In what type of infection would they be useful?
- Would they be indicated for so-called critical colonisation or definite classic infection of the ulcer?
- How deeply does their action penetrate into the ulcer? Would they only be useful for superficial infections of the ulcer and how would superficial be defined?

They would need to be non-toxic to keratinocytes and fibroblasts and not induce antimicrobial resistance.

In cases of local infection where there is a sudden onset of a limited ring or flare of cellulitis that is not spreading, is it appropriate to use a topical antimicrobial alone without a systemic antibiotic?

WJ: This is a valid question, and one which could and should be answered by a randomised controlled trial. We currently do not know the extent to which topical agents will be effective against limited bacterial invasion.

WJ: *Standard swabs are of limited value in determining the numbers and species of bacteria present should never be used in isolation to determine whether or not antibiotics should be given.*

ME: *Undiagnosed and untreated infection can destroy the diabetic foot in 24 hours, and the early warning signs of infection may be very subtle and masked by neuropathy or ischaemia.*

ME: Infection is the major problem of the diabetic foot. Undiagnosed and untreated infection can destroy the diabetic foot in 24 hours. The diabetic foot is complicated by the presence of neuropathy and ischaemia. The early warning signs of infection in the diabetic foot may be very subtle and masked by neuropathy or ischaemia, either or both of which may prevent evidence of Galen's signs and symptoms of rubor, calor, dolor and loss of function. Furthermore, diabetic patients are immunosuppressed. The neuropathy and ischaemia of the diabetic foot reduces local resistance to invading bacteria. Thus even a limited ring of cellulitis is significant and is an indication for systemic antibiotic therapy in patients with diabetes. Furthermore, antibiotics are prescribed even more readily for the diabetic neuroischaemic foot (as opposed to the neuropathic foot) as untreated infection often leads rapidly to necrosis and major amputation.

In open wounds it is understood that the greater the number of bacterial species (accepted pathogens or not) that can be identified on a standard swab, the greater the chance of delayed healing. Should we take weekly swabs to check species numbers until granulation tissue is evident and surface area reduction is well under way to inform the use of topical antimicrobials?

WJ: Standard swabs are of limited value in determining the numbers and species of bacteria present and the results should never be used in isolation to determine whether or not antibiotics should be given. Surface sampling is of value in defining the presence of, and antibiotic sensitivity of, certain robust organisms, such as *Staphylococcus aureus*, but it is otherwise a practice which is grossly overused.

The number of organisms present in or on a wound is primarily a feature of its chronicity; local ischaemia/tissue devitalisation; and previous antibiotic exposure. There are no data that I know of to indicate that the number of different species present on sampling is an independent predictor of the likelihood that any or all are contributing to delayed healing. There are similarly no data yet to show that the extent of colonisation by any one pathogenic species — as determined by quantitative or semi-quantitative microbiology — is associated with either delayed healing or subsequent clinical infection of diabetic foot ulcers. While few laboratories currently have the resources to undertake such studies, this question of the significance of the size of the bacterial burden is, however, a pretty fundamental one and could, and should, be addressed by properly designed studies.

The results of surface swabs should not, therefore, be used to determine the use of antimicrobials – whether administered topically or systemically. The only exception to this rule is the use of mupirocin for nasal carriage of MRSA. Available evidence is that colonisation of diabetic foot ulcers by MRSA (and other resistant organisms) is not, however, associated with a worse outcome and does not therefore require specific therapy (Hartemann-Heurtier et al, 2004) and should not influence antibiotic choice unless there is clinical evidence of infection.

ME: There is considerable controversy concerning the use of swabs in the diabetic foot. The importance of bacterial load as a predictor of healing in patients with diabetic foot ulcers was investigated in a small pilot study, in diabetic patients with no evidence of clinical infection (Browne et al, 2001). The authors demonstrated that if bacterial load in the ulcer was greater than 1.0×10^6 colony-forming units/g tissue, healing was impaired. Thus, taking weekly swabs may be useful but it is a very labour intensive approach. Quantitative microbiology is not carried out routinely. It may be possible to use swabs for this purpose but tissue specimens may be preferable, although more difficult to obtain especially in the diabetic neuroischaemic foot. However, this approach has great potential and needs further investigation. WUK

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