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A review of the microbiology, antibiotic usage and resistance in chronic skin wounds

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Chronic leg and foot wounds represent an increasing burden to healthcare systems as the age of the population increases. The deep dermal tissues of all chronic wounds harbour microorganisms, however, the precise interaction between microbes in the wounds and impaired healing is unknown. With regard to antibiotic therapy, there is a lack of evidence concerning its effectiveness, optimal regimens or clinical indications for treatment. Despite this lack of evidence, antibiotics are frequently a feature of the management of chronic wounds and these patients receive significantly more antibiotic prescriptions (both systemic and topical) than age and sex-matched patients. Current guidelines for antibiotic prescribing for such wounds are often based on expert opinion rather than scientific fact and may present difficulties in interpretation and implementation to the clinician. Although the increasing prevalence of antibiotic resistance is widely recognized, the relationships between antibiotic resistance, chronic wound microbiology and rationales for antibiotic therapy have yet to be determined. This review discusses the role of microbes in chronic wounds from a clinical perspective with particular focus on the occurrence of bacteria and their impact on such wounds. The evidence and role of antibiotics in the treatment of such wounds are outlined and current practice of antibiotic usage for chronic wounds in the primary care setting described. The implications of antibiotic usage with regard to antibiotic resistance are also considered.

Keywords: wound infection, wound healing, antibacterials

Introduction

Chronic leg and foot ulcers are non-healing wounds that occur due to a breakdown in the underlying physiology of the leg. This breakdown is frequently associated with venous, arterial or metabolic factors.[1] The wounds are a significant cause of morbidity; studies in the UK have estimated the point prevalence of leg and foot ulcers to be in the region of 1.48/1000 population[2] and there is clear evidence that prevalence increases with advancing age[2–4] with up to 36/1000 population in those over 65 years old.[5] The annual prevalence of venous leg ulcers alone has been estimated to be 1.69% in those aged 65 years and over.[6]

The role of microbes in chronic wounds

The impact of microorganisms on chronic wounds has been extensively studied and reviewed using different approaches to elicit their possible role in non-healing. These have ranged from highlighting the occurrence of particular species[7] or groups of organisms,[8] to assessing the impact of microbial populations on clinical outcomes.[9] In many cases, studies are difficult to compare due to the use of different methods of specimen collection and microbial analysis as well as differences in patient demographics and in the aetiology and infection status of ulcers.[10] In addition, clinical analyses tend to be limited in scope and based on assumptions regarding relative pathogenicity.

The microflora of leg and foot ulcers is usually polymicrobial and recent studies using molecular techniques have emphasized the complex ecology of these wounds.[11,12] Using conventional techniques, the mean number of bacterial species per ulcer has been found to range from 1.6 up to 4.4.[13–16] Hansson *et al.*[17] observed that 86% of ulcers with no clinical signs of infection contained more than one bacterial species.

Staphylococcus aureus and coagulase-negative staphylococci have been the predominant organisms isolated from both prospective, purpose-collected samples and retrospective analysis

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of clinical investigations. *S. aureus* has been reported in frequencies varying from 43% of infected leg ulcers[18] to 88% of non-infected leg ulcers[17] whereas *Staphylococcus epidermidis* has been reported in 14% of venous ulcer specimens[19] and 20.6% of diabetic foot ulcers (DFUs).[15] *Pseudomonas aeruginosa* is another frequently identified organism and has been found in 7–33% of ulcers.[14,17,20] A number of other aerobic species have also been reported, including *Escherichia coli*,[15,17–21] *Enterobacter cloacae*,[17–19,21] *Klebsiella* species,[15,17–19,21] *Streptococcus* species,[7,9,15–21] *Enterococcus* species[15–17,20,21] and *Proteus* species.[16–21] This is by no means an exhaustive list, but is illustrative of the range of aerobic bacteria that exist in chronic wounds.

In addition to aerobes, anaerobic organisms are frequently identified in wounds, albeit with considerable variation. Trengove *et al.*[22] found obligate anaerobes in one-quarter of chronic leg ulcer samples, whilst Ge *et al.*[21] found they constituted only 6% of DFU wound isolates. However, a focused study by Bowler & Davies[18] found anaerobes in 73% of non-infected leg ulcers and 82% of infected leg ulcers. The most common isolates found in both the infected and non-infected leg ulcers were *Peptostreptococcus* species and pigmented and non-pigmented *Prevotella/Porphyromonas* species.[18] *Finegoldia magna* (previously classified as *Peptostreptococcus magnus*) was found by Hansson *et al.*[17] to be present in 19.6%, and *Peptoniphilus asaccharolyticus* in 9.8% of non-infected venous leg ulcers. Kontiainen & Rinne[16] found that clinical swabs sent for analysis, presumably from infected or assumed infected wounds, yielded obligate anaerobic rods (mainly *Bacteroides* species) from 12% of ulcers and anaerobic cocci (peptostreptococci) from 8%. Ge *et al.*[21] found *Bacteroides*, *Peptostreptococcus* and *Prevotella* species to be the most frequently isolated obligate anaerobes in mild or moderately infected DFUs.

The continuity of the microbial profile of chronic wounds over time is unclear from the limited literature that has examined this issue. Hansson *et al.*[17] considered the microflora of chronic wounds to be a relatively stable entity having found that 90% of ulcers that were followed for 4 months, or until healing, contained at least one resident organism that was isolated from all monthly swabs. Furthermore, Gilchrist & Reed[23] considered chronic wounds to have stable microbial populations, following the observation that once a species was present, it generally remained so under hydrocolloid dressings, with the exception of the transient appearance of *P. aeruginosa*. However, closer examination of their data shows that 85% of wounds acquired new aerobes and 45% new anaerobes over the 8 week study period. Trengove *et al.*[22] logged the occurrence of new bacterial groups appearing in wounds after initial swabs had been taken. They found at least one new bacterial group present in subsequent swabs in 82% of patients, and thus concluded that the microbial populations of chronic wounds alter over time. Each of these studies suggests that although there may be a degree of stability for some microbial populations, the chronic wound appears to be a dynamic environment. However, there are to date no definitive studies of bacterial succession within chronic wounds, the influence of antibiotics on this succession, or of the interactions between bacterial succession and healing.

Infection status of chronic wounds

The interaction between ulcer and bacteria can be stratified into four levels: contamination, colonization, critical colonization and infection.[24] Whilst, contamination and colonization by microbes are not believed to inhibit healing, the line between colonization and infection can be difficult to define. The term 'critical colonization' has been used to describe the stage at which bacteria begin to adversely affect wound healing.[24] Moreover, the underlying pathogenesis of chronic wounds may result in wounds of different aetiologies being differently affected by bacteria.[20,25,26]

A range of clinical criteria have been used to define infection in chronic wounds. The Consensus Development Conference on Diabetic Foot Wound Care[27] agreed that a DFU should be considered infected when there are purulent secretions or the presence of two or more signs of inflammation (erythema, warmth, tenderness, heat, induration). Guidelines for the management of chronic venous leg ulcers produced by the British Association of Dermatologists and the Royal College of Physicians,[28] recommend that infection should be considered if one of the following is present: pyrexia, increased pain, increasing erythema of surrounding skin, lymphangitis or rapid increase in ulcer size. It is accepted that chronic wounds by their very nature may not always display the classic symptoms of infection (pain, erythema, oedema, heat and purulence) and it has been suggested that an expanded list, including signs specific to secondary wounds (such as serous exudate plus concurrent inflammation, delayed healing, discolouration of granulation tissue, friable granulation tissue, foul odour and wound breakdown) be employed to identify infection.[29]

Microbiologically, a critical bacterial load, synergic relationships between bacterial species and the presence of specific pathogens have all been proposed as indicators of infection. The presence of microbes *per se* is not indicative of wound infection. However, the possibility that a critical microbial load might directly affect the healing outcome in both acute and chronic wounds has been considered for several decades, with a direct relationship first being demonstrated by Bendy *et al.*[30] in 1964. Since then, work carried out by Robson[31] and others has led to the widely-held opinion that non-healing is associated with a bacterial load of more than 10^5 bacteria per gram of tissue.

The concept of bacterial synergy which recognizes the importance of interspecies interactions has been purported to occur in chronic wounds through studies such as that by Bowler & Davies.[18] They found the growth and pigmentation of some Gram-negative anaerobes to be enhanced by some facultative bacteria through the provision of an essential, unidentified growth factor. Furthermore, they found significantly greater numbers of anaerobes in infected ulcers compared with non-infected ones. The authors go on to argue that although enhanced virulence due to synergy between bacterial species has not been directly demonstrated in these wounds, there is evidence of it in other infections such as acute necrotizing soft tissue infections and hence it is likely to occur in the wound environment.

With regard to specific pathogens, beta-haemolytic streptococci,[7,31] *S. aureus*,[20] Enterobacteriaceae[20] and *Pseudomonas* species[20,22] have all been implicated as having potentially adverse effects on wound healing. The impact of these species may vary in different settings, for example, over 60% of arterial and diabetic ulcers colonized with *S. aureus* went on to develop an infection compared with only 20% of venous ulcers similarly colonized.[20]

In summary, microorganisms are identified in the deep tissue of all chronic wounds, yet the role they play and the impact of

specific species on wound longevity are unclear. The distinction between infected and colonized wounds has to be considered on a clinical basis and not by microbiological analysis due to the universal colonization of chronic wounds.[32] Microbial analysis can be of benefit when considered in concert with clinical observations to confirm causative organisms and their sensitivities,[33] and so enable refinement of antibiotic regimens.[32] Clinical diagnosis of infection can, however, also be problematic due to the nature of the wounds and this uncertainty may lead to the unnecessary use of antibiotics.

Antimicrobial treatment of chronic wounds

The evidence for antibiotic treatment

Whilst the mainstay of treatment of chronic wounds is designed to address the underlying causes, e.g. the use of compression bandages for venous leg ulcers, antibiotics are frequently prescribed to these patients. In 2000, O'Meara et al.[34] published a systematic review of wound care management, including the use of antimicrobial agents, with the objective of systematically assessing 'the clinical- and cost-effectiveness of systemic and topical antimicrobial agents in the prevention and healing of chronic wounds'. The inclusion criteria required studies to be randomized trials or prospective non-randomized trials with a concurrent control group. Only six studies examining the use of systemic antibiotics for chronic foot or leg ulcers met the review's inclusion criteria. Moreover, there were still many methodological problems with the included studies, for example only two had undertaken *a priori* sample size calculations. The six included studies also differed with regard to the aetiology of ulcers and their infection status. Two studies included only venous leg ulcers and two only diabetic foot ulcers, whereas the remaining two included ulcers of mixed aetiology. The inclusion/exclusion policy for wounds with clinical signs of infection was only clearly defined in two studies; as an inclusion criterion for one study and an exclusion criterion for the other. The outcome measure of all studies was, however, an objective measure of wound healing and not the resolution of infection.

Searching the literature generated since the publication of the O'Meara et al. report, two further relevant studies on systemic antibiotics in chronic wounds were identified. The search used extended search terms that covered systemic antibiotics, including generic names, and chronic wound terms of specific and non-specific aetiology. MESH headings and text were used, where appropriate, and the following databases searched: Medline, ISI Web of Science, EMBASE, CINAHL, Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, British Nursing Index and SIGLE. Only English language publications, from the years 2000 to 2004, that were randomized studies with a concurrent control group and clinical outcome were included.

The two studies identified in the updated search were by Lipsky et al.[35] and Siami et al.[36] Both of these included chronic ulcer patients as only one sub-group of the study population. Lipsky et al.[35] investigated the efficacy of linezolid compared with ampicillin-sulbactam/co-amoxiclav in the treatment of diabetic foot infections including infected ulcers. In this randomized study, no difference in efficacy between treatments was seen for all diabetic foot infections. However, when analysed by

diagnosis, infected ulcers ($n = 245$) had significantly higher clinical cure 15–21 days after completion of treatment with linezolid compared with aminopenicillin/beta-lactamase inhibitor (81% versus 68%, $P = 0.018$). Siami et al.[36] investigated the efficacy of clinafloxacin versus piperacillin–tazobactam in patients with a range of skin and soft tissue infections (including 76 patients with infected diabetic foot ulcerations) and failed to demonstrate any difference in the clinical cure rates 6–14 days post-therapy for evaluable diabetic foot patients ($n = 54$, 51.7% versus 48.0% for clinafloxacin and piperacillin–tazobactam, respectively).

The conclusion drawn by O'Meara et al.[34] concerning systemic antibiotics was that insufficient evidence exists for their use in wound healing, and until such data does, other criteria may be used to guide the use of antibiotics, such as cost minimization. In addition, our updated search of the literature found that conclusive studies regarding the use of systemic antibiotics have not been published in more recent years. Hutchinson et al.[37] also found inadequate data available to address the relative effectiveness of antibiotic regimens for serious diabetic foot infections including spreading cellulitis and osteomyelitis. They were also unable to find sufficient information to determine whether antibiotics are more effective than placebo for superficial or skin deep ulcers. There is also a lack of evidence regarding the optimal duration of treatment.[32]

Recommendations for antibiotic treatment

Numerous recommendations (based on expert opinion) exist regarding the use or avoidance of antibiotics for chronic skin wounds, and these differ according to ulcer aetiology. Importantly, there is a much lower tolerance of suspected infection in diabetic foot ulcers due to the risk of amputation and subsequent morbidity and mortality. Thus, the early use of antibiotics at signs of infection is generally advocated,[26,38] with some even advocating their use in uninfected ulcers.[39] In contrast, recommendations with regard to venous ulcers advocate antibiotic use solely in the presence of clinical signs or symptoms of infection.[28,40]

Highlighting the difficulties for the clinician, the International Working Group on the Diabetic Foot[41] recommends a complex antibiotic strategy which involves intravenous and/or possibly oral use of empirical broad-spectrum antibiotics in the presence of deep foot infections. The list of regimens suggested includes ampicillin/sulbactam, ticarcillin/clavulanate, co-amoxiclav, clindamycin and a quinolone, second or third generation cephalosporin and a quinolone, and metronidazole with a quinolone.[41] These guidelines are clearly difficult to interpret and implement in practice. The clinical guidelines on Type 2 diabetes by Hutchinson et al.[37] recommend only that ulcers with extensive cellulitis and/or osteomyelitis should be treated with intensive, systemic antibiotics. They comment that the polymicrobial nature of diabetic foot wounds would suggest use of a broad-spectrum antibiotic, but conclude that there is insufficient evidence to distinguish between the relative effectiveness of different antibiotic regimens. An update of these guidelines, by the UK National Institute for Clinical Excellence in 2004, is no more specific, recommending only that patients with non-healing or progressive ulcers with clinical signs of active infection receive intensive, systemic antibiotics.[42] The SIGN guidelines for chronic leg ulcers are equally general, again recommending that systemic antibiotics only be instituted when there is clinical

evidence of infection.[40] Guidelines from the British Association of Dermatologists and The Royal College of Physicians on the management of chronic venous leg ulcers recommend treatment with systemic penicillin upon ulcer infection with beta-haemolytic streptococci, whereas cellulitis caused by other organisms should be treated according to bacteriological sensitivity.[28]

Antibiotic use in clinical practice

Despite the scarcity of evidence supporting the effectiveness of antibiotics, they are still widely used in the treatment of chronic wounds. A Swedish audit showed 26.6% of chronic wound patients (leg and foot ulcers, pressure ulcers, post-operative and traumatic wounds which had not healed in 6 weeks) were receiving systemic antibiotics at the time of the study whereas a further 33.5% not receiving antibiotics at the time of the study, had done so in the previous 6 months. In total, therefore, 60.1% of chronic wound patients had received at least one antibiotic in the 6 month period.[43]

In the UK, investigation of the prescription of antibiotics for chronic wounds of all aetiologies in the community using the General Practice Morbidity Database for Wales (GPMD) for the year 2000 found that over two-thirds (68.3%) of patients with chronic wounds received at least one systemic antibiotic during the year, compared with less than one-third (29.4%) of age, sex and general-practice matched non-wound patients. Chronic wound patients received significantly more antibiotics than matched non-wound patients: means (range) of 2.3 (0–22) and 0.6 (0–14) antibiotic prescriptions per person per year, respectively (data in preparation).

Furthermore, the GPMD data showed those antibiotics prescribed significantly more frequently to chronic wound patients than non-wound, matched patients to be flucloxacillin, co-amoxiclav, cefaclor, cefalexin, erythromycin, trimethoprim, metronidazole and ciprofloxacin. In addition, significantly more flucloxacillin, co-amoxiclav and metronidazole were prescribed for chronic wound patients in chronic-wound-specific visits (i.e. visits for which the sole diagnosis or treatment recorded referred to a chronic wound) than the non-wound patients received for all visits.

Topical antimicrobials in wound care

The focus of this review is the use of systemic antibiotics in wound care. However, it is of interest to briefly comment on topical preparations with antimicrobial activity. These preparations include both topical antibacterials (for example, silver sulfadiazine, fusidic acid and metronidazole) and topical antiseptics (such as sodium chloride, chlorhexidine and povidone-iodine).[44]

Previous authors have commented that the use of topical preparations outweighs the available evidence and that this is an area which requires further study.[45] Studies in support of their use were found by O'Meara *et al.*[34] and in our updated search of the literature. O'Meara *et al.*[34] identified research of acceptable methodological standard that indicated the following may be beneficial to wound healing: allopurinol, dimethyl sulphoxide, silver sulfadiazine and silver zinc allantoinate cream. An initial improvement was also seen with both povidone-iodine hydrocolloid and silver-impregnated charcoal dressings, but neither of these maintained their advantage

until the end of the study periods. From our updated search of the literature (conducted as previously described for systemic antibiotics but using appropriate topical antibacterial and antiseptic terms), one recent study was found which provides further evidence in this area. Fumal *et al.*[46] investigated the effect of povidone-iodine, silver sulfadiazine and chlorhexidine digluconate on both the healing rate and histological properties of clinically non-infected chronic leg ulcers ($n = 51$). This open, randomized trial in which patients had two similar ulcers and acted as their own control found povidone-iodine solution to significantly increase ulcer healing rate at 6 weeks and significantly decrease time-to-healing compared with control. Silver sulfadiazine and chlorhexidine digluconate both showed slightly increased healing rates and decreased time-to-healing but neither showed significant improvement compared with the controls.

The benefit of topical antimicrobials may, theoretically, be due to their ability to deliver high local concentrations of antibiotic irrespective of vascular supply.[32] Further benefits which have been cited include the avoidance of adverse systemic effects,[32,47] and a low incidence of resistance.[47] However, others argue that topical antibiotics are a major driving force behind the development of antibiotic resistance.[48,49] There are also concerns regarding toxicity to human cells,[50] and sensitization, the incidence of which varies considerably between substances.[51]

Overall, published guidelines on the treatment of chronic wounds do not recommend the use of topical antimicrobials: guidelines for DFUs recommend only systemic antibiotics for infections,[41,42] and SIGN guidelines on the care of chronic leg ulcers specifically advise against the use of topical antimicrobials, as they are frequent sensitizers and have no effect on healing.[40] They do, however, state that short course metronidazole gel for odoriferous ulcers might be a possible exception.[40] Despite these guidelines, data from the GPMD suggest that topical antimicrobials are frequently prescribed to patients with chronic wounds. For example, patients with chronic wounds received 185 silver sulfadiazine and 223 topical metronidazole prescriptions per 1000 patients per year, compared with non-wound patients who received less than 5 prescriptions per 1000 patients per year for each of these compounds (data in preparation).

Antibiotic resistance and chronic wounds

Whilst the role of microorganisms in chronic wounds and the antibiotic treatment of chronic wounds have been discussed, their relationship with antibiotic resistance is an important public health issue which has yet to be fully investigated. The combination of increasing numbers of the population who are at risk of developing chronic wounds, together with the increasing prevalence of antibiotic resistance, makes this a highly pertinent issue. The polymicrobial nature of chronic wounds is likely to provide an appropriate environment for genetic exchange between bacteria. Indeed, the first two cases of vancomycin-resistant *S. aureus* in the United States were both isolated from chronic wound patients.[52,53]

It is hardly surprising that antibiotic-resistant organisms have been found to colonize and infect chronic wounds. Colsky *et al.*[54] found as many as half of all *S. aureus* isolates from hospitalized dermatology patients with leg ulcers to be methicillin-resistant

S. aureus (MRSA) and more than one-third of *P. aeruginosa* isolates to be resistant to ciprofloxacin. A study by Tentolouris *et al.*[13] in a diabetic foot clinic found 40% of *S. aureus* isolated from non-limb-threatening infected foot ulcers to be MRSA; giving MRSA a prevalence of 15% in all DFU patients with infected ulcers. Furthermore, there were significantly more MRSA isolates from patients who had received prior antibiotic therapy, compared with those that had not. A follow-up study, in the same clinic, identified a similar proportion of methicillin resistance in the *S. aureus* isolates, but showed that the prevalence of MRSA in foot ulcers had almost doubled over a 3 year period to 30% of all DFU patients with ulcer infection.[55] Ge *et al.*[21] investigated resistance in bacterial isolates from infected DFUs, from patients who had not received antibiotics during the previous fortnight, and found 12% of *S. aureus*, 46% of *S. epidermidis* and 45% of *S. haemolyticus* to be methicillin-resistant. They also found high levels of resistance to erythromycin in most species of Gram-positive organisms. The previously mentioned Swedish audit of all chronic wounds by Tammelin *et al.*[43] also found 12.5% of *S. aureus* isolates and 21.7% of *Pseudomonas* species isolates to be resistant to a clinically relevant antibiotic.

Different populations of wound patients can show wide variation in the level of antibiotic resistance encountered. For example, a prospective study of uninfected chronic venous leg ulcers from 66 patients who had received no antibiotics in the previous month identified very low levels of antibiotic resistance; only two patients were found to have MRSA [7.7% of those patients colonized with *S. aureus* ($n = 26$)].[11] In contrast, a separate, retrospective investigation of leg and foot ulcer swabs sent for analysis at the PHLS in Cardiff, from wounds presumed to be infected or having prolonged non-healing, demonstrated much higher levels of MRSA: 36% of patients with *S. aureus* (unpublished data). The underlying reason for these differences are unknown and could be multi-factorial, including such factors as prior antibiotic therapy and the level of contact with healthcare institutions.

Chronic wound patients are clearly a high-risk group for the acquisition, carriage and dissemination of antibiotic-resistant organisms. Day & Armstrong[56] reviewed the limited evidence on risk factors for the carriage of MRSA in diabetic foot wounds. While they found no studies that had directly addressed this issue, suggested risks include cross-contamination of wounds from the patients themselves, inanimate objects or health care personnel, long-term use of antibiotics, prior hospitalization and severity of illness (which may increase exposure to MRSA endemic environments, such as hospitals and nursing homes). The risk that wound patients carrying antibiotic-resistant organisms pose to others is also unknown. However, dressing changes alone have been shown to disperse significant numbers of bacteria into the air.[57] The extent of this dispersal varies according to the type of dressing involved and is slow to decline.[57] Wound patients are also clearly a group of patients who have a high level of contact with health care staff and could themselves act as a reservoir for cross-contamination. High prevalence of antibiotic resistance, especially MRSA, affects treatment decisions concerning wounds and raises the question of whether and when empirical regimens should cover these resistant organisms.[58] Whilst the additional impact of antibiotic-resistant organisms on wound healing is not known, overall, the morbidity, mortality and cost associated with infections in hospital patients caused by antibiotic-resistant

organisms has been shown to be 1.3- to 2-fold higher than infections caused by antibiotic-sensitive organisms.[59]

It is clear from the literature that expert opinion suggests that antibiotics have an important role to play in the treatment of clinically infected chronic wounds. However, there are no conclusive scientific studies to support antibiotic use, let alone those that might definitively guide antibiotic choice, dose and duration. The use of antibiotics is not risk-free for the individual with both the immediate risk associated with anaphylactic reactions[60] and the longer term prospect of antibiotic use making co-morbidities more difficult to treat. For example, the use of macrolides and metronidazole up to 10 years previously have, respectively, been associated with clarithromycin and metronidazole resistance in *Helicobacter pylori* isolates.[61] In addition, antibiotic resistance in the general population is a continuing and growing concern. The contribution made to the development, maintenance and dissemination of resistance by those antibiotics issued for chronic wounds is not yet known, although there is reason to believe that the chronic wound patient population may be of importance due to the high levels of antibiotic prescribing to these patients, the degree of microbial load associated with their lesions and the potential they provide for dissemination of resistant organisms to others. MRSA and other resistant organisms have been isolated from both infected and colonized chronic wounds, however, the true prevalence and impact on the wider community are, again, not known. Research needs to be undertaken to elicit the interactions between microbes, antibiotics and antibiotic resistance in chronic wounds for the benefit of both chronic wound patients and the population in general.

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