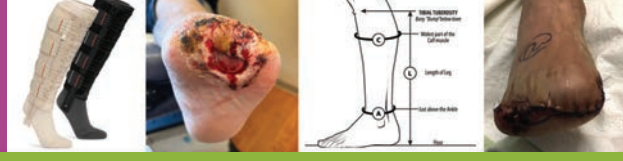

Antimicrobial Resistance and Stewardship in Wound Management

It's all about using the right antibiotic, for the right patient, at the right time, with the right dose, and the right route, causing the least harm to the patient and future patients.

BY WINDY COLE, DPM AND EMMA WOODMANSEY, PHD

Introduction

It has been well-established that control of bioburden is of utmost importance for wound management to be successful. Chronic wounds often have been open for many weeks, months, and sometime years. The longer a wound remains open, the greater the likelihood that the spectrum of wound bacteria will move in a trajectory of increasing severity (Figure 1).[1,2] If left unchecked, the number of bacteria in the tissue can reach pathological levels, tipping the scale from contamination to infection, leading to tissue destruction, abscess formation, and ultimately osteomyelitis.[1] In the case of spreading infections, these can rapidly lead to sepsis in elderly or immunocompromised patients.[3-5]

Even at lower levels, bacteria in wounded tissues can contribute to disruption of the healing cascade. The causation is multifactorial. Firstly, metabolically active bacteria compete with tissue cells for oxygen and nutrients that are essential in supporting the process of wound repair and regeneration.[6] Additionally, certain bacterial species generate exotoxins and endotoxins

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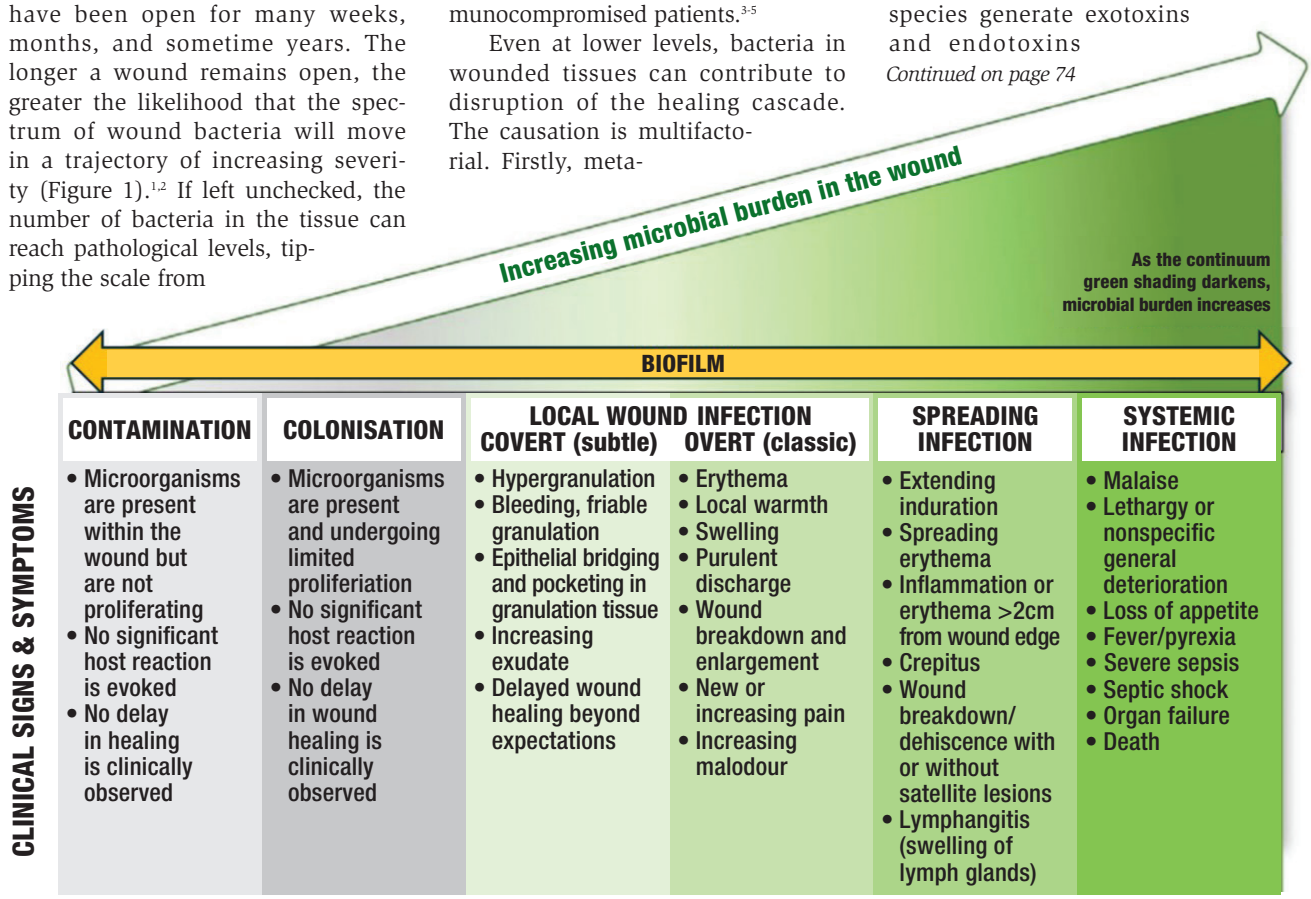
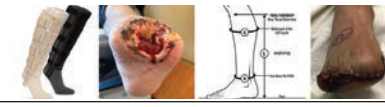


Figure 1: The wound infection continuum with the spectrum of microbial burden from least to most. Modified from IWII 2022[2]



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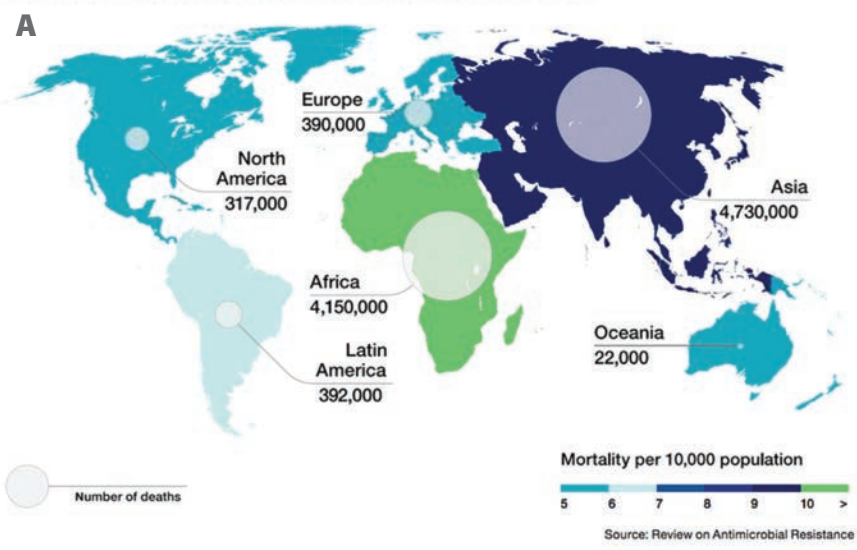
diffuse into the wound milieu. Bacterial endotoxins cause gram-negative sepsis, while exotoxins are peptides that are mostly secreted by Gram-positive bacteria.[7]

These antigenic substances are released at a constant low rate from inside bacteria with discharge levels increasing during bacterial cell lysis.[7] Additionally, these bacterial toxins can lead to dysregulation of immunity, and impairment of cellular functions such as collagen cross-linking and deposition potentially contribute to delayed wound healing.[7]

Matrix metalloproteinases (MMPs) are endopeptidases enzymes found in tissue. These substances are instrumental in wound healing. MMPs direct cell–cell and cell–matrix interactions through the release of cytokines, growth factors, and other biological active substances found in the extracellular matrix (ECM).[8]



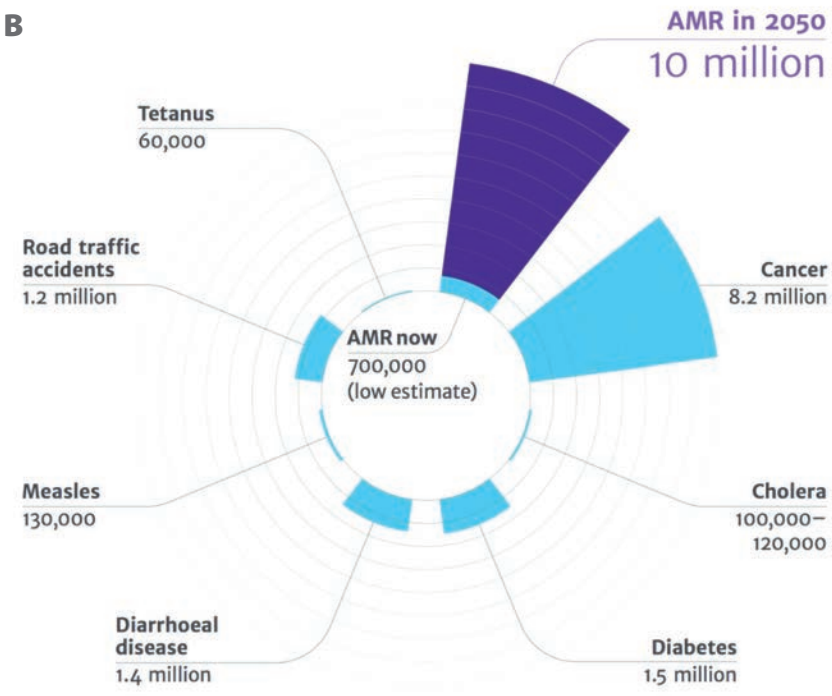


Figure 2: (A) Worldwide deaths attributed to AMR by the year 2050, (B) yearly deaths attributable to AMR by 2050 compared to other health conditions[18]

In acute wound healing, at controlled levels, MMPs are extremely beneficial but when dysregulation arises, tissue breakdown occurs, and development of a chronic wound ensues.[9] Additionally, bacterial pathogens can secrete proteases themselves, leading to further degradation of the ECM.[10]

The secret to MMP activity is the right type, in the right amount, at the right time. Therefore, controlling bacterial contamination can also help to regulate MMP production and prevent levels from tipping the scale toward destruction of healthy tissue.

Over 80% of non-healing chronic wounds contain a biofilm.[11] This is detrimental to wounds in two main ways—firstly due to the impact of the presence of biofilms on delayed wound healing[12,13] and secondly due to their ability to evade both the immune response and antimicrobial treatment.[14-16] Acute or planktonic infections are managed by systemic antibiotics and or topical antimicrobials; however, if biofilm is present, these treatments do not clear the residual tolerant biofilm bacteria, resulting in a reservoir for re-infection leading to frequent and recurrent infections.[17]

Given the deleterious effects that heavy bacterial loads can have on tissue health and wound healing, it's no wonder that HCPs routinely turn to antibiotics as a first line therapy in wound management. However, the frequent use of systemic antibiotic therapy has given rise to some rather serious long-term sequelae. Herein, the author will examine the current state of antimicrobial resistance in wound care and discuss the importance of including an antibiotic stewardship program as part of the wound care algorithm.

Antimicrobial Resistance (AMR)

The world is facing a crisis due to the rising rate of bacterial resistance as a direct result of the over-utilization of antibacterial agents.[18] Antibiotics, antivirals, antifungals, and antiparasitics are some of the most prescribed agents and have served as the cornerstone of modern medicine for decades. Due to indiscriminate and somewhat inappropriate overuti-

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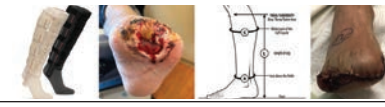

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lization of these agents, antimicrobial resistance (AMR) has become a growing concern worldwide. AMR is a result of genetic changes that occur in pathogens over time after repeated exposure to antimicrobial agents.[19]

Prior treatment with commonly-used antibiotics has been linked to increases in risk of developing infections.[22] Additionally, evidence exists that misuse of antibiotics can lead to an uptick in patient morbidity, extend the length of hospital stays, and increase overall healthcare costs.[20]

Worldwide deaths attributed to AMR are also on the rise with estimates reaching catastrophic levels in some nations by 2025 and are predicted to be far greater than many other causes of death such as road traffic accidents, diabetes, or even cancer by 2050—less than 30 years' time (Figure 2).[18]

In the presence of AMR, antimicrobial treatments can become ineffective, leading to infections that are recalcitrant, thus increasing the risk of disease spread and mortality. The looming tsunami that is AMR is creating the need for more potent and expensive drugs. But the pharmaceutical industry has not been able to keep up with this demand for the development of new antibiotics to expand treatment options in the face of resistant microbial infections. Thus, AMR has led to significant rising global healthcare costs.[20] AMR infections in the United States alone have an estimated cost of $55 billion/year—$20 billion for healthcare and $35 billion for loss of productivity.[18]

An analysis on data from outpatient center visits in 2014 noted that 266.1 million courses of antibiotics were dispensed from U.S. community pharmacies.[21] This equates to more than five prescriptions written each year for every six people in the United States alone, with Azithromycin and Amoxicillin among the most prescribed antibiotics.[21] This value was similar in 2022, with 236 million antibiotic prescription in outpatient settings (Figure 3).[22]

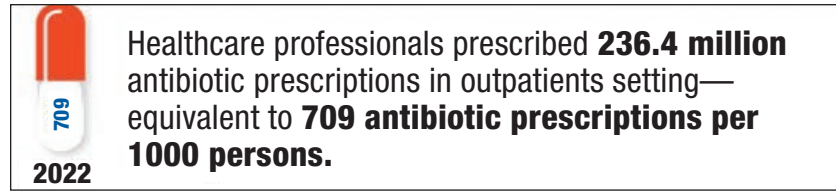

Figure 3: Number of outpatient antibiotic prescriptions in the United States, 2022[22]

Hard-to-heal wounds often remain open for many weeks or months; thus there is an inherent risk for bacterial levels to increase and infections to ensue.

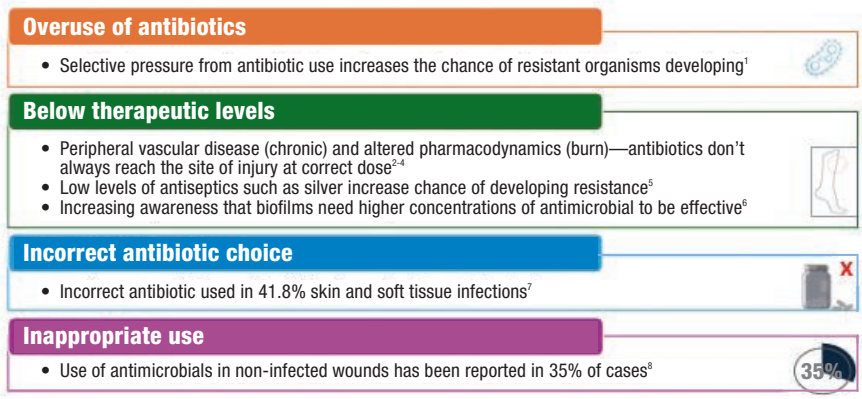

Figure 4: Reasons for increasing antimicrobial resistance in wounds[23,27-30,32-34]

Antimicrobial Use and Misuse in Wound Management

There are a number of reasons why antimicrobial resistance is increasing in wound care; these are discussed below and summarized in Figure 4.

The most obvious reason is the overuse of antibiotics, which leads to an increase in the selective pressure or the likelihood that bacteria can develop resistance to treatments.[23] Chronic wound patients seen in the outpatient care setting receive a greater number of antibiotic prescriptions when compared to their age- and gender-matched counterparts without wounds.[24] More specifically, studies have shown that 53.3% to 71% of patients with chronic wounds are prescribed at least one wound-related antibiotic at some point during their outpatient wound care journey.[25]

Hard-to-heal wounds often remain open for many weeks or months; thus there is an inherent risk for bacterial levels to increase and infections to ensue. Healthcare practitioners treating complex, chronic wounds may therefore use multiple rounds of oral and/or intravenous (IV) antibiotic therapy, although serial and prolonged courses of antibiotics can lead to the development of antimicrobial resistance, making subsequent wound infections increasingly difficult to treat.[23] Persistent and recurrent infections as a result of biofilm presence in chronic wounds,[11,26] further increase this cycle of repeated treatment due to their ability to evade both antimicrobial treatments and the immune response.[14-16]

Moreover, using antimicrobials or antibiotics at below an effective dose concentration allows microorganisms to survive and genetically change rapidly to resist the antimicrobials; this lower dose may be as a result of systemic antimicrobial treatments not reaching the site of infection at

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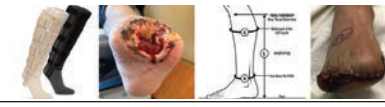

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the correct dose due to pharmacodynamic changes as seen following burn injury, or from reduced vascular supply to the site as seen in many chronic wound patients, or it may be as result of treatment with a level of antimicrobial in cleansers or dressings below effective levels.[3,27-32]

Empirical treatment based on best-guess as to the causative organism can lead to incorrect antibiotic choice. A recent study reporting more than 41% of skin and soft tissue infections received the incorrect antibiotic, highlighting the need for the mantra… start smart, then focus antimicrobial treatments once the causative organism is determined.[33]

The inappropriate use of antimicrobials in wounds when not indicated drives an increasing risk for developing AMR. The CDC has estimated that a minimum of 30% of prescribed antibiotics given in the outpatient setting are unnecessary.[35] Furthermore, a recent audit of infected wounds across northern Europe highlighted inconsistencies in appropriate treatment, with antimicrobial use in 35% of wounds even though they were considered not infected and conversely antibiotics not being used in 41% of wounds that were identified as infected.[34]

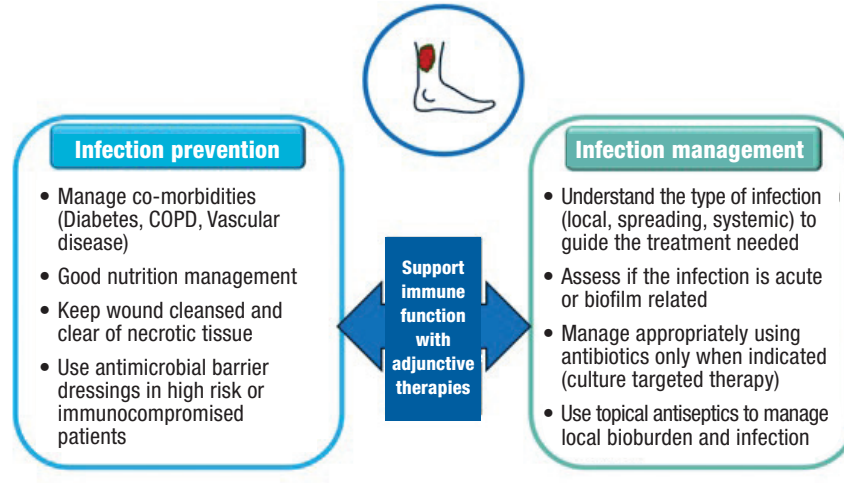

Figure 5: Infection prevention and management strategies incorporating appropriate antimicrobial use[92,3,23,26,40,42-45]

likely to be isolated from long-term care facilities than in the community. Interestingly, this data highlighted a shift in prevalence of the dominant causative organisms from Gram positive organisms such as MRSA, VRE, and Clostridium difficile in 1987 to MDR Pseudomonas aeruginosa, Acinetobacter baumannii, and Enterobacteriaceae producing extended spectrum beta lactamases (ESBL); and in 2015, highlighting the increasing issue of MDRO Gram negative species faced across healthcare.[37] Inappropriate prescribing of antimicrobials is one of the contributing factors to such findings but other factors, including advancing age (>70 years), presence of chronic wounds, implanted medical devices, and previous antibiotic use all are significant risk factors in development of MDR infection.[37]

Patients with a wound have an increased chance of developing an infection caused by resistant bacteria/fungi the longer the wound is open, and the larger the wound size.[36]

Appropriate Infection Management Strategies

Infection Prevention

Optimization of the wound environment through improving blood flow, controlling contributing co-morbidities, removal of necrotic tissue, maintaining a moist wound environment, off-loading, and managing bacterial levels in the tissues is the cornerstone of good wound management and can help to prevent infection developing (Figure 5).[40,41]

Antimicrobials should only be used prophylactically to prevent infection in wounds at high risk of contamination (i.e., contaminated/dirty surgical procedures) or when the patient has a high risk of infection such as with immunocompromised patients, for example, as a result of diabetes, immune disorders, or chemotherapy.[2,45]

Infection Management

Healthcare providers often rely on clinical signs and symptoms (Figure 1) to determine the presence of wound infection[2,42]; however, understanding of these is variable, which can cause confusion over when to use antimicrobial treatments.[34] Recent studies have also shown that clinical signs and symptoms are often unreliable markers of high bacterial presence, biofilm, and infection in chronic wound patients.[46] In this study, Le, et al. leveraged a fluorescence imaging device to identify wounds with bacterial load of >104 CFUs; in 85% of the wounds imaged clinical signs and symptoms did not correlate to the levels of bacteria seen with the validated imaging device.[46]

Moreover, clinical markers are somewhat difficult to ascertain in

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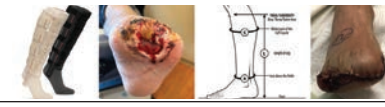

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certain patient populations such as the elderly, immunocompromised patients, and dark-skinned individuals as are those caused by low-level biofilm infection.[26,42,47,48]

Education and simplified tools to support HCPs identify these more subtle clinical signs of infection and are key to understanding when to intervene with antimicrobials. Current guidance advises, where possible, that heavy bacterial load and local infection should be managed locally with topical antimicrobials such as silver, iodine, and polyhexanide biguanide (PHMB). Systemic antibiotics should be reserved for treating spreading or systemic infections supported by topical antimicrobials to continue to tackle the infection locally.[2,3,42]

Antiseptics and Antimicrobials

The use of antiseptics to minimize surgical infections was recognized by Joseph Lister in 1868.[49] He used carbolic acid to reduce surgical wound infections such as gas gangrene. Today, many different antiseptics are available to health practitioners in a plethora of formats, including antiseptic cleansing solutions, gels, and antimicrobial dressings, to help minimize the spread of microorganisms.[2,44]

Antiseptics can be combined with novel delivery mechanisms or matrices to further support wound management and healing.

Antimicrobial dressings, if providing a sufficient (cidal) and sustained level of antimicrobial agent, can provide a barrier to ingress and egress of bacteria from a wound, specifically by killing the organisms before they can transfer through the dressing.[3,50] This is particularly important when culprit organisms are resistant to antibiotics in order to minimize spread from a colonized/infected wound to other health care workers or patients. Furthermore, some topical antimicrobial dressings have been shown to be effective against bacteria in biofilms,[51-54] which can minimize the impact on delayed healing and inflammation and break the cycle of recurrent infections posed by wound biofilms.[17]

Antiseptics can be combined with novel delivery mechanisms or matrices to further support wound management and healing. Cadexomer iodine, for example, consists of 0.9 w/w iodine within starch beads which physically expand on contact with exudate. This not only affords exudate absorption (up to seven times the weight of the beads) and sloughing action but also in turn allows the sustained availability of iodine proportionate to the wound exudate level, with the product changing color from brown to yellow/white when the antimicrobial is exhausted and needs changing.[51] This physical expansion is one of the proposed mechanisms responsible for the disruption observed with cadexomer iodine against biofilm structure.[51,52,54,55]

Another example is when antimicrobials are suspended in matrices. One such commercially available product (Puralply AM (PPAM) (Organogenesis Inc., Canton, MA) is composed of a native cross-linked extracellular matrix containing PHMB indicated for the management of chronic and acute ulcers of various etiologies. PPAM falls under the cellular and acellular matrix-like product (CAMP) category. The cross-linked type 1 collagen contained in PPAM is coated with PHMB. Published studies have shown that consistent use of PPAM may assist in the elimination and/or prevention of accumulation of bacterial bioburden and the possibility of biofilm formation/reformation.[56,57]

Alternatives to Traditional Antimicrobial Treatments in Wound Management

New adjunctive technologies and treatments are showing promising results as part of a wound management toolkit alongside topical antimicrobials and systemic antibiotics to further reduce the barriers of infection and support healing in chronic wounds. This is not a comprehensive list, but simply a cross section of therapeutics that are currently available or in various stages of research and development.

Topical oxygen therapy (TOT) is an umbrella term for several modalities for topically administering oxygen to wounds or ulcers to promote tissue healing.[58]

Topical Oxygen Therapy

Topical oxygen therapy (TOT) is an umbrella term for several modalities for topically administering oxygen to wounds or ulcers to promote tissue healing.[58] TOT is advocated as an adjunct to good standard of care when a hard-to-heal wound has failed to reduce in size by more than 40% to 50% within one month using good standard of care alone.[58,59] Moreover, TOT use is endorsed and recommended by international expert guidance including the IWGDF, WHS, and the ADA,[58-62] with potential benefits highlighted across any non-healing wound.[58,63,64]

Continuous Topical Oxygen Therapy (cTOT) is one form of TOT that delivers a continuous low flow of low-pressure oxygen to the wound, 24 hours a day, 7 days a week. A growing body of high-level evidence advocates the use of cTOT as a beneficial adjunct to wound healing in hypoxic wounds, with substantive meta-analysis and RCT level evidence in DFUs[65-71] supported by wider real-world evidence in DFU[72-76] and across other chronic wound etiolo-

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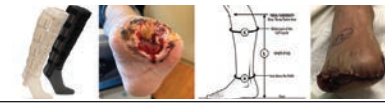

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gies, including leg ulcers (venous and arterial) and other traumatic or surgical non-healing chronic wounds.[77-81]

From an infection perspective, in addition to the impact on healing, oxygen plays an important role in the immune response in wounds, supporting immune cell activity, cell migration, and bacterial killing via the reactive oxygen species.[82] The production of nitric oxide is also oxygen dependent, and has increasing interest in its role in vasodilation and angiogenesis combined with an antimicrobial and antibiofilm effect.[82,83] Moreover, recent pre-clinical evidence investigating the effect of cTOT on biofilms has shown a direct impact on metabolism in bacterial biofilms,[84] in essence waking up biofilm bacteria form their state of hibernation, particularly towards the center of a biofilm structure, which may hold the potential to increase the susceptibility of biofilm bacteria to antibiotics.[85,86]

Cold atmospheric plasma therapy (CAP) is a new approach to wound management gaining interest around the world.

Fatty Acids

Throughout history, animal fats and vegetable oils products have been employed for medicinal purposes. Fatty acids (FAs) are membrane phospholipids having influence over the inflammatory response in tissues, thus aiding in skin structure integrity, tissue regeneration, and immunological status.[87] Fatty acids can control the invasion of microorganisms, decreasing the chance of tissue infection during wound repair.[88] In animal studies, essential fatty acids have been noted to support the essential elements of the wound healing cascade. Lania, et al. found that rat wounds treated with topical FA (sunflower oil) had higher IGF-1, a known mitogenic influence on keratinocytes, and increased IL-6 levels, a pro-inflammatory cytokine that resolves inflammation, than the control animals.[89] These healing qualities make FAs attractive agents for use in topical wound treatments.

A novel marine Omega FA containing multimodal wound matrix (OMC™), (Omeza, Sarasota, FL) has shown promise in decreasing bacterial contamination and supporting wound area reduction in patients with hard-to-heal wounds of varying etiologies. This anhydrous conformable wound matrix contains cold water-fish Omega FA peptides and other non-cytoxic components.

The potential biological effects of this omega fatty acid-containing wound matrix was evaluated as part of a small investigation into the utility in the treatment of chronic, hard-to-heal wounds of the lower extremity. This case series included one diabetic foot ulcer and two venous leg ulcers. The mean baseline wound age was 24 weeks with a mean baseline wound size of 8.61 cm2. The mean wound area reduction of all wounds in the 6-week observation period was 82%. The two VLUs healed during the study period. The TWAR of the DFU was 53% at 6-weeks when the patient was lost to follow-up due to a geographic relocation. Fluorescence imaging showed clearance of pathologic levels of bacterial contamination over the course of the study for all subjects.[90]

Chelating Agents

Transitional metals such as nickel, iron, zinc and manganese are micronutrients essential for the normal metabolic functions of all organisms. When the equilibrium of these essential metals is disrupted, physiological disorders such as microbial infection can ensue. Microorganisms such as fungi and bacteria must sequester metals from their host to manifest virulence.[91] Microbes produce specific chelating substances to aid in the uptake and transfer of essential metal from the environment or their host.[92]

Innate to the human immune system is the ability to segregate certain metal ions as a way of limiting bacterial growth and proliferation in a process referred to as nutritional immunity.[93] Although in patients with certain comorbidities and/or immunodeficiencies, the ability to disturb the metal metabolism of microorganisms may be attenuated.[93] Chronic wound patients may be particularly susceptible to infections due to their immunocompromised status. Thus, therapies that can mimic nutritional immunity could have significant value in this patient population.

Chelating agents have a high binding affinity to metal ions. Thus, wound care therapies containing chelants have emerged with utility in obstructing the vital biologic processes of planktonic bacteria. These agents work through the blockage and sequestration of metal ions, starving bacteria and other microorganisms of the metal ions they require for adhesion, cellular viability, growth, replication, and virulence.[94]

Ethylenediaminetetraacetic acid (EDTA) has shown antimicrobial/antibiofilm activity through chelation of calcium, magnesium, iron, and zinc to destabilize bacteria cell walls, leading to cell destruction.[95] Advanced wound dressings containing EDTA are commercially available. ColActive Plus (Hartmann USA, Rock Hill, SC) is a matrix product containing collagen, sodium alginate, carboxylmethylcellulose (CMC), and EDTA. The EDTA in the dressing removes zinc to inhibit the activity of bacteria and matrix metalloproteinases (MMPs), thus creating a suitable environment for wound healing.[96]

Cold Plasma

Cold atmospheric plasma therapy (CAP) is a new approach to wound management gaining interest around the world. Plasma, the fourth state of matter, is composed entirely or partially of ionized gas. Plasma is formed by breaking apart the gas molecules or detaching electrons from polyatomic and/or monoatomic gas.[97] Cold plasma has been used in the fields of medicine and agriculture

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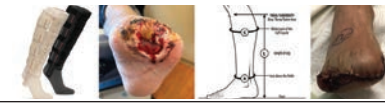

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as an antimicrobial agent. CAP potency is derived from its ability to inactivate cellular processes of bacteria through the generation of reactive oxygen and nitrogen species (RONS).[98] These RONS decompose the cellular envelop by lipid peroxidation, destroying the bacteria through oxidizing cellular proteins, nucleic acid, and carbohydrates.[98]

The robust inactivation of microorganisms created during cold plasma therapy has given rise to their increased utilization as an antimicrobial therapy.[99] Studies have shown that CAP has low cytotoxicity, demonstrating that direct exposure of plasma protects chronic wound tissue proliferation but terminates infection by destroying biofilm.[99]

Because of its non-invasive character, CAP has been praised and encouraged to be used in a range of therapeutic regimens, including chronic wounds with high levels of bacterial contamination.[100] Investigations by Maisch, et al. illustrated the successful use of CAP treatment to decolonize wounds containing methicillin-resistant Staphylococcus aureus (MRSA) and Escherichia coli without causing any tissue damage.[101]

Although wound care therapies that leverage CAP are in the early stages of development and scientific investigation, interest in this therapy has seemingly opened new doors in the area of wound management with its potential to tackle the significant challenge of antibiotic-resistant strains of bacteria.

Postbiotics

Postbiotics are defined as a "preparation of inanimate microorganisms and/or their components that confer a health benefit on the host". Also known as 'non-viable probiotics' or 'inactivated probiotics,' postbiotic agents may contain intact inanimate microbial cells, or cell fragments with or without metabolites.[102] The use of postbiotic agents has shown a positive impact on the maintenance of skin health by promoting the growth of beneficial bacteria and inhibiting the growth of harmful bacteria.[102] There is a growing amount of research being conducted into the potential application of postbiotics to other areas such as wound management.

While probiotics have shown to have benefit for accelerating skin le-

Figure 6: Essential steps toward antibiotic stewardship

sions in vitro, there are regulatory and safety concerns.[103] One of the main potential advantages of using postbiotic preparations in human therapeutics is that the microbial biomass is inanimate. Hence, postbiotic use is not constrained to the same health and safety measures that have been designed for products that include live microbes.

Recent research by Nam, et al. illustrated the positive impact of the postbiotic preparation of Lactococcus chungangensis on wound-healing in the context of diabetes mellitus.[104] It has been postulated that postbiotics can improve wound healing by modulating the inflammatory phase, increasing collagen and elastin deposition, limiting harmful bacteria levels, and enhancing angiogenesis.[104] Further research using supernates and lysates of various probiotic bacterial cultures have been shown in vitro to inhibit the growth of key wound pathogens such as Staphylococcus aureus, Streptococcus pyogenes and Pseudomonas aeruginosa and Acinetobacter baumannii, with some bacterial extracts reducing the toxicity of S. aureus and St. pyogenes against skin cells.[105]

Postbiotic application appears to be a promising strategy to decrease pathologic levels of bacteria in chronic wounds, but additional investigations are needed to fully understand the mechanism of action and utility across wound types.

Nitric Oxide

Nitric Oxide (NO) is a naturally occurring messenger molecule found in tissues that plays a crucial role in wound healing.[106] NO is instrumental in the regulation of three significant aspects of the wound healing process: inflammation, vascular homeostasis, and bacterial clearance. NO is also an agent with no known resistance.[107] This combination of effects has made NO a tantalizing contender as a treatment for emerging wound care therapies, especially for the treatment of diabetic foot ulcers. Alterations in NO production are often seen in the presence of diabetes. Low levels of NO in this patient population have been linked to impaired wound healing and the development of chronic wounds. Study evidence has shown that diabetic wound fluid has significantly lower levels of NO than healthy wound fluid.[108]

Dating back to the 1990s, the study of NO as a wound healing therapeutic focused on the generation of NO from both endogenous and exogenous sources.[109] The production of NO from endogenous sources has focused on L-arginine supplementa-

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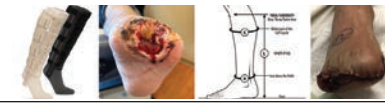

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tion, as L-arginine is the immediate precursor to NO production.[110] It has been postulated that the body cannot make adequate amounts of arginine during times of stress and tissue injury. Therefore, adding L-arginine as a dietary supplement to the low levels of endogenous stores could maximize NO production leading to improved wound repair and regeneration.[110]

Supplying exogenous NO to a chronic wound in its gaseous form either directly or through NO-releasing gels or dressings has also shown promise. In a published report, Schanuel, et al. used a combination of a NO-releasing hydrogel and film that produced enhanced wound contracture, improved collagen production, lower bacteria count, and a lessened inflammatory stage. The investigators concluded that due to the controlled manner of NO release, this combination of treatments had an additive beneficial effect on wound healing.[111]

A similar impact on wound healing was observed in a pilot study using a NO-producing dressing in DFUs versus standard care alone. A significantly improved wound area reduction in the NO dressing group at 12 weeks compared to current best clinical practice was reported.[112]

NO in various formats has shown promising antimicrobial and antibiofilm properties, making this a useful target molecule for infections management and wound healing, coupled with the fact that to date no antimicrobial resistance has been reported with this intervention.[83]

Understanding of the usefulness of NO as a wound healing therapeutic is still growing. There appears to be much variation in the level and delivery of NO to have the optimal benefit based on the route of administration and implementation.[83,113] Researchers are dedicated to gaining a true understanding of how best to harness the potential benefits of NO as a wound management therapy.

Antibiotic Stewardship Programs

Antibiotic stewardship (AMS) is a term used to describe "coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen,"[113] or put simply "The right antibiotic, for the right patient, at the right time, with the right dose, and the right route, causing the least harm to the patient and future patients".[114]

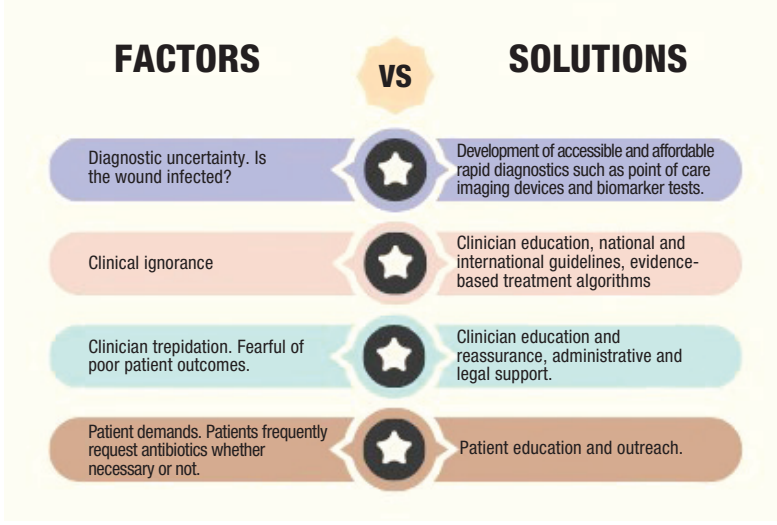

Figure 7: Key factors to address to tackle the misuse of antimicrobials in patients with wounds

Organized antimicrobial stewardship programs can offer concise, evidence-based guidance on the choice of antibiotic, dose, route of administration, and duration of treatment and should be an essential part of every medical facility including wound care centers. A systematic review and meta-analysis by Schuts, et al., illustrated that implementing Antimicrobial Stewardship Programs has been associated with reduced rates of antimicrobial use, decreases in antimicrobial resistance, lower infection rates, better clinical outcomes, attenuated hospital stays, and lower costs of care.[115] Essential steps toward antibiotic stewardship are illustrated in Figure 6.

Furthermore, establishing international AMS goals is an important step in driving change and preventing AMR globally. The World Health Organization (WHO) have published practical guidance on antimicrobial stewardship interventions incorporating clinician and patient education, directives on antibiotic use, and approvals and measures and audits to guide success.[116]

A comparison study conducted by Al-Omari and colleagues evaluated the results of implementing an AMS program in a large hospital system in Saudi Arabia.[117] The investigators compared a one-year baseline period prior to AMS implementation to a four-year follow-up after adoption of the AMS program, with a reported reduction in consumption and cost of several broad-spectrum antimicrobial agents. Additionally, lower incidence of healthcare-associated infections were reported throughout the hospital system.[117] Similar quality measures for antibiotic prescribing can be adopted by wound care clinicians, outpatient wound centers, and other wound care facilities to determine if antibiotic prescribing patterns meet appropriateness standards.

Variability in management of infected wounds highlights opportunities to aid more effective diagnosis and treatment. Wound care clinicians may struggle to determine when it is clinically appropriate to use various antimicrobials safely and effectively as there remains unclear guidance on antimicrobial use and accessible diagnostic tools in this space (Figure 7).

There is a growing need for systematic approaches to educate and support wound care providers in developing evidence-based guidelines for prescribing and administering antimicrobial therapies. Incorporation of support tools or evidence-based pathways into practice may enhance confidence in management of local infection, balanced with appropriate antimicrobial use, potentially minimizing resistance and improving outcomes.

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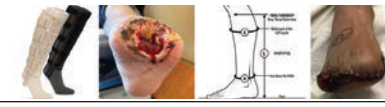

Antimicrobial Resistance *(from page 82)*

Conclusion

Antimicrobial resistance is a growing worldwide healthcare concern. There is a growing call to action for the development of formalized antimicrobial stewardship programs in all sectors of healthcare. Education around diagnosis is key across health professionals, especially as the relationship between the wound bacterial load and clinical signs of infection is not always clear-cut in hard-to-heal wounds. Furthermore, when there are no signs of infection in non-healing wounds, culturing and systemic antibiotic therapy are not recommended. However, clinicians should consider good wound bed preparation practices to reduce the microbial contamination and reduce biofilm communities, including wound debridement and topical evidenced-based topical antimicrobials.

The development of novel antimicrobial agents or interventions is of keen interest in the wound healing space to aid providers in improving the closure rates of microbial contaminated wounds. Future research should focus on furthering the development of alternative or adjunctive antimicrobial treatments in non-healing wounds and building evidence-based pathways that recognize the multi-faceted approach to infection management required in wound care. **PM**

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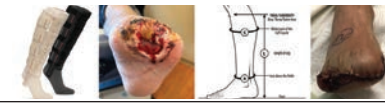

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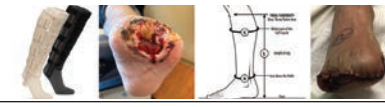

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Dr. Woodmansey is Global Clinical Director, Natrox Wound Care, Inotec AMD Ltd. She is a scientist with a positive, enthusiastic approach to delivery in the healthcare field and responsible for clinical and medical wound care strategy within a global medical devices company.