RESEARCH

The use of hypochlorous acid in an OXA-48 multiple drug-resistant *Enterobacteriacea*-infected lower leg wound – a case study

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Resistance among pathogenic bacteria to standard antimicrobial agents used for chemotherapy has emerged as a major public health concern globally and is expanding at an alarming rate. The problem is further compounded by the inappropriate and irrational use of antimicrobials, which has driven the emergence of multidrug-resistant (MDR) infection. Here, we present a case on OXA-48 *Klebsiella pneumoniae* wound infection, a carbapenemase-producing *Enterobacteriaceae* MDR Gram-negative bacteria that was treated successfully with hypochlorous acid gauze dressings retained with crepe bandages. This approach was successful in eradicating the OXA-48 infection, and further instrumental in the control of inflammation, which allowed the wound to heal completely within 60 days.

S Afr J Plast Reconstr Aesthet Surg Burns 2021;4(1):10-12. https://doi.org/10.7196/SAJPRASB.2021.v4i1.58

Of all antibiotics that are prescribed, 30% are unnecessary, according to the Centers for Disease Control and Prevention in the USA.[1] With extensive and often avoidable antibiotic use, an increasing number of bacterial strains have become antibiotic resistant, some to multiple drugs (multidrug-resistant; MDR).[2] An even more serious threat is the spread of Gram-negative pathogens that are resistant to essentially all available antibiotic drugs.[3] The slow pace of drug development necessitates careful stewardship of currently available antibiotics, and highlights the role of medical professionals to maximise the utility of available drugs.[4] Wound infections with MDR bacteria pose an ever-increasing challenge to the clinician, as the choice of antimicrobial drugs to treat these infections becomes more limited. Here we describe a case of wound infection that was successfully treated with hypochlorous acid (HOCl), thus limiting the use of antibiotics.

Case study

An 89-year-old female was admitted to the frail care centre of a retirement home with an inflamed open wound measuring 7 × 4 cm, after plate removal and debridement of her left ankle. A fracture repair was performed 2 months prior to admission, due to a fall at her place of residence. Her general medical examination revealed no signs of systemic sepsis. Initial care consisted of pain medication and absorbent dressings for a serosanguinous exudate that was present in the wound. Despite the wound care regimen, over the ensuing 15 days the wound area expanded in size to 13 × 4 cm, with an area of necrosis on the inferior part of the wound. A tissue sample was then taken for microscopy, culture and sensitivity. The culture revealed OXA-48 positive carbapenemase-producing *Klebsiella pneumoniae* (extended-spectrum beta-lactamase (ESBL) positive) that displayed multidrug resistance. The only antibiotic against which the organism demonstrated sensitivity was amikacin, an aminoglycoside antibiotic that is usually administered intravenously. As the frail care unit could not administer intravenous antibiotics, a decision was made to treat the wound with HOCl dressings. For the first 2 weeks these dressings were applied three times per week, and for the next 6 weeks, the dressing frequency was twice per week.

The dressing technique consisted of non-sterile clean gauze that was saturated thoroughly with Thoclor Labs Trifectiv Plus Wound and Burn Care HOCl 350 mg/L. The dressings were firmly applied to all areas of the wound, and dry gauzes were applied on top of the saturated gauze. No occlusive dressings were applied, as prior experience indicated that this usually causes maceration in the wound and surrounding tissue. For the first two dressing changes, the dried gauze was removed carefully from the wound to allow for any necrotic tissue that may be present in the wound to be removed by the gauze (wet-to-dry debridement). After the first dressing, the patient reported a significant reduction in pain and odour. Inflammation was reduced, and the quantity of wound exudate reduced significantly by the third dressing (after 1 week). Once the exudate had stopped, a single layer of Jelonet was applied directly onto the wound, followed by the Trifectiv-saturated gauze. This ensured that no discomfort occurred when the old dressing was removed. Complete healing occurred by day 60 (Fig. 1). Follow-up wound swab analysis revealed complete eradication of the OXA-48 *K. pneumoniae*, and that no other organisms were present.

Fig. 1 shows the infected ankle wound resulting from surgery to remove an ankle plate. After 15 days, the wound appeared septic and

Fig. 1. Progression of wound infection with OXA-48 positive carbapenemase-producing Klebsiella pneumoniae *wound infection and subsequent healing in an 89-year-old female.*

inflamed, with necrosis by day 0, when HOCl dressings were started. Thereafter, application of HOCl (3 × per week for the first 2 weeks, thereafter twice per week) resulted in a reduction of inflammation and resolution of the infection. The wound was mostly healed after 8 weeks of HOCl treatment.

Discussion

In order to provide a wound with the best environment to heal, it is important to eradicate bacterial infection and any bacterial biofilms, as well as remove all necrotic material, together with controlling inflammation.[5] Limiting and finally eradicating wound infection can be substantively undermined by infection with drug-resistant bacteria. New strains of drug resistance are regularly reported, and it is estimated that MDR bacteria cause up to 800 000 deaths per year worldwide.[6] Carbapenem-resistant *Enterobacteriaceae* (CRE) are Gram-negative bacteria resistant to the carbapenem class of antibiotics, which are considered the drugs of last resort for such infections. Resistance is mediated by an enzyme called a carbapenemase that inactivates the antibiotic, with phenotypic resistance ranging from moderate to severe. *Enterobacteriaceae* are common infectious bacteria and include *Escherichia coli*, *Klebsiella*, *Salmonella*, *Shigella* and *Yersinia pestis.* Experts fear CRE as the new 'superbug'.[7] Carbapenemase-producing *K. pneumoniae* bacteria are a group of emerging highly drug-resistant Gram-negative bacilli causing infections associated with significant morbidity and mortality.[8] First described in 2004 in Turkey, OXA-48 is a variant carbapenemase-producing *Enterobacteriaceae* (CPE) that has recently started to spread worldwide.[9] OXA-48 is a carbapenemase produced by a growing number of CPE isolates, and is of major concern owing to its difficulty in detection, association with treatment failure and high dissemination rate.[10,11]

A high level of OXA-48 resistance is associated with co-production of an ESBL.[12] If antiseptics are needed to control the microbiological load of the wound, these products should be effective in eradicating the wound infection, not cytotoxic to viable wound cells and not prone to the development of resistance against their use. Commonly used disinfectants such as povidone iodine, hydrogen peroxide, citric acid and chlorhexidine have all been reported to be cytotoxic.[13-16] As a result, these agents can have a negative effect on wound healing, and there has also been reported resistance to them.[17] Necrotic tissue itself also impairs healing, as it provides a rich growth environment for bacteria, increasing the chance of infection and so increasing inflammation in the wound. The tissue necrosis can be the result of long-standing infection, wound exposure to the environment, non-viable tissue, ischaemia or a result of trauma.

Hence it is essential that all necrotic material be removed from the wound, through either sharp or wet-to-dry dressing debridement, as the presence of non-viable tissue prevents the control of infection.[18]

HOCl is a naturally occurring, powerful oxidation/reduction agent[19] that is normally produced by white blood cells in the human body as the main ingredient used by the innate immune systems to destroy harmful micro-organisms. HOCl has strong microbiocidal properties that can be exploited for wound healing, as no long-term resistance against its use has been described.[19] Thoclor Labs Trifectiv Plus Wound and Burn Care HOCl has been demonstrated to have high bactericidal efficacy against a variety of organisms, including methicillin-resistant *Staphylococcus aureus*.[20] HOCl has a strong anti-inflammatory effect.[21] Excessive inflammation is at the centre of the process that leads to a delay in wound healing, and it is therefore essential that inflammation be kept under control during the healing phase.[22] HOCl modulates inflammation through its effect on nuclear factor kB and activator protein-1 of monocytes. It also has a strong inhibitory effect on interleukin-6, one of the main inflammatory cytokines.[21] The final effect of this is a reduction in pain and swelling, which promotes wound healing.[22] Thoclor Labs HOCl has also been proven to have no cytotoxic effect. The absence of any cytotoxic effect is an important component in its ability to promote healing in wounds.[23]

Conclusion

This case study demonstrates that it is possible to treat a severe antibiotic-resistant wound infection using Thoclor Labs' Trifectiv Plus Wound and Burn Care. Not only was the OXA-48 positive *K. pneumoniae* infection

successfully eradicated, but a simplified dressing regimen consisting of gauze, Trifectiv Plus Wound and Burn Care and crepe bandages proved highly effective in reducing inflammation. Wet-to-dry debridement for the first few dressing changes was instrumental in ridding the wound of necrotic material, which also facilitated infection control. In the absence of systemic sepsis, it is advisable to treat wound infection with a new generation of poly potential antiseptics such as Trifectiv Plus hypochlorous acid, which has been demonstrated not only to be bactericidal against MDR bacteria, but also to have no cytotoxicity effect on the cells of the wound. Furthermore, its strong anti-inflammatory effect is likely also an essential element in wound healing.

Acknowledgements. None.
Author contributions. HR: wrote manuscript; BK: scientific advisor; JN: clinician who treated case study.
Funding. None.
Conflicts of interest. HR is director: Trifectiv Pty Ltd; BK is scientific advisor to Trifectiv Pty Ltd.

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Accepted 1 February 2021.