

Challenging wounds, improving outcomes

Biofilm management with topical oxygen therapy

FOREWORD

Evidence has proven the positive effects of topical oxygen therapy on chronic, hard-to-heal wounds (Harding, 2016). It is becoming widely accepted that hard-to-heal wounds contain biofilm and that the presence of biofilm delays and/or prevents healing (WUWHS, 2016).

The aim of this document is to inform practitioners about the issue of biofilm and how it affects wound chronicity, as well as how topical oxygen therapy may help to resolve stalled healing. Evidence provided in this document suggests that topical oxygen therapy can help in the management of biofilm in chronic wounds.

EXPERT PANEL

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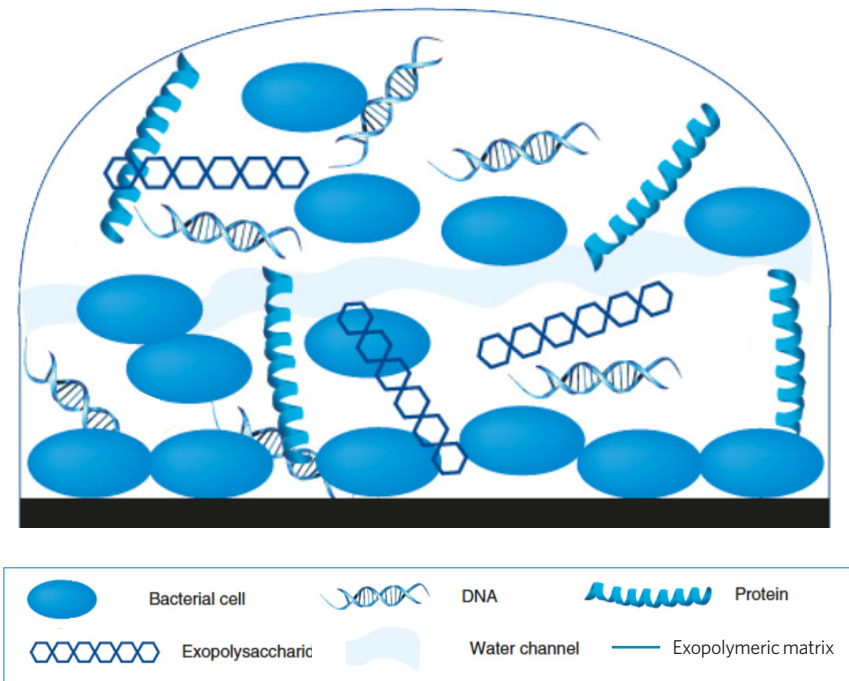
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WHAT IS BIOFILM?

The classic definition of biofilm is a structured community of bacteria growing on a surface. Biofilms are dynamic communities living within a protective, self-made matrix of sugars and proteins. The surface-associated nature of a biofilm induces changes in bacterial gene expression that differentiate biofilm from standard wound infection. Biofilms are characterised by significant tolerance to antibiotics and biocides, while remaining protected from host immunity (IWII, 2016). Biofilm formation can also be influenced by environmental factors, such as oxygen and nutrient availability (Maric & Vraneš, 2007).

Biofilm can start to form within hours, and mature within 2–4 days of initial colonisation, becoming very tightly attached to extracellular matrix components or the wound bed and making them difficult to remove by surface irrigation or superficial debridement (Swanson et al, 2014). As biofilm formation progresses, bacteria become increasingly resistant to antibiotics, antiseptics and disinfectants, making disruption and eradication difficult. While not all biofilms are 'bad', pathogenic biofilms are detrimental and delay wound healing.



Biofilm structure (adapted from Rabin et al, 2015)

BIOFILM AND WOUND CHRONICITY

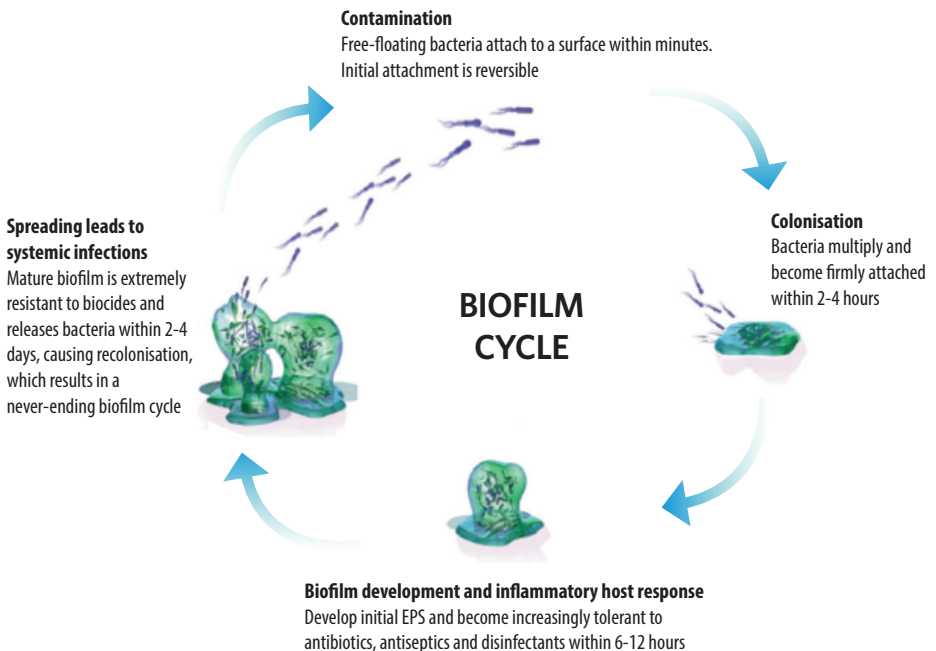
Pathogenic biofilm is a major barrier to wound healing. As such, biofilm is associated with wound chronicity and has been found to be present in the majority of chronic, non-healing wounds.

Estimates on the presence of biofilm vary, with current figures putting the presence of biofilm anywhere between 60 and 100% of non-healing wounds. It is thought that the 'true' prevalence is closer to 100% (WUWHs, 2016).

Traditional methods of biofilm eradication include:

- Debridement
- Antiseptics/topical antimicrobials
- Systemic antibiotics

However, biofilm removal (and preventing biofilm reformation) is notoriously difficult. The bacterial community residing in biofilm can be extremely resistant to antimicrobials, and even silver dressings have been found to be least effective on biofilm (Jamal et al, 2015). This means that novel solutions are needed, particularly given the increasing issue of antibiotic resistance.



HOW TO DETECT BIOFILM

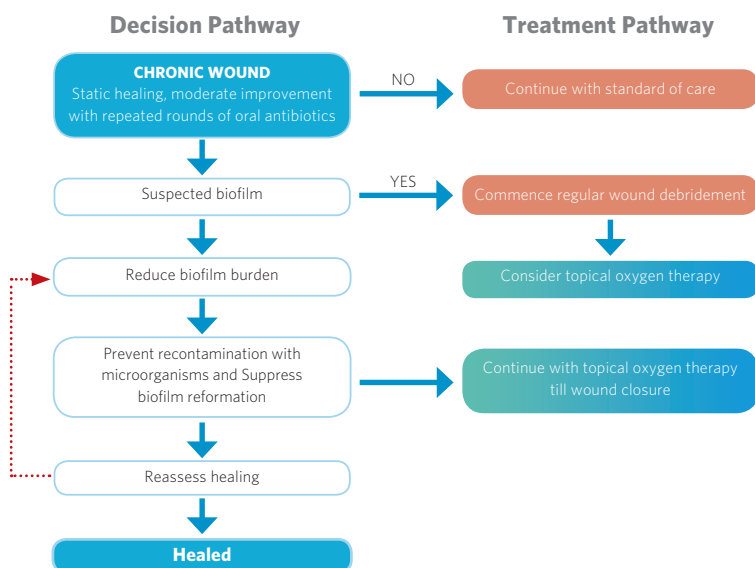
Biofilm is not visible to the naked eye and there is no reliable visual means for diagnosis. In practice, this means that identifying biofilm is often based on subjective clinical experience. Research on wound samples indicates that, while some wounds with biofilm may display common visual characteristics (e.g. a shiny or slimy wound surface), there is no conclusive visual indicator (IWII, 2016).

Biofilm-based infections are different from acute infections in that they may not induce characteristic signs of infection (temperature, redness, swelling, etc). Many wounds that appear to be healthy and 'uninfected' to the naked eye are shown via laboratory investigation to have biofilm present that contributes to stalled healing; biofilm can also form in deep wound tissue where it is not visible (IWII, 2016). While their clinical presentation is different, a biofilm-based infection is still pathogenic.

It therefore may be more helpful to consider biofilm in all chronic wounds where:

- Appropriate antimicrobial treatment has failed
- Healing is delayed despite optimal wound management and health support
- Granulation is poor or friable hypergranulation is present
- Low-level chronic inflammation, or increased exudate/moisture are present

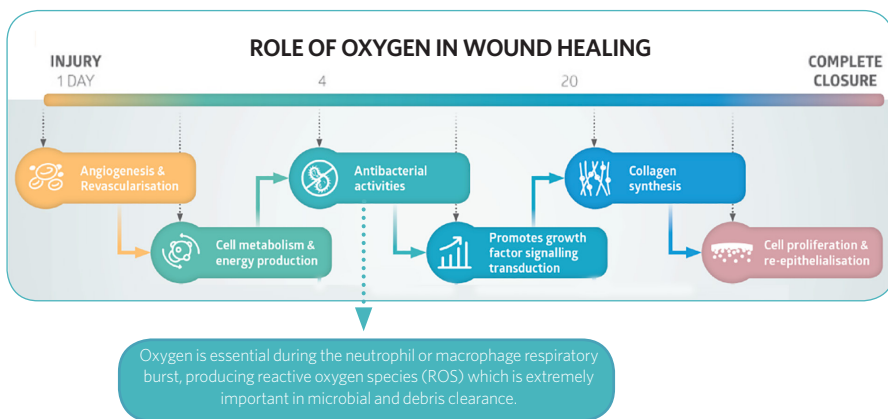
POTENTIAL BIOFILM MANAGEMENT STRATEGY



THE ROLE OF OXYGEN

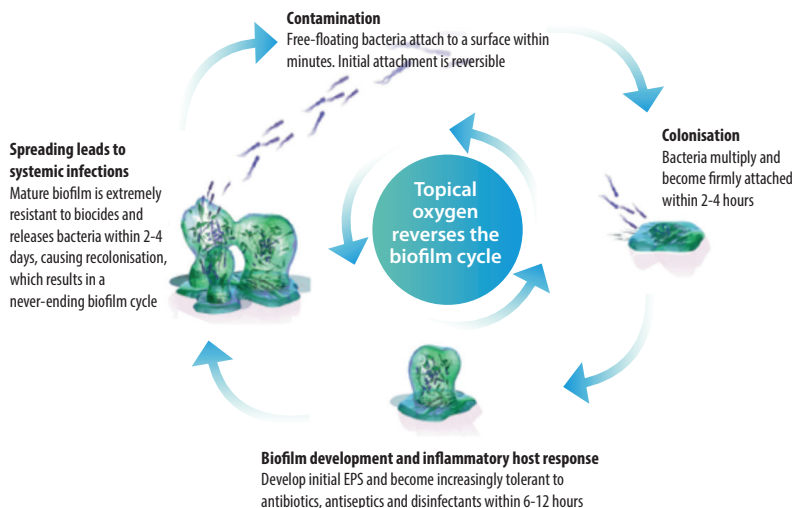
Oxygen is critical to all stages of wound healing, and hypoxia (lack of oxygen) has a significant impact on wound chronicity. Among the effects of hypoxia are reduced antimicrobial activity of phagocytes due to reduced ROS production (Wounds UK, 2017).

Low oxygen levels impair the ability of immune cells to generate the reactive oxygen species used to kill bacteria that colonise wounds, increasing the risk of biofilm formation. As they grow, bacteria also use oxygen and worsen hypoxia, creating a vicious circle of non-healing.



Chronic wounds with mature biofilm require additional measures to restore local oxygen balance.

THE POTENTIAL ROLE OF TOPICAL OXYGEN IN THE MANAGEMENT OF BIOFILMS



THE ROLE OF NATROX®

NATROX® Oxygen Wound Therapy (Inotec AMD Ltd) is an innovative, simple and lightweight device that has been clinically proven to deliver 98% pure humidified oxygen direct to the wound bed.

It has been proven to have a positive effect on healing in a variety of challenging and hard-to-heal chronic wounds. There is emerging evidence to suggest that this may be useful as part of a biofilm-based management pathway.

The device optimises treatment by providing an active therapy that can be maintained 24 hours a day, 7 days a week until the wound is healed. It is battery-operated, portable, discreet and silent, which enables the patient to continue with their daily activities with minimal disruption.



STUDY RESULTS

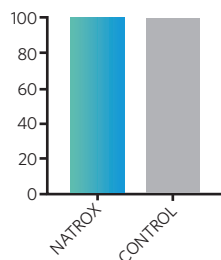
NATROX RCT

A recent randomised controlled trial (RCT) compared the effect of NATROX Oxygen Wound Therapy to standard best practice care in patients with non-healing diabetic foot ulcers (DFUs) (Yu et al, 2016). Two groups of patients were followed for 8 weeks, with one group receiving standard of care and the other treatment with NATROX. Both groups received weekly wound measurements.

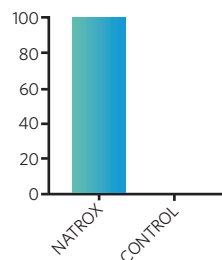
Ulcers were graded according to the University of Texas diabetic wound classification system, classified as grade 0–3. At baseline, groups were well matched in terms of wound size and demographics.

NATROX was found to have a positive effect on healing even the most severe chronic ulcers in the trial. The study found that Grade I ulcers are likely to heal with best practice standard of care. Adding NATROX therapy was found to make a significant difference in the healing of Grade II and III ulcers. Healing was found to be rapid, with significant improvements noted within 2 weeks.

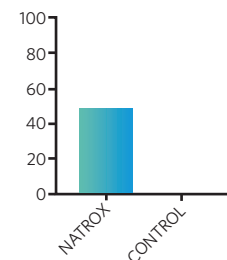
A: % of Healed Grade I Ulcers



B: % of Healed Grade II Ulcers



C: % of Healed Grade III Ulcers



■ NATROX ■ Control

NATROX BIOFILM STUDY

Having observed the rapid effect of NATROX on the wounds, follow-up research was carried out to assess the effect of topical oxygen on wound biofilm. Patients were recruited with a DFU that had been present for more than 4 weeks but less than 52 weeks. NATROX Oxygen Wound Therapy was added to their standard care. The wounds were photographed weekly and for swabbed for biofilm analysis by 16S rDNA sequencing. Bacterial relative abundance was determined for the most abundant 1% genera and classified according to respiratory habit.

In non-responders, the wound microbiome was found to be anaerobic and unchanging. However, in patients whose wounds healed, the wound microbiome changed over the course of NATROX therapy and transitioned into a flora dominated by aerobic genera.

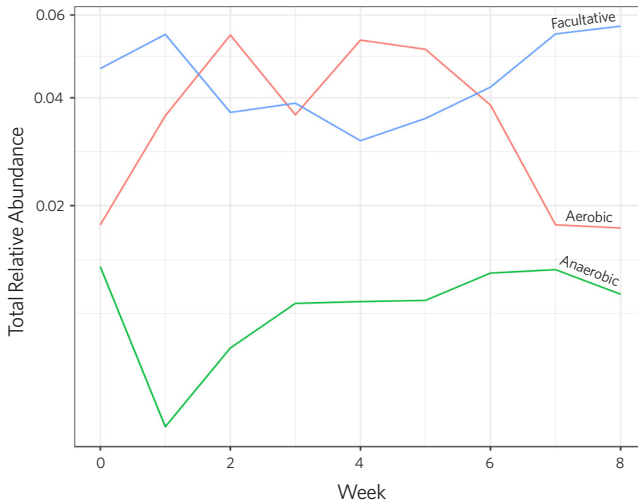
CLINICAL IMAGES OF RESPONDER



The wound on presentation



The wound at week 8



Sequencing analysis of wound biofilm genera over time, classified according to respiratory habit. There is an almost equal representation of aerobic and anaerobic genera at Time 0 (prior to application of Natrox), but topical oxygen causes a rapid increase in the number of aerobic genera found in wounds by week 2. Facultative anaerobes like *Staphylococcus* spp. are assumed to switch from anaerobic to aerobic respiration with the application of topical oxygen, such that their overall abundance in wounds does not change significantly over time.

TIPS IN PRACTICE

- If biofilm is suspected and the wound has not responded to standard of care (reduction in area by 40–50% after 4 weeks), consider treatment with NATROX.
- Within the first 2 weeks of NATROX treatment, exudate may increase. Dressing choice and dressing change frequency should be adjusted to account for this increase. After 2 weeks, exudate levels should reduce.
- The wound may also initially increase in size during the first 2 weeks of treatment, before becoming smaller and progressing to closure.
- It is vital to properly prepare the wound before treatment via a structured wound bed preparation regimen (e.g. TIME; Dowsett & Newton, 2005) in order to ensure the wound is adequately debrided, and to facilitate full contact between the device and the wound bed.
- It is important to protect the skin (e.g. from pressure damage). The tubing should be carefully positioned and may need to be cushioned, particularly in the early stages of treatment and when used in conjunction with offloading (i.e. in diabetic foot ulcers) or compression therapy (i.e. in venous leg ulcers).
- NATROX should not be used in conjunction with creams or similar topical treatments, as these can act as a barrier to oxygen absorption.
- After the wound has closed, it may be useful to consider continuing treatment for a short duration to ensure the skin has fully healed and to reduce risk of recurrence – it may be helpful to use the Leg Club model, which does not classify a wound as officially ‘healed’ until 2 weeks after wound closure, due to the fragility of the healed tissue (Lindsay, 2004). The Leg Club model relates to venous leg ulcers, but the concept may also be helpful in other chronic wound types.

SUMMARY

Biofilm has been found to be present in the vast majority of chronic wounds, and to be responsible for delayed or failed healing (WUWHS, 2016).

Topical oxygen therapy, particularly in a portable form capable of delivering continuous oxygen in a patient-friendly manner, has been found to be beneficial in treating hard-to-heal wounds and resolving stalled healing (Harding, 2016).

Evidence has suggested that using NATROX Oxygen Wound Therapy has a positive effect, not only on healing in hard-to-heal wounds, but on changing the wound environment to tackle biofilms. Therefore, NATROX may be beneficial in hard-to-heal wounds as part of a biofilm-based wound care regimen.

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