Slow-healing wounds have a negative impact on patient wellbeing, are challenging for clinicians to manage and are costly to the health economy (Frykberg and Banks, 2015). This guide discusses Woulgan® Bioactive Beta-Glucan (Woulgan), a new active healing treatment that has been shown to kick-start healing in slow-healing wounds. Woulgan contains the active ingredient 2% soluble beta-glucan, which has immuno-modulating properties beneficial to healing.

THE IMPACT OF SLOW WOUND HEALING: HEALTH ECONOMICS AND HUMAN COST
The financial burden of treating slow-healing wounds is significant; treating a wound costs on average between €6,000 and €10,000 per year (Posnett et al, 2009), and the annual NHS cost of managing wounds and associated comorbidities is around £5.3 billion (Guest et al, 2015). With an ageing population and rising incidence of comorbid conditions that induce wounds (e.g. diabetes, vascular disease, obesity), these costs are set to spiral.

It is well recognised that the majority of slow-healing wounds become stuck in the early stages of wound healing, known as the inflammatory phase. This prevents the wound from progressing to the proliferation/granulation phase (Gibson et al, 2009). Timely resolution of the inflammation phase is crucial for the wound healing process, thus reducing associated healthcare and human costs.

Slow-healing wounds are more likely to develop complications, which places a heavy demand on resources and significantly drives up the costs of treatment. Wound complications contribute to longer and more intensive treatment, extended hospital stays, readmission, and specialist medical or even surgical intervention (Dowsett, 2015). Delayed healing also has a great human cost, impairing health related quality of life – including physical, mental, psychosocial and spiritual/cultural wellbeing, and leading to lost productivity in the workplace (Dowsett, 2015).

Behind the science
Inflammation and macrophages
Biopsies from slow-healing wounds and animal models of delayed healing show characteristics such as a prolonged or stagnated inflammation phase. Because of this, inflammation is often perceived as the problem in wound healing, yet this is an oversimplification. While dampening the inflammatory response can, in some cases, benefit hard-to-heal wounds, new understanding of wound healing pathophysiology suggests the key step is the resolution (not the inhibition) of the inflammatory response and the transition into the proliferative phase. This transition relies on the pro-inflammatory macrophages.

Several publications have hypothesised that targeting macrophages in slow-healing wounds may be effective, as this cell type is central in the normal wound healing process and is key to resolving the inflammation phase rather than just suppressing it. Across the phases of wound healing, the presence of active macrophages is essential (Table 1). Macrophages provide signal molecules important for healing and orchestrating the wound-healing process (Brancato and Albina, 2011). They also boost host defences, remove dead cells, and support cell proliferation and tissue restoration after a wound occurs (Koh and DiPietro, 2011).

It is recognised that macrophages in elderly patients and diabetics do not function optimally, are less responsive to the environment and respond poorly to surrounding signal molecules. This contributes to a greater risk of slow-healing and chronic progression in this patient group.

INTRODUCING WOULGAN BIOACTIVE BETA-GLUCAN
A moist wound-healing environment has long been recognised as the foundation for optimal wound healing. Woulgan provides typical gel properties, being at least 80% water, thus offering a moist wound healing environment that rehydrates necrotic tissue and aids in autolytic debridement (King et al, 2017). Woulgan combines these properties with the medicinal substance soluble beta-glucan (SBG®), which has macrophage activating properties. SBG is extracted from Saccharomyces-cerevisiae (baker’s yeast), by a patented method (King et al, 2017). Thus, Woulgan enhances or reactivates slowed healing by stimulating the immune system, while at the same time contributing to a environment for moist wound healing (King et al, 2017).

WOULGAN AND MACROPHAGE ACTIVATION
The interaction between beta-glucans and cell-signalling to initiate the immune response is well documented in literature; however, beta-glucans are fairly new to the wound care field (Wounds UK, 2018). SBG has the ability to stimulate the immune system and activate white blood cells, in particular macrophages (Raa, 2015). In doing so, it has positive effects on angiogenesis, cell proliferation and wound contraction throughout the course

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SBG’s activation of white blood cells, primarily macrophages, results in:

- Increased phagocytic activity and killing of bacteria or other microbial organisms.
- Increased production and release of signalling molecules (cytokines) and growth factors that contribute to wound healing. This improves the function of macrophages, which coordinate various stages in the healing process (Wounds UK, 2018).

**M1 and M2 macrophages**

In the early phases of normal wound healing the macrophages display pro-inflammatory functions and are referred to as m1 macrophages. In the later stages, they alter their function, becoming more anti-inflammatory, and are then termed m2 macrophages. A consensus exists to suggest this transition from m1 to reparatory m2 macrophages is crucial for the resolution of the inflammation phase.

In chronic wounds the elevated number of dead inflammatory cells, debris and often the presence of bacteria, needs to be cleared in order for wounds to proceed to the next stage of healing. This is performed by m1 macrophages via phagocytosis. It is this process that triggers macrophages to switch phenotype, from m1 to m2, ensuring progress to the proliferation phase and orchestrating healing. When macrophages are activated by beta-glucan they will be more efficient in their phagocytic capabilities and bacterial killing, thus cleansing the wound of dead cells and pathogenic microbes. Activated macrophages from SBG stimulation are shown to express a range of cytokines and growth factors which support the cell proliferation, wound contraction, angiogenesis and deposition of the extracellular matrix, all associated with the later stages of wound healing and m2 macrophage functions. Thus beta-glucan contributes to a “good” and balanced inflammatory response rather than a detrimental one, ultimately leading to resolution of the inflammation and progression onto the later stages of the healing cascade.

**WOULGAN IN CLINICAL PRACTICE**

Woulgan is a treatment for both acute and chronic wounds where healing is slow, or is anticipated to be slower than normal, or is at high risk of becoming stalled (Box 1).

Woulgan is indicated for use in dry or medium-exuding, partial- or full-thickness wounds, including:

- Diabetic foot ulcers
- Leg ulcers
- Pressure ulcers
- Open post-operative wounds
- Partial thickness burns
- Graft and donor sites
- Abrasions and lacerations

**Table 1. The role of macrophages in the different wound-healing phases**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Cells involved</th>
<th>Function and activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemostasis</td>
<td>Platelets</td>
<td>Clotting</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Macrophages, Neutrophils</td>
<td>Tissue macrophages&lt;br&gt; • alarms and attracts neutrophils to wound bed&lt;br&gt; • phagocytise debris&lt;br&gt; • produce cytokines and growth factors</td>
</tr>
<tr>
<td>Proliferation</td>
<td>Macrophages, Fibroblasts, Myofibroblasts, Keratinocytes</td>
<td>Macrophages&lt;br&gt; • produce signal molecules for angiogenesis&lt;br&gt; • activate fibroblasts to collagen production&lt;br&gt; • attract and activate myofibroblasts for wound contraction&lt;br&gt; • produce growth factors for cell proliferation</td>
</tr>
<tr>
<td>Remodelling</td>
<td>Fibroblasts, Macrophages, Fibrocytes</td>
<td>Fibrocytes are “clones” of macrophages and fibroblasts, aiding collagen-tissue modulation</td>
</tr>
</tbody>
</table>

**Box 1. Checklist of wound conditions suitable for treatment with Woulgan**

- Dry to medium-exuding
- Partial- to full-thickness. Full-thickness wounds might not heal with secondary intention
- Fibrin – up to 75% of the wound surface can be covered with dry or moist fibrin. The gel properties will dissolve the fibrin
- Necrosis – the wound can be covered with up to 75% yellow or black necrotic tissue. Before applying Woulgan debride according to local practice
- Fistulas – Woulgan can be used in fistulas, although some fistulas will not heal without surgery
- Tendons and bones can be exposed. Woulgan will not harm these structures, but when tendon and bone are visible, the wound might not heal with secondary intention
- Undermining – can be present

**Box 2. Recognised indicators of slow-healing (Vowden, 2011)**

- Insufficient, no or negative change in size after 4 weeks of best practice optimal care (i.e. <50% reduction for DFUs, or a 20–40% reduction for VLUs)
- No or negative change in exudate
- No change or increase in slough
- No or negative change in pain
- No or negative change in quality of life
**USING WOULGAN: DECISION PATHWAY**

Clinicians should know when to escalate treatment in slow-healing wounds. The algorithm (Figure 1), developed by a UK expert working group, outlines a decision pathway for the timely use of Woulgan as an active therapy in the context of appropriate standard wound care (Wounds UK, 2018). It is recommended to initiate Woulgan treatment after 4 weeks if the response to optimal standard care is not satisfactory. For patients or wounds at high risk of delayed healing at initial assessment (e.g. immunosuppressed patients, or patients with obesity or diabetes), Woulgan may be considered earlier. For patients with poorly perfused wounds or other underlying conditions, these should be identified and addressed appropriately before Woulgan is initiated. Thereafter, the patient and wound should be assessed every 4 weeks (Frykberg and Banks, 2015).

**Three courses of action may follow assessment (Wounds UK, 2018):**

1. If improvements are evident, initiate a second 4-week period or until healed. After 8 weeks of Woulgan treatment, assess healing and return to standard of care if appropriate.
2. If the healing slows or plateaus again, start another 4-week period of Woulgan treatment, assess and continue if improvements are seen on next assessment.
3. If no improvements are seen or the wound deteriorates, Woulgan treatment should be discontinued. Assess possible reasons for deterioration – e.g. patient condition, clinical infection, changes in use of compression/off-loading/use of cleansing agents or cover dressings.

**EVIDENCE FOR USE**

SBG has been found to have a significantly positive effect in the treatment of diabetic foot ulcers, leading to significantly increased healing compared to control (See Figure 2; Zykova, 2014). A real world clinical evaluation of 300 patients with mixed aetiology ulcer wounds found 24-week healing rates of 92% (Woulgan) versus for 46% (standard care) (Hunt, 2018). Furthermore, the mode of action of SBG in Woulgan has been investigated in several diabetic mouse models. Overall healing, angiogenesis, cell proliferation and wound contraction outcomes were studied and compared to placebo. SBG had positive effects on all the studied parameters and significantly outperformed existing products in this mouse model. The enhanced cell proliferation and angiogenesis may be explained by activation of macrophages by SBG stimulation (Table 3).

**BENEFITS OF TREATMENT WITH WOULGAN**

**Cost savings**

Economic modelling (Zykova, 2014) shows using Woulgan results in significant savings vs standard care (Table 2). Because Woulgan is intended for use on hard-to-heal and slow-healing wounds, the long-term savings could be even greater (Hunt, 2018).
Patient considerations

Hard-to-heal and slow-healing wounds can have a devastating impact on patient well-being and quality of life. While the ultimate goal for patients may be long-term healing, in the short-term they may be more preoccupied with reducing symptoms that impair health-related quality of life, such as pain, malodour, or inability to perform usual daily activities (Wounds International, 2012). Patients who cannot maintain or increase activity levels may see their wound status deteriorate (e.g. where mobility is part of managing co-morbid conditions) and need additional costly treatments. Prolonged and escalated care is associated with anxiety and depression and low patient adherence (Wounds International, 2012).

CONCLUSION

There is a developing body of pre-clinical and clinical evidence for the role of SBG in wound care (Table 3). Woulgan offers a way to ‘re-start’ macrophage activity and move wounds trapped in the inflammation phase into the proliferation stage. Woulgan is a clinically and cost-effective active therapy for slow-healing wounds (Cutting et al, 2017), and as such, it is included in the NHS Drug Tariff.

Table 3. Clinical experience with Woulgan for different wound types

<table>
<thead>
<tr>
<th>Description</th>
<th>DFUs</th>
<th>LUs</th>
<th>PUs</th>
<th>Other</th>
<th>Published (✔/✘)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised, comparator trial; 60 pts</td>
<td>✔</td>
<td></td>
<td></td>
<td>✔</td>
<td>Zykova et al, 2014</td>
</tr>
<tr>
<td>Trial with control arm, UK; 300 pts</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>Hunt, 2018</td>
</tr>
<tr>
<td>Randomised controlled trial, UK; 42 pts</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Case series, UK; 39 pts</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>King et al, 2017</td>
</tr>
<tr>
<td>Case series, UK; 2 pts</td>
<td></td>
<td></td>
<td></td>
<td>✔</td>
<td>Welch, 2014</td>
</tr>
<tr>
<td>Case series, Nordic countries; 30-40 pts</td>
<td></td>
<td></td>
<td></td>
<td>✔</td>
<td>Predota-Glowacka and Hartin, 2018; Håland et al, 2018</td>
</tr>
<tr>
<td>Survey, UK and Germany; 150 pts</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>Oral presentation at Pareto Health Care Seminar 2015</td>
</tr>
<tr>
<td>Online survey, Norway; 58 pts</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td></td>
<td>Oral presentation at NiFS 2015; Engstad and Skjaeveland, 2015</td>
</tr>
<tr>
<td>PMCF study with control arm; 80pts</td>
<td></td>
<td>✔</td>
<td></td>
<td></td>
<td>✔</td>
</tr>
</tbody>
</table>

DFU = diabetic foot ulcer; LU = leg ulcer; PMCF = post market clinical follow up; pts = patients; PU = pressure ulcer.

REFERENCES

Hunt SD (2018) J Wound Care 27(9): 620-30