Appropriate use of soluble beta-glucan in the management of slow-healing wounds: round table recommendations

KEY WORDS
- Advanced therapies
- Immunomodulation
- Macrophages
- Slow-healing wounds
- Soluble beta-glucan
- Stalled wounds

Slow-healing, chronic 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). Woulgan is a newly available wound care gel containing the active ingredient 2% soluble beta-glucan. Beta-glucan has immunomodulating properties and has been shown to kick-start the healing of slow-healing wounds. A working group of key opinion leaders met in January 2018 to determine the potential role of Woulgan gel in slow-healing wounds, such as diabetic foot ulcers, pressure ulcers and venous leg ulcers, and to develop a decision pathway for clinical practice to support clinicians in escalating treatment promptly to avoid unnecessary impact on patient wellbeing and costs. The group's consensus recommendations on appropriate use are presented here.

JACQUI FLETCHER (CHAIR)
Independent Nurse Consultant

SIMON BARRETT
Humber Teaching NHS Foundation Trust, East Riding of Yorkshire and North Yorkshire

LYNNE HEPWORTH
Tissue Viability Nurse, South West Yorkshire Partnership Foundation Trust, West Yorkshire

DUNCAN STANG
Podiatrist and National Diabetes Foot Co-ordinator, NHS Lanarkshire, Lanarkshire

JOY TICKLE
Tissue Viability Nurse Specialist, Shropshire Community Health NHS Trust, Shropshire

ROS THOMAS
Deputy Head of Podiatry, ABMULHB, Morriston Hospital in Swansea, Wales

DONNA WELCH
Principal Podiatrist Diabetes at City Health Care Partnership CIC Hull

The NHS cost of treating chronic or slow-healing wounds and associated comorbidities is £5.3 billion per annum (Guest et al, 2015), and wound healing demands are predicted to rise with an increasing older population with long-term conditions and more complex needs (Dowsett, 2015a). The increasing economic cost of chronic wounds is due to hospital and facility costs (such as specialist care, diagnostics and treatment) and associated healthcare professional time. The economic burden of slow-healing wounds also extends to patient costs in terms of out-of-pocket payments (e.g. travel) and lost productivity if they can no longer work because of their wound (Wounds International, 2013; Dowsett, 2015a). Slow-healing wounds also have a negative impact on health-related quality of life (e.g. physical, mental, psychosocial and spiritual/cultural wellbeing; Wounds International, 2012) as patients may require increased care and support, becoming more dependent on healthcare time (Dowsett, 2015a).

Careful initial assessment and repeated evaluation of therapy are needed to recognise and assess the factors relating to the complexities of wound healing (Brambilla et al, 2015). It is well-established that wound healing is complex and multi-factorial (Brambilla et al, 2015): there can be patient factors (e.g. comorbidities, complications, medication and self-care delaying access to specialist care), wound factors (e.g. size, duration, location, infection), factors relating to clinical service delivery (e.g. competency of the healthcare professional), and various biophysiological factors (Vowden, 2011).

It can be a challenge to initiate effective therapeutic strategies in a timely and cost-effective manner to manage the patient's symptoms and expectations and achieve healing. Part of an effective strategy is to understand when wound progress is slower than expected and escalation of an advanced treatment alongside optimal care is required.

Woulgan is a wound care gel containing 2% soluble beta-glucan (SBG), which has immunomodulating properties and has been shown to kick-start the healing of slow-healing wounds (Skjæveland and Engstad, 2013). This article considers the round table recommendations for the use of Woulgan of key opinion leaders in the UK.

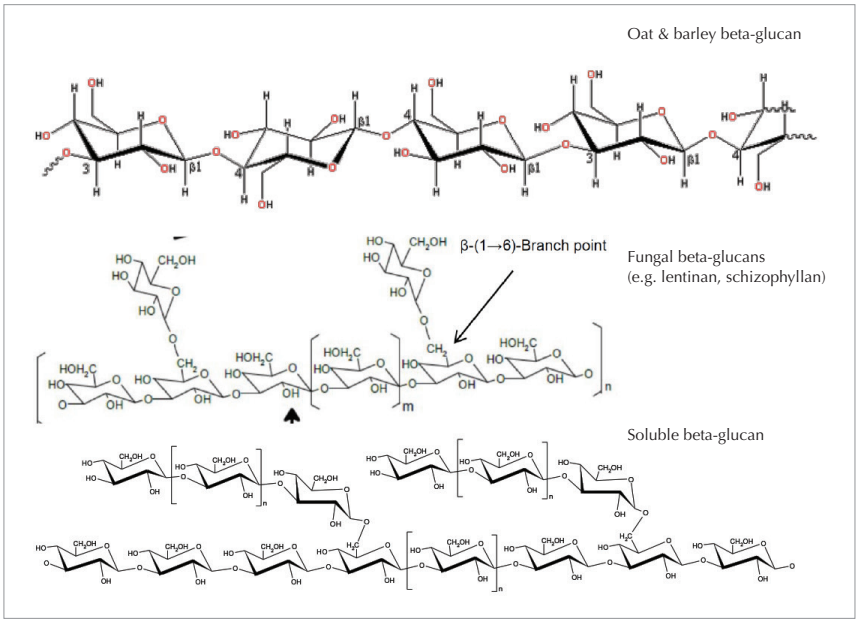

Figure 1. Structural composition of different beta-glucans

Box 1. Beta-glucan fish food.

Waste products from the beer manufacturing process that were rich in yeast beta-glucans were added as a feed additive for industrial fishing. Fish that were fed beta-glucan-rich feed had a stronger immune response and survived disease compared to fish that were not (Vetvicka et al, 2013).

BETA-GLUCANS

Beta-glucans, or compounds that are primarily beta-glucans, have been used for medical purposes in the Far East for more than 2,000 years. These compounds have been recognised in Western medicine in the last century as a result of their ability to modulate the innate immune system, particularly through the action on white blood cells (monocytes and macrophages) (Di Luzio, 1983; Brown and Gordon, 2003; Chen and Seviour, 2007) following their use in fishing industry (*Box 1*). Beta-glucans are polysaccharides, long chains of glucose molecules of different length, structure and, therefore, function (*Figure 1*). They harbour pathogen-associated molecular structures (PAMPs) that activate the innate immune response. Beta-glucans can be found in different micro-organisms but are mainly found in yeast and fungi. The bioactivity of beta-glucans is determined by their source and structure, for example, beta-glucan from yeast is demonstrated to be superior in activating macrophages compared to other beta-glucans (Seljelid et al, 1981).

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. Beta-glucan 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 (Leibovich and Ross, 1975; Delavary et al, 2011).

Chronic wounds appear to stagnate in the early stages of wound healing, also known as the inflammation 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. Phagocytosis of dead cells and debris moves the wound from the inflammation phase and into the proliferation phase (Roy, 2009). For diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs), the healing process can be further compromised:

- For people with diabetes, macrophages have a lower production of neurotransmitters and growth factors (Zykova et al, 2000; Zykova et al, 2004). In slow-healing DFUs, fibroblast cells and macrophages undergo a premature ageing process — senescence. Senecent cells respond poorly to signalling molecules and have a far lower cell-proliferation rate than normal cells (Mendez et al, 1998; Loots et al, 1999)
- The altered local environment in VLUs causes a net increase in proliferative macrophages before the tasks of resolving the inflammation are completed (MacLeod and Mansbridge, 2016)
- Poor macrophage functionality is also true, to some extent for the older population.

Continual signalling from microorganisms and the immune and host cells in chronic wounds leads to the macrophages becoming tolerant and unreactive to these signals. However, it has been shown that these 'tolerised' macrophages can be partially restored following beta-glucan stimulation (Novakovic et al, 2016). Beta-glucans can restart the healing process by improving the likelihood of resolving the inflammation phase and progressing to the proliferation stage of healing.

INTRODUCING WOULGAN

Woulgan gel is an active therapy of 2% SBG derived from yeast for slow-healing wounds, which provides a moist wound environment.

Declaration of interest
This article was supported by Woulgan.

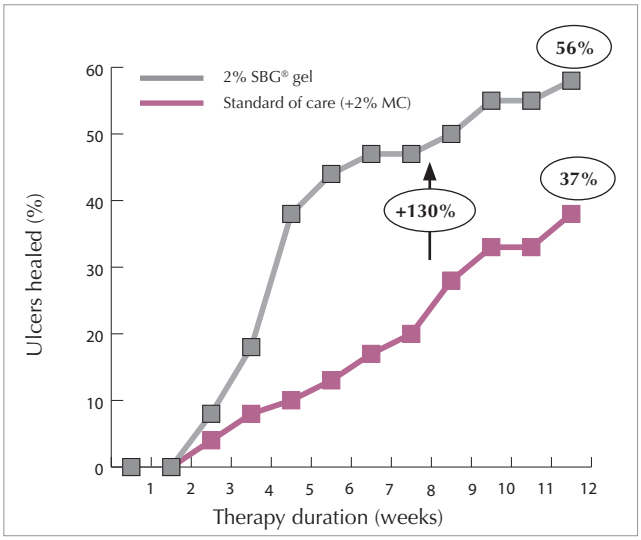

Figure 2. Healing of diabetic foot ulcers using 2% soluble beta-glucan (SBG) gel (*n*=60) versus standard care in a randomised, controlled trial (Zykova et al, 2014)

In pre-clinical trials with diabetic mice, the SBG group showed increased wound contraction, cell proliferation and angiogenesis compared to the control group (Skjæveland and Engstad, 2013). The clinical effect of SBG is also documented in a 12-week blinded, randomised comparator trial in 60 patients with DFUs (Zykova et al, 2014). The SBG group had a shorter median healing time, and a significantly higher proportion of healed ulcers at week 8 compared to controls. Over the 12 weeks, the proportion of ulcers healed was higher in the SBG group than the control, suggesting Woulgan may be favourable to use to kick-start healing (*Figure 2*). *Table 1* is a summary of published or ongoing reasearch of Woulgan in DFUs, LUs, pressure ulcers (PUs) and other stalled wounds of different aetiologies.

WOULGAN: INDICATIONS

Woulgan is a specialist-initiated treatment that can be used by a generalist following appropriate guidance for ongoing treatment. Woulgan is indicated when wound healing is slower than expected, or in wounds where healing has the potential to stall in DFUs, PUs, open post-operative wounds, grafts and donor sites, partial thickness burns and abrasions and lacerations. It is indicated for use on wounds with low to moderate levels of exudate. If an infection is present, the infection should be treated according to local guidelines before Woulgan is initiated. However, Woulgan can be used in conjunction with prophylactic antimicrobial therapies in high-risk individuals.

USING WOULGAN: DECISION PATHWAY

Clinicians should know when to escalate treatment in slow-healing wounds. The algorithm (*Figure 3*) outlines a decision pathway for using Woulgan as an advanced therapy in the context of appropriate standard wound care. Standard care for wound management should include a thorough holistic assessment of the patient and wound by a competent healthcare professional following a structured, formalised process, such as TIME (Schultz et al, 2003) or the Triangle of Wound Assessment (Dowsett et al, 2015b). Following assessment and wound bed preparation, i.e. cleansing and debridement, treatment of infection, exudate management and periwound skin care, and management of aetiology and comorbidities (Schultz et al, 2003; Harries et al, 2016) (e.g. suitable off-loading for a DFU), the patient and wound should be assessed regularly every 4 weeks (Frykberg and Banks, 2016).

Table 1. Clinical experience with Woulgan for different wound types.

Description	DFUs	LUs	PUs	Other	Published (✓/✘)
Randomised, comparator trial; 60 pts	✓				✓ Zykova et al, 2014
Case series, UK; 39 pts	✓	✓	✓		✓ King et al, 2017
Case series, UK; 2 pts	✓				✓ Welch, 2017
Randomised controlled trial, UK; 42 pts	✓				✘ Data on file (Biotec); Oral presentation at 46th EASD Annual Meeting, Stockholm, Sweden, 2010
Online survey, Norway; 58 pts	✓	✓	✓	✓	✓ Oral presentation at NIFS 2015; Engstad and Skjaeveland, 2015
Survey, UK and Germany; 150 pts	✓	✓	✓	✓	✓ Oral presentation at Pareto Health Care Seminar 2015
Trial with control arm, UK; 300 pts	✓	✓	✓	✓	✘ Results expected in 2018
Case series, Nordic countries; 30–40 pts	✓	✓	✓	✓	✘ Results expected in 2018
PMCF study with control arm; 80 pts	✓				✘ Ongoing

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

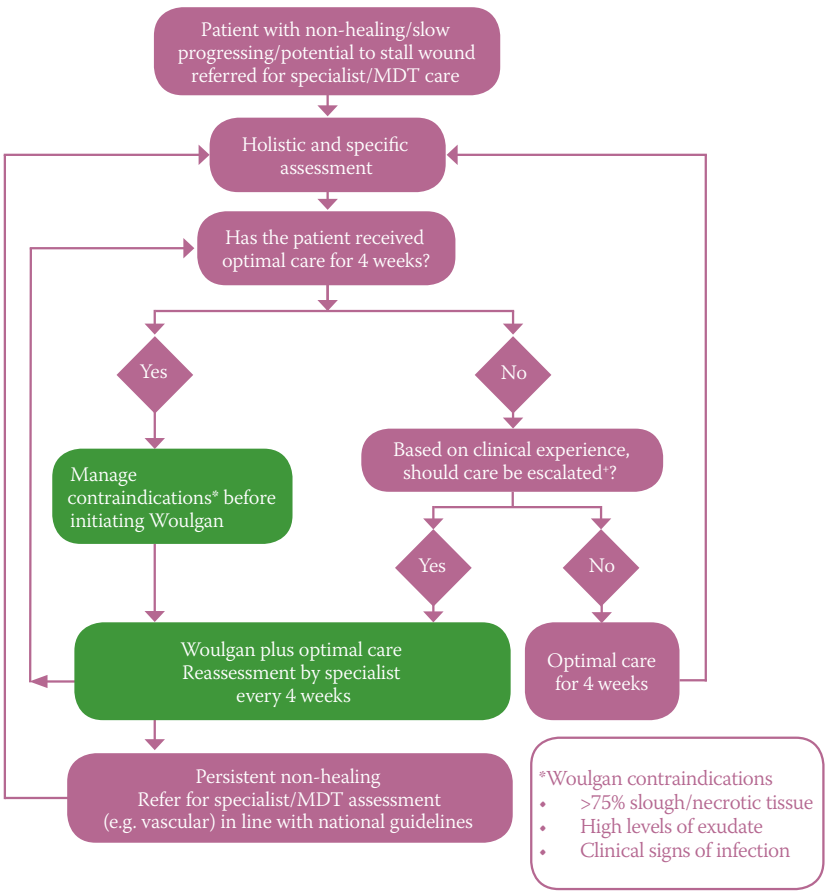

Figure 3. Decision pathway for implementing Woulgan into clinical practice

Patients under consideration for compression therapy (e.g. patients with VLUs should undergo vascular assessment, such as determining ankle–brachial pressure index (ABPI) (Scottish Intercollegiate Guidelines Network [SIGN], 2010; Wounds UK, 2016). There is currently no approved standard care for PUs because of the complex and less-defined nature of the PU categories; however, it is sensible to suggest that standard care would include performing a risk assessment using a recognised tool, optimising nutrition and mobility (Wounds UK, 2017) and implementing measures to redistribute pressure (NICE, 2014; NPUAP, EPUAP, PPPIA, 2014).

Woulgan should be considered after 4 weeks of best practice optimal care if the wound has not responded substantially to treatment (*Figure 3*). It is widely accepted that a 50% change in DFU area after 4 weeks of observation is a robust predictor of healing at 12 weeks (Sheehan et al, 2003; Frykberg and Banks, 2016). For VLUs, a 20–40% reduction in wound area within 2–4 weeks is predictive of healing (Flanagan, 2003; Harding et al, 2011). The recognised indicators of slow-healing can include (Vowden et al, 2008):

- Insufficient, no or negative change in size (i.e. <50% reduction in DFU area, or a 20–40% reduction in VLU area after 4 weeks of best practice optimal care)
- 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.

For patients or wounds at high risk of delayed healing at initial assessment (e.g. immunosuppressed patients, or patients with obesity or diabetes) (Vowden et al, 2008), 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.

The decision to prescribe and initiate Woulgan should be made by an appropriate competent practitioner in consultation with the patient, according to local policy. However, subsequent application of Woulgan may be continued by any qualified practitioner who has adequate clinical training and support, and follows the guidance for use.

An appropriate dressing to cover the wound following Woulgan application is considered essential. A dressing conducive to moist wound healing should be selected as per the local formulary. The chosen dressing should meet the patient's needs and manage other existing wound symptoms (e.g. appropriate to the exudate level).

SUMMARY

Beta-glucan is a well-described immuno-modulatory compound influencing the innate immune response but is new to wound care; however, there is a developing body of pre-clinical and clinical evidence for the role of SBG in wound care (*Table 1*). The decision pathway (*Figure 3*) provides guidance on wound assessment, management, and Woulgan application and review, and helps clinicians to determine when to escalate treatment with Woulgan. Research has shown Woulgan is

a clinically and cost-effective (Cutting, 2017) active therapy for slow-healing wounds, as such, it is included in the NHS Drug Tariff. National guidance on when to initiate second-line or advanced treatment would be advantageous.

CONCLUSION

Woulgan should be considered after 4 weeks of optimal care in patients with a slow-healing wound, and could be considered earlier for patients at high risk of delayed wound healing. Macrophages can become tolerant to cell signalling of the innate immune response due to age, underlying comorbidities or over-activation from pathogenic bacteria. Woulgan presents an approach to 're-start' macrophage activity and move wounds that may be stalled in the inflammation phase into the proliferation stage. WUK

REFERENCES

Brambilla R, Hurlow J, Landis S, Wolcott R (2016) *Innovations in hard-to-heal wounds. World Union of Wound Healing Societies.* Available at: www.wuwhs2016.com/files/WUWHS_H2H_CR_Web.pdf (accessed 17.04.18)

Brown GD, Gordon S (2003) Fungal beta-glucans and mammalian immunity. *Immunity* 19(3):311–5

Chen J, Seviour R (2007) Medicinal importance of fungal beta-(1--> 3), (1--> 6)-glucans. *Mycol Res* 111(Pt 6): 635–52

Cutting KF (2017) The cost-effectiveness of a novel soluble beta-glucan gel. *J Wound Care* 26(5): 228–34

Delavary BM, Van der Veer WM, et al (2011) Macrophages in skin injury and repair. *Immunobiology* 216(7): 753–62

Di Luzio NR (1983) Immunopharmacology of glucan: a broad spectrum enhancer of host defence mechanisms. *Trends Pharmacol Sci* 4: 344–7

Dowsett C (2015a) Breaking the cycle of hard-to-heal wounds: balancing cost and care. *Wounds Int* 6 (2):17–21

Dowsett C, Protz K, Drouard H, Harding KG (2015b) *Triangle of Wound Assessment.* Available at: www.woundsinternational.com/made-easys/view/triangle-wound-assessment (accessed 17.04.18)

Engstad RE, Skjaeveland I (2015) Possibility of beta-glucan containing product induced acceleration of the wound healing process (EP351). Presented at *51st European Association for the Study of Diabetes.* 14–18 September, Stockholm, Sweden

Flanagan M (2003) Improving accuracy of wound measurement in clinical practice. *Ostomy Wound Manage* 49(10): 28-40

Frykberg RG, Banks J (2016) Management of diabetic foot ulcers: a review. *Federal Practitioner* 33(2): 16-23

Gibson D, Cullen B, Legerstee R, et al (2009) MMPs Made Easy. *Wounds International* 1(1): Available at: www.woundsinternational.com/made-easys/view/mmps-made-easy-1 (accessed 17.04.18)

Guest J, Ayoub N, McIlwraith et al (2015) Health economic burden that wounds impose on the National Health Service in the UK. *BMJ* 009283

Harding K, Armstrong DG, Barrett S et al (2011) *International Consensus. The Role of Proteases in Wound Diagnostics. An Expert Working Group Review.* Available at: www.woundsinternational.com/media/issues/419/files/content_9869.pdf (accessed 17.04.18)

Harries RL, Bosanquet DC, Harding KG (2016) Wound bed preparation: TIME for an update. *Int Wound J* 13 (Suppl S3): 8–14

King B, Barrett S, Cutting KF (2017) Clinical evaluation of a bioactive beta-glucan gel in the treatment of 'hard-to-heal' wounds. *J Wound Care* 26(2): 58–63

Leibovich SJ, Ross R (1975) The role of the macrophage in wound repair. A study with hydrocortisone and antimacrophage serum. *Am J Pathol* 78(1): 71–100

Loots MAM, Lamme EN, et al (1999) Cultured fibroblasts from chronic diabetic wounds on the lower extremity (non-insulin-dependent diabetes mellitus) show disturbed proliferation. *Arch Dermatologic Res* 29(2–3): 93–9

MacLeod AS, Mansbridge JN (2016) The innate immune system in acute and chronic wounds. *Adv Wound Care (New Rochelle)* 5(2): 65–78

Mendez MV, Stanley A et al (1998) Fibroblasts cultured from venous ulcers display cellular characteristics of senescence. *J Vasc Surg* 28(5): 876–83

NICE (2014) *Pressure Ulcers: Prevention and Management (CG179).* NICE, London. Available at: www.nice.org.uk/guidance/cg179 (accessed 16.04.18)

Novakovic B, Habibi E, Wang SY et al (2016) Beta-glucan reverses the epigenetic state of LPS-induced immunological tolerance. *Cell* 167(5): 1354–68

NPUAP, EPUAP, PPPIA (2014) National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel and Pan Pacific Pressure Injury Alliance. Prevention and treatment of pressure ulcers: quick reference guide. *Cambridge Media*: Perth, Australia

Roy S (2009) Resolution of inflammation in wound healing: significance of dead cell clearance. *Advances Wound Care* 1: 253-8

Schultz GS, Sibbald RG, Falanga V, et al (2003) Wound bed preparation: a systematic approach to wound management. *Wound Repair Regen* 11(2): Suppl S1-28

Scottish Intercollegiate Guidelines Network (2010) Management of chronic venous leg ulcers. A national clinical guideline 120. Edinburgh: *SIGN*. Available at: www.sign.ac.uk (accessed 12.04.18)

Seljelid R, Bogwald J, Lundwall A (1981) Glycan stimulation of macrophages *in vitro*. *Exp Cell Res* 131: 121-9

Sheehan P, Jones P, Caselli A et al (2003) Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. *Diabetes Care* 26(6):1879-82

Skjæveland I, Engstad RE (2013) Can the activation of the body's own key cells in wound healing, WOUND MACROPHAGES, make a positive contribution in the treatment of chronic wounds? *Sår* 21(4)

Vetvicka V, Vannucci L, Sima P (2013) The Effects of β – glucan on fish immunity. *N Am J Med Sci* 5(10): 580–8

Vowden P, Apelqvist J, Moffatt C (2008) Wound complexity and healing. In: European Wound Management Association (EWMA). Available at: http://ewma.org/fileadmin/user_upload/EWMA.org/Position_documents_2002-2008/EWMA_08_Eng_final.pdf

Vowden P (2011) *Hard-to-Heal Wounds Made Easy.* Available at: www.woundsinternational.com/media/issues/514/files/content_10140.pdf (accessed 17.04.18)

Welch D (2017) A clinical evaluation of Woulgan® Biogel in the management of non-infected diabetic foot ulcerations. *Diabetic Foot Journal* 20(1): 43–7

Wounds International (2012) *International Consensus. Optimising Wellbeing in People Living with a Wound. An Expert Working Group Review.* Available at: www.woundsinternational.com/media/issues/554/files/content_10309.pdf (accessed 17.04.18)

Wounds International (2013) *International Consensus. Making the Case for Cost-Effective Wound Management.* Available at: http://www.woundsinternational.com/consensus-documents/view/international-consensus-making-the-case-for-cost-effective-wound-management www. woundsinternational.com (accessed 17.04.18)

Wounds UK (2016) *Best Practice Statement: Holistic Management of Venous Leg Ulceration.* Available at: www.woundsinternational.com/media/issues/554/files/content_10309.pdf (accessed 17.04.18)

Wounds UK (2017) *Consensus Document. Recognising, Managing and Preventing deep tissue injury (DTI).* Available at: www.wounds-uk.com/supplements/recognising-managing-and-preventing-deep-tissue-injury-dti (accessed 17.04.18)

Zykova SN, Jenssen TG, et al (2000) Altered cytokine and nitric oxide secretion in vitro by macrophages from diabetic type II-like db/db mice. *Diabetes* 49: 1451–8

Zykova SN, Svartberg J, et al (2004) Release of TNF-alpha from *in vitro*-stimulated monocytes is negatively associated with serum levels of apolipoprotein B in patients with type 2 diabetes. *Scand J Immunol* 60(5): 535–42

Zykova SN, Balandina KA, et al (2014) The macrophage stimulating agent soluble yeast beta 1,3/1,6-glucan as a topical treatment of diabetic foot and leg ulcers: a randomised, double blind, placebo-controlled phase II study. *J Diabetes Investigation* 5(4): 392–9