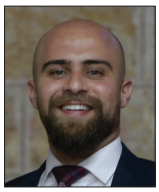
Addressing wound chronicity factors: UrgoClean Ag® and UrgoStart® case studies

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Chronic wounds are a perennial problem in clinical practice and place a burden on patients, their families and healthcare providers. By addressing factors that contribute to chronicity (slough, biofilm, elevated levels of metalloproteinases and impaired angiogenesis), in addition to managing a patient's comorbidities, nutritional status and lifestyle, there is a greater chance of healing. This article discusses the mechanisms by which UrgoClean Ag and UrgoStart support a healthy wound environment, along with two case studies of their use in practice.

Chronic wounds have been referred to as a 'silent epidemic', afflicting a growing number of the global population (Gottrup, 2004). These wounds are not only increasing the burden on healthcare providers and systems but they also have a devastating effect on patients and their families (Frykberg and Banks, 2015). People affected by chronic wounds are more likely to be older, have underlying chronic disorders and be at additional risk for further complications (Iversen et al, 2009). In a retrospective cohort study of outpatients with chronic wounds (mean age 75 years), patient mortality was an estimated 28% over a 2-year period (Escandon, et al, 2011). This is much higher than the 4% mortality rate reported for 75–79 year olds without chronic wounds, suggesting a higher risk of death in the wounded population (Escadon, et al, 2011).

The estimated socioeconomic cost of chronic wounds is 2–4% of the health budget in Western countries (Trostrup et al, 2013). This is expected to increase over time as a consequence of population ageing, as older people have a greater risk of developing comorbidities, including compromised venous flow, atherosclerosis, diabetes, renal impairment, lymphoedema, rheumatological disease, poor nutritional status, local pressure over prominent bones and ischaemia (Trostrup et al, 2013).

Factors contributing to chronicity

Devitalised tissue

The presence of nonviable tissue plays a prominent role in chronicity. Necrotic tissue consists dead or devitalised cells, tissue and cellular debris. Slough — which consists of fibrin, pus, leucocytes, microorganisms and proteinaceous materials — is created by the immune-mediated clearance of the wound (Percival and Suleman, 2015).

Nonviable tissue provides an optimum environment for the multiplication of microorganisms that prolong the inflammatory phase of healing and can act as a reservoir for biofilms (Dowsett and Ayello, 2004; Percival and Suleman, 2015).

Biofilms

In biofilms, planktonic bacteria, fungi, and other microorganisms, aggregate to form micro colonies that are encapsulated in a self-produced extracellular polymeric substance (EPS) which surrounds the growing colony and acts as a protective barrier against the host immune response and makes them tolerant to antimicrobial agents (Trostrup et al, 2013; Bjarnsholt et al, 2017). The abundant neutrophils and macrophages that surround biofilms secrete high levels of reactive oxygen species and matrix metalloproteinases (MMPs), triggering a chronic inflammatory response (Philips et al, 2012). Biofilms also stimulate an inflammatory response, increasing vascular permeability, oedema and exudate production, which may be interrelated with slough production (Wolcott et al, 2008).

MMPs

The high levels of MMPs in chronic wounds create a hypoxic environment within the wound bed, resulting in increased proteolysis and triggering a chronic inflammatory response (Moor et al, 2009; Philips et al, 2012). Although MMPs play a pivotal role in wound healing, the increased levels of these enzymes cause the degradation and destruction of proteins, such as growth factors and extracellular

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matrix (ECM), which are required for healing (Gibson et al, 2009).

Angiogenesis

New blood vessel formation, or angiogenesis, is a critical event in the wound healing process. It is the process that involves the growth of new capillaries to form granulation tissue (Honnegowda et al, 2015). In acute wounds, new capillaries become visible in the wound bed as granulation tissue within the first few days. This acts as an environment for proliferating blood vessels, migrating fibroblasts and new collagen (Tonnesen et al, 2000) Furthermore, the proliferating capillaries supply the growing tissue with oxygen and micronutrients but also remove catabolic waste products (Honnegowda et al, 2015). In chronic wounds, angiogenesis is impaired, leading to further tissue damage resulting from chronic hypoxia and impaired micronutrient delivery with subsequent poor formation of new blood vessels and decreased entry of inflammatory cells and their growth factors (Brem et al, 2003; Honnegowda et al, 2015). Interestingly, specific defects have been identified in diabetic ulcers, venous ulcers and arterial ulcers, most importantly, deficiency of the vascular endothelial growth factor which stimulates the formation of blood vessels, acts as an endothelial cell mitogen and chemotactic agent, as well as induces vascular permeability (Bao et al, 2009; Johnson et al, 2014)

Addressing factors causing chronicity

It is difficult to overcome the problems — slough, biofilm, elevated levels of MMPs and impaired angiogenesis — that contribute to wound chronicity. In addition to managing the patient as whole (comorbidities, nutrition, lifestyle, etc), clinicians need to manage factors that impede the healing process.

Desloughing

Desloughing removes dead and devitalised tissue, as well as excess MMPs and biofilms (Milne, 2015). The effective removal of slough using a method that is as fast and safe as possible should enable the wound to return to a healthy state that supports the healing cascade (Dowsett and Ayello, 2004). Delayed desloughing is a primary cause of delayed healing (Shultz et al, 2003). Desloughing of chronic wounds is, therefore, a critical component of wound bed preparation to facilitate healing (Vowden and Vowden, 2011).

While the debridement of eschar usually involves techniques such as sharp and surgical debridement, desloughing is more often achieved by conservative methods, such as the use of local dressings that promote autolysis and safe mechanical methods (Grothier, 2015). Mechanical debridement has traditionally been associated with the practice of wet-to-dry dressings that are non-selective and painful for patients (Davies, 2004). However, more modern approaches, such as polyacrylate fibre dressings, offer safer and more effective methods to remove this debris from the wound bed (Milne, 2015).

Supporting angiogenesis

Fibroblasts synthesise collagen and organise the components of the ECM and are essential for angiogenesis. It is important to select a dressing that facilitates fibroblast migration to the wound bed and/or fibroblast proliferation, as this will enhance the production of ECM and collagen, thereby supporting other cells involved in healing and aiding contraction of the wound (Wiegand et al, 2019). Local modulation of MMPs is also useful in the management of chronic wounds (Richard et al, 2012). Certain non-adherent dressings are not only atraumatic upon removal but interact locally with cells in the wound microenvironment, thereby promoting a healthy environment for healing (Bernard et al, 2005).

Supporting a healthy wound environment

UrgoClean Ag and UrgoStart

UrgoClean® is an absorbent cohesive dressing developed specifically for desloughing wounds (Meaume et al, 2012). It is suitable for use on sloughy and exuding wounds. It consists of polyacrylate non-woven fibres that absorbs exudate and traps slough and has an acrylic core that provides the dressing with its tensile strength (Eloy et al, 2010). The pad is coated with a soft adherent lipido-colloid layer (TLC Technology) that promotes healing and enables atraumatic removal (Trudigan et al, 2014).

UrgoClean Ag® is composed of the same materials as UrgoClean, with the addition of silver sulfate to the TLC matrix. In contact with the wound exudate, the silver sulfate breaks down (Ag2S04 -> 2 Ag+ + S042) and releases the Ag+ ion, while the CarboxyMethylCellulose particles swell to form a surface hydrocolloidal film. It is suggested that this controlled supply of Ag+ at the surface into the lipido-colloid gel guarantees a constant antibacterial activity, strictly in contact with the wound (Laboratoires URGO, 2009). The poly-absorbent fibres mechanically break down the extracellular polymeric substances in the biofilm while the Ag+ ions exert an antimicrobial action (Bisson et al, 2013).

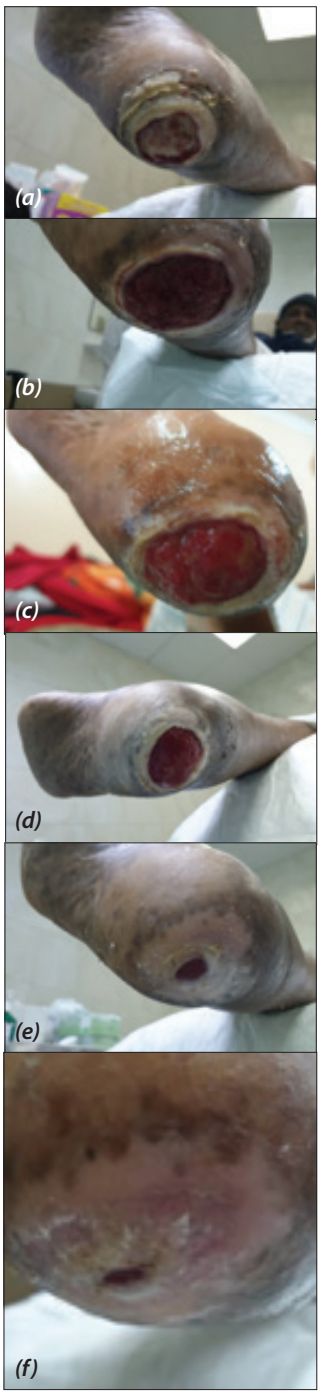

Figure 1a–f. Case study 1 – diabetic foot ulcer. From top: on presentation; day 7; day 10 ; day 13; day 25; and day 34.

Table 1. Results of the Explorer study (Edmonds et al, 2018).

	TLC plus NOSF	TLC only	Results
Wound closure, n (%)	60 (48%)	34 (30%)	18 percentage points difference, 95% CI: 5–30; adjusted odds ratio 2.60, 95% CI: 1.43–4.73; P=0.002
Time to closure by week 20, days (range)	180 (163–198)	120 (110–129)	TLC-NOSF shortened the mean time to closure by 60 days compared to an advanced neutral dressing (P=0.029)

Evidence for use

Various *in vitro* and *in vivo* studies were conducted to establish the efficacy of this UrgoClean Ag — these are discussed in details in a previously published article in *Wounds Asia* (Galea, 2018a), including a non-comparative exploratory clinical study in the local management of chronic wounds from the desloughing phase, where all treated wounds were considered to be debrided after 3 weeks and the median relative decrease of the sloughy tissue, at week 6 was between 75% and 89% (Meaume et al, 2012). In a randomised, controlled, open-labelled clinical study involving chronic wounds with more than 70% of the wound bed covered with slough at baseline, the relative reduction of slough tissue was significantly higher in the UrgoClean group than in the control group (-65.3% vs -42,6%; *P*=0.013) and the percentage of debrided wounds was also significantly higher in the test group (52.5% vs 35.1%; *P*=0.033) (Meaume et al, 2014).

Furthermore, in a prospective, multicentre, non-comparative clinical trial, Dalac et al (2016) showed effective debridement properties that were documented (62.5% relative reduction of sloughy tissue at week 4; 58.8% of debrided wounds at week 4) and improvement of the periwound skin status was noted (healthy for 28.6% of the patients at week 4 vs 2.7% at baseline). Moreover, Desroche et al (2016), in a study that was designed to evaluate the antibacterial activity of UrgoClean Ag against biofilm of methicillin-resistant *Staphylococcus aureus* (MRSA), resulted in a significant decrease of the biofilm population by a log reduction of 4.6, after 24 hours of exposure where the antibiofilm activity was maintained for 7 days with reduction values up to 4 log (reduction of biofilm superior to 99.99%).

In studies conducted in the early nineties, it was shown that sucrose octasulfate protects fibroblast growth factor and induces dermal fibroblast and keratinocyte proliferation in quiescent cultures (Burch and McMillan, 1991; Desai et al, 1995). In view of this, experiments were conducted to identify how this molecule could be used in the management of skin ulcers. Nano-oligosaccharide factor (NOSF) — the active component of which is sucrose octasulfate — is an innovative compound derived from the chemical oligosaccharide family that has demonstrated MMP-inhibiting properties. It promotes healing in leg ulcers, pressure ulcers, diabetic foot ulcers and recurring wounds (White et al, 2015). *In vitro* studies have established the efficacy of TLC-NOSF (UrgoStart®) in MMP inhibition and neovascularisation enhancement (Coulomb, 2008). More recently, randomised controlled trials of TLC-NOSF in chronic wounds have reported significant reductions in healing times and improved health-related quality of life (Bohbot, 2010; Meaume et al, 2014; 2017, Münter et al, 2017).

A recent double-blind trial conducted in five countries (France, Spain, Italy, Germany and the UK) across 43 hospitals with diabetic foot clinics found the NOSF dressing to be effective, safe and easy to use (Edmonds et al, 2018). It significantly improved the closure of neuroischaemic diabetic foot ulcers when compared to standard care *[Table 1]*.

Interestingly, in the NOSF group, 65% (46/71) of wounds with a duration of less than 6 months closed compared to just 25% (14/55) of longer-standing wounds. This suggests that earlier adoption of UrgoStart provides better results (Galea, 2018b). Reactions to the Explorer randomised controlled trial, which demonstrated faster healing of neuroischaemic diabetic foot ulcers, have been very promising (Tucker, 2018).

Recommendations for use

The National Institute for Health and Care Excellence (NICE, 2019) in the UK recommends using UrgoStart for the treatment of diabetic foot ulcers and leg ulcers. Having reviewed the evidence, the committee agreed that UrgoStart had demonstrated efficacy and cost-effectiveness, and had a positive impact on health-related quality of life (NICE, 2019). The International Working Group on the Diabetic Foot recommends considering the use of sucrose octasulfate-impregnated dressings in the management of chronic wounds (Schaper et al, 2019).

Case studies

Case 1

A male patient presented to the clinic with a

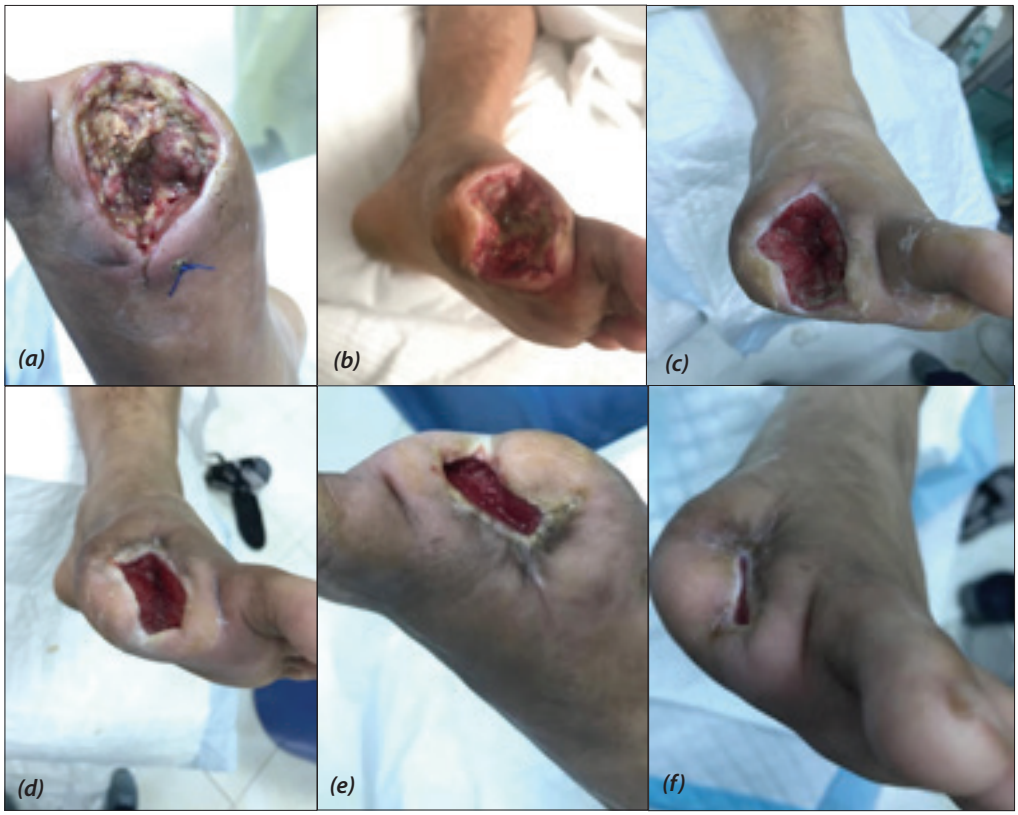

Figure 2a–f. Case study 2 – non-healing infected wound following hallux amputation . From top: on presentation; day 2; day 10 ; day 23; day 29; day 54.

diabetic foot ulcer. He had been diagnosed with diabetes 20 years previously and had peripheral neuropathy. On presentation (June 13, 2019), the ulcer on the right heel was >5 cm^2 and was mostly covered in slough. There were signs of local infection, including malodour and high levels of exudate. The presence of biofilm was suspected and a wound swab was taken that later revealed the presence of *Pseudomonas aeruginosa*. UrgoClean Ag was applied to manage the local infection and slough *[Figure 1a]* and was changed every 3 days.

The ulcer showed marked improvement at each dressing change *[Figure 1b–c]*. On June 26, the wound was free from signs of infection and the surrounding callus was debrided *[Figure 1d]*. At this point, UrgoStart was initiated. Rapid improvement was seen thereafter *[Figure 1e]*; on August 17, the wound had reduced in size to 0.2 cm^2 *[Figure 1f]*. The wound had completely closed 6 weeks after treatment was initiated.

Case 2

A 50-year-old female patient presented with a non-healing, infected wound following hallux amputation. She had long-standing diabetes and hypertension. Her wound was highly exudative, malodorous, sloughy and measured 3 cm^2 *[Figure 2a]*. The patient had a pain score 8 out of 10. Her wound had previously been managed with traditional wet gauze with saline.

UrgoClean Ag was applied to manage the local infection and slough and was changed every day for 3 days. By day 3, there was were noticeable improvements in pain level, signs of infection and percentage slough in the wound bed *[Figure 2b]* and the frequency of dressing changes was extended to every 3 days.

On January 17, the wound was free from infection and UrgoStart was initiated *[Figure 2c]*. Healthy granulation tissue developed and a the wound area reduced significantly over the following 3 weeks *[Figure 2d–e]*. On March 3, the wound measured 0.5 cm^2 *[Figure 2f]* and on March 20 (10 weeks after commencing treatment) was completely closed.

Conclusion

The management of chronic wounds is a perennial challenge for clinicians. However, new treatment modalities, such as UrgoClean Ag and UrgoStart, are proving effective in the management of slough and biofilms, reducing healing times and enhancing health-related quality of life.

Acknowledgement

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foot disease. Available at: https://iwgdfguidelines.org/guidelines (accessed 24.01.20)

Schultz G, Sibbald G, Falanga V et al (2003) Wound bed preparation: a systematic approach to wound management. *Wound Repair Regen* 11(Suppl 1): 1–28

Tonnesen MG, Feng X, Clark RA (2000) Angiogenesis in wound healing. *J Investig Dermatol Symp Proc* 5(1): 40–6

Trostrup H, Bjarnsholt T, Kirketerp-Moller K et al (2013) What is new in the understanding of non healing wounds epidemiology, pathophysiology, and therapies. *Ulcers* 2013 Jan 1: 625934

Trudigan J, Law P, Tarbox B (2014) Evaluation of UrgoClean® for the treatment of sloughy, exuding wounds. *Wounds UK* 10(1): 56–62. Available at www.wounds-uk.com (accessed 24.01.20)

Tucker ME (2018) Dressing Hastens Neuroischemic Diabetic Foot Ulcer Healing. *Medscape* 3 January 2018 (accessed 24.01.20)

Vowden K, Vowden P (2011) Debridement made easy. *Wounds UK* 7(4 Suppl): 1–4. Available at www.wounds-uk.com (accessed 24.01.20)

White R, Cowan T, Glover D (2015) *Supporting evidence-based practice: A clinical review of TLC healing matrix*. 2nd edn. MA Healthcare Ltd, London

Wiegand C, Abel M, Hipler UC, Elsner P (2019) Effect of non-adhering dressings on promotion of fibroblast proliferation and wound healing in vitro. *Sci Rep* 9(1): 4320

Wolcott RD, Rhoads DD, Dowd SE (2008) Biofilms and chronic wound inflammation. *J Wound Care* 17(8): 333–41

References

Bao P, Kodra A, Tomic-Canic M et al (2009) The role of vascular endothelial growth factor in wound healing. *J Surg Res* 153(2): 347–58

Bernard FX, Barrault C, Juchaux F et al (2005) Stimulation of the proliferation of human dermal fibroblasts in vitro by a lipidocolloid dressing. *J Wound Care* 14(5): 215–20

Bisson JF, Hidalgo-Lucas S, Bouschbacher M, Tomassin L (2013) Effects of TLC-Ag dressings on skin inflammation. *J Dermatol* 40(6): 463–70

Bjarnsholt T, Eberlein T, Malone M, Schultz G (2017) Management of wound biofilm made easy. *Wounds International* May 2017: 1–6. Available at www.woundsinternational.com (accessed 24.01.20)

Bohbot S (2010) Management of venous leg ulcers with two active wound dressings. Protocol of a randomized clinical trial. *J WOCN* 37(3): S57

Brem H, Jacobs T, Vileikyte L et al (2003) Wound-healing protocols for diabetic foot and pressure ulcers. *Surg Technol Int* 11: 85–92

Burch RM, McMillan BA (1991) Sucralfate induces proliferation of dermal fibroblasts and keratinocytes in culture and granulation tissue formation in full thickness skin wounds. *Agents Actions* 34(1–2): 229–31

Coulomb B (2008) Evaluation de la matrice imprégnée de NOSF (nano-oligosaccharide factor), dans un modèle de reconstruction dermique in vitro. *J Plaies Cicatris* 14: 54–7

Dalac S, Sigal L, Addala A et al (2016) Clinical evaluation of a dressing with poly absorbent fibres and a silver matrix for managing chronic wounds at risk of infection: a non comparative trial. *J Wound Care* 25(9): 531–8

Desroche N, Dropet C, Janod P, Guzzo J (2016) Antibacterial properties and reduction of MRSA biofilm with a dressing combining polyabsorbent fibres and a silver matrix. *J Wound Care* 25(10): 577–84

Davies P (2004) Current thinking on the management of necrotic and sloughy wounds. *Prof Nurse* 19(10): 34–6

Desai UR, Vlahov IR, Pervin A, Linhardt RJ (1995) Conformational analysis of sucrose octasulfate by high resolution nuclear magnetic resonance spectroscopy. *Carbohydr Res* 275(2): 391–401

Dinh T, Tecilazich F, Kafanas A et al (2012) Mechanisms involved in the development and healing of diabetic foot ulceration. *Diabetes* 61(11): 2937–47

Dowsett C, Ayello E (2004) TIME principles of chronic wound bed preparation and treatment. *Br J Nurs* 13(Sup3): S16-23

Edmonds ME, Foster AV, Sanders L (2008) *A Practical Manual of Diabetic Foot Care*. 2nd edn. Blackwell, Oxford

Edmonds M, Lázaro-Martínez JL, Alfayate-García JM et al (2018) Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial. *Lancet Diabetes Endocrinol* 6(3): 186–96

Eloy R, Clermont G, Nicot D, Morel N (2010) *Mechanism of Action of UrgoClean*. Poster presentation. Available at: https://bit.ly/2tT18va (accessed 24.01.20)

Escandon J, Vivas AC, Tang J et al (2011) High mortality in patients with chronic wounds. *Wound Repair Reg* 19(4): 526–8

Frykberg RG, Banks J (2015) Challenges in the treatment of chronic wounds. *Adv Wound Care* 4(9): 560–82

Galea E (2018a) Moving the chronic wound along the healing trajectory. *Wounds Asia* 5(2): 39–43. Available at: www.woundsinternational.com (accessed 24.01.20)

Galea E (2018b) A breakthrough in the management of neuroischaemic diabetic foot ulcers. *Diabetic Foot Journal Middle East* 4(1): 46–9. Available at: www.woundsinternational.com (accessed 24.01.20)

Gibson D, Cullen B, Legerstee R et al (2009) MMPs Made Easy. *Wounds International* November 2009 (Suppl): 1–6. Available at: www.woundsinternational.com (accessed 24.01.20)

Grothier L (2015) Improving clinical outcomes and patient experience through the use of desloughing. *Br J Community Nurs* 20(Suppl 9): S25–31

Gottrup F (2004) A specialized wound-healing center concept: importance of a multidisciplinary department structure and surgical treatment facilities in the treatment of chronic wounds. *Am J Surg* 187(5A): S38–43

Honnegowda TM, Kumar P, Udupa EG et al (2015) Role of angiogenesis and angiogenic factors in acute and chronic wound healing. *Plast Aesthet Res* 2(4): 243–9

Iversen MM, Tell GS, Riise T et al (2009) History of foot ulcer increases mortality among individuals with diabetes: ten-year follow-up of the Nord-Trøndelag Health Study, Norway. *Diabetes Care* 32(12): 2193–9

Johnson KE, Wilgus TA (2014) Vascular endothelial growth factor and angiogenesis in the regulation of cutaneous wound repair. *Adv Wound Care* 3(10): 647–61

Laboratoires URGO (2009) Product File.

Meaume S, Perez J, Rethore V et al (2012) Management of chronic wounds with an innovative absorbent wound dressing. *J Wound Care* 21(7): 315–22

Meaume S, Dissemond J, Addala A et al (2014) Evaluation of two fibrous wound dressings for the management of leg ulcers: Results of a European randomised controlled trial (EARTH RCT). *J Wound Care* 23(3): 105–16

Meaume S, Truchetet F, Cambazard, F et al (2012) A randomized, controlled, double-blind prospective trial with a Lipido-Colloid Technology-Nano-Oligo Saccharide Factor wound dressing in the local management of venous leg ulcers. *Wound Repair Regen* 20(4): 500–11

Meaume S, Dompmartin A, Lok C et al; CHALLENGE Study Group (2017) Quality of life in patients with leg ulcers: results from CHALLENGE, a double-blind randomised controlled trial. *J Wound Care* 26(7): 368–79

Milne J (2015) Wound-bed preparation: the importance of rapid and effective desloughing to promote healing. *Br J Nurs* 24(Suppl 20): S52–8

Moor AN, Vachon DJ, Gould LJ (2009) Proteolytic activity in wound fluids and tissues derived from chronic venous leg ulcers. *Wound Repair Regen* 17(6): 832–9

Münter KC, Meaume S, Augustin M et al (2017) The reality of routine practice: a pooled data analysis on chronic wounds treated with TLC-NOSF wound dressings. *J Wound Care* 26(Suppl 2): S4–15

National Institute for Health and Care Excellence (2019) *Medical Technologies Guidance 42. UrgoStart for treating diabetic foot ulcers and leg ulcers*. Available at: www.nice.org.uk/guidance/MTG42 (accessed: 24.01.20)

Percival SL, Suleman L (2015) Slough and biofilm: removal of barriers to wound healing by desloughing. *J Wound Care* 24(11): 498–510

Phillips PL, Wolcott RD, Fletcher J, Schultz GS (2012) Biofilms Made Easy. *Wounds International* 1(3): 1–6. Available at www.woundsinternational.com (accessed 24.01.20)

Richard JL, Martini J, Faraill MB (2012) Management of diabetic foot ulcers with a TLC-NOSF wound dressing. *J Wound Care* 21(3): 142–7

Schaper NC, van Netten JJ, Apelqvist J et al; International Working Group on the Diabetic Foot (2019) *IWGDF Guidelines on the prevention and management of diabetic*