JWC International Consensus Document

Implementing TIMERS: the race against hard-to-heal wounds

Tissue

Inflammation/infection

Moisture

Edge

Regeneration

Social factors

KLOX TECHNOLOGIES MiMedx NEXT SCIENCE BREAK THROUGH BIOFILM MEDLINE Organogenesis Empowering Healing SILVERLON essity

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Foreword

In July 2018, the authors of this document met in the Royal Borough of Windsor to discus hard-to-heal wounds. The two-day meeting resulted in this consensus document. It is a very difficult area to examine; even the starting point is complicated. What is a non-healing wound? Or is that a chronic wound? Or a hard-to-heal wound? Is this different for every wound type? Does the definition vary by aetiology? Probably. By region? Possibly. A favourite was wanting to ask the panel if there is such a thing as a chronic, hard-to-heal or non-healing wound, or are they wounds that haven't been assessed and treated with a good standard of care (SoC) from the beginning? Then there were the difficult ethical questions,such as should you stop treating the wound of a non-adherent patient?

Over the two days, these questions and many others were examined at length. Here we are going to try and summarise the main points of this consensus. In terms of what to call these wounds, it was decided hard-to-heal was the most appropriate—not wanting to put the emphasis on non-healing, that all starts off a little negative. There is also a body of literature out there, and in the document, on when you would consider a wound to be hard-to-heal. This was quite a tough one;in diabetic foot ulcers (DFU) <50% reduction over four weeks is considered hard-to-heal. In venous leg ulcers (VLU) the value is <40% and in pressure ulcers (PU) the value is <20–40%. Obviously, aetiology plays a big role. Here it is recommended that any wound that has not healed by 40–50% after four weeks of good SoC should be considered a hard-to-heal wound and alternative strategies should be sought, often via referral to a wound care specialist or multidisciplinary team (MDT).

Of course the wound may have been present for much longer, as the patient may have avoided—or thought they did not require—treatment; however, the baseline recommended here is from the first documented visit for the wound.

A 10-step approach in the management pathway required for each wound is outlined in Section 4. This also includes how to treat palliative wounds in a maintenance fashion:

1. Holistic patient assessment: physical, psychological, spiritual and social needs. This must include and identify the underlying pathophysiological cause(s) and risk factor(s)
2. Wound assessment: measurement
3. Decide the desired outcome (healing or maintenance) and care plan
4. Address/manage the underlying pathology or plan maintenance care
5. Implement local wound care according to WBP/TIME, etc or maintenance/palliative care
6. Follow-up, reassessment and measurement
7. Modify the care pathway and refer if necessary to specialists or MDT
8. Patient/family education throughout the SoC
9. Discharge or transition to maintenance treatment to prevent recurrence
10. Record actions/outcomes at every episode of care.

This consensus panel also recommends updating TIME to TIMERS, adding regeneration/repair of tissue (R) and, importantly and often overlooked, social factors (S). S is an overarching theme, as patient factors are crucial to healing. The new framework, discussed in Section 5, provides structured approaches to managing wounds and identifies where advanced adjunctive therapies should be considered along with SoC.

Another important point raised was bioburden, especially biofilm. It is becoming generally accepted that hard-to-heal chronic wounds contain biofilm and that treating this could be a key factor in pushing the wound toward a healing state.

There are many other important points, including: the more understanding/agreement the patient has about their care plan, the more likely they are to adhere; use of medical jargon should be avoided; and ethically, it is not acceptable to withdraw or stop therapy that is recommended in best-practice statements, even if the wound has not progressed.

We enjoyed the meeting and discussion and hope you find this consensus informative and useful.

Rachel Webb and Camila Fronzo

Section 1. Introduction

Hard-to-heal wounds are a challenge for the patient, the health professional and health-care systems. Chronic wounds create poor health and personal issues for the patient and substantial costs to health-care systems.[1,2] There are known issues in the delivery of health care and in patient engagement with their therapy. An international panel of experts met in July 2018 to discuss the challenges with wounds that do not heal over extended time periods. This consensus statement summarises the outcome of the meeting and recommends approaches to addressing the delivery of care and patient engagement.

The prevalence of chronic wounds is estimated at between 1% and 2% in developed countries.[3] However, there is wide variation in the reported prevalence and incidence of chronic wounds worldwide and within each care setting.[4] The most prevalent wounds are venous leg ulcers (VLU), pressure ulcers (PU) and diabetic foot ulcers (DFU)[5–7] in people aged >60.[8–10] A percentage of wounds may not heal completely for a year or more,[11,12] and this places a significant burden on health-care systems and economies. In the context of this consensus statement, complete healing means full epithelial resurfacing and discharge, or transition to patient-management strategies to prevent recurrence.

Hard-to-heal wounds consume disproportionate amounts of medical products—devices and medicines—and the time of health professionals. Despite the relative standardisation of management for chronic wounds, healing rates vary considerably.[13–18] DFUs classified as stage 4 according to the Wound, Ischemia, and foot Infection (WIfI) system[19] may take up to a mean of 190 days to heal.[20] VLUs properly managed with 12 weeks of compression have healing rates of 32 to 55%; at 24 weeks, up to 68% may heal.[21–24] Furthermore, between 12% and 47% of VLU patients managed over 12 months may not heal.[10,25–28] Healing rates with compression bandaging over more extended periods of up to 420 days can reach around 90%[12] and over 500 days, 93%.[29]

> ## Key points
>
> - Hard-to-heal wounds affect the patient's quality of life, as well as being a burden on the health-care system
> - Incidence of hard-to-heal wounds is rising as the age of the population increases
> - Patient-related factors that influence outcomes include comorbidities, severity of the underlying condition and adherence
> - Correct treatment at an early stage could prevent many hard-to-heal wounds
> - Provider-related factors include awareness of treatment options available, the influence of external wound-healing inhibitors such as biofilm and availability of products
> - This document addresses the challenge of long-term, hard-to-heal wounds—those that do not close after care for up to a year or more

Up to 10% of patients with diabetes have a DFU and the lifetime incidence is reported to be 19%, but may be as high as 34%.[30,31] Furthermore, the prevalence of diabetes is increased in the elderly[32] population, resulting in an increase in the prevalence and incidence of DFU. Lower extremity ulcers including DFU may last for up to 13 months with estimates that nearly 40% of patients have a recurrence, within one year of their DFU healing.[31] Healing times in more severe DFU are worse than in less severe ulcers[19,33] and referral times are longer.[34,35]

Analysis of The Health Improvement Network (THIN) database of patient records managed by primary care in the UK has identified deficiencies in delivery of care for VLU and DFU related to diagnosis[1] and appropriate wound management.[1,2] Referrals may take place in months rather than the recommended days.[36] Over a 12-month period, approximately 50% of PUs may heal. However, the proportion of PUs that heal is inversely proportional to its category. In Guest et al,[37] all category I PUs healed over the 12-month audit period, but the likelihood of a category IV or unstageable PU healing was less than 20%.[37]

There may be significant deficiencies in the knowledge among nurses,[38–40] an issue recognised by many.[41] A survey of community nurses in Ireland found that more than half did not use Doppler to assess ankle-brachial pressure index (ABPI) in the assessment of VLU patients.[42] Differences[43] and deficiencies in referral and care have been noted in other countries.[44–46]

Patient engagement is an important part of the equation and may be affected if they cannot understand the reason(s) for the management of their wounds.[47] This will likely lead to poor adherence to the care plan and poor healing. Often, the evidence for efficacy of many medical products is limited and of poor quality[48] and carers find managing chronic wounds challenging.[49]

There is a variable understanding among general practitioners (GPs) about the underlying causes of chronic wounds and incomplete understanding of the organisation of care pathway structures.[50,51] A study from four European countries showed that not all GPs identify specialised practitioners to refer patients to, and many are unaware of clinical guidelines and protocols.[50,51] These factors are highly likely to be contributors to poor healing outcomes and to be mirrored in health-care systems worldwide.

Patients with chronic wounds suffer increased morbidity and decreased quality of life (QoL).[52–67]

There have been and are numerous studies assessing the financial cost of hard-to-heal, chronic wounds, of many different types.[57–67] These assessed parameters including nursing time and length of stay in hospital, along with how severity increases costs, some examples are shown in Table 1.

A number of factors may influence the likelihood of a wound healing. Variation in delivery of care affects outcomes. The skill level of the health professional, particularly outside specialist centres, may be insufficient to ensure optimal treatment.[68–70] Diagnosis,[71] referral[36] and delivery of a recognised standard of care (SoC) may be suboptimal.[10,71–74] The diagnosis and management of the underlying condition may vary. For example, the application of compression bandages is known to be variable[75] and the outcomes in plantar neuropathic DFU are significantly affected by the type of offloading[76,77] used, which varies considerably,[78] particularly as the foot changes shape.[79] Patients with severe ischaemia may not have vascular reconstruction.[36] These variations may be compounded by different guidelines that present similar advice on care, but may vary to the point of contradicting each other, leading to confusion in implementation.[80,81]

Patient-related factors that influence outcomes include comorbidities—there is a correlation between the worst wounds and the sickest patients, as patients with multiple comorbidities are the ones that often fail to heal[82]—severity of the underlying condition, illness beliefs[83] and adherence to the care plan. Adherence to the care plan[84] is considered a key factor in successful management of chronic ulcers.

This consensus statement addresses the challenge of long-term, hard-to-heal wounds—those that do not close after care for up to a year or more. Importantly, we emphasise the need to assess patients quickly and intervene early with the optimal SoC to increase the probability that a wound will heal.

This working document addresses general principles and provides guidance intended to

Table 1. Examples of the cost of hard-to-heal wounds

Aetiology and situation	Costs
VLU >grade 1 UK[37]	£7600 (2015/2016)
PU >grade 1 UK[37]	£7800 (2015/2016)
VLU >grade 1 UK[37]	>£8500 (2015/2016)
VLU Community care, Germany	€9060 (2014)
Chronic wounds Medicare	>US$52 billion (2014)
Hospital acquired PU US	US$8041 per ulcer
DFU[61]	US$44,200 yearly
DFU Europe[36]	€10,000 yearly
VLU—venous leg ulcers; PU—pressure ulcer; DFU—diabetic foot ulcer	

maximise the likelihood that wounds that have not healed over extended periods will progress. It should be read and implemented in conjunction with the clinician's local guidelines. It brings theory and practice together and offers areas of reflection that allow the reader to review the information and then decide where and how to use it to underpin their own practice.

Section 2. Identification of hard-to-heal wounds

Chronic wounds start by either direct trauma to tissue already compromised by underlying pathology or by breakdown of tissue under unbroken skin. Patients with diabetic neuropathy may not be aware of the trauma—pressure, friction, shear or penetrating/other injury—that has led to the wound. Patients with undiagnosed venous disease may notice abrasion or laceration, but not understand the seriousness of the wound. In instances when the wound does not heal and the patient does not understand its seriousness, they may attempt self-care before seeking advice from a health professional. In many cases, that would be a GP or physician who may have limited knowledge of wound care.

Wounds can fail to heal due to a lack of understanding/awareness of the importance of establishing and treating the underlying pathophysiology, which has either caused the wound or provides significant barriers to healing. It is important that these factors are addressed or managed to optimise healing outcomes. Crucially, a 'hard-to heal' wound needs to be flagged by a health professional before intervention can take place. The key to effective care is application of SoC, including identification of risk factors, monitoring outcomes and recognition of the correct course of action if the wound responds or it does not.

Risk factors for hard-to-heal wounds

Fig 1 summarises the risk factors associated with hard-to heal wounds. Risk factors may be characterised as disease state and pathophysiology specific to the wound aetiology; clinical risk factors not specific to the aetiology; and patient-related and non-clinical risk factors.

Disease state and pathophysiology

Details of pathophysiology are discussed in section 3 and are summarised here.

> ### Key points
>
> - An approach needs to be taken that is designed to identify hard-to-heal wounds and the action that should be taken
> - The most important risk factor for developing a VLU is underlying chronic venous disease
> - Diabetes may lead to a number of risk factors for ulcer formation, including peripheral neuropathy, peripheral arterial disease and a history of previous DFU
> - Critical risks for the formation of a PU are the forces of pressure, friction and shear
> - A wound that has not reduced in size by >40–50% at 4 weeks should be regarded as hard-to-heal and be referred to a specialist wound practitioner or a complex wound clinic

Venous leg ulcers

The most important risk factor for developing a VLU is underlying chronic venous disease that leads to chronic venous insufficiency, a spectrum of diagnoses of increasing complexity classified by the Comprehensive Classification System for Chronic Venous Disorders (CEAP).[85,86] Other classification systems for chronic venous disease have been developed.[87]

Chronic venous disease leads to haemodynamic changes[88,89] that increase intravenous blood pressure in the deep, superficial and/or perforator systems. Venous insufficiency or muscle pump deficiency reduce the effectiveness of return of blood to the heart, and defects in the intravenous valves lead to venous reflux and blood pooling in the lower extremities. The high venous pressure caused by pooling stimulates chronic inflammation that eventually makes the skin break down to form a VLU. Effective management of VLU addresses venous hypertension with external compression and potentially venous intervention.

Diabetic foot ulcers

Diabetes may lead to a number of risk factors for ulcer formation. Key risks are:[90]

Fig 1. Risk factors for hard-to-heal wound formation. Note: the more factors a patient has, the more likely the wound will not heal

Presentation of wound/lesion/ulcer

No ← → Yes

Risk factors associated with hard-to-heal wounds

Obesity	Diabetes	Cancer
Older age	Arterial disease	Systemic medication
Poor nutrition	Venous disease	Radiation
Genetics	Neuropathy	Psychosocial
Smoking	Chronic inflammation	Patient adherence
Anaemia	Lymphatic insufficiency	Patient economic status
Hypoxia	Oedema (if on lower limbs)	Demographic factors
Comorbidities	Immune suppression or disease	Behavioural factors
		Immobilisation

Pressure ulcer
Leg ulcer
Diabetic foot ulcers
Peripheral arterial disease

Risk of a hard-to-heal wound
Address underlying cause
Modify risk factors where possible

Healing

Maintenance care
When underlying cause and risk factors cannot be sufficiently altered to facilitate healing

1. Peripheral neuropathy (sensory, motor and autonomic neuropathy)
    a) Sensory: reduces or eliminates touch sensation and nociception
    b) Motor: foot deformity as a result of distal nerve damage, causing small muscle wasting and muscle atrophy. The protective fat pads over the heel and metatarsal heads become displaced, and atrophy exposing bony prominences to pressure damage and callus formation could lead to ulceration
    c) Autonomic: leads to lack of sweating, dry skin, cracking and endothelial dysfunction
2. Peripheral arterial disease (PAD) leading to ischaemia
3. A history of previous DFU.

A number of classification systems for DFU have been developed, including PEDIS (perfusion, extent, depth, infection, sensation),[91] by the International Working Group on the Diabetic Foot (IWGDF), SINBAD (site, ischaemia, neuropathy, bacterial infection, area, depth)[33] and Wound Ischaemia and Foot Infection (WIfI).[92] DFU are, however, generally classified by the Wagner and University of Texas systems.[93–95] These classification systems effectively stratify the ulcer by the level of risk it presents. Risk stratification for a DFU is a critical input for planning and delivering care.

Arterial ulcers

The main risk factor for arterial or ischaemic ulcers is arterial disease manifested as poor blood supply to the extremities and low partial pressure of oxygen in tissue.

Pressure ulcers

A triumvirate of aetiology-specific factors create critical risks for the formation of PU.[96] These are the forces of pressure, friction and shear. Pressure deforms tissue and may occlude blood supply. Pressure causes direct damage to tissue faster than ischaemia does[97–99] and leads to shear forces, which deform tissue structures over bony prominences. Tissue that has been starved of blood supply may be damaged by reperfusion injury from reactive oxygen molecules when the patient is moved to re-establish blood supply. Shear forces also arise from the effects of friction at the skin surface, which causes lateral skin deformity and shear damage.[100] Moisture increases the friction of skin, exacerbating the effects of friction-related deformity.[101] A previous PU is a further risk factor for new PU formation. Traditionally, PU are classified by a grading system that takes account of the depth and severity of skin damage.[96]

Clinical risk factors

A wide range of clinical factors not directly related to the aetiology[102] of the wound are risks for hard-to-heal wounds. These include: the number of concurrent wounds of any aetiology; obesity; increasing age; poor nutritional status; diabetes; local or systemic hypoxia; ischaemia[103] and arterial supply to the lower extremities indicated by the 6-minute walking test; arterial hypertension; dyslipidaemia and metabolic syndrome;[104] critical limb ischaemia;[105] the presence of biofilm; clinical infection; genetic factors; smoking; lymphatic insufficiency; chronic inflammatory disorders; cancer; immune suppression or immunological disorders; and systemic medications. Wound size greater than 10cm^2 and ulcer duration greater than 12 months[106] are independent prognostic factors.

Non-clinical risk factors

They include: psychosocial factors;[107] educational attainment and its relationship to understanding the care needs of the wound; patient beliefs; dementia; depression; social support; adherence to or concordance with care pathway;[108,109] the impact of the care pathway on the patient's activities of daily living (AoDL); patient choice; patient's own goals; quality of life (QoL); previous experience of treatment; mobility; reduced ability to self-care as a result of comorbidities and/or frailty; sleep disorders; environment and living conditions, including distance from the clinical setting and living alone; access to care; and patient's economic situation where, for example, travel to a clinical centre or treatment is self- or part-funded. It may not be possible to address all of the patient's non-clinical risk factors. Patient-related risk factors and their management are addressed in Section 6.

Service-delivery factors

There is increasing evidence for sub-optimal service delivery in which wounds are not managed using best practice. Examples include: inadequate diagnosis; failure to identify the wound type; not using best practice for managing underlying pathology; poor selection of dressings; and lack of adequate, health professional education and training.

Patient management

Measurement of the reduction in wound surface area at four weeks is an accepted marker for progression to wound closure.[110–114] Past research involving lower extremity ulcers has demonstrated that a <40% reduction at four weeks for a VLU and <50% reduction at four weeks for a DFU indicates the ulcer is refractory to the current treatment plan.[111–114] Other studies have confirmed that PUs with <20–40% change in size over initial 2–4 weeks provide a reliable indication that the wound is not responding to treatment.[115] These metrics provide wound care clinicians with an expected trajectory of healing, 40–50% reduction at four weeks, that can be reasonable applied to all wounds. At this stage, a change in management or reevaluation of aetiology is warranted; furthermore, wounds that fail to close by at least 40–50% over four weeks of a good SoC are not likely to heal fully without more specific

intervention. Such wounds require more focused and intensive intervention.

Here we introduce a modified, best-practice system—TIMERS—designed to ensure that Tissue, Inflammation/Infection, Moisture balance, wound Edge, Regeneration of tissue and Social factors are addressed.

Risk factors (Section 2) must be identified, as should the underlying pathophysiology (Section 3) and a wound assessment, along with a full holistic assessment of the patient (Section 4), all must be completed. A care plan should be agreed with the patient and implemented, with primary focus on modifying the underlying pathophysiology and risk factors, and providing local wound care according to the principles of TIMERS. Follow-up and measurement of the wound size/volume should be carried out over a period of four weeks. At the 4-week juncture, a wound that has satisfactorily reduced in surface area by at least 40–50% should continue on the elected care plan, with ongoing monitoring and measurement. Should the healing trajectory of this wound fall below the expected progression (at least 40–50% reduction), then the patient should be referred to specialist health professionals or a complex wound clinic.

Section 3. Pathophysiology of hard-to-heal wounds

The majority of hard-to-heal wounds are associated with risk factors, as discussed in *Section 2*. In addition to patient-related, non-clinical factors, and to clinical risk factors not directly related to the wound, a critical feature is the presence of an underlying endogenous pathophysiological cause.

Acute wounds may be characterised broadly as those with an identifiable acute external cause, little to no causative pathophysiology, and thus a controlled inflammatory response[116] and largely predictable healing. In contrast, chronic, hard-to-heal wounds are characterised by a physiological barrier to recovery before the breach in the skin appears, an underlying pathophysiology, chronic inflammation,[117–119] and a mostly unpredictable healing trajectory. The inflammatory impact of the presence of biofilm[120] is overlaid on the patient's pathophysiology. Clinically, these differences mean that acute wounds are usually treated by managing the wound environment and the risk of infection, whereas chronic wounds also require a focus on and management of the underlying pathophysiology and risk factors. *Fig 2* shows the major molecular factors that need to be addressed to allow optimal healing.

From underlying cause to wound: the tissue breakdown pathway

Excellent overviews of the chronic wound pathophysiology may be found in a number of reviews.[119,121,122] It is critical to manage the underlying cause to encourage healing. The cycle of relentless chronicity must be broken to manage and reduce the persistent inflammatory state and encourage conditions that are conducive to healing.[123]

Endogenous tissue-breakdown mechanisms, common to all skin ulceration, have three main components:

1. Tissue-destructive enzymes, principally matrix metalloproteinases (MMPs)

2. An oxidative environment caused by reactive oxygen species (ROS)

3. Impaired endogenous control mechanisms that modulate enzyme activities.

These mechanisms are capable of destructive tissue breakdown leading to wound formation, the key driver of which is a chronic inflammatory stimulus driven by the nature of the aetiological causes.[117,119,124,125] Chronic stimulation of the endothelial lining of blood vessels[117] sets up a persistent cycle of leukocyte adhesion to the vessel walls,[117] extravasation of leukocytes and accumulation of neutrophils and macrophages, creating a complex, persistent inflammatory state. The expression of inflammatory cytokines and growth factors is disturbed compared with acute wounds,[126–128] leading to over-expression of several proteases[129] such as MMP-1, MMP-9 and MMP-8, elastase and plasminogen activators (PA).[130–134] PAs activate plasmin, an important activator of MMP[135] and ROS[136,137] in tissue. PA is expressed in non-ulcerated skin of patients with chronic venous disease, possibly indicating its role in the development of VLU.[138] Exacerbating the effects of the over-expression of proteases capable of degrading dermal extracellular matrix (ECM) is the concomitant down-regulation of the inhibitors that keep the protease activity in check:
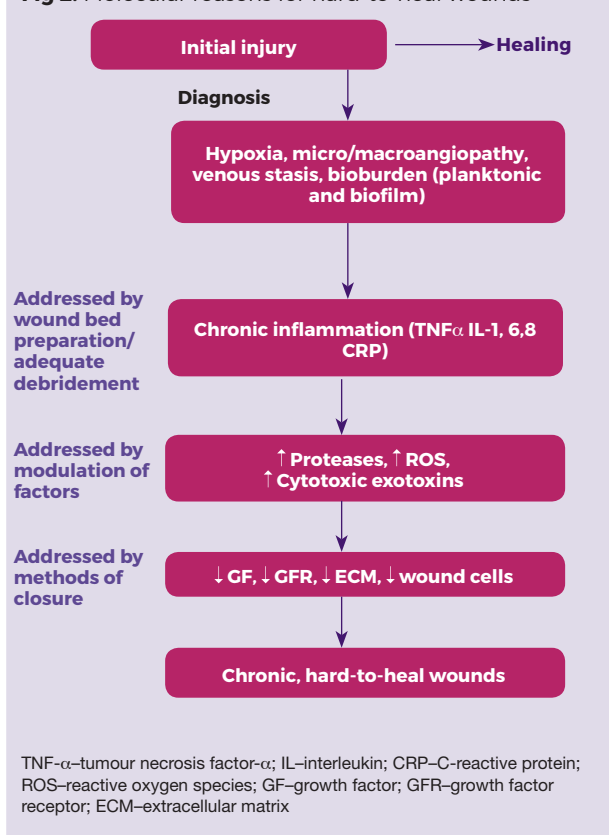
tissue inhibitor of metalloproteinase-1 (TIMP-1) and TIMP-3.[139–142] Together, the effect of higher levels of proteases and reduced expression of TIMPs contributes significantly to wound chronicity. Fibroblasts become quiescent/senescent[143,144] or themselves may have over-express of collagenase, elastase and stromelysin, and reduced levels of TIMP-1 and TIMP-3.[145] Fibroblast senescence has been associated with slow healing.[146,147] The overexpression of proteinases and ROS is responsible for creating a dysfunctional ECM with reduced integrin binding[148] that does not support cell migration and wound healing.

Biofilm in hard-to-heal wounds

Biofilm is a complex polymicrobial community of microorganisms embedded in a predominantly extracellular polymeric substance (EPS) that protects the microbes from antimicrobial activity (Box 1). Biofilm is now believed to be ubiquitous in chronic wounds,[149,150] and once removed, is able to reform quickly,[151] unless prevented from doing so. Biofilm has been recognised as an important contributor to the hard-to-heal status of chronic wounds.[120] While there is no direct clinical evidence from chronic, hard-to-heal wounds that biofilm is solely responsible for poor or non-healing, there is a wealth of evidence that implicates biofilm in wound chronicity.[149] The consensus is that biofilm stimulates chronic inflammation,[152] thereby adding to the burden of endogenous inflammatory stimulus. Biofilm expresses inflammatory signals[153] that attract neutrophils[154,155] and may interfere with neutrophil function, causing inappropriate degranulation releasing proinflammatory cytokines.[156] Biofilm inhibits activation of the complement cascade,[157] induces microRNAs that inhibit tight junction proteins that maintain skin barrier function,[158] reduces the effect of host defences[159] and affects pH and local oxygen concentrations.[160,161] Preclinical

Fig 2. Molecular reasons for hard-to-heal wounds

Initial injury → Healing

Diagnosis

↓

Hypoxia, micro/macroangiopathy, venous stasis, bioburden (planktonic and biofilm)

↓

Addressed by wound bed preparation/ adequate debridement

Chronic inflammation (TNFα IL-1, 6,8 CRP)

↓

Addressed by modulation of factors

↑Proteases, ↑ROS, ↑Cytotoxic exotoxins

↓

Addressed by methods of closure

↓GF, ↓GFR, ↓ECM, ↓wound cells

↓

Chronic, hard-to-heal wounds

TNF-α–tumour necrosis factor-α; IL–interleukin; CRP–C-reactive protein; ROS–reactive oxygen species; GF–growth factor; GFR–growth factor receptor; ECM–extracellular matrix

evaluations of healing in wounds with biofilm have shown impaired healing.[162] Overall, current opinion supports the importance of biofilm as a mediator of chronicity in hard-to-heal wounds.[163] Furthermore, biofilm begins to reform after debridement within 24 hours.[164]

Hard-to-heal ulcer cells: can they heal a wound?

Fibroblasts explanted from chronic, hard-to-heal VLU tissue grow significantly more slowly than fibroblasts from acute wounds or normal skin. Chronic wound fibroblasts respond less well to

Box 1. Biofilm: what you need to know

Biofilm is a polymicrobial community of organisms embedded in a complex extracellular polymeric substance (EPS) that protects the organisms from host-derived and medical antimicrobial activity. Organisms in biofilm are tolerant of systemic and topical antimicrobial agents, which are restricted from gaining access to the organisms, and by alterations in the metabolism of organisms in biofilm. It has also been shown that biofilm contains fungi as well as bacteria.[338] There is no point-of-care diagnostic test for wound biofilm and it is not possible to make a definitive diagnosis of wound biofilm by eye, so it is possible that a wound affected by biofilm will not be identified as such. A wound that is impeded by biofilm but is not managed as such adds cost to the care and continued poor QoL for patients.

The determination that a wound is not healing because of biofilm is based on research that established biofilm is present on over 70% of all chronic wounds,[149] and by eliminating other possible causes of non-healing through the implementation of a high standard of care that addresses identified risks and underlying causes and by observation of surrogate signs for biofilm. Chronic wounds by definition generally present with biofilm in the wound which should be addressed at the initial encounter. Signs that a wound is likely to be hard-to-heal because of the presence of biofilm include:

History of or current recalcitrance to antibiotic or antimicrobial treatment
Treatment failure, even with appropriate antibiotic or antimicrobial treatment
Delayed healing
Cycles of recurrent infection/exacerbation
Excessive moisture and wound exudate
Low-level chronic inflammation
Low-level erythema

Box 2. What is cell senescence?

Senescence is a cell state related to the number of cell divisions that a cell has experienced. During every cell division, a part of the chromosomal structure—the telomere—shortens until a limit is reached. The limit, known as the Hayflick limit, determines when a cell will be subject to programmed cell death ('apoptosis'). As telomeres shorten, the cell's proliferative potential is reduced.

inflammatory cytokines and MMPs.[167] A chronic wound in which unregulated chronic inflammation exsists is likely to have experienced several cycles of cell division, each of which will have led to telomere shortening and increasing the proportion of wound cells that are senescent. Senescent fibroblasts are now considered important contributors to the chronicity of ulcers, and these characteristics of senescence help provide a mechanism. Box 2 explains cell senescence.

Hard-to-heal wounds are also likely to be related to impaired proliferation as a result of senescence following normal ageing or accelerated cell proliferation in the inflammatory wound environment. Biofilm may also play a role in increased senescence in wound cells through stress and secreted factors that target and usurp host cellular pathways.[168] However, as noted in Agren et al's study,[165] cell proliferation may not be abolished completely. There is no point-of-care diagnostic to identify senescence in chronic ulcers; however, it is reasonable to assume that at least a proportion of cells in a wound are senescent. This implies that, in many, if not most ulcers, the cells are able to mount a proliferative response, which will contribute to healing. Clinically, the strategy must be to provide the wound environment most conducive to healing for the cells in the wound. The strategy is accurate patient and wound assessment, wound bed preparation (WBP) and TIMERS, as discussed in Section 4.

platelet-derived growth factor BB (PDGF-BB). Moreover, fibroblasts from leg ulcers of a longer duration show morphology consistent with aged or senescent fibroblasts.[165] Studies show that neonatal fibroblasts, which have a high proliferative rate, are impaired in the presence of VLU wound fluid.[166] In addition, senescent cells have an altered phenotype—senescence-associated secretory phenotype (SASP)—which relates to increased expression of

Section 4. Fundamentals of standard of care

The most important components of an effective SoC are:

- Early intervention
- Accurate assessment and diagnosis of the patient and wound
- Optimal patient and wound management strategy
- Appropriately-skilled health professionals
- Early referral to specialists.

A patient managed without delay using the optimum care plan is more likely to heal.[169] The speed of healing diminishes with increasing age of the patient,[170,171] which is associated with alterations in the expression of growth factors,[169] MMPs,[172] tissue inhibitor of matrix metalloproteinases (TIMPs),[173] elastase,[133] and reduced deposition of ECM constituents.[174] Wound healing also diminishes with increased wound age.[175]

The healing response is controlled by risk factors and comorbidities (Section 2) that are independent of the inherent capacity of the tissue to repair. In order for SoC to be effective, it must modify the risk factors and the effects of comorbidities, as well as deliver care that optimises the probability of healing.

Optimal wound healing occurs when the same effective SoC is delivered across the whole care pathway as the patient transitions between health professionals and care settings. The care pathway defines who does what, with which products/devices, using which methods and services, and in which care settings. It is well-established that the high standard of care delivered through a multidisciplinary team (MDT) approach leads to better outcomes.[64,169,176–178] Although the evidence may be relatively weak, effective multidisciplinary communication is likely to lead to better care.[179]

A number of expert international, national and local guidelines have been produced specific to the main wound aetiologies and to processes in the wound management pathway and as general guidelines that cover most major wound types. Health professionals should refer to these guidelines, appropriate to their health-service delivery, for best

Key points

- Standard of care (SoC) is crucial for wound healing and a series of international, national and local guidelines are available for health professionals to refer to
- SoC must modify the risk factors and the effects of comorbidities, as well as deliver care that optimises the probability of healing
- Optimal wound healing occurs when the same SoC is delivered across the whole care pathway
- A 10-step approach in the management pathway required for each wound is outlined in this section

practice. A list of guidelines is provided in *Box 2* (note that this is not a complete set of guidelines, but is intended to illustrate examples that cover all aspects of a good SoC). Health professionals are advised to consult their local health-care providers for information on guidelines used in their clinic, region or country and adopt those. Where recommended guidelines have not been identified, health professionals should select the most appropriate from those presented, or conduct a search for guidelines relevant to their circumstances.

Wound management pathway and process guidelines

There are a number of management and process pathway guidelines, including Biofilm Guidelines: The Global Wound Biofilm Expert Panel,[120] Infection Guidelines: The International Wound Infection Institute (IWII);[180] WBP and TIME;[181,182] see Box 3.

The overarching SoC for any wound comprises a logical set of actions informed by the requirements of effective care. These actions are:

1. Holistic patient assessment: physical, psychological, spiritual and social needs. This

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Box 3. Best-practice guidelines to consider if local/national guidelines are not available.

Wound bed preparation and TIME

Wound bed preparation: TIME for an update[171]
Management of chronic wounds: diagnosis, preparation, treatment and follow-up[172]

Infection and biofilm

Consensus guidelines for the identification and treatment of biofilms in chronic nonhealing wounds The Global Wound Biofilm Expert Panel[120]
Wound Biofilm: current perspectives and strategies on biofilm disruption and treatments[253]
Wound infection in clinical practice: The International Wound Infection Institute (IWII)[180]
Sepsis: recognition, diagnosis and early management. NICE guidelines [339]

DFU

Diabetic foot problems: prevention and management NICE guidelines[194]
Prevention and management of foot problems in diabetes: a summary guidance for daily practice International Working Group on the Diabetic Foot (IWGDF)[199]
Local management of diabetic foot ulcers. (WUWHS)[340]
Identifying and treating foot ulcers in patients with diabetes: saving feet, legs and lives JWC consensus document[93]
A clinical practice guideline for the use of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers[341]

Pressure ulcers

PU Guidelines. EPUAP, NPUAP, PPPIA[96]

Lower limb and odema

Management of venous leg ulcers: Clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. Society for Vascular Surgery; American Venous Forum[342]
Wound Healing Society 2015 update on guidelines for venous ulcers. WHS[198]
Management of patients with venous leg ulcer: challenges and current best practice. EWMA[81]
Best Practice Statement: Holistic management of venous leg ulceration. Infectious Diseases Society of America[343]
Wound healing society 2014 update on guidelines for arterial ulcers. WHS[344]
Standards of practice for lymphoedema services British Lympology Society.[345]

Assessment

Best Practice Statement: Improving holistic assessment of chronic wounds. London: Wounds UK, 2018[346]

Note: this list is not comprehensive and many others are available

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must include and identify the underlying pathophysiological cause(s) and risk factor(s)
2. Wound assessment: measurement
3. Decide the desired outcome (healing or maintenance) and care plan
4. Address/manage the underlying pathology or plan maintenance care
5. Implement local wound care according to WBP/TIME, etc or maintenance/palliative care
6. Follow-up, reassessment and measurement
7. Modify the care pathway and refer if necessary to specialists or MDT
8. Patient/family education throughout the SoC
9. Discharge or transition to maintenance treatment to prevent recurrence
10. Record actions/outcomes at every episode of care.

In some cases, steps 1 and 2 overlap and may not take place in that order; however, all should be performed before a treatment/maintenance care plan can be successful.

A suggested timeline for treatment and referral is outlined in *Fig 3*. Wound management should be conducted by an individual wound care or tissue viability specialist. The expected skill-set for this individual includes:
- Revisit holistic assessment
- Establish the underlying cause
- Identify barriers (pathophysiology and risk factors) to healing
- Referral to a complex wound clinic or MDT, as appropriate

The specialist individual should be competent to undertake the steps involved in TIME:
- Debride using autolytic, enzymatic, mechanical, sharp, ultrasound or larval debridement
- Treat local or systemic infection and ensure the biofilm pathway is followed
- Ensure adequate moisture levels by selecting the appropriate dressing
- Provide an environment for encouraging wound edge advancement.

The specific steps in the management pathway required for each wound and each wound type must

Fig 3. Timeline for suggested treatment and referral

First presentation: Day 1

A wound of four-week duration (including four weeks of treatment) and identification as 'hard-to-heal'
Same timeframe/indications for specialist complex clinics

At four weeks/30 days 40–50% decrease
Indicators to failed treatment include: Clinically ↓ , ↑ Exudate, ↑ Devitalised tissue, ↑ or new onset Pain,
progression or recurrent infection, ↑ Maceration

Referral required

Individual specialist (limited skill-set/access to therapies)

Complex wound clinics: multidisciplinary teams

be tailored to the patient and wound, and at every stage of wound progression. Different wound types/aetiologies require different approaches to diagnosis and management of the underlying causes and risk factors. Outside of the common chronic wound types (arterial ulcers, DFU, PU and VLU), a number of other underlying conditions also predispose a wound to become hard-to-heal.[183,184] These include: Marjolin's ulcer, associated with squamous cell carcinoma; pyoderma gangrenosum, a non-infectious, inflammatory skin disease often associated with Crohn's disease, colitis ulcerosa, rheumatoid arthritis and other conditions; radiotherapy causing radionecrosis; erysipelas; mycosis fungoides, a form of cutaneous T-cell lymphoma; and the infection-related Buruli ulcer, caused by *Mycobacterium ulcerans*. These should also be managed in the same way as other hard-to-heal wound aetiologies and follow a referral-and-treatment pathway. The specific details of their treatment are outside the scope of this document. Basic wound easement is outlined in Fig 4.

1. **Holistic patient assessment.** A wound may be

hard-to-heal because of factors that are local to the wound, affect the limb or anatomy more generally, or are related to the whole patient and their beliefs and environment. All these factors should be identified by discussion with the patient. Holistic assessment identifies past medical history, assesses the limb or anatomy and records the wound history.[185] Factors to assess include medical history, comorbidities, obesity, functional status, mobility, ankle reflex, smoking, medications, laboratory parameters and vital signs, nutrition, and an assessment of the ability of the patient to adhere to an agreed care plan.[121] In obtaining this information, staff should help identify pathological causes and risk factors (ie comorbidities, life style), although further information or testing may be required, as outlined below.

Risk factors. Include parameters identified in the patient assessment and pathophysiology (*Fig 1*). Identifying the risk factors that are the dominant influencers of non-healing is critical to effective management of the patient.

Fig 4. Fundamentals of wound assessment and referral

Holistic assessment: *international/local guidelines/best practice statements, Patient risk factors of a hard-to-heal wound, additional assessment (eg venous duplex, biopsy)*
Wound assessment: *volume, extent, area, exudate*

Diagnosis: *refer on if appropriate/required*

Treatment: *standard to best practice, including wound bed preparation, initiation of biofilm prevention/treatment, TIMERS wound assessment, control oedema, refer to local formulary*

Patient-centred outcomes: *healing or maintenance (this needs to be a multidisciplinary team approach)*

Modifying these risk factors where possible will increase the chances that the wound will heal. **Pathophysiological cause(s)**. Diagnostic procedures, alongside patient history, should be used to identify the underlying pathophysiology of the wound. Minimally, an assessment of vascular status should be made. A range of methods are available to achieve this: pulse palpation, ABPI, toe pressure and radiological imaging, including duplex Doppler ultrasound, MRI and computed tomography (CT) imaging. An ABPI <0.8 or 0.9 may indicate arterial involvement, but care should be taken with patients with diabetes who may have hardened arteries that will lead to a false, high ABPI value. In this case, the patient should undergo more detailed vascular assessment using methods other than ABPI. Where significant peripheral arterial disease (PAD) is identified or suspected, the patient should be referred to a vascular specialist before debridement and compression are implemented. Oedema, which may be related to the underlying pathophysiology or to comorbidities such as congestive heart

failure, lymphatic failure and medication, should be assessed. Compression, although not strictly contraindicated, is a relative contraindication in congestive heart failure. Foot ulcers should be examined for the presence of diabetes-related causes, such as neuropathy. A number of methods are available to achieve this, including the simple Ipswich touch test that requires no equipment; touch perception using monofilaments; vibration perception threshold; or more complex electromechanical tests.[93] The classification of the wound at this stage may be neuropathic or neuroischaemic. Particular care should be taken to distinguish a PU on the foot in a person with diabetes and a DFU, because of the requirements of different MDTs needing to be involved.[93]

2. **Wound assessment and measurement.** Parameters that should be assessed include depth, volume, extent, area, exudate (amount and type), location, appearance, temperature, odour, overt and subclinical infection and structural deformity. The presence and relative

amounts of different tissue types in the wound should be assessed. These include slough, necrosis, granulation tissue, and epithelial cells. Wound size (depth and area) should be measured using the best available method. Size can be measured using simple methods, such as a tape measure and sterile cotton tipped applicator—more detailed methods include tracing and planimetry, or advanced electronic devices such as Tissue Analytics's wound management platform, capable of accurately photographing, tracking and analysing patient wounds, with automatically calculated metrics that include measured depth and area, and the creation of an electronic record for the patient notes.[186] Wound volume can be estimated by covering the wound with a plastic film and injecting a gel, to be sucked out and measured. It is important to use the clock method to indicate undermining etc. Infection should be identified based on clinical signs:[180] redness, swelling, heat, pain, presence of pus, malodour and, in the case of DFU where osteomyelitis is suspected, probing to bone. Osteomyelitis may be present in a DFU without overt clinical signs of inflammation; imaging should be used to rule out osteomyelitis.[121] Please note that overt signs and symptoms of biofilm are not always present and should be considered early in treatment before clinical signs of infection present. Specimens for microbiological analysis should be taken.[121] Surface swabbing is considered the minimum level of sampling and tissue biopsy is regarded by some as the standard. When swabbing, the wound must be cleansed first and the swab taken under/along the wound edges. Pus may also be collected for microbiological analysis. Results from microbiological analysis will not confirm or refute the presence of infection, but are used to guide antimicrobial therapy. This is why all wound culture results should be clinically correlated when determining the necessity for initiating antimicrobial therapy. Infection is a clinical diagnosis of tissue invasion by microbes

that have elicited a host-defensive, inflammatory reaction. It is distinct from colonisation or contamination. Biofilm is likely to be present in almost all chronic wounds, but cannot yet be diagnosed, other than by biopsy and microscopy.[120] Where biofilm is determined to be a cause of a hard-to-heal wound, a biofilm-management pathway should be implemented at the initial stages of treatment, as discussed later.

3. **Decide the desired outcome (healing or maintenance) and care plan.** Assessment provides the input to the decision on the desired outcome. In many cases, this will be a healed wound. However, an alternative may be maintenance of the patient where healing is unrealistic, for example in a critically-ill patient at the end of life, in which case management may be focused on maintaining dignity, managing wound symptoms such as infection, pain, exudate and reducing odour. Limb amputation may be a desired outcome if healing is unrealistic and the patient prefers it or when the risk of complications related to an open wound is higher than the risks of amputating. The desired outcome determines the care plan, the elements of which should state how the patient and wound will be managed, using which methods and involving the appropriate health professionals through referral, if necessary. The desired outcome and associated care pathway should be agreed with the patient and their assent to adherence to it gained.

4. **Address/manage the underlying pathology.** Clinicians should refer to the guidelines for the recognised standards of care for managing the underlying pathology. In the case of VLU, the standard is to manage oedema and venous hypertension using compression,[81,187] delivered by using one of a number of different methods including short- or long-stretch elastic bandaging, hosiery, pneumatic devices, or

inelastic products such as Unna boot or orthostatic wraps (Circaid, Medi; JOBST FarrowWrap, Essity T/A BSN medical). Patients should undergo venous imaging to identify if there is any venous disease which, when corrected, would increase the rate of healing and reduce risk of recurrence. VLU healing was significantly higher in a 450-subject randomised controlled trial (RCT) with early venous reflux ablation (EVRA) to correct venous disease and compression, compared with compression alone.[188–190] Hosiery may be used for post-healing prevention of recurrence and higher compression is more effective than lower.[191] Long-term follow-up outcomes from the EVRA trial, evaluated in the ESCHAR trial, shows that recurrence was reduced in patients who underwent EVRA.[192]

For an uninfected DFU, the standard is offloading and management of diabetes. Offloading may be achieved with a number of different approaches, including simple shoes, orthotics, removable walker boots or non-removable total contact casts (TCC). Clinical outcomes are better with non-removable offloading devices,[193] especially in non-adherent patients. Ischaemic DFU and patients with PAD should be assessed for a possible vascular intervention to reinstate blood supply if indicated and before any sharp debridement. In patients in whom the ABPI is <0.8 and >0.5, the practitioner should determine whether the PAD or venous disease is the predominant factor in hard-to-heal wounds and manage the patient accordingly. Patients in whom ABPI is <0.5 should have revascularisation if access to the skills and service is available; some authorities advocate referral to a vascular specialist for any abnormal ABPI. The standard for managing the underlying cause with PU is pressure relief or reduction, which may be achieved by frequent repositioning and/or the use of pressure-relieving products such as cushions, pads, mattresses, and advanced beds with automated alternating inflation of pneumatic cells.
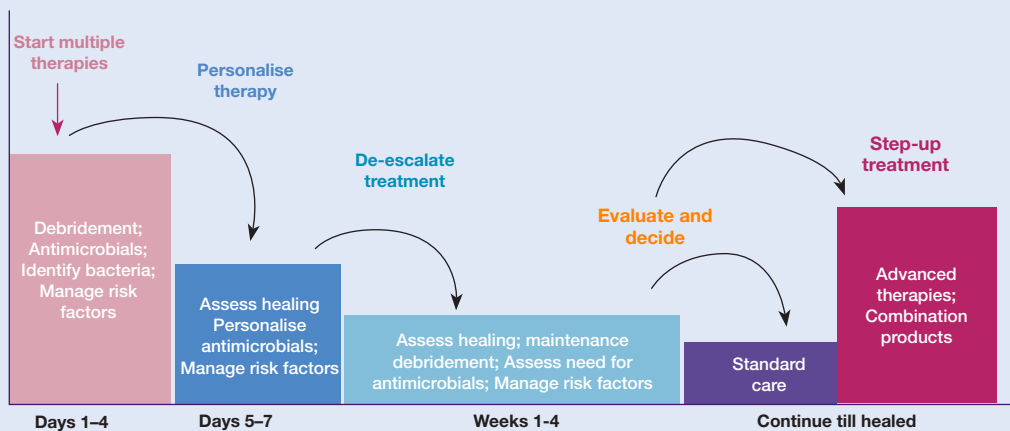
5. **Implement local wound care according to WBP/TIME, etc.** The fundamentals of local wound care are summarised in the acronym TIME, which stands for tissue, infection/inflammation, moisture imbalance, wound and edge.[181]

Note: this consensus panel recommends updating TIME to TIMERS, integrating regeneration/repair of tissue (R) and social factors (S). The new framework, discussed in Section 5, along with the main elements of TIME, provides structured guidance on approaches to managing wounds and identifies where advanced adjunctive therapies should be considered alongside standard care.

6. **Follow-up, reassessment and measurement**. A patient with a hard-to-heal wound should be followed up and re-assessed at every dressing change and/or treatment episode. Where the wound has not responded, the re-assessment should evaluate risk factors, comorbidities and underlying causes. In cases where the response is <40–50% at four weeks, it is appropriate to consider causes that may not be readily visible to the naked eye on clinical assessment, including malignancy. The appropriate diagnostic tests, for example, biopsy and histology, should be considered and the patient referred. Measurement of the wound size is mandatory at each dressing change and photography should be considered as part of the patient records. Some assessments conducted at the initial presentation may not be necessary; an example is ABPI, which is unlikely to change significantly over a short period. However, if ABPI was the only vascular assessment method used at presentation, referral for more detailed vascular assessment by duplex ultrasound or other

Fig 5. Proposed step-down and then step-up biofilm pathway. Adpated from Schultz et al.[120]

Start multiple therapies

Personalise therapy

De-escalate treatment

Evaluate and decide

Step-up treatment

Debridement; Antimicrobials; Identify bacteria; Manage risk factors

Assess healing Personalise antimicrobials; Manage risk factors

Assess healing; maintenance debridement; Assess need for antimicrobials; Manage risk factors

Standard care

Advanced therapies; Combination products

Days 1–4   Days 5–7   Weeks 1-4   Continue till healed

perfusion assessments is warranted. If the patient receives revascularisation procedures, retesting for maintenance of blood flow should be done within 30 days of the intervention. If maintenance/palliative pathway was followed, check if this is meeting the goals set, such as pain control, management of exudate, prevention of infection. Also check for unexpected deterioration.

7. **Modify the care pathway and referral**. Implementing a high SoC will recognise that the current management pathway is ineffective or less effective than expected. The individual wound care specialist or tissue viability specialist should then escalate care to a complex wound clinic and/or MDT. In the case of DFU, guidelines state that a patient newly diagnosed with a DFU should be referred early[36] and, in some guidelines, within 24 hours to the MDT.[194] Best practice, and the recommendations in this consensus, stress that chronic, hard-to-heal wounds of all types should be managed by health professionals in a multi-professional service structure. The MDT is defined by the skill set and clinical procedures required, not the profession

of the members and must be multi-professional and characterised by strong internal communication. Other specialities that may be integrated into a DFU MDT include podiatric skills, endocrinology and nutrition. The MDT may be stratified by the level of care[195] that may be delivered and a 3-level structure. Competencies recommendations for a DFU MDT have been made by the IWGDF. A recommended clinical skills mix required for effective inpatient management of DFU has also been made.[196] The skills are:

- Performing haemodynamic and anatomic vascular assessment and revascularisation
- Performing neurological workup
- Performing site-appropriate deep culture to direct antibiotic therapy
- Performing bone assessment, for example, X-ray or CT scans
- Wound assessment and staging/grading of infection and ischaemia
- Performing bedside and intraoperative incision and debridement to decompress abscesses
- Initiate and modify culture-specific and patient-appropriate antibiotic therapy
- Performing postoperative monitoring to

reduce recurrence and reinfection

- Provide basic foot care education through the care pathway.

The integration of these skills should also be considered whenever possible in the development of MDTs at outpatient complex wound clinics. Unfortunately, these are not generally established for management of patients in the community, but are common in the acute setting, for example, a surgical team. This does not mean that referral can be ignored when a wound does not respond as the objective of the care plan states. The patient should be referred for specialist management using either escalated diagnosis and assessment tools, clinical interventions that require differently skilled practitioner(s), or advanced products that require different skill levels. Referral to the MDT or specialist is indicated by non-responsiveness to SoC and/or when the wound status has worsened.

Examples of interventions that may require different skill levels include surgical debridement for a patient who has been managed using autolytic or mechanical debridement, vascular reconstruction, microbiology and infection control where wound infection is suspected, or plastic surgery. The biofilm pathway[120] is a case where referral may be required. Referral to an MDT may not be necessary, but patients managed in the biofilm pathway must have at least a tailored management plan. The reader is directed to the consensus for further detail on the biofilm pathway.

It is generally assumed, based on the available evidence, that all chronic wounds contain biofilm.[149] *Fig 5* shows a schematic of how it is suggested that the biofilm care pathway is implemented.[120] The pathway follows well-established principles based on the natural history of biofilms and clinical practice in managing them. The pathway relies on assumptive early intervention with a de-escalating series of steps to remove as much biofilm as possible and prevent its regrowth. From around day one to day four, implement multi-modal therapies, including: aggressive debridement if indicated, biofilm directed topical antimicrobials and systemic antibiotics; however, systemic antibiotics should be backed up with microbiological data. The next stage, up to approximately one week, is assessment of response, further debridement appropriate to the wound and personalised antimicrobial therapy. As the wound improves, treatment is de-escalated up to approximately four weeks. In the de-escalation phase, inflammation and healing are assessed, maintenance debridement implemented, antimicrobial strategy reassessed, and host factors are managed. The pathway may follow different paths at four weeks (depending on clinical response) until full closure, if that is the stated aim of the care plan. Where the wound shows potential for closure, then SoC is continued. Where the wound does not show promise of closure, through a reduction in size, treatment is stepped up, with the introduction of advanced products and continued standard care. If maintenance/palliative pathway is to be followed, the full MDT needs to be involved with any decision to palliate the patient.

8. **Educate the patient and family**. Education should be provided throughout the entire care pathway. In brief, the level of the patient's understanding of their condition and their ability to learn about it and its care should be determined. The health professional should tailor education to the patient and consider the need to educate others in the patient's family and social group in order to facilitate a greater degree of adherence and improve outcomes. If a maintenance/palliative pathway was followed, ensure patient's family/carer is involved in any decision-making.

9. **Discharge or transition to prevention therapy.**

In patients for whom all risk factors have been controlled but wound healing is not a realistic outcome, and this has been discussed and agreed with specialists, transition to maintenance or palliative therapy may be implemented. It is not acceptable to stop treatment for patients who are not expected to heal. Patients must continue to receive a high standard of care to alleviate symptoms that affect QoL and activities of living, and to prevent the wound deteriorating. In these cases, and where possible, the patient should receive care for the underlying pathology, including offloading, compression therapy, management of friction and shear forces or pressure relief, where indicated. Infection should be managed according to the TIME principles. Debridement should be done where indicated; wound moisture should be managed to maintain a healthy moisture balance in the wound and to manage leakage of exudate from the wound. Pain and odour should also be managed. The patient should be followed up as required, and care appropriate to the patient and wound should be delivered. The use of advanced therapies, as outlined in *Section 5* of this document, may not be appropriate clinically or economically. It is critical that this wound-management pathway is discussed in detail with the patient before embarking on it. Both the patient and the clinician must be fully appraised of the implications and be in agreement.

Once a wound has healed, if there are no underlying factors that predispose the patient to further ulceration or wound formation, then they will be discharged from care. Recurrence in chronic wounds with underlying causes, particularly VLU and DFU, is high. Strategies to prevent recurrence should be implemented. For VLU, continued elastic medical compression should be used for life.[197] The level of compression may be lower than that for the treatment phase.[198] Although higher compression is more effective, patients often find adhering to continued use challenging. Patients should have undergone venous assessment to determine the need for EVRA. For DFUs, the fundamentals of prevention of recurrence in plantar neuropathic DFU are continuous offloading, education, diabetes control, regular foot inspections and early intervention when signs of pre-ulcerated tissue are identified.[199] In patients with healed PU, focus on pressure relief and reduction, management of friction and shear, skin care and repositioning, along with management of comorbidities, should be used.

10. **Record keeping.** Meticulous recording of all patient interactions, interventions and outcomes with dates must be kept.

Diagnostics and assessment tools

There are few diagnostic tools specific to wound management applications available. A non-invasive method to visualise organisms in wounds as an aid to debridement is Moleculight (Smith & Nephew), which uses violet light to induce autofluorescence. A red or cyan fluorescence signals when bacteria are present, due to the presence of endogenous porphyrins or pyoverdine. Cyan is typically associated with the presence of *Pseudomonas aeruginosa*. Organisms distributed on the wound surface can be easily identified and their removal monitored.[200,201] Another non-invasive imaging system that has been used in assessing DFUs among other medical applications is hyperspectral imaging (HSI). Using the method, the visible and near infrared spectral range, has been shown to provide information on the physiological parameters, with high spatial and spectral resolution.[202,203]

A way to assess the microbiome (what microorganisms are present) of a wound is DNA sequencing, a diagnostic service offered by a number of different companies. It is a highly specific and sensitive technology that may be appropriate to countries and health-care systems with very developed health-care such as the US and some EU

and Pacific Rim countries. The output includes details on the organisms found and their relative proportions and a suggested wound-management plan based on the results, although cost and availability could be an issue.

There is no point-of-care tool to identify biofilm and best practice is biopsy, microscopy, or swabbing, although swabbing will not identify the absence of biofilm. Access to a diagnostic microbiology laboratory may not be possible in many locations, and biopsy is a specialised procedure that requires a specifically-trained practitioner. Where microbiology laboratory services and a health professional trained in biopsying are not available, other indicators of the presence of biofilm should be used.

There is no tool to predict whether or not a wound is likely to heal based on its biochemistry or metabolites. The principal method for wound diagnosis and measurement of healing is high-quality clinical observation and ongoing assessment by a health professional skilled in the area. Diagnostic methods that assist in determining the diagnosis of wounds include: vascular assessment with imaging technology, such as duplex ultrasound scanning; blood pressure in the extremities (for example toes); transcutaneous oxygen measurement; and near infrared spectroscopy (NIRS) of the oxygenation of blood. Neuropathy may be assessed, as discussed in the sub-section on identification of underlying causes. In patients at risk of PU formation, a tool is available to measure the presence of extravascular fluid, so-called subepidermal moisture (SEM), by measuring impedance. SEM is a marker of potentially harmful pathology developing in at-risk skin and typically identifies these changes before they become clinically observable by eye.[204] The use of this test may drive earlier intervention and prevent the formation of PU in at-risk patients.

Section 5. Advanced and adjunctive product use: when and how?

I t is important that every health professional understands the signs and indications that referral is necessary. In primary care, SoC consistent with the competencies in that setting should be used for two to four weeks and the progress of the wound monitored, although this is always dependent on the ability to treat the wound on presentation. This consensus panel recommends that a wound that does not reduce in size 40–50% by week four should be referred to a wound care specialist or complex wound clinic. This period to see evolution before referral does not go against strategies for early detection of complications. If criteria exist suggesting that the patient is at risk due to the wound, or that the wound may benefit from an early specialised treatment, a pathway for immediate referral should be activated. This may vary from country to country.

Health professionals should identify desired objectives and outcomes within timeframes to meet realistic goals for the patient. Where these are not met, the patient should be referred to the appropriate MDT/ advanced care setting. Advanced therapies appropriate to the competencies in the complex wound clinic/MDT should be deployed based on the outcomes of patient and wound assessment. Advanced adjunctive therapies are most likely to be used by complex wound clinics/MDTs because of the advanced skills in those settings.

The care pathway that the referred patient should follow is outlined in Section 4 on SoC, best practice for common wound types is outlined in Box 4. The 10 steps are the same; the implementation is more complex. The diagnostics will provide a more detailed assessment of the underlying factors that prevent healing, informing the therapies to be used. The treatments used in the care pathway are more discriminating than those at the primary care level and must be prescribed and used by health professionals with certified competencies in these complex therapies.
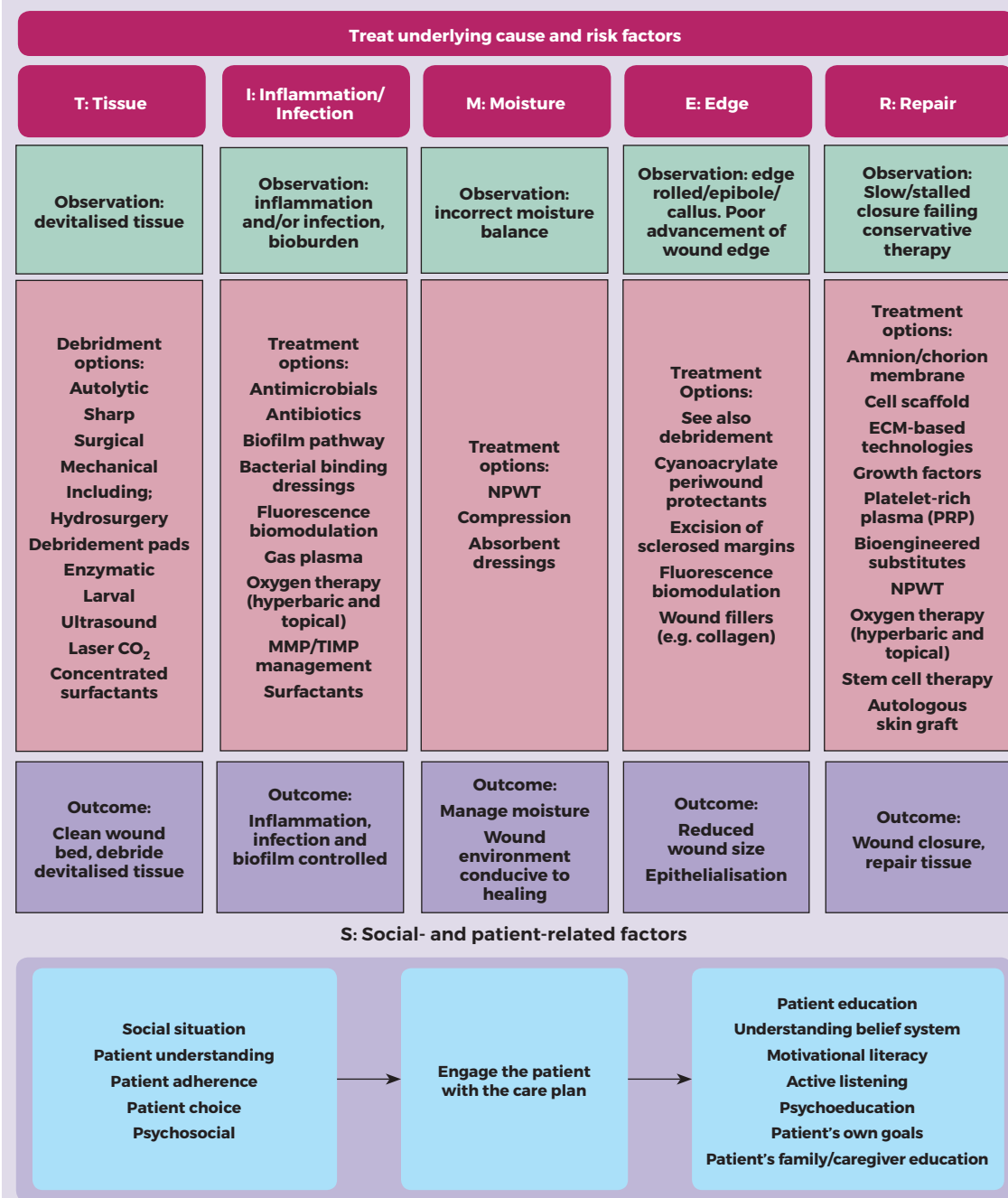
Key points

- We suggest updating TIME to TIMERS, adding repair/regeneration (R) and social factors (S)
- S is an overarching theme, as patient factors are crucial to healing
- When the desired outcomes and timeframes are not met, the patient should be referred to the appropriate multidisciplinary team (MDT) or advanced care setting
- Each element of TIMERS is supported by recommendations for advanced therapies and approaches, with evidence that they will meet the clinical goals

The first step in the care pathway is holistic patient assessment, clear identification of the underlying causes and risk factors, followed by wound assessment and measurement. The more detailed assessments used in a complex wound clinic/MDT will guide the definition of the desired outcome and care plan and how the patient and wound will be managed.

TIMERS

The TIME concept is a framework focused on management of specific, important parameters of the wound. When a wound does not respond, even when its management is guided by TIME, other factors that have an impact on outcomes must be recognised. This consensus panel recommends updating TIME to recognise these factors with the integration of repair/ regeneration (R) and social factors (S). The new framework provides structured guidance on approaches to managing wound parameters and it identifies where advanced adjunctive therapies should be considered alongside standard care. TIME becomes TIMERS:

Fig 6. TIMERS framework for managing hard-to-heal wounds. Diagnosis and holistic assessment, as well as social- and patient-related factors, are the foundation on which treatment should be based

Treat underlying cause and risk factors				
T: Tissue	**I: Inflammation/ Infection**	**M: Moisture**	**E: Edge**	**R: Repair**
Observation: devitalised tissue	Observation: inflammation and/or infection, bioburden	Observation: incorrect moisture balance	Observation: edge rolled/epibole/ callus. Poor advancement of wound edge	Observation: Slow/stalled closure failing conservative therapy
Debridment options: Autolytic Sharp Surgical Mechanical Including; Hydrosurgery Debridement pads Enzymatic Larval Ultrasound Laser CO_2 Concentrated surfactants	Treatment options: Antimicrobials Antibiotics Biofilm pathway Bacterial binding dressings Fluorescence biomodulation Gas plasma Oxygen therapy (hyperbaric and topical) MMP/TIMP management Surfactants	Treatment options: NPWT Compression Absorbent dressings	Treatment Options: See also debridement Cyanoacrylate periwound protectants Excision of sclerosed margins Fluorescence biomodulation Wound fillers (e.g. collagen)	Treatment options: Amnion/chorion membrane Cell scaffold ECM-based technologies Growth factors Platelet-rich plasma (PRP) Bioengineered substitutes NPWT Oxygen therapy (hyperbaric and topical) Stem cell therapy Autologous skin graft
Outcome: Clean wound bed, debride devitalised tissue	Outcome: Inflammation, infection and biofilm controlled	Outcome: Manage moisture Wound environment conducive to healing	Outcome: Reduced wound size Epithelialisation	Outcome: Wound closure, repair tissue

S: Social- and patient-related factors

Social situation Patient understanding Patient adherence Patient choice Psychosocial	→	Engage the patient with the care plan	→	Patient education Understanding belief system Motivational literacy Active listening Psychoeducation Patient's own goals Patient's family/caregiver education

T: tissue viability
I: infection/inflammation
M: moisture balance
E: wound edge
R: repair/regeneration
S: social- and patient-related factors.

TIMERS is a general framework (*Fig 6*) to guide care at all competency levels in all settings. Although relevant to all care settings, the details of wound management would vary according to each setting and health professional competencies.

The risk of complications is elevated when a wound is open.[205] The window of opportunity to minimise the likelihood of complications by encouraging the wound to heal is short; for example, a DFU that remains open for 30 days is associated with a 4.7-fold increase in the likelihood of infection and warrants an early intervention mind-set.[205]

Identification and management of social- and patient-related factors perfuses the entire TIMERS framework. Management of the underlying causes and risk factors is supported by a high SoC, using evidence-based, symptomatically-guided treatment for each of the components.

A wound that has been referred to a complex wound clinic/MDT may be managed with one or more modality, including adjunctive advanced therapies. The cost of advanced therapies may seem high; however, expensive therapy is any therapy that does not work, is not matched to the clinical goal, or is inappropriate for the patient. Such therapies lead to prolongation of the wound, low adherence and potentially adverse outcomes. Advanced treatment does not mean expensive treatment when used appropriately.

Definition of advanced therapy

The European Wound Management Association (EWMA) has defined advanced therapies for wound management as therapies that are based on novel

> **Box 4. Best practice for the most common wound types**
>
> *Venous leg ulcer*
> Compression therapy and venous intervention
> *Pressure ulcer*
> Pressure reduction, relief and redistribution
> *Diabetic foot ulcer*
> Offloading and management of diabetes
> *Arterial ulcer*
> Vascular reconstruction
>
> All can be aided by disruption of wound microbiota
>
> The overarching standard of care is holistic assessment and accurate diagnosis, leading to management of the underlying causes and pathophysiology using best practice according to expert guidelines

principles or technologies with a range of modes of action supported by comparative evidence.[206] Advanced therapies are categorised in the EWMA statement according to the technology that underpins them. The categories are: materials; cell and tissue engineering; physical and biophysical; sensors; and IT-related.

This consensus document categorises advanced therapies for wound management functionally in relation to the symptoms and clinical goals under TIMERS. Each of the six elements of TIMERS is supported by recommendations for advanced therapies and approaches, with evidence that they will meet the clinical goals.

Advanced therapy considerations

The size and location of the wound must be considered in the choice of any product, but particularly in the choice of advanced therapies. Their effectiveness could be compromised if, for example, a tissue equivalent is used on a plantar DFU and the patient is non-adherent to offloading. Wound healing located over a pressure point in most cases cannot be achieved without appropriate offloading. Effective, yet costly, treatment options should be avoided in situations where patient non-adherence

ensures treatment failure. Careful discussion with the patient and a clear understanding of their social situation and personal goals are required to assure that an appropriate product is used. Many products are incompatible with, and should not be used in, an infected wound. In these cases, therapy should be directed at addressing infection/biofilm. Commissioning of treatment services by the regional or national health services may also be a factor in the choice and use of advanced products.

Advanced therapies are not available to, approved in or affordable by all care settings. They may be covered financially by a health-care system only when a defined response threshold has been reached. An example is select Medicare Administrative Contractors (MAC), which will cover specific advanced therapies only after the wound has been managed for four weeks using SoC or other conservative measures. Some health-care systems require their clients to pay in full or in part for their treatment if their deductibles have not been met, and this may limit the use of treatment, particularly those priced higher per unit or treatment episode than less advanced wound care products.

The components of TIMERS

For each component of TIMERS, clinical intervention is defined along with functionally-linked therapies or processes (*Fig 6*). The outcome for each component is defined. Guidance on when not to use therapies is provided. The sixth component, 'S', is discussed in full in *Section 6*. T, I, M and E are similar to the equivalent components of TIME with regard to their definition, meaning and the goals of therapy.[181]

Tissue

The focus is on the presence of devitalised or non-viable tissue that does not contribute to healing and may play a role in delaying healing or facilitating infection. The clinical observation is the presence of such tissue and the goal is to eliminate it. Mechanical or sharp debridement is a more intensive or invasive

form of WBP than autolytic/enzymatic debridement, or cleansing with liquid products. Past studies, including two multicentre RCTs, have demonstrated and confirmed that sharp debridement is safe and effective in stimulating healing of recalcitrant wounds, especially when combined with advanced therapies.[207–210] However, the type of debridement methods employed needs to be determined by the patient's clinical circumstances and preferences, and by variations in clinical skills.

Considerations for debriding the wound

Before debriding, considerations include: the health professional's competence; tissue type (for example, slough, necrosis, hard eschar); presence of biofilm and implementation of the biofilm pathway; wound location and depth; presence of ischaemia; the underlying cause; the duration of the debridement process; site of the devitalised tissue; and use of immunosuppressants. Where debridement is being contemplated, any patient use of anticoagulants should be considered a possible contraindication before sharp debridement. Where the wound area is very large or the international normalised ratio (INR) is >2.5, sharp debridement may be contraindicated. Anticoagulant therapy can extend the duration of a clinic visit, because of the need to ensure that all post-debridement bleeding has stopped.

When not to debride

Aggressive, excisional sharp debridement should not be conducted where PAD has been diagnosed if ABPI is <0.5. The lack of perfusion and consequent ischaemia compromise the patient's ability to heal, and debriding, particularly surgically, is likely to exacerbate the wound. Debridement can be conducted if revascularisation is possible and successful. Non-viable, necrotic tissue can be removed carefully, while avoiding the underlying viable tissue. If pyoderma gangrenosum is suspected and diagnosed, the inflammatory component should be adequately suppressed medically before engaging in conservative sharp debridement, since these ulcer types when left

untreated can exhibit pathergy, where it worsens in response to minor trauma.

Advanced and other therapy options for debridement

Sharp or surgical debridement: a surgical blade is used to cut tissue from the wound with an appropriate local or general anaesthetic. Patients with peripheral neuropathy may not require anaesthesia and this must be guided by clinical assessment of nociception. Non-viable tissue, biofilm, slough, foreign bodies and callus can be removed efficiently from the wound edge and base until healthy bleeding tissue is seen. However, it should be noted that it has been proven that debridement does not completely remove biofilm, but only provides a window of opportunity for continuation of biofilm-directed therapies.[64,211] A key advantage is speed and the control to remove the majority of non-viable tissue in one clinic visit versus autolytic debridement, which can take weeks to months.

Autolysis: autolytic debridement uses the patient's own endogenous proteolytic enzymes produced by phagocytic cells to degrade devitalised tissue. A dressing that seals the wound is applied. The natural accumulation of wound fluid in the wound space moistens the environment, allowing the proteases to work. A number of dressings can act in this manner, including Cutimed Sorbact Hydroactive (Essity T/A BSN medical) and HydroClean plus (Hartmann). Advantages include the selectivity of endogenous proteases, which are controlled by inhibitors such as TIMPs and others that prevent degradation of healthy tissue and the atraumatic painlessness of the process. The disadvantage of autolysis is the extended time required to debride the wound. Progress must be monitored by removing the dressings and reapplying, if necessary. Autolytic debridement may be combined with mechanical debridement to facilitate WBP. The role of autolytic debridement to manage a chronic wound is limited, due to the impaired physiology of the chronic wound milieu. Non-surgical methods are appropriate for patients who cannot withstand or do not want surgery.

Chemical debridement: a number of antiseptic preparations have been suggested as chemical debriders, such as Santyl (Smith & Nephew) or Octenidine (Schülke), may be used.[212]

Larval debridement/biosurgery: larvae of the greenbottle fly (*Lucilia sericata* or *Lucilia cuprina*) remove moist slough by excreting proteolytic enzymes to digest non-viable tissue and ingesting the liquefied tissue.[213] Larval debridement is atraumatic. The specificity of larval debridement for non-viable tissue is thought to be based on the patient's endogenous protease inhibitors, as for autolytic debridement. The enzymes that digest devitalised tissue are inhibited by the endogenous inhibitors in healthy tissue. Disadvantages include the time required to debride, squeamishness on the part of the patient, its inability to remove callus, and the availability of larvae.

Mechanical debridement: a number of debridement methods that use mechanical energy to remove tissue are available:

- Debridement pads, for example, Debrisoft (Lohmann & Rauscher) and UCS Debridement (Medi), have recently been adopted for their ease of use, rapid results and relatively painless use. Sloughy tissue including biofilm in the wound and eczematous surrounding skin may be debrided using monofilament pads
- Hydrosurgery (Versajet, Smith & Nephew), a pressurised water jet or whirlpool, is used to clean the wound.[214] Debridement is rapid and largely atraumatic to healthy tissue
- Ultrasonic debridement,[214] where the energy for tissue disruption is provided by acoustic waves. Ultrasound delivered with saline, for example, Ultrasonic Assisted Wound Debridement (Söring), causes cavitation in tissue to disrupt slough and necrotic tissue. Non-contact ultrasound (for example, MIST, Cellularity)[214] uses an atomised

saline spray to assist debridement. A clinical study of the healing effect of MIST demonstrated significantly improved wound closure in recalcitrant DFU compared with SoC, although in this study MIST was not used as a debridement modality.[215] Ultrasonic debridement may reduce viable counts of Meticillin-resistant *Staphylococcus aureus* (MRSA); however, the reported effect is small, based on *in vitro* studies.[216] Ultrasonic debridement is relatively painless, but the equipment is expensive and may not be easily available.

Note: the older traumatic method of wet-to-dry dressings is now not recommended.

Inflammation and infection

The focus in this component is on bioburden management, and in particular the biofilm pathway. Health professionals should refer to the details of the pathway in *Section 4* and to the published biofilm pathway consensus.[120]

Considerations for controlling inflammation and bioburden

Health professionals should be informed about the antibiotic stewardship policy of their health-care provider.

Stewardship policies may recommend antibiotics for specified clinical diagnoses based on the known resistance profiles of organisms endemic to the facility and local environment. The policy may also specify a cycle of rotation of antibiotics to prevent organisms being exposed over long periods to the same antibiotic, which can increase the likelihood that new resistance will evolve. It may further specify antibiotics to be used in cases where resistant organisms have been isolated.

In general, topical antibiotics alone are not recommended for wound care, because this potential pressure may favour the emergence of antibiotic resistance developing in wound microbes. In this regard, a more novel antimicrobial approach could be

considered, such as the use of antibiofilm/antimicrobial combinations to disaggregate biofilms, thus improving the effectiveness of the applied antibiofilm agent.

Generally, organisms are rarely resistant to or tolerate antiseptics, except in biofilm phenotype. Antiseptics, such as hypochlorous acid, clear planktonics and are helpful after debridement to slow the biofilm reformation, but do not effectively disaggregate the biofilm EPS, especially with short exposure times of less than 5 minutes.[120] Infrequent examples of antiseptic resistance or tolerance include silver resistance mediated by carriage of plasmid-borne silver resistance genes[217,218] or intrinsic tolerance related to the structure of organisms.[219] *De novo* development of silver resistance appears to be rare.[218] In cases of resistance or tolerance, an alternative antiseptic should be used.

Health professionals should be aware of the signs and symptoms of inflammation. The classical signs include redness, oedema, heat and pain. A wound may have exudate that signifies inflammation. This may include large volumes of exudate or purulent exudate. Furthermore, signs of inflammation may be less evident because of skin pigmentation or the underlying disease. Patients with diabetes may not show all the classical signs. The simple expedient of measuring the patient's core temperature may reveal inflammation, and laboratory investigations for inflammation markers such as C-reactive protein (CRP) may be indicated.

Inflammation and infection are conditions that prevent healing. There is no clinical situation in which not managing inflammation and infection is warranted.

Advanced therapy options for controlling inflammation and bioburden

Biofilm pathway: recommended to manage bioburden and its contribution to inflammation in hard-to-heal wounds. Briefly, the first stage is early intervention with aggressive debridement and topical antiseptics with detailed microbiology, followed by de-escalation to assessment of response, further debridement and personalised antimicrobial therapy.[120] Over four weeks

inflammation and healing are assessed, maintenance debridement implemented, antimicrobial strategy re-assessed, and host factors are managed. If at four weeks healing has not progressed, advanced treatments are introduced (Fig 5).

Manage underlying pathology: inflammation may be caused by chronic underlying pathology that stimulates blood vessels in a classical inflammatory cascade. The assessment of the patient should include detailed analysis of the underlying causes. These should be managed over the entire duration of treatment using the best available methods consistent with clinical and patient needs.

Antimicrobials and antibiotics: a number of options for antimicrobial treatment in the biofilm pathway are available. These include topical antiseptics, dressings that physically adsorb or absorb and retain organisms (such as bacterial binding dressings), innovative antimicrobial therapies, biofilm disrupting technology, and systemic antibiotics.

Antiseptics: a broad range of antiseptics (also known as antimicrobial barriers) are available including iodine, chlorhexidine, polyhexamethylene biguanide (PHMB), silver (metallic, nanocrystaline, ionic), octenidine, reactive oxygen, and hypochlorous acid. Most antiseptics are represented by a large number of products in a variety of forms from several manufacturers, that allow the optimal treatment for the patient to be chosen. For example, Silverlon, is an bactericidal nylon fabric wound dressing where each strand is uniformly plated with pharmaceutical grade silver. The dressing, when kept moist, continually provides sustained release 24/7 of ionic silver (Ag+) of up to 70ppm and ensures the eradication of wound pathogens without staining or discolouration of the wound. A recent publication show a significant reduction (60%) of SSI.[220] The silver ions reduce bacteria by interfering with thiol groups within cellular respiratory enzymes, interfering with bacterial cell division and inactivating DNA and by damaging the

bacterial cell wall to allow leakage of cell electrolytes and increasing permeability to allow entry of more silver ions.[221] Examples of products containing antiseptics are:
- Hypochlorous acid. Hydrocyn Aqua (Vigilenz); Nexodyn (APR); Puracyn (Innovacyn); Revamil Wound Dressing; Octenilin Wound Gel (Schülke)
- Iodine. Inadine (KCI); Iodoflex (Smith & Nephew)
- PHMB. Activheal range (Advanced Medical Solutions); Kendall AMD range (H&R); Suprasorb X+P; PuraPly AM (PHMB on native ECM, Organogenesis); HMB (Lohmann & Rauscher)
- Reactive oxygen. SurgihoneyRO (H&R Healthcare)
- Silver. Silverlon (Argentum). Oxysalts (Ag3+: Crawford Healthcare); Maxorb Ag (Medline); Optifoam Ag+ Foam Dressing (Medline); Aquacel Ag (Convatec).

Physical mode of action: physical modes of action include adsorption onto the structure of the product and absorption into the 3-dimensional structure of a product, combined in some products with antimicrobial action. Examples include:
- Bacterial-binding dressings (Cutimed Sorbact, Essity T/A BSN medical). The bacterial-binding dressing contains Sorbact Technology, a hydrophobic fatty acid derivative which gives the dressings their highly hydrophobic properties. Hydrophobic bacteria and fungi[222,223] become rapidly and irreversibly bound in the dressing and are removed at dressing change, preventing the further release of exotoxins and the release of endotoxins upon bacterial cell death.[224,225] These offer infection management and prevention due to their purely physical mode of action. The bacterial-binding dressing has been used successfully to manage DFU[226] and surgical site infection.[227]
- Activated carbon. It has long been used as a filter for volatile small molecules, such as those that cause odour. Electrostatic forces enable activated carbon to attract and bind microorganisms and kill them. These properties have been exploited in

Zorflex (Zorflex), made from 100% activated carbon, which has shown promise in a case series of leg ulcers[228]

- Gas plasma. The antimicrobial action of gas plasma for planktonic and biofilm[229] microorganisms, including ESKAPE pathogens, is well-established.[230–233] Gas plasma is created at the point of care by a high-voltage electric arc in the chosen gas and kills organisms by the action of reactive oxygen species.[234,235] Gas plasma may stimulate healing[236] through enhanced angiogenesis[237] and local tissue perfusion.[238,239] Gases used include ambient air and argon. The devices reduce the temperature of the plasma at the point of generation from several thousands of degrees Celsius to a harmless temperature for delivery to tissue. Cold argon plasma treatment may reduce the antibiotic sensitivity of MRSA *in vitro*;[240] testing of interactions may be warranted. Examples of gas plasma therapies indicated for wound management include the Adtec Healthcare Steriplas argon plasma device[241] and MicroPlaSter[242]

- Fluorescence biomodulation. Fluorescence biomodulation uses fluorescent wavelengths of light to manage inflammation in a process known as fluorescence biomodulation, or photobiomodulation. Light from a monochromatic light-emitting diode (LED) is transmitted from a hand-held device into a topical light-absorbing molecule (LAM, also known as chromophores) formulation placed over the treatment area. The LED light with a single peak wavelength between 440 and 460nm stimulates fluorescent wavelengths of light emitted from the LAM into the tissue, where it exerts control of bacterial bioburden[243] and photobiomodulation effects.[244, 245] Mitochondria are reported to be the principal cellular site of response to the photobiomodulation.[246–249] The biological effects include: altered gene expression; expression of protective, anti-apoptotic, antioxidant and pro-proliferation gene products;[250] nitric oxide;[245]

increased blood vessel counts;[248] and increased cell proliferation. The LumiHeal device (Klox Technologies) has been evaluated in a real-life setting of 100 patients with chronic wounds, including VLU, DFU and PU. The intervention led to a positive efficacy profile in promoting wound healing and reactivating the healing process,[251,252] as well as in QoL outcomes. It was also proved to be safe. A case series in VLU supports the use of this technology[243]

- Biofilm disruption technology. The EPS of biofilm is responsible for maintaining the 3-dimensional structure of biofilm with organisms distributed within it, and is largely responsible for the resistance and tolerance of organisms to antimicrobial intervention in biofilm.[253] Disruption of biofilm by focusing on EPS is recommended as a paradigm shift in the effective management of biofilm.[253] A number of biofilm disruption products exist, from the family of Xbio line of products from Next Science (BlastX gel SurgX sterile gel, TorrentX wound wash, Bactisure), while concentrated surfactants (Plurogel, Medline) to disrupt bioflim have been developed. The antimicrobial wound gel with the non-toxic Xbio technology deconstructs the bacterial biofilm EPS matrix, destroys bacteria within the gel through the high osmolarity created in the wound and a surfactant that induces cell and spore lysis, and defends from recolonisation, while maintaining a moist wound environment.[254] The gel has been shown to inhibit biofilm formation by wound bacteria *in vitro* and *in vivo*, eliminate established biofilm infection, and reduce bacterial counts in biofilm by 6 to 8 $\log^{10}$ CFU/disc.[255] It is indicated for the management of wounds such as PU, partial- and full-thickness wounds, DFU, leg ulcers and postoperative wounds. Alone or in combination with SoC, the gel has been shown to be effective in disrupting wound biofilm and improving healing outcomes in recalcitrant wounds.[256,257] Concentrated surfactant gel, for example PluroGel

(Medline), also helps manage biofilm and infection. Slough and biofilms within the wound are held together, and to the wound bed, to a major extent by non-covalent forces, which have a tendency to be disrupted by a surfactant's amphiphilic polymer structure. *In vitro* studies demonstrate that the non-cytotoxic, water-soluble gel is able to disperse microbial aggregates, disrupt mature biofilms, and prevent *de novo* biofilm growth.[258,259] *In vitro* models also show that the micelle-based matrix formed by the concentrated surfactant gel may interfere with quorum-sensing pathways in microbes which are essential for biofilm development.[260]

Hyperbaric oxygen therapy has been shown to increase the O_2 concentration in blood,[261] and evidence suggests it may be useful in the treatment of some infections, including in deep and recalcitrant infections such as necrotising fasciitis, and osteomyelitis, as well as aiding healing in burn patients and reducing amputation rates in patients with DFUs.[262,263] It is thought HBOT promotes the healing of infections by an number of mechanisms, including direct bacteriostatic/bactericidal effects and enhancement of the immune systems.[263]

Moisture balance

The focus should be on management of moisture in order to create a balanced, moist wound environment for healing.

Considerations for moisture balance

Excessive exudate production, or too little exudate or moisture in a wound, leads to disrupted healing and potential damage to the surrounding skin. Considerations include the exudate characteristics with respect to its amount, colour, odour, viscosity, possible constituents and appearance.[264] The periwound skin should be assessed for potential damage or compromise. The potential impact of other products used in wound care should be considered, for example, a dressing that is unable to retain fluid under

pressure may be unsuitable for use under compression. Viscous exudate requires managing differently to thin watery exudate, as products that readily manage thin exudate may become blocked by viscous exudate, reducing dressing uptake and leading to pooling. Purulent, haemopurulent or seropurulent exudate may signify infection. Colour and odour may be indicators of microbial influence on the wound, including biofilm and infection. The constituents of exudate may include proteases that can damage compromised skin. An algorithm for dressing selection based on the characteristics of exudate is available.[265]

The patient should be considered in selecting an appropriate moisture-management strategy. Exudate leakage and soiling can adversely affect the patient's QoL and that of those around them; it also increases the likelihood of pathogens gaining access to the wound.[265] Dressing change frequency should be considered in the light of the ability of the patient to attend clinic or get access to community nursing services.

Oedema management with compression therapy may be challenging in patients with a history of cardiac failure, arterial insufficiency, and patients unable to tolerate compression therapy.

Management of moisture is a critical step in an effective SoC. If not implemented, the wound may become too dry or too wet and the surrounding skin may be damaged by exudate that spreads from the wound. Ineffectively managed moisture and exudate may leak from the dressing and contaminate secondary dressings and compression products, as well as the patient's clothing and environment. A moisture-balanced wound environment is widely regarded as optimal for wound healing once all other factors have been managed. There is no situation where moisture should not be managed and balanced in a wound.

Advanced and other therapy options for managing moisture

Dressings are the most commonly-used approach to manage exudate and moisture. Health professionals

should be familiar with the characteristics of dressings available in their health-care system in order to select the product that best matches the patient, wound and exudate assessment.

Management of oedema should be considered as part of moisture management—oedema reduction is a key element of effective wound management. Oedema may be managed with compression unless contraindicated, in which case diuretics may be appropriate. A patient with lymphoedema should be referred to the lymphoedema team for specialist management.

Low-viscosity exudate may be managed using one of a wide variety of absorbent dressings, including foams, fibrous products such as gelling fibres, superabsorbent dressings and NPWT. High-viscosity exudate may be managed with dressings or methods designed specifically for such exudate. An example of such a dressing is Mepilex XT (Mölnlycke Health Care) and Cutimed Siltec (Essity T/A BSN medical). Low-viscosity exudate in moderate-to-highly exuding wounds is suitable for management with superabsorbent dressings, such as the Cutimed range (Essity T/A BSN medical) and the Optilock range (Medline). These types of dressing are indicated for acute and chronic wounds, to absorb and retain exudate.

High volumes of exudate can rapidly overwhelm dressings, even those with high absorption and retention capacity. An alternative is NPWT; some examples include Renasys Touch (Smith & Nephew) and VAC Therapy (KCI, an Acelity company). High-viscosity exudate can be managed with NPWT using instillation in combination with specifically-designed foam dressings with large channels. The large channels allow the exudate to pass through and be removed from the wound surface. An example is VAC Instill Therapy System (KCI), combined with a reticulated open-cell foam dressing, Veraflo Cleanse Choice (KCI).[266,267] Many other examples of NPWT, including portable versions, are available: Advance (Mölnlycke Health Care), Avelle (ConvaTec), Invia Motion (Medela), Nanova (KCI), PICO (Smith & Nephew), SNaP (KCI), and Venturi Avanti (Talley Group).

Low moisture may be addressed using products that donate fluid to the wound. Hydrogels; gel-type dressings, such as ActiFormCool (L&R) and Cutimed Sorbact Hydroactive (Essity T/A BSN medical) are suitable for this use. In a wound that is expressing small amounts of fluid, it may be sufficient to cover the wound with a moisture-retaining, occlusive dressing, such as a hydrocolloid (DuoDERM ConvaTec; Suprasorb H (Lohmann & Rauscher), to provide the moist wound environment known to facilitate healing.

Management of wound proteases

Where excessive production of proteases is suspected, a number of options are available for reducing their effect. These include sacrificial substrate, for example, Promogran (KCI); absorption and retention, such as superabsorbent dressings, including Cutimed Sorbion range (Essity T/A BSN medical), the Aquacel range (ConvaTec), Durafiber (Smith & Nephew); or inhibition of proteases, for example, UrgoStart (Urgo Medical), Puracol Collagen dressings (Medline) Suprasorb C, a collagen filler (Lohmann & Rauscher).

Edge

In full-thickness wounds and many large wounds, epithelial resurfacing takes place from the wound edge. Monitoring the epithelial margin of the wound guides the approach to management, in order to optimise the conditions required. The quality of the wound bed is key to epithelial advancement from the wound margins, and WBP focuses on this.

Considerations for wound edge management

WBP is a prerequisite for epithelial advancement. The edge of the wound should be assessed for the need to debride and for the possible need for therapies to accelerate re-epithelialisation. Other considerations include wound size and depth, the nature and duration of the wound, and patient-related parameters, including psychosocial factors, accessibility, environment and adherence to the care path.

In a wound for which the clinical objective is healing, it is important to account for the role of the wound edge. As with other aspects of TIMERS, for which debridement is a possible intervention, caveats described above apply. It is highly unlikely that epithelial advancement from the margins will occur if high levels of exudate production, the underlying pathology, biofilm, and infection have not been addressed. Focus must be on these aspects first.

Advanced and other therapy options for reducing wound size

The wound margins should be excised if required as indicated by callus formation or devitalised tissue. Where epithelial advancement is slow, a number of options for accelerating it are available. These include tissue equivalent or living-skin equivalent products, such as allogeneic cellular graft products, including Alloskin (Allosource), autologous split-thickness skin grafts, epithelial punch grafts and regulatory protein-containing tissue equivalents, such as dehydrated Human Amnion/Chorion Membrane allografts (dHACM; EpiFix, MiMedx) or bioengineered skin substitutes (BLCC; Apligraf, or HDS; Dermagraft, Organogenesis). In cases where the wound bed does not present with the optimal granulation tissue to receive skin grafts (for example, if stagnant slough is present), the ulcer may benefit from autologous punch grafting. Although some pinch or punch grafts may not adhere to the wound bed, they release growth factors, signal molecules and cells that enhance epithelial resurfacing and reduce pain.[268–270] Other options include the previously-covered photobiomodulation device LumiHeal (Klox) and protease-modulating technologies.

Repair and regeneration

The focus here is encouraging wound closure by: providing a matrix to support cell infiltration; stimulating cell activity using signal molecules or growth factors; delivering oxygen therapy; or using stem cells.

Considerations for repair and regeneration

A hard-to-heal wound is likely to respond to therapy only once risk factors have been addressed. The risk factors are those identified in the patient and wound assessment process of a high SoC. Critical factors include the underlying pathology, infection, biofilm, and patient-related factors.

When not to manage wound repair with advanced therapies

It must be established that the wound is not responding to SoC and that the clinician has addressed all the risk factors identified. Management of repair with advanced therapies should not be implemented until risk factors are addressed. Some, but not all, authorities limit the use of advanced therapies to use on wounds that have responded to SoC by less than 50% at four weeks. The National Institute for Health and Care Excellence (NICE) in the UK advises against the use of some advanced therapies, based on efficacy and/or health economic grounds,[271,272] although this is not a universally held opinion.

Advanced therapy options for wound repair

A wide range of options for advanced therapy of chronic, hard-to-heal wounds is available. Different technologies are available to select from, based on the suitability of a technology for the wound and patient characteristics. Technologies include topically- and systemically-delivered interventions, such as: oxygen (systemically-delivered); growth factor preparations; nitric oxide and sucrose octasulphate; tissue equivalent products; NPWT; systemic pharmacotherapy; and protein-based nutritional supplements, such as ProMod and Juven (Abbott).

Topical interventions

● Nitric oxide (NO). A two-component gel dressing (ProNOx1, Edixomed) that generates and delivers NO directly to the wound has recently been shown to reduce wound area significantly more than SoC alone in a real-world, open-label, multicentre RCT in DFU.[272] The study offers

preliminary evidence of efficacy that requires confirmation in an RCT that assesses complete wound closure

- Oxygen therapy. Oxygen therapy is delivered either topically or systemically. HBOT is given via breathing air with a high, partial pressure of oxygen in a closed chamber (respiratory HBO: rHBO). Health Quality Ontario found in its health technology assessment (HTA) that rHBO in conjunction with SoC improves wound healing in DFU[273] and may offer benefits in AU management,[274] possibly through reduction in MMP levels[275] as a result of reduced recruitment of neutrophils.[276] Local oxygen therapies deliver an oxygen-rich atmosphere to the wound area, either by topical continuous delivery of non-pressurised (normobaric) oxygen (CDO) through small cannulas or thin tubes (Natrox/Epiflo) to wound dressings, or by small chamber-based constant pressure devices (TWO$_2$/TO$_2$).[261]

- Growth factors (GF). GFs may be delivered to a wound as a gel (Becaplermin, Smith & Nephew) or as autologous platelet-rich plasma (PRP). PRP may be presented as pure PRP or with other cells, with or without a fibrous matrix such as fibrin.[206] The mode of action is stimulation of cell activity and migration by providing signalling molecules that may be deficient in the wound. Some authorities do not recommend use of PRP in wound healing,[206] and a systematic review concluded that DFU may benefit.[277,278] However, the evidence of its effect is of low quality and requires confirmation in well-designed RCTs[278]

- Sucrose octasulfate. Previously known as nano-oligosaccharide fraction (NOSF), sucrose octasulfate is a constituent of UrgoStart, which has recently completed a multicentre RCT in 240 hard-to-heal, non-infected, neuropathic DFU, which demonstrated statistically significantly greater complete wound closure at 20 weeks than did SoC alone[279]

- Tissue equivalents (TE) and living skin equivalents (LSE). Presentations of TE and LSE include: decellularised tissue matrices; placental-based grafts; bioengineered matrices manufactured from solubilised ECM constituents, with or without added cells; cell culture-based grafts; and collagen products. Products may be allogeneic or xenografts, presented as sheets or powder, and be supplied dehydrated or hydrated. The mode of action for these technologies is provision of a scaffold to enable cellular infiltration into the wound space. Matrices may be temporary and require repeated application, or integrated into the healed tissue and remodelled over an extended time period. Overall, skin grafting for the management of DFU is associated with increased healing compared with SoC alone[280]

- Placental-based grafts. Amniotic and chorion layers are used in these products. DHACM (MiMedx) is an example that retains over 280 unique regulatory proteins present in the amnion/chorion tissue after processing.[281,282] These bioactive proteins extracted from dHACM have been shown to stimulate proliferation of human microvascular endothelial cells and recruit mesenchymal stem cells[283] *in vitro* and *in vivo*,[281,285] all of which aid in the wound-healing process. Clinical evaluations have demonstrated the efficacy of dHACM in Wagner grade I and II DFU[209,210, 284–288] and VLU[289,290]

- Bioengineered technologies. Many products are available in this category of advanced technology. Examples include Dermagraft and Apligraf (both Organogenesis). Dermagraft is a cryopreserved, 3-dimensional human dermal substitute (HDS) composed of human fibroblasts, an ECM and a bioabsorbable polyglactin mesh scaffold which may be serially applied to a wound without the need for removal of the product from the wound and is indicated for DFU.[291] Apligraf, a bioengineered bilayered living cellular construct (BLCC) indicated for VLU and DFU, has an outer layer of human epidermal keratinocytes, and an inner layer of human dermal fibroblasts contained within a collagen matrix.[292,293] BLCC has been shown to induce a shift to healing through

modulation of inflammatory and GF signalling, keratinocyte activation and attenuation of Wrt/β-catenin signalling in VLU.[293] Both have been shown to offer health economic benefit in the management of DFU as a result of lower amputation rates, fewer days' hospitalisation and fewer emergency department visits than conventional care[294]

● ECM-based technologies. Products based on collagen and other ECM constituents have been evaluated in chronic wounds. Collagen-based products include Puracol (Medline),[295] Biobrane (Smith & Nephew), Suprasorb C (L&R) and PuraPlyAM (Organogenesis), a native structured ECM-based technology coated with an anti-microbial (PHMB). Hyaluronan (HA) has been shown to be involved in wound healing, with its functions modulated by its molecular weight, including control of inflammation and cellular functions.[296,297] HA esterified with benzyl alcohol (HYAFF) is the key constituent in the bilayer, fibrous, non-woven product, Hyalomatrix (Medline), with a semi-permeable silicone outer layer. In the wound, hydrated Hyalomatrix de-esterifies to deliver HA. Hyalomatrix has been extensively evaluated in clinical studies and shown to enhance healing in a range of chronic wounds;[298–302] reduce scarring in full-thickness burns[302] and in scar revision;[303] and offer rapid healing in large skin-loss injuries.[304]

● Cell-based grafts. Stem cell therapy and cultured epithelial cells are in this category. Cultured autologous epithelial cell grafts include Epicel (Genzyme), Epidex (Euroderm) and MySkin (Altrika).[305]

In considering the use of advanced methods based on autologous grafting or tissue-equivalent and bioengineered products in the management of

VLU specifically, the health professional should refer to a systematic review which found that bilayered grafts enhanced healing compared with dressings.[306] However, studies conducted on other products were subject to high likelihood of bias[307]

● NPWT. Already discussed in relation to debridement, NPWT may be used to stimulate in-filling of the wound and is associated with enhanced take of skin grafts or cutaneous substitutes. A large number of publications attest to the efficacy of NPWT in chronic wounds. A possible mechanism is microdeformation of tissue by either continuous sub-atmospheric pressure or repeated cycles of low and normal pressure, thus creating a physical stimulus for tissue growth

● Other therapies: following systematic review, Pentoxifylline has been recommended for the management of hard-to-heal VLU.[308]

Not all therapies are available in all countries.

Social- and patient-related

The 'S' of TIMERS envelops the entire framework and recognises the importance of patient engagement in increasing the likelihood of healing. Social and patient factors are discussed in full detail in *Section 6*.

Extreme long-term, non-responsiveness

The care plan should be continued in the event of extreme long-term, non-responsiveness. Ethically, it is not acceptable to withdraw or stop therapy that is recommended in best-practice statements, even if the wound has not measurably progressed. Treatment should continue in order, as a minimum, to prevent deterioration, and the healing expectations of the health professional and patient should be managed accordingly. This entails redefining or repriorsitisation of patient and clinical goals.

Section 6. Management of patient-related factors

The 'S' component of TIMERS (*Fig 6*) focuses on the social situation and patient-related factors. The over-arching social situation and patient-related factors are critical in ensuring the most effective management of wounds and must be considered alongside all the other components of TIMERS. Importantly, the first step in the TIMERS framework is to conduct a holistic patient assessment and diagnostic investigations to identify all the risk factors associated with the wound and the patient. These investigations should clearly identify the non-clinical, patient-related risk factors. Manageable risk factors may include educating the patient using language and materials that they can understand. Uncontrollable risk factors may include the patient's living conditions, where they live and dementia. In assessing social- and patient-related risk factors, it is important to distinguish between those that may be addressable by the health professional and those that cannot and must be accepted.

Non-clinical social- and patient-related risk factors may be classified as: psychosocial factors, factors that affect adherence, physical and comorbidity factors, and extrinsic factors.

Psychosocial factors

For the care pathway to be successful, agreement on its implementation—effectively, a form of 'contract'—is required between the health professional and the patient. Psychosocial factors[107] that can negatively impact on the ability of a patient to reach such an agreement are related to the patient's ability to understand the care plan. Factors that may affect this include the patient's educational attainment level and health literacy (HL). Levels of HL may be low and add cost to health care,[309] because their wounds are less likely to heal.[310] Factors can also relate to the health professional and may include the inability of the clinician to explain adequately, the over-use of medical jargon and an unwillingness to engage constructively with the patient's social situation. Medical language can be difficult to understand, leading to potential misunderstandings about the

Key points

- Social- and patient-related factors are likely to influence the outcome of the management of hard-to-heal wounds
- The panel identified psychosocial factors, factors that affect adherence, physical and comorbidity factors, and extrinsic factors
- The more understanding and agreement the patient has about their care planm the more likely they are to adhere
- Use of medical jargon should be avoided

wound and what has caused it. Hence, a health professional's use of medical jargon could also lead to poor adherence. The patient's beliefs will be driven by this understanding and will be affected by their previous experience of management of the wound. The social support available to the patient from family and friends may be insufficient to facilitate effective understanding of the care plan. Dementia and depression are also important. Dementia may make understanding of the care plan and the needs of the wound impossible for the patient, and in this situation social support is critical.

Factors that affect adherence

A critical part of managing hard-to-heal, and indeed healing wounds and any other medical condition, is the patient following the agreed care path, a major driver of success.[108,311] Debate among health professionals on the exact terminology to use in relation to how well the care plan is followed exists.[312–314] The terms 'adherence', 'concordance' and 'compliance' have been used and, at the time of writing, these terms remain in use in different countries and settings. 'Adherence' refers to the degree to which the care plan is followed by the patient, whereas 'concordance' is related to the degree to which the patient and the health professionals have agreed the plan.[315] Throughout this document, the term 'adherence' has been used for consistency. The reader should understand that this

term as used here has a meaning analogous to 'concordance' or 'compliance' in the context of how the care path is followed. The term 'compliance', which implies following instructions rather than acting with agreement,[315] has fallen out of favour in the UK, as it does not promote patient/clinician partnership.

Factors that may reduce adherence include the patient's own goals, which may differ from those of the health professional and may be unrealistic.[316] Additionally, the goals for the patient may be different among individual health professionals.[317] These factors will influence whether or not the patient receives care that they are happy with and to which they are prepared to adhere. For the care plan to succeed, the goals must align. If goals do not align, the patient is likely to feel less empowered and in control of their part of the care plan. This is likely to affect adherence.[317] Patients may also harbour dissatisfaction with the continuity of their wound management as they see it.[318] The impact of the care plan on the patient's activities of daily living (AoDL) must be considered. Past experience may have shown the patient that a certain treatment was painful or 'did not work'. Whether the failure of a previous care plan was down to the care plan itself or the patient's adherence to it should be teased out. Adherence is affected by how the care plan affects QoL, which is often severely diminished by a chronic wound.[56] QoL is strongly influenced by four factors in VLU patients: social function; domestic activities; cosmesis; emotional status.[318] Clinical factors that influence health-related QoL (HRQoL) include pain, itching, altered appearance, sleep loss, functional limitation and disappointment with treatment.[319] QoL markers, which are influenced by symptoms, may improve when wounds progress or heal. Previous experience and the goals of treatment are important factors in the choice that the patient will make about treatment and this must be considered.

Physical and comorbidity factors

Patient mobility is important, in particular where it is required for self-care, or mobility contributes to the action of the treatment. Compression for chronic venous disease is an example of where movement of the calf muscle pump by foot flexion or walking creates pressure spikes in the veins that assist the return of blood to the heart,[320] and it is important that the type of compression selected will work with the patient's physical abilities. The patient may need to contribute to self-care by re-applying products or monitoring the foot when their sight is affected by retinopathy, impairing their ability to see the wound or foot clearly. Comorbidities may adversely affect the patient's ability to walk or confine them to a chair or bed. An elderly patient may be frail and/or arthritic and unable to grip objects effectively. Sleep disorders may affect the patient's cognition and daily activities and reduce the effectiveness of the care plan.

Extrinsic factors

These are indirect factors that may be uncontrollable or not addressable by the practitioner and may have to be largely accepted. Examples are the patient's environment and living conditions,[321] the distance from their home to the clinical setting, living alone, social isolation, and access to care (although this may be addressable). Other risk factors include the patient's economic situation where, for example, travel to a clinical centre or treatment is self- or part-funded.

Management of social and patient-related risk factors

Modification of social and patient-related risks is necessary to encourage the patient to agree to and engage with the care plan.

Psychosocial factors

The health professional must present a care plan that can be understood by the patient, taking into account their ability to understand potentially complex medical and clinical concepts and language. The better the patient understands and agrees with their treatment, the more likely they are to follow the agreed care plan.[322,323] Health professionals must also have

enough information about the patient's belief system, perhaps influenced by their past experience and the advice and guidance of others—clinically qualified and lay—to tailor the plan to the patient in a way that they believe it will be effective. This may require discussions with the patient's social support system. Educating the patient and others is a critical factor: education should be delivered simply and the health professional must carefully explain why the steps of the care plan are needed. A patient with dementia or depression will rely heavily, if not totally, on their social support system for the effectiveness of the care plan.

Psychosocial factors are important and many are difficult to modify; these can be modified if appropriate; however, skills are used and it could be suggested that a social worker or psychologist should be part of the MDT. It should be noted that psychology can play a significant part, not only for the patient, but also in improving the clinician's care, so everyone benefits

Adherence

The patient's level of adherence should be assessed. Adherence to the care plan is heavily influenced by a number of factors,[108,324–326] including the patient's belief systems, impact on AoDL and QoL, previous experience of care and pain, either at dressing change or from the treatment generally.[327] The health professional must ensure that the objectives of the care plan are the same as those of the patient, otherwise a disempowered patient and non-adherence are the likely outcomes.[328] This requires active listening on the part of the health professional and a two-way exchange of information:[329]

● Assimilate the patient's comments and wishes
● Check for clear understanding
● Ask clarifying questions
● Re-check for understanding
● Formulate a plan that aligns with the comments and wishes
● Agree the plan with the patient

● Use motivational interviewing to maximise the likelihood of adherence.

The care plan may need specific interventions and methods to meet the goals for AoDL and symptom management, including pain at all stages of the care pathway, to encourage adherence. However, it should be noted that the evidence for interventions to improve adherence/concordance does not appear to show benefit.[330]

The care plan for a chronic, hard-to-heal wound is likely to need input from the MDT or group of health professionals, and this must be recognised. A decision to move from active therapy of the wound to maintenance must be agreed by the MDT. The patient themselves may decide that they no longer want the outcome that is preferred by a health professional. If the patient decides to move to a maintenance therapy plan, the implications and consequences must be clearly communicated to the patient. The plan will include managing wound symptoms such as infection, exudate, pain and odour, rather than the explicit objective of closing the wound.

Physical and comorbidity factors

Treatment that fits the patient's physical abilities should be implemented as far as possible. A treatment that requires physical activity will be ineffective for a patient who is unable to engage in the required level of activity. If the patient is unable to administer self-care, then arrangements must be considered for the care to be administered by a trusted carer who may be a health professional, family member or friend. This person must be educated about what is needed and why, and how to deliver the care. An example is daily foot inspections in an obese patient with diabetes and retinopathy. A patient who does not have retinopathy may be able to inspect their own feet using a mirror mounted on a wall or on a stick. Comorbidities must be managed as far as possible and their compatibility with adherence assessed. Sleep disorders, similarly, should be addressed if possible. If the patient sleeps in a chair because she/he cannot climb stairs to the bedroom, then the care should

accommodate this, with, for example, advice on support, positioning and leg elevation.

Extrinsic factors

Although little may be done about the distance of the patient's home from the clinic, it may be possible to arrange for local volunteer services to help the patient with low- or no-cost transport to the clinic when needed. The impact of leg clubs on VLU healing, although supported by low-quality evidence, appears to be positive[331–334] and encouraging the patient to attend such groups for social interaction, and care is likely to be beneficial. Patients who attend leg clubs perceive the benefits to be sociability, enabling, knowledge and experience, interpersonal

relationships, and caring and quality.[333] Either community nurses supported by advanced practice clinics via telehealth technology[334] or dedicated hospital- or community-based clinics for patients with wounds may in the future also contribute to better outcomes.[335,336] The key factor is access to high-quality, best practice, patient-centred care to improve outcomes.[337]

In summary, social- and patient-related factors are likely to influence the outcome of the management of hard-to-heal wounds. Despite the evidence for some interventions and strategies being of low quality, the panel recommends that these factors should be addressed.

References

1. Guest JF, Fuller GW, Vowden P. Venous leg ulcer management in clinical practice in the UK: costs and outcomes. Int Wound J 2018; 15(1):29–37. https://doi.org/10.1111/iwj.12814

2. Guest JF, Fuller GW, Vowden P. Diabetic foot ulcer management in clinical practice in the UK: costs and outcomes. Int Wound J 2018; 15(1):43–52. https://doi.org/10.1111/iwj.12816

3. Gottrup F. 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 2004; 187(5 5A):S38–S43. https://doi.org/10.1016/S0002-9610(03)00303-9

4. Graves N, Henry z. The prevalence and incidence of chronic wounds: a literature review. Wound Practice & Research: Journal of the Australian Wound Management Association 2014; 22(1):4-12, 14–19

5. Phillips TJ, Dover JS. Leg ulcers. J Am Acad Dermatol 1991; 25(6):965–987. https://doi.org/10.1016/0190-9622(91)70295-D

6. Piaggesi A. Research development in the pathogenesis of neuropathic diabetic foot ulceration. Curr Diab Rep 2004; 4(6):419–423. https://doi.org/10.1007/s11892-004-0050-4

7. Apollonio A, Antignani PL, Di Salvo M et al. A large Italian observational multicentre study on vascular ulcers of the lower limbs (Studio Ulcere Vascolari). Int Wound J 2016; 13(1):27–34. https://doi.org/10.1111/iwj.12216

8. Abbade LP, Lastória S. Venous ulcer: epidemiology, physiopathology, diagnosis and treatment. Int J Dermatol 2005; 44(6):449–456. https://doi.org/10.1111/j.1365-4632.2004.02456.x

9. Hall J, Buckley HL, Lamb KA et al. Point prevalence of complex wounds in a defined United Kingdom population. Wound Repair Regen 2014; 22(6):694–700. https://doi.org/10.1111/wrr.12230

10. Guest JF, Ayoub N, McIlwraith T et al. Health economic burden that wounds impose on the National Health Service in the UK. BMJ Open 2015; 5(12):e009283. https://doi.org/10.1136/bmjopen-2015-009283

11. Marston WA, Crowner J, Kouri A, Kalbaugh CA. Incidence of venous leg ulcer healing and recurrence after treatment with endovenous laser ablation. J Vasc Surg Venous Lymphat Disord 2017; 5(4):525–532. https://doi.org/10.1016/j.jvsv.2017.02.007 Medline

12. Harrison MB, VanDenKerkhof EG, Hopman WM et al. The Canadian Bandaging Trial: Evidence-informed leg ulcer care and the effectiveness of two compression technologies. BMC Nurs 2011; 10(1):20. https://doi.org/10.1186/1472-6955-10-20

13. Ukat A, Konig M, Vanscheidt W, Münter KC. Short-stretch versus multilayer compression for venous leg ulcers: a comparison of healing rates. J Wound Care 2003; 12(4):139–143. https://doi.org/10.12968/jowc.2003.12.4.26490

14. Watson JM, Kang'ombe AR, Soares MO et al. VenUS III: a randomised controlled trial of therapeutic ultrasound in the management of venous leg ulcers. Health Technol Assess 2011; 15(13):1–192. https://doi.org/10.3310/hta15130

15. Weller CD, Evans SM, Staples MP et al. Randomized clinical trial of three-layer tubular bandaging system for venous leg ulcers. Wound Repair Regen 2012; 20(6):822–829. https://doi.org/10.1111/j.1524-475X.2012.00839.x

16. Harding K, Aldons P, Edwards H et al. Effectiveness of an acellular synthetic matrix in the treatment of hard-to-heal leg ulcers. Int Wound J 2014; 11(2):129–137. https://doi.org/10.1111/iwj.12115

17. Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Healing diabetic neuropathic foot ulcers: are we getting better? Diabet Med 2005; 22(2):172–176. https://doi.org/10.1111/j.1464-5491.2004.01375.x

18. Thomas DR, Diebold MR, Eggemeyer LM. A controlled, randomized, comparative study of a radiant heat bandage on the healing of stage 3–4 pressure ulcers: A pilot study. J Am Med Dir Assoc 2005; 6(1):46–49. https://doi.org/10.1016/j.jamda.2004.12.007

19. Mills JL Sr, Conte MS, Armstrong DG et al.The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIfI). J Vasc Surg 2014; 59(1):220-34.e1-2. https://doi.org/10.1016/j.jvs.2013.08.003

20. Mathioudakis N, Hicks CW, Canner JK et al. The Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIfI) classification system predicts wound healing but not major amputation in patients with diabetic foot ulcers treated in a multidisciplinary setting. J Vasc Surg. 2017; 65(6):1698-1705.e1. https://doi.org/10.1016/j.jvs.2016.12.123

21. Tinkler A, Hotchkiss J, Nelson EA, Edwards L. Implementing evidence-based leg ulcer management. Evid Based Nurs 1999; 2(1):6–8. https://doi.org/10.1136/ebn.2.1.6

22. Iglesias C, Nelson E, Cullum N et al. VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers. Health Technol Assess 2004; 8(29):iii. https://doi.org/10.3310/hta8290

23. O'Brien JF, Grace PA, Perry IJ et al. Randomized clinical trial and economic analysis of four-layer compression bandaging for venous ulcers. Br J Surg 2003; 90(7):794–798. https://doi.org/10.1002/bjs.4167

24. Lyon RT, Veith FJ, Bolton L, Machado F; Venous Ulcer Study Collaborators. Clinical benchmark for healing of chronic venous ulcers. Am J Surg 1998; 176(2):172–175. https://doi.org/10.1016/S0002-9610(98)00136-6

25. De Sanctis MT, Belcaro G, Cesarone MR et al. Treatment of venous ulcers with pentoxifylline: a 12-month, double-blind, placebo controlled trial. Microcirculation and healing. Angiology 2002; 53 Suppl 1:S49–S51

26. Milic DJ, Zivic SS, Bogdanovic DC et al. Risk factors related to the failure of venous leg ulcers to heal with compression treatment. J Vasc Surg 2009; 49(5):1242–1247. https://doi.org/10.1016/j.jvs.2008.11.069

27. Brambilla R, Aloisi D, Weingard I, Fioruzzi M et al. VERUM – a European approach for successful venous leg ulcer healing: implementation of a comprehensive therapy concept (VERUM) in daily practice. EWMA J 2013; 13:19–23.

28. Ashby RL, Gabe R, Ali S, Adderley U et al. Clinical and cost-effectiveness of compression hosiery versus compression bandages in treatment of venous leg ulcers (Venous leg Ulcer Study IV, VenUS IV): a randomised controlled trial. Lancet 2014; 383(9920):871–879. https://doi.org/10.1016/S0140-6736(13)62368-5

29. Milic DJ, Zivic SS, Bogdanovic DC et al. A randomized trial of the Tubulcus multilayer bandaging system in the treatment of extensive venous ulcers. J Vasc Surg 2007; 46(4):750–755. https://doi.org/10.1016/j.jvs.2007.04.062

30. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA 2005; 293(2):217–228. https://doi.org/10.1001/jama.293.2.217

31. Armstrong DG, Boulton AJ, Bus SA. Diabetic Foot Ulcers and Their Recurrence. N Engl J Med 2017; 376(24):2367–2375. https://doi.org/10.1056/NEJMra1615439

32. International Diabetes Diabetes Federation. Diabetes Atlas. 2013; (sixth edn) https://tinyurl.com/ybq5h7uy (accessed 18 January 2019)

33. Ince P, Abbas ZG, Lutale JK et al. Use of the SINBAD classification system and score in comparing outcome of foot ulcer management on three continents. Diabetes Care 2008; 31(5):964–967. https://doi.org/10.2337/dc07-2367

34. NHS Digital. National Diabetes Foot Care Audit - 2014-2016 [Internet]. https://tinyurl.com/ycjtvys9. (accessed 18 January 2019)

35. Smith-Strøm H, Iversen MM, Igland J et al. Severity and duration of diabetic foot ulcer (DFU) before seeking care as predictors of healing time: A retrospective cohort study. PLoS One 2017; 12(5):e0177176. https://doi.org/10.1371/journal.pone.0177176

36. Prompers L, Huijberts M, Apelqvist J et al. Delivery of care to diabetic patients with foot ulcers in daily practice: results of the Eurodiale Study, a prospective cohort study. Diabet Med 2008; 25(6):700–707. https://doi.org/10.1111/j.1464-5491.2008.02445.x

37. Guest JF, Fuller GW, Vowden P, Vowden KR. Cohort study evaluating pressure ulcer management in clinical practice in the UK following initial presentation in the community: costs and outcomes. BMJ Open 2018; 8(7):e021769. https://doi.

org/10.1136/bmjopen-2018-021769

38 Zarchi K, Latif S, Haugaard V et al. Significant differences in nurses' knowledge of basic wound management - implications for treatment. Acta Derm Venereol 2014; 94(4):403–407. https://doi.org/10.2340/00015555-1770

39 Hughes M. Wound infection: a knowledge deficit that needs addressing. Br J Nurs 2016; 25(6 suppl):S46–S51. https://doi.org/10.12968/bjon.2016.25.6.S46

40 Welsh L. Wound care evidence, knowledge and education amongst nurses: a semi-systematic literature review. Int Wound J 2018; 15(1):53–61. https://doi.org/10.1111/iwj.12822

41 Haram R, Ribu E, Rustøen T. The views of district nurses on their level of knowledge about the treatment of leg and foot ulcers. J Wound Ostomy Continence Nurs 2003; 30(1):25–32 .

42 Barrett S, Cassidy I, Graham MM. National survey of Irish community nurses' leg ulcer management practices and knowledge. J Wound Care 2009; 18(5):181–190. https://doi.org/10.12968/jowc.2009.18.5.42172

43 Fincke BG, Miller DR, Christiansen CL, Turpin RS. Variation in antibiotic treatment for diabetic patients with serious foot infections: A retrospective observational study. BMC Health Serv Res 2010; 10(1):193. https://doi.org/10.1186/1472-6963-10-193

44 Habib SH, Biswas KB, Akter S et al. Cost-effectiveness analysis of medical intervention in patients with early detection of diabetic foot in a tertiary care hospital in Bangladesh. J Diabetes Complications 2010; 24(4):259–264. https://doi.org/10.1016/j.jdiacomp.2008.12.005

45 Cavanagh P, Attinger C, Abbas Z et al. Cost of treating diabetic foot ulcers in five different countries. Diabetes Metab Res Rev 2012; 28 Suppl 1:107–111. https://doi.org/10.1002/dmrr.2245

46 Manu C, Lacopi E, Bouillet B et al. Delayed referral of patients with diabetic foot ulcers across Europe: patterns between primary care and specialised units. J Wound Care 2018; 27(3):186–192. https://doi.org/10.12968/jowc.2018.27.3.186

47 Searle A, Gale L, Campbell R et al. Reducing the burden of chronic wounds: Prevention and management of the diabetic foot in the context of clinical guidelines. J Health Serv Res Policy 2008; 13(3_suppl Suppl 3):82–91. https://doi.org/10.1258/jhsrp.2008.008011

48 Jeffcoate WJ, Lipsky BA, Berendt AR et al. Unresolved issues in the management of ulcers of the foot in diabetes. Diabet Med 2008; 25(12):1380–1389. https://doi.org/10.1111/j.1464-5491.2008.02573.x

49 Varga MA, Holloway SL. The lived experience of the wound care nurse in caring for patients with pressure ulcers. Int Wound J 2016; 13(2):243–251. https://doi.org/10.1111/iwj.12279

50 Garcia-Klepzig JL, Sánchez-Ríos JP et al. Perception of diabetic foot ulcers among general practitioners in four European countries: knowledge, skills and urgency. J Wound Care 2018; 27(5):310–319. https://doi.org/10.12968/jowc.2018.27.5.310

51 Manu C, Lacopi E, Bouillet B et al. Delayed referral of patients with diabetic foot ulcers across Europe: patterns between primary care and specialised units. J Wound Care. 2018; 27(3):186-192. https://doi.org/10.12968/jowc.2018.27.3.186.

52 Franks PJ, Moffatt CJ, Doherty DC et al. Longer-term changes in quality of life in chronic leg ulceration. Wound Repair Regen 2006; 14(5):536–541. https://doi.org/10.1111/j.1743-6109.2006.00160.x

53 Goodridge D, Trepman E, Embil JM. Health-related quality of life in diabetic patients with foot ulcers: literature review. J Wound Ostomy Continence Nurs 2005; 32(6):368–377. https://doi.org/10.1097/00152192-200511000-00007

54 World Union of Wound Healing Societies (WUWHS), Florence Congress, Position Document. Local management of diabetic foot ulcers. Wounds International, 2016

55 Fejfarová V, Jirkovská A, Dragomirecká E et al. Does the diabetic foot have a significant impact on selected psychological or social characteristics of patients with diabetes mellitus? J Diabetes Res 2014;2014:1–7. https://doi.org/10.1155/2014/371938

56 Green J, Jester R, McKinley R, Pooler A. The impact of chronic venous leg ulcers: a systematic review. J Wound Care 2014; 23(12):601–612. https://doi.org/10.12968/jowc.2014.23.12.601

57 Augustin M, Brocatti LK, Rustenbach SJ et al. Cost-of-illness of leg ulcers in the community. Int Wound J 2014; 11(3):283–292. https://doi.org/10.1111/j.1742-481X.2012.01089.x

58 Guest JF, Ayoub N, McIlwraith T et al. Health economic burden that different wound types impose on the UK's National Health Service. Int Wound J 2017; 14(2):322–330. https://doi.org/10.1111/iwj.12603

59 Nussbaum SR, Carter MJ, Fife CE et al. An Economic Evaluation of the Impact, Cost, and Medicare Policy Implications of Chronic Nonhealing Wounds. Value Health 2018; 21(1):27–32. https://doi.org/10.1016/j.jval.2017.07.007

60 Dreyfus J, Gayle J, Trueman P et al. Assessment of Risk Factors Associated With Hospital-Acquired Pressure Injuries and Impact on Health Care Utilization and Cost Outcomes in US Hospitals. Am J Med Qual 2018; 33(4):348-358. https://doi.org/10.1177/1062860617746741

61 Chan B, Cadarette S, Wodchis W et al. Cost-of-illness studies in chronic ulcers: a systematic review. J Wound Care. 2017; 26(sup4):S4–S14. https://doi.org/10.12968/jowc.2017.26.Sup4.S4

62 White BA, Dea N, Street JT et al. The Economic Burden of Urinary Tract Infection and Pressure Ulceration in Acute Traumatic Spinal Cord Injury Admissions: Evidence for Comparative Economics and Decision Analytics from a Matched Case-Control Study. J Neurotrauma 2017; 34(20):2892–2900. https://doi.org/10.1089/neu.2016.4934

63 Bauer K, Rock K, Nazzal M et al. Pressure Ulcers in the United States' Inpatient Population From 2008 to 2012: Results of a Retrospective Nationwide Study. Ostomy Wound Manage 2016; 62(11):30–38

64 Driver VR, Fabbi M, Lavery LA, Gibbons G. The costs of diabetic foot: the economic case for the limb salvage team. J Am Podiatr Med Assoc 2010; 100(5):335–341. https://doi.org/10.7547/1000335

65 McInnes AD. Diabetic foot disease in the United Kingdom: about time to put feet first. J Foot Ankle Res 2012; 5(1):26. https://doi.org/10.1186/1757-1146-5-26

66 Rinkel WD, Luiten J, van Dongen J et al. In-hospital costs of diabetic foot disease treated by a multidisciplinary foot team. Diabetes Res Clin Pract 2017; 132:68–78. https://doi.org/10.1016/j.diabres.2017.07.029

67 Öien RF, Forssell H, Ragnarson Tennvall G. Cost consequences due to reduced ulcer healing times—analyses based on the Swedish Registry of Ulcer Treatment. Int Wound J 2016; 13(5):957–962. https://doi.org/10.1111/iwj.12465

68 Edwards J, Mitchell A, Bayat A et al. A comparative study of nurses' wound care knowledge in two areas. J Community Nursing 2005; (online).

69 Ousey K, Chadwick P, Cook L. Diabetic foot or pressure ulcer on the foot? Wounds UK 2011; 7(3):105–108

70 Vowden P, Vowden K. Diabetic foot ulcer or pressure ulcer? That is the question. Diabetic Foot Canada 2016; 4:26–29.

71 McIntosh C, Ousey K. A survey of nurses' and podiatrists' attitudes, skills and knowledge of lower extremity wound care. Wounds UK 2008; 4(1):59–68.

72 Akhtar S, Schaper N, Apelqvist J, Jude E. A review of the Eurodiale studies: what lessons for diabetic foot care? Curr Diab Rep 2011; 11(4):302–309. https://doi.org/10.1007/s11892-011-0195-x

73 Harding K. Challenging passivity in venous leg ulcer care - the ABC model of management. Int Wound J 2016; 13(6):1378–1384. https://doi.org/10.1111/iwj.12608

74 Heyer K, Protz K, Augustin M. Compression therapy—cross-sectional observational survey about knowledge and practical treatment of specialised and non-specialised nurses and therapists. Int Wound J 2017; 14(6):1148–1153. https://doi.org/10.1111/iwj.12773

75 Moffatt CJ, Edwards L, Collier M et al. A randomised controlled 8-week crossover clinical evaluation of the 3M Coban 2 Layer Compression System versus Profore to evaluate the product performance in patients with venous leg ulcers. Int Wound J 2008; 5(2):267–279. https://doi.org/10.1111/j.1742-481X.2008.00487.x

76 Health Quality Ontario. Fibreglass total contact casting, removable cast walkers, and irremovable cast walkers to treat diabetic neuropathic foot ulcers: a health technology assessment. Ont Health Technol Assess Ser 2017; 17(12):1–124

77 Elraiyah T, Prutsky G, Domecq JP et al A systematic review and meta-analysis of off-loading methods for diabetic foot ulcers. J Vasc Surg. 2016; 63(2 Suppl):59S-68S.e1-2

78 Raspovic A, Landorf KB. A survey of offloading practices for diabetes-related plantar neuropathic foot ulcers. J Foot Ankle Res 2014; 7(1):35. https://doi.org/10.1186/s13047-014-0035-8

79 Johnson M, Newton P, Goyder E. Patient and professional perspectives on prescribed therapeutic footwear for people with diabetes: A vignette study. Patient Educ Couns 2006; 64(1-3):167–172. https://doi.org/10.1016/j.pec.2005.12.013

80 Scott IA, Glasziou PP. Improving the effectiveness of clinical medicine: the need for better science. Med J Aust 2012; 196(5):304–308. https://doi.org/10.5694/mja11.10364

81 Franks PJ, Barker J, Collier M et al. Management of patients with venous leg ulcer: challenges and current best practice. J Wound Care 2016; 25(Sup6 Suppl 6):S1–S67. https://doi.org/10.12968/jowc.2016.25.Sup6.S1

82 Vowden P. Hard-to-heal wounds. Made Easy. Wounds International 2011; 2(4):1–6

83 Hjelm K, Nyberg P, Apelqvist J. Gender influences beliefs about health and illness in diabetic subjects with severe foot lesions. J Adv Nurs 2002; 40(6):673–684. https://doi.org/10.1046/j.1365-2648.2002.02427.x

84 Armstrong DG, Lavery LA, Kimbriel HR et al. Activity Patterns of Patients With Diabetic Foot Ulceration: Patients with active ulceration may not adhere to a standard pressure off-loading regimen. Diabetes Care 2003; 26(9):2595–2597. https://doi.org/10.2337/diacare.26.9.2595

85 Eklöf B, Rutherford RB, Bergan JJ et al. Revision of the CEAP classification for chronic venous disorders: Consensus statement. J Vasc Surg 2004; 40(6):1248–1252. https://doi.org/10.1016/j.jvs.2004.09.027

86 Rabe E, Pannier F. Clinical, aetiological, anatomical and pathological classification (CEAP): gold standard and limits. Phlebology: The Journal of Venous Disease 2012; 27(1_suppl Suppl 1):114–118. https://doi.org/10.1258/phleb.2012.012s19

87 Vasquez MA, Rabe E, McLafferty RB et al. Revision of the venous clinical severity score: Venous outcomes consensus statement: Special communication of the American Venous Forum Ad Hoc Outcomes Working Group. J Vasc Surg 2010; 52(5):1387–1396. https://doi.org/10.1016/j.jvs.2010.06.161

88 Meissner MH, Moneta G, Burnand K, et al. The hemodynamics and diagnosis of venous disease. J Vasc Surg. 2007;46 Suppl S:4S–24S

89 Lee BB, Nicolaides AN, Myers K et al. Venous hemodynamic changes in lower limb venous disease: the UIP consensus according to scientific evidence. Int Angiol 2016;35(3):236–352

90 Boulton AJ. The pathway to foot ulceration in diabetes. Med Clin North Am 2013 Sep;97(5):775–790. https://doi.org/10.1016/j.mcna.2013.03.007 Medline

90 Tiftikcioglu BI, Bilgin S, Duksal T et al. Autonomic Neuropathy and Endothelial Dysfunction in Patients With Impaired Glucose Tolerance or Type 2 Diabetes Mellitus Medicine (Baltimore) 2016; 95(14): e3340. https://doi.org/10.1097/MD.0000000000003340

91 Schaper NC. Diabetic foot ulcer classification system for research purposes: a progress report on criteria for including patients in research studies. Diabetes Metab Res Rev 2004; 20(S1 Suppl 1):S90–S95. https://doi.org/10.1002/dmrr.464

92 Zhan LX, Branco BC, Armstrong DG, Mills JL Sr. The Society for Vascular Surgery lower extremity threatened limb classification system based on Wound, Ischemia, and foot Infection (WIfI) correlates with risk of major amputation and time to wound healing. J Vasc Surg 2015; 61(4):939–944. https://doi.org/10.1016/j.jvs.2014.11.045

93 Ousey K, Chadwick P, Jawien A et al. Identifying and treating foot ulcers in patients with diabetes: saving feet, legs and lives. J Wound Care. 2018; 27(Sup5):S1-S52. https://doi.org/10.12968/jowc.2018.27.Sup5.S1

94 Frykberg RG. Diabetic foot ulcers: pathogenesis and management. Am Fam Physician 2002; 66(9):1655–1662

95 Lavery LA, Armstrong DG, Harkless LB. Classification of diabetic foot wounds. J Foot Ankle Surg 1996; 35(6):528–531. https://doi.org/10.1016/S1067-2516(96)80125-6

96 European Pressure Ulcer Advisory Panel (EPUAP), National Pressure Ulcer Advisory Panel (NPUAP), Pan Pacific Pressure Injury Alliance (PPPIA). Prevention and Treatment of Pressure Ulcers: Quick Reference Guide. Emily Haesler (ed). Cambridge Media, 2014

97 Reger SI, Ranganathan VK, Orsted HL et al. Shear and friction in context. In International review. Pressure ulcer prevention: pressure, shear, friction and microclimate in context. A consensus document. Wounds International, 2010

98 Gefen A, Farid KJ, Shaywitz I. A review of deep tissue injury development, detection, and prevention: shear savvy. Ostomy Wound Manage 2013; 59(2):26–35

99 Gefen A, Weihs D. Cytoskeleton and plasma-membrane damage resulting from exposure to sustained deformations: A review of the mechanobiology of chronic wounds. Med Eng Phys 2016; 38(9):828–833. https://doi.org/10.1016/j.medengphy.2016.05.014

100 Strong P, Smit HJ. Adapting fast and slow: force-related tissue damage. Wounds UK 2018; 14(3):22–25.

101 Gefen A. How do microclimate factors affect the risk for superficial pressure ulcers: A mathematical modeling study. J Tissue Viability 2011; 20(3):81–88. https://doi.org/10.1016/j.jtv.2010.10.002

102 Fife CE, Horn SD, Smout RJ et al. A predictive model for diabetic foot ulcer outcome: The Wound Healing Index. Adv Wound Care 2016; 5(7):279–287. https://doi.org/10.1089/wound.2015.0668

103 Vowden P, Vowden K. The importance of detecting lower-limb ischaemia. Wounds International 2016;7(4):6–9.

104 Jockenhöfer F, Gollnick H, Herberger K et al. Aetiology, co-morbidities and cofactors of chronic leg ulcers: retrospective evaluation of 1 000 patients from 10 specialised dermatological wound care centers in Germany. Int Wound J 2016; 13(5):821–828. https://doi.org/10.1111/iwj.12387

105 Honda Y, Hirano K, Yamawaki M et al. Wound healing of critical limb ischemia with tissue loss in patients on hemodialysis. Vascular 2017; 25(3):272–282. https://doi.org/10.1177/1708538116673015

106 Harding KG, Moore K, Phillips TJ. Wound chronicity and fibroblast senescence - implications for treatment. Int Wound J 2005; 2(4):364–368. https://doi.org/10.1111/j.1742-4801.2005.00149.x

107 Finlayson K, Edwards H, Courtney M. The impact of psychosocial factors on adherence to compression therapy to prevent recurrence of venous leg ulcers. J Clin Nurs 2010; 19(9-10):1289–1297. https://doi.org/10.1111/j.1365-2702.2009.03151.x

108 Moffatt C, Kommala D, Dourdin N, Choe Y. Venous leg ulcers: patient concordance with compression therapy and its impact on healing and prevention of recurrence. Int Wound J 2009; 6(5):386–393. https://doi.org/10.1111/j.1742-481X.2009.00634.x

109 Annells M, O'Neill J, Flowers C. Compression bandaging for venous leg ulcers: the essentialness of a willing patient. J Clin Nurs 2008; 17(3):350–359. https://doi.org/10.1111/j.1365-2702.2007.01996.x

110 Sheehan P, Jones P, Caselli A et al. 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 2003; 26(6):1879–1882. https://doi.org/10.2337/diacare.26.6.1879

111 Margolis DJ, Gelfand JM, Hoffstad O, Berlin JA. Surrogate end points for the treatment of diabetic neuropathic foot ulcers. Diabetes Care 2003; 26(6):1696–1700. https://doi.org/10.2337/diacare.26.6.1696

112 Coerper S, Beckert S, Küper MA et al. Fifty percent area reduction after 4 weeks of treatment is a reliable indicator for healing—analysis of a single-center cohort of 704 diabetic

patients. J Diabetes Complications 2009; 23(1):49–53. https://doi.org/10.1016/j.jdiacomp.2008.02.001

113 Cardinal M, Eisenbud DE, Phillips T, Harding K. Early healing rates and wound area measurements are reliable predictors of later complete wound closure. Wound Repair Regen 2008; 16(1):19–22. https://doi.org/10.1111/j.1524-475X.2007.00328.x

114 Snyder RJ, Cardinal M, Dauphinée DM, Stavosky J. A post-hoc analysis of reduction in diabetic foot ulcer size at 4 weeks as a predictor of healing by 12 weeks. Ostomy Wound Manage 2010; 56(3):44–50

115 Günes, U.Y. A prospective study evaluating the pressure ulcer scale for healing to assess Stage II, Stage III and Stage IV Pressure Ulcers. Ostomy Wound Manage 2009,55(5):48-52

116 Schultz GS, Davidson JM, Kirsner RS et al. Dynamic reciprocity in the wound microenvironment. Wound Repair Regen 2011; 19(2):134–148. https://doi.org/10.1111/j.1524-475X.2011.00673.x

117 Chen WY, Rogers AA. Recent insights into the causes of chronic leg ulceration in venous diseases and implications on other types of chronic wounds. Wound Repair Regen 2007; 15(4):434–449. https://doi.org/10.1111/j.1524-475X.2007.00250.x

118 Trengove NJ, Bielefeldt-Ohmann H, Stacey MC. Mitogenic activity and cytokine levels in non-healing and healing chronic leg ulcers. Wound Repair Regen 2000; 8(1):13–25. https://doi.org/10.1046/j.1524-475x.2000.00013.x

119 Bergan JJ, Schmid-Schönbein GW, Coleridge Smith PD, Nicolaides AN, Boisseau MR, Eklof B. Chronic venous disease. Minerva Cardioangiol 2007; 55(4):459–476

120 Schultz G, Bjarnsholt T, James GA et al. Consensus guidelines for the identification and treatment of biofilms in chronic nonhealing wounds. Wound Repair Regen 2017; 25(5):744–757. https://doi.org/10.1111/wrr.12590

121 Frykberg RG, Banks J. Challenges in the Treatment of Chronic Wounds. Adv Wound Care (New Rochelle). 2015 1; 4(9):560-582.

122 Schultz GS, Davidson JM, Kirsner RS et al. Dynamic reciprocity in the wound microenvironment. Wound Repair Regen 2011; 19(2):134–148. https://doi.org/10.1111/j.1524-475X.2011.00673.x

123 Chi YW, Raffetto JD. Venous leg ulceration pathophysiology and evidence based treatment. Vasc Med 2015; 20(2):168–181. https://doi.org/10.1177/1358863X14568677

124 Smith PD, Thomas P, Scurr JH, Dormandy JA. Causes of venous ulceration: a new hypothesis. BMJ 1988; 296(6638):1726–1727. https://doi.org/10.1136/bmj.296.6638.1726

125 Nwomeh BC, Yager DR, Cohen IK. Physiology of the chronic wound. Clin Plast Surg 1998; 25(3):341–356

126 Mast BA, Schultz GS. Interactions of cytokines, growth factors, and proteases in acute and chronic wounds. Wound Repair Regen 1996; 4(4):411–420. https://doi.org/10.1046/j.1524-475X.1996.40404.x

127 Raffetto JD. Pathophysiology of chronic venous disease and venous ulcers. Surg Clin North Am 2018; 98(2):337–347. https://doi.org/10.1016/j.suc.2017.11.002

128 Ligi D, Mosti G, Croce L et al. Chronic venous disease – part I: Inflammatory biomarkers in wound healing. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease 2016; 1862(10):1964–1974. https://doi.org/10.1016/j.bbadis.2016.07.018

129 Loots MA, Lamme EN, Zeegelaar J et al. Differences in cellular infiltrate and extracellular matrix of chronic diabetic and venous ulcers versus acute wounds. J Invest Dermatol 1998; 111(5):850–857. https://doi.org/10.1046/j.1523-1747.1998.00381.x

130 Trengove NJ, Stacey MC, Macauley S et al. Analysis of the acute and chronic wound environments: the role of proteases and their inhibitors. Wound Repair Regen 1999; 7(6):442–452. https://doi.org/10.1046/j.1524-475X.1999.00442.x

131 Amato B, Coretti G, Compagna R et al. Role of matrix metalloproteinases in non-healing venous ulcers. Int Wound J 2015; 12(6):641–645. https://doi.org/10.1111/iwj.12181

132 Rao CN, Ladin DA, Chilukuri K et al. Alpha 1-antitrypsin is degraded and non-functional in chronic wounds but intact and functional in acute wounds: the inhibitor protects fibronectin from degradation by chronic wound fluid enzymes. J Invest Dermatol 1995; 105(4):572–578. https://doi.org/10.1111/1523-1747.ep12323503

133 Herrick S, Ashcroft G, Ireland G et al. Up-regulation of elastase in acute wounds of healthy aged humans and chronic venous leg ulcers are associated with matrix degradation. Lab Invest 1997; 77(3):281–288

134 Rogers AA, Burnett S, Lindholm C et al. Expression of tissue-type and urokinase-type plasminogen activator activities in chronic venous leg ulcers. Vasa 1999; 28(2):101–105. https://doi.org/10.1024/0301-1526.28.2.101

135 Danø K, Andreasen PA, Grøndahl-Hansen J et al. Plasminogen activators, tissue degradation, and cancer. Adv Cancer Res 1985; 44:139–266. https://doi.org/10.1016/S0065-230X(08)60028-7

136 Moseley R, Hilton JR, Waddington RJ et al. Comparison of oxidative stress biomarker profiles between acute and chronic wound environments. Wound Repair Regen 2004; 12(4):419–429. https://doi.org/10.1111/j.1067-1927.2004.12406.x

137 Zamboni P, Scapoli G, Lanzara V et al. Serum iron and matrix metalloproteinase-9 variations in limbs affected by chronic venous disease and venous leg ulcers. Dermatol Surg 2005; 31(6):644–649. https://doi.org/10.1097/00042728-200506000-00005

138 Peschen M, Rogers AA, Chen WY, Vanscheidt W. Modulation of urokinase-type and tissue-type plasminogen activator occurs at an early stage of progressing stages of chronic venous insufficiency. Acta Derm Venereol 2000; 80(3):162–166. https://doi.org/10.1080/000155500750042880

139 Lobmann R, Ambrosch A, Schultz G et al. Expression of matrix-metalloproteinases and their inhibitors in the wounds of diabetic and non-diabetic patients. Diabetologia 2002; 45(7):1011–1016. https://doi.org/10.1007/s00125-002-0868-8

140 Subramaniam K, Pech CM, Stacey MC, Wallace HJ. Induction of MMP-1, MMP-3 and TIMP-1 in normal dermal fibroblasts by chronic venous leg ulcer wound fluid. Int Wound J 2008; 5(1):79–86. https://doi.org/10.1111/j.1742-481X.2007.00336.x

141 Derosa G, D'Angelo A, Tinelli C et al. Evaluation of metalloproteinase 2 and 9 levels and their inhibitors in diabetic and healthy subjects. Diabetes Metab 2007; 33(2):129–134. https://doi.org/10.1016/j.diabet.2006.11.008

142 Saito S, Trovato MJ, You R et al. Role of matrix metalloproteinases 1, 2, and 9 and tissue inhibitor of matrix metalloproteinase-1 in chronic venous insufficiency. J Vasc Surg 2001; 34(5):930–938. https://doi.org/10.1067/mva.2001.119503

143 Mendez MV, Stanley A, Park HY et al. Fibroblasts cultured from venous ulcers display cellular characteristics of senescence. J Vasc Surg 1998; 28(5):876–883. https://doi.org/10.1016/S0741-5214(98)70064-3

144 Healey C, Forgione P, Lounsbury KM et al. A new in vitro model of venous hypertension: the effect of pressure on dermal fibroblasts. J Vasc Surg 2003; 38(5):1099–1105. https://doi.org/10.1016/S0741-5214(03)00556-1

145 Campisi J. The role of cellular senescence in skin aging. J Investig Dermatol Symp Proc 1998; 3(1):1–5. https://doi.org/10.1038/jidsymp.1998.2

146 Stanley A, Osler T. Senescence and the healing rates of venous ulcers. J Vasc Surg 2001; 33(6):1206–1211. https://doi.org/10.1067/mva.2001.115379

147 Harding KG, Moore K, Phillips TJ. Wound chronicity and fibroblast senescence - implications for treatment. Int Wound J 2005; 2(4):364–368. https://doi.org/10.1111/j.1742-4801.2005.00149.x

148 Agren MS, Werthén M. The extracellular matrix in wound healing: a closer look at therapeutics for chronic wounds. Int J Low Extrem Wounds 2007; 6(2):82–97. https://doi.org/10.1177/1534734607301394

149 Malone M, Bjarnsholt T, McBain AJ et al. The prevalence of biofilms in chronic wounds: a systematic review and meta-analysis of published data. J Wound Care 2017; 26(1):20–25. https://doi.org/10.12968/jowc.2017.26.1.20

150 Johani K, Malone M, Jensen S et al. Microscopy visualisation confirms multi-species biofilms are ubiquitous in diabetic foot ulcers. Int Wound J 2017; 14(6):1160–1169. https://doi.org/10.1111/iwj.12777

References

151 Wolcott RD, Rumbaugh KP, James G et al. Biofilm maturity studies indicate sharp debridement opens a time-dependent therapeutic window. J Wound Care 2010; 19(8):320–328. https://doi.org/10.12968/jowc.2010.19.8.77709

152 World Union of Wound Healing Societies (WUWHS), Florence Congress, Position Document. Management of Biofilm. Wounds International 2016

153 Wolcott RD, Rhoads DD, Dowd SE. Biofilms and chronic wound inflammation. J Wound Care 2008; 17(8):333–341. https://doi.org/10.12968/jowc.2008.17.8.30796

154 Bjarnsholt T, Kirketerp-Møller K et al. Why chronic wounds will not heal: a novel hypothesis. Wound Repair Regen 2008; 16(1):2–10. https://doi.org/10.1111/j.1524-475X.2007.00283.x

155 Fazli M, Bjarnsholt T, Kirketerp-Møller K et al. Quantitative analysis of the cellular inflammatory response against biofilm bacteria in chronic wounds. Wound Repair Regen 2011; 19(3):387–391. https://doi.org/10.1111/j.1524-475X.2011.00681.x

156 Percival SL, Bowler PG. Biofilms and their potential role in wound healing. Wounds 2004; 16:234–240.

157 Shiau A, Wu C. The inhibitory effect of Staphylococcus epidermidis slime on the phagocytosis of murine peritoneal macrophages is interferon-independent. Microbiol Immunol 1998; 42(1):33–40. https://doi.org/10.1111/j.1348-0421.1998.tb01966.x

158 Roy S, Elgharably H, Sinha M et al. Mixed-species biofilm compromises wound healing by disrupting epidermal barrier function. J Pathol 2014; 233(4):331–343. https://doi.org/10.1002/path.4360

159 Trøstrup H, Lerche C, Christophersen L et al. Immune modulating topical S100A8/A9 inhibits growth of Pseudomonas aeruginosa and mitigates biofilm infection in chronic wounds. Int J Mol Sci 2017; 18(7):1359. https://doi.org/10.3390/ijms18071359

160 de Beer D, Stoodley P, Roe F, Lewandowski Z. Effects of biofilm structures on oxygen distribution and mass transport. Biotechnol Bioeng 1994; 43(11):1131–1138. https://doi.org/10.1002/bit.260431118

161 Lawrence JR, Swerhone GD, Kuhlicke U, Neu TR. In situ evidence for microdomains in the polymer matrix of bacterial microcolonies. Can J Microbiol 2007; 53(3):450–458. https://doi.org/10.1139/W06-146

162 Schierle CF, De la Garza M, Mustoe TA, Galiano RD. Staphylococcal biofilms impair wound healing by delaying reepithelialization in a murine cutaneous wound model. Wound Repair Regen 2009; 17(3):354–359. https://doi.org/10.1111/j.1524-475X.2009.00489.x

163 Cutting KF, Wolcott R, Dowd SE, et al. Biofilms and significance to wound healing. In: Percival S, Cutting KF (eds). The microbiology of wounds. CRC Press, Taylor and Francis Group, 2010

164 Attinger C1, Wolcott R. Clinically addressing biofilm in chronic wounds. Adv Wound Care (New Rochelle) 2012; 1(3):127–132. https://doi.org/10.1089/wound.2011.0333

165 Agren MS, Steenfos HH, Dabelsteen S et al. Proliferation and mitogenic response to PDGF-BB of fibroblasts isolated from chronic venous leg ulcers is ulcer-age dependent. J Invest Dermatol 1999; 112(4):463–469

166 Mendez MV, Raffetto JD, Phillips T et al. The proliferative capacity of neonatal skin fibroblasts is reduced after exposure to venous ulcer wound fluid: A potential mechanism for senescence in venous ulcers. J Vasc Surg 1999; 30(4):734–743. https://doi.org/10.1016/S0741-5214(99)70113-8

167 Pedro de Magalhães J, Chainiaux F, de Longueville F et al. Gene expression and regulation in H2O2-induced premature senescence of human foreskin fibroblasts expressing or not telomerase. Exp Gerontol 2004; 39(9):1379–1389. https://doi.org/10.1016/j.exger.2004.06.004

168 Wolcott R. Are chronic wounds, chronic infections? J Wound Care 2016; 25(Sup10):S3–S3. https://doi.org/10.12968/jowc.2016.25.Sup10.S3

169 Alavi A, Sibbald RG, Mayer D et al. Diabetic foot ulcers. J Am Acad Dermatol 2014; 70(1):1.e1–1.e18. https://doi.org/10.1016/j.jaad.2013.06.055

170 Ashcroft GS, Mills SJ, Ashworth JJ. Ageing and wound healing. Biogerontology 2002; 3(6):337–345. https://doi.

org/10.1023/A:1021399228395

171 Ashcroft GS, Horan MA, Ferguson MW. The effects of ageing on wound healing: immunolocalisation of growth factors and their receptors in a murine incisional model. J Anat 1997; 190(3):351–365. https://doi.org/10.1046/j.1469-7580.1997.19030351.x

172 Ashcroft GS, Horan MA, Herrick SE et al. Age-related differences in the temporal and spatial regulation of matrix metalloproteinases (MMPs) in normal skin and acute cutaneous wounds of healthy humans. Cell Tissue Res 1997; 290(3):581–591. https://doi.org/10.1007/s004410050963

173 Ashcroft GS, Herrick SE, Tarnuzzer RW et al. Human ageing impairs injury-induced in vivo expression of tissue inhibitor of matrix metalloproteinases (TIMP)-1 and -2 proteins and mRNA. J Pathol 1997; 183(2):169–176. https://doi.org/10.1002/(SICI)1096-9896(199710)183:2%3C169::AID-PATH915%3E3.0.CO;2-Q

174 Ashcroft GS, Horan MA, Ferguson MW. Aging is associated with reduced deposition of specific extracellular matrix components, an upregulation of angiogenesis, and an altered inflammatory response in a murine incisional wound healing model. J Invest Dermatol 1997; 108(4):430–437. https://doi.org/10.1111/1523-1747.ep12289705

175 Fife CE, Horn SD, Smout RJ et al. A Predictive Model for Diabetic Foot Ulcer Outcome: The Wound Healing Index. Adv Wound Care 2016; 5(7):279–287. https://doi.org/10.1089/wound.2015.0668

176 Buggy A, Moore Z. The impact of the multidisciplinary team in the management of individuals with diabetic foot ulcers: a systematic review. J Wound Care 2017; 26(6):324–339. https://doi.org/10.12968/jowc.2017.26.6.324

177 Moore Z, Butcher G, Corbett LQ et al. Exploring the concept of a team approach to wound care: Managing wounds as a team.. J Wound Care 2014; 23(5 Suppl.):S1–S38. https://doi.org/10.12968/jowc.2014.23.Sup5b.S1

178 Atkin L, Critchley A. The leg ulceration pathway: impact of implementation. Wounds UK 2017; 13(4):107–112

179 Suva G, Sharma T, Campbell KE, Sibbald RG, An D, Woo K. Strategies to support pressure injury best practices by the inter-professional team: A systematic review. Int Wound J 2018; 15(4):580–589. https://doi.org/10.1111/iwj.12901

180 International Wound Infection Institute (IWII) Wound infection in clinical practice. Wounds International 2016

181 Harries RL, Bosanquet DC, Harding KG. WBP: TIME for an update. Int Wound J 2016; 13(S3 Suppl 3):8–14. https://doi.org/10.1111/iwj.12662

182 Gupta S, Andersen C, Black J et al. Management of chronic wounds: diagnosis, preparation, treatment and follow-up. Wounds 2017 Sep;29(9 suppl):S19–S36

183 Patel GK, Grey JE, Harding KG. Uncommon causes of ulceration. BMJ 2006; 332(7541):594–596. https://doi.org/10.1136/bmj.332.7541.594

184 Labropoulos N, Manalo D, Patel NP et al. Uncommon leg ulcers in the lower extremity. J Vasc Surg 2007; 45(3):568–573.e2. https://doi.org/10.1016/j.jvs.2006.11.012

185 Atkin L, Critchley A. The leg ulceration pathway: impact of implementation. Wounds UK 2017; 13(4):107–112.

186 Tissue Analytics. Wound assessment and management platform. https://tinyurl.com/y8ygk6qk (accessed 18 January 2019)

187 Ashby RL, Gabe R, Ali S, Saramago P et al. VenUS IV (Venous leg Ulcer Study IV) – compression hosiery compared with compression bandaging in the treatment of venous leg ulcers: a randomised controlled trial, mixed-treatment comparison and decision-analytic model. Health Technol Assess 2014; 18(57):1–294. https://doi.org/10.3310/hta18570

188 Gohel MS, Heatley F, Liu X, Bradbury A et al. A Randomized Trial of Early Endovenous Ablation in Venous Ulceration. N Engl J Med 2018; 378(22):2105–2114. https://doi.org/10.1056/NEJMoa1801214

189 Tang TY, Walsh SR, Chong TT et al. Results of the EVRA trial will be a game-changer for the management of every venous ulcer. Phlebology 2018; 33(10):660–662. https://doi.org/10.1177/0268355518791886

190 Davies HOB, Bradbury AW. The EVRA trial: new hope for people with venous leg ulcers? Eur J Vasc Endovasc Surg. 2018; pii: S1078-5884(18)30504-5. [Epub ahead of print] https://doi.org/10.1016/j.ejvs.2018.07.030

191 Milic DJ, Zivic SS, Bogdanovic DC, et al. A randomized trial of class 2 and class 3 elastic compression in the prevention of recurrence of venous ulceration. J Vasc Surg Venous Lymphat Disord 2018; 6(6):717–723. https://doi.org/10.1016/j.jvsv.2018.06.009

192 Gohel MS, Barwell JR, Taylor M et al. Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial. BMJ 2007; 335(7610):83. https://doi.org/10.1136/bmj.39216.542442.BE

193 Lewis J, Lipp A. Pressure-relieving interventions for treating diabetic foot ulcers. Cochrane Database Syst Rev 2013; (1):CD002302. https://doi.org/10.1002/14651858.CD002302.pub2

194 NICE Guideline. NG19. Diabetic foot problems: prevention and management. 2015; https://tinyurl.com/ksslts5. (accessed 18 January 2019)

195 International Working Group on the Diabetic Foot (IWGDF). How to organise a diabetic foot clinic. 2007; https://tinyurl.com/y76sxmjf. (accessed 18 January 2019)

196 Wukich DK, Armstrong DG, Attinger CE et al. Inpatient management of diabetic foot disorders: a clinical guide. Diabetes Care 2013; 36(9):2862–2871. https://doi.org/10.2337/dc12-2712

197 Rabe E, Partsch H, Hafner J et al. Indications for medical compression stockings in venous and lymphatic disorders: An evidence-based consensus statement. Phlebology: The Journal of Venous Disease 2018; 33(3):163–184. https://doi.org/10.1177/0268355516689631

198 Marston W, Tang J, Kirsner RS, Ennis W. Wound healing society 2015 update on guidelines for venous ulcers. Wound Repair Regen 2016; 24(1):136–144. https://doi.org/10.1111/wrr.12394

199 IWGDF. Prevention and management of foot problems in diabetes: a summary guidance for daily practice. 2015. https://tinyurl.com/ybplmyxh (accessed 18 January 2019)

200 Blackshaw EL, Jeffery S. Efficacy of an imaging device at identifying the presence of bacteria in wounds at a plastic surgery outpatients clinic. J Wound Care 2018; 27(1):20–26 https://doi.org/10.12968/jowc.2018.27.1.20

201 Rennie MY, Lindvere-Teene L, Tapang K, Linden R. Point-of-care fluorescence imaging predicts the presence of pathogenic bacteria in wounds: a clinical study. J Wound Care 2017; 260(8):452–460. https://doi.org/10.12968/jowc.2017.26.8.452

202 Wild T, Becker M, Winter J et al. Hyperspectral imaging of tissue perfusion and oxygenation in wounds: assessing the impact of a micro capillary dressing. J Wound Care 2018; 27(1):38–51. https://doi.org/10.12968/jowc.2018.27.1.38

203 Rutkowski R, Schuster M, Unger J et al. Hyperspectral imaging for in vivo monitoring of cold atmospheric plasma effects on microcirculation in treatment of head and neck cancer and wound healing. Clinical Plasma Medicine 2017 7-8:52–57. https://doi.org/10.1016/j.cpme.2017.09.002

204 Moore Z, Patton D, Rhodes SL, O'Connor T. Subepidermal moisture (SEM) and bioimpedance: a literature review of a novel method for early detection of pressure-induced tissue damage (pressure ulcers). Int Wound J 2017; 14(2):331–337. https://doi.org/10.1111/iwj.12604

205 Lavery LA, Armstrong DG, Wunderlich RP et al. Risk factors for foot infections in individuals with diabetes. Diabetes Care 2006; 29(6):1288–1293. https://doi.org/10.2337/dc05-2425

206 Piaggesi A, Låuchli S, Bassetto F et al. Advanced therapies in wound management: cell and tissue based therapies, physical and bio-physical therapies smart and IT based technologies. J Wound Care 2018; 27(Sup6a Suppl 6):S1–S137. https://doi.org/10.12968/jowc.2018.27.Sup6a.S1

207 Wilcox JR, Carter MJ, Covington S. Frequency of debridements and time to heal: a retrospective cohort study of 312 744 wounds. JAMA Dermatol 2013; 149(9):1050–1058. https://doi.org/10.1001/jamadermatol.2013.4960

208 Williams D, Enoch S, Miller D et al. Effect of sharp debridement using curette on recalcitrant nonhealing venous leg ulcers: A concurrently controlled, prospective cohort study. Wound Repair Regen 2005; 13(2):131–137. https://doi.org/10.1111/j.1067-1927.2005.130203.x

209 Tettelbach W, Cazzell S, Reyzelman AM et al. A confirmatory study on the efficacy of dehydrated human amnion/chorion membrane dHACM allograft in the management of diabetic foot ulcers: A prospective, multicentre, randomised, controlled study of 110 patients from 14 wound clinics. Int Wound J 2019; 16(1):19–29. https://doi.org/10.1111/iwj.12976

210 Tettelbach W, Cazzell S, Sigal F A multicentre prospective randomised controlled comparative parallel study of dehydrated human umbilical cord (EpiCord) allograft for the treatment of diabetic foot ulcers. Int Wound J 2019; 16(1):122–130. https://doi.org/10.1111/iwj.13001

211 Phillips, P. W. (2010). Biofilms Made Easy. Wounds International 1(3), 1–6

212 McDonnell G, Russell AD. Antiseptics and disinfectants: activity, action, and resistance. Clin Microbiol Rev 1999; 12(1):147–179. https://doi.org/10.1128/CMR.12.1.147

213 Smith AG, Powis RA, Pritchard DI, Britland ST. Greenbottle fly (Lucilia sericata or Lucilia cuprina) remove moist slough by excreting proteolytic enzymes to digest non-viable tissue and ingesting the liquefied tissue. Biotechnol Prog 2006; 22(6):1690–1696. https://doi.org/10.1021/bp0601600

214 Bekara F, Vitse J, Fluieraru S et al New techniques for wound management: A systematic review of their role in the management of chronic wounds. Arch Plast Surg 2018; 45(2):102-110. https://doi.org/10.5999/aps.2016.02019

215 Ennis WJ, Foremann P, Mozen N et al. Ultrasound therapy for recalcitrant diabetic foot ulcers: results of a randomized, double-blind, controlled, multicenter study. Ostomy Wound Manage 2005; 51(8):24–39

216 Conner-Kerr T, Alston G, Stovall A et al. The effects of low-frequency ultrasound (35 kHz) on methicillin-resistant Staphylococcus aureus (MRSA) in vitro. Ostomy Wound Manage 2010; 56(5):32–43

217 Percival SL, Woods E, Nutekpor M et al. Prevalence of silver resistance in bacteria isolated from diabetic foot ulcers and efficacy of silver-containing wound dressings. Ostomy Wound Manage 2008; 54(3):30–40

218 Percival SL, Bowler PG, Russell D. Bacterial resistance to silver in wound care. J Hosp Infect 2005; 60(1):1–7. https://doi.org/10.1016/j.jhin.2004.11.014

219 Klaus T, Joerger R, Olsson E, Granqvist CG. Silver-based crystalline nanoparticles, microbially fabricated. Proc Natl Acad Sci USA 1999; 96(24):13611–13614. https://doi.org/10.1073/pnas.96.24.13611

220 Krieger BR, Davis DM, Sanchez JE, et al. The use of silver nylon in preventing surgical site infections following colon and rectal surgery. Diseases of the colon and rectum 2011; 54(8):1014–1019. https://doi.org/10.1097/DCR.0b013e31821c495d

221 Marx DE, Barillo DJ Silver in medicine: The basic science. Burns 2014; 405:S9–S18. https://doi.org/10.1016/j.burns.2014.09.010

222 Ljungh Å, Wadström T. Growth conditions influence expression of cell surface hydrophobicity of staphylococci and other wound infection pathogens. Microbiol Immunol 1995; 39(10):753–757. https://doi.org/10.1111/j.1348-0421.1995.tb03267.x

223 Robertson E. Treatment of Candida infection with a fungus adsorbing dressing. Sår 2007;1:26.

224 Cutting K, McGuire J. Safe bioburden management: A clinical review of DACC technology Journal of Wound Care 2015; 24(5):1–32

225 Ljungh, A., Yanagisawa, N., Wadström, T. Using the principle of hydrophobic interaction to bind and remove wound bacteria. J Wound Care 2006; 15: 4, 175–180.

226 Haycocks S, Chadwick P, Guttormsen K. Use of a DACC-coated antimicrobial dressing in people with diabetes and a history of foot ulceration. Wounds UK 2011; 7(11):108–114.

227 Totty JP, Bua N, Smith GE et al. Dialkylcarbamoyl chloride (DACC)-coated dressings in the management and prevention of wound infection: a systematic review. J Wound Care 2017;

References

26(3):107–114. https://doi.org/10.12968/jowc.2017.26.3.107

228 Murphy N. Reducing infection in chronic leg ulcers with an activated carbon cloth dressing. Br J Nurs 2016; 25(12):S38–S44. https://doi.org/10.12968/bjon.2016.25.12.S38

229 Matthes R, Lührman A, Holtfreter S et al. Antibacterial activity of cold atmospheric pressure argon plasma against 78 genetically different (meca, luk-P, agr or capsular polysaccharide type) Staphylococcus aureus strains. Skin Pharmacol Physiol 2016; 29(2):83–91. https://doi.org/10.1159/000443210

230 Wiegand C, Beier O, Horn K et al. Antimicrobial impact of cold atmospheric pressure plasma on medical critical yeasts and bacteria cultures. Skin Pharmacol Physiol 2014; 27(1):25–35. https://doi.org/10.1159/000351353

231 Wiegand C, Fink S, Hipler UC et al. Cold atmospheric pressure plasmas exhibit antimicrobial properties against critical bacteria and yeast species. J Wound Care 2017; 26(8):462–468. https://doi.org/10.12968/jowc.2017.26.8.462

232 Brun P, Bernabè P, Marchiori C et al. Antibacterial efficacy and mechanisms of action of low power atmospheric pressure cold plasma: membrane permeability, biofilm penetration and antimicrobial sensitization. J Appl Microbiol 2018; 125(2):398–408. https://doi.org/10.1111/jam.13780

233 Ulrich C, Kluschke F, Patzelt A et al. Clinical use of cold atmospheric pressure argon plasma in chronic leg ulcers: A pilot study. J Wound Care 2015; 24(5):196–203. https://doi.org/10.12968/jowc.2015.24.5.196

234 Mols M, Mastwijk H, Nierop Groot M, Abee T. Physiological and transcriptional response of Bacillus cereus treated with low-temperature nitrogen gas plasma. J Appl Microbiol 2013; 115(3):689–702. https://doi.org/10.1111/jam.12278

235 Kondeti VS, Phan CQ, Wende K et al. Long-lived and short-lived reactive species produced by a cold atmospheric pressure plasma jet for the inactivation of Pseudomonas aeruginosa and Staphylococcus aureus. Free Radic Biol Med 2018; 124:275–287. https://doi.org/10.1016/j.freeradbiomed.2018.05.083

236 Isbary G, Stolz W, Shimizu T et al. Cold atmospheric argon plasma treatment may accelerate wound healing in chronic wounds: Results of an open retrospective randomized controlled study in vivo. Clin Plasma Med 2013; 1(2):25–30. https://doi.org/10.1016/j.cpme.2013.06.001

237 Arndt S, Unger P, Berneburg M et al. Cold atmospheric plasma (CAP) activates angiogenesis-related molecules in skin keratinocytes, fibroblasts and endothelial cells and improves wound angiogenesis in an autocrine and paracrine mode. J Dermatol Sci 2018; 89(2):181–190. https://doi.org/10.1016/j.jdermsci.2017.11.008

238 Kisch T, Helmke A, Schleusser S et al. Improvement of cutaneous microcirculation by cold atmospheric plasma (CAP): Results of a controlled, prospective cohort study. Microvasc Res 2016; 104:55–62. https://doi.org/10.1016/j.mvr.2015.12.002

239 Kisch T, Schleusser S, Helmke A et al. The repetitive use of non-thermal dielectric barrier discharge plasma boosts cutaneous microcirculatory effects. Microvasc Res 2016; 106:8–13. https://doi.org/10.1016/j.mvr.2016.02.008

240 Lührmann A, Matthes R, Kramer A. Impact of cold atmospheric pressure argon plasma on antibiotic sensitivity of methicillin-resistant Staphylococcus aureus strains in vitro. GMS Hyg Infect Control. 2016; 11:Doc17

241 Isbary G, Morfill G, Schmidt HU et al. A first prospective randomized controlled trial to decrease bacterial load using cold atmospheric argon plasma on chronic wounds in patients. Br J Dermatol 2010; 163(1):no. https://doi.org/10.1111/j.1365-2133.2010.09744.x

242 Arndt S, Schmidt A, Karrer S, von Woedtke T. Comparing two different plasma devices kINPen and Adtec SteriPlas regarding their molecular and cellular effects on wound healing. Clin Plasma Med 2018; 9:24–33. https://doi.org/10.1016/j.cpme.2018.01.002

243 Nikolis A, Grimard D, Pesant Y et al. A prospective case series evaluating the safety and efficacy of the Klox BioPhotonic System in venous leg ulcers. Chronic Wound Care Management and Research 2016; 3:101–111. https://doi.org/10.2147/CWCMR.S104391

244 Nielsen ME, Devemy E, Jaworska J, Scapagnini G. Photobiomodula¬tion by low energy chromophore-induced fluorescent light. Abstract presented at SPIE BiOS, San Francisco, CA, USA; 28 January 2017.

245 de Freitas LF, Hamblin MR. Proposed mechanisms of photobiomodu¬lation or low-level light therapy. IEEE J Sel Top Quantum Electron 2016 May;22(3):348–364. https://doi.org/10.1109/JSTQE.2016.2561201 Medline

246 Kuffler DP. Photobiomodulation in promoting wound healing: a review. Regen Med 2016; 11(1):107–122. https://doi.org/10.2217/rme.15.82

247 Kim HP. Lightening up Light Therapy: Activation of Retrograde Signaling Pathway by Photobiomodulation. Biomol Ther (Seoul) 2014; 22(6):491–496. https://doi.org/10.4062/biomolther.2014.083

248 Tatmatsu-Rocha JC, Tim CR et al. Mitochondrial dynamics (fission and fusion) and collagen production in a rat model of diabetic wound healing treated by photobiomodulation: comparison of 904 nm laser and 850 nm light-emitting diode (LED). J Photochem Photobiol B 2018; 187:41–47. https://doi.org/10.1016/j.jphotobiol.2018.07.032

249 Scapagnini G, Marchegiani A, Rossi G et al. Management of all three phases of wound healing through the induction of fluorescence biomodulation using fluorescence light energy. Proc SPIE 2019; In Press. https://tinyurl.com/y48a57dz (accessed 20 February 2019)

250 Hashmi JT, Huang YY, Osmani BZ, et al. Role of low-level laser therapy in neurorehabilitation. PM R 2020; 2(12 Suppl. 2):S292–S305.

251 Romanelli M, Piaggesi A, Scapagnini G et al. EUREKA study – the evaluation of real-life use of a biophotonic system in chronic wound management: an interim analysis. Drug Des Devel Ther 2017; 11:3551–3558. https://doi.org/10.2147/DDDT.S142580

252 Romanelli M, Piaggesi A, Scapagnini G, et al. Evaluation of fluorescence biomodulation in the real-life management of chronic wounds: EUREKA trial. J Wound Care. 2018; 27(11):744–753. https://doi.org/10.12968/jowc.2018.27.11.744

253 Snyder RJ, Bohn G, Hanft J et al. Wound Biofilm: Current Perspectives and Strategies on Biofilm Disruption and Treatments. Wounds 2017; 29(6):S1–S17

254 Next science. Blast X. Data on file https://www.nextscience.com/blastx-wound-gel/ (accessed 17 january 2019)

255 Miller KG, Tran PL, Haley CL et al. Next science wound gel technology, a novel agent that inhibits biofilm development by gram-positive and gram-negative wound pathogens. Antimicrob Agents Chemother 2014; 58(6):3060–3072. https://doi.org/10.1128/AAC.00108-14

256 Wolcott R. Disrupting the biofilm matrix improves wound healing outcomes. J Wound Care 2015; 24(8):366–371. https://doi.org/10.12968/jowc.2015.24.8.366

257 Kim D, Namen Ii W, Moore J et al. Clinical Assessment of a Biofilm-disrupting Agent for the Management of Chronic Wounds Compared With Standard of Care: A Therapeutic Approach. Wounds 2018; 30(5):120–130

258 Yang Q, Schultz GS, Gibson D. A Surfactant-Based Dressing to Treat and Prevent Acinetobacter Baumannii Biofilms. J Burn Care Res 2018; 39(5):766–770. https://doi.org/10.1093/jbcr/irx041

259 Percival SL, Mayer D, Salisbury AM. Efficacy of a surfactant-based wound dressing on biofilm control. Wound Repair Regen 2017; 25(5):767–773. https://doi.org/10.1111/wrr.12581

260 Ghatak P, Mathew-Steiner SS, Pandey P, Roy S, Sen CK. A surfactant polymer dressing potentiates antimicrobial efficacy in biofilm disruption. Nature Scientific Reports. 2018; 8:873.

261 Gottrup F, Dissemond J, Baines C. Use of oxygen therapies in wound healing: focus on topical and hyperbaric oxygen treatment J Wound Care 2017; 26(Sup5):S1–S43. https://doi.org/10.12968/jowc.2017.26.Sup5.S1

262 C.-E. Chen, J.-Y. Ko, C.-Y. Fong, R.-J. Juhn, Treatment of diabetic foot infection with hyperbaric oxygen therapy, Foot Ankle Surg. 16 (2) (2010) 91–95.

263 Memar MY, Yekani M, Alizadeh N, Baghi HB. Hyperbaric oxygen

therapy: Antimicrobial mechanisms and clinical application for infections. Biomed Pharmacother 2018; 109:440–447. https://doi.org/10.1016/j.biopha.2018.10.142

264 Tickle J. Wound exudate assessment and management: a challenge for clinicans. Br J Nurs 2015; 24(Sup20 Suppl 20):S38–S43. https://doi.org/10.12968/bjon.2015.24.Sup20.S38

265 White R. Wound dressings and other topical treatment modalities in bioburden control. J Wound Care 2011; 20(9):431–439. https://doi.org/10.12968/jowc.2011.20.9.431

266 Kim PJ, Applewhite A, Dardano AN et al. Use of a Novel Foam Dressing With Negative Pressure Wound Therapy and Instillation: Recommendations and Clinical Experience. Wounds 2018; 30(3 suppl):S1–S17

267 Téot L, Boissiere F, Fluieraru S. Novel foam dressing using negative pressure wound therapy with instillation to remove thick exudate. Int Wound J 2017; 14(5):842–848. https://doi.org/10.1111/iwj.12719

268 Nordström A, Hansson C. Punch-grafting to enhance healing and to reduce pain in complicated leg and foot ulcers. Acta Derm Venereol 2008; 88(4):389–391 .

269 Fourgeaud C, Mouloise G, Michon-Pasturel U et al. Interest of punch skin grafting for the treatment of painful ulcers. J Mal Vasc 2016; 41(5):329–334. https://doi.org/10.1016/j.jmv.2016.08.002

270 Conde Montero E, Guisado Muñoz S, Pérez Jerónimo L et al. Martorell Hypertensive Ischemic Ulcer Successfully Treated With Punch Skin Grafting. Wounds 2018; 30(2):E9–E12

271 NICE. Pressure ulcers: prevention and management. Clinical guideline CG179. 2014; https://tinyurl.com/lg2rmk2 (Accessed 18 January 20190

272 Edmonds ME, Bodansky HJ, Boulton AJ et al. Multicenter, randomized controlled, observer-blinded study of a nitric oxide generating treatment in foot ulcers of patients with diabetes-ProNOx1 study. Wound Repair Regen 2018; 26(2):228–237. https://doi.org/10.1111/wrr.12630

273 Health Quality Ontario. Hyperbaric oxygen therapy for the treatment of diabetic foot ulcers: a health technology assessment. Ont Health Technol Assess Ser 2017; 17(5):1–142

274 Heyboer M 3rd, Grant WD, Byrne J et al. Hyperbaric oxygen for the treatment of nonhealing arterial insufficiency ulcers. Wound Repair Regen 2014; 22(3):351–355. https://doi.org/10.1111/wrr.12176

275 Zhang Q, Gould LJ. Hyperbaric oxygen reduces matrix metalloproteinases in ischemic wounds through a redox-dependent mechanism. J Invest Dermatol 2014; 134(1):237–246. https://doi.org/10.1038/jid.2013.301

276 Kendall AC, Whatmore JL, Winyard PG et al. Hyperbaric oxygen treatment reduces neutrophil-endothelial adhesion in chronic wound conditions through S-nitrosation. Wound Repair Regen 2013; 21(6):860–868. https://doi.org/10.1111/wrr.12108

277 Hirase T, Ruff E, Surani S, Ratnani I. Topical application of platelet-rich plasma for diabetic foot ulcers: A systematic review. World J Diabetes 2018; 9(10):172–179. https://doi.org/10.4239/wjd.v9.i10.172

278 Martí-Carvajal AJ, Gluud C, Nicola S et al. Growth factors for treating diabetic foot ulcers. Cochrane Database Syst Rev 2015; (10):CD008548. https://doi.org/10.1002/14651858.CD008548.pub2

279 Edmonds M, Lázaro-Martínez JL, Alfayate-García JM et al. 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 2018; 6(3):186–196. https://doi.org/10.1016/S2213-8587(17)30438-2

280 Santema TB, Poyck PP, Ubbink DT. Skin grafting and tissue replacement for treating foot ulcers in people with diabetes. Cochrane Database Syst Rev 2016; 2(2):CD011255. https://doi.org/10.1002/14651858.CD011255.pub2

281 Koob TJ, Lim JJ, Zabek N, Massee M. Cytokines in single layer amnion allografts compared to multilayer amnion/chorion allografts for wound healing. J Biomed Mater Res B Appl Biomater 2015; 103(5):1133–1140. https://doi.org/10.1002/jbm.b.33265

282 Koob TJ, Lim JJ, Massee M, Zabek N, Denozière G. Properties of dehydrated human amnion/chorion composite grafts: Implications for wound repair and soft tissue regeneration. J Biomed Mater Res B Appl Biomater 2014 Aug;102(6):1353–1362. https://doi.org/10.1002/jbm.b.33141 Medline

283 Massee M, Chinn K, Lim JJ, Godwin L et al. Type I and II Diabetic Adipose-Derived Stem Cells Respond In Vitro to Dehydrated Human Amnion/Chorion Membrane Allograft Treatment by Increasing Proliferation, Migration, and Altering Cytokine Secretion. Adv Wound Care 2016; 5(2):43–54. https://doi.org/10.1089/wound.2015.0661

284 Koob TJ, Rennert R, Zabek N, Massee M, Lim JJ, Temenoff JS, Li WW, Gurtner G. Biological properties of dehydrated human amnion/chorion composite graft: implications for chronic wound healing. Int Wound J. 2013; 10(5):493–500.

285 Maan ZN, Rennert RC, Koob TJ, Januszyk M, Li WW, Gurtner GC. Cell recruitment by amnion chorion grafts promotes neovascularization. J Surg Res. 2015; 193(2):953–962.

286 Zelen CM, Serena TE, Denoziere G, Fetterolf DE. A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. Int Wound J 2013; 10(5):502–507. https://doi.org/10.1111/iwj.12097

287 Zelen CM, Gould L, Serena TE et al. A prospective, randomised, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ul. Int Wound J 2015; 12(6):724–732. https://doi.org/10.1111/iwj.12395

288 Zelen CM, Orgill DP, Serena T et al. A prospective, randomised, controlled, multicentre clinical trial examining healing rates, safety and cost to closure of an acellular reticular allogenic human dermis versus standard of care in the treatment of chronic diabetic foot ulcers. Int Wound J 2017; 14(2):307–315. https://doi.org/10.1111/iwj.12600

289 Serena TE, Carter MJ, Le LT et al. A multicenter, randomized, controlled clinical trial evaluating the use of dehydrated human amnion/chorion membrane allografts and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers. Wound Repair Regen 2014; 22(6):688–693. https://doi.org/10.1111/wrr.12227

290 Bianchi C, Cazzell S, Vayser D et al. A multicentre randomised controlled trial evaluating the efficacy of dehydrated human amnion/chorion membrane (EpiFix ®) allograft for the treatment of venous leg ulcers. Int Wound J 2018; 15(1):114–122. https://doi.org/10.1111/iwj.12843

291 Marston WA, Hanft J, Norwood P et al. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. Diabetes Care. 2003; 26(6):1701–1705.

292 Steinberg JS, Edmonds M, Hurley DP Jr, King WN. Confirmatory data from EU study supports Apligraf for the treatment of neuropathic diabetic foot ulcers. J Am Podiatr Med Assoc. 2010; 100(1):73–77.

293 Stone RC, Stojadinovic O, Rosa AM, et al. A bioengineered living cell construct activates an acute wound healing response in venous leg ulcers. Sci Transl Med. 2017;9(371). eaaf8611

294 Rice JB, Desai U, Ristovska L et al. Economic outcomes among Medicare patients receiving bioengineered cellular technologies for treatment of diabetic foot ulcers. J Med Econ 2015; 18(8):586–595. https://doi.org/10.3111/13696998.2015.1031793

295 Driver V, French M, Cain J et al. The Use of Native Collagen Dressings on Chronic Lower Extremity Wounds: Case Studies. Presented at SAWC. Tampa, FL. 2007

296 Chen WJ, Abatangelo G. Functions of hyaluronan in wound repair. Wound Repair Regen 1999; 7(2):79–89. https://doi.org/10.1046/j.1524-475X.1999.00079.x

297 Aya KL, Stern R. Hyaluronan in wound healing: Rediscovering a major player. Wound Repair Regen 2014; 22(5):579–593. https://doi.org/10.1111/wrr.12214

298 Alvarez OM, Makowitz L, Patel M. Venous ulcers treated with a hyaluronic acid extracellular matrix and compression therapy: interim analysis of a randomized controlled trial. Wounds 2017;

29(7):E51–E54

299 Caravaggi C, Grigoletto F, Scuderi N. WBP With a Dermal Sub-stitute (Hyalomatrix PA) Facilitates Re-epithelialization and Healing: Results of a Multicenter, Prospective, Observational Study on Complex Chronic Ulcers (The FAST Study). Wounds 2011; 23(8):228–235

300 Uccioli L, Giurato L, Ruotolo V et al. Two-step autologous graft-ing using HYAFF scaffolds in treating difficult diabetic foot ulcers: results of a multicenter, randomized controlled clinical trial with long-term follow-up. Int J Low Extrem Wounds 2011; 10(2):80–85. https://doi.org/10.1177/1534734611409371

301 Voigt J, Driver VR. Hyaluronic acid derivatives and their heal-ing effect on burns, epithelial surgical wounds, and chronic wounds: A systematic review and meta-analysis of randomized controlled trials. Wound Repair Regen 2012; 20(3):317–331. https://doi.org/10.1111/j.1524-475X.2012.00777.x

302 Erbatur S, Coban YK, Aydın EN. Comparision of clinical and histo-pathological results of hyalomatrix usage in adult patients. Int J Burns Trauma 2012; 2(2):118–125

303 Faga A, Nicoletti G, Brenta F et al. Hyaluronic acid three-dimensional scaffold for surgical revision of retracting scars: a human experimental study. Int Wound J 2012; 10(3):329–335. https://doi.org/10.1111/j.1742-481X.2012.00981.x

304 Onesti MG, Fino P, Fioramonti P et al. Reconstruction after skin cancer excision through a dermal induction template: our ex-perience. Int Wound J 2016; 13(2):198–203 https://doi.org/10.1111/iwj.12255

305 Tubo R. Fundamentals of Cell-Based Therapies, In: Principles of Regenerative Medicine, Atala A, Boyce WB, Lanza R, Thomson JA, Nerem RM (eds). 2008 https://doi.org/10.1016/B978-0-12-369410-2.X5001-3

306 Brown-Etris M, Shields DK, Galluzzi KE et al. Preliminary clinical outcomes on the use of composite cultured skin for the healing of venous ulcers. 13th Annual Symposium on Ad-vanced Wound Care and 10th Annual Medical Research Forum on Wound Repair; 2000, 1–4 April; Dallas, Texas. 2000:D5

307 Jones JE, Nelson EA, Al-Hity A. Skin grafting for venous leg ulcers. Cochrane Database Syst Rev 2013; (1):CD001737

308 NICE. Clinical Knowledge Summary Leg Ulcer–Venous. 2017; https://tinyurl.com/y8n7oo9k (accessed 18 January 2019)

309 Eichler K, Wieser S, Brügger U. The costs of limited health liter-acy: a systematic review. Int J Public Health 2009; 54(5):313–324. https://doi.org/10.1007/s00038-009-0058-2

310 Margolis DJ, Hampton M, Hoffstad O et al. Health literacy and diabetic foot ulcer healing. Wound Repair Regen 2015; 23(3):299–301. https://doi.org/10.1111/wrr.12311

311 Annells M, O'Neill J, Flowers C. Compression bandaging for venous leg ulcers: the essentialism of a willing patient. J Clin Nurs 2008; 17(3):350–359. https://doi.org/10.1111/j.1365-2702.2007.01996.x

312 Anderson I. Nurses' understanding of the terms compliance and concordance. Leg Ulcer Forum J 2007; 21(Autumn):21–25.

313 Moffatt CJ. Understanding patient concordance in the man-agement of leg ulcers. Nurs Times 2014; 100(32):58

314 Moffatt CJ. Perspectives on concordance in leg ulcer man-agement. J Wound Care 2004b; 13(6):243–248. https://doi.org/10.12968/jowc.2004.13.6.26894

315 Snowden A, Marland G. No decision about me without me: concordance operationalised. J Clin Nurs 2013; 22(9-10):1353–1360. https://doi.org/10.1111/j.1365-2702.2012.04337.x

316 McCaughan D, Sheard L, Cullum N et al. Patients' perceptions and experiences of living with a surgical wound healing by secondary intention: A qualitative study. Int J Nurs Stud 2018; 77:29–38. https://doi.org/10.1016/j.ijnurstu.2017.09.015

317 European Patient Forum. Patient Empowerment Campaign. 2018; https://tinyurl.com/y7wvadoc (accessed 18 January 2019)

318 Smith JJ, Guest MG, Greenhalgh RM, Davies AH. Measuring the quality of life in patients with venous ulcers. J Vasc Surg 2000; 31(4):642–649. https://doi.org/10.1067/mva.2000.104103

319 Hareendran A, Bradbury A, Budd J et al. Measuring the impact of venous leg ulcers on quality of life. J Wound Care 2005; 14(2):53–57. https://doi.org/10.12968/jowc.2005.14.2.26732

320 World Union of Wound Healing Societies (WUWHS). Principles of best practice: Compression in venous leg ulcers. A consensus document. MEP Ltd, 2008

321 309   Franks PJ, Bosanquet N, Connolly M et al. Venous ulcer healing: effect of socioeconomic factors in London. J Epidemiol Community Health 1995; 49(4):385–388. https://doi.org/10.1136/jech.49.4.385

322 Upton D, Upton P. Psychology of wounds and wound care in clinical practice. Springer International Publishing, 2015.

323 Cameron C. Patient compliance: recognition of factors involved and suggestions for promoting compliance with therapeutic regimens. J Adv Nurs 1996; 24(2), 244–250

324 Two-component compression: Concordance, evidence and clinical use. 2nd Edition London: Wounds International 2017; Supplement.

325 Edwards LM. Why patients do not comply with compression bandaging. Br J Nurs 2003; 12(Sup2 Suppl):S5–S16. https://doi.org/10.12968/bjon.2003.12.Sup2.11327

326 Mudge E, Holloway S, Simmonds W, Price P. Living with venous leg ulceration: issues concerning adherence. Br J Nurs 2006; 15(21):1166–1171. https://doi.org/10.12968/bjon.2006.15.21.22374

327 Briggs M, Closs SJ. Patients' perceptions of the impact of treatments and products on their experience of leg ulcer pain. J Wound Care 2006; 15(8):333–337. https://doi.org/10.12968/jowc.2006.15.8.26941

328 Weiss M, Britten N. What is concordance? Pharm J 2003; 271:493.

329 International Best Practice Statement: Optimising patient involvement in wound management. Wounds International 2016.

330 Weller CD, Buchbinder R, Johnston RV. Interventions for help-ing people adhere to compression treatments for venous leg ulceration. Cochrane Database Syst Rev 2016; 3(3):CD008378. https://doi.org/10.1002/14651858.CD008378.pub3

331 Abu Ghazaleh H, Artom M, Sturt J. A systematic review of com-munity Leg Clubs for patients with chronic leg ulcers. Prim Health Care Res Dev 2018 Aug; 1–10. https://doi.org/10.1017/S1463423618000610

332 Lindsay E. The Lindsay Leg Club Model: a model for evidence-based leg ulcer management. Br J Community Nursing 2004; 9(Sup2):S15–S20 324

333 Stephen-Haynes J. The Leg Club model: a survey of staff and members' perceptions of this model of care. J Wound Care 2010; 19(9):380–387. https://doi.org/10.12968/jowc.2010.19.9.78220

334 Sood A, Granick MS, Trial C et al. The Role of Telemedicine in Wound Care. Plast Reconstr Surg 2016; 138(3 Suppl):248S–256S. https://doi.org/10.1097/PRS.0000000000002702

335 Flaherty E. Setting up a community nurse-led healed leg ulcer clinic. Br J Nurs 2005; 14(Sup3 Suppl 3):S14–S20. https://doi.org/10.12968/bjon.2005.14.Sup3.18606

336 Franks PJ, Moffatt CJ, Connolly M et al. Community leg u- Pass-man MA, Marston WA et al. American Venous Forum. Manage-ment of venous leg ulcers: Clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg 2014; 60(2 Suppl):3S–59S. https://doi.org/10.1016/j.jvs.2014.04.049

343 Lipsky BA, Berendt AR, Cornia PB et al. 2012 infectious diseases society of america clinical 203 Wounds UK. Best Practice State-ment: Holistic management of venous leg ulceration. Wounds UK.

344 Federman DG, Ladiiznski B, Dardik A et al. Wound healing soci-ety 2014 update on guidelines for arterial ulcers. Wound Repair Regen 2016 Jan;24(1):127–135. https://doi.org/10.1111/wrr.12395

345 British Lymology Society. Standards of practice for lymphoe-dema services. 2016; https://tinyurl.com/yd4kqo73 (accessed 18 January 2019)

346 Best Practice Statement: Improving holistic assessment of chronic wounds. Wounds UK, 2018.

Notes

Contact **Anthony Kerr** to get involved in further International consensus documents

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