

**Supporting evidence-  
based practice:  
a clinical review of  
TLC technology**

An educational supplement  
in association with



# Contents

Foreword	3
Evidence-based dressing selection	4
Pre-clinical evidence	9
The clinical evidence for dressings with TLC technology	11
Dressings with TLC-Ag technology	22
Dressings with TLC-NOSF technology	27
References	33



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# Foreword

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**T**he requirements for evidence-based wound care have been evident for some years, despite continuing confusion over the definition and nature of this ‘evidence’, while the hierarchy of clinical evidence remains a topic of heated debate. Nonetheless, practitioners are faced with the inescapable task of compiling and evaluating all available evidence before making clinical judgements.

This review aims to provide clinicians, pharmacists and all others involved in the dressings supply chain with a thorough summary and assessment of the evidence relating to Urgo’s TLC range of wound dressings. While the compilation of this review has been financially supported by Urgo, it has been written with total academic freedom. Urgo’s philosophy of exhaustive clinical research manifests in the relative wealth of evidence now available, with more scheduled for publication this year. The emphasis here is on the word ‘relative’, for in order to understand this review, it is essential to consider the context in which it has been written.

In the ‘modern age’ of wound care, since George Winter’s key publications on moist wound healing in the early 1960s, dressings have been designed to support a moist wound interface. The growth of the industry that provides these products has been parallel to the development of a clinical specialty in many countries.

A variety of experts, both clinical and scientific, have striven to produce evidence in support of interventions and clinical observations. It has become apparent that wound healing is not as straightforward as first thought, requiring the reaching of various milestones along the path to healing — if, indeed, healing is the clinical objective. Thus, early goals include the debridement of slough and necrotic tissues and the control of infection. Later, the main objectives are promotion of granulation and re-epithelialisation. This is especially evident in ‘chronic’ wounds, such as leg ulcers, pressure ulcers and diabetic foot ulcers.

In the past three decades, millions of patients have benefitted from the use of modern wound dressings, and the evidence base reflects their clinical use. While early experiences warranted a case-by-case approach, thereafter, clinical trials were conducted — mainly against dry gauze, the standard of the day. It must be remembered that while many now decry the gauze comparator, such dressings are still widely used in many health care systems. It is also vital to emphasise that the evidence for dry dressings remains very weak, considering current financial constraints and efforts to cut costs through restricting the use of ‘modern’ dressings.

The following compilation of clinical evidence covers Urgo’s entire range of lipidocolloid wound dressings, known as the TLC range. There are randomised, controlled clinical trials, observational studies, and a number of cases and case cohorts; these involve many thousands of patients and a wide variety of wound types and clinical challenges. This evidence is collated and presented for your information, to assist you in making judgements on clinical use, purchasing and formulary processes. It is vital in such circumstances that you look at and appraise the totality of the evidence. Every effort has been made to present it here.

# Evidence-based dressing selection

A wide range of considerations determine dressing selection. Taking into account the wound type, the patient's holistic needs and his or her own clinical experience, the practitioner will then look to the literature for guidance. To support practitioners with their decision-making, this supplement provides an in-depth review of the evidence on Urgo's Technology Lipido-Colloid range of dressings. Its objective is to summarise the literature, as opposed to critiquing it

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**W**hen faced with a plethora of dressings, how does the clinician decide which product to use? Clearly, clinical knowledge, based on experience complemented by evidence from the literature, will be the largest factor influencing the decision. The clinician will start by assessing both the wound (type, duration, size, exudate level, pain, presence of malodour, condition of the surrounding skin) and the patient (age, medical history, comorbidities, psychosocial factors) and will then consider the potential effectiveness of the selected product, evidenced by clinical outcomes and demonstrated cost-effectiveness. Naturally, the type/nature of the wound and stage of healing will also influence product selection and management options.

## Identifying a chronic wound

The phases of the wound healing process are well known. For the purposes of this supplement, it is assumed that acute wounds such as minor burns, surgical wounds, lacerations and other traumatic injuries generally follow the three key stages of the healing trajectory — inflammation, proliferation and maturation — with little deviation.

Chronic wounds, in contrast, do not progress through these phases in an orderly and timely sequence<sup>1</sup> and generally fail to heal in 4–6 weeks despite the provision of standard care. Chronic wounds become 'stuck' in the inflammatory stage. In acute wounds, the inflammatory process serves to limit blood loss, kill invading bacteria, dispose of devitalised tissue and promote an environment that is conducive to tissue growth.<sup>2</sup> In addition, matrix metalloproteinases (MMPs), which are protein-digesting enzymes, help remove dead and devitalised tissue. Their number is kept in check by tissue inhibitors of metalloproteinases (TIMPs), thereby preventing undue protease damage to healthy

tissue. In chronic wounds, however, such anti-protease activity is diminished, resulting in significantly elevated levels of proteases. Studies have shown that chronic wounds can contain up to 65 times more proteases than acute wounds.<sup>3</sup> The ensuing excessive MMP activity effectively stalls the healing process. Proliferation of keratinocytes, fibroblasts and endothelial cells is slowed or blocked. The MMPs degrade key components of the extracellular matrix (fibronectin, fibrin and collagen) as well as the viable marginal tissue, and impair the expression of growth factors. Similarly, the release of reactive oxygen species is much higher in chronic than acute wounds. This not only results in the degradation of viable tissue but also local ischaemia.<sup>4,5</sup> In this way, inflammation is prolonged and healing delayed, with potentially devastating consequences for the patient, and huge resource implications for the individual, the health service and employers (Box 1).

### Box 1. Impact of chronic wounds<sup>9,178</sup>

- **Financial impact:** chronic wounds are estimated to cost the NHS at least £1 billion per annum<sup>179–181</sup>
- **Nursing resource:** community nurses spend up to 50% of their time managing chronic wounds<sup>182</sup>
- **Social isolation of the patient:** due to malodour and/or exudate
- **Patient lost working days:** while waiting for treatment and/or because of malodour and exudate problems and potential complications
- **Reduced quality of life:** as a result of the above reasons

Patient risk factors that may predispose a wound to become chronic include incontinence, undermining, peri-wound maceration, infection, oedema, chronic venous insufficiency or arterial disease of the lower leg, diabetes, chemotherapy, steroids and the presence of a wound biofilm. If any of these risk factors are present, the clinician must ensure that prevention measures are taken



and the factors that may cause the wound to become chronic are addressed. This is of particular relevance to the management of MMPs, where effective 'rebalancing' of MMPs in the wound bed will 'kick-start' healing in a chronic wound.

So how can the clinician determine if the dressing is having this desired effect? One indicator that a treatment is effective is a >40% reduction in area in the first 2–3 weeks of treatment as this indicates that the wound is healing.<sup>6</sup> In fact, a 20–40% wound area reduction at 3–4 weeks has been demonstrated to be highly predictive of complete closure at 20–24 weeks in leg ulcers.<sup>7,8</sup> Thus, if a wound (treated or not) has not shown signs of progression from the inflammatory stage to the proliferative stage within this time frame, it could have become chronic.<sup>9</sup>

### Management of chronic wounds

Evidence has shown that, for many patients, managing the symptoms of a wound is as important, if not more so, than promoting healing. The results of a multinational, multicentre trial undertaken in 2008<sup>10</sup> showed that wound pain, both ongoing and/or during dressing removal/procedures, was the most distressing and stressful aspect of having a wound. Impaired mobility, difficulties with bathing, leakage, malodour, bandage/dressing slippage and skin trauma were also considered important. These findings support those of other studies.<sup>11–14</sup>

Therefore, the objective of treatment is not only to treat the underlying aetiology of the wound (with pressure-redistributing equipment for pressure ulcers, offloading for diabetic foot ulcers or compression therapy for venous and mixed aetiology ulcers), but also to select a dressing that will promote a wound environment that is conducive to healing and acceptable to the patient. To achieve this, a dressing will need to:

- Maintain a good moisture balance at the wound/dressing interface
- Allow gaseous exchange
- Provide thermal insulation
- Form a barrier to bacteria
- Be non-toxic and non-irritant
- Not cause pain or trauma at removal
- Require minimal disturbance or replacement.<sup>15,16</sup>

Other desired properties include the ability to remove or inactivate proteolytic enzymes, remove excess exudate and devitalised tissue, have an antimicrobial effect and control malodour.

Inevitably, no one dressing has all of these prop-

erties and, as the patient progresses to the stated goals (healing or symptom management), the functions that will determine dressing selection, such as moisture balance, pain relief, management of infection or wound bed preparation, will change. When selecting a dressing, the clinician will therefore seek to identify one that can best meet the patient's individual needs at that particular time. As stated above, the selection will be based on clinical knowledge, clinical experience and appraisal of the published evidence. Only in this way can it be claimed to be evidence based.

### Evidence-based dressing selection

Published evidence for the efficacy of an intervention can be found through a number of resources:

- National Institute for Health and Clinical Excellence (NICE)
- Professional bodies — for example, the World Union of World Healing Societies (WUWHS) and the European Wound Management Association (EWMA)
- Health databases (CINAHL, PubMed)
- Cochrane database for systematic reviews, York Centre for Review and Dissemination.

Received wisdom on clinical evidence is that it falls into a hierarchy depending on the type of study undertaken.<sup>17</sup> The hierarchy of evidence and associated grading recommendations relate to the strength of the literature (Box 2). Meta-analyses of RCTs, followed by the randomised controlled trial (RCT), are considered to provide the best evidence for the efficacy of a treatment intervention. However, there is an ongoing debate about our apparent over-reliance on RCTs for constructing the evidence base in wound care, with some arguing that the narrow inclusion/exclusion criteria used mean the findings are not necessarily applicable to the 'real-life events that lie beyond the study confines' and that other levels of evidence should also be used to inform practice.<sup>18</sup>

While no one denies that a well-conducted meta-analysis (or RCT) can produce robust results, or argues that studies at all levels of the evidence

#### Box 2. Hierarchy and source of clinical evidence<sup>25</sup>

- Meta-analyses of well-designed randomised controlled trials
- Randomised controlled trials
- Evidence from well-designed, non-randomised controlled trials, such as cohort studies
- Case control studies
- Case series studies
- Expert opinion

hierarchy are equally valid, there is concern that the findings of some RCT/meta-analyses relating to wound care treatments do not support widely accepted empirical evidence. For example, a recent Cochrane Systematic Review concluded that there is insufficient evidence to support the use of silver dressings,<sup>19</sup> even though it is a popular (and by association effective) antimicrobial in both primary and secondary care. Indeed, meta-analyses have even concluded that there is little or no compelling evidence of a significant difference in healing times between wounds treated with traditional and modern dressings!<sup>20</sup>

Such findings may be due to a wide variety of factors including methodological inconsistencies between the various studies analysed, methodological flaws within individual studies, inadequate sample sizes, short follow-up periods, non-blinded assessment of outcomes, poorly-defined control groups, and the subjectivity of those who decree the evidence to be 'inconclusive.'

One of the most notorious examples of a poor methodological design is the recent VULCAN RCT, where the investigators inappropriately tested the efficacy (ulcer healing) of silver-donating dressings over 12 weeks in patients with leg ulcers showing no clinical signs of infection or bacterial colonisation.<sup>21</sup> The finding that there were no significant differences in healing outcomes between the silver dressing and the cheaper, non-silver comparator is already being used as a rationale to remove silver dressings from wound formularies.

In response to such confusion about what actually constitutes evidence in wound care, the European Wound Management Association (EWMA) Patient Outcome Group (POG) produced useful guidance on how to conduct quality trials.<sup>1</sup> The document acknowledges that very few wound care products have a sufficiently large market to justify the expense and time needed to implement a RCT. It proposes that generic or 'me-too' products, which abound in wound care, can be assessed by the process of equivalence, stating that only when a product is significantly different from anything that has already been approved is a new comparative clinical trial likely to be required. The implication is that observational (clinical) studies are sufficient in such circumstances.

The document also states that traditional endpoints (wound closure, wound area reduction and healing time) do not reflect the entire patient experience or even the primary indications of certain

dressings, and proposes that other endpoints, such as the presence of wound infection, pain and change in wound condition (e.g., exudate levels, malodour etc.), can be equally valid, although they should be predefined and, wherever possible, measured in a way that can be validated independently. There is a very strong case for 'outcomes' research and pragmatic trials in wound management.<sup>22</sup>

In summary, while case studies, observational studies and clinical studies may not be perceived to be 'high value' in terms of evidence level and grading, in wound care, where demonstrable outcomes can influence practice, they are invaluable to the practitioner and, ultimately, the patient.

### **The evidence for Urgo wound management products**

Urgo provides a range of dressings that can meet the management requirements of most acute and chronic wounds (Table 1). Unique to the range is Technology Lipido-Colloid (TLC), which is based on the impregnation of hydrocolloid (carboxymethyl-cellulose) and petroleum jelly into either a fine polyester mesh or a soft-adherent layer. According to the manufacturer, as exudate is absorbed, the hydrocolloid particles become hydrated and interact with the petroleum jelly to form a lipidocolloid gel that creates a moist environment within the wound, thereby promoting healing. As first identified by Winter,<sup>23</sup> moisture is required for granulation tissue formation as epithelial cells cannot easily migrate across the wound surface if it is dry.

The newly formed granulation tissue is extremely fragile, so care must be taken to ensure it does not adhere to the dressing and become damaged at dressing removal. To prevent this, the mesh present in some of the TLC dressings has a small pore size (500µm) through which granulation tissue cannot migrate. As a result, the dressing does not adhere to the newly formed tissue, with a significantly reduced likelihood of trauma — and, in turn, bleeding and pain — at dressing change (Fig 1a and Fig 1b). A key advantage of TLC dressings is that, depending on the one used, they can be left in place for up to 14 days as they are non-adherent.<sup>24</sup>

When in contact with the wound, the permanently open mesh pores prevent any risk of occlusion and allow exudate to drain into a secondary dressing, reducing the risk of maceration of the surrounding skin. The continuous yarn composition ensures that no fibres are shed into the wound (Fig 1c and Fig 1d).



**Table 1. Dressings with Technology Lipido-Colloid (TLC)**

Dressing	Description	Indications
<b>Dressings with TLC technology</b>		
<b>Urgotul</b>	Non-occlusive, non-adhesive, flexible lipido-colloid dressing comprising a polyester mesh impregnated with hydrocolloid and petroleum jelly particles	Wounds with no or low exudate levels at the granulation/epithelialisation stage: burns, <sup>14,24,40,60,61</sup> skin grafts, <sup>60</sup> skin tears, <sup>183,184</sup> donor sites, <sup>60</sup> traumatic wounds, <sup>14,24,52,53,61</sup> postoperative wounds, <sup>14,24,40,52</sup> amputation stumps, <sup>40</sup> paediatric wounds, <sup>61</sup> leg ulcers, <sup>14,24,40,66,67</sup> pressure ulcers, <sup>14,24,40</sup> diabetic foot ulcers, <sup>14,24,78</sup> epidermolysis bullosa <sup>63,64</sup> Can also be used in cavity wounds, under compression, <sup>67</sup> under NPWT <sup>55</sup> and combined with an absorbent dressing. Can be left in place for up to 14 days, <sup>24</sup> although the secondary dressing will still need to be changed
<b>Urgotul Duo</b>	As for Urgotul, but combined with a protective absorbent pad, thereby avoiding the need for a secondary dressing	As for Urgotul, but is particularly suitable for awkward places <sup>41,43</sup>
<b>Urgotul Duo Border</b>	As for Urgotul Duo, but also includes a semi-permeable backing with an adhesive border	As for Urgotul Duo <sup>185</sup>
<b>UrgoCell TLC</b>	Soft-adherent lipido-colloid foam dressing. Comprises a soft-adherent TLC layer, an absorbent polyurethane foam pad and a protective semi-permeable polyurethane backing	Low to moderately exuding wounds at the granulation/epithelialisation stage <sup>186</sup> such as pressure ulcers <sup>85</sup> and leg ulcers etc. <sup>68-71,187</sup> Particularly recommended for wounds with fragile surrounding skin Can be used under compression <sup>68,71</sup>
<b>Dressings with TLC technology and silver (TLC-Ag)</b>		
<b>Urgotul SSD</b>	Same properties as Urgotul, but impregnated with silver sulphadiazine	Wounds with no or low exudate levels showing signs of infection or critical colonisation such as burns, <sup>122-124,188</sup> abdominal wounds, <sup>132</sup> paediatric wounds, <sup>124</sup> skin grafts, <sup>125</sup> postoperative and traumatic wounds, <sup>106</sup> and diabetic foot ulcers <sup>130</sup> Can also be used in cavity wounds, under compression and can be combined with an absorbent dressing
<b>Urgotul Silver</b>	Same properties as Urgotul but impregnated with silver	Wounds with no or low exudate levels showing signs of infection or critical colonisation <sup>128</sup> Can also be used in cavity wounds, under compression and can be combined with an absorbent dressing
<b>Urgotul Duo Silver</b>	As for Urgotul Duo, but also impregnated with silver	As for Urgotul Silver, but particularly suitable for wounds in awkward places
<b>UrgoCell Silver</b>	As for UrgoCell, but impregnated with silver	Low to moderately exuding wounds with signs of infection or critical colonisation. <sup>128,129</sup> Particularly recommended for wounds with a damaged surrounding skin Can be used under compression <sup>129</sup>
<b>Dressings with TLC technology and protease inhibitor (TLC-NOSF)</b>		
<b>UrgoStart Contact</b>	As for Urgotul, but also impregnated with the matrix metalloproteinase (MMP) inhibitor NOSF	Chronic or recurring wounds with no or low exudate levels, diabetic foot ulcers, <sup>166,189</sup> pressure ulcers, venous leg ulcers, <sup>155,190</sup> acute wounds that have become chronic. <sup>169,170,172</sup> Can also be used in cavity wounds, under compression <sup>155</sup> and can be combined with an absorbent dressing
<b>UrgoStart</b>	As for UrgoCell TLC, but also impregnated with the matrix metalloproteinase (MMP) inhibitor NOSF	Low to moderately exuding chronic or recurring wounds, <sup>148-150,191</sup> venous leg ulcers, <sup>156,159,192</sup> pressure ulcers <sup>162,193,194</sup> diabetic foot ulcers, <sup>195</sup> arterial wounds <sup>168,196,197</sup> and acute wounds that have become chronic. <sup>170,171,177</sup> Can be used under compression <sup>156,159</sup>

In this way, TLC dressings meet many of the requirements of the ideal dressing. TLC dressings are indicated for acute and chronic wounds with no to moderate levels of exudate.

This supplement summarises the evidence from RCTs, comparative and non-comparative clinical studies, observational studies and *in vitro* studies on the efficacy, tolerability and acceptability of the TLC dressing range. Poster evidence is also included when the findings are likely to be of particular value to clinicians or there is no published peer-reviewed data relating to the use of TLC on a particular wound type. In all, the efficacy, tolerability and safety of TLC dressings have been evaluated in more than 35,000 patients drawn from 170 clinical

areas across Europe. In addition, over 600 clinicians were involved in these evaluations (Table 2).

This body of clinical evidence amounts to seven RCTs involving 618 subjects, 14 observational studies on 34,943 patients (some evaluated several TLC products) and 21 other clinical studies involving a further 942 patients. When pooled together, the results provide ‘good’ evidence, as defined by Evans,<sup>25</sup> that TLC dressings promote healing and prevent pain and trauma at dressing change.

The results of these studies, and those described in the following chapters, demonstrate the wound-closing, exudate management, pain management and infection control properties of these dressings.



Fig 1a. Removal of traditional dressings



Fig 1b. Removal of Urgotul



Fig 1c. Structure of traditional dressings

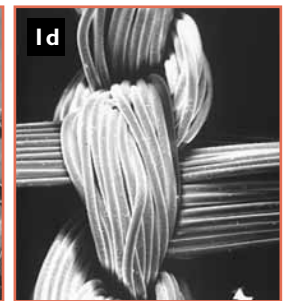


Fig 1d. Structure of Urgotul

Table 2. Summary of studies undertaken

Product	Type of study	Number of patients	Wound types
Urgotul	3 randomised	144	Acute and chronic wounds: burns, donor sites, skin grafts, skin tears, traumatic wounds, postoperative wounds, leg ulcers, pressure ulcers, diabetic foot ulcers, epidermolysis bullosa. Used in combination with NPWT and compression bandaging
	1 observational	5850	
	11 clinical studies	554	
Urgotul Duo	1 clinical study	43	Acute and chronic wounds
UrgoCell	1 observational	2842	Venous leg ulcers
	3 clinical studies	138	
Urgotul SSD	1 randomised	68	Burns
	2 clinical studies	81	
Urgotul Silver	1 randomised	102	Venous leg ulcers
UrgoCell Silver	1 clinical study	45	Venous leg ulcers
UrgoStart Contact	1 randomised	117	Chronic wounds (venous leg ulcers, diabetic foot ulcers)
	1 clinical study	34	
UrgoStart	1 randomised	187	Chronic wounds (leg ulcers, pressure ulcers)
	2 clinical studies	47	
	3 observational	3315	
TLC dressings	9 observational	22,936	Acute and chronic wounds
Total number of patients in clinical studies on TLC dressings		36,503	





# Pre-clinical evidence

**L**ong before any wound dressing prototype is put onto a patient, many *in vitro* tests are conducted in the laboratory. Each test is designed to evaluate a particular performance characteristic — for example, exudate handling,<sup>26</sup> the bacterial barrier properties,<sup>27</sup> the toxicity of dressing constituents and the full formulation,<sup>28</sup> plus the dressing's antimicrobial activity.<sup>29</sup> As a result, anyone with experience in wound care will have encountered and, in many cases be guided by, the evidence available from *in vitro* tests.

Fibrogenesis is an important mechanism in wound repair. Fibroblasts (a dermal cell type) play a key role in producing extracellular matrix components that are vital for granulation tissue and, later, wound closure and remodelling.<sup>30</sup> In chronic wounds, where prolonged inflammation has disrupted normal healing, altered fibroblast functions can lead to fibrosis, oxidative stress and impaired closure.<sup>31</sup> It follows that any intervention that is likely to 'normalise' fibroblast function will elicit noticeable clinical responses, which suggests that a dressing that can stimulate fibroblast proliferation will promote wound healing. *In vitro* experiments have investigated the effects of TLC dressings on fibroblast viability and proliferation. The results show that they simulate these activities.

## Effects on fibroblasts

The first *in vitro* study to assess the effect of TLC dressings on fibroblasts looked specifically at whether or not it modified their behaviour. The effects of Urgotul and five other non-adhesive wound-contact dressings — Adaptic (then produced by Johnson & Johnson), tulle gras Lumiere (Solvay Pharma), Mepitel (Mölnlycke Healthcare), Ialuset (Genevrier Laboratories) and Physiotulle (Coloplast) — on cultured human fibroblast were evaluated. Fibroblasts were taken from healthy volunteers aged 12, 32 and 51 years. The MTT assay was used to assess fibroblast viability. (MTT is a colourimetric assay that assesses the overall activity of cells.) Cultures in monolayer were used to study fibroblast morphology and growth. To characterise the effects of the dressings on cell phenotype, fibroblasts were seeded within collagen gels and labelled for alpha-SM and F-actin, which are markers of myofibroblast differentiation. (During

the wound healing process, fibroblasts transform into myofibroblasts, which have contractile properties that facilitate wound closure.) Fibroblast cells were exposed to the dressing samples for 1 and 3 days.

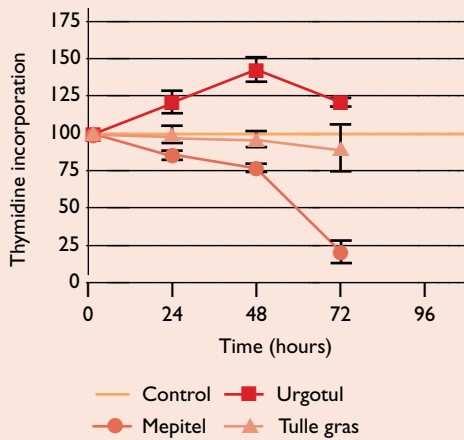
The results demonstrated that, for all skin ages, Urgotul, Mepitel, Physiotulle and tulle gras had no significant effects on cell growth on day 3, whereas cell proliferation was significantly reduced with Adaptic and Ialuset ( $p < 0.05$ ). Changes in cell morphology were noted with these two dressings, with the fibroblasts appearing round in shape on day 3, which is indicative of cell death. Cells in contact with Urgotul, Mepitel, Physiotulle and tulle gras demonstrated the same bipolar and elongated morphology as did the controls, again indicating that the dressing did not have any cytotoxic effects. However, only fibroblasts exposed to Urgotul exhibited long stress fibres, which is a precursor to transformation into myofibroblasts.<sup>32</sup>

The next step was to assess the effect of Urgotul on fibroblast proliferation. An *in vitro* study therefore compared the level of fibroblast proliferation achieved with Urgotul with that of two similar comparators: soft-silicone wound-contact dressing (Mepitel) and tulle gras. Proliferation was determined by whether or not there was an increase in tritiated thymidine incorporation in the DNA of replicating normal human dermal fibroblasts (a validated assay for evaluating the rate of fibroblast proliferation.) In addition, cell viability/cytotoxicity was assessed using the MTT assay. Finally, following contact with the dressings, fibroblasts were also visualised using confocal laser microscopy.

In terms of cell proliferation, of all the dressings Urgotul was associated with the highest levels of thymidine incorporation at all time points tested (24, 48, 76 and 96 hours). The difference was most marked at 48 hours ( $p < 0.01$ ), when it was 45% greater than in the controls (cultures with no dressings). Mepitel was associated with an overall non-significant tendency to reduce cell proliferation, although this became significant when the medium was not changed every 24 hours (Fig 2).

The MTT results confirmed Viennet et al.'s results, showing that none of the test dressings significantly modified the overall metabolic activity of the fibroblast culture. However, visual observa-

**Fig 2. Urgotul was associated with stimulation of fibroblast proliferation<sup>33</sup>**



tion of the cell layers showed clear differences: very little of the print pattern of the net comprising the Urgotul and Mepitel dressings was apparent on the cell layer, whereas with tulle gras the cell layer appeared to be significantly damaged, indicating that it was cytotoxic to fibroblasts.

Finally, cells treated with Urgotul and Mepitel had a normal morphology, whereas those from tulle gras samples were abnormal and often rounded. However, following exposure to Urgotul, the density of the dividing fibroblast cells increased when compared with the other dressings, again confirming that it stimulates proliferation in these experimental conditions.<sup>33</sup>

The third *in vitro* study (presented as a poster) focused on cytotoxicity, but this time with Atrauman (Paul Hartmann) as the comparator. Here, the MTT assay was repeated three times using three

different batches of Atrauman. Results confirmed the above findings that Urgotul does not have a cytotoxic effect on normal human dermal fibroblasts at any time point (24, 48 and 72 hours). In contrast, Atrauman clearly decreased fibroblast viability after 24 hours, and presented a cytotoxic effect after 24, 48 and 72 hours with two different batches and after 72 hours with the third batch.<sup>34</sup>

This activity was also demonstrated on UrgoCell TLC.<sup>35</sup> MTT assay and assessment of tritiated thymidine incorporation, followed by confocal laser microscopy, demonstrated that UrgoCell TLC is not toxic to cells, and that it significantly stimulates cultured fibroblast proliferation after 24 hours ( $p < 0.001$ ), 48 hours ( $p < 0.001$ ) and 72 hours ( $p < 0.05$ ) when compared with the control.

### Effects on collagen

The effect of Urgotul on extracellular matrix protein production was also explored, again using normal human dermal fibroblasts. (Pro)collagen 1 and fibronectin were quantified by specific immunoenzymatic assays (ELISA) and the extracellular matrix organisation was visualised by immunofluorescence microscopy, after immunolabelling of type 1 collagen, type III collagen or fibronectin. Results showed that the fibroblasts in contact with Urgotul produced significantly more soluble (pro) collagen 1 than the control (180% of the control;  $p < 0.01$ ). This result was validated by a confirmation test using the same methodology. The results also show that it stimulated production of hyaluronic acid,<sup>36</sup> which helps promote cell proliferation. This is a key early stage of dermal repair, giving an insight into how TLC dressings can facilitate healing.<sup>37,38</sup>

**Table 3. Summary of *in vitro* evidence for TLC dressings**

Authors	Urgo product	Comparative product(s)	Main results
Viennet C. et al <sup>32</sup>	Urgotul	Tulle gras, Adaptic, Mepitel, laluset, Physiotulle	Cell proliferation reduced with Adaptic and laluset
Bernard FX et al <sup>33</sup>	Urgotul	Mepitel, Tulle Gras	Urgotul stimulates fibroblast proliferation by 45% Mepitel showed a tendency to reduce cell proliferation
Juchaux F. et al <sup>34</sup>	Urgotul	Atrauman	Atrauman is cytotoxic to fibroblasts
Bernard FX et al <sup>35</sup>	UrgoCell TLC	None	UrgoCell TLC stimulates fibroblast proliferation
Bernard FX et al <sup>36</sup>	Urgotul	None	Urgotul stimulates (pro)collagen I production by 43%



# The clinical evidence for dressings with TLC technology

As seen from the *in vitro* evidence, neutral TLC dressings create a moist environment that stimulates fibroblast proliferation. Furthermore, their non-adherent properties are designed to avoid pain and trauma to newly formed tissue at dressing removal, which can delay healing. For patients, the prospect of uninterrupted healing and pain-free dressing removal can greatly improve quality of life. While this may sound aspirational, numerous clinical studies at all levels of the evidence hierarchy show that TLC dressings regularly achieve these desired clinical outcomes in different wound types as discussed below.

## Acute and chronic wounds

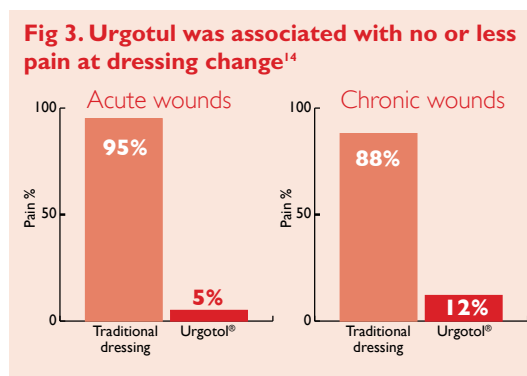
Evidence relating to outcomes achieved in acute and chronic wounds is discussed first. A large-scale multicentre observational study, which involved almost 6,000 patients with acute or chronic wounds,<sup>14</sup> clearly demonstrates that Urgotul reduces pain at dressing change. The prevalence of pain at dressing change was measured, and the use of Urgotul evaluated for any reduction in this. At the screening visit, patients experiencing moderate or severe pain at dressing change were identified using a simple four-point pain scale. Those who met this criterion then self-evaluated in a questionnaire pain intensity and frequency during subsequent wound care procedures. Dressings in use at baseline included mostly simple wet or dry gauze dressings, paraffin gauze, hydrocolloids or foams. A second questionnaire enquired about the practitioner's approach to the management of a painful wound. Acute wounds (2914) comprised traumatic injuries, burns and post-surgical wounds. Chronic wounds (2936) were mainly leg ulcers, but also included pressure ulcers, diabetic foot ulcers and chronic post-traumatic/post-surgical wounds.

In all, 80% (n=2308) of patients with acute wounds and 80% (n=2341) with chronic wounds reported moderate or severe pain at dressing removal at the screening visit. Of these, 1879 switched to Urgotul during the treatment period (1023 with acute wounds and 856 with chronic wounds). Median follow-up periods were 10 and 23 days for

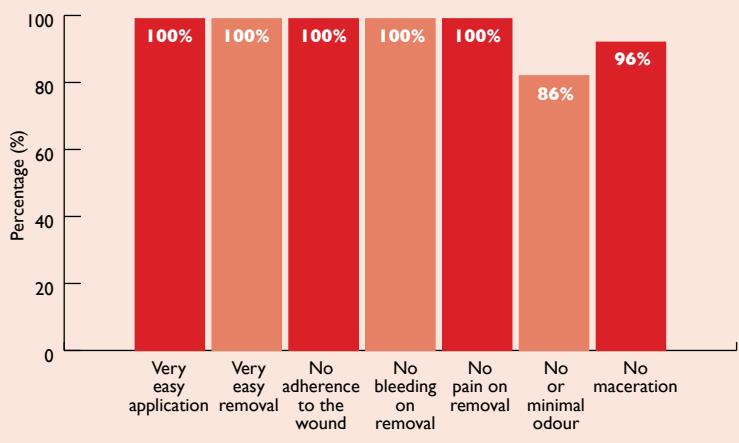
acute and chronic wounds respectively. Compared with the period before the switch, 95% of patients with acute wounds and 88% with chronic wounds reported no pain or less pain at dressing change (Fig 3). Furthermore, 83% of patients stated that, since switching to Urgotul, they felt substantially less anxious before treatments, while 80% of patients with acute wounds and 71% with chronic wounds stated that they wished to continue with this dressing.

A smaller study undertaken, in Spain, involving 28 patients with acute wounds (n=7), chronic wounds (n=10) and burns (n=11) found that Urgotul was highly efficacious and caused either no or minimal pain at dressing change. The wounds, which were mostly located on the lower limb, were assessed until full healing occurred. Previous treatments used included sterile gauze, 'greasy' gauze, hydrocolloids and foams. Surface area was measured using planimetry. Mean baseline measurements were 20.91cm<sup>2</sup> ± 24.63 (range 0.50–62.16) for acute wounds and 5.18cm<sup>2</sup> ± 3.22 (1.78–10.83) for chronic wounds. The mean baseline duration of chronic wounds was 24.6 months. For burns, the mean duration was 7.5 days ± 8.9 (1–30) and the mean surface area was 37.5cm<sup>2</sup> ± 90.0 (2.1–308).

All of the wounds healed. Chronic wounds healed in a mean of 67.8 days ± 40.9 (28–130), acute wounds in a mean of 11.0 days ± 6.6 (3–24) and burns in a mean of 20.3 days ± 3.0. None of the burns developed clinical signs of infection. The dressing, which was almost always non-adherent, was considered to be very easy/easy to both apply



**Fig 4. Acceptability of TLC dressing (Urgotul)<sup>24</sup>**



and remove at every dressing change. No local adverse events were reported.<sup>39</sup>

The first study on Urgotul undertaken in the UK confirmed its efficacy and acceptability.<sup>24</sup> This single-centre, 4-week clinical study involved 22 patients with acute (n=12) or chronic (n=10) wounds. Chronic wounds comprised sacral pressure ulcers, venous/arterial ulcers, a diabetic foot ulcer and a traumatic haematoma on the skin. Acute wounds comprised burns, postoperative abdominal wounds, traumatic wounds and cellulitis. Wound area was measured by tracing and photography. Average baseline surface areas were 84.36cm<sup>2</sup> (1.35–290) for the acute wounds and 26.68cm<sup>2</sup> (3.54–59) for chronic wounds.

Seven of the acute wounds healed in a mean time of 15 days (range 7–20), while one chronic wound healed in 10 days and the rest showed a 'marked reduction' in size. Good results were also reported for acceptability. All nurses agreed that Urgotul was 'very easy' to apply because of its flexibility and conformability, and 'very easy' to remove, even after 14 days in one instance. Furthermore, they all gave the highest score ('very good') for conformability, which is noteworthy as the wounds varied in type, depth, shape and part of the anatomy. (In one patient the base and sides of a full-thickness, abdominal wound were carefully but easily laid with Urgotul under V.A.C. [KCI] to prevent ingrowth of granulation tissue into the V.A.C. foam, a commonly encountered problem in practice). Similarly, all dressing removals were atraumatic (no bleeding occurred), and no patients experienced pain at dressing change. There were no treatment-related adverse events.

While dressing change frequency was not measured, Urgotul was left in place for 6–7 days on average, saving nursing time and avoiding excessive disturbance of the wound. Full results for acceptability of the Urgotul dressing are given in Fig 4.

A 4-week multicentre clinical trial reported good efficacy, acceptability and tolerability for Urgotul in a similar patient population that also included patients with partial-thickness burns.<sup>40</sup> The sample comprised 92 patients with acute wounds (n=34), leg ulcers (n=24), other chronic wounds (n=14), or burns (n=20). Wounds were measured by planimetry and photography. Mean baseline surface areas were 19.1cm<sup>2</sup> (± 21.0) for the acute wounds, 19.1cm<sup>2</sup> (± 35.5) for the leg ulcers and 10.3cm<sup>2</sup> (± 7.2) for the other chronic wounds (primarily five pressure ulcers and four amputation stump wounds).

Eleven acute wounds, three leg ulcers and two other chronic wounds healed within 4 weeks. In the remaining wounds, the surface area decreased, on average, by 76%, 64% and 44% respectively. Conformability was considered appropriate in almost all acute wounds, but less so in the chronic wounds, where it was classed as poor in 11% and 14% of changes respectively. However, of the 771 dressing changes undertaken, application was considered easy/very easy in ≥90% of acute wounds and other chronic wounds, and in ≥80% of leg ulcers. Almost all (>96%) dressing removals were easy/very easy, with no pain recorded in just over three quarters of dressing removals for each wound type (range 76–79%). The prevalence of adhesion, maceration, malodour and bleeding was very low.

Nineteen of the burn injuries healed in 5–19 days (mean 11.0 ± 4.5). Conformability was considered good/very good in 61% of dressing changes, reflecting the challenge of dressing burns located on the hand and fingers. Of the 97 dressing changes undertaken, application and removal were considered easy/very easy in 81% and 80% respectively. Again, the prevalence of maceration, malodour and bleeding was low.

For all wound types, safety was good, with only seven adverse events: two cases of peri-wound erythema, which were dressing related and resulted in both patients dropping out of the study, and one case each of peri-wound ulceration, overgranulation, bleeding, pain and inflammation, and pain/dressing adhesion.

The success of Urgotul led to the development of Urgotul Duo. This has all of the properties of Urgotul plus a light absorbent pad, which avoids



the need for a secondary dressing in wounds with low exudate. This reduces the risk of peri-wound maceration or excoriation, which delay healing.

A multicentre clinical study<sup>41</sup> reported similar efficacy, tolerability and acceptability results as those for Urgotul. The sample comprised 43 hospitalised patients with acute (trauma) (n=27) or chronic wounds (leg ulcers/pressure ulcers) (n=16). The acute wounds had been previously treated with a wound contact layer dressing, paraffin gauze or a hydrocolloid, the leg ulcers with a hydrocolloid or alginate, and the pressure ulcers with hydrocolloids or alginates.

Forty patients were evaluated for 4 weeks; the three withdrawals were non-dressing related. Wound area was measured by planimetry and photography. Mean baseline wounds areas were 13.4cm<sup>2</sup> (± 16.6) for the acute wounds, 7.6cm<sup>2</sup> (± 4.6) for the leg ulcers and 8.5 (± 4) for the pressure (mostly heel) ulcers.

Twenty-three wounds (53%) healed by the end of the 4-week study period (20 acute wounds and three chronic wounds). The acute wounds healed in a mean of 17.4 days (±8.1) and the chronic wounds in a mean of 25 days (two leg ulcers) and 21 days (pressure ulcer). By the end of the treatment period, the wound surface area had reduced by 94%, 76% and 75% for acute wounds, leg ulcers and pressure ulcers respectively. The dressing also improved any inflammation of the peri-wound skin, which either disappeared or improved to 'healthy' in 83% of acute wounds, 57% of leg ulcers and 100% of pressure ulcers.

Conformability was considered 'very good' in 76% of acute wound and 83% of leg ulcer dressing applications, but in only 59% of pressure ulcer applications, although it was never 'poor'. The nurses considered the dressing either very easy/easy to apply/remove at almost every dressing change. Similarly, pain was not experienced at most dressing removals (89% or better in all wound types) and was 'marked' in 1.7% of acute wounds. Adhesion was 'marked' in only 2.8% of acute wounds. There was no bleeding in ≥91% of wounds at dressing change, or any confirmed dressing-related adverse events. During this study dressings were changed, on average, every 2.5 to 2.8 days, although in some cases nurses were able to leave them in place for up to 8 days. Secondary dressings were rarely needed at acute wound dressing changes (2%), but more often for leg ulcers (14%) and pressure ulcers (21%). As a result, nurses considered the dressing application

and changing times to be shorter in 75% of cases and operations to be facilitated in 84% of cases.<sup>41</sup>

The acceptability of a range of TLC dressings (mostly Urgotul Duo) was further demonstrated in a large-scale (but as yet unpublished) study involving 1448 patients, which reported that TLC dressings are highly conformable and thus easy to apply in acute and chronic wounds initially judged to be 'difficult to dress'.<sup>42</sup> Wound types included traumatic injuries, postoperative wounds, pressure ulcers, leg ulcers, burns and 'other'. At baseline, two-thirds of the wounds were painful and 31% bled easily. TLC dressings applied mainly comprised Urgotul Duo (49%), UrgoCell (12%) and UrgoCell Lite (27%) (the latter is not yet available in the UK). The dressings achieved the highest score for conformability in 82% to 87% of applications to ulcers/traumatic and postoperative wounds respectively and in over 75% of applications to burns and other wound types.

The evidence that Urgotul Duo reduces the need for secondary dressings suggests it may have economic benefits. An observational multicentre study was conducted to compare the resource utilisation with Urgotul with that of Urgotul Duo in four emergency departments in France.<sup>43</sup> The study involved 305 outpatients with predominantly traumatic wounds treated with either Urgotul Duo (n=166 patients) or Urgotul (n=139) for 2 weeks. Demographic data and wound characteristics for the two groups were similar. The study population was mainly male, with an average age of 34.9 years.

Wounds treated with Urgotul were significantly more likely to require secondary dressings compared with Urgotul Duo: 98% versus 12% (p<0.001). Further investigation found that use of secondary dressings with Urgotul Duo was largely attributed to one emergency department, which recorded a higher incidence of bleeding at dressing removal.

Acceptability results also favoured Urgotul Duo over Urgotul:

- 88% of nurses considered that Urgotul Duo saved them time
- 98% reported that care was easier
- 100% said they preferred Urgotul Duo.

These results demonstrate that use of Urgotul Duo can produce cost savings by avoiding the need for secondary dressings.

In May 2010, Urgo launched new Urgotul in the UK, which is a more flexible and conformable version of Urgotul. Anecdotal reports suggested that Urgotul tended to slip when applied to vertical surfaces such as the digits or thigh, to epidermolysis

bullosa wounds and paediatric wounds. To overcome this, the manufacturer has increased the conformability of the dressing, so that it stretches and moves with the body, thereby avoiding the risk of slippage.

A multicentre clinical study involving 44 patients with acute (n=32) and chronic wounds (n=12) reported that the conformability of new

Urgotul is generally better than that of original Urgotul, particularly in relation to children and surgical wounds. Acute wounds comprised postoperative wounds, traumatic injuries, partial-thickness burns and amputation sites. Chronic wounds comprised leg ulcers, pressure ulcers and 'other'. Mean baseline wound surface areas were 21.64cm<sup>2</sup> ± 25.30 (range 1.63–89.64, median 9.38) and

**Table 4. Summary of main outcomes of clinical studies involving the use of TLC dressings**

Study	Sample size	Wound types	Product used	Outcome measures	Key results
Meaume et al. <sup>14</sup>	5850 patients	Acute and chronic wounds	Urgotul	Incidence of pain at dressing change	At baseline, incidence was 80% for both acute and chronic wound types. After switching to Urgotul, 95% of patients with acute wounds and 88% with chronic wounds reported no or less pain
Meaume et al. <sup>40</sup>	92 patients	Acute and chronic	Urgotul	Efficacy, tolerability and acceptability	11/34 acute wounds, 3/24 leg ulcers, 2/14 other chronic wounds healed in 4 weeks. Wound surface area of leg ulcers and other chronic wounds reduced by 64% and 44% respectively. 19/20 burns healed in 5–19 days. For all wound types, the dressing was very easy/easy to apply and remove in >80% of dressing changes, with no pain at removal in >73%. Safety was good
Coudert et al. <sup>43</sup>	305 patients	Mainly traumatic	Urgotul Duo versus Urgotul	Compare resource utilisation between the two dressings	Wounds treated with Urgotul were significantly more likely to require a secondary dressing (p<0.001). A large majority of nurses considered that it saved them time (88%) and made care easier to deliver (98%). Cost savings were produced by avoiding the need for secondary dressings
Ma et al. <sup>53</sup>	28 patients	Full-thickness traumatic digital wounds	Urgotul versus gauze	Healing time and wound size	Wounds treated with Urgotul healed significantly faster (p=0.024). Fewer dressing changes were required
Tan et al. <sup>60</sup>	25 patients	Partial-thickness burns and skin graft donor sites	Urgotul versus tulle gras	Efficacy and acceptability	Mean healing time was significantly faster for Urgotul (p<0.05). 100% of the nurses considered 'very easy' to use/change and remove versus 0% for tulle gras. Bleeding at first dressing change was observed in twice as many tulle-gras sites as Urgotul: 100% vs 52% (p<0.05)
Letouze et al. <sup>61</sup>	100 children	Burns and other wounds (principally traumatic and postoperative)	Urgotul	Reduction in pain levels	Faces scale and VAS results indicated there was limited pain at dressing change. Objective pain scale results suggest that at most dressings (50–65%) children did not cry, move or become restless, regardless of wound type
Meaume et al. <sup>66</sup>	91 patients	Venous leg ulcers plus compression bandaging	Urgotul versus DuoDERM E (also known as Granuflex)	Efficacy, tolerability and acceptability	Efficacy for the two dressings was similar but there was a significant difference in favour of Urgotul for ease of removal, reduction in malodour, maceration and pain at removal (p<0.001)
Dereure et al. <sup>68</sup>	2532 patients	Venous leg ulcers plus compression bandaging	Urgocell	Concordance with compression therapy and acceptability of the dressing	64% of respondents self-reported that they wore their compression bandages each day. 82% of patients considered that their wounds either healed or improved. High scores for tolerance and acceptability



6.61cm<sup>2</sup> (± 3.12) (range 2.19–13.40, median 6.05) for acute and chronic wounds respectively. Previous treatments included hydrocolloids, foams, contact layers, alginates, greasy gauze or 'other' dressings. Wounds were measured by planimetry and photography.

Efficacy of new Urgotul was good, although it should be noted that 10 patients with acute wounds were excluded from the efficacy analysis, primarily due to lack of planimetric data. Seventeen acute wounds and three chronic wounds healed. The mean healing times were 14.2 days (± 7.7) and 26.3 days (± 2.9) respectively. Acute wounds reduced by an average of 78% and chronic wounds by average of 42% during the 4-week study period. Two adverse events (infection and infected necrotic tissue) were reported in patients with acute wounds only, one of which resulted in discontinuation with treatment.

Conformability was reported to be good/very good in 93% of acute wound dressing changes and 85% of chronic wound dressing changes, while the dressing was considered to have stayed in place at 89% of evaluations. In addition, the clinicians considered new Urgotul to be more conformable than Urgotul at 73% of dressing changes respectively in all patients who had used it before entry into the study. There was no pain in 87% of dressing changes, with moderate bleeding being reported in only 8%.<sup>44</sup>

### Traumatic wounds

Assuming there are no complicating comorbidities and depending on the patient's age, traumatic wounds often progress through the stages of the healing process in an orderly and timely fashion, although the speed of healing will depend on the cause of injury, the degree of tissue loss and the anatomical site. Wounds should be cleansed to remove any debris and potential contaminations, and then dressed with a non-adherent dressing in order to keep the area moist and avoid pain at dressing change. A dressing that can accelerate healing and achieve a good cosmetic effect is desired.<sup>45-51</sup>

A small, independent, clinical study that compared the effectiveness and acceptability of five dressings on traumatic and surgical wounds showed that Urgotul achieved faster than expected healing rates.<sup>52</sup> This study, which took place in an orthopaedic outpatient department in the UK, assessed: Mepitel (Mölnlycke), N-A Ultra (then pro-

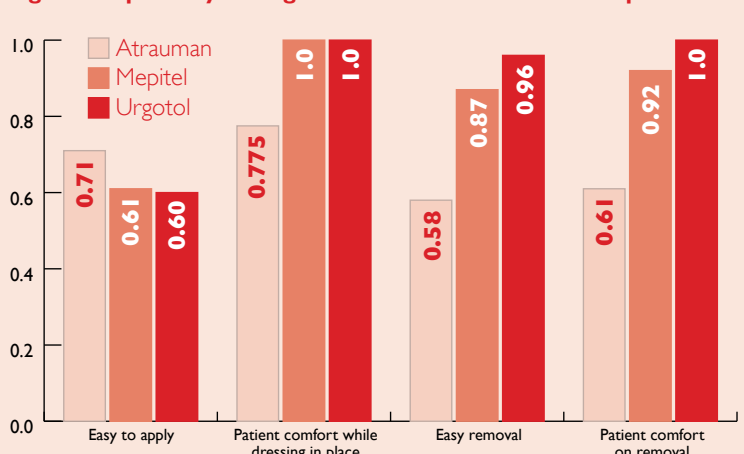


*Traumatic wound at presentation (Fig 5a). Healing was achieved after 23 days (Fig 5b)*

duced by Johnson & Johnson), Urgotul, Atrauman (Paul Hartmann) and Tegapore (3M). All patients who attended the department with superficial wounds healing by secondary intention received one of the five dressing for a 2-week period. The different dressings were allocated on a rotational basis, based on five 2-week allotments. Fifty-two patients participated, with wounds including digital amputation, digital crush injury, toenail avulsion, skin tear, laceration, post-surgical cellulitis, post-surgical incision and pretibial laceration. Seven patients received Atrauman, 13 patients received Mepitel, eight received N-A Ultra, nine received Tegapore and 15 received Urgotul. Forty-six wounds had either healed or were healing at the study end, although details are not given.

Results showed that Urgotul required the least dressing changes. Tegapore and Atrauman required the most dressing changes per patient (mean of 4.6 and 4.4 respectively) and N-A Ultra, Mepitel and Urgotul the least (mean of 2.4, 1.8 and 1.7 respectively). Ease of application was comparable for all five dressings. However, there were variations in ease of removal, with Urgotul achieving the high-

**Fig 6. Acceptability of Urgotul versus Atrauman and Mepitel<sup>52</sup>**



est score (being 'easy' to remove in 96% of cases), closely followed by Mepitel and N-A Ultra, while Atrauman and Tegapore had the lowest scores as they dried and adhered to the wound bed in 16% and 22% of cases respectively. Only with Urgotul did patients always consider themselves 'comfortable' during dressing removal.

Urgotul achieved faster than expected healing rates, particularly following toenail avulsions, and appeared to facilitate autolytic debridement of superficial slough and necrosis. The investigator concluded that, of the five dressings, Urgotul achieved the best results on wounds in areas that are more sensitive, difficult to dress, with changing exudate levels and superficial slough and necrosis. Results are summarised in Fig 6.<sup>52</sup>

Another independent study — this time a randomised controlled trial (RCT) undertaken in Hong Kong — provides more detailed data showing that Urgotul accelerates healing of traumatic wounds.<sup>53</sup> Patients attending an emergency department with full-thickness traumatic digital wounds were randomised to receive either Urgotul or gauze (the control). The outcome measures were the time taken to



**Amputation stump treated with NPWT and Urgotul (Fig 7a). The wound has almost healed after 19 days (Fig 7b)**

heal the wounds and the wound size at each dressing change. Over a 7-month period, 28 patients participated (16 experimental and 12 control), allowing a 5% level of significance at a power of 60%. Wound size was determined by regular tracing. Full healing was defined as complete epithelialisation.

No patients withdrew from the study or were lost to follow-up. Most patients were male (75%) and healthy, with a mean age of 32.5 years ( $\pm 17.1$ ). Both groups were comparable at baseline in terms of patient demographics and wound characteristics. Results show that wounds treated with Urgotul experienced a greater reduction in size and healed faster. The average healing time was 12.1 days ( $\pm 3.3$ , range 7–20) in the Urgotul group and 16.8 days ( $\pm 5.1$ , range 9–21) in the control group, representing a statistically significant difference in favour of Urgotul ( $p=0.024$ ). The authors suggest that the fewer dressing changes required for Urgotul will not only avoid traumatising the wound, but also produce savings in both time and resources. Unfortunately, due to an outbreak of severe acute respiratory syndrome (SARS) in Hong Kong at the time of the study, the number of admissions dropped, resulting in the low statistical power, limiting the generalisability of the findings.

### Negative pressure wound therapy

Negative pressure wound therapy (NPWT), also known as topical negative pressure (TNP), is widely regarded as an extremely effective (albeit expensive) method of promoting healing in a wide range of acute and chronic wounds. In most NPWT systems, a polyurethane or polyvinyl alcohol foam dressing is placed between the wound and the device, but there is a risk that granulation tissue can grow through the foam, causing trauma and pain at removal.<sup>54</sup> To avoid this, a wound contact layer can be used under the NPWT foam. It is proposed that Urgotul's small mesh size prevents such growth, increasing the likelihood of painless removal.

This was confirmed in a trial in which patients being managed with NPWT experienced substantially less pain at dressing change after using Urgotul under NPWT.<sup>55</sup> Sixty-six patients with 42 acute and 24 chronic wounds given Urgotul plus NPWT (V.A.C., KCI) were followed-up for an average of 17 days. At baseline, pain was noted between two consecutive dressing changes in 66% of patients, even though 60% were receiving oral analgesics, and was either 'moderate' or 'marked' in 69% of dressing care procedures. During the treatment period with





Urgotul plus NPWT these percentages fell to 34% and 13% respectively. Patients considered the combination easy/very easy to remove in 95% of dressing changes, and there was no adherence in 88% of removals. No or minor bleeding was reported in 91% of dressing changes. Finally, the appearance of the surrounding skin improved from inflamed, oedematous, eczematous or macerated to 'healthy' in 18 patients. No Urgotul-related adverse events were reported. It appears, therefore, that dressing changes were less painful when NPWT is used with Urgotul because granulation tissue did not adhere to the wound bed.

### Grafts

If there has been a loss of a large percentage of skin — for example, as a result of a burn or soft-tissue trauma — then split-thickness skin grafting may be required. The ensuing donor site wound will be treated as an acute wound, and so will require a dressing that maintains a moist environment, is non-adherent, absorbent, easy to apply and remove, and helps relieve postoperative pain.<sup>56-58</sup> Traditionally, paraffin gauze (or tulle gras) was used for this purpose, with an absorbent secondary dressing,<sup>59</sup> but this often dries out and adheres to the wound, causing pain and trauma at dressing removal.

An independent, open-label, randomised, intra-individual comparison trial found that, compared with tulle gras, Urgotul was not only associated with more painless dressing removals, but also significantly faster healing times for both burn injury and the graft donor sites.<sup>60</sup> Twenty-five patients were recruited into the study over 6 months. Partial-thickness burns selected for comparison were of similar depth, as assessed by two blinded observers; all grafts were harvested at a fixed depth. Each patient had two burns (or one large burn divided by an imaginary line), one of which was dressed with tulle gras and the other with Urgotul plus a standard secondary dressing. The same treatment protocol applied to the donor sites. In this way, each patient acted as his or her own control. Two blinded observers used photography and planimetry to assess wound healing every week for a mean of 3 months.

Two patients were lost to follow-up, so 23 (92%) were followed up. The mean age was 44 years (range 23–65) and the mean areas dressed with Urgotul and tulle gras were 118cm<sup>2</sup> and 112cm<sup>2</sup> respectively.

The mean time to complete epithelialisation was significantly faster with Urgotul than tulle gras: 9.6 days (range 7–14) versus 11.9 days (7–21) respec-



**A 75-year-old woman presenting with a basocellular carcinoma on the nose, which was treated with a graft (Fig 8a). The wound after 7 days of treatment (Fig 8b)**

tively ( $p<0.05$ ). Furthermore, 100% of the nurses considered Urgotul 'very easy' to use/change at each dressing change, compared with 0% for tulle gras, while the latter was 'difficult' to use in 13% of dressing changes. Bleeding at the first dressing change was observed in twice as many tulle-gras sites as Urgotul: 100% versus 52% ( $p<0.05$ ). During the treatment period, significant bleeding occurred in 17% of tulle gras dressing changes but in none of the Urgotul ones. Finally, none of the Urgotul dressing changes were 'very painful' (defined as intolerable pain requiring extra analgesia), compared with 35% per cent of the controls. Pain was more likely to be 'minimal' with Urgotul than tulle gras: 65% versus 26% respectively ( $p<0.05$ ). No adverse events were reported.<sup>60</sup>



**A 72-year-old patient presenting with a mixed aetiology leg ulcer of 18 months' duration: wound appearance after grafting (Fig 9a). Progression of healing after 8 weeks of treatment with Urgotul (Fig 9b)**



**One-year-old child presenting with a partial-thickness burn on the inside of the arm (Fig 10a). Following treatment with Urgotul there is full epithelialisation on day 15 (Fig 10b)**

### Paediatric wounds

Most wounds presenting in children are acute, generally burns, traumatic injuries and surgical wounds. Given the anxiety wounds are likely to cause children (and their parents), plus the potential sociopsychological consequences, it is vital that dressings are easy to apply and that removal is pain free. The stature of young children also makes it essential that dressings are conformable, so that they can fit into small, awkward places when necessary.

A 4-week clinical study conducted in both France (11 centres) and Germany (5 centres) involving children with burns or other acute and chronic wounds found that removal of Urgotul was atraumatic, with limited pain and adhesion.<sup>61</sup> A total of 100 children (aged 1–12 years) with 77 burns (29% superficial partial-thickness, 71% deep partial-thickness) and 23 'other' wounds (principally traumatic, postoperative and burns sequelae, but also postoperative necrotic and recent pressure under



**A 13-month-old child presenting with a traumatic wound on the forehead following a road traffic accident (Fig 11a). The wound healed after 7 days (Fig 11b)**

plaster) participated. Analgesia was administered at 21% of the documented 529 dressing changes undertaken on all wounds in the two countries. Children assessed their pain at dressing change using either the faces scale (children aged over 3 years) or a visual analogue scale (VAS) where 0mm =no pain and 100mm =very painful (children aged over 6 years). In addition, nurses assessed pain in those aged 1–6 using both the objective pain scale (four items: crying, motion, restlessness and verbal/non-verbal expression) and the VAS.

At a majority of dressing changes (59%) the children selected the 'smiling faces' on the faces scale, while the mean VAS values ranged between 0.9mm and 10.1mm, depending on the country and the wound type. These VAS values were very similar to those noted by the nurses (1.1–6.7mm) and supported the investigators' qualitative evaluation.

Results for the objective pain scale show that most dressing changes (50–65%) did not cause the children to cry, move, or become restless, regardless of wound type.

The nurses' evaluations (both objective and subjective) showed that Urgotul was associated with either no pain or moderate pain at almost every dressing change. The vast majority of dressing applications/removals were either easy or very easy, with minimal bleeding or adherence. Conformability was largely good/very good for nearly 90% of all dressings changes.<sup>61</sup>

### Epidermolysis bullosa

*Epidermolysis bullosa* (EB) is a group of inherited skin conditions that result in potentially extensive skin lesions and blistering following minimal trauma. The open lesions are susceptible to infection. Skin management is mainly supportive, and predominantly comprises good wound care. Given the fragility of the skin and mucous membranes in these patients, a non-adherent, atraumatic dressing must be used to avoid pain at dressing change wherever possible and so improve quality of life.

The largest published wound care study involving this patient group found that use of Urgotul improved healing rates and reduced pain at dressing change when compared with the previous treatment regimen.<sup>62</sup> This clinical study involved 20 patients (11 adults and nine children aged over 12 months), of whom half had previously used other non-adherent dressings or petrolatum gauze. The target lesion had been present for 1–45 days (mean  $8.8 \pm 12.1$ ).



**Non-Herlitz junctional epidermolysis bullosa on a 9-month-old child (Fig 12a). Same wound after 7 weeks of treatment with Urgotul (Fig 12b)**

Nineteen of the 20 EB lesions healed in a mean 8.7 days ( $\pm 8.5$ ); 50% of the sample stated this was shorter than with the previous dressing. Excellent results were also reported for acceptability, with 91% of dressing changes being pain free and no reports of very severe pain. Indeed, 75% of patients stated that dressing changes were less painful than with the previous dressing. Analgesia (paracetamol) was only needed before 13% of dressing changes. Correspondingly, dressing removal was easy/very easy in 98% of cases, with strong adhesion being reported in only three dressing changes. Mild bleeding was reported in only five patients in 18 dressing changes. Based on these findings, 11 patients (55%) concluded that their quality of life had improved following use of Urgotul. Most of the adults and all of the children said they felt less apprehensive about the procedure than they had with their previous dressing. Nineteen of the 20 patients said they would use the dressing again.<sup>63</sup>

While these results demonstrate that Urgotul is a valuable treatment modality for patients with EB, its lack of tact and flexibility may rarely result in slippage, and thus wound extension, when used on large areas. Furthermore, the Urgotul range did not include a size big enough for the large lesions often seen in EB. A study involving 14 patients (nine adults and five children), presented as a poster, found that new Urgotul (which is available in a wider range of sizes, including a 20 x 30cm) was considered more comfortable and associated with a better quality of life than previous dressings used, including Urgotul.<sup>64</sup> Prior to the study, all patients had used either a non-adherent soft sili-

cone primary dressing or Urgotul. Compared with their previous dressing, 50% of patients said their quality of life had improved, 33% said the new dressing was less painful, 33% considered it more comfortable, and 17% felt less apprehensive at dressing change. Thirty-three per cent found that dressing changes were quicker. All patients considered new Urgotul to be very easy/easy to apply and its conformability to be very good/good. In all, 75% were willing to continue using new Urgotul on all of their wounds.<sup>64</sup>

### Venous leg ulceration

Venous leg ulcers are the most prevalent of all chronic wounds, with a reported incidence of 1 and 2 per 1000 of the general population.<sup>65</sup> Compression bandaging is the gold standard therapy for venous and mixed aetiology ulcers. However, clinical studies show that TLC dressings, when used in conjunction with compression, can promote healing still further.

The first 8-week RCT to investigate the use of Urgotul with compression showed that, although efficacy was similar, it was significantly more acceptable to patients than the hydrocolloid comparator.<sup>66</sup> Ninety-one patients with venous or mixed aetiology ulcers were randomised to receive either Urgotul (n=47) or DuoDERM E (known in the UK as Granuflex, ConvaTec) (n=44) in combination with high compression bandages. Results showed that efficacy of the two dressing was similar in terms of healing rates and healing times. In terms of acceptability, there was a significant difference in favour of Urgotul (ease of removal, maceration, odour and pain on removal) over the comparator ( $p < 0.002$ ). In addition, fewer dressing changes were made per week in the Urgotul group ( $2.31 \pm 0.45$  versus  $2.54 \pm 0.57$  [mean  $\pm$  SD;  $p = 0.047$ ]).<sup>66</sup>



**A 78-year-old female patient presenting with bilateral, circumferential leg ulcers (Fig 13a). The same wounds after 6 weeks of treatment with Urgotul (Fig 13b)**

The efficacy of Urgotul plus four-layer compression bandaging was also demonstrated in a clinical study, which again confirmed its acceptability to patients and clinicians.<sup>67</sup> Thirty-six patients with venous leg ulcers, 84% of which were indolent or deteriorating, were treated with Urgotul plus a four-layer multilayer compression bandaging system (K-Four, Urgo). Wound area was measured by planimetry and photography.

At the final visit (week 12), 18 patients had healed in 46.8 days ( $\pm 27.4$ ) of treatment. Of the 16 patients whose ulcer had not healed, the area decreased by a mean of 49.3%, from a mean of 15.2cm<sup>2</sup> to 7.3cm<sup>2</sup>. The average wear time was 6.7 days ( $\pm 2.3$ ), which the authors say is close to the ideal of 7 days required for cost-effective community leg ulcer care. There was only one dressing-related adverse event (skin irritation around the wound), which resolved spontaneously without the need to exclude the patient from the study. Once again, the dressing was 'very easy' to apply/remove in almost all cases, with very little pain, adherence or bleeding at removal. Conformability was rated as 'very good' in 96% of dressing changes.

There was also an improvement in the condition of the surrounding skin: at baseline, only 17.1% had a healthy surrounding skin, whereas at the study end it was considered healthy/normal in 50% of dressing changes and compromised in some way (dry/scaly, macerated, erythematous, oedematous) in 50%.<sup>67</sup>

In other circumstances, healing may be delayed in exuding venous leg ulcers, despite compression. Other studies have investigated the effect on chronic leg ulcers of combining compression therapy with UrgoCell, a foam dressing with TLC. The results show this combination was generally efficacious, acceptable and well tolerated. These results are summarised briefly below.

An observational study conducted in general practice settings in France showed that the combination of UrgoCell and compression was not only efficacious, but also helped to improve concordance rates.<sup>68</sup> The sample comprised 2532 consecutive patients with venous leg ulcers who were about to receive a non-adherent primary wound dressing (almost always UrgoCell). At baseline, 64% of the patients who had access to compression said they regularly wore it, indicating the difficulties in achieving concordance. However, this increased to 80% at the follow-up visit at least 3 weeks later.

The mean ulcer length at baseline was 5.3cm  $\pm$  4.1 (range 0.1–35.0) and the mean duration was 9

months  $\pm$  15 (0–240). After an average of 32.4 days, the mean reduction in ulcer length was 38% (median 33%), while 14% of the ulcers healed and 71% improved. Either no or minimal pain was experienced at removal in 94% of dressing removals. High scores were also reported for tolerability, conformability and acceptability.

The next study, also multicentre and clinical, involved 43 patients with non-healing venous or mixed aetiology ulcers given this treatment combination for a maximum of 6 weeks.<sup>69</sup> Results show that the mean baseline area of 10.71cm<sup>2</sup> ( $\pm 7.31$ ) had reduced by 38%, to 7.67cm<sup>2</sup> ( $\pm 9.27$ ), by the study end. The dressing was well accepted; four treatment-related adverse events, mainly 'erosion' and eczema lesions, were reported, but none required discontinuation with treatment.

Similar results were obtained in a slightly larger clinical study<sup>70</sup> on UrgoCell Adhesive (which is not yet available in the UK), involving 50 patients who had chronic wounds with a mean duration of 7 months. Ulcers were measured by planimetry and photography. Previous dressings used were another hydrocolloid, foam, alginate or greasy gauze. Following treatment with the new dressing combination, six patients healed in a mean of 28  $\pm$  8 days. For the group as a whole, the surface area reduced by a mean of 47%, from a mean baseline surface area of 8.34cm<sup>2</sup> ( $\pm 6.95$ , range 0.8–30.7), during the 6-week study period. The investigators considered that 72% of the wounds had improved. The new dressing was also associated with an improvement in the condition of the peri-wound skin, which was considered healthy in 28% at inclusion versus 36% of study end. There were only four (unspecified) dressing-related local adverse events. Again, good results were reported for all acceptability parameters, with nearly 90% of dressing removals being pain-free.

The next study was conducted after UrgoCell was improved by the inclusion of a soft-adherent TLC layer (UrgoCell TLC), with a view to making it more conformable and easy to use. This multicentre clinical study,<sup>71</sup> presented as a poster, involving 45 patients with venous or mixed aetiology leg ulcers found that the mean baseline area, 13.15cm<sup>2</sup> ( $\pm 10.54$ , range 1.96–45.02), reduced by 37.4% ( $\pm 52.2$ ) after 6 weeks of treatment. (Wounds were measured by planimetry and photography.) Two ulcers healed. In addition, scores for ease of use and conformability were excellent, while pain during dressing removal was minimal or non-existent in nearly 98% of cases.



Diabetic foot ulcer at inclusion (Fig 14a). Same ulcer after 15 weeks of treatment with Urgotul (Fig 14b)

### Diabetic foot ulcers

The prevalence of foot ulcers among people diagnosed with diabetes mellitus is estimated as 4–10%.<sup>72</sup> The major aetiologies of diabetic foot ulcers are neuropathy, peripheral vascular disease and neuroischaemia. Approximately half of all diabetic foot ulcers become infected over the course of therapy.<sup>73</sup> Diabetic foot ulcers are a severe complication of diabetes, and are associated with a reduced quality of life, morbidity and premature mortality.<sup>74</sup> They are also associated with 85% of major amputations.<sup>75</sup> Standard treatment comprises debridement, offloading, treatment/prevention of infection and use of modern wound dressings to promote a moist environment.<sup>76,77</sup>

A multicentre 6-week clinical study involving 35 patients with diabetic foot ulcers provides preliminary evidence on the efficacy and acceptability of Urgotul.<sup>78</sup> Mean baseline ulcer surface area was 13cm<sup>2</sup>, measured by planimetry. The mean ulcer duration was 5.2 months. The surrounding skin was healthy in only 21%. Thirteen patients healed completely, while there was a 55% reduction in mean wound surface for the group as a whole. An improvement in the condition of the surrounding skin was noted in all but three patients. Conformability was almost always (99%) regarded as very

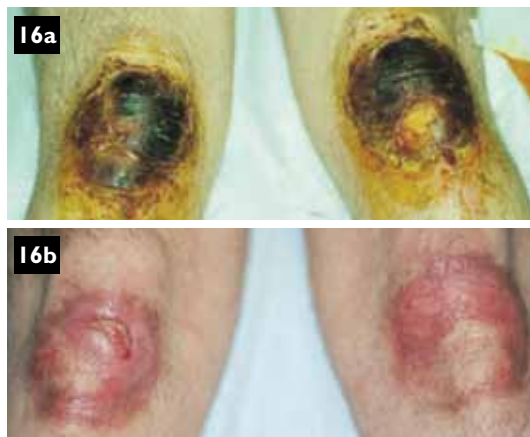


A 84-year-old patient with a category 3 pressure ulcer of 4 weeks' duration on a knee stump (Fig 15a). Healing was achieved after 6 weeks (Fig 15b)

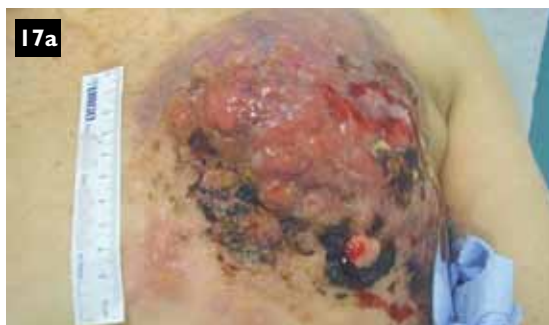
good/good. Only one adverse event (erysipelas of the right lower limb) was reported but this was not considered to be dressing related.

### Other wounds

TLC dressings have been evaluated on a number of other wounds such as bullous pemphigoid,<sup>79</sup> deep caustic burns,<sup>80</sup> pyoderma gangrenosum,<sup>81,82</sup> cancerous wounds,<sup>83</sup> post-tattoo,<sup>84</sup> pressure ulcers.<sup>85</sup>



Caustic burn resulting follow contact with wet cement (Fig 16a). Complete wound healing after 72 days (Fig 16b)



A 65-year-old woman presenting with breast cancer (Fig 17a). The same wound after 12 months of radiotherapy, chemotherapy and TLC dressings (Fig 17b)

# Dressings with TLC-Ag technology

All wounds — acute and chronic — contain microorganisms, but this does not mean that they are infected.<sup>86</sup> In chronic wounds, the presence of devitalised tissue can result in colonisation by a variety of microorganisms, but this is only regarded as problematic if there is a host reaction (characterised by the clinical symptoms of critical colonisation or infection), which will delay healing.<sup>87</sup> While the number of bacterial species present in the wound is not necessarily an indicator of infection, the presence of four or more groups increases the risk,<sup>88</sup> as does, of course, host susceptibility<sup>89</sup> and the presence of certain pathogens and pathogenic species, such as *Staphylococcus aureus*, *Streptococcus* species, anaerobes and *Pseudomonas aeruginosa*.<sup>90</sup>

The concepts of critical colonisation and infection are based on the level of host response to the pathogens present in the wound. While there is no universally agreed definition of critical colonisation, it is proposed that a wound is critically colonised when the bacteria delay healing with subtle signs of a host reaction or inflammation but no overt signs of infection — for example, when the wound margins fail to contract, exudate levels increase, the wound bed is predominantly sloughy and, possibly, granulation is friable and bleeds easily at dressing change. In contrast, infection is associated with damage to the host, with the classic signs including pain, erythema, heat, oedema, malodour, cellulitis, delayed healing and wound breakdown.<sup>91,92</sup>

More recently, it has been proposed that all chronic wounds contain biofilms,<sup>93</sup> although this has yet to be proven. Most bacteria grow when attached to a surface, such as the host tissue, and the numbers and species of bacteria multiply to become a stable, self-sustaining, polymicrobial community (the biofilm) that is encased within a matrix of extracellular polymers. A host inflammatory response then occurs, resulting in the recruitment of excess neutrophils, pro-inflammatory cytokines and excessive host-derived proteases, which provide the biofilm with a constant source of nutrients.<sup>94</sup> The biofilm has an evolutionary ability to adapt to its environment and avoid the immune system and resist antibiotics, thereby ensuring its survival. As time passes, the aerobic

and anaerobic bacteria in the biofilm increase their pathogenic effect, potentially causing infection and delaying healing still further.<sup>95</sup>

Topical antimicrobials can be used to prevent and treat infection in high-risk patients. In addition, the various antiseptics contained within most of these dressings will reduce the bioburden, thereby helping the host to regain control. Topical antimicrobials have an advantage over systemic antibiotics in that they are not associated with resistance, and have a broader antimicrobial spectrum and much lower sensitisation rates.<sup>96</sup> While best practice guidelines are still in development, it is prudent to restrict use to a maximum of 3–4 weeks before re-assessing the patient, depending on local protocols. Topical antimicrobials should only be used while the signs of critical colonisation or local infection are resolving. If the infection becomes systemic, then antibiotics must be applied.

Silver has a broad antimicrobial effect against both Gram-positive and Gram-negative bacteria, including *Pseudomonas aeruginosa*, meticillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus (VRE), as well as some fungi, viruses and protozoa.<sup>97</sup> It is thought to bind to and damage microbial cell walls, inhibit replication and reduce metabolism and growth.

The safety and tolerability profile of silver is good. While there is evidence that some silver dressings are cytotoxic to keratinocytes *in vitro*,<sup>98,99</sup> this effect is less marked *in vivo* and *ex vivo* as the silver is dispersed by the blood circulation and deposited in the liver and kidney, from where it is presumably eliminated from the body in the urine.<sup>100,101</sup> The potential for bacterial resistance to silver has also been raised,<sup>102,103</sup> but recorded occurrences are very rare.<sup>104</sup>

Silver has therefore been incorporated into TLC dressings to give them antimicrobial properties. Silver sulphadiazine (3.75%) has been added to Urgotul to produce Urgotul SSD, and silver ion (3.5%) to Urgotul to produce Urgotul Silver. Both are indicated for the treatment of non to low exuding acute (burns, skin abrasions, traumatic injuries, second-degree burns) and chronic wounds showing signs of infection or critical colonisation. They can also be used on more heavily exuding wounds



when in combination with an absorbent dressing.

Three unpublished large-scale observational studies demonstrate that clinicians have used these TLC-Ag dressings on over 8,000 patients with critically colonised and/or locally infected acute and chronic wounds, with the results indicating that they were well accepted by both clinicians and patients.<sup>105-107</sup>

Despite the widespread acceptance of silver dressing in clinical settings, the lack of multiple, large-scale, high-quality trials on silver dressings — and thus robust efficacy data — has raised concern among commissioners that the expense incurred by their routine use may not be justified.<sup>19</sup> Such concern was fuelled by the VULCAN RCT,<sup>21</sup> which reported that silver dressings are no more effective than low-adherent dressings in healing venous leg ulcers, even though there is nothing to indicate in the study that the dressings were applied to critically colonised or infected ulcers, indicating that its methodology was flawed. Clearly, a more considered approach to the literature is warranted.

This chapter therefore provides substantial evidence from the laboratory trials and clinical studies that dressings with TLC-Ag can help improve wounds with signs of critical colonisation or infection.

### In vitro evidence

Following the launch of Urgotul SSD, *in vitro* research, presented in a poster, investigated the bactericidal properties (based on minimal inhibitory concentration, MIC) of silver sulphadiazine against 117 strains of bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). (The MIC test determines the degree of antimicrobial activity of a material against a specific bacterium.) Results revealed it produced low MIC values, demonstrating that silver sulphadiazine is bactericidal against a large amount of the strains tested, including those with known antibiotic resistance.<sup>108</sup>

Further *in vitro* studies showed that Urgotul SSD has minimal cytotoxic effects on human dermal cells. In a comparative, independent, laboratory study involving five silver dressings — Acticoat (Smith & Nephew), Aquacel Ag (ConvaTec), Con-treet Foam (Coloplast), PolyMem Silver (Aspen Medical) and Urgotul SSD (Urgo) — PolyMem Silver and Urgotul SSD had the least cytotoxic effects on human keratinocyte and fibroblast monolayer cultures. The cultured skin cells were 'relatively safe' in the presence of these two dressings,

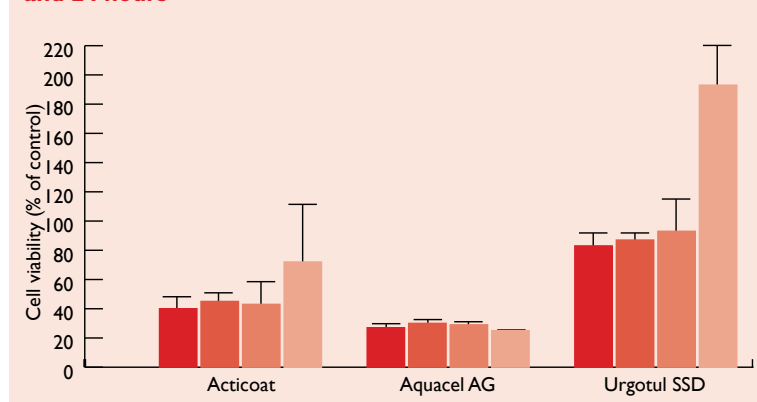
but died when exposed to the other three. In fact, the biological activity of Urgotul SSD was comparable to that of a non-silver dressing control (Aquacel) on the keratinocyte monolayer (Fig 18).<sup>109</sup>

Silver has been shown to inhibit biofilm formation *in vitro*.<sup>110-115</sup> *In vitro* research, as yet available only as posters, demonstrated the efficacy of TLC technology containing silver (TLC-Ag) in destroying *S. aureus* and *P. aeruginosa* biofilms. Based on bacterial counts, one study showed that TLC-Ag killed 98% of *P. aeruginosa* biofilms and 99.9% of *S. aureus* biofilms, with a maximum effect after 1 and 2 days respectively. These results were confirmed by scanning electron microscopy (SEM).<sup>116</sup> A second laboratory study, which focused on Urgo-Cell Silver, confirmed these results, finding that it destroyed 100% and 98% of *P. aeruginosa* and *S. aureus* biofilms, respectively, within 24 hours. Dressing samples were also exposed to the biofilms for 2, 4 and 7 days. Results show that changing the dressing after 2 days (as indicated in the manufacturer's instructions for use) sustained the antimicrobial effect. Again, these antimicrobial effects were confirmed by scanning electron microscopy.<sup>117</sup>

### Burns

Burns are traumatic wounds that may be caused by exposure to thermal extremes, caustic chemicals, electricity, radiation or direct heat. Pain can be severe, particularly in superficial burns. Infection is the main cause of morbidity and death. The main aims of management are therefore to reduce pain between and during dressing change, prevent infection and restore form, function, and feeling.<sup>118</sup>

**Fig 18. Fibroblast cell viability after dressing treatments for 2, 4, 6 and 24 hours<sup>109</sup>**





**Partial-thickness burn on the hand, caused by boiling water, on a 18-month-old child (Fig 19a). Healing was achieved after 7 days of treatment with Urgotul SSD (Fig 19b)**

Traditionally, silver sulphadiazine cream was used to prevent or treat infection in burns, but its use prolongs healing,<sup>119</sup> inactivates enzyme debriding agents<sup>120</sup> and has cytotoxic effects.<sup>121</sup> It also requires daily dressing changes. To counter these effects, silver sulphadiazine has been incorporated into dressings, with a view to facilitating a slow, but sustained, release of silver sulphadiazine.

Urgotul SSD is a silver sulphadiazine-impregnated TLC dressing that delivers a known dose of silver sulphadiazine to the wound and reduces dressing change frequency (when compared with the cream). Its efficacy in burn injuries has been largely proven.

In a multicentre clinical study, Carsin et al. found that its use either resulted in healing or enabled skin grafting in hospitalised patients with recent (<24 hours) partial-thickness burns.<sup>122</sup> Mean baseline surface area was 192.7cm<sup>2</sup> (± 151.1, range 30–629). Of the 41 patients included, 24 healed in a mean of 10.8 ± 4.3 days (range 5–21) and 13 had a skin graft within a mean of 11.5 days (range 4–24). None developed a secondary infection



**Partial-thickness burn on the face (Fig 20a). Appearance after 7 days of treatment with Urgotul SSD (Fig 20b)**

during the 4-week study period, even though swabs results identified *S. aureus* in eight patients. It is noteworthy that seven of these eight patients healed; the eighth patient was withdrawn due to the development of eschar on the treated wound. The mean dressing change frequency was 1.73 days (range 1–5).

Nurses scored the dressing highly in terms of acceptability, and it was almost always considered easy/very easy to remove with no/slight bleeding. There was no or slight adherence at 82% of dressing changes. Conformability was considered very good/good at approximately two-thirds of dressing changes (73%). Only one adverse event was reported: pain on the third day of treatment but this did not warrant discontinuation.<sup>122</sup>

An independent randomised controlled trial (RCT) that compared Urgotul SSD with 1% silver sulphadiazine not only confirmed the dressing's efficacy but also showed it was associated with lower pain scores than the comparator treatment.<sup>123</sup> Sixty-eight patients with partial-thickness burns of less than 15% total body surface area were randomised to receive either Urgotul SSD (n=34) or 1% silver sulphadiazine (n=34). Both groups had comparable demographic data and wound characteristics at baseline. Statistically significant differences in favour of Urgotul SSD were reported in terms of mean healing times (10 ± 4 days versus 12 ± 6 days respectively, p<0.05) and pain scores (recorded 30 minutes after each dressing change using a 0–10 visual analogue scale) (3 ± 1 versus 6 ± 2, p<0.05). Fewer patients treated with Urgotul SSD required analgesia (p=0.04). The mean follow-up times at the outpatient burn clinic were significantly shorter for the Urgotul SSD patients (p=0.03). The authors state that the Urgotul SSD group required less frequent dressing changes.

Good results have also been reported in paediatric burns. An independent, retrospective cohort study that compared Urgotul SSD with Contreet Ag (also known as Biatain Ag) (Coloplast) reported that it provided near-painless wound management, and was highly acceptable to children with partial- or full-thickness burns.<sup>124</sup> Two comparable groups of 20 children were evaluated. Analgesia was administered only before dressing change in accordance with the physician's preference. Pain results slightly favoured Urgotul SSD, with pain being absent or slight in 92% of dressing changes compared with 85% for Contreet Ag, while the results for acceptability were comparable for the





two dressings. However, Urgotul SSD was considered 'very easy' to apply and remove in 49% and 73% of dressing changes respectively, versus 35% and 56% for the control group.<sup>124</sup>

## Grafts

When removing a dressing to determine graft take, care must be taken to avoid adherence as this will traumatise the new vascularity of the graft. A non-adherent dressing is therefore advised. Urgotul SSD has been shown to prevent adherence and thus painful dressing changes in ulcers following grafting. A poster presentation states that 10 patients whose post-necrotic angiodermatitis skin grafts were dressed with Urgotul SSD experienced less pain at dressing change.<sup>125</sup> Dressing change frequency was every 2 days for the first 8 days and then twice weekly, thereby reducing the risk of mechanical trauma to the graft and aiding healing. Necrotic angiodermatitis is a painful, lower extremity, ischaemic ulcer associated with poorly controlled hypertension.<sup>126</sup> Treatment comprises excision and grafting, while management includes infection control.<sup>126,127</sup> None of the graft sites developed an infection.

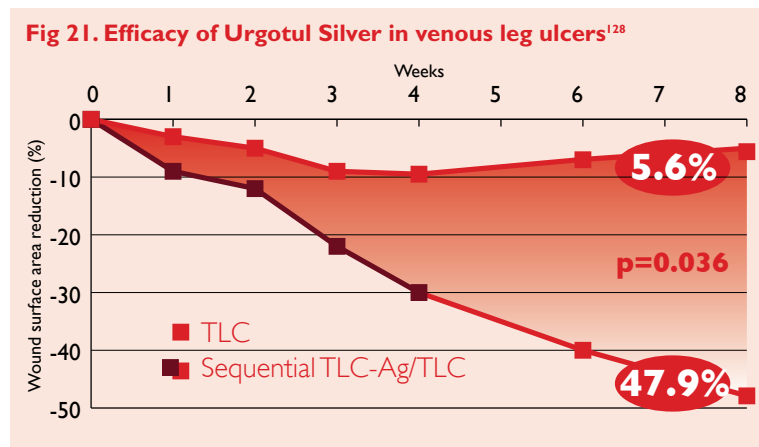
## Venous leg ulcers

Urgotul Silver is impregnated with silver ions. These are not released into the wound, but are instead maintained within the lipidocolloid gel (this mechanism of action is similar to Urgotul SSD). The antibacterial effect only occurs when the gel comes into contact with the wound. UrgoCell Silver is a foam version of Urgotul Silver, and is indicated for low to moderate exudate levels. The clinical studies outlined below show that TLC-Ag dressings aid healing in chronic wounds showing signs of infection or critical colonisation.

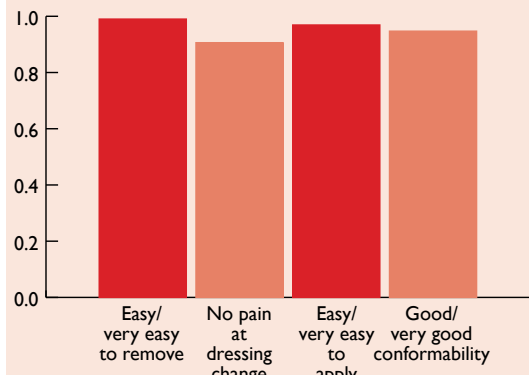
A multi-centre, open-label RCT found that Urgotul Silver, worn under compression bandaging, promoted healing of critically colonised venous leg ulcers, when compared with a non-silver control (Urgotul).<sup>128</sup> A total of 102 patients from 24 centres with at least three of the following signs of critical colonisation — pain between two consecutive dressing changes, peri-wound erythema, oedema, malodour and heavy exudation — were included in the efficacy analysis. The treatment period lasted 8 weeks, with patients in the treatment group (n=52) receiving Urgotul Silver for the first 4 weeks and then Urgotul for the following 4 weeks. The control group (n=50) received Urgotul for 8 weeks. Wound

surface area was measured objectively by planimetry and photography. The mean baseline wound areas were 22.3cm<sup>2</sup> (± 20.4, median 16.3) and 17.5cm<sup>2</sup> (± 14.4, median 12.6) for the treatment and control groups respectively. The two groups were comparable at baseline. In the investigators' opinion, a large majority of all ulcers (79%) were 'stagnating or aggravating'. Three patients dropped out before the first week following withdrawal of consent, aggravation of the ulcer and an intercurrent event, so the ITT analysis was performed on 99 patients. Twenty-eight patients dropped out of the study, primarily due to ulcer aggravation (n=11) and local adverse events (n=13). Most of these (n=20) were in the control group, and five were possibly dressing related.

Results show greater efficacy for Urgotul Silver throughout the study period. At week 4, wound area in the Urgotul Silver group reduced on average by 6.5 ± 13.4cm<sup>2</sup> (median 4.2cm<sup>2</sup>) compared with 1.3 ± 9.0cm<sup>2</sup> (median 1.1cm<sup>2</sup>) for the control (p=0.023). The same trends were observed when surface area evolutions were expressed as a percentage reduction from baseline. By week 8, median ulcer area regression was 47.9% in the Urgotul Silver group versus 5.6% in the controls (p=0.036). Interestingly, after week 4, when Urgotul Silver was replaced with Urgotul, the mean ulcer area in this group continued to decrease, whereas no clinically relevant change was noted in the control group, which used Urgotul throughout the study period. By week 8, the mean ulcer size reduction was 5.9cm<sup>2</sup> for the treatment group compared with 0.8cm<sup>2</sup> for the control group, representing a marked statistically significant difference (p=0.002). Results also showed that ulcers treated with this dressing were less likely to be still criti-



**Fig 22. Acceptability of TLC-Ag dressing (UrgoCell Silver)<sup>129</sup>**



cally colonised at week 4 than the controls (61% versus 83%). Indeed, compared with baseline, there was a significant reduction in the number of clinical signs of infection in the wounds dressed with Urgotul Silver versus the control ( $-2.5 \pm 1.5$  versus  $-1.0 \pm 1.4$ ;  $p < 0.001$ ).

There was no difference in the number of adverse events ( $n=11$ ) in each group, and the authors were unable to determine whether or not they were

dressing related. Four patients from the treatment group and five from the control group discontinued treatment because of them. These results are particularly interesting in the light of the VULCAN debate as they provide clear evidence that Urgotul Silver promotes healing when compared with a non-adherent neutral control when used on the appropriate wound types.<sup>128</sup>

In 2006, a multicentre clinical study assessed the efficacy of UrgoCell Silver under compression bandaging in venous leg ulcers, although here efficacy was defined not only as the reduction in the wound size but also as a reduction in the clinical signs of critical colonisation.<sup>129</sup> The results showed that this dressing performed well for both outcomes. Forty-five patients with 3–5 signs of critical colonisation (spontaneous pain between dressing changes, peri-wound erythema, malodour, oedema and heavy exudation) and a mean venous ulcer surface area of  $12.6\text{cm}^2 (\pm 10.0)$  (range 2.6–48) were included in the study. Wound size was determined by tracing and photography. By week 4, only 10 patients still had three or more of these symptoms — a highly significant reduction ( $p < 0.001$ ). Similarly, at week 4 the mean percentage reduction in ulcer size was 35% ( $\pm 58\%$ , median 33%), which was also highly significant ( $p < 0.001$ ). Of the 45 ulcers, five healed and 30 improved. The dressing was left in place for 2.6 days on average, and even up to 13 days in one case.



**A 66-year-old male with a venous leg ulcer on the left leg that had been progressively worsening for 14 months (Fig 23a). After 15 weeks of treatment, the venous ulcer had healed (Fig 23b)**

### Other wounds

The antimicrobial properties of TLC technology with silver dressings have also been demonstrated on other wound types, including diabetic foot ulcers,<sup>130</sup> malignant wounds,<sup>83</sup> complex wounds,<sup>131</sup> abdominal wounds,<sup>132,133</sup> frostbite wounds,<sup>134</sup> post-traumatic wounds,<sup>135,136</sup> and rhinophyma.<sup>137</sup>

**Table 5. Summary of main outcomes of clinical studies involving the use of TLC-Ag dressings**

Study	Sample size	Wound types	Product used	Outcome measures	Key results
Muangman et al. <sup>123</sup>	68 patients	Partial-thickness burns	Urgotul SSD versus 1% silver sulphadiazine	Efficacy	Healing times and pain scores significantly favoured Urgotul SSD ( $p < 0.05$ )
Lazareth et al. <sup>128</sup>	102 patients	Critically colonised venous leg ulcers	Urgotul Silver versus Urgotul	Efficacy, tolerability and acceptability	At week 8, there was a significantly greater reduction in wound size in the Urgotul Silver group ( $p = 0.002$ ) as well as fewer clinical signs of critical colonisation ( $p < 0.001$ ). No difference in terms of local adverse events and tolerability



# Dressings with TLC-NOSF Technology

**T**he role played by matrix metalloproteinases (MMPs) in perpetuating wound chronicity is described earlier in this supplement. To summarise, the increased levels of MMPs (along with pro-inflammatory cytokines and reactive oxygen species) observed in chronic wound exudate results in the degradation of the extracellular matrix and inactivation of growth factors. In this way, the wound is maintained in an uncontrolled inflammatory state, which delays or stalls tissue repair, cellular proliferation and angiogenesis.<sup>3,138,139</sup> A dressing that is capable of sequestering excess MMPs from chronic wound exudate may therefore help to produce an anti-inflammatory effect and thus benefit healing.<sup>140</sup>

To achieve this, Urgo has produced a range of dressings that incorporate the MMP inhibitor nano-oligosaccharide factor (NOSF) into the lipidocolloid matrix of TLC dressings; the resulting combination is termed TLC-NOSF. According to the manufacturer, when in contact with wound exudate, the polysaccharide structure of NOSF partially dissolves to form a colloidal substance that binds onto all surfaces of the wound. The NOSF then interacts with the MMPs in the wound exudate, inhibiting and neutralising their activity.<sup>141,142</sup> Urgo proposes that controlling excess MMP activity in this way helps to 'kick start' the healing process.

Dressings in the TLC-NOSF range comprise UrgoStart Contact (a contact layer with TLC-NOSF) and UrgoStart (a soft-adherent foam dressing with TLC-NOSF). Like all TLC dressings, they are non-adherent and promote a moist wound environment.<sup>24</sup>

By rekindling the healing process in a previously recalcitrant wound, TLC-NOSF improves quality of life. This was illustrated in a French observational study involving 1005 outpatients with non-healing venous leg ulcers, which showed that patients experienced less pain/discomfort and anxiety/depression, as well as greater mobility, following treatment with TLC dressings including TLC-NOSF; they were also better able to perform their usual day-to-day activities.<sup>143</sup>

The efficacy and safety of TLC-NOSF dressings have been demonstrated in various laboratory and clinical trials, described below.

## *In vitro* evidence

The effectiveness of TLC-NOSF in reducing MMP activity has been demonstrated *in vitro*. A laboratory study, reported in a poster, used a normal human dermal fibroblast culture to compare the effect of the TLC-NOSF dressing (UrgoStart Contact) on overall MMP activity at 24 hours. Results (based on chemofluorescent staining) show that the TLC-NOSF dressing significantly reduced overall MMP activity when compared with a control.

The investigators then used the ELISA assay kit to measure the effect of the TLC-NOSF (UrgoStart Contact) on MMP-1, MMP-2 and MMP-9 levels in supernatants of U937 human macrophages and normal human epidermal keratinocytes exposed to it for 24 hours. (Keratinocytes and macrophages express MMP-2, MMP-1 and MMP-9 respectively.) Again, there was a significant reduction in levels of all three MMPs when compared with the control.<sup>141</sup> As stated above, MMP levels, particularly MMP-2 and MMP-9, are raised in chronic wounds,<sup>3,144,145</sup> while MMP-1, MMP-2 and MMP-9 all degrade collagen.<sup>146</sup>

These results are supported by another *in vitro* study,<sup>142</sup> in which a TLC-NOSF dressing (UrgoStart) was placed over a three-dimensional dermal equivalent that had formed following the incorporation of normal human dermal fibroblasts into a collagen matrix. The culture media were analysed on days 2, 4 and 8. Results showed that the TLC-NOSF dressing had inhibited the enzymatic activity of MMP-2 and MMP-9 (gelatinases) and MMP-1 and MMP-8 (collagenases) on day 4. (MMPs can be either collagenases or gelatinases, and both degrade collagen.)<sup>146</sup> This effect was maintained until day 8 in the gelatinases but not in the collagenases. As stated above, gelatinase (MMP-2 and MMP-9) levels are particularly high in chronic wounds. The investigators propose that the effects demonstrated in this dermal equivalent model are likely to be similar to those occurring in an *in vivo* dressing application.

Finally, comparative *in vitro* experiments involving human umbilical venous endothelial cells, reported in a poster,<sup>147</sup> demonstrated that NOSF enhanced the proliferation and migration of these cells at 24 hours, following the creation with a pipette of a 'continuous lesion' across the monolayer, when compared with a control.

These three studies suggest that TLC-NOSF has the potential to inhibit MMP activity, stimulate the proliferation and migration of endothelial cells and thus allow the wound to progress through the healing process.

### Chronic wounds

Evidence is emerging of the clinical efficacy of TLC-NOSF dressings in promoting healing in chronic wounds where the prognosis for healing was previously poor. Large-scale clinical studies involving patients with a wide range of wound types, and which therefore reflect the real-life clinical environment, give a good insight of the benefits the dressing can offer patients and practitioners.

The largest observational study on the use of UrgoStart, which cites data from 2052 patients attending 483 wound centres across Germany, found that it helped to accelerate healing, with a median 75% reduction in wound surface area across the entire sample, and was acceptable to patients.<sup>148</sup> Patients with wounds that were not showing any signs of healing and who had the following risk factors for compromised healing (diabetes mellitus, clinical obesity, immobility, congestive cardiac insufficiency and renal insufficiency) were included in the study. Wounds comprised venous leg ulcers (58%), pressure ulcers (9%), arterial leg ulcers (8%), diabetic foot ulcers (5%), fungating wounds (1%) and other (19%). All patients with venous leg ulceration wore some form of compression therapy. Dressings used prior to entry into the study comprised gauze, dry compress, alginate, TLC dressings, foam, hydrocolloid, silver dressings and other. Patients were followed up for a maximum of 8 weeks.

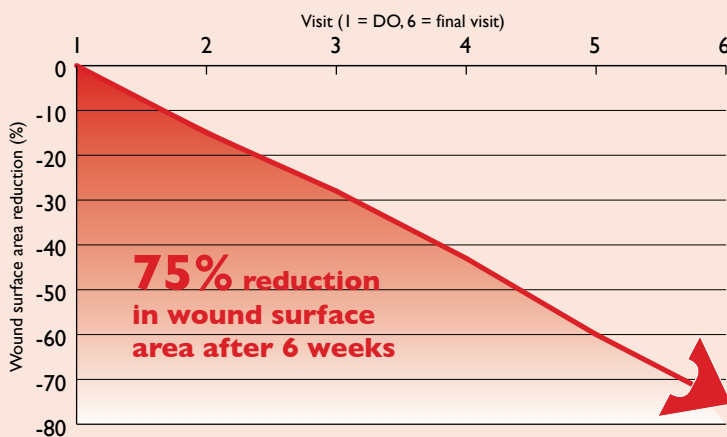
Combining all wound types, the median baseline wound surface area of 10cm<sup>2</sup> reduced to 2cm<sup>2</sup> by the study end — a median reduction of 75%. This effect was most marked in pressure ulcers. Twenty-eight per cent of ulcers healed.

Fifty-nine per cent of the sample completed a questionnaire enquiring about the acceptability of the dressing. Of these, 58% stated that they never/rarely and 23% that they occasionally experienced pain at dressing removal, while 96% reported that the dressing was very comfortable/comfortable. Ninety-four per cent of patients were very satisfied/satisfied with the dressing. Of the entire sample, 30 patients (1.5%) reported adverse events, most of which were dressing related, primarily oedema, erythema and itching.<sup>148</sup>

Another large observational study, this time involving 1185 patients, found that use of UrgoStart was associated with a progression towards healing in difficult-to-heal wounds of varying aetiologies. The investigators used an assessment tool, which allocates individual scores for the wound surface area, wound healing stage, exudate level and presence of spontaneous pain, to produce an overall score. Wounds comprised venous leg ulcers (67.5%), diabetic foot ulcers (10.2%), pressure ulcers (8.5%), angiodermatitis (1.9%) and other (11.9%). Of the wounds, 21% had been present for over 6 months, 64% were recurrent and 70% were stagnating or deteriorating. The average follow-up time was 44 ± 25 days. The overall scores reduced by an average of approximately 50% for all wound types, with an improvement noted as soon as 2 weeks. The benefit was most marked for non-arterial wounds of less than 6 months' duration.<sup>149</sup>

These results are supported by a smaller multicentre observational study involving 78 inpatients (mean age 39.5 years) from 17 hospitals, which found that UrgoStart kick-started healing in patients with chronic wounds with risk factors including arteriopathy of the lower limb, immobility, diabetes, malnutrition and general corticotherapy. Wound types included leg ulcers (41%), pressure ulcers (27%), surgical wounds and chronic traumatic wounds (16%), diabetic foot ulcers (14%) and other (2%). Previous dressings used included wound contact layers, alginates and foams. The mean baseline wound surface area was 34.3cm<sup>2</sup>. Following treatment with UrgoStart, the clinicians considered the reduction in wound surface area to be very satisfactory/satisfactory in 86% cases. Similarly, dressing absorption, ease of application and conformability,

**Fig 24. Observational study involving 2052 patients<sup>148</sup>**



and non-adherence to the wound were considered very satisfactory/satisfactory in 97%, 98.5% and 98.2% of cases, respectively.<sup>150</sup>

## Venous leg ulcers

The gold standard treatment for venous and mixed aetiology leg ulcers is compression bandaging,<sup>151</sup> but adjuvant therapy with a dressing that can rebalance MMPs levels can also aid healing.<sup>152</sup>

Confirmation of the efficacy of the TLC-NOSF dressing first comes in the form of a randomised controlled trial (RCT) in which the control was the protease-inhibitor, Promogran (Systagenix Wound Management); both products were used under compression. The study was conducted in 22 French hospitals and five UK wound specialist centres. Fifty-seven patients with non-healing venous leg ulcers were randomised to receive the TLC-NOSF (UrgoStart Contact) dressing and 60 to the control. Both groups were comparable for ulcer severity parameters at baseline. Wounds were regularly measured by planimetry and photography. Twenty-four patients in the control group and 17 in the NOSF group withdrew, mainly because of withdrawal of consent, ulcer aggravation, and local adverse events. All randomised patients were included in the intention-to-treat (ITT) analysis (ie, all those allocated to a treatment were included in the analysis regardless of whether or not they received or adhered to the intervention). As almost all patients (93%) had been concordant with compression therapy during the study, the results can be attributed to the use of UrgoStart Contact during the study period.

Percentage reduction in ulcer area was selected as the primary outcome (and evaluated blindly) because it is a predictor of progression to healing in chronic wounds.<sup>8,153,154</sup> Absolute reduction in ulcer area and healing rates were also measured. The NOSF group achieved a significantly larger ulcer area reduction, percentage area reduction and healing rates at 12 weeks compared with the control. The mean wound area at baseline was  $10.9\text{cm}^2 \pm 9.3$  (median 8.1). The median wound area reduced by 54.4% and 12.9% in the TLC-NOSF (UrgoStart Contact) and control groups respectively ( $p=0.0286$ ). The mean absolute reduction in wound area was  $2.3\text{cm}^2 \pm 10.2$  (median: 4.2) versus  $0.2\text{cm}^2 \pm 10.4$  (median 1.0) at study end for the UrgoStart Contact and control groups respectively ( $p=0.01$ ).

In all, 56% of ulcers in the TLC-NOSF group achieved a 40% reduction in wound area compared with 35% in the control group ( $p=0.022$ ) in

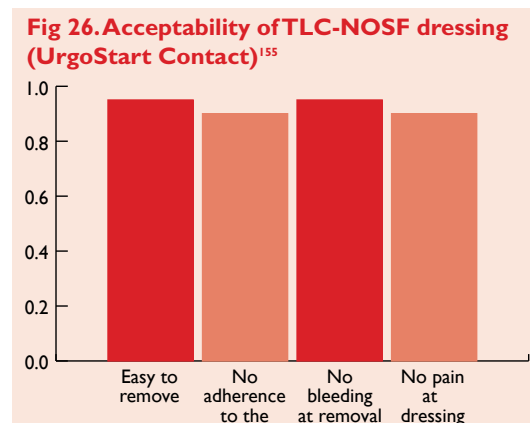


*An 87-year-old patient presented with two leg ulcers of 12 months' duration on her left leg (Fig 25a). Complete healing was achieved after 16 weeks (Fig 25b)*

a median of 42 and 84 days respectively. Interestingly, sub-group analysis showed that ulcers of >6 months' duration in the TLC-NOSF group were significantly more likely to achieve a  $\geq 40\%$  reduction than those in the control group: 55% versus 26%. (More than 56% of ulcers had been present for >6 months at baseline and 61% were recurrent.) Finally, the mean healing rate was significantly higher in the TLC-NOSF group than in the control group:  $-0.016 \pm 0.285\text{cm}^2/\text{day}$  (median  $-0.056$ ) versus  $+0.075 \pm 0.475\text{cm}^2/\text{day}$  (median  $-0.015$ ) respectively ( $p=0.029$ ).

Six patients discontinued treatment because of adverse events in the treatment group (UrgoStart Contact) versus 14 in the controls. Pain and infection occurred more frequently in the control group than in the TLC-NOSF (UrgoStart Contact) group: 18 versus 5. Interestingly, pain has been reported as an adverse event in other Promogran studies.<sup>152</sup> Only one patient in the TLC-NOSF group developed an infection. Acceptability data showed that dressing changes were also slightly more acceptable to patients in the TLC-NOSF group.<sup>155</sup>

This RCT's results are confirmed by the findings of a recently completed multicentre clinical study, as yet only available as a poster, on the efficacy of



TLC-NOSF (UrgoStart foam dressing) on venous leg ulcers when used in combination with compression therapy.<sup>156</sup> Over 6 weeks, 22 patients underwent regular assessments including clinical evaluations, area tracing and photography. The mean baseline wound surface area was 9.29cm<sup>2</sup>; all of the ulcers had granulation tissue covering over 50% of the wound bed. Three patients healed in an average of 4 weeks, while for the sample as a whole the mean baseline wound area reduced by mean of 56%. Four dressing-related adverse events were reported: infection (n=1), eczema (n=1), ulceration (n=2).<sup>156</sup>

Foam dressings are often used in the management of low to moderately exuding chronic wounds, including leg ulcers.<sup>157</sup> Although foam dressings differ in composition and clinical performance varies between brands, there is as yet no strong evidence that any single neutral foam dressing is more efficacious than the others. Indeed, a RCT that compared two foam dressings (Allevyn Hydrocellular, Smith & Nephew versus Mepilex, Mölnlycke Health Care) plus compression in the management of 156 patients with chronic venous leg ulcers reported similar healing rates in both groups.<sup>158</sup>

Urgo has risen to the challenge and has conducted an unique double-blind RCT comparing the efficacy of UrgoStart (foam dressing with NOSF) with that of a 'neutral' foam (UrgoCell TLC) in the management of chronic venous leg ulcers under compression.<sup>159</sup> Efficacy was based on the reduction in wound surface area, measured by planimetry, after 8 weeks of treatment. Secondary outcomes were the percentage of ulcers whose surface area reduced by 40% after 8 weeks, tolerability, acceptability and effects of the dressings on quality of life. The study population, which comprised 187 patients (inpatients and outpatients) from 45 centres, was randomised to receive one of the two foam dressings.

Results show that both groups were comparable at baseline. The average baseline wound surface

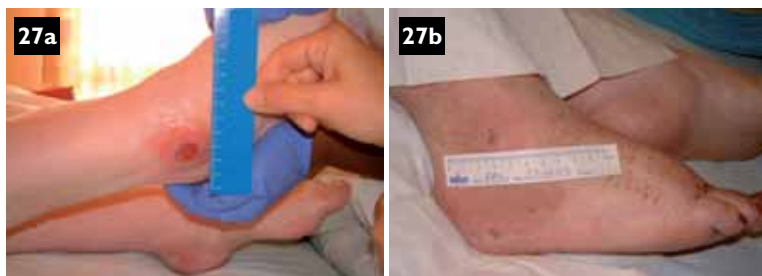
area was 16.8 ± 15.7cm<sup>2</sup>; 54.5% of ulcers had a surface area larger than 10cm<sup>2</sup>. After 8 weeks, there was a highly significant difference between the two groups in the median percentage reduction in ulcer area: 58.3% for UrgoStart versus 31.6% for Urgocell TLC group (p=0.0021). The difference in median absolute values after 8 weeks was also highly significant in favour UrgoStart: 6.13cm<sup>2</sup> versus 3.26cm<sup>2</sup> (p=0.0038). Furthermore, significantly more of the ulcers in the UrgoStart group had reduced by 40% in surface area by then: 65.6% versus 39.4% (p=0.0003), which as stated is highly predictive of wound closure at 20–24 weeks. Rate of healing was more than twice as fast with NOSF: 10.83mm<sup>2</sup>/day versus 5.15mm<sup>2</sup>/day (p=0.0056).

In terms of the other outcome measures, no significant differences were observed in terms of tolerability and acceptability. However, there was a significant difference in favour of Urgostart in two of the five quality-of-life parameters assessed (using the EuroQuol 5D questionnaire): pain (p=0.022) and anxiety-depression (p=0.037).<sup>159</sup> For the first time, a foam dressing (UrgoStart) has demonstrated a superior efficacy over another foam dressing.

## Pressure ulcers

Pressure ulcers are caused by unrelieved pressure, shear, or friction. Increased age, reduced mobility, impaired nutrition, vascular disease, incontinence and the skin condition at baseline consistently emerge as risk factors,<sup>160</sup> although no one factor can be identified as having more weight over another. Given these risk factors, patients are often elderly and have impaired mobility and comorbidities. While the gold standard treatment is pressure redistribution, wound dressings also play a central role<sup>161</sup> as they can be used to maintain a moist environment, prevent critical colonisation or infection and, as in the case of TLC-NOSF dressings, maintain a healthy balance of proteases and cytokines within the wound.

As yet, only one study — recently completed and thus still unpublished — has assessed the efficacy and tolerability of UrgoStart on pressure ulcers.<sup>162</sup> It found that the foam dressing helped to promote healing in wounds with a poor prognosis, in this case category 3 pressure ulcers (EPUAP classification). This 6-week open multicentre study involved 25 patients with pressure ulcers, which were mainly located on the heels and sacrum. Patients underwent standardised weekly clinical, planimetric (area tracings) and photographic assessments. The mean baseline sur-



**27a** A 61-year-old patient presenting with a pressure ulcer of 12 months' duration (Fig 27a). The same ulcer after 5 weeks of treatment with UrgoStart (Fig 27b)



face area of 6.56cm<sup>2</sup> reduced to 4.19cm<sup>2</sup> at week 6, a mean reduction of 43.8%. Three ulcers healed completely in a mean of 27 days. Two adverse events (overgranulation) occurred in the same patient.

### Diabetic foot ulcers

Diabetic foot ulcers are the most common cause of non-traumatic lower limb amputation in the western world, with the risk being 15–46 times higher in patients with diabetes than in those without the disease.<sup>163,164</sup> Amputation is normally a result of complications following ulceration. Aetiology can be multifactorial, including peripheral arterial disease, sensory and autonomic neuropathy, structural deformity and limited joint mobility. Treatment centres on offloading to avoid further trauma, but again dressings are required to promote an environment that promotes healing. Indeed, biopsies have shown that the concentration of MMPs is up to 65-fold higher in diabetic foot ulcers than in traumatic wounds, with MMP-2 and MMP-9 being six- and 14-fold higher respectively.<sup>165</sup>

A dressing that can inhibit MMPs, and thus rebalance the relationship between MMPs and tissue inhibitors of metalloproteinases (TIMPs) will therefore be a useful adjunct to offloading.

A recently completed and thus still unpublished multicentre clinical study involving 34 patients with University of Texas classification grade 1A (i.e. non-infected, non-ischaemic, superficial) neuropathic plantar wounds ulcers showed that TLC-NOSF (UrgoStart Contact) promoted healing and was well accepted by both practitioners and patients. Baseline surface area was 2.7 ± 2.4cm<sup>2</sup> (range 0.46–8.63, median 1.85). Planimetric data (for 32 patients) showed that 10 wounds had healed after 12 weeks of treatment, while the mean reduction in wound surface area for the entire group was 62.7 ± 49.8% (median 82.7). The above 10 wounds healed in a mean of 61.7 days ± 21.4 (range 31–91, median 57.5). Final evaluation showed that a large majority of wounds either healed (31%) or improved (50%). Of the remainder, 13% stagnated and 6% deteriorated. Three local adverse events were recorded (aggravation of wound [n=1] and maceration [n=2]), but none led to discontinuation with treatment.

High scores were reported for the acceptability parameters, with the dressing being regarded as easy/very easy to remove at 99.7% of dressing changes, with hardly any reports of adherence or bleeding. Application was considered easy/very easy in 96% and conformability very good/good in



*Diabetic foot ulcer (Fig 28a). Healing was achieved after 10 weeks with UrgoStart (Fig 28b)*

85% of dressing changes, respectively.<sup>166</sup> Dressing conformity is an important consideration for diabetic foot ulcers as the dressing will need to stay in place under footwear while also being exposed to pressure when the patient is walking.<sup>166</sup>

### Arterial ulcers

Prolonged peripheral arterial occlusive disease leads to poorly nourished skin, increasing its vulnerability to trauma and infection. The poor supply of oxygen and nutrients can severely impair healing.<sup>167</sup> Treatments include medication to promote arterial perfusion, angioplasty or reconstructive surgery.

TLC-NOSF technology has been shown to promote healing in arterial leg ulcers that have not responded to revascularisation procedures including angioplasty and stenting. This case series, which as yet is available as a poster, involved 15 patients with stage IV peripheral arterial disease who had 17 wounds that had not healed for a mean of 9.8 months (range 2–34) after the revascularisation procedure. Sixteen wounds had been treated with at least two different dressings before the TLC-NOSF regimen (UrgoStart) was started. The average baseline wound size was 22.5cm<sup>2</sup> (range 3–74.6) All wounds were treated with UrgoStart for an average of 6.5 weeks (range 2–14). Thirteen wounds either healed (n=7) or improved (n=6), with a mean surface area reduction of 72% (range 49–91). One wound remained static and three wounds deteriorated: two because of local infection and one because of maceration following cutting of the dressing.<sup>168</sup>

### Acute wounds that have become chronic

These wounds are often traumatic in origin, and so are particularly prone to infection due to the presence of devitalised tissue, foreign bodies and bacteria. Risk factors for delayed healing include old age, poor vascular supply and comorbidities such as



**A 93-year-old woman presenting with a tibial laceration (Fig 29a). Healing was achieved after 9 weeks with UrgoStart Contact (Fig 29b)**

diabetes. TLC-NOSF dressings have been studied and proved to be effective in a number of such wounds, including:

- Dehiscid abdominal wounds<sup>169-171</sup>
- Pre-tibial laceration<sup>172</sup>
- Post-traumatic or post-surgical wounds<sup>173-177</sup>
- Pilonidal sinus.<sup>176</sup>

### Conclusion

This supplement demonstrates that there is extensive evidence, from *in vitro* to double-blind RCTs,

to support the TLC dressing range. The pre-clinical scientific data clearly shows that TLC dressings promote fibroblast proliferation and collagen production, two of the prerequisites for healing. This is supported by clinical studies, much of which reflect the challenges of real-life practice, showing that use of TLC dressings either achieves full wound closure or accelerates healing in a broad range of wound types. In addition, the tolerability and acceptability data consistently show that the dressing scored highly in terms of comfort and ease of use, with the minimal pain and bleeding experienced at dressing removal reflecting its non-adherent properties.

Some dressings in the TLC range contain silver or the MMP inhibitor, NOSF. Again, both *in vitro* and clinical evidence provide strong efficacy data, showing that they promote healing in chronic wounds and/or those that are critically colonised or infected.

Taken as a whole, the evidence on the TLC dressing range shows that it meets the twin objectives of promoting wound healing and improving quality of life.

**Table 6. Summary of main outcomes of clinical studies involving the use of TLC-NOSF dressings**

Study	Sample size	Wound types	Product used	Outcome measures	Key results
Munter et al. <sup>148</sup>	2052 patients	Chronic wounds of various aetiologies	UrgoStart	Efficacy, acceptability and tolerability	Median surface area reduced from 10cm <sup>2</sup> to 2cm <sup>2</sup> (75%) over 8 weeks. 81% never/rarely/occasionally experienced pain at dressing removal. 94% of patients were very satisfied/satisfied with the dressing. Only 1.5% of patients experienced adverse events.
Kerihuel et al. <sup>149</sup>	1185 patients	Chronic wounds of various aetiologies	UrgoStart	Efficacy	Assessment tool scores were used to represent the overall condition of the wound. Scores reduced by a mean of 50% for all wound types over a mean of 44 days.
Schmutz et al. <sup>155</sup>	117 patients	Chronic venous leg ulcers	UrgoStart Contact versus Promogran	Efficacy, tolerability and acceptability	Median wound area reduced by 54.4% and 12.9% at 12 weeks in the UrgoStart Contact and Promogran groups respectively (p=0.0286). 56% of ulcers in the UrgoStart Contact group achieved a 40% reduction in surface area versus 35% for Promogran (p=0.022). Mean healing rate was also significantly higher in the UrgoStart Contact group (p=0.029). Pain and infection occurred more frequently in the control group: 18 versus 5. Acceptability results were better in the UrgoStart Contact group.
Meaume et al. <sup>159</sup>	187 patients	Chronic venous/mixed aetiology leg ulcers	UrgoStart versus Urgocell TLC	Efficacy, tolerability and acceptability	There was a highly significant difference between the two groups in the median percentage reduction in ulcer area after 8 weeks: 58.3% for UrgoStart versus 31.6% for Urgocell TLC (p=0.0021). The median ulcer size at week 8 in wounds treated with UrgoStart was half that of those treated with the comparator: 3.26cm <sup>2</sup> versus 6.13cm <sup>2</sup> (p=0.0038). Significantly more ulcers in the UrgoStart group reduced by 40% in surface area: 65.6% versus 39.4% (p=0.0003). The healing rate was twice as fast with UrgoStart: 10.83mm <sup>2</sup> /day versus 5.15mm <sup>2</sup> /day (p=0.0056). There were no significant difference between the groups in terms of tolerability and acceptability.





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