ACELLULAR MATRICES FOR THE TREATMENT OF WOUNDS

an expert working group review
FOREWORD

Currently there is no definitive paper or guideline on the use of acellular matrices in acute and chronic wounds. To begin to address this, an expert working group convened in New York, USA in July 2010 to review current knowledge of acellular matricies and their rationale for use.

The recommendations in this document are based on the consensus opinion of the group and the available evidence. They aim to help both generalist and specialist clinicians decide when to use and how to select an appropriate acellular matrix. This document also aids understanding of how these products may be classified within the rapidly growing range of tissue-engineered products that are indicated for wound healing.

Acellular matrix products can be used in a wide variety of applications, including burns and reconstructive surgery, soft tissue and abdominal wall repair and as internal implants for orthopaedic use in joint resurfacing and tendon repair. This document focuses on the use of acellular matrices (or scaffolds) in hard-to-heal wounds such as diabetic foot ulcers, venous leg ulcers and pressure ulcers.

Dr Gerit Mulder
Acellular matrices and wound healing

Wound healing is a dynamic process involving interactions between cells, extracellular matrix (ECM) and growth factors that reconstitutes tissue following injury.1

The extracellular matrix (ECM) plays an important role in tissue regeneration and is the major component of the dermal skin layer. The composition of ECM includes proteoglycans, hyaluronic acid, collagen, fibronectin and elastin. As well as providing a structural support for cells, some components of the ECM bind to growth factors, creating a reservoir of active molecules that can be rapidly mobilised following injury to stimulate cell proliferation and migration.2 In many chronic wounds, increased levels of inflammatory cells lead to elevated levels of proteases that appear to degrade the ECM components, growth factors, protein and receptors that are essential for healing.3

Recognition of the importance of the ECM in wound healing has led to the development of wound products that aim to stimulate or replace the ECM. These tissue-engineered products comprise a reconstituted or natural collagen matrix that aims to mimic the structural and functional characteristics of native ECM.4 When placed in the wound bed, the three-dimensional matrix provides a temporary scaffold or support into which cells can migrate and proliferate in an organised manner, leading to tissue regeneration and ultimately wound closure.

It is important to differentiate native ECM, a key component of the dermal layer, from a collagen matrix product that is applied to a wound bed

Tissue-engineered products may be cellular (contain living cells) or acellular (biologically inert) and sourced from:

- **Biological** tissue:
  - animal (eg equine/bovine/porcine)
  - human (eg cadaveric skin)
  - plant (eg containing oxidised regenerated cellulose/collagen)

- **Synthetic** materials

- **Composite** materials (containing two or more components, which may be biological or synthetic).

The terms biological (ie synthesised by nature), synthetic (ie derived from man-made materials) or composite (ie derived from a mix of materials of various origin) are preferable to general terms such as ‘natural’, ‘organic’, or ‘biomatrix’.

Acellular matrices may be animal- or human-derived, with all cells removed during manufacture, or they may be synthetic or composite, where cells are naturally not present from the outset. These matrices or tissue scaffolds provide a collagen structure for tissue remodelling, while the removal of viable cells aims to minimise or prevent an inflammatory or immunogenic response.5

Given current knowledge, the ideal acellular matrix is one that most closely approximates the structure and function of the native ECM it is replacing
Different types of tissue-engineered products exist and there is confusion around the terminology used. Products may be classified as skin substitutes, xenografts, allografts or collagen dressings. Alternatively, these products may be described as biological dressings in that they function as a protective wound cover. However, while most wound dressings need to be changed frequently, matrices provide a scaffold for tissue repair and therefore must remain in the wound for a sufficient length of time.

Product classification is determined by the product’s primary mechanism of action. In Europe, most acellular matrix products are classified as Class III medical devices and must be identified by the CE mark. In the US, the FDA regulates these as medical devices that require clearing via the 510(k) process to demonstrate safety (for definitions of medical devices in the US and Europe see Table 1). Those sourced from donated skin are classified as human bank tissue (eg Alloderm®, LifeCell). However, many new products do not fit into existing categories and matters are further complicated when a product combines two or more regulated elements (ie drug, device or biological product). At present there are no unified controls for combination products.

One way in which acellular matrices may function is as a biological modulator. This term was introduced by the consensus group to help overcome confusion around different products. A biological modulator is a material or substance derived from biological or synthetic sources that influences biological processes such as wound healing.

### Table 1 | Definition of ‘medical device’

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<tr>
<th>US Food and Drug Administration</th>
<th>European Union Legal Framework</th>
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| “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is:  
- recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,  
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or  
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.”  
“Section 201(h) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321(h))” | “Any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for purpose of:  
- diagnosis, prevention, monitoring, treatment or alleviation of disease  
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap  
- investigation, replacement or modification of the anatomy or of a physiological process  
- control of conception  
and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted function by such means;”  
Excerpt from Directive 2007/47/EC |
While tissue-engineered products offer increasingly important strategies for managing complex wounds, potential drawbacks include the risks of infectious agent transfer and immunological rejection. Furthermore, the manufacturing process, transport, storage, etc, of these products have major cost implications, which mean that their current clinical use remains limited. However, the development and introduction of more advanced products and better understanding of individual product characteristics will lead to better outcomes, enabling appropriate product selection and clearer assessment of cost-effectiveness.

In addition to clinical considerations, when selecting an acellular matrix product, clinicians should consider the following device-specific issues:
- Is the product animal/human-derived, synthetic or composite?
- How is the product manufactured?
- What is the rate of degradation of the product?
- Is the product sterile or aseptically processed?

Concerns for the clinician and patient include:
- Risk of possible viral transmission/infection, rejection/allergenic reaction
- Religious/cultural/social issues (eg objections to the use of animal products)
- Impurity of products (eg non-sterile).

**COMPOSITION**
Acellular matrix products differ mainly in the source of cells and tissue materials and methods used during manufacture. A variety of animal- and human-derived products are available:

**Products derived from animal sources** (xenografts) are developed by harvesting living tissue (eg dermis, small intestine submucosa, pericardium, etc) from various donor animals (eg porcine, equine or bovine) at different stages of development. The tissue materials are subsequently processed to remove the cells (decellularisation), leaving the collagen matrix. Products derived from animal sources may consist of the tissue scaffold only (eg Unite® BioMatrix Collagen Wound Dressing, Synovis) or may be combined with synthetic materials to create a composite product (eg INTEGRA® Bilayer Matrix Wound Dressing, Integra LifeSciences).

**Products derived from human sources**, ie donated human cadaver skin (allografts), undergo various processes to remove the cells and deactivate or destroy pathogens (eg AlloDerm®, Lifecell; GraftJacket®, Wright Medical).

It is important that healthcare professionals know the constituents of individual products. They have a duty to explain to patients the nature and purpose of any proposed treatment, along with any risks attached. Where appropriate, informed consent should be obtained.

**MANUFACTURING PROCESS**
Acellular matrices are engineered using a range of chemical and mechanical processes. The ultimate goal is to remove all cellular components using a non-damaging process that maintains the structure and function of the source tissue. The more compatible the final product is to host ECM, the less likely it will elicit an adverse reaction. The steps used in the manufacture of individual products, however, may degrade the structure of the source tissue or strip out growth factors that are bound to ECM components. This may result in rapid degradation and reabsorption of the matrix by the host and lead to scar tissue formation. An adverse reaction...
may be indicated by inflammation with accumulation of cells around the edges of the matrix, preventing cellular or vascular infiltration (encapsulation)\(^8\). The ideal response is minimal inflammation and gradual degradation of the matrix over time with complete integration with the host tissue. How a product is manufactured may therefore be more important to product function than the source, species and location from which the tissue has been taken. Manufacturing may involve the following processes.

**Crosslinking**

The process of stabilising collagen (crosslinking) involves the creation of links between individual strands of collagen. This inhibits degradation of the collagen by proteases (eg matrix metalloproteinases [MMPs]) and prolongs its presence in the wound\(^5\). The nature of the crosslinking bonds varies according to the processes used. Some traditional methods using chemical (eg aldehydes) or mechanical processes, heat or radiation may allow very little control over the degree of crosslinking. Such processes may produce bonds that are very short and inflexible, which may inhibit cell migration and vascular regeneration, while residual chemicals in the product may produce an inflammatory response causing the matrix to be rapidly reabsorbed\(^5\).

Newer processes have been shown to produce elastic crosslinks that are more pliable and less prone to enzymatic breakdown\(^4\). Data from animal models also suggest that if a matrix is flexible rather than rigid, cells can migrate more rapidly and proliferate in an organised manner similar to normal tissue regeneration\(^9\). The type of crosslinking may therefore have a direct effect on product durability in the wound and treatment outcomes\(^10\). In a published case study, a stabilised xenograft was shown to withstand enzyme activity in a patient with a chronic ulcer and high level of infection and inflammation\(^10\).

In comparison, non-crosslinked products may be degraded by proteases more quickly and replaced by scar tissue\(^5\). However some next generation products have been shown, when implanted, to be associated with rapid revascularisation without scar tissue formation and a low inflammatory or immunological response, but are not crosslinked\(^11\).

**Sterilisation**

Sterilisation is important to reduce the risk of disease transmission and is required for FDA clearance of all animal-derived products. However, residual chemicals used during the sterilisation process (eg ethylene oxide [EtO] or gluteraldehyde) may produce an inflammatory response within the host tissue and radiation may damage the matrix, causing it to be broken down and absorbed too quickly\(^5\). Newer sterilisation methods using a tested liquid chemical (ethylene dichloride [EDC]) are being developed that preserve the collagen structure in the tissue while eliminating the risk of disease\(^5\). Most human-derived acellular products are aseptically processed and are not terminally sterile.

**Preservation and shelf-life**

The preservation media or solution used will affect product stability and overall shelf-life. In addition, this may be affected by the regulatory conditions in individual countries as well as the known chemical degradation of the product. Shelf-life may vary from 18 months to five years. Products that have off-the-shelf availability, can be stored at room temperature and require minimal preparation, offer advantages to both clinicians and patients in decreasing operating time and avoiding donor site morbidity\(^23\).

A saline rinse prior to application may help to minimise an inflammatory response in the host tissue by removing any residual chemicals used in the preservation process. Manufacturers’ directions for preparation and use should be followed
Understanding mode of action

The mechanisms by which acellular matrices promote wound healing remain to be elucidated and there is ample scope for further research.

It is known from the literature that chronic or hard-to-heal wounds are characterised by a disrupted or damaged ECM that cannot support wound healing. Treatment strategies that are designed to replace the absent or dysfunctional ECM may be beneficial\(^3\). As a result, there is renewed interest in collagen-based advanced wound care products.

In chronic wounds, there is an excess of MMPs and reduced growth factor activity. Together these result in the degradation of the ECM. For wound healing to occur the balance between protease and growth factor activity needs to be adjusted\(^3\). Research has demonstrated that topically applied collagen-based products can initiate wound healing by binding to and inactivating harmful proteases, while encouraging angiogenesis and formation of granulation tissue\(^1^4\).

Current information about the mode of action of acellular matrices is largely based on preclinical data, mainly from research focusing on a porcine-derived small intestinal submucosa (SIS) wound matrix. These data show that matrices may:
- Act as a scaffold to support cell ingrowth and granulation tissue formation\(^1^5\)
- Have receptors that permit fibroblasts to attach to the scaffold\(^1^6\)
- Stimulate angiogenesis\(^1^7\)
- Act as a chemoattractant for endothelial cells\(^1^8\)
- Contain/protect growth factors\(^1^9\).

When used as an implant, the acellular matrix appears to be fully incorporated into the wound. However, when used in a chronic wound, the matrix is eventually displaced and is not fully incorporated. As such, the role of acellular matrices in chronic wounds is not fully understood. It has been suggested that they act as a biological cover that modulates the wound environment to promote normal wound healing\(^2^0,2^1\) (Figure 1).

**Figure 1** Suggested mode of action of collagen-based acellular matrix products\(^2^0,2^1\)

Note: the optimal response will be achieved using a matrix that is closest to the tissue it is replacing.

**Biological modulator**

A material or substance derived from biological or synthetic sources that influence biological processes such as wound healing.

**Chronic wounds contain high levels of MMPs which can:**
- Degrade the ECM and growth factors
- Increase inflammatory response
- Reduce cell responsiveness in the wound
- Delay wound healing

**Treat using an acellular matrix that closely resembles native ECM. This may act as a scaffold for:**
- MMPs to bind to and break down collagen in the product
- Epithelial cells, fibroblasts and vascular endothelial cells to migrate into and proliferate
- Reduced levels of MMPs to be released back into wound as collagen matrix breaks down, rebalancing protease and growth factor levels in the wound

**Enhanced wound healing environment, where matrix has been replaced by new collagen with remodelling of ECM**

In chronic wounds, an acellular matrix wound product should be in as complete contact as possible with the wound surface to be effective.
Rationale for use

Currently available acellular wound matrix products are listed in the Appendix, page 13. It should be noted that this information is taken directly from the manufacturers’ websites, and anyone using these products should always consult the specific manufacturer’s instructions, taking into consideration important factors, such as allergy and wound infection.

All products should be used in conjunction with manufacturers’ instructions and/or recommendations

Acellular matrices should be considered in wounds that are unresponsive to traditional wound management modalities or present as a complex surgical wound. Factors to consider will be dependent on the wound type, underlying aetiology, patient suitability and treatment goal. In a non-healing chronic wound (eg diabetic foot ulcer), for example, an acellular matrix may be selected to replace the damaged ECM, fill the defect and optimise the wound environment for healing.

The use of different products is influenced by a number of external factors, including availability, single or multiple applications, ease of use and cost/reimbursement. In addition, it is important to consider the clinical setting in which the matrix is to be applied (eg in the operating theatre or outpatient clinic) as well as the expertise and level of training required (Table 2).

**APPLYING THE MATRIX**

The following should be considered prior to application:
- Protocol for first application (eg wound bed preparation/TIME22,23)
- Methods of attachment (ie sutures, Steri-strips or staples)
- The use of appropriate dressings to cover the matrix.

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**Table 2 | Experienced practitioner tips for each stage of the procedure**

<table>
<thead>
<tr>
<th>Pre-application</th>
<th>Application</th>
<th>Post-application (maintenance period)</th>
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| ■ Assess patient suitability  
- Perform a comprehensive assessment of the patient and the wound  
- Establish a diagnosis  
- Address social and cultural issues | ■ Prevent/minimise product contamination and bacterial overgrowth  
- Ensure correct handling of product according to manufacturer’s instructions  
- Avoid intraoperative recontamination (eg change gloves between procedures) | ■ Disrupt as little as possible  
- Minimise dressing changes (should not be disturbed for at least 1 week. Early inspection increases the risk of displacement)  
- If displaced, remove and apply a new matrix  
- Staples should not be left in for more than 1 week (7 days)  
- Sutures can be left for a maximum of 14 days  
- Steri-strips can be left for 1–2 weeks  
- Trim the edges of the product that dry and lift during the healing process | ■ Secure matrix using staples; Steri-strips (eg for patients with sensitive surrounding skin); sutures (caution is needed not to lift or pucker skin/disrupt product). Consider anaesthesia  
- Size matrix - excess matrix should be trimmed using scissors (see also Use in large wounds p8)  
- Ensure appropriate wound dressing selection  
- The matrix should be covered with a non-adherent primary dressing, bolster and/or padding (eg in moderate to heavily exudating wound)  
- Use a secondary dressing to hold the matrix and wound dressings in place  
- Consider the use of an appropriate topical antimicrobial  
- Consider fenestrated (meshed) product, eg:  
- when the wound has a large surface area or is very deep, requiring negative pressure wound therapy (NPWT)  
- when it is necessary for fluid to drain, especially if heavily exudating | ■ Exclude ischaemia/infection and uncontrolled bacterial burden/allergy  
- Address underlying aetiology to maximise healing potential (eg control exudate/bacterial burden; ensure adequate offloading/compression/pressure reduction; reduce steroids/inflammation)  
- Perform adequate and appropriate wound bed preparation (eg debridement)  
- Ensure patient concordance (eg those with diabetic foot problems, those requiring compression) |
The landmarks towards achieving a successful outcome include:

- No clinical signs of infection or bioburden, eg purulence, sliminess, unexpected malodour (Note: some products that contain keratin produce an odour when wet)
- Formation of granulation tissue, reduction in wound size and re-epithelisation
- Removal of the method of attachment (ie staples, sutures or Steri-strips).

When the matrix is still present in the wound bed, it may produce a different appearance to normal granulation (eg the tissue may not have the typical bright red appearance; if silver dressings are used, it may look dry, silver/black in colour with no signs of infection). It is important to know what the wound should look like when it is reviewed post-application and to be able to identify when the wound is progressing normally (Figure 4) and when further intervention is needed (Figure 5).
Complications
The actions below are recommended should the following complications occur:
- **Infection:** remove acellular matrix, control the infection and apply a new matrix following adequate wound bed preparation.
- **Detached or displaced matrix:** remove matrix and assess to establish the reasons for failure. Perform adequate wound bed preparation before applying a new matrix.
- **Excessive inflammation/allergic reaction:** remove and do not reapply a new matrix.
- **Failure to heal/lack of effect:** reassess the wound and the patient. When the wound is not healing the matrix may be displaced and there may be an increase in wound size.

A significant increase in pain after application may indicate a reaction to the product or infection

Use in large/exuding wounds
When the wound is very large, multiple sheets may be needed to cover the entire wound bed. There should be slight overlap with the wound edges and the matrix may need to be secured to reduce risk of displacement. Many chronic wounds are often accompanied by infection and excessive amounts of exudate, making matrix fixation difficult. A fenestrated (meshed) acellular matrix can be used to allow the fluid to drain from the wound. The level of exudate will affect the choice of secondary dressing for an optimal moist wound environment. If there is excessive moisture, such as maceration of the wound edges, the matrix should not be applied until the exudate level has been controlled.

Use with adjunctive therapies
The use of an acellular matrix combined with other treatments may permit progression to the next stage. For example, negative pressure wound therapy (NPWT) may help to control excessive exudate and hold the matrix in place to maximise contact with the wound bed. When using NPWT a fenestrated (meshed) matrix should be application and a non-adhesive contact layer must be placed between the matrix and the foam dressing.

It is important to know whether other products can be used successfully in combination with the matrix

Achieving optimal outcomes
Appropriate and careful product selection is critical to achieve optimal patient outcomes. The decision to use a particular product may be based on a number of structural, biological and clinical factors (Table 3).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>The ideal properties of an acellular matrix for hard-to-heal wounds</th>
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<tbody>
<tr>
<td><strong>Structural</strong></td>
<td><strong>Biological</strong></td>
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<tr>
<td>Closely resembles native ECM (eg retains natural architecture and key components for wound healing)</td>
<td>Provides barrier to infection (i.e. innate immunity)</td>
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<tr>
<td>Minimal storage/preparation needed and long shelf-life</td>
<td>Resistant to proteolytic enzyme degradation</td>
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<tr>
<td>Terminally sterile (ie cannot transmit viral or other agents)</td>
<td>Promotes optimal cell activity for rapid revascularisation and tissue regeneration</td>
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Evaluating the clinical evidence for use

Acellular matrices have been used extensively in burns, when the primary goal is to restore function and have an expanding role in the treatment of chronic wounds. There is also an increasing range of acellular products for use as surgical implants in abdominal, plastic and reconstructive surgery.

Understanding the clinical advantages and limitations of individual products is crucial to effective use and patient outcomes. However, there is currently limited published data that reaches a sufficient level of evidence (see Box 1: Wound Healing Society guidelines for the treatment of chronic wounds) and few comparisons of products in different indications, in particular chronic and problematic wounds that are hard to heal.

HARD-TO-HEAL WOUNDS

The most common types of wound that fit into this category are:

- Diabetic foot ulcers
- Lower extremity venous ulcers
- Ulcers of mixed aetiology
- Pressure ulcers.

Appropriate treatment using an acellular matrix may result in faster or more complete healing than standard treatment in hard-to-heal wounds. This is further supported by a retrospective evaluation of the use of an acellular collagen product derived from equine pericardium in chronic full-thickness wounds of varying aetiology. Despite being unresponsive to previous treatment approaches, all wounds achieved complete closure without complications.

The low complication rate supports the theory that acellular matrices are less likely to cause an immunological response than cellular products that contain cross-species cellular components. Both acellular xenografts and allografts appear to modulate the wound environment by reducing the inflammatory activity to stimulate tissue regeneration. However, more extensive and controlled clinical studies are needed to provide a better understanding of their mechanisms of action and role in the treatment of hard-to-heal wounds.

Diabetic foot ulcers (DFUs)

A number of studies have been performed in patients with diabetes and lower extremity ulcers (foot, ankle or leg) using porcine collagen derived from small intestine submucosa (SIS) and a human-derived dermal matrix (Table 4). A more recent prospective series has studied the use of equine pericardium in neuropathic diabetic foot ulcers (DFUs). These studies suggest acellular matrices may promote wound healing when compared to conventional treatments. However, there are no large-scale studies and it is difficult to make direct comparisons of the results. All studies have shown that these products are safe and can achieve complete wound closure in both partial and full-thickness wounds, including when bone and/or tendon are exposed (Table 4). In addition, they may be used with split-thickness skin grafts to achieve complete closure in deep wounds. Long-term studies are needed to assess the quality of the regenerated tissue and re-ulceration rate in all wound types.

Prior to application, appropriate debridement of non-viable tissue is vital for optimal wound healing. For deep wounds that are irregular, or demonstrate tunnels or undermining, a flowable tissue matrix (micronised) can be applied with a syringe into tunnels or extensions. When using a sheet-form matrix, this will need to be cut to size so that it overlaps the wound margins. In addition, NPWT may be used in combination with an acellular matrix to promote healing in the management of non-healing diabetic foot ulcers. Appropriate offloading is also necessary to achieve wound healing.
Table 4 | Summary of evidence for diabetic foot wounds

<table>
<thead>
<tr>
<th>Product used</th>
<th>Wound type</th>
<th>Publication</th>
<th>Type of study</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Human-derived allograft (GraftJacket®) vs hydrogel wound dressing (Curasol®)</td>
<td>Diabetic lower extremity wounds</td>
<td>Briggs SA et al Orthopedics 2004; 27 (1 Suppl): s145-49</td>
<td>Prospective, randomised controlled, multicentre (n=73)</td>
<td>All patients were treated with sharp debridement. 20 patients were given one application of the allograft. At 4 weeks, there was a statistically significant reduction in ulcer size in the allograft treated group compared with the debridement only group (controls); wound closure was 73% vs 34%. At 12 weeks, 85% of patients in the allograft group were healed compared with only 5% in controls.</td>
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<td>Forcine small intestine submucosa xenograft (Oasis®) vs becaplermin wound gel (Regranex®)</td>
<td>DFUs (chronic, full-thickness)</td>
<td>Niezgoda et al. Adv Skin Wound Care 2005, 18(5): 258-66</td>
<td>Prospective, randomised controlled, multicentre (n=73)</td>
<td>At 12 weeks 49% (18/37) of patients receiving SIS xenograft were healed vs 28% (10/36) of patients receiving daily treatment of the gel (p=0.055). Subgroup analysis showed that in patients with wounds on the planter surface, 53% of SIS xenograft patients healed compared with 14% of gel-treated patients. No significant difference was found in mean time to healing between treatment groups (p=0.245).</td>
</tr>
<tr>
<td>Human-derived allograft (GraftJacket®) + moist wound therapy</td>
<td>DFUs (neuropathic)</td>
<td>Martin BR et al. Int Wound J 2005; 2(2): 161-65</td>
<td>Prospective case series (n=17)</td>
<td>82.4% (14/17 of wounds) measuring mean 8.9±3.2 cm² healed in the 20-week evaluation period.</td>
</tr>
<tr>
<td>Silicone membrane/ reconstituted bovine collagen matrix (INTEGRA™ Bilayer Matrix) and split-thickness skin grafts (STSG) to replace silicone layer</td>
<td>DFUs (with exposed bone and tendon)</td>
<td>Silverstein G. J Foot Ankle Surg 2006, 45(4):28-33</td>
<td>Retrospective case series (n=5)</td>
<td>All 5 patients with diabetes had extensive soft tissue defects. Following surgical debridement a non-fenestrated version was applied. Dressing changes were carried out weekly. Shock absorbent dressing was used. At 12 weeks 39% (2/5) of wounds were healed. No significant differences were observed for matrix incorporation, 100% granulation and complete healing. Mean time to complete healing was 13.8 weeks.</td>
</tr>
<tr>
<td>Human-derived allograft (GraftJacket®) + mineral oil soaked compression bandage</td>
<td>Diabetic lower extremity wounds</td>
<td>Briggs SA. Int Wound J 2006; 3(3):181-87</td>
<td>Prospective, randomised controlled (n=28)</td>
<td>All patients were treated with sharp debridement. At week 16: 12/14 allograft treatment group healed vs 4/14 in control group. Uner area, depth, volume and number of ulcer healed achieved statistical significance in favour of the allograft treatment arm (p=0.001).</td>
</tr>
<tr>
<td>Human-derived allograft (GraftJacket®) + hydrogel wound dressing (Curasol®)</td>
<td>Diabetic lower extremity wounds</td>
<td>Winters CI, et al. Adv Skin Wound Care 2008; 21(8): 375-81</td>
<td>Retrospective multicentre (n=75)</td>
<td>Total 100 wounds of which 91 (91%) in 67 patients healed. Patients treated with multiple modalities to attain wound closure. No significant differences were observed for matrix incorporation, 100% granulation and complete healing. Mean time to complete healing was 13.8 weeks.</td>
</tr>
<tr>
<td>Human-derived allograft (micronised) (GraftJacket® Xpress Scaffold)</td>
<td>DFUs with sinus tract</td>
<td>Briggs SA et al. Foot Ankle Spec 2009; 2(2):67-72</td>
<td>Retrospective series (n=12)</td>
<td>At 12 weeks 10/12 patients achieved complete healing. Average time to healing was 8.5 weeks.</td>
</tr>
<tr>
<td>Human-derived allograft (GraftJacket®) + silver-based non-adherent dressing vs standard of care</td>
<td>DFUs</td>
<td>Reyzelman et al. Int Wound J 2009; 6(3): 196-208</td>
<td>Prospective randomised controlled multicentre (n=86)</td>
<td>At 12 weeks study in which 47 patients were randomised to allograft group and 39 patients to control group. Complete healing was 69.6% (n=32) and 53.2% (n=21) for allograft and control groups respectively. No significant difference was found in mean time to healing between treatment groups (p=0.05). Subgroup analysis showed that in patients with wounds on the planter surface, 53% of SIS xenograft patients healed compared with 14% of gel-treated patients. No significant difference was found in mean time to healing between treatment groups (p=0.245).</td>
</tr>
<tr>
<td>Silicone membrane/ reconstituted bovine collagen matrix (INTEGRA™ Bilayer Matrix)</td>
<td>Infected DFU with exposed bone and tendon</td>
<td>Clerici et al. Int J Lower Extrem Wounds 2009; 8(4):289-92</td>
<td>Case report</td>
<td>62 year old female patient with an acute deep foot infection. Following surgical debridement, NPWT and amputation of the distal metatarsal, a collagen bilayered matrix was applied. At 8 weeks there was complete healing. A 3-month review revealed no stump complications with preservation of maximal foot length.</td>
</tr>
<tr>
<td>Equine pericardium xenograft (Unite®)</td>
<td>DFUs (neuropathic)</td>
<td>Fleischill et al. J Am Pod Med 2009; 99(4); 301-05</td>
<td>Prospective pilot case study</td>
<td>23 consecutive patients with 34 foot wounds. Surgical debridement prior to application of xenograft. At time of xenograft removal (mean 2.9 weeks), 30 (94%) wounds had improved. 15 wounds (47%) healed at 12 weeks.</td>
</tr>
<tr>
<td>Bovine-derived xenograft (MATRIDERM®)</td>
<td>DFU</td>
<td>Cervelli et al. Int Wound J (2010); 7(4):291-96</td>
<td>Prospective case report</td>
<td>A 65 year old male patient with DFU. Following treatment with antibiotics and surgical debridement, xenograft applied. There was immediate pain reduction; complete wound healing was achieved, which was associated with an excellent aesthetic result.</td>
</tr>
<tr>
<td>Silicone membrane/ reconstituted bovine collagen matrix (INTEGRA™ Bilayer Matrix)</td>
<td>DFUs (lower extremity salvage)</td>
<td>Iorio M et al. Plast Reconstr Surg 2010; 8 (Epub ahead of print)</td>
<td>Retrospective review (n=105 patients with 121 wounds)</td>
<td>Collagen bilayer matrix found to be a viable option when used for reconstruction and stable closure in patients at low risk of amputation. For patients at high-risk of amputation, the rate of salvage may not be improved with the use of a collagen bilayer matrix.</td>
</tr>
</tbody>
</table>
Venous leg ulcers
A systematic review of randomised controlled trials (RCTs) of a variety of wound dressings for chronic venous ulcer\textsuperscript{35} was conducted to determine whether more modern advanced wound dressings further improve the healing of venous ulcers over simple wound dressings. This found that of the 20 RCTs identified, five showed significance for ulcer healing, including a study by Mostow and colleagues using a porcine collagen matrix derived from small intestine submucosa (SIS)\textsuperscript{36} (Table 5).

Mixed arterial/venous and vasculitic ulcers
Ulcers related to numerous underlying aetiologies may present particular challenges for clinicians and are costly to treat. These wounds are often slow to heal and associated with high levels of pain, inflammation and tissue necrosis\textsuperscript{10}. The use of an acellular matrix has been shown to be effective in this subset of patients with lower extremity ulcers and can help to reduce the level of pain and increase quality of life\textsuperscript{10,37} (Table 6).

Pressure ulcers
There is currently limited evidence on the use of acellular matrices in patients with pressure ulcers. Typically, non-healing pressure ulcers may present as partial or full-thickness wounds with or without exposed bone and tendon. In wounds with undermined areas a micronised injectable acellular matrix may provide an alternative to surgical treatment of pressure ulcers\textsuperscript{38}.

| Table 5 | Summary of evidence for venous leg ulcers |
| --- | --- | --- | --- |
| Product used | Wound type | Publication | Type of study | Outcomes |
| Porcine small intestine submucosa (SIS) xenograft (Oasis\textsuperscript{®}) + compression therapy vs compression therapy alone (standard of care) | VLUs | Demling et al. Wounds 2004; 16(1): 18-22 | Interim analysis. Prospective randomised controlled multicentre (n=84) | At 12 weeks 71% of ulcers healed with SIS xenograft (applied weekly) compared to 46% with the compression therapy only group (p=0.018). |
| Porcine small intestine submucosa (SIS) xenograft (Oasis\textsuperscript{®}) + compression therapy vs compression therapy alone | VLUs (> 1 month duration) | Mostow et al. J Vasc Surg 2005; 41(5): 837-43 | Prospective, randomised controlled multicentre (n=120 with at least 1 VLU) | At 12 weeks 55% of the wounds in the SIS xenograft group were healed compared with 34% in the standard care group (p=0.0196). There were no recurrences in the six-month follow in the SIS treated group. |

| Table 6 | Summary of evidence for mixed arterial/venous ulcers and other aetiologies |
| --- | --- | --- | --- |
| Product used | Wound type | Publication | Type of study | Outcomes |
| Porcine small intestine submucosa (SIS) xenograft (Oasis\textsuperscript{®}) vs hyaluronic acid (HA) biomaterial (Hyaloskin) | Mixed arterial/venous ulcers | Romanelli et al. Int Wound J 2007; 4(1): 3-7 | Randomised prospective single centre (n=54) | 50 patients completed the study. At 16 weeks, complete wound closure achieved in 21 patients (82.6%) in SIS xenograft group compared to HA group. Patients treated with SIS xenograft reported significantly greater comfort (p<0.01), less pain (p<0.05) and less frequent dressing changes (p<0.05) compared to HA treated group. |
| Equine pericardium xenograft (Unite\textsuperscript{®}) vs human acellular dermal matrix (GraftJacket\textsuperscript{®}) | Vasculitic ulcer | Mulder G, Lee D. Int J Lower Extremity Wounds 2009; 8(3): 157-61 | Case report | 56 year old man with bilateral foot ulcers associated with severe cryoglobulinemia and vasculitis. Surgical debridement and application of xenograft to all lateral and right medial wounds; half of left medial covered with allograft. Pain reduction at 1 week. At week 4, all xenograft sites improving. All xenograft-treated wounds healed by week 7. Further 3 months to heal left medial wound. |
| Equine pericardium (Unite\textsuperscript{®}) plus injectable collagen glycosaminoglycan matrix (INTEGRA\textsuperscript{TM} Flowable Matrix) for largest defect and use of a silicone free collagen-glycosaminoglycan product (INTEGRA\textsuperscript{TM} Wound Dressing) for areas of exposed tendon | Lower extremity ulcers associated with scleroderma and Raynaud’s Disease | Mulder G, Lee D. Wounds 2009; 21(11):297-301 | Case report | 39 year old man with bilateral full thickness ulcers associated with scleroderma. Surgical debridement and application of xenograft (plus combination therapy where applicable). Dressings left intact for 1 week. Patient had significantly less pain. At 12 days all wounds were progressing towards closure. At 8 weeks following surgery all but the largest of wounds had fully closed without complications |

NB: Studies listed in date order
FUTURE RESEARCH

There is a need for comparisons of clinical effectiveness and cost to enable appropriate use of products and to challenge current gold standard treatments.

Wounds that fail to heal can negatively impact on the patient’s quality of life and have important cost implications for health services. Where wounds are less likely to heal with routine standard of care, there may be a role for advanced wound therapies such as acellular matrices. Potential benefits and low complication rates of these products, which when combined with the cost advantages of a single or infrequent application, minimal preparation/storage and long shelf-life, may make them a viable treatment option for patients with chronic ulcers.

Achieving the appropriate level of evidence

Future data to be sought from:
- Prospective, multicentre, randomised controlled trials
- Comparative studies between 2 or more products
- Long-term follow up studies
- Economic studies
- Effectiveness and efficacy studies (life experience)

REFERENCES

7. Enoch S, Shaaban H, Duran KW. Informed consent should be obtained from patients to use products (skin substitutes) and dressings containing biological material. J Med Ethics 2005; 31: 2-6.
<table>
<thead>
<tr>
<th>Company/manufacturer</th>
<th>Product</th>
<th>Source</th>
<th>Indicated for</th>
<th>Shelf-Life*/Storage</th>
<th>Crosslinking</th>
<th>Sterilisation process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acell Inc/Medline</td>
<td>Matrix™ Wound Care Matrix</td>
<td>Porcine urinary bladder matrix</td>
<td>+</td>
<td>2 years Room temperature</td>
<td>None</td>
<td>Electron beam irradiation</td>
</tr>
<tr>
<td>AM Scientific/Brennen Medical</td>
<td>LZ-DERM™</td>
<td>Porcine dermis</td>
<td>+</td>
<td>Room temperature</td>
<td>Aldehyde Sterile (method undocumented)</td>
<td></td>
</tr>
<tr>
<td>Cook Medical</td>
<td>BioDesign™ (Surgisis®) Hernia Graft</td>
<td>Porcine small intestine submucosa (SIS)</td>
<td>+</td>
<td>18 months Room temperature</td>
<td>None</td>
<td>Ethylene oxide</td>
</tr>
<tr>
<td>Coviden</td>
<td>Permacol</td>
<td>Porcine dermis</td>
<td>+</td>
<td>Room temperature</td>
<td>HDMI Gamma irradiation</td>
<td></td>
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<tr>
<td>Davol Inc/Bard</td>
<td>CollaMend Implant</td>
<td>Porcine dermis</td>
<td>+</td>
<td>Room temperature</td>
<td>EDC Ethylene oxide</td>
<td></td>
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<tr>
<td>Davol Inc/Bard</td>
<td>XenMatrix™ Surgical Graft</td>
<td>Porcine dermis</td>
<td>+</td>
<td>Room temperature</td>
<td>None</td>
<td>Electron beam irradiation</td>
</tr>
<tr>
<td>Dr. Suwelack Skin &amp; Health Care AG/EuroSurgical</td>
<td>MATRIDERMA™</td>
<td>Bovine dermis</td>
<td>+</td>
<td>5 years Room temperature</td>
<td>None</td>
<td>Gamma irradiation</td>
</tr>
<tr>
<td>Dr. Suwelack Skin &amp; Health Care AG/Medline</td>
<td>Puracol® Plus Microscaffold Collagen (Puracol® Plus Ag.)</td>
<td>Bovine collagen</td>
<td>+</td>
<td>3 years Room temperature</td>
<td>None</td>
<td>Supplied sterile (method undocumented)</td>
</tr>
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<td>Euroresearch</td>
<td>BIOPAD™ Collagen Wound Dressing</td>
<td>Equine flexor tendon</td>
<td>+</td>
<td>Store in a dry place away from heat sources</td>
<td>None</td>
<td>Gamma irradiation</td>
</tr>
<tr>
<td>HealthPoint Ltd./Cook Biotech, Inc</td>
<td>OASIS™ Wound Matrix</td>
<td>Porcine small intestine submucosa (SIS)</td>
<td>+</td>
<td>2 years Room temperature</td>
<td>None</td>
<td>Ethylene oxide</td>
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<tr>
<td>Integra LifeSciences</td>
<td>INTEGRAS™ Matrix Wound Dressing</td>
<td>Bovine tendon collagen and glycosaminoglycan</td>
<td>+</td>
<td>2 years Room temperature</td>
<td>Glutaraldehyde Ethylene oxide</td>
<td></td>
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<tr>
<td>LifeCell</td>
<td>Strattice™ Reconstructive Tissue Matrix</td>
<td>Porcine dermis</td>
<td>+</td>
<td>Room temperature</td>
<td>None</td>
<td>Electron beam irradiation</td>
</tr>
<tr>
<td>Mesynthes</td>
<td>Endoflex™ Dermal Template</td>
<td>Poppy-submucosal layers of ovine forestomach</td>
<td>+</td>
<td>Room temperature</td>
<td>None</td>
<td>Ethylene oxide</td>
</tr>
<tr>
<td>Synovis Orthopedic and Woundcare, Inc.</td>
<td>Unitet® Biomatrix Collagen Wound Dressing</td>
<td>Equine pericardium</td>
<td>+</td>
<td>3 years Room temperature</td>
<td>EDC EDC</td>
<td></td>
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<tr>
<td>Synovis Orthopedic and Woundcare, Inc.</td>
<td>Vetenet® Collagen Matrix</td>
<td>Bovine pericardium</td>
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<td>Controlled room temperature</td>
<td>None</td>
<td>Sodium hydroxide</td>
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<tr>
<td>TEI Biosciences</td>
<td>PrMatix™ Dermal Repair Scaffold</td>
<td>Fetal bovine derms</td>
<td>+</td>
<td>3 years Room temperature</td>
<td>None</td>
<td>Ethylene oxide</td>
</tr>
<tr>
<td>TEI Biosciences</td>
<td>SurgiMend®/SurgiMend® Segural Hernia Repair Matrix</td>
<td>Fetal bovine dermis</td>
<td>+</td>
<td>3 years Room temperature</td>
<td>None</td>
<td>Ethylene oxide</td>
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### Xenograft Collagen Grafts

<table>
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<tr>
<th>Company/manufacturer</th>
<th>Product</th>
<th>Source</th>
<th>Indicated for</th>
<th>Shelf-Life*/Storage</th>
<th>Crosslinking</th>
<th>Sterilisation process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davol Inc/Bard</td>
<td>XenMatrix™ Surgical Graft</td>
<td>Bovine dermis</td>
<td>+</td>
<td>Room temperature</td>
<td>None</td>
<td>Electron beam irradiation</td>
</tr>
<tr>
<td>Dr. Suwelack Skin &amp; Health Care AG/EuroSurgical</td>
<td>MATRIDERMA™</td>
<td>Bovine dermis</td>
<td>+</td>
<td>5 years Room temperature</td>
<td>None</td>
<td>Gamma irradiation</td>
</tr>
</tbody>
</table>

### Allografts

<table>
<thead>
<tr>
<th>A.C.I. Medical/HANS Biomed</th>
<th>SureDerm™ Acellular Dermal Graft</th>
<th>Human dermis</th>
<th>+</th>
<th>-</th>
<th>2 years Refrigeration necessary</th>
<th>None</th>
<th>Supplied sterile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davol Inc/Bard</td>
<td>AlloMax™ Surgical Graft</td>
<td>Human dermis</td>
<td>+</td>
<td>-</td>
<td>No refrigeration required</td>
<td>None</td>
<td>Tutoplast® process and low-dose gamma irradiation</td>
</tr>
<tr>
<td>LifeCell</td>
<td>AlloDerm® Regenerative Tissue Matrix</td>
<td>Human dermis</td>
<td>+</td>
<td>-</td>
<td>2 years Refrigeration upon receipt</td>
<td>None</td>
<td>Aseptically processed</td>
</tr>
<tr>
<td>Mentor</td>
<td>NeoForm™</td>
<td>Human dermis</td>
<td>+</td>
<td>-</td>
<td>5 years Room temperature</td>
<td>None</td>
<td>Tutoplast® process and low-dose gamma irradiation</td>
</tr>
<tr>
<td>Musculoskeletal Transplant Foundation/ Ethicon</td>
<td>FlexHD® Acellular Hydrated Dermis</td>
<td>Human dermis</td>
<td>+</td>
<td>-</td>
<td>Ready to use Room temperature</td>
<td>None</td>
<td>Aseptically processed (passes the US Pharmacopea Standard 71 for sterility)</td>
</tr>
<tr>
<td>Musculoskeletal Transplant Foundation/ Synthes CMF</td>
<td>DermaMatrix Acellular Dermis</td>
<td>Human dermis</td>
<td>+</td>
<td>-</td>
<td>3 years Freeze dried Room temperature</td>
<td>None</td>
<td>Aseptically processed (passes the US Pharmacopea Standard 71 for sterility)</td>
</tr>
<tr>
<td>Wright Medical Technology, Inc</td>
<td>GraftJacket® Regenerative Tissue Matrix Ulcer Repair</td>
<td>Human dermis</td>
<td>+</td>
<td>-</td>
<td>2 years Freeze dried, refrigerate upon receipt</td>
<td>None</td>
<td>Aseptically processed</td>
</tr>
</tbody>
</table>

### Synthetic Acellular Dermal Replacements

<table>
<thead>
<tr>
<th>Integra LifeSciences</th>
<th>INTEGRAS™ Bi-layer Matrix Wound Dressing</th>
<th>Bi-layered bovine tendon collagen and glycosaminoglycan with a polysiloxane (silicone) membrane</th>
<th>+</th>
<th>+</th>
<th>2 years Room temperature</th>
<th>Aqueous gluteraldehyde Irradiation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Integra LifeSciences</td>
<td>INTEGRAS™ Dermal Regeneration Template</td>
<td>Bi-layered bovine tendon collagen and glycosaminoglycan with a polysiloxane (silicone) membrane</td>
<td>+</td>
<td>-</td>
<td>2 years Store flat and refrigerate</td>
<td>Glutaraldehyde Gamma irradiation</td>
<td></td>
</tr>
</tbody>
</table>

*Shelf-life is cited when known.

**APPENDIX | Acellular wound matrix products available in US and/or Europe**

All information has been checked against manufacturers' websites. Please refer to individual product literature for use.
THE HEALING TOUCH IS BACK IN YOUR HANDS

THE PEGASUS PATCH IS BACK

Pegasus Biologics is now Synovis Orthopedic & Woundcare. Our proven product reputation and legacy of hard science for soft tissue moves forward with Synovis — and on to you — placing advanced collagen wound dressings in your hands to support the healing of complex wounds.

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> Supports a healthy wound bed for the healing of chronic and complex wounds — learn more.
> Flexibly crosslinked collagen dressing, enzymatic resistant and single application only for most wounds. — learn more.

Let's get reacquainted
Meet your new Synovis Orthopedic and Woundcare team to learn more about our core technologies and discover all our new group has to offer.

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