QUICK GUIDE

SKIN SUBSTITUTES FOR THE MANAGEMENT OF HARD-TO-HEAL WOUNDS

WOUNDS | INTERNATIONAL

INTRODUCTION TO SKIN SUBSTITUTES

Skin substitutes offer an increasingly important resource for managing complex wounds and have become a commonplace tool within wound care. The term 'skin substitutes' is an umbrella term for the wide range of biological dressings and biological matrices, which facilitate the repair and/or regeneration of the skin through various mechanisms. Skin substitutes can be divided into two broad categories:

1. Biological dressings
2. Biological matrices.

Depending on the layer(s) of the skin that the skin substitute aims to mimic to facilitate the regeneration process, biological matrices can be further classified as either[1,2]:

- Dermal matrices
- Epidermal-dermal matrices.

Umbrella terms for skin substitutes:

- Tissue scaffolds or tissue-engineered products
- Cellular and/or tissue-based products (CTPs) or cellular, acellular and matrix-like products (CAMPs).

These matrices* act as a stable, often biodegradable, three-dimensional scaffold that stimulates and replaces the function of the damaged extracellular matrix (ECM). This promotes the formation of granulation tissue (and eventual re-epithelialisation) by allowing host and/or seeded cells to attach, migrate, and proliferate as the wound progresses towards closure. These products also behave as biological modulators by delivering or augmenting the production of cytokines and growth factors to facilitate wound healing[2].

*Disclaimer: The Mode of Action (MoA) for many of these products is based on *in vitro* data, along with some animal based studies. The bilayer cellular construct has studied the MoA in a chronic venous leg ulcer patient population.

BIOLOGICAL DRESSINGS

Biological dressings are temporary wound coverings that perform some of the functions of the epidermis (i.e. protect from mechanical trauma, infection and fluid loss), thereby maintaining a moist environment to facilitate wound healing[2,3].

A group of international experts[4] suggested the term 'biological dressings' to differentiate these products from other wound dressings, as they act as biomodulators by augmenting the wound environment through the release of active growth factors and other biomolecules that can regulate endogenous cells in a wound environment[5].

CURRENT USE IN PRACTICE AND RATIONALE FOR USE

Clinical guidelines deem advanced therapies, such as skin substitutes, to be a suitable adjunct to standard of care (SOC) for hard-to-heal lower extremity wounds and chronic wounds — i.e. wounds that fail to respond to SOC alone and fail to close or reduce in size by approximately 40–50% (depending on wound type) within 4 weeks[2,6,7].

By this definition, skin substitutes are indicated for the treatment or management of chronic and hard-to-heal wounds, such as:

- Diabetic foot ulcers (DFUs)
- Pressure ulcers (PUs)
- Venous leg ulcers (VLUs)
- Arterial ulcers
- Mixed aetiology ulcers
- Wounds secondary to trauma
- Post-surgical wounds
- Other wound aetiologies.

Natural placental tissue is a rich source of ECM proteins (e.g. collagens I, III, IV, VI, proteoglycans, glycoproteins), growth factors, cytokines, and viable endogenous cells, including mesenchymal stem cells that support the wound-healing process. These components influence cell differentiation, hormone/protein production, and basement membrane remodelling, making them beneficial for managing complex, chronic, non-healing wounds.

Dermal matrices can be formed of varying layers to act as durable skin substitutes and are designed to provide a stable three-dimensional matrix to promote the formation of granulation tissue. Their duration may be influenced by many factors related to the wound bed, including but not limited to: bacterial load, non-viable tissue, debris, levels of exudate and the presence of inflammatory cells.

Dermal matrices can be further divided into the following categories:

- Acellular dermal matrices (ADM)
- Dermal skin substitutes (DSS)
- Small intestinal submucosa (SIS).

Epidermal-dermal matrices are bi-layered products comprised of a stable three-dimensional dermal matrix layer to promote the formation of granulation tissue and an epidermal layer that stimulates re-epithelialisation.

These products can be classified as:

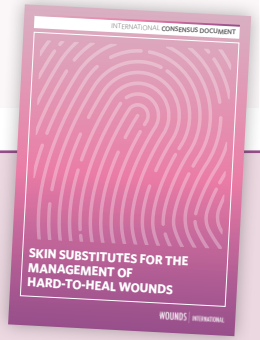
- Dermal regeneration template (DRT)
- Bilayer cellular construct (BLCC).

Cellularity is considered an important discriminator between skin substitute products unless the tissue is immunologically privileged, as the presence of allogenic cells increases the rejection risk and manufacturing complexity. A summary of each of the subcategories within biological dressings and biological matrices, along with their cellularity is presented in Box 1.

Box 1. Placental-derived allografts in current use

- **Epidermal tissue transplants (amniotic/placental-derived)**
  - Dehydrated human amniotic membrane (dHAM) – Acellular
  - Cryopreserved placental membrane with viable cells (vCPM) – Cellular
  - Dehydrated human amnion-chorion membrane (dHACM or dACM) – Acellular
  - Hypothermically stored amniotic membrane (HSAM) – Cellular
  - Hypothermically stored chorion membrane (HSCM) – Cellular
- **Dermal matrices**
  - Acellular Dermal Matrices (ADM) – Acellular
  - Dermal skin substitutes (DSS) – Cellular
  - Small intestinal submucosa (SIS) – Acellular
- **Epidermal-dermal matrices**
  - Bi-layered cellular construct (BLCC) – Cellular
  - Dermal regeneration template (DRT) – Acellular

Scan the QR code to access Mulder G et al (2024) Skin substitutes for the management of hard-to-heal wounds.



TIPS FOR PRODUCT SELECTION

- All treatment decisions should be underpinned by thorough and accurate assessment, using a structured assessment tool such as TIMERS[8], considering the patient holistically in terms of their overall health, needs and preferences, as well as their wound
- It is important that clinicians are knowledgeable about the biomaterials within the product that they would like to use and the stage of wound healing that they would like the product to help modulate
- Wound bed preparation is an important consideration in optimising product use and outcomes
- Wherever possible, clinical consideration needs to be based on evidence, to ensure best practice and consistency of care for patients; however, evidence may still be lacking in some areas, and local guidance along with clinical judgement should be used
- It is important to carry out all treatment in accordance with the manufacturer's instructions and guidelines or recommendations
- Prior to commencing treatment, practical factors and treatment goals should be considered
- Treatment goals should be reviewed and progress assessed as treatment continues. The milestones towards achieving a successful outcome may include:
  - No clinical signs of acute infection or bioburden (e.g. purulence, sliminess or unexpected malodour)
  - Formation of granulation tissue
  - Re-epithelialisation
  - Reduction in wound size
  - Successful removal of the method of attachment (i.e. staples, sutures or wound closure strips).

References

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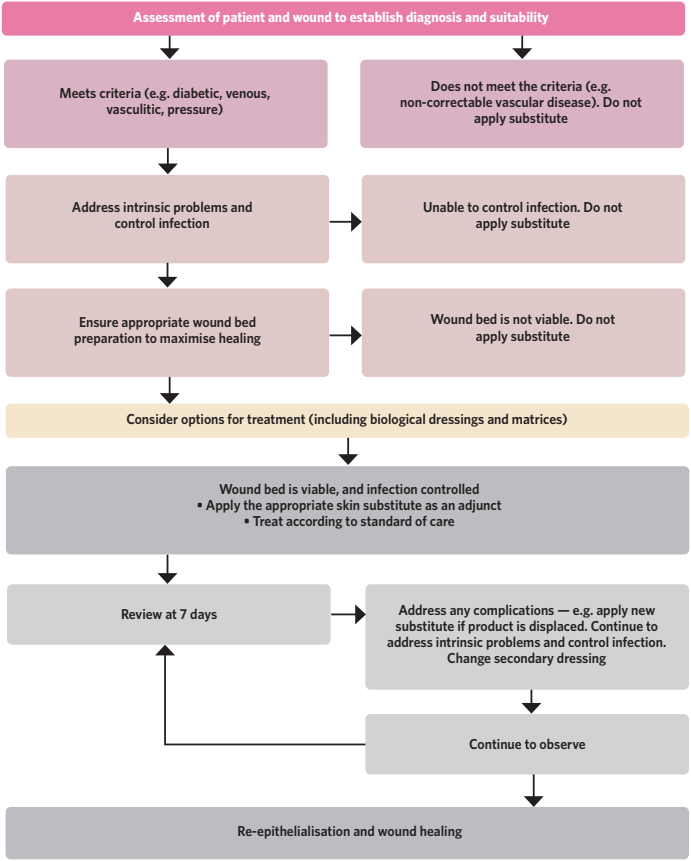
PATHWAY FOR CARE IN PRACTICE



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