JWC International Consensus Document

Best practice for wound repair and regeneration

use of cellular, acellular and matrix-like products (CAMPs)

SUPPORTED BY

AROA BioTissue Surgical COOK BIOTECH INTEGRA LIFE SCIENCES MIMEDX Organogenesis Empowering Healing

Panel chair

Stephanie Wu, DPM, MSc, FACFAS, Dean, Dr William M Scholl College of Podiatric Medicine; Professor, Department of Podiatric Surgery and Applied Biomechanics, Center for Stem Cell and Regenerative Medicine, Rosalind Franklin University of Medicine and Science, Illinois, US

Authors

Marissa Carter, PhD, MA, MAPWCA, President, Strategic Solutions Inc, Montana, US

Windy Cole, DPM, CWSP, Director, Wound Care Research, Kent State University, Ohio, US

Roselle Crombie, MD, Department of Surgery, Yale New Haven Health System, Connecticut, US

Daniel L. Kapp, MD, Chief of Plastic Surgery, Palm Beach Gardens Medical Center, Florida, US

Paul Kim, DPM, MS, Professor, Department of Plastic Surgery, University of Texas Southwestern, Texas, US

Catherine Milne, APRN, MSN, ANP/ACS-BC, CWON-AP, Connecticut Clinical Nursing Associates, Connecticut, US

Joseph Molnar, MD, PhD, FACS, Professor of Plastic and Reconstructive Surgery and Regenerative Medicine, Wake Forest University School of Medicine, North Carolina, US

Jeffrey Niezgoda, MD, FACHM, MAPWCA, CHWS, Founder and President Emeritus, AZH Wound and Hyperbaric Center, Wisconsin, US

Kevin Woo, PhD, RN, NSWOC, WOCC, FAPWCA, Professor, Queen's University, Ontario, Canada

David Zabel, MD, FACS, Chief of Plastic and Reconstructive Surgery, Christiana Care Health System, Affiliated Faculty Department of Biomedical Engineering, University of Delaware, Delaware, US

Rose Hamm, Medical Writer, Adjunct Associate Professor of Clinical Physical Therapy, University of Southern California, California, US

Review panel

David Armstrong, Professor of Surgery; Director, USC Limb Preservation Program, California, US

Alan J Bock, DPM, MS, Palmetto State Surgical Podiatry Associates, South Carolina, US

Baljit Dheansa, Consultant Burns and Plastic Surgeon and Honorary Senior Lecturer, Queen Victoria Hospital, East Grinstead, UK

Vickie Driver, DPM MS FACFAS FAAWC, System Chief, Wound Care and Hyperbaric Medicine, Inova Heart and Vascular Institute, Virginia, US

Paul Glat, MD, Chief of Plastic Surgery, St Christopher's Hospital for Children, Philadelphia, Pennsylvania, US

John Lantis II, MD, Chief and Professor of Surgery, Mount Sinai West Hospital and the Icahn School of Medicine, New York, US

Lydia Masako Ferreira, PhD, MD, Professor of Plastic Surgery, Universidade Federal de Sao Paulo, Sao Paulo, Brazil

Mark Melin, MD, FACS, RPVI, FACCWS, M Health Fairview Wound Healing Institute, Edina, Minnesota, US

Keyur Patel, DO, CHWS, FAPWCA, FACHM, Medical Director and Principal Investigator, Three Rivers Wound and Research Center, Florida, US

Elia Ricci, MD, Difficult Wound Healing Unit, St Luca's Clinic, Turin, Italy

Richard Simman, MD, FACS, FACCWS, Professor of Surgery, University of Toledo, College of Medicine and Life Sciences, Ohio, US

John Steinberg, DPM, FACFAS, Professor, Department of Plastic Surgery, Georgetown University School of Medicine, Washington DC, US

William Tettelbach, MD, FACP, FIDSA, FUHM, MAPWCA, CWSP, Adjunct Assistant Professor, Duke University School of Medicine, Undersea and Hyperbaric Medicine; Adjunct Professor, Western University of Health Sciences, Podiatric Medicine and Surgery, Salt Lake City, Utah, US

Dot Weir, RN, CWON, CWS, Clinician and Educator, Saratoga Hospital Center for Wound Healing and Hyperbaric Medicine, New York, US

Contents

Foreword	S4
Aims and terminology	S5
Chapter 1: Introduction	S8
Chapter 2: Categorisation and effect on host tissue	S11
Chapter 3: Principles of care and clinical objectives	S15
Chapter 4: Guidelines for use	S17
Chapter 5: Barriers to implementation	S23
Chapter 6: Summary	S28
References	S29

This document was supported by Aroa Biosurgery, BioTissue Inc, Cook Biotech Inc, Integra LifeSciences, MiMedx and Organogenesis

Suggested citation for this document: Wu S, Carter M, Cole W et al. Best practice for wound repair and regeneration: use of cellular, acellular and matrix-like products (CAMPs). J Wound Care 2023; 32(4 Suppl B):S1–S32

Head of Projects: **Camila Fronzo and Chris Beck**
Associate Publisher: **Tracy Cowan**
Projects Editor: **Benjamin Wakefield**
Design: **Fonthill Creative**
Managing Director: **Anthony Kerr**

www.journalofwoundcare.com
www.mamedcomms.com

To sponsor or if you have an idea for the next *JWC* international consensus document, please contact Anthony Kerr anthony.kerr@markallengroup.com
+44 (0)7979 520828

MA Healthcare

Published by: **MA Healthcare Ltd, St Jude's Church, Dulwich Road, London, SE24 0PB, UK**
Tel: +44 (0)20 7501 6726
Web: www.markallengroup.com

Cover Image: Anusorn via Adobe Stock

Foreword

There are currently over 80 biomaterials derived from autologous, allogeneic, synthetic and xenogeneic sources, or a combination of any or all these types of materials, available for soft-tissue coverage to effect wound closure. Often generically referred to as cellular and/or tissue-based products (CTPs), they are manufactured under various trade names and marketed for a variety of indications.

In July 2022, an expert panel of 11 key opinion leaders from the US and Canada met in New York, US, to discuss how CTPs work. The aim was to promote awareness and increase understanding of CTPs, as well as give recommendations on best practice for their use in relation to patient selection, wound bed preparation, product application, post-application care and follow-up wound management.

This consensus document, which is based on the discussion at the meeting, aims to help simplify what health professionals report can be a confusing range of options for CTPs. It describes the principles of wound management and offers insight on how to implement the 'R' (Repair/Regeneration) in the TIMERS acronym,[1] with the goal of improving patient outcomes.

Over the 2-day expert-panel meeting, many topics relating to CTPs were discussed at length. These included:

- Definitions, categorisation and mode of action of CTPs
- Best practice for determining when to initiate treatment with CTPs to achieve optimum results
- A checklist or algorithm to support the best use of CTPs
- Management of patient comorbidities that can affect healing outcomes
- Obstacles to the implementation of CTPs, as well as recommendations on how to overcome these obstacles
- Potential strategies for increasing awareness and access to CTPs in emerging markets.

When developing the guidelines, the consensus document authors focused on the clinical and scientific evidence available to define best practice for the use of CTPs on hard-to-heal wounds. The panel acknowledged that the term 'CTP' no longer captures the diversity of available biomaterials and the bioengineering advancements of the past two decades. Instead, the panel proposed a new term, cellular, acellular and matrix-like products (CAMPs), and gave the following definition:

'A broad category of biomaterials, synthetic materials or biosynthetic matrices that support repair or regeneration of injured tissues through various mechanisms of action.'

Given the international focus of this document, the regional availability of CAMPs and the varying levels of knowledge among health professionals worldwide, this publication should be read and implemented in conjunction with local guidelines. It should also be noted that this document is intended to expand on and be synergistic with the 2019 *Journal of Wound Care* (*JWC*) international consensus document 'Implementing TIMERS: the race against hard-to-heal wounds' and not to replace it.

We hope you find this document informative and that it helps make a difference in practice.

***Stephanie Wu**, DPM, Panel Chair*

1. Atkin L, Bucko Z, Montero EC et al. Implementing TIMERS: the race against hard-to-heal wounds. J Wound Care. 2019;28(3S3):S1–S49. https://doi.org/10.12968/jowc.2019.28.sup3a.S1

Aims and terminology

The purpose of this *Journal of Wound Care* (*JWC*) international consensus document is to improve understanding of biological technologies used in the repair and regeneration of soft tissue as part of wound management. It is a follow-up to the 2019 *JWC* consensus document[1] that developed the TIMERS acronym. In addition to tissue (T), inflammation/infection (I), moisture balance (M) and edges (E), TIMERS goes a step further to capture repair/regeneration (R) and social factors (S) as critical components of comprehensive care for patients with hard-to-heal wounds.

This new consensus document, derived from an expert panel meeting held in July 2022, outlines the elements of best practice, based on the research evidence on biological technologies and the panel's clinical judgement and experience. The content is based primarily on experience in the US, where this technology is more commonly available. However, a secondary goal is to increase awareness of its use in the rest of the world. Transparency of the information provided was achieved through a rigorous review process by an international group of key opinion leaders with experience in these products.

1. Atkin L, Bucko Z, Montero EC et al. Implementing TIMERS: the race against hard-to-heal wounds. J Wound Care. 2019;28(3S3):S1–S49. https://doi.org/10.12968/jowc.2019.28.sup3a.S1

Glossary

Acellular tissue component A non-cellular component in the extracellular matrix (eg, vesicles, proteins, filaments, granules and collagen); these are not contained in cells but do affect cellular activity

Acellular Not containing any cells; in the context of CAMPs, describes tissue in which the cells have been removed but the support structure or matrix left in place

Adnexal structures of the skin Specialised dermal structures with sensory, contractility, lubrication and heat-loss functions; they include the pilosebaceous unit (hair follicle and sebaceous gland), arrector pili (smooth muscles that control hair position), sweat glands and nails

Allogeneic Tissue taken from an individual of the same species

Allograft Tissue harvested from a donor of the same species as the recipient but not genetically the same

Anabolic process The constructive or building-up aspect of metabolism in which molecules, such as amino acids or proteins, are created from smaller units

Angiogenesis The formation of new capillaries from existing blood vessels, which involves the migration, growth and differentiation of endothelial cells

Amnion A membrane that encases and covers the embryo in the uterus

Amniotic fluid The fluid that fills the amnion, causing it to expand into the amniotic sac that protects the developing embryo

Antigenicity The ability of a foreign body or antigen to induce an immune response by interacting with a specific antibody or T-cell receptor

Atypical wound A wounds that cannot be defined using one of the primary non-healing categories, such as diabetic foot ulceration

Autograft A tissue graft harvested from one part of the body and transferred to another part of the same individual—in this context, either split-thickness or full-thickness skin harvested with a sharp instrument (scalpel or dermatome) and immediately applied to a wound surface

Autolysis The process by which the body uses its own enzymes to break down or lyse non-viable tissue

Biofilm A community of bacteria that attaches to a surface, such as human tissue, and forms a protective layer or film composed of extracellular polymeric substances, polysaccharides and structural proteins, which serves as a protective encasement for the bacteria

Biomaterial A natural or synthetic product that haa been engineered to interact with the components of living tissue to affect a therapeutic procedure; in this context, these aim to enhance or support repair or regeneration of injured tissue

Bioresorbable Material that is able to be naturally absorbed by the body over a period of time

Biosynthesis The process by which simple components are converted into complex compounds by a living organism—in this context, it describes a CAMP material that is manufactured from biologically available monomers or subunits using an industrial, controlled process

Bolster dressing A material that is placed over a graft or CAMP and secured sufficiently to stop the soft tissue beneath it moving, thereby preventing shear between the graft or CAMP and the wound surface

CAMP Cellular, acellular and matrix-like product, also referred to as a cellular/tissue product (CTP)

Catabolic process The metabolic process in which larger structures are broken down into smaller particles

Cultured epidermal autograft The process of using a small biopsy of an individual's skin to collect keratinocytes, expand the number of those cells in a laboratory and reapply them to the wound with either a petrolatum gauze or dermis-like substitute cover dressing

Cell surface receptors Proteins that are embedded in the cellular membrane and have two functions: to recognise and bind a signalling molecule (or ligand) to the cell membrane and to communicate the extracellular signals to the intracellular pathways, thereby affecting the cellular activity

Chemokine Specialised messenger protein molecule that directs the migration of white blood cells to infected or injured tissue; chemokines are a subgroup of cytokines

Class III medical device A medical device deemed to pose a high risk to the patient, requiring premarket approval (US) or conformity assessment (EU)—to ensure their safety and efficacy to the US Food and Drug Administration (FDA), these products undergo the PMA process of scientific review, which includes submission of clinical data to support the claims made for the device

Collagen The primary structural protein that makes up the extracellular matrix, a component of the body's connective tissue

Cytokine A general category of protein molecule that is secreted by cells and uses chemical signals to influence intercellular interactions and communication—subgroups are named in relation to either the cells that produce them (eg, lymphokine and monokine) or their activity (chemokines that attract cells by chemotaxis or interleukins that are made by one leucocyte and act on other leucocytes). Cytokines can be either pro-or anti-inflammatory

Dehiscence Separation of previously approximated wound edges as a result of failure to heal, usually occuring 5–8 days after surgery

Differentiated cell A cells that has changed in form to perform a specific function

Downregulation Decrease in cellular response through molecular stimulation

Dynamic reciprocity An ongoing bidirectional interaction between cells and the surrounding environment provided by the extracellular matrix—it is an integral part of the wound healing process, as it causes cells to differentiate, proliferate, migrate and survive

Enzyme A protein that works as a catalyst to increase the rate at which a cellular activity takes place without itself being altered

Exosome Extracellular vesicle secreted by almost all cell types to aid many cellular functions, including intercellular communication, cell differentiation and proliferation, angiogenesis, stress response and immune signalling

Extracellular signalling Cues from molecules that transmit specific information to target cells and therefore affect the receiving cell activity

Extracellular matrix The network of proteins and other molecules found between cells that give support and structure to cells and tissues in the body

Fenestration The placement of small holes or slits in donor skin for grafting; this allows donor skin to be stretched so that it can cover a larger wounded area, and it enables fluid to drain through the holes, rather than collecting between the donor skin and the receptive wound bed

Fibronectin A glycoprotein in the extracellular matrix that binds to other extracellular matrix proteins and plays a key role in cell adhesion, growth, migration and differentiation, all of which are important parts of wound healing

Full-thickness wound Loss of the epidermis and all of the dermis, exposing the hypodermis and/or deeper structures

Glycosaminoglycan Long negatively-charged polysaccharides that attract water and are used as lubricants throughout the body; they also bind and present growth factors and other signalling molecules to cells, which helps direct cellular activity and intracellular communication

Growth factor Polypeptide secreted by certain cells that can influence other cells in the body to grow and reproduce

Hyaluronic acid (hyaluronan) A glycosaminoglycan located in the extracellular matrix of the skin that can bind and retain water; it is a key factor in the moisture loss of ageing skin

Immunogenicity The ability of cells, tissues or foreign bodies to invoke an immune response

Intercellular signalling Communication between cells to determine and regulate their activities; this is primarily a function of exosomes

Intracellular signalling Communication by the organelles within a cell to dictate its biochemical functions

Matrix-like products Natural or synthetic or a combination of materials that act as a functional molecular template to facilitate the repair and regeneration of tissue

Meshing The process of passing donor skin through a mechanical device (mesher) that perforates the skin so that it can be stretched to a larger area; this allows fluid to drain through the holes and places more skin edges in contact with the wound bed

Moist wound healing The practice of maintaining an optimal moist wound environment to promote normal healing processes

Non-differentiated cells Immature cells in the body that have not yet specialised for a specific function (also known as stem cells)

Non-viable Dead cells that are incapable of living, developing or reproducing; CAMPs can contain viable and/or non-viable cells, depending on their production and preservation processes

Nucleic acid Chemical compounds within the cell that carry information, especially for directing protein synthesis; the two major classes are deoxyribonucleic acid (DNA) and ribonucleic acid (RNA)

Occlusive dressing An airtight and watertight dressing that prevents loss or absorption of fluid from a wound and serves as a barrier to the external environment

Organelle Macromolecule within a cell that regulates cellular biochemical functions, including anabolic and catabolic reactions, pH regulation, protein production and motility, fatty acid synthesis and oxidation, removal of waste products and storage of genetic information

Partial-thickness wound Loss of the epidermis and part of the dermis; this may be classified as superficial or deep, depending on the dermal structures that are affected

Polyglactin A synthetic bioresorbable material used to fabricate scaffolding mesh for CAMPs

Protease An enzyme that breaks down protein

Proteoglycans Proteins that are heavily glycosylated or have carbohydrate molecules attached to them

Scaffold Three-dimensional extracellular matrix analogues—natural, synthetic or a combination of the two—that contribute to cell adhesion, proliferation and differentiation and are compatible with neovascularisation (an essential process for keeping cells alive)

Semi-occlusive dressing A dressing that allows air to move through the material but does not allow moisture or environmental contaminants to penetrate the wound

Senescence The loss of a cell's ability to divide and grow

Sharp debridement Selective removal of devitalised tissue using forceps, scalpel, curettes and scissors in a non-surgical setting, such as the bedside, outpatient clinic or home—may include use of topical analgesics and oral or intravenous pain relief

Surgical debridement Removal of devitalised tissue (using forceps, scalpel, curettes, scissors or high-powered water jet) in the operating room with the patient under general or local anaesthesia

Tenascin Glycoprotein that is abundant in the extracellular matrix

Thrombospondin A family of glycoproteins that have antiangiogenic functions

Transcription factor A protein that controls the rate of transcription of genetic information from DNA to RNA, thereby regulating genes to ensure they are expressed in the desired cells at the desired time and in the desired amount

Typical wound Commonly encountered wound, including, but not limited to, arterial and venous leg ulcers, pressure ulcers, lacerations, surgical incisions, dehiscence or burns

Upregulation Increase in cellular response through molecular stimulation

Viable Cells that are capable of living, developing or reproducing; in the context of this document, CAMPs containing viable or living cells

Vitronectin A glycoprotein in the serum, extracellular matrix and bone that promotes cell adhesion and spreading

Xenograft A tissue graft harvested from a donor of a different species from the recipient

Chapter 1: Introduction

Over the past six decades, several milestones in wound management have had a major impact on the care of patients with hard-to-heal wounds, starting with the understanding of moist wound healing that was first published in the landmark study by George Winter in 1962.[1,2] Acceptance of the concept of moist wound healing led to the next milestone, the development of wound dressings that create the optimal moisture in the wound environment for healing to occur, beginning with transparent films and hydrogels and progressing to occlusive or semi-occlusive dressings and, more recently, to advanced dressings that interact with the wound surface to absorb exudate or hydrate the wound.[3] Moist wound healing, in conjunction with aggressive and appropriate routine debridement of devitalised tissue, has become the standard of care for hard-to-heal wounds.

Key points

- Many biomaterials were first introduced for clinical use in the 1970s, with a variety approved since the turn of the century
- Most biomaterials are marketed under the 510(k) approval, meaning they have been cleared by the US Food and Drug Administration (FDA) as safe and effective; at present, only four have premarket approval (PMA) from the FDA, which involves a more rigorous process of scientific and regulatory review and is reserved for class III or high-risk medical devices
- Initially, this technology was referred to as skin substitutes, but the terminology evolved, with this category of product being termed cellular and/or tissue-based products (CTPs)
- This consensus document, which is based on an expert panel discussion, aims to address the previous absence of universal guidelines for the use of CTPs
- To reflect the innovations of the past two decades, this document proposes a new definition for this technology, as well as a new name: cellular, acellular and tissue-based products (CAMPs)

Historical developments in wound management

Debridement

Methods of mechanical and enzymatic debridement have been developed as alternatives to sharp and surgical debridement. A major milestone was the use of pulsed lavage with suction for the removal of exudate and debris (first used by the military in the 1960s and made available as a portable unit in the 1980s), which eventually replaced whirlpool therapy, especially when the negative effects of placing a dependent oedematous extremity in warm water and the possible increased risk of infection were understood.[4–6]

Negative pressure wound therapy

When negative pressure wound therapy (NPWT) became available in the late 1990s, it revolutionised wound care, especially that of large wounds with deeper spaces producing high amounts of exudate.[7–9] The use of NPWT has been further advanced with the development of NPWT with instillation for wounds with heavy bioburden delaying closure.[10] Other developments have included single-use topical NPWT for surgical incisions to reduce infection rates and prevent dehiscence[11,12] and disposable devices that provide NPWT in situations where the larger battery-powered units cannot be deployed.[13]

Biomaterials

The late 1990s also saw the first bioengineered bilayered skin, dermal regenerative products and commercial xenograft for wound repair in humans (Apligraf, Organogenesis, Canton, MA, US; Integra Dermal Regeneration Template, Integra LifeSciences, Princeton, NJ, US; Oasis, Smith+Nephew, Fort Worth, TX, US). Since then, there has been significant research and development in biomaterials, both viable and non-viable. Hard-to-heal partial- and full-thickness wounds, surgical wounds, burns or other extensive wounds are often treated with this technology—specifically, cellular, acellular and matrix-like products (CAMPs)—a milestone that has occurred in parallel with the development of advanced dressings.

While autologous skin grafts (split- or full-thickness) and flaps remain the gold-standard for wound closure,[14,15] biomaterials provide some of the same qualities as autografts for the treatment of

extensive burns, surgical wounds, acute traumatic wounds and hard-to-heal wounds such as diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs).[16,17] Haddad[18] defined the most important functions of skin substitutes as:

- Prevention of wound infection
- Maintenance of a moist wound environment
- Replacement of normal skin to restore function and aesthetics .

Other qualities of biomaterials that compare to those of skin grafts (and normal skin) include their:[6,19]

- Ability to protect the wound from the external environment
- Prevention of fluid loss
- Support of cell proliferation, differentiation and migration
- Lack of antigenicity, toxicity and immunogenicity
- Promotion of inflammatory modulation
- Durability, malleability and flexibility.

The first reported clinical application of placental tissue in modern medicine was in the early 1900s, when it was applied for tissue grafting.[20] The use of synthetic substitutes to assist in the closure of full-thickness burn wounds was first introduced in the 1940s, when it consisted of a thin synthetic sponge material placed on a debrided full-thickness burn wound. The sheet was left in place and trimmed away or 'removed fractionally' as autografts became available.[21]

Biomaterials, initially termed skin substitutes, were first available in the 1970s with the introduction of cultured epidermal autografts (CEAs), a process by which the patient's keratinocytes are multiplied *in vitro* and then applied as a graft to cover a wound.[22]

The first dermal substitutes became available in the early 1980s as a result of the work of Eugene Bell, a pioneer in regenerative medicine[23,24] who reported the development of a living skin-equivalent graft 'consisting of fibroblasts cast in collagen lattices and seeded with epidermal cells.'[25]

The term 'tissue engineering' was coined in 1987 by the US National Science Foundation, and the first manufactured skin construct with dermis and epidermis was approved for marketing in 1998.[26]

In 2001, a bioresorbable polyglactin mesh scaffolding seeded with human dermal fibroblasts was introduced.[27] Since then, many biomaterials for wound care have been developed, tested and approved for marketing throughout the world by the regulatory agencies listed in *Box 1*.[26]

At the suggestion of the Alliance of Wound Care Stakeholders, the original terminology for these products evolved to refer to this category as cellular and/or tissue based products (CTPs), and it was subsequently recognised as such by the Centers for Medicare and Medicaid Services (CMS) via a Local Coverage Determination (LCD) in 2016.[28] CTPs were added to the CMS Healthcare Common Procedure Coding System (HCPCS) in 2019.[29] Meanwhile, the literature began to discuss these products, and their indications, techniques and outcomes, as CTPs.[30,31]

Approval

The majority of the biomaterials have been marketed under 510(k) approval, meaning that the US Food and Drug Administration (FDA) has given the manufacturer clearance to market the product as safe and effective, and post-market trials have been conducted.[32] However, there is some indication that the level of evidence for these trials is lower than for premarket approval (PMA), which is the FDA rigorous process of scientific and regulatory review to evaluate the effectiveness of high-risk or Class III medical devices.[33] At present, only three CAMPs have PMA approval by the FDA (*Box 2*).

Box 1. Regulatory agencies approving biomaterials[26]

- Australian Therapeutic Goods Administration
- European Medicines Agency and European Commission
- Health Canada
- Japanese Ministry of Health, Labour and Welfare; Pharmaceuticals and Medical Devices Agency
- South Korean Ministry of Food and Drug Safety (under Pharmaceutical Affairs Act)
- US Food and Drug Administration (FDA)

Box 2. CAMPs that currently have PMA approval

- Apligraf (Apligraf, Organogenesis, Canton, MA, US)
- Dermagraft (Organogenesis, Canton, MA, US)
- Integra Dermal Regeneration Template (Integra LifeSciences, Princeton, NJ, US)

Need for international guidance

Although there has been extensive literature on the use of biomaterials on a variety of wounds, universal guidelines do not exist to define best practice for their application to hard-to-heal wounds, although CTPs were discussed in the 2019 *Journal of Wound Care (JWC)* TIMERS international consensus document.[34] The July 2022 expert panel discussion, convened to develop this document, focused on the clinical and scientific evidence to develop such guidelines, which are intended to expand on TIMERS[34] and not to replace it. Some of the potential benefits of advanced products that were considered in the panel discussion included decreased length and cost of treatment, fewer minor and major amputations (in lower-extremity DFUs); as well as decreased emergency department visits and hospital readmissions.[35] It is also important to understand that this discussion was not based on payment structure or FDA approval for guidance on their use.

Introducing a new definition

After a lengthy panel discussion on the composition, activity, complexity and mechanisms of action of the products, it was acknowledged that the term CTP no longer captured the innovations of the past two decades and had become insufficient to reflect the mechanisms of action and the diversity of bioactive materials. Therefore, the following all-encompassing definition was suggested:

'A broad category of biomaterials, synthetic materials or biosynthetic matrices that support repair or regeneration of injured tissues through various mechanisms of action.'

To better capture the diversity of products, the consensus panel selected the term 'cellular, acellular and matrix-like products (CAMPs)', an acronym that will be used throughout this document to refer to the products being discussed. For clarification, acellular products in this context refers to products that have had all cells removed from the tissue as part of their processing; acellular activity refers to actions of tissue components that are not cells, such as growth factors, cytokines, extracellular vesicles and other proteins.

This definition separates CAMPs from dressings, which do not directly affect cellular activity, and includes materials that have extracellular matrices (ECMs) as a component. CAMPs also include products previously referred to as skin substitutes. The panel clarified that a tissue injury being treated with a CAMP can be the result of a surgical procedure and not just the subcutaneous and epidermal/dermal repair of hard-to-heal wounds.

Because the field is changing and dynamic, with new products being introduced and existing products being altered or removed from the market, the panel elected to discuss products in categories rather than by specific brand names. The intention is to increase the longevity of this document, so that it is not soon outdated. Finally, it should be noted that products need to be examined for their individual characteristics and used according to their appropriate category.

Chapter 2: Categorisation and effect on host tissue

The CAMPs consensus panel considered categorisation, activity on host tissue and evidence-based practice.

Categorisation

Other groups have proposed categorising CAMPs according to variable characteristics, such as cellularity (cellular or acellular),[36] replaced region (epidermal, dermal or both)[16] or source (autologous, allogeneic, xenogeneic or biosynthetic).[16] Evan Davison-Kotler designed a factorial algorithm for categorising skin substitutes (the term used in his work) according to four characteristics:

- Cellularity (cellular or acellular)
- Replaced region (epidermal, dermal or both)
- Layering (single layer or bilayer)
- Material (natural, synthetic or both).[37]

However, this algorithm does not address repair or regeneration of deeper tissue, such as in a hernia, fistula or joint, rather than an integumentary defect—nor does it include matrices designed to provide and/or stimulate production of scaffolding for tissue growth.

Noting the weaknesses of these classifications, the panel proposed a categorisation system for CAMPs based on their composition (*Table 1*). This divides products first into cellular, acellular and matrix-like categories. They are then divided into either autograft, allograft and xenograft subcategories for cellular and acellular products, or natural and synthetic subcategories for matrix-like products. Cellular products are then further divided by whether the cells are viable or non-viable.

Table 1. Compositional categorisation of cellular, acellular and matrix-like products (CAMPs)

Category	Subcategory
Cellular	· Autograft (viable) · Allograft (viable or non-viable) · Xenograft (viable or non-viable)
Acellular	· Allograft · Xenograft
Matrix-like	· Natural · Synthetic

Key points

- The consensus panel considered that previous methods of categorising biomaterial products had inherent weaknesses, and so propose a new categorisation into cellular, acellular and matrix-like
- When in contact with host tissue, CAMPs can modulate intracellular signalling, intercellular communication and extracellular/scaffolding activities
- They also contain or stimulate activity of growth factors and regulatory proteins, which play a major role in the processes required for tissue regeneration
- Although there is a large body of clinical evidence and cost-effectiveness data on CAMPs, there are few comparative studies on their relative efficacy and no systematic reviews to determine which category might be better for a particular pathology

Activity on host tissue

The viable or living cells used in allograft and autograft products can be either differentiated cells, such as fibroblasts and keratinocytes, or non-differentiated cells, such as stem cells, as in living amniotic tissue or autologous micrografts.[38]

Although not well understood for all of the individual products, modulation of the following three activities may occur when a bioactive material is placed in contact with the host tissue:[39,40,41]

- Intracellular signalling
- Intercellular communication (between the cells in the graft and the cells in the host tissue)
- Extracellular matrix (ECM)-linked or scaffolding activities.

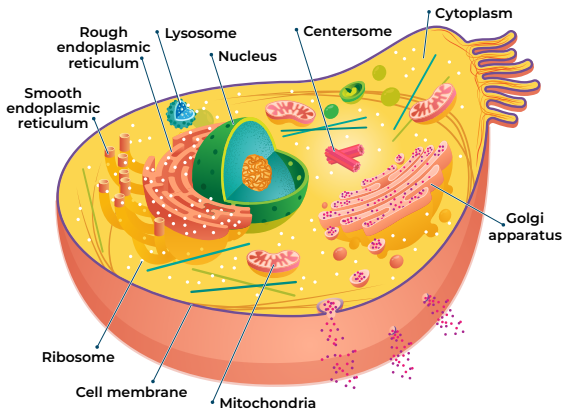
A wide spectrum of growth factors and/or matrix molecules has been identified in the individual products; these bioactive structures play critical roles in regulating tissue development and growth. Epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), keratinocyte growth factor (KGF), transforming growth factor alpha and beta (TGF-α and TGF-β), vascular endothelial growth factor (VEGF) and tissue inhibitors of metalloproteinases (TIMPs) are some of the regulatory proteins that play essential roles in the signalling, communication and physiological

processes required for healthy tissue regeneration, including cell migration, proliferation and recruitment.

Although most CAMPs have overlapping or multiple effects, an understanding of these is a critical part of clinical decision-making about which product to use. It is also important to recognise that an individual product's characteristics and possible effects do not necessarily correlate with its efficacy for a given indication, such as a DFU or venous leg ulcer (VLU).

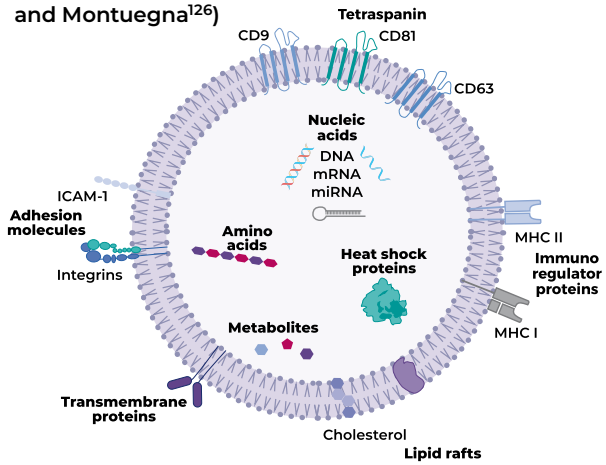
Fig 1. Cell organelles (adapted from National Health Genome Research Institute[125])

VectorMine via AdobeStock



Organelles are macromolecules contained within the cell that regulate cellular biochemical functions. Important cell organelles include the nuclei (for storage of genetic information), mitochondria (for production of chemical energy) and ribosomes (for assembly of proteins)

Fig 2. Exosome components (adapted from Valencia and Montuegna[126])



Exosomes are extracellular vesicles secreted by almost all cell types to aid many cellular functions. They contain molecules such as nucleic acids, proteins or lipids.

Intracellular signalling

The wound healing cascade is a precisely orchestrated sequence of cellular and acellular (or non-cellular) activity that depends on:

- Concentration and timing of chemical signal delivery
- Target cell receptor availability
- Degradation rate
- Messenger half-life
- pH
- Presence of enzymes (eg, proteases) in the wound.[42]

Cells produce interleukins, cytokines and chemokines, which drive the intercellular signalling involved in wound repair. When these key cells are not present or do not produce the necessary components (at which point the cells are termed senescent), wound healing stalls.[43]

When applied into a wound, CAMPs have the potential to re-establish an ideal wound healing environment capable of supporting host cells or recruiting alternative cells, which either produce or activate the intrinsic proteins required for wound closure.[48]

Intracellular signalling, which occurs between the organelles (*Figure 1*) located within a cell, precisely regulates the cellular biochemical functions, including anabolic and catabolic reactions, pH regulation, protein production and motility, fatty acid synthesis and oxidation, removal of waste products and storage of genetic information.[44]

The timely and successful function of a cell depends on the communication between the organelles to maintain metabolic coordination, primarily through membrane contact sites. This is key to cell survival and effective functioning, which allows wound healing to occur without detriment or undue delay.[44]

Extracellular communication

Exosomes (*Figure 2*) are extracellular vesicles secreted by almost all cell types to aid many cellular functions, including intercellular communication, cell differentiation and proliferation, angiogenesis, stress response and immune signalling—all processes that are necessary for normal wound healing.[45]

Exosomes may contain a variety of proteins, lipids, cell surface receptors, enzymes, cytokines, transcription factors and nucleic acids that modulate the cellular activity involved in tissue regeneration.[45] When exosomes interact with other cells, their contents may be transferred to the target cell, thereby altering the physiological state of the recipient cell.

By introducing exosomes into injured tissue (either by stem cells, adipose cells or extracted exosomes in a hydrogel), the activity of the recipient cells can be upregulated in such a way that the factors that inhibit wound healing, such as chronic inflammation, are diminished, and the processes necessary for wound healing, such as angiogenesis and collagen synthesis, are stimulated. Therefore, the introduction of exosomes for intercellular communication can accelerate healing.[46,47]

Extracellular matrix activities

ECM components—including fibronectin, glycosaminoglycans (GAGs), proteoglycans, thrombospondin, tenascin, vitronectin and collagens—create a scaffolding or structural integrity for the dermal cells involved in wound healing.

The ECM also facilitates cellular and acellular signal transduction between keratinocytes and fibroblasts during all phases of healing.[48] This signalling modulates the action of cytokines, chemokines and growth factors, thereby mediating the interactions among cells; between cells; between cells and the matrix; or between the ECM proteins.[49]

Dynamic reciprocity, defined as the ongoing bidirectional interaction among the cells and the surrounding environment provided by the ECM, is an integral part of the wound healing process that causes cells to differentiate, proliferate, migrate and survive.[50]

Another function of ECM is the promotion of communication between keratinocytes and fibroblasts, which are responsible for the formation and maintenance of the adnexal structures (hair follicles, sweat glands and innervations). When the adnexal structures are destroyed, the epidermis cannot self-regenerate because of the loss of stem-cell sources.[48]

Hyaluronic acid, a GAG that is prevalent in the ECM, has the capacity to retain water.[51] The synthesis of hyaluronic acid increases during tissue injury and wound healing. This regulates several aspects of tissue repair, such as the activation of inflammatory cells to enhance the immune response. Hyaluronic acid and other GAGs are also involved in the fibroblast and endothelial cell response to injury.[52]

Therefore, when exogenous ECM is added to injured tissue, it may facilitate the wound healing process by retaining moisture and upregulating the cellular responses.[53]

Hyaluronic acid is a basic component of amniotic fluid present in placental tissues and, therefore, plays an important role in fetal health, presumably by influencing the activity of various growth factors and signalling molecules during wound healing.[54] Growth factors that are commonly present in amniotic fluid include EGF, TGF-α and TGF-ß, insulin-like growth factor I (IGF-I), erythropoietin (EPO), granulocyte colony-stimulating factor (GCSF) and macrophage colony-stimulating factor (MCSF).[55,56] In addition, heavy chain-hyaluronan/pentraxin 3 (HC-HA/PTX3) has been identified by Tseng et al. as a key biological ECM component within the cryopreserved amniotic membrane that is both anti-inflammatory and anti-scarring.[57] With maternal permission, the placental tissues can be donated for processing into sheet grafts using any of several different methods. Because the tissue can contain epithelium, basal membrane, compact layer and fibroblast layers, products containing amnion and amniotic fluid can also contain stem cells, ECM and regulatory cytokines, all of which support tissue growth and modulate inflammation in utero.[58,59] In wound management, placental products are used primarily for coverage. The way in which the tissue is preserved may play a critical role in what portions of the placental products are enhanced.[60–62]

The ECM is especially relevant in the maturation phase of wound healing. How this phase takes place determines if the tissue heals by repair or by regeneration. Repair is defined as follows:

'A closure process where fibroblasts bridge the wound gap by organising their ECM differently from the healthy status.'[48]

This can result in more disorganised scarring and diminution of biological function. Regeneration is defined as follows:

'The organisation of the ECM that will appear indistinguishable from the healthy status.'[48]

The role of CAMPs, including enzyme-responsive systems, in wound management is to reinforce the wound's innate healing mechanisms that create dynamic reciprocity and thereby support the reestablishment of the wound healing processes and help restore normal tissue function, whether that is epidermal, dermal, connective or fascial.[63]

Evidence-based practice

Randomised controlled trials (RCTs) play a pivotal role in the FDA's process for determination and approval of a product for marketing and distribution. RCTs compare a given product used in combination with standard of care with provision of standard of care alone, usually for a specific diagnosis (for example, acellular xenograft plus standard of care for a DFU).[64] However, the quality and quantity of evidence among the different categories of products (and for products within categories) varies, which is not necessarily a reflection on product efficacy, defined as its ability to produce a desired or intended result. In addition, standard of care can differ among RCTs and may be poorly documented.[65,66]

There is a large body of evidence in the literature on the use of CAMPs. This includes a number of health-economic studies with intense patient and wound scrutiny, all of which support the healing efficacy and financial advantages of CAMPs. Although RCTs comprise the highest level of evidence, they sometimes also have inclusion/exclusion criteria that preclude their being reflective of the real-world experience.[67] For example, trials need to include more information on patients' socioeconomic status, ethnicity, comorbidities and medications—information that would aid health professionals in applying research findings to their patient populations.[68] In addition, there are few comparative studies demonstrating superiority of one CAMP over another, and there are no systematic reviews comparing products to determine which category might be better for a particular pathology. Differences in product composition and the proprietary processing methods used by manufacturers make each CAMP unique, creating a need for more comparative studies.

There is limited information in the literature to help guide health professionals in making decisions about which product to use for a particular indication. The panel feels strongly that there needs to be continued support for research to better understand the physiological effects and/or mechanism of action of CAMPs. Given the limited literature mentioned above, when a provider is considering a CAMP for patient care, factors that contribute to the clinical experience need to be taken into account, and the judgements needed to make an optimal decision should be factored in. This requires:

- Understanding of the composition and potential action of the product and its components
- Thorough patient evaluation
- In-depth wound assessment to determine what the wound needs for healing to progress
- Adequate wound bed preparation involving debridement of all non-viable tissue[69]
- Specific patient-centred goals.

Health professionals are also advised to carefully review the indications and contraindications provided by each product's manufacturer.

While the panel acknowledges that institution formularies and cost-effectiveness are considerations in clinical decision-making, selection should be based primarily on clinical rather than economic or organisational needs. The ability of staff to provide follow-up care may also need to be considered.

Chapter 3: Principles of care and clinical objectives

CAMPs can be used in the management of wounds of almost all aetiologies: typical and atypical wounds, surgical incisions (both dermal and deep), traumatic injuries, acute wounds and hard-to-heal and complex wounds. There is also growing evidence for the use of CAMPs in dermatological disorders.[70]

Key points

- CAMPs can be used on wounds of all aetiologies, from surgical, to atypical, to hard to heal; there is also evidence for their use in dermatological conditions
- This therapy should be initiated when a wound has failed to respond to standard of care and the patient's risk factors and comorbidities have been addressed
- Application earlier than is often currently the case can be considered, providing the above criteria have been met
- Treatment goals for CAMPs are to provide structural support, stimulate epithelial cell migration and angiogenesis, enhance surgical closure, maintain or improve joint performance, increase tensile strength, reduce the risk of recurrence and minimise scar tissue

Principles of wound care

The basic principles of caring for patients with wounds are described in the *JWC* TIMERS consensus document (*Table 2*).[34] The TIME paradigm has been universally accepted as referring to:

- Tissue (debridement of devitalised tissue)
- Inflammation and Infection (adequate treatment of infection including biofilm)
- Moisture (management of moisture to create an environment conducive to healing)
- Edges (treatment of edges to facilitate full wound closure).

The TIMERS consensus panel added two critical aspects of wound management to this paradigm:

- Repair and regeneration
- Social and patient-related factors.

Table 2. TIMERS framework[34]

Aspect	Clinical characteristic	Management options	Outcome objectives
T: Tissue	Devitalised tissue	Debridement	Clean wound bed
I: Inflammation and infection	Inflammation and/or infection, bioburden	Primarily topical antimicrobials, antibiotics and antibiofilm treatment, cleansing with surfactants	Control of inflammation, infection and biofilm
M: Moisture	Incorrect moisture balance	Dressings to hydrate dry tissue; absorbent dressings or negative pressure wound therapy and/or compression therapy to manage excess moisture	Moisture management and creation of a wound environment conducive to healing
E: Edge	Rolled edges, epibole, callus, hypergranulation tissue and poor advancement	Debridement, silver nitrate, or pressure for hypergranulation	Reduction in wound size; epithelialisation
R: Repair and regeneration	Slow, stalled closure despite provision of standard of care	Advanced therapies, including CAMPS	Wound closure; tissue repair
S: Social and patient-related factors	Psychosocial factors; physical factors and comorbidities; extrinsic factors	Specialist care for comorbdities. Patient education; active listening; patient empowerment and activation; motivational interviewing and literacy	Patient concordance and adherence to treatment; increased patient satisfaction with care

In relation to ECM activities, repair/regeneration can be enhanced with the use of advanced therapies, such as oxygen therapy, biophysical agents, NPWT, energy therapies, topical interventions and CAMPs. The CAMPs consensus panel advises that these interventions be implemented when the wound is not responding to standard of care for a given aetiology and the patient-specific risk factors and underlying conditions have been addressed.

Although there is medical evidence supporting the initiation of CAMPs if the progression towards closure of a DFU stalls after 30 days of standard of care,[67,71–73] the average time to application of the first CAMP on a Medicare patient with a hard-to-heal DFU is >69 days.[74] The CAMPs consensus panel strongly recommends that earlier consideration of CAMP application, particularly within 30 days of the initial DFU clinic visit or the initiation of the acquisition and approval process, may benefit patient outcomes and have economic value[35,74] (this will be discussed in more detail in Chapter 4).

The social- and patient-related factors of TIMERS include psychosocial factors that affect adherence to the care plan, social support of family and caregivers, cognitive status and ability to understand instructions, impact of the care plan on activities of daily living and quality of life, mobility, environment and living conditions. Social habits, such as smoking and vaping,[75–77] alcohol intake and illicit/non-prescribed drug use, also need to be considered when selecting and applying interventions, especially if the patient is unwilling or unable to cease habits that will negatively impact treatment efficacy. Global funding issues may inhibit the use of CAMPs in some places where government coverage is not available and there are not third-party payers.

Another critical factor affecting treatment outcomes is communication between primary care physicians and other specialists involved in the patient's care. These not only include vascular surgeons, plastic surgeons, endocrinologists, rheumatologists, dermatologists and podiatrists, but also allied health professionals who may be involved in regular wound monitoring and treatment plan changes, such as nurses, physical therapists, lymphoedema specialists, nutritionists and diabetic educators.

Discussion is sometimes complicated by the different classification systems used for specific wound aetiologies, such as the Wound, Ischaemia and Foot Infection (WIFI) and Wagner classifications for DFUs and staging for pressure injuries/ulcers, and the fact that some wounds have mixed aetiologies.

Best practice requires an interdisciplinary team approach, with effective communication between members, based on the understanding that the patient is the most important part of the team.

Clinical objectives

The panel recommends that CAMPs, as well as serving as a barrier, should be used to achieve the following clinical outcomes:

- Structural support for soft-tissue deficits, as well as a barrier against the external environment
- Stimulation of angiogenesis and matrix production
- Coverage of deep structures
- Epithelial cell migration
- Binding/inactivation of proteases and protection of endogenous growth factors
- Enhancement of surgical closure
- Improvement in and maintenance of functional performance, such as joint range of motion and increased tensile strength
- Reduced risk of wound recurrence
- Improved cosmetic appearance by minimising scar tissue[61,62]

All these outcomes have been observed to be associated with CAMP application. This is based on the cellular and acellular actions supported by CAMPs, along with the other factors that promote healing

Chapter 4: Guidelines for use

This chapter presents guidelines for using CAMPs, covering preparation for application, application, reapplication care and cessation of treatment.

Preparation for application

As with any medical procedure, application of a CAMP product should be preceded by a thorough assessment to optimise the patient for wound closure. This assessment includes, but is not limited to, the components given in *Box 3*.[78] Meanwhile, the wound assessment should include appraisal of the:

- Wound location
- Wound dimensions (length, width and depth)
- Any undermining and tracks
- Tissue type(s) present
- Periwound skin
- Exudate
- Oedema
- Wound edges
- Malodour
- Pain
- Signs of infection/inflammation
- Exposure of deep structures.[78]

Box 3. Aspects of patient assessment[78]

- Patient history, including medical and psychiatric history for any comorbidities that may impede wound healing
- Pain levels
- Medications (prescription, herbal o over-the-counter)
- Allergies that may be specific to the CAMP being considered for use
- Nutritional status
- Laboratory values pertinent to wound healing
- Vascular perfusion status
- Blood glucose control for patients with diabetes or pre-diabetes
- Alcohol consumption; smoking or vaping status; or use of other tobacco products, such as chewing tobacco; drug habits
- Past wound care and response to it
- Functional status and use of any assistive devices
- Vocational and recreational activities, including requirements and limitations
- Cultural and religious beliefs
- Social support if patient is housebound or level of care if patient is in a facility
- Any other risk factors that may affect the patient's healing potential

Key points

- A comprehensive holistic patient and wound assessment must be completed before CAMPs are applied
- Wound bed preparation, with adequate debridement, is required before application; lack of or insufficient debridement will result in CAMP failure
- Patients must be given information and education on CAMPs before application; it is vital to manage patient expectations beforehand, and any religious or philosophical concerns or objections should be discussed
- Informed written patient consent must be gained before initiating treatment with CAMPs
- The manufacturer's instructions or protocol for use must always be adhered to
- During application, ensure there is full contact between the CAMP and the wound bed, with no dead spaces in which fluid can accumulate
- If the wound fails to progress after application, further comprehensive holistic assessment is required; if necessary, discontinue treatment or apply a different CAMP product with a new treatment objective

Wound location is important, because the amount of pressure that might be incurred or motion present can create friction and/or shear between the CAMP and the host tissue, increasing the risk of failure.

The Enhanced Recovery After Surgery (ERAS) protocol is an evidence-based approach that aims to minimise the stress of surgery, improve outcomes, promote quicker recovery and reduce hospital length of stay.[79,80] The guidelines, which incorporate preoperative, intraoperative and postoperative care, begin with optimising the patient's physical status before surgery.[81] Although there are ERAS guidelines for multiple surgical specialties, there are none for wound management. The panel concurs that the development of protocols similar to ERAS would be beneficial for patients with wounds.

The well-documented factors that can impede wound healing must be acknowledged and addressed

Table 3. Factors that impede wound healing, adapted from Hamm[110]

Infection · Bacterial · Biofilm · Fungal · Viral
Elevated pH of the wound bed[111]
Medications · Anticoagulants (these can prolong bleeding or delay onset of inflammatory phase) · Antirejection and immunosuppressive medications · Calcium channel blockers · Non-steroidal anti-inflammatory drugs (NSAIDs) · Steroids
Comorbidities · Anaemia · Arterial insufficiency · Cardiac disease (eg, right-side heart failure) · Coagulopathies · Chronic oedema (eg, venous, lymphatic or traumatic) · Chronic renal disease · Diabetes · Hypothermia · Obesity · Protein energy malnutrition · Pulmonary/respiratory diseases · Rheumatologic disorder · Vitamin/mineral deficiencies (eg, vitamins A, C, D, B12; copper; manganese; zinc)
Moisture due to incontinence, perspiration or wound drainage
Mechanical forces (shear, friction, pressure)
Cancer therapies · Cancer-related surgery with lymph-node resection and subsequent lymphoedema · Chemotherapy (topical and systemic) · Radiation
Autoimmune disorders (both the disease and the medication)
Negative psychological states (eg, stress, anxiety and depression)
Lifestyle factors · Alcohol abuse (>4 drinks/day in men, 3 drinks/day in women) · Factitious behaviours · Smoking and vaping
Foreign bodies, including synthetic and orthopaedic materials

to optimise outcomes (*Table 3*). The standard of care for pressure, arterial, venous and diabetic foot ulcers is an integral part of patient care and so must be implemented. To optimise outcomes, it is vital that patients adhere to standard of care throughout the course of treatment with a CAMP product (*Table 4*). Once the assessment is complete and the underlying conditions have been addressed, wound bed preparation with adequate wound debridement is required before the CAMP is applied. Lack of adequate debridement of the wound bed will ultimately lead to CAMP failure.

Patient education

It is vital that patients are given information and education on CAMPs before application. This should include the basics of CAMP technology and instruction on post-application care and activity restrictions. Before application, discussions with patients should aim to manage their expectations. Any allergies and religious or philosophical objections to any of the product ingredients will also need to be discussed. Consent for treatment required for the procedure, especially if surgery is involved, must be reviewed and signed. The panel recommends that every institution or provider have a CAMP-specific consent form that lists the risks and benefits of the products. Any out-of-pocket expenses that may be incurred by the patient should also be disclosed before treatment.

Preparing the wound

Wound bed preparation is critical for successful outcomes with CAMPs. As defined in the TIMERS consensus document,[34] this includes adequate debridement of non-viable tissue using the most efficient method that can be tolerated by the patient, taking into account patient pain levels, haemostasis, equipment available and scope-of-practice constraints. Exceptions to aggressive debridement include:

- Pyoderma gangrenosum that has not been treated with immunosuppressive therapy[82,83]
- Non-infected stable eschar (defined as eschar that is attached at all edges with no fluctuance) on the lower extremity of a non-ambulatory patient

- Patient with a terminal illness or in palliative care
- Arterial wounds with dry, attached eschar that have not yet been adequately revascularied, ankle brachial pressure index (ABPI) under 0.5 and international normalised ratio (INR) over 2.5 — note that caution is recommended for sharp debridement and, before revascularisation, only infected tissue should be debrided.[34]

The panel agrees that, in each of these situations, CAMPs application should be deferred until the underlying condition is addressed and the wound bed is adequately prepared. Failure to do this could result in need for a future application of the CAMP.

Inflammation and infection, especially excess biofilm, need to be resolved through debridement, use of topical antiseptics and personalised antimicrobial therapy.[84] Technologies are available that can assess bacterial load through fluorescent imaging[85–87] or measure biomarkers of healing potential, such as growth factors, interleukins, MMPs and TIMPs.[88,24] These studies may be useful in determining the optimal time for CAMP application, especially for the surgical patient. There are also technologies that may be able to assess the adequacy of tissue perfusion and oxygenation using near-infrared imaging (NIRS).[89]

Moisture balance is critical to CAMP application and is discussed in the next section. If excessive drainage is present in the wound as a result of local or extremity oedema, the plan of care must include absorbent dressings and adequate safe compression. If oedema is the result of a systemic disorder, treatment of the underlying pathology is imperative and diuretics may be indicated; if the oedema is lymphatic in origin, referral to a lymphedema specialist is advised.[34] Regardless of its cause, oedema must be resolved and reduced before a CAMP is applied.

One of the indications for CAMPs, particularly for stalled wounds, is to reestablish an environment in the wound bed that encourages epithelial migration. Therefore, attention to the wound edges is part of pre-application care, which includes removal of callus or other non-viable tissue containing senescent cells. The status of the wound edges, wound depth, presence of undermining and tissue type are all factors in CAMP selection.

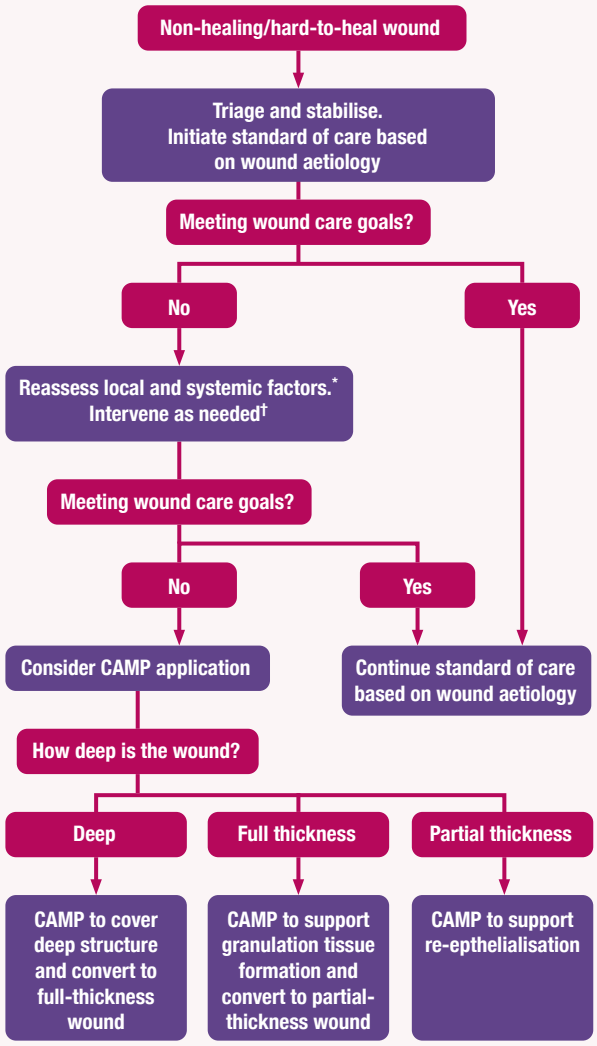
It is important to note the differences between using CAMPs on surgical patients—for example, after surgical debridement or in conjunction with a surgical procedure—and using them on patients with hard-to-heal wounds in non-surgical settings, such as outpatient clinics, long-term care facilities or acute

Table 4. Recommended best practice for wounds

Aetiology	Recommendation
Arterial	Before revascularisation: dry dressing and protective footwear, gentle debridement of infected and/or non-viable tissue only, after revascularisation: debridement into viable bleeding tissue when tissue perfusion supports healing, moist wound healing (with protective moist dressings over exposed bone and tendon), adaptive footwear for any amputations performed as a result of critical limb ischaemia
Venous	Appropriate non-invasive anatomic diagnosis (eg, venous reflux ultrasound), vascular referral for management of venous insufficiency/deficit repair, assessment of arterial perfusion—compression tailored to specific venous aetiology, debridement, moist wound healing with appropriate absorbent dressings, ankle exercises to strengthen the gastrocsoleus muscle and activate the venous pump
Pressure	Pressure redistribution with appropriate support surfaces and repositioning, debridement, moist wound therapy, optimised nutrition, management of incontinence, mobility training
Diabetic foot	Maximal data-driven offloading of affected area, blood glucose control, debridement, moist wound therapy, vascular assessment (ankle- or toe-brachial index), nutrition counselling, oedema management
Atypical	Biopsy to confirm the diagnosis, treatment of the underlying pathology, debridement, moist wound therapy, edema management if present

settings. Both the underlying comorbidities and factors that may impede wound healing must be addressed. There may be differences in the method of debridement required, type of tissue present, wound depth and treatment goals, all of which will influence CAMP selection and wound management dressing—for example, with NPWT potentially being selected for a surgical wound or occlusive dressings under compression for lower extremity wounds.

Fig 3. Decision-making flowchart for CAMP application



*For example, biopsy and X-ray; †for example, vascular intervention

The decision-making process for determining if and when a patient is appropriate for CAMP application is illustrated in *Figure 3*, with the final goal for every wound being full closure with return to optimal function.

Application

The wound diagnosis, tissue type and size influence the decision about when to apply a CAMP. The patient condition, as determined during the pre-application triage, also influences when the product can be applied. However, this decision is not based on wound duration. If, following use of standard of care based on its aetiology, a hard-to-heal wound fails to progress through a timely healing sequence, additional wound assessments (eg, cultures, biopsies, laboratory tests and imaging) may be indicated to detect the underlying factors impeding wound healing. If none are identified, more aggressive debridement and CAMP application are indicated.

A comparative study by Tettelbach et al. involving patients with lower extremity diabetic foot ulcers showed that earlier and more aggressive debridement and use of advanced care with a placental product resulted in overall better outcomes compared with standard of care alone without advanced care.[74]

For surgical wounds, the use of CAMPs in conjunction with surgical wound excision has resulted in better cosmetic outcomes, reduced scarring and improved function.[3,90] For wounds where vital structures (major arteries and veins, vascular grafts, nerves and organs) are exposed, it is strongly advised that the appropriate surgeon is consulted to develop a care plan that will protect the structures while wound closure is facilitated.

For both surgical and non-surgical wounds, it is recommended that all non-viable tissue be debrided and the bacteria load appropriately managed immediately before application of the CAMP.

Every CAMP manufacturer has specific protocols for its product, which should be studied before and adhered to during application. This may include hydrating the product with normal saline if the product has been dehydrated or cryopreserved. However, there are some general guidelines for all

CAMPs. Selection of an appropriate CAMP depends on the patient's age, wound location, wound size, tissue type and expected outcomes. In most cases, a CAMP size that will achieve full coverage of the wound surface is selected.

During application, the CAMP is placed directly onto the wound bed, with care taken to ensure that full contact is maintained between the product and the wound surface; there must be no dead spaces in which fluid can accumulate between the CAMP and the wound surface. The product is then secured with a bolster dressing, NPWT[91] or compression, as well as, in most cases, sutures, staples or wound-closure strips to prevent slippage, which typically results from friction and/or shearing forces and may lead to CAMP failure. Meshing and fenestration can also be beneficial where there is high risk of fluid accumulation under the product.

After the product is firmly affixed, a non-adherent cover dressing may be applied, with the primary purpose of maintaining moisture balance. This also prevents adherence to the CAMP if the dressing needs to be changed before the next application. If wound bed preparation has been adequate, antimicrobial dressings should not be necessary. Use of cytotoxic antiseptic products (Dakin's solution, povidone iodine or acetic acid) is not typically recommended, especially in higher concentrations, as they may be harmful to any cells in either the cellular CAMP or the healthy host tissue.[92–94]

Finally, there must be adequate offloading, pressure redistribution, shear reduction and oedema management with compression, depending on the initial vascular assessment and wound diagnosis.

Based on clinical experience, a CAMP is typically left in place after the first application for 7–14 days, or as needed, depending on the product. However, the time period needs to be individualised based on holistic assessment of the patient and wound and the manufacturer's recommendation for use. If a CAMP is used with NPWT, early engraftment may occur, with an earlier need for reapplication. At every subsequent visit, an interval reassessment should be performed to determine the following:

- Efficacy of the product
- Any changes in the wound bed indicative of infection
- Presence of visible angiogenesis and/or epithelialisation
- Any collection of fluid under the CAMP
- Periwound skin reactions
- Patient adherence to the care plan.

If there is progression towards closure, the assessment needs to reflect the changes in wound size and tissue type, and it should determine what new treatment goals might be required. If the wound is not improving, the patient's underlying issues, such as blood glucose control, change in perfusion, bacterial load, activity limitations and adherence to compression or offloading—need to be re-assessed to determine the possible cause of the poor response.

Two relatively new technologies that might aid assessment pre- and post-application are:

- NIRS, which measures the percentage of oxygenated blood that reaches the wound bed and gives information on hypo- and hyper-perfusion and neovascularisation, both of which influence wound healing potential and flap patency[95–97]
- Fluorescence imaging, which can provide information on the presence, location and type of bacteria in a wound—information that can be used to predict healing potential, identify factors impeding wound healing and guide treatment plans.[85,86,98,99]

Neither technology has gained wide use, and more validation of their clinical value and efficacy is recommended.

A study by Ferrari et al. found that infection was the only variable significantly associated with failure of a dermal matrix on surgical wounds created in the treatment of skin cancer. This emphasises the importance of idenitfying and treating infection when using CAMPs.[100] If the wound is not progressing as expected at the time of follow-up after the first application, it may be prudent to confer with another wound specialist or clinical expert.

Reapplication care

Most CAMPs are placed on wounds multiple times, although the recommended number of applications may vary according to the individual product and its manufacturer's recommendation.[61,62,72,101] Re-application often occurs weekly or every other week, based on the wound's closure rate and appearance and the manufacturer's recommendations for use. In some cases, an immediate improvement may not be evident after the first application. In surgical cases, some products are reapplied only if grafting or incorporation of the CAMP into the tissue has failed. For hard-to-heal wounds being treated in an outpatient clinic, reapplication may not be appropriate if there is no improvement.

When reapplying a CAMP, all of the components of pre- and post-application care described above must be implemented, especially adequate debridement of non-viable tissue.

Provision of patient and caregiver education after each application is key to the success of treatment. This must include information on the aspects in *Box 4*.

Possible restrictions on activities of daily living depend on the wound location—for example, if it is on the knee or ankle, ambulation may be limited or specific equipment may be required to protect the CAMP's integrity by eliminating the potential for shear. If the CAMP is on the lip, the restrictions may relate to eating and drinking. The provider needs to factor in adequate time to discuss these issues with the patient and caregivers. If the patient is cared for in a long-term care facility or by home health, specific instructions should be conveyed to the staff to avoid inadvertent disturbance of the product.

Cessation of treatment

The decision to terminate CAMP application, which may or may not be the completion of wound care, is based on the following conditions:

- The goals set for treatment have been achieved
- There are clinical signs of infection; however, the use of CAMP can be resumed after the infection has been successfully treated
- The wound is not progressing as expected—holistic re-assessment to identify the underlying factors impeding wound healing is advised; once these issues have been resolved, the CAMP can be reapplied
- Adequate outcomes have not been achieved with the recommended applications of a CAMP
- The patient is allergic or hypersensitive to the product; if the offending ingredient in the product can be identified, an alternative CAMP may be considered
- The patient is transitioned to palliative care.

If the goals set at the time of the initial CAMP application are met (for example, a tissue defect is filled in), a different CAMP may be indicated to meet new objectives, such as re-epithelialisation with full wound closure. The initial treatment may not always be the best one, as wounds are dynamic and change with time. Therefore, clinical experience and judgment are the best guidelines for deciding whether to stop using a product or change to a different one.

Box 4. Priorities to be highlighted in patient education

- Maintaining dressing integrity by keeping it clean, dry and intact
- Limiting joint motion or tissue movement in areas over which a CAMP has been placed
- Using offloading devices for DFUs
- Using pressure-redistribution surfaces for pressure injuries/ulceration
- Adhering to compression therapy for venous leg ulceration
- Informing the provider of clinical signs suggestive of infection, such as increased drainage, malodour, pain or periwound erythema
- Ensuring clinical signs of infection are treated

Chapter 5: Barriers to implementation

The panel acknowledged that there can be obstacles to the use of CAMPs in the treatment of patients with hard-to-heal, complex or surgical wounds. This chapter identifies these hurdles and offers strategies and suggestions to help providers overcome them. Some of the impediments are specific to the US, but others are universal. However, the panel has tried to make these suggestions appropriate for all medical settings, provider scopes of practice and social concerns.

Key points

- Barriers to implementation of CAMPs, including storage requirements, lack of access and facility regulations, can be overcome with practical measures, careful budgeting and presenting evidence on their cost-effectiveness
- The CAMP selected can have its own financial implications due to factors such as size, application costs (for example, relating to debridement) and variations in expiration date
- Effective interdisciplinary communication, fast referral to specialists, expeditious payer approval and the prompt application, as recommended in this consensus document when indicated, can all increase the cost-effectiveness of CAMP therapy
- More research evidence is needed on the comparative benefits of CAMPs, their long-term outcomes and the potential for cost savings; more randomised controlled trials and, ultimately, systematic reviews are needed

Institutional impediments

Storage

Some CAMPs, particularly viable cellular products, have specific storage requirements to maintain product integrity and protect their shelf life. In some cases, underutilised space within a facility can be designated for CAMP storage; if none is available, capital equipment should be budgeted for. Note that the products do not require large storage spaces, but the appliance used for storage must be monitored to ensure the correct temperatures are maintained, as required for facility procedures. This is especially important for cellular products that are more expensive, have a shorter shelf life and require more attention in relation to handling, storage and preparation for application. Some commercial companies will assist in providing possible storage solutions.

Facility regulations

Before a CAMP is put on a facility formulary, it must be shown to conform to committee regulations and restrictions. This can be achieved by evidencing its cost-effectiveness and added value, such as:[69,74]

- Fewer inpatient hospital days
- Shorter healing times
- Lower infection and amputations rates
- Improved quality of life.

An understanding of the value analysis committee's criteria for approving a new product is critical in preparing a CAMP presentation.

Institutional policies may require tracking of products for inventory control that holds everyone involved in acquiring and using the products accountable for their purchase, storage and use. Additional regulatory tracking is required for products derived from human sources. Products that have serial numbers need to be registered in a log so that each item can be tracked from the decision to apply, purchase order and receipt of the product to application of the product on the patient. A logging system is needed for these products, regardless of the setting in which the patient is being treated. This is not only to account for each individual product; it is also informational in the case of a product recall—in summary, it is part of best practice.

Access

The availability of CAMPs can be affected by both location (rural versus urban) and care setting (hospital versus long-term care facility or office-based practice), as well as access to providers who are competent in their use. All wound-care providers are encouraged to identify and establish rapport with experienced specialists within a location for referrals about the management of underlying comorbidities; this will help achieve the optimal use of CAMPs. This is especially important if surgical debridement is needed before application but the facility does not have operating rooms, as well as for patients who have underlying comorbidities that need to be treated by specialists other than the

wound-care provider—for example, the vascular surgeon, rheumatologist or dietitian. If surgical debridement is not feasible due to lack of access to an operating room, application of the CAMP should be deferred until optimal wound bed preparation can be achieved with other methods. A CAMP should not be placed on a wound that is not adequately prepared.

Financial implications

Reimbursement

Payment will differ among third-party payers, which varies according to country, insurance and Medicare local coverage determinations (LCDs), including the need for prior authorisation, copayments (products are covered by a specific payer) and evidence/documentation required for reimbursement. Providers need to work closely within their payer systems to optimise coverage for their patients and to be familiar with what product is covered, how many procedures are allowed and bundling regulations, among other factors. Providers can empower patients, family members and caregivers to advocate for patients by providing them with the contact information they need to communicate within the payer systems and the medical information to justify treatment.

Product selection

Choosing the most appropriate product can have financial implications—for example, ordering the size that best fits the wound, considering the cost differential of the various products, matching the product to best achieve the desired physiological response and carefully checking the expiration date on the packaging are important for financial feasibility. Determining the need for debridement in the operating room versus at the bedside or in the clinic is critical, not only for outcomes, but also for cost analysis and reimbursement. Finally, the terminology used in documentation needs to be specific, so that all parties have a clear understanding of the patient and wound condition on which the clinical decision is based, as well as any secondary dressings and adjunctive therapies used in the treatment plan

Provider concerns

Clinical decision-making about the use of CAMPs is based on experience, knowledge and education. These should reflect the organisation's or facility's competency standards, which should cover patient selection, application, post-procedural care and documentation. Providers need to know the scope of practice determined by the state or governing agency for their professions, as well as any restrictions set by governmental agencies for provider billing codes. They also need to ensure there is consistency of care across the settings in which a patient is seen and between the caregivers providing care and monitoring the wound.

Patient outcomes can be optimised and costs for facilities saved with professional actions such as:

- Good communication across the care continuum
- Referral to specialists, such as vascular teams, rheumatologists or dietitians, when required
- Networking with other clinicians
- Expeditious payer approval so that earlier treatment can be initiated.

Communication between providers and payers must lead to decisions that are made in the patient's best interest and not based on economics.

Financial benefits of earlier application

There is a need for more universal education about the role of CAMPs in improving the care of patients with hard-to-heal wounds, especially in underserved parts of the world. This should demonstrate how earlier use of CAMPs, rather than after lack of response to standard of care, can improve healing, economic and functional outcomes, with reductions in treatments and provider hours spent on each patient yielding net cost savings.[69,74] However, it should also help providers recognise when a wound is not responding to CAMP therapy and then discontinue treatment, as this is a critical part of the overall cost containment for individual patients.

According to a retrospective analysis of Medicare data from 2015 to 2018, the average time to the first application of a CAMP was greater than 69 days.[35]

Improved DFU outcomes were observed when CAMPs were started earlier, within the range of 30–45 days from the initial visit. Once initiated, the CAMP should be applied routinely every 7–14 days, or as needed, depending on the product, until the wound either resolves or becomes refractory to this therapy. That only 9.2% of Medicare patients being treated with a CAMP received the product in accordance with stated parameters for use indicates that further education on appropriate use of CAMPs is required.[35]

Social determinants

Smoking, vaping, alcohol misuse, poor nutrition, factitious behaviour and poor adherence are contraindications for CAMP application and need to be identified before application. Counselling and psychological support must be provided before therapy is initiated, to optimise outcomes and prevent product failure or wound recidivism.

Lifestyle, diet and religious concerns need to be recognised and discussed openly, so that the plan of care includes options that will accommodate any issues raised. Socioeconomic concerns, including coverage for treatment, logistical issues relating to getting to and from appointments and family support, also need to be addressed using whatever means are available within the community to aid patient care. The panel recognised that coverage, availability and support services vary among communities and countries, and these guidelines are offered with that understanding.

Regulatory evidence

The panel acknowledges that regulations vary depending on the following:

- Regulatory agency in each country and the evidence required for product approval
- Regulatory controls that apply to a particular product, based on clinical trials, wound aetiology and settings for application
- Endpoints used in the clinical trials and the subsequent conclusions made—for example, healing times instead of recurrence or cost analysis
- Settings for the clinical trials.

Specifically, there is a concern that recurrence is usually studied on a short-term basis (for example, 3 months), whereas data collected over longer periods would be beneficial in determining patient and cost benefits. Achieving patient adherence and follow-up care for a year is challenging, but it may be critical in drawing conclusions about data. The setting for clinical trials, such as inpatient versus outpatient, will also affect the conclusions on cost-effectiveness and product efficacy, while the outcomes used to make clinical decisions will vary between the different country agencies. Benchmarks are not standardised, and the ones used in clinical trials in the hospital setting tend to be those used to get product approval, which subsequently affects availability for patients in all settings.

Rationale

Evidence-based medicine is defined as 'a systematic approach to clinical problem solving, which allows the integration of the best available research evidence with clinical expertise and patient values'. It requires that clinicians do the following:[102,103]

- Apply evidence summaries to clinical practice
- Develop and/or update selected systematic reviews, meta-analyses and evidence-based guidelines in their areas of expertise
- Enrol patients in studies that advance treatment, diagnosis and prognosis.

Much of the literature on CAMPs is based on case studies or trials comparing the use of one product with standard of care for one diagnosis. Standard of care is not always well-documented or consistent between studies. There is a paucity of clinical trials comparing one CAMP with another CAMP (a need that is expressed by multiple authors) and few systematic reviews for what is classified as a complex intervention in healthcare.[104] Guise et al. suggested a method of developing a systematic review or meta-analysis for complex interventions that starts with identifying a need and then doing a literature review, followed by gathering expert opinion from a

Table 5. Systematic reviews or meta-analyses on skin substitutes or cellular tissue products for wound healing

Study	Focus	Conclusion
Pham et al. (2007)[121]	Comparison of the safety and efficacy of bioengineered skin substitutes versus biological skin replacements and/or standard dressing methods in the management of burns	Bioengineered skin substitutes are as safe and as efficacious as biological skin replacements or topical agents/wound dressings
Langer and Rogowski (2009) [109]	Cost-effectiveness of growth factors and tissue-engineered artificial skin for treating hard-to-heal wounds	Some growth factors and tissue-engineered artificial skin products have favorable cost-effectiveness ratios in selected patient groups with hard-to-heal wounds
Ellis and Kulber (2012)[112]	Use of acellular dermal matrix in forearm, wrist and hand reconstruction	Clinical indications for acellular dermal matrix have increased; hand surgeons continue to find innovative uses to solve upper-extremity surgical problems; more comparative prospective trials are needed
Felder et al. (2012)[113]	Outcomes and effectiveness of different skin substitutes for healing hard-to-heal foot ulcers	Living cell-based skin substitutes are effective for increasing the rate of complete healing in hard-to-heal foot ulcers; acellular skin substitutes show promise but require further research
Jones et al. (2013)[116]	Effect of skin grafts on the treatment of venous leg ulcers	Bilayer artificial skin in conjunction with compression bandaging increases healing of venous leg ulcers compared with a simple dressing plus compression
Paggiaro et al. (2016)[119]	Role of biological skin substitutes in the treatment of Stevens-Johnson syndrome and its related diseases	Biological dressings were found to be effective in reducing mortality, perhaps through increased epithelialisation, reduced water loss and decreased risk of infection
Santema et al. (2016a)[107]	Benefits and harms of skin grafting and tissue replacement for treating foot ulcers in people with diabetes	Effect of skin grafts and tissue replacements in conjunction with standard of care results in an increase in healing rate of foot ulcers and slightly fewer amputations in people with diabetes compared with standard of care alone
Santema et al. (2016b)[123]	Effectiveness of skin substitutes on ulcer healing and limb salvage in the treatment of diabetic foot ulcers (goes into greater detail about studies reviewed for the Cochrane review above)	Skin substitutes plus standard of care increase the likelihood of complete ulcer closure compared with standard of care alone
Tchero et al. (2017)[124]	Use of five regeneration matrices (Integra, Nevelia, Matriderm, Pelnac, Renoskin) as reported in clinical trials	An overall low failure rate suggested that bioengineered skin products provide a suitable support and microenvironment for healing of diabetic foot ulcers, with low recurrence rates
Porzionato et al. (2018)[122]	Systematic review of the development of grafts from decellularised human tissues/organs	N/A
Gordon et al. (2019)[106]	Efficacy of healing diabetic foot ulcers with biologic skin substitutes	Biological dressings are more effective than standard-of-care dressings in healing diabetic foot ulcers by 12 weeks
Paggiaro et al. (2019)[120]	Comparison of allograft skin with other skin substitutes that have been used in the treatment of burns	No differences were detected for the use of allograft skin versus other skin substitutes (noted that most of the study methods had a high risk of bias)

Table 5. Systematic reviews or meta-analyses on skin substitutes or cellular tissue products for wound healing (continued)

Study	Focus	Conclusion
Hoogewerf et al. (2020)[115]	Which topical treatments are most effective in healing facial burns, improving scars, decreasing complications and improving quality of life	Low-certainty evidence that skin substitutes might slightly reduce time to >90% healing compared with non-specified antibacterial agento; other factors studied had inconclusive evidence
Liang et al. (2020)[117]	Efficacy and safety of amniotic membrane for the healing of split-thickness graft donor sites	Uuse amniotic membrane for treating split-thickness graft donor sites was safe and effective
Snyder et al. (2020)[108]	Technology assessment of clinical literature on the various skin substitute products available in the US, suggesing best practice for future studies	There were 76 commercially available skin substitutes; studies rarely reported clinical outcomes (eg, amputation or recidivism) or patient-related outcomes (eg, pain, return to function, exudate or odour); of papers studies, 22 were randomised controlled trials, of which 12 had a low risk of bias
Ghio et al. (2021)[114]	Survival of skin-substitute grafts through clinical observations indicating that epithelial stem cells persisted in the skin substitutes	Multiple combinations of culture and production conditions could result in the formation of a new epithelial stem cell niche in a bilamellar skin substitute
Lorincz et al. (2022)[118]	Effectiveness of therapeutic modalities in the treatment of pediatric second-degree burns, compared with the use of silver sulphadiazine	Only three trials compared silver sulphadiazine with the same skin substitute, with 'a tendency for faster healing times and a reduced complication rate linked to biosynthetic, silver foam and amnion membrane dressings; there was a substantial difference between the number of dressing changes, associated with less pain and narcosis and shorter treatment duration

Terms used in this table reflect those used in the systematic reviews and meta-analyses cited.

panel of experts and ending with a 'broad international peer review' and final consensus.[104]

Levels of evidence were first developed in 1979 by the Canadian Task Force on the Periodic Health Examination and have undergone several modifications since then.[105] All of the modifications list systematic studies and meta-analyses as the strongest level of evidence. *Table 5* lists the systematic reviews and/or meta-analyses identified using 'skin substitutes' and 'cellular tissue products for wound healing' as the search words. Common considerations in these studies include the need for:

- Studies on the relative benefits of different CAMPs[106,107]
- Studies on the long-term implications of these products
- Studies to determine the financial considerations for their use[106,107]
- Better-designed and better–reported RCTs for their use on specific diagnoses[108]
- More recent systematic reviews.

Numerous case studies, retrospective studies, prospective studies and clinical trials have evaluated the efficacy of the many CAMPs currently available, but they have yet to be included in systematic reviews and are too numerous to summarise here.

Given their high cost, evidence on the cost-effectiveness of CAMPs is a major factor in gaining institutional approval for their use. However, providers and payers need to consider not only the cost of the product, but also the total cost of care for patients with hard-to-heal wounds.[74,109] The panel considered that, in the US, the current reimbursement climate is negatively affecting innovation in the development and use of CAMPs, and that, to demonstrate value, a paradigm is needed that actually states value matters.

Chapter 6: Summary

Since the introduction of biomaterial products for wound healing in the early 1970s, understanding of their effects has increased, and a plethora of these products has been developed. These products have been classified according to their cellularity (cellular vs acellular), source (autograft vs allograft vs xenograft) and material (natural vs synthetic). This led the expert panel for this consensus document to adopt the following definition for them:

'A broad category of biomaterials, synthetic materials or biosynthetic matrices that support repair or regeneration of injured tissues through various mechanisms of action'.

This was shortened to cellular, acellular and matrix-like products (CAMPs).

While CAMPs differ in composition, they provide human tissue that has been injured, either as a result of a disease, trauma or surgery, with the following benefits:

- Structural support for soft tissue through the stimulation of angiogenesis and matrix production, as well as coverage of deep structures
- Migration of epithelial cells
- Enhancement of surgical closure
- Improvement of functional outcomes
- Improvement in cosmetic appearance.

The success of any CAMP application depends on an appropriate and thorough patient evaluation, treatment of all underlying disorders, adequate wound bed preparation and comprehensive patient and caregiver education. This consensus document identifies impediments to their use in the current medical environment and suggests possible solutions for this. The panel recognises that, although the literature supports the use of CAMPs in the treatment of hard-to-heal wounds, burns, surgical wounds and some skin disorders, more good-quality research is needed to provide robust evidence on their benefits and to determine their efficacy and cost-effectiveness. This level of evidence is critical to obtain universal acceptance and availability of the products.

Consensus panel recommendations

1. There needs to be ongoing support for research to better understand the physiological effect and modes of action of CAMPs
2. Although institution formularies and cost-effectiveness are considerations in clinical decision-making, selection of CAMPs should be based primarily on clinical, not economic or organisational, need
3. The average time for first application of a CAMP on a Medicare patient with a hard-to-heal diabetic foot ulcer is over 69 days. Earlier application, even within 30 days of presentation, should be considered if the patient has not responded to standard of care, their risk factors have been addressed and the underlying aetiology and comorbidities treated
4. Discussion about the initiation of CAMPs requires an interdisciplinary approach
5. Key clinical objectives for the use of CAMPs include provision of structural support for tissue deficits and promotion of tissue regeneration and remodelling, with sustained healing, a good aesthetic outcome and increased tensile strength
6. Development of protocol(s) similar to the Enhanced Recovery After Surgery (ERAS) guidance would be beneficial for use in wound management
7. Following a comprehensive holistic assessment, wound bed preparation with adequate debridement is essential to achieve a good outcome with CAMPs
8. Safe but aggressive debridement of non-viable tissue is critical before application of any CAMP regardless of aetiology
9. All patients must receive education about CAMPs, their ingredients, mode of action and what to expect before application
10. Every institution should give patients a CAMP-specific consent form identifying the risks and benefits to sign in advance
11. Research studies need to have longer follow-up periods to determine full patient and cost benefits of CAMPs
12. The current reimbursement system in the US is negatively affecting innovation in CAMP development. To demonstrate value, a paradigm is needed that actually states that value matters

References

1. Winter GD. Formation of the scab and the rate of epithelization of superficial wounds in the skin of the young domestic pig. Nature. 1962;193:293–294
2. White E. The murky beginnings of the moist wound healing movement. Wounds UK. 2020;16(3):90. https://doi.org/10.1007/s12663-016-0880-z
3. Jones J. Winter's concept of moist wound healing: a review of the evidence and impact on clinical practice. J Wound Care. 2005;14(6):273–276. https://doi.org/10.12968/jowc.2005.14.6.26794
4. Tobias AM, Chang B. Pulsed irrigation of extremity wounds: a simple technique for splashback reduction. Ann Plast Surg. 2002;48(4):443–4. https://doi.org/10.1097/00000637-200204000-00019
5. Bath MF, Seresh R, Davies J, Machesney MR. Does pulsed lavage reduce the risk of surgical site infection? A systematic review and meta-analysis. J Hospital Infections. 2021;118:32–39
6. Gibbs KA, Hamm RL. Pulsed lavage with suction. In: Hamm R (ed). Text & atlas of wound diagnosis & treatment. New York (NY): McGraw Hill Education; 2019. p475–486
7. Bota O, Martin J, Hammer A et al. Microvascular Research. Microvasc Res. 2022;140:104301. https://doi.org/10.1016/j.mvr.2021.104301
8. Borgquist O, Ingemansson R, Malmsjö M. Individualizing the use of negative pressure wound therapy for optimal wound healing: a focused review of the literature. Ostomy Wound Manage. 2011;57(4):44–54
9. Pappalardo V, Frattini F, Ardita V, Rausei S. Negative pressure therapy (NPWT) for management of surgical wounds: effects on wound healing and analysis of devices evolution. Surg Technol Int. 2019;34:56–67
10. Kim PJ, Attinger CE, Constantine T et al. Negative pressure wound therapy with instillation: International consensus guidelines update. Int Wound J. 2020;17(1):174–186. https://doi.org/10.1111/iwj.13254
11. Nherera LM, Saunders C, Verma S, Trueman P, Fatoye F. Single-use negative pressure wound therapy reduces costs in closed surgical incisions: UK and US economic evaluation. J Wound Care. 2021;30(S5):S23–S31. https://doi.org/10.12968/jowc.2021.30.sup5.s23
12. Saunders C, Nherera LM, Horner A, Trueman P. Single-use negative-pressure wound therapy versus conventional dressings for closed surgical incisions: systematic literature review and meta-analysis. BJS Open. 2021;5(1):zraa003. https://doi.org/10.1093/bjsopen/zraa003
13. Armstrong DG, Marston WA, Reyzelman AM, Kirsner RS. Comparative effectiveness of mechanically and electrically powered negative pressure wound therapy devices: a multicenter randomized controlled trial. Wound Repair Regen. 2012;20(3):332–341. https://doi.org/10.1111/j.1524-475x.2012.00780.x
14. Singh M, Nuutila K, Kruse C, Robson MC, Caterson E, Eriksson E. Challenging the conventional therapy: emerging skin graft techniques for wound healing. Plast Reconstr Surg. 2015;136(4):524e–530e. https://doi.org/10.1097/prs.0000000000001634
15. Simman R, Phavixay L. Split-thickness skin grafts remain the gold standard for the closure of large acute and chronic wounds. J Am Col Certif Wound Spec. 2011;3(3):55–9. https://doi.org/10.1016/j.jcws.2012.03.001
16. Dai C, Shih S, Khachemoune A. Skin substitutes for acute and chronic wound healing: an updated review. J Dermatol Treat. 2020;31(6):639–648
17. Bay C, Chizmar Z, Reece EM et al. Comparison of skin substitutes for acute and chronic wound management. Sem Plast Surg. 2021;35:171–180
18. Haddad AG, Giatsidis G, Orgill DP et al. Skin substitutes and bioscaffolds: temporary and permanent coverage. Clin Plastic Surg. 2017;44:627–634. https://doi.org/10.1016/j.cps.2017.02.019.
19. Goodarzi P, Falahzadeh K, Nematizadeh M et al. Tissue engineered skin substitutes. Adv Exp Med Biol. 2018;1107:143–188. https://doi.org/10.1007/5584_2018_226
20. David JS. Skin transplantation with a review of 550 cases at the Johns Hopkins Hospital. Johns Hopkins Med J. 1910;15(307):307–98
21. Chardack W, Martin MM, Jewett TC, Boyer BE. Synthetic substitutes for skin. Plast Reconstr Surg. 1962;30(5):554–567
22. Lucich EA, Rendon JL, Vlerio IL. Advances in addressing full-thickness skin defects: a review of dermal and epidermal substitutes. Regen Med. 2018;13(4):443–446. https://doi.org/10.2217/rme-2017-0047.
23. Bell E, Ehrilich HP, Sher S et al. Development and use of a living skin equivalent. Plast Reconstr Surg. 1981;67(3):386–392
24. Bell E, Sher S, Hull B et al. The reconstitution of living skin. J Invest Dermatol. 1983;81(1):S2–S10
25. Bell E, Erlich HP, Buttle DJ, Nakatsuji T. A living tissue formed in vitro and accepted as a full thickness skin equivalent. Science. 1981;211:1042–1054
26. Oberweis CV, Marchal A, Lopez-Ruiz E, Galvez-Martin P. Tissue engineering, Part B. 2020;26(2):181–196. https://doi.org/10.1089/ten.TEB.2019.0315
27. Hart CE, Loewen-Rodriguez A, Lessem J. Dermagraft: use in the treatment of chronic wounds. Adv Wound Care. 2012;1(3):138–141. https://doi.org/10.1089/wound.2011.0282
28. US Food and Drug Administration. Website. 2020. www.fda.gov (accessed 10 March 2023)
29. Bolton AJM, Armstrong DG, Kirsner RS, Attinger CE, Lavery LA, Lipsky BA et al. Diagnosis and management of diabetic foot complications. Arlington (VA): American Diabetes Association; 2018
30. Center for Medicare and Medicaid Services. Wound applications of cellular and/or tissue based products (CTPs), lower extremities. 2022. www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdId=36690&ver=30 (accessed 10 March 2023)
31. Schaum KD. Fiction or fact: reimbursement for cellular and/or tissue-based products for skin wounds. Adv Skin Wound Care. 2019;32(2):55–57. https://doi.org/10.1097/01.ASW.0000550738.26041.c5.
32. Hughes OB, Rakosi A, Macquhae F et al. A review of cellular and acellular matrix products: indications, techniques, and outcomes. Plast Reconstr Surg. 2016;138(S3):138S–147S. https://doi.org/10.1097/PRS.0000000000002643
33. Abdo J, Ortman H. Biologic and synthetic cellular and/or tissue-based products and smart wound dressings/coverings. Surg Clin North Am. 2020;100(4):741–756. https://doi.org/10.1016/j.suc.2020.05.006
34. Atkin L, Bucko Z, Montero EC et al. Implementing TIMERS: the race against hard-to-heal wounds. J Wound Care. 2019;28(S3):S1–S49
35. Armstrong DG, Tettelbach WH, Chang TJ, et al. Observed impact of skin substitutes in lower extremity diabetic ulcers: lessons learned from Medicare Database (2015-2018). J Wound Care. 2021;30(S7). https://doi.org/10.12968/jowc.2021.30.sup7.s5
36. Barbul A, Gelly H, Masturzo A. The health economic impact of living cell tissue products in the treatment of chronic wounds: a retrospective analysis of Medicare claims data. Adv Skin Wound Care. 2020;33(1):27–34. https://doi.org/10.1097/01.ASW.0000581588.08281.c1
37. Davison-Kotler E, Sharma V, Kang NV, Garcia-Gareta E. A universal classification system of skin substitutes inspired by factorial design. Tissue Engineering. 2018;24(4):279–288. https://doi.org/10.1089/ten.TEB.2017.0477
38. De Francesco F, Graziano A, Trovato L et al. A regenerative approach with dermal micrografts in the treatment of chronic ulcers. Stem Cell Rev Rep. 2017;13(1):139–148. https://doi.org/10.1007/s12015-016-9692-2
39. Falanga V. Wound healing and its impairment in the diabetic foot. Lancet. 2005;366(9498):1736–1743. https://doi.org/10.1016/S0140-6736(05)67700-8
40. Hunt TK, Hopf H, Hussain Z. Physiology of wound healing. Adv Skin Wound Care. 2000;13(S2):6–11
41. Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic-Canic M. Growth factors and cytokines in wound healing. Wound Repair Regen. 2008;16(5):585–601. https://doi.org/10.1111/j.1524-475x.2008.00410.x
42. Werner S, Greenwald MB. Wound healing: an orchestrated process of cell cycle, adhesion, and signaling. Reference Module in Life Sciences. 2016;3:216–222. https://doi.org/10.1016/B978-0-12-821618-7.00213-3
43. Luttrell T. Healing response in acute and chronic wounds. In: Hamm R (ed). Text & Atlas of Wound Diagnosis & Treatment. New York (NY): McGraw Hill Education; 2019. p15–66
44. Jain A, Zoncu R. Organelle transporters and inter-organelle communication as drivers of metabolic regulation and cellular homeostasis. Molecular Metabolism. 2022;60(6):101481. https://doi.org/10.1016/j.molmet.2022.101481
45. Hade MD, Suire CN, Suo Z. Mesenchymal stem cell-derived exosomes: applications in regenerative medicine. Cells. 2021;10(8):1959. https://doi.org/10.3390/cells10081959
46. Li D, Wu N. Mechanism and application of exosomes in the wound healing process in diabetes mellitus. Diabetes Res Clin Pract. 2022;109882. https://doi.org/10.1016/j.

diabres.2022.109882
47. Lou R, Chen J, Zhou F et al. Exosome-cargoes microRNAs: potential therapeutic moldcules for diabetic wound healing. Druf Discovery Today. 2022;20. https://doi.org/10.1016/j.drudis.2022.07.008.
48. Urciuolo F, Casale C, Imparato G, Netti PA. Bioengineered skin substitutes: the role of extracellular matrix and vascularization in the healing of deep wounds. J Clin Med. 2019;1. https://doi.org/10.3390/jcm8122083
49. Olczyk P, Mencner L, Komosinska-Vassey K. The role of extracellular matrix components in cutaneous wound healing. Biomed Res Int. 2014;747584. https://doi.org/10.1155/2014/747584.
50. Schultz GS, Dvidson JM, Kirsner RS et al. Dynamic reciprocity in the wound microenvironment. Wound Repair Regen. 2011;19(2):134–148. https://doi.org/10.1111/j.1524-475X.2011.00673.x
51. Wu G, Kam J, Bloom JD. Hyaluronic acid basics and rheology. Facial Plast Surg Clin North Am. 2022;30(3):301–308. https://doi.org/10.1016/j.fsc.2022.03.004
52. Papakonstantinou E, Roth M, Karakiulakis G. Hyaluronic acid: the role in skin aging. Dermatoendocrinology. 2012;4(3):253–258. https://doi.org/10.4161/derm.21923
53. Panayi AC, Haug V, Liu Q et al. Novel application of autologous micrografts in a collagen-glycosaminoglycan scaffold for diabetic wound healing. Biomed Mater. 2021;16(3). https://doi.org/10.1088/1748-605x/abc3dc
54. Nyman E, Huss F, Nyman T, Junker J, Kratz G. Hyaluronic acid, an important factor in the wound healing properties of amniotic fluid: in vitro studies of re-epithelialisation in human skin wounds. J Plast Surg Hand Surg. 2013;47(2):89–92. https://doi.org/10.3109/2000656x.2012.733169
55. DCunha AR, Jehangir S, Rebekah G, Thomas RJ. Human amniotic membrane vs collagen in the treatment of superficial second-degree burns in children. Wounds. 2022;34(5):135–140. https://doi.org/0.25270/wnds/2022.135140
56. Castellanos G, Bernabe-Garcia A, Moraleda JM, Nicolas FJ. Amniotic membrane application for the healing of chronic wounds and ulcers. Placenta. 2017;59:146–153. https://doi.org/10.1016/j.placenta.2017.04.005
57. Tseng SC. HC-HA/PTX3 purified from amniotic membrane as novel regenerative matrix: insight into relationship between inflammation and regeneration. Invest Ophthalmol Vis Sci. 2016;57(5):ORSFh1–8. https://doi.org/10.1167/iovs.15-17637
58. Klama-Baryla D, Rojczk E, Kitala D et al. Preparation of placental tissue transplants and their applications in skin wound healing and chosen bullous diseases – Stevens-Johnson syndrome and toxic epidermal necrolysis treatment. Int Wound J. 2020;17(2):491–507
59. Robson MC, Krizek TJ. The effect of human amniotic membranes on the bacteria population of infected rat burns. Ann Surg. 1973;177(2):144–149. https://doi.org/10.1097/00000658-197302000-00003
60. Cooke M, Tan EK, Mandrycky C, He H, O'Connell J, Tseng SC. Comparison of cryopreserved amniotic membrane and umbilical cord tissue with dehydrated amniotic membrane/chorion tissue. J Wound Care. 2014;23(10):465–474. https://doi.org/10.12968/jowc.2014.23.10.465
61. Caputo WJ, Vaquero C, Monterosa A et al. A retrospective study of cryopreserved umbilical cord as an adjunctive therapy to promote the healing of chronic, complex foot ulcers with underlying osteomyelitis. Wound Repair Regen. 2016;24(5):885–93. https://doi.org/10.1111/wrr.12456
62. Raphael A. A single-centre, retrospective study of cryopreserved umbilical cord/amniotic membrane tissue for the treatment of diabetic foot ulcers. J Wound Care. 2016;25(S7):S10–S17. https://doi.org/10.12968/jowc.2016.25.sup7.s10
63. Brouns JEP, Dankers PYW. Introduction of enzyme-responsivity in biomaterials to achieve dynamic reciprocity in cell-material interactions. Biomacromolecules. 2021;22:4–23
64. Liu Y, Panayi AC, Bayer LR, Orgill DP. Current available cellular and tissue-based products for treatment of skin defects. Adv Skin Wound Care. 2019;32(1):19–25
65. Wilcox JR, Carter MJ, Covingron S. Frequency of debridements and time to heal: a retrospecitive cohort study of 321744 wounds. JAMA Dermatol. 2013;149(9):1050–1058
66. Carter MJ, Fife CE. Clinic visit frequency in wound care matters: data from the US Wound Registry. J Wound Care. 2017;26(S1):S4–S10
67. Gurtner GC, Garcia AD, Bakewell K, Alarcon JB. A retrospective matched-cohort study of 3994 lower extremity wounds of multiple etiologies across 644 institutions comparing a bioactive human skin allograft, TheraSkin, plus standard of care, to standard of care alone. Int Wound J. 2020;17(1):55–64. https://doi.org/10.1111/iwj.13231
68. Gethin G, Ivory JD, Connell L et al. External validity of randomized controlled trials of interventions in venous leg ulceration: a systematic review. Wound Repair Regen. 2019;27:702–710. https://doi.org/10.1111/wrr.12756
69. Tettelbach WH, Cazzell SM, Hubbs B, Jong JL, Forsyth RA, Reyzelman AM. The influence of adequate debridement and placental-derived allografts on diabetic foot ulcers. J Wound Care. 2022;31(S9):S16–S26. https://doi.org/10.12968/jowc.2022.31.sup9.s16.
70. Nilforoushzadeh MA, Amirkhani MA, Khodaverdi E, Razzaghi Z, Afzali H, Izadpanah S, Zare S. Tissue engineering in dermatology - from lab to market. Tissue Cell. 2022;74:101717. https://doi.org/10.1016/j.tice.2021.101717
71. Armstrong DG, Galiano RD, Orgill DP et al. Multi-centre prospective randomised controlled clinical trial to evaluate a bioactive split thickness skin allograft vs standard of care in the treatment of diabetic foot ulcers [published correction appears in Int Wound J. Int Wound J. 2022;19(4):932–944. https://doi.org/10.1111/iwj.13759.
72. Driver VR, Lavery LA, Reyzelman et al. A clinical trial of Integra Template for diabetic foot ulcer treatment. Wound Repair Regen. 2015;23(6):891–900. https://doi.org/10.1111/wrr.12357
73. Sheehan P, Jones P, Caselli A et al. Percent change in wound area of diabetic foot ulcers over a 4-week period is robust predictor of complete healing in a 12-week prospective trial. Diabetes Care. 2003;26(6):1879–1882. https://doi.org/10.2337/diacare.26.6.1879
74. Tettelbach WH, Armstrong DG, Chang TJ et al. Cost-effectiveness of dehydrated human amnion/chorion membrane allografts in lower extremity diabetic ulcer treatment. J Wound Care. 2022;31(S2). https://doi.org/10.12968/jwc.2022.31.sup2.s10
75. Jaleel Z, Blasberg E, Troiano C et al. Association of vaping with decreased vascular endothelial growth factor expression and decreased microvessel density in cutaneous wound healing tissue in rats. Wound Repair Regen. 2021;29(6):1024–1034. https://doi.org/10.1111/wrr.12945
76. Liu Z, Zhang Y, Youn JY, Zhang Y, Makino A, Yuan JX, Cai H. Flavored and nicotine-containing E-cigarettes induce impaired angiogenesis and diabetic wound healing via increased endothelial oxidative stress and reduced NO bioavailability. Antioxidants (Basel). 2022;11(5):904. https://doi.org/10.3390/antiox11050904
77. Mitri A, Lin G, Waldman RA, Grant-Kels JM. Effects of tobacco and vaping on the skin. Clin Dermatol. 2021;39(5):762–771. https://doi.org/10.1016/j.clindermatol.2021.05.004
78. Hamm R. Examination and evaluation of the patient with a wound. In: Hamm R (ed). Text & Atlas of Wound Diagnosis & Treatment. New York (NY): McGraw Hill Education; 2019. p67–97
79. Smith TW Jr, Wang X, Singer MA, Godellas CV, Vaince FT. Enhanced recovery after surgery: a clinical review of implementation across multiple surgical subspecialties. Am J Surg. 2020;219(3):530–534. https://doi.org/10.1016/j.amjsurg.2019.11.009
80. Spencer P, Scott M. Implementing enhanced recovery after surgery across a United States health system. Anesthesiol Clin. 2022;40(1):1–21. https://doi.org/10.1016/j.anclin.2021.11.011
81. Altman AD, Helpman L, McGee J et al. Enhanced recovery after surgery: implementing a new standard of surgical care. Can Med Assoc J. 2019;191(17):E469–E475
82. Chan MC, Janes C, Patel M, Ellis S, Lantis JC. The use of cellular- and/or tissue-bsed therapy for the management of pyoderma gangrenosum: case series and review of the literature. Wounds. 2021;33(6):161–168
83. Anaeme AN, Darnall AR, Anaeme K. Clinical efficacy of human split-thickness skin allograft in patients with pyoderma gangrenosum: a case series. Wounds. 2022;34(6):165–174
84. Schultz G, Bjarnsholt T, James GA et al. Global Wound Biofilm Expert Panel. Consensus guidelines for the identification and treatment of biofilms in chronic nonhealing wounds. 2017;25(5):744–757. https://doi.org/10.1111/wrr.12590
85. Oropallo AR, Andersen C, Abdo R, Hurlow J, Kelso M, Melin M, Serena TE. Guidelines for Point-of-care fluorescence imaging for

detection of wound bacterial burden based on Delphi consensus. Diagnostics (Basel). 2021;11(7):1219. https://doi.org/10.3390/diagnostics11071219
86. Hurley CM, McClusky P, Sugrue RM, Clover JA, Kelly JE. Efficacy of a bacterial fluorescence imaging device in an outpatient wound care clinic: a pilot study. J Wound Care. 2019;28(7):438–443. https://doi.org/10.12968/jowc.2019.28.7.438
87. Li S, Renick P, Senkowsky J, Nair A, Tang L. Diagnostics for wound infections. Adv Wound Care (New Rochelle). 2021;10(6):317–327. https://doi.org/10.1089/wound.2019.1103
88. Lindley LE, Stojadinovic O, Pastar I, Tomic-Canic M. Biology and biomarkers for wound healing. Plast Reconstr Surg. 2016;138(S3):18S–28S. https://doi.org/10.1097/prs.0000000000002682
89. Li S, Mohamedi AH, Senkowsky J, Nair A, Tang L. Imaging in chronic wound diagnostics. Adv Wound Care (New Rochelle). 2020;9(5):245–263. https://doi.org/10.1089/wound.2019.0967
90. Bemenderfer TB, Anderson RB, Odum SM, Davis WH. Effects of cryopreserved amniotic membrane-umbilical cord allograft on total ankle arthroplasty wound healing. J Foot Ankle Surg. 2019;58(1):97–102. https://doi.org/10.1053/j.jfas.2018.08.014
91. Diehm YF, Fischer S, Gazyakan E et al. Negative pressure wound therapy as an accelerator and stabilizer for incorporation of artificial dermal skin substitutes – a retrospective, non-blinded, and non-randomized comparative study. J Plast Recon Aesth Surg. 2021;74(2):357–363. https://doi.org/10.1016/j.bjps.2020.08.041
92. Vick LR, Propst RC, Bozeman R, Wysocki AB. Effect of Dakin's solution on components of a dermal equivalent. J Surg Res. 2009;155(1):54–4. https://doi.org/10.1016/j.jss.2008.08.007
93. Barreto R, Barrois B, Lambert J et al. Addressing the challenges in antisepsis: focus on povidone iodine. Int J Antimicrob Agents. 2020;56(3):106064. https://doi.org/10.1016/j.ijantimicag.2020.106064
94. Chen Q, Zhou K. Acetic acid use in chronic wound healing: a multiple case series. J Wound Ostomy Continence Nurs. 2022;49(3):286–89. https://doi.org/10.1097/won.0000000000000863
95. Landsman A. Visualization of wound healing progression with near infrared spectroscopy: a retrospective study. Wounds. 2020;32(10):265–271
96. Weingarten MS, Neidrauer M, Mateo A et al. Prediction of wound healing in human diabetic foot ulcers by diffuse near-infrared spectroscopy: a pilot study. Wound Repair Regen. 2010;18(2):180–5. https://doi.org/10.1111/j.1524-475x.2010.00583.x
97. Starr NC, Slade E, Gal TJ et al. Remote monitoring of head and neck free flaps using near infrared spectroscopy tissue oximetry. Am J Otolaryngol. 2021;42(1):102834. https://doi.org/10.1016/j.amjoto.2020.102834
98. Hill R, Woo K. A prospective multisite observational study incorporating bacterial fluorescence information into the UPPER/LOWER wound infection checklists. Wounds. 2020;32(11):299–308
99. DasGupa T, Rashleigh L, Zhou K et al. Use of a fluorescence imagin device to detect elevated bacterial loads, enhance antimicrobial stewardship, and increase communication across inpatient complex wound care teams. Wounds. 2022;34(7):A15
100. Ferrari B, Reffiani C, Francomano M et al. Clinical factors influencing the outcomes of an acellular dermal matrix for skin cancer treatment: a retrospective study. Adv Skin Wound Care. 2020;33(7):367–374
101. Lantis JC, Snyder R, Reyzelman AM et al (PriMatrix Study Group). Fetal bovine acellular dermal matrix for the closure of diabetic foot ulcers: a prospective randomised controlled trial. J Wound Care. 2021;30(Sup7):S18–S27. https://doi.org/10.12968/jowc.2021
102. Masic I, Miokovic M, Muhamedagic B. Evidence based medicine - new approaches and challenges. Acta Inform Med. 2008;16(4):219–25. https://doi.org/10.5455/aim.2008.16.219-225
103. Division of Internal Medicine. Evidence-based medicine. 2023. www.hopkinsmedicine.org/gim/research/method/ebm.html (accessed 10 March 2023)
104. Guise J, Butler ME, Chang C et al. AHRQ series on complex intervention systematic reviews – paper 6: PRISMA-CI extension statement and checklist. J Clin Epidemiol. 2017;90:43–50. https://doi.org/10.1016/j.jclinepi.2017.06.016
105. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg. 2011;128(1):305–310. https://doi.org/10.1097/PRS.0b013e318219c171
106. Gordon AJ, Alfonso AR, Nicholson J, Chiu ES. Evidence for healing diabetic foot ulcers with biologic skin substitutes: a systematic review and meta-analysis. Ann Plast Surg. 2019;83(S4):S31–S44. https://doi.org/10.1097/SAP.0000000000002096
107. Santema TB, Polyck PPC, Ubbink DT. Skin grafting and tissue replacement for treating foot ulcers in people with diabetes. Cochrane Database of Systematic Reviews. 2016;2:CD011256. https://doi.org/10.1002/14651858.cd011255.pub2.
108. Snyder K, Sullivan N, Margolis D, Schoelles K. Skin substitutes for treating chronic wounds (AHRQ Technology Assessments). Rockville (MD): Agency for Healthcare Research and Quality; 2020
109. Langer A, Rogowski W. Systematic review of conomic evaluations of human cell-derived wound care products for the treatment of venous and diabetic foot ulcers. BMC Health Serv Res. 2009;9:115. https://doi.org/10.1186/1472-6963-9-115
110. Hamm R (Ed). Text & atlas of wound diagnosis and treatment. 2nd edn. New York: McGraw Hill Education. 2019;321–346
111. Percival SL, McCarty S, Hunt JA, Woods EJ. The effects of pH on wound healing, biofilms, and antimicrobial efficacy. Wound Repair Regen. 2014;22(2):174–86. https://doi.org/10.1111/wrr.12125
112. Ellis CV, Kulber DA. Acellular dermal matrices in hand reconstruction. Plast Reconstruct Surg. 2012; 130(S5):256S–269S. https://doi.org/10.1097/PRS.0b013e318265a5cf
113. Felder JM, Goyal SS, Attinger CE. A systematic review of skin substitutes for foot ulcers. Plast Reconstr Surg. 2012; 130(1):145–164. https://doi.org/10.1097/PRS.0b013e318254b1ea
114. Ghio SC, Larouche K, Doucet EJ, Germain L. The role of cultured autologous bilayered skin substitutes as epithelial stem cell niches after grafting: a systematic review of clinical studies. Burns Open. 2021; 5:56–66. https://doi.org/10.1016/j.burnso.2021.02.002
115. Hoogewerf CJ, Hop MJ, Nieuwenhuis MK et al. Topical treatment for facial burns. Cochrane Database of Syst Rev. 2020; 7. https://doi.org/10.1002/14651858.CD008058.pub3
116. Jones JE, Nelson EA, Al-Hity A. Skin grafting for venous leg ulcers. Cochrane Database of Syst Rev. 2013; 31. https://doi.org/10.1002/14651858.CD001737.pub4
117. Liang X, Zhou L, Yan J. Amniotic membrane for treating skin graft donor sites: a systematic review and meta-analysis. Burns. 2020; 46(3):621–629. https://doi.org/10.1016/j.burns.2019.09.010.
118. Lorincz A, Varadi A, Hegy P et al. Paediatric partial-thickness burn therapy: a meta-analysis and systematic review of randomized control trials. Life (Basel). 2022; 12(5):619. https://doi.org/10.3390/life12050619
119. Paggiaro AO, Filho M, de Carvalho V et al. The role of biological skin substitutes in Stevens-Johnson syndrome: systematic review. Plast Surg Nurs. 2016; 38(3):121–127. https://doi.org/10.1097/PSN.0000000000000234
120. Paggiaro AO, Bastianelli R, Carvalho VF et al. Is allograft skin the gold standard for burn skin substitute? A systematic literature review and meta-analysis. J Plast Reconstr Aesthet Surg. 2019; 72(8):1245–1253. https://doi.org/10.1016/j.bjps.2019.04.013
121. Pham C, Greenwood J, Cleland H et al. Bioengineered skin substitutes. Burns. 2007;33(8):946–57. https://doi.org/10.1016/j.burns.2007.03.020
122. Porzionato A, Stocco E, Barbon S et al. Tissue-engineered grafts from human decellularized extracellular matrices: a systematic review and future perspectives. Int J of Molec Sci. 2018; 18;19(12):4117. https://doi.org/10.3390/ijms19124117
123. Santema TB, Poyck PPC, Ubbink DT. Systematic review and meta-analysis of skin substitutes in the treatment of diabetic foot ulcers: highlights of a Cochrane systematic review. Wound Rep Regen/ 2016; 24:737–744. https://doi.org/10.1111/wrr.12434
124. Tchero H, Herlin C, Bekara F et al. Failure rates of artificial dermis products in treatment of diabetic foot ulcers: a systematic review and network meta-analysis. Wound Rep Regen. 2017; 25(4)691–696. https://doi.org/10.1111/wrr.12554
125. National Human Genome Research Institute. Organelle. 2023. www.genome.gov/genetics-glossary/organelle (accessed 14 March 2023)
126. Valencia K, Montuenga LM. Exosomes in liquid biopsy: tissue nanometric world in the pursuit of precision oncology. Cancers (Basel). 2021;13(9):2147. https://doi.org/10.3390/cancers13092147

JWC International Consensus Document

MA Healthcare

SUPPORTED BY

AROA

BioTissue Surgical

COOK BIOTECH

INTEGRA LIFE SCIENCES

MIMEDX

Organogenesis Empowering Healing