Skin Substitutes for Burn Wounds

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Daniel Popp, Christian Tapking,
and Ludwik K. Branski

10.1 Introduction

Progress in the care of severely burned patients has been achieved over the past decade and led to significantly decreased morbidity and mortality [1]. Mortality decrease could be seen especially in the severely burned children population [2]. The main fields of improvement in burn care have been (1) fluid resuscitation and early patient management, (2) control of infection, (3) modulation of the hypermetabolic response, and (4) surgery and wound care [3].

10.2 Burn Wound Care

Extensive burn injuries are characterized by a local and systemic inflammatory as well as by a hypermetabolic response. Inflammatory mediators, produced and released by infiltrating immune cells, and toxins of wound-colonizing microorganisms would lead to burn sepsis if burn eschar is not removed. Early excision and early wound coverage are generally accepted as standard of care since the early 1970s [4]. Debridement of the burn wound and eschar should be done as soon as possible after the patient has been resuscitated and stabilized. That would be usually within the first 48–72 h postburn. It has been shown that early excision significantly reduces blood loss, amount of circulating endotoxin levels, hypermetabolic response, wound infection, overall hospital stay, and ultimately postburn morbidity and mortality [5–8].

As an effective alternative to surgical and nonsurgical standard of care in partial- and full-thickness burns, Debriding Gel Dressing (DGD) (NexoBrid®, formerly also known as Debrase®), a bromelain-based enzymatic agent, can be used safely and is nowadays widely used in burn centers [9, 10].

For partial-thickness burn wounds, silver sulfadiazine (SSD) has been the standard of care for many years. In the last three to four decades, a huge variety of new dressing came onto the market [11]. Nowadays, they are standard of care due to the below-mentioned superiority compared over SSD. In partial-thickness burn wounds, the wound coverage should provide an occlusive, moist environment conducive to wound healing and preventive to infection. The ultimate goal is to decrease treatment time, pain, and discomfort.

D. Popp · L. K. Branski (✉)
Division of Plastic, Aesthetic and Reconstructive Surgery, Department of Surgery, Medical University of Graz, Graz, Austria
e-mail: danpopp@utmb.edu; lubransk@utmb.edu

C. Tapking
Department of Surgery, Shriners Hospital for Children-Galveston, University of Texas Medical Branch, Galveston, TX, USA

Department of Hand, Plastic and Reconstructive Surgery, Burn Trauma Center, BG Trauma Center Ludwigshafen, University of Heidelberg, Heidelberg, Germany
e-mail: chtapkin@utmb.edu

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10.3 Skin Substitutes

Skin is a highly complex organ. The two highly specialized layers of the skin contribute to their function as a whole as follows: The epidermis serves as a barrier against vaporization and bacteria. The dermis provides mechanical strength and elasticity. Loss of that barrier function leads to a loss of fluid and protein. The loss of the epidermis makes the tissue prone for inflammation, bacterial colonization, infection, and sepsis. Prolonged wound healing leads to higher rates of scarring [12].

Despite the known benefits of early autografting [4], in many cases it is not safe, as in unstable patients or if not enough donor sites are available due to extensive burns, or simply not possible, as on the battlefield, in mass casualties, or due to limited operating room resources. In these circumstances the burn surgeon needs to resort to alternatives, either for temporary covering or as a definitive dermal replacement.

The ideal skin substitute is constantly available off the shelf; is durable, flexible, and easy to handle; can be applied in one single operation; provides an effective barrier layer to prevent water and heat loss as well as to bacterial invasion; does not become hypertrophic; is nonantigenic; grows with children; is cost efficient; and provides permanent wound coverage but unfortunately to date also does not exist [12].

Generally, skin substitutes can be classified based on their usage (temporary vs. permanent) and on their origin (biologic vs. synthetic). Many of them can be applied in the treatment of partial-thickness as well as full-thickness burns.

In this chapter, we elucidate a selection of currently available skin substitutes for temporary and (semi-) permanent coverage. We describe the origin of the material (biologic, synthetic, combination) and indications of its application (either for partial-thickness or for full-thickness burn wounds). Furthermore, we outline the current study situation and illustrate product-related characteristics and limitations.

10.3.1 Temporary Skin Substitutes: Clinical Use, Advantages, Limitations, Prospects

10.3.1.1 Biological Tissues

Human Allograft (Cadaver Skin)

Fresh allograft skin possesses many of the ideal features of a biologic dressing, wherefore it is the "gold standard" for temporary coverage of extensive full-thickness burn wounds when not enough autologous tissue is available. It basically replaces the lost physiologic barrier and reduces water, electrolyte, and protein loss; prevents wound desiccation; suppresses microbial proliferation; is nonimmunogenic; and prepares the wound bed for definitive wound coverage and can serve as an indicator as to if the wound bed is ready for autografting. This can be crucial, as in large burns successful autografting can be essential for survival [13]. It also reduces pain, which makes occupational and physiotherapy easier for the patient.

Human allograft skin can be used as viable tissue up to 14 days when kept refrigerated at 4 °C and the nutrient solution is changed frequently [14]. Cryopreserved skin can be used up to 5 years [15]. It can also be used in a nonviable state after lyophilization [16].

Viable allograft fulfills its role as a biologic cover usually for 3–4 weeks until it gets rejected. Furthermore, meshed allograft is used as an overlay for widely meshed autograft (overlay technique) [17].

Glycerolized allograft is useful as permanent coverage for partial-thickness burns until re-epithelialization occurs. It is particularly useful in scald burns of children, as it makes dressing changes easy and less painful [18]. Following FDA and AATB regulations [19], the use of human cadaveric skin is generally considered safe. Nevertheless, there is still a risk for transmitting viral diseases, especially CMV. But with regard to the benefits, these risks are clinically negligible [20].

Human Amnion

Human amniotic membrane has been used for centuries as a biological wound dressing. After the first report of its usage in skin transplantations by Davis in 1910 [21], Sabella [22] described the use of amnion in burn patients.

Beneficial effects as faster wound epithelialization, lower rate of burn wound infections, pain relief, fluid loss, and scar reduction as well as shortening of the hospital stay have been proven [23, 24]. Furthermore it is easy to handle for the surgeon and adheres well to the wound bed [25].

Amnion is usually used as viable tissue. Since amnion is gained from living donors, consent has to be taken prior to caesarean section. Apart from that, it has to undergo a very similar process as allograft skin and is screened for any viral or bacterial diseases prior to grafting. Furthermore, the donor is screened to prevent transmission of diseases [17] and finally it is sterilized. Those standardized procedures provide safe usage and make amnion broadly available for specialized burn care providers [26]. When preserved in glycerol, it is a long-time storable nonviable biologic dressing that is enormously valuable in developing countries due to its cost-effectiveness [27].

Recently, there has been a method developed to preserve amnion/chorion that can be stored for up to 5 years under ambient conditions and though keep its biologic activity [28–30]. The nonviable and sterilized product still contains growth factors, chemokines, and other regulatory proteins that are important for wound healing, in much higher concentrations compared to other processing methods. The two-layer composition seems to contribute to that, especially chorion [31]. Dehydrated human amnion/chorion membrane (dHACM) is commercially available (EpiFix; AmnioFix; EpiBurn; MiMedx Group, Inc., Marietta, GA) and has been used to treat partial-thickness burns as well as full-thickness burns as a temporary treatment and also as overlay [32, 33]. Moreover, it is an ideal scaffold for stem cells in tissue engineering [34].

At our institution, until present, we use amnion mainly for second-degree facial burns because of its advantageously good plasticity. In a previous study, notably less frequent dressing changings and related patient comfort at no higher infection rate with comparable cosmetic outcome were seen when compared to topical antimicrobials [35].

Xenograft

Among the different animal skins being studied in the past, only pig skin turned out to be useful due to its histologic structure close to human skin [36, 37]. It shows very little immunologic properties and gets more "ejected" by epithelialization underneath than rejected and should rather be classified as dressing [38]. It provides similar beneficial effects as allograft, but does not show vascularization or capillary ingrowth [39] and therefore xenografts cannot be used to prove readiness of the wound for autografting [40]. In some populations they might also not be used due to ethnic or religious reasons [41] and there is a theoretic risk of zoonoses. Porcine xenograft can be used as a temporary cover for partial-thickness as well as for full-thickness burns or for coverage of donor sites. It is processed and stored similar to allograft [42, 43].

10.3.1.2 Synthetic and Biosynthetic Materials

Up to date there exists a huge variety of synthetic wound dressings. The below mentioned are a selection of dressings routinely used at our institution.

Biobrane®

Biobrane® (Bertek Pharmaceuticals Inc., Morgantown, WV, USA) is a bilayer biosynthetic composite wound dressing, consisting of porcine-derived collagen chemically bound to a nylon mesh that is partially embedded into an ultrathin porous silicone. The silicone film serves as a semipermeable epidermal substitute that allows wound water vapor but still maintains a moist healing environment and serves as a bacterial barrier. Its translucent properties allow for wound judgment without removing the product, and its flexibility enables its usage over joints. Sera and blood clot within this matrix and firmly adhere the fabric to the wound bed until epithelialization occurs and Biobrane® can be easily removed [3, 13, 44, 45]. It accelerates wound healing and

lowers pain overall and during dressing changes in partial-thickness burns [45]. It is a safe alternative to allograft as a temporary coverage in third-degree burn wounds when applied to thoroughly debrided, noninfected wound beds. A further advantage is that early mobilization can be performed, while after allograft transplantation the patient or at least the burned area has to be immobilized for a few days. That has clear benefits especially in hand and extremity burns. Overall costs seem not to differ significantly, even though if applied faster than, e.g., allograft, OR time can be saved [13, 46, 47]. It has to be changed usually after 10 days. For some reason, it is currently off the market. There are already existing products that claim to be its successor, but there is still a lack of clinical data [48].

TransCyte

TransCyte (Advanced Tissue Sciences, La Jolla, CA, USA) is also a bilayer biosynthetic composite wound dressing with similar properties as Biobrane with additional neonatal in vitro-cultured human fibroblasts integrated into the nylon mesh. Those fibroblasts secrete human dermal collagen, matrix proteins, and growth factors [49, 50]. It can also be used for treatment of partial-thickness burn wounds as well as a temporary substitute for full-thickness wounds [51–54]. There is evidence that it leads to faster re-epithelialization and fewer dressing changes when compared to Biobrane [50], but it is currently also off the market, probably due to high costs.

Suprathel®

Suprathel® (PolyMedics Innovations GmbH, Denkendorf, Germany) is a synthetic copolymer membrane that serves as a temporary replacement of the epithelium and imitates the same. It contains mainly DL-lactide (>70%); the other components are trimethylene carbonate and ε-caprolactone. The membrane features a porosity of 80% that enables exudate to drain and it can be elongated up to 2.5 times of its size, which gives the product a very good plasticity. Furthermore it supports wound healing and re-epithelialization [55].

Once applied after meticulous debridement of the wound, it attaches nicely to the moist wound bed. At our institution, we cover it with at least one layer of paraffin gauze under normal gauze to absorb the wound fluid. During healing, it becomes—at least partly—transparent, which allows the physician to judge the wound without removing the membrane. It will consecutively detach from the areas that already show epithelialization and should be trimmed in a circular manner until the whole wound has healed and it can be peeled off painless.

The major advantages of this product are its potent pain-reducing potential and its excellent handling. However, it is quite expensive compared to allogenic material or other products, used for second-degree burns [55, 56].

Especially in patients with extensive burns, STSGs can be saved for coverage of third-degree burns when Suprathel® is applied to the second-degree burn wounds [57]. It may be used not only for superficial partial-thickness burns, but also for mixed-depth partial-thickness burns [58]. Furthermore, it can be used also in an outpatient setting for adults as well as for children [56].

Mepilex® Ag

Mepilex Ag® (Mölnlycke Healthcare, Göteborg, Sweden) is an absorbable, silver-coated foam pad. Its innermost silicone layer Safetec® prevents adhesion to the wound bed and therefore reduces pain during dressing changes while the silicone foam absorbs exudate, yet keeps the wound in a moist condition. The broad-spectrum antimicrobial effect of Mepilex® Ag is due to therein comprised silver-sulfate ions and activated carbon [59]. Dressing changes need to take place usually every 3–7 days but are quite easy to handle and relatively pain free compared to dressings without a silicone layer. It furthermore may increase healing time and is more cost efficient than for example Suprathel® ($0.8/cm^2 vs. $0.56/cm^2) [56, 60]. At our institution it is the standard of care for superficial burn wounds.

Aquacel®

The first Aquacel® (ConvaTec Inc., Greensboro, North Carolina, USA) contains a core hydrofiber

layer with carboxymethylcellulose and carboxymethylation [61]. An update was Aquacel® Ag, which includes ionic silver. The controlled release of ionic silver absorbs fluids to form a cohesive gel [62]. It provides an antimicrobial protection and protects the wound for up to 14 days [63]. A dressing, which is slightly larger than the wound, is placed on the wound and covered with a sterile secondary layer. Aquacel® is used for burn injuries as well as for chronic wounds and was shown to be safe and effective in partial-thickness burns [61, 64]. Especially in chronic wounds, which tend to develop infections, Aquacel® Ag was proven to decrease wound size and rate of infections [65]. Aquacel® was shown to be more cost effective than other dressings, because it normally does not require a lot of dressing changes [62]. Furthermore, Aquacel® seems to increase the comfort for patients and nurses [66].

10.3.2 Dermal Replacements/ Analogues

10.3.2.1 Biologic Materials

Split-Thickness Skin Graft (STSG)

Split-thickness skin grafts (STSG) are typically indicated for temporary or permanent coverage of cutaneous defects [67]. It consists of epidermis and parts of the dermis, depending on the graft thickness (0.2–0.7 mm). STSG are harvested with a dermatome (constant pressure at a 45° angle to the skin) from thigh or back and other areas, if necessary [68]. Some of the dermal skin appendages remain at the donor site. After harvesting, the graft may be meshed or Meek technique is used and then placed on the clean wound. The STSG can be kept in moist gauze and hydrated until ready to be applied [69]. STSG are well known and accepted for soft-tissue coverage, especially in burns and plastic surgery reconstruction, but also in ulcers [70]. STSG are usually fixed via staples or (sometimes) with sutures. For large sheet grafts, to leave the graft uncovered to allow rolling of fluids is an option [71]. Grafts initially survive via diffusion until a subsequent revascularization occurs. A major limitation of STSG is its often unsatisfying functional and cosmetic results, which affects the patients' quality of life especially when used in exposed or joint areas. Hypertrophic scarring and poor elasticity and scar contractures are common problems [72]. In order to increase cosmetic and functional results, dermal matrices such as described below have been developed [73, 74]. Nevertheless, STSG remain the gold standard by now.

1. Indications
   Immediate coverage of clean soft-tissue defects and accelerated wound healing
   Prevention of scar contracture and enhanced cosmetic in superficial wounds
   Immediate coverage of burn defects and reduced fluid loss from the wounds
2. Contraindications
   Infected wounds or necrotic tissue
   Exposure of tendons or bones
   Exposure of blood vessels or nerves
3. Donor-site morbidity
   The donor site, which is often a large surface of the body, heals by epithelialization and is expected to heal like any abrasion [75]. It needs to be kept in mind that skin grafting produces a wound at the donor site which enlarges the unprotected wound area [75, 76]. It has been shown that scarring in donor site is proportional to the thickness of the graft and to the occurrence of infections [77]. Intensive itching may occur due to exposed nerve endings. It has been shown that returning harvested skin, which is not needed, to the donor site may decrease healing time and wound morbidity [78].

Mesh

The technique of meshing was introduced by Tanner et al. in 1963 [79]. To increase the coverable surface, the STSG can be enlarged up to a 1:4 ratio. Larger ratios can be difficult to handle, because the skin tends to curl on itself. Meshing can be performed by hand or the STSG is placed on a plastic sheet and rolled through a machine which cuts the skin sheet on several points, so that a net with preset interstices is pro-

duced [80]. The interstices prevent an accumulation of the fluid, which leads to better and safer healing [81]. The location and size of the wound as well as possible donor site determine the meshing ratios [80].

Meek first described this technique in 1958 [82] and it was later modified by other authors [79, 83, 84]. The expansion is efficient and effective. STSG are placed on a cork plate, which is then cut vertically and horizontally into 1 × 1 to 3 × 3 mm squares. The grafts are then transferred to a carrier with aluminum foil backing, the cork plate is removed, and the graft is sprayed with an adhesive spray. After waiting for 5–8 min, the aluminum foil is expanded and the graft can be placed on the wound. An expansion ratio up to 1:9 may be reached. This technique allows to cover larger wounds and if there is a lack of donor sites. That is why severely burned patients can often benefit from this technique [83, 85].

Acellular Dermal Matrix

Alloderm® (Life Cell Corporation, Branchburg, NJ, USA) is an acellular human matrix, which is processed from cadaveric dermis and does not contain epithelial elements [86]. The substitute is freeze-dried, which allows the graft to adapt to the dermal structure, and screened for potentially transmissible pathogens [72, 87]. Comparable to Integra®, Alloderm® is placed over the wound after full excision of nonviable tissue. The dermal matrix incorporated with the patients' own tissue and a thin layer of split-thickness skin graft is placed on top of the Alloderm® graft. Since the cells have been removed, Allograft® is not rejected by the immune system [88]. The outcome is similar to other dermal replacements with favorable results [89]. Recent studies have shown that Alloderm®, aside from burns [88], is also suitable for breast reconstructions, head and neck reconstructions, and abdominal wall/hernia surgery [90, 91]. Since Alloderm® contains elastin and collagen, there is less tension and increased elasticity compared to other dermal substitutes, which results in a less contractions [73].

10.3.3 Biosynthetic Materials

10.3.3.1 Integra

Integra® (Integra Life Sciences Corporation, Plainsboro, NJ, USA) consists of two layers: one bovine tendon collagen matrix and one silicone layer. The silicone layer, which prevents water loss and protects the dermis, is peeled away during wound healing and the bovine layer integrates with the human skin [92]. It is used as a dermal skin substitute and placed over the wound after full excision of nonviable tissue. After initial healing of approximately 3 weeks, a thin autograft is placed onto the neo-dermis [92]. In several studies, Integra® seemed to have a better outcome regarding wound healing time compared to autograft, allograft, or xenograft, but had a higher rate of infections than other substitutes such as Biobrane® [77, 93, 94]. Long-term use and outcomes and outcomes in terms of length of hospital stay, cosmetic results, and functional outcome are mentioned to be favorable [95]. In very large burns, it can be used under widely meshed autografts (4:1–10:1) with an overlay (e.g., allograft or Biobrane).

10.3.3.2 Matriderm

Matriderm® (MedSkin solutions Dr. Suwelack AG, Billerbeck, Germany) is a highly porous membrane composed of three-dimensionally coupled collagen and elastin. The collagen is gained from a bovine dermis and the elastin from a bovine nuchal ligament by hydrolysis [72]. After being sterilized and freeze-dried, Matriderm® can be stored at room temperature [72]. Matriderm® can be engrafted in a one-step procedure with a thin skin graft after full excision of the nonviable tissue [96]. Due to its good dermal wound bed preparation with extensive formation of rete ridges and capillary loops, the skin barrier and elasticity are close to the normal human skin, which is surrounding the wound [72, 97, 98]. It is reported to have minimal complications and good clinical outcomes and was proved valuable in restoring skin elasticity and skin barrier [72]. Survival rate is reported similar to other dermal matrices [99, 100].

10.4 Partial- Versus Full-Thickness Burns: Using the Right Substitute

Given the huge number of different skin substitutes available, the selection of product to use for a certain patient is always an individual decision based on the experience and personal preference of the surgeon. The clinician has to take the advantages and disadvantages of the product into account and ultimately, in the era of cost pressure on our healthcare system, cost-effectiveness. Given the fact that procedure time makes up around 40% of operating room time in a burn OR [101], not only material costs but also applicability in a timely manner have to be considered.

All abovementioned temporary substitutes are used at our institution. In partial-thickness facial burns—especially in children—amnion is a good option, as well as for hand burns. Here, also Suprathel is a very good alternative. If infection is present, biologic products or products containing silver may be preferred in combination with frequent dressing changes and/or debridements. For full-thickness burns, our standard of care is either allograft or xenograft until enough donor sites are available, even though the above mentioned are used if needed. In the end it may vary between institutions and every clinician has his or her preferred products.

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