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The use of allograft skin in burn care

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The article reviews the current methods and indications for the use of allograft skin in the management of burns, as well as the prospects for application of the allografts in tissue engineering.

Keywords: burns, allograft skin, skin bank, cryopreserved skin, glycerol-preserved skin.

Despite a downward trend in the incidence of thermal injury in developed countries [1], the requirements for a favorable outcome of its treatment are constantly rising. Even patients with extensive deep burns and thermal inhalation injury have a chance to recovery thanks to advances in current critical care, the tactics involving an early excision of necrotic tissue, and the use of bio-engineered products for skin replacement.

One of the most serious obstacles for a surgeon to overcome while treating a severely burnt patient is the lack of autologous skin resources for grafting. According to literature reports, such a problem arises in cases when a deep burn covers more than 60 % of the total body surface area (TBSA) [2, 3]. A widespread use of bio-engineered skin substitutes could have solved the problem; however, despite all the efforts being made, a "test-tube skin" that would be available and meet all the requirements has not yet been

created. Layered autologous keratinocytes that have been developed since late 70s of the XX century have certain shortcomings such as a long period of culturing (3-5 weeks), low viability after being transferred to an excised wound, and, moreover, an extremely high cost [4, 5].

Currently, the maximum area of a lost skin that could be reconstructed depends on the widely used grafting techniques potentially sparing the autologous skin, namely, mesh grafts, MEEK-technique, autologous skin micro-grafting [3, 6]. A surgical approach in the treatment of extensive burns involves the multiple uses of donor sites. Meanwhile, their re-epithelialization takes certain time, at least a week, in most favorable setting. As a rule, the pace of the burn eschar staged excision outstrips the donor site re-epithelialization rate. Thus, the problem of temporary covering the excised wounds acutely arises. For these purposes, various types of wound dressings have been used, including hydrophobic ointment dressings, semipermeable polyurethane coatings (Epigard®, Syspur-derm®). Despite a widespread use of commercially available in this country skin grafting products obtained from animal skin (the freeze-dried or lyophilized porcine skin *Xenoderm*), and synthetic temporary covers for burn wounds, the deep burns of over 40-50% of TBSA are nearly predetermine a fatal outcome. A relatively affordable and highly effective resource for overcoming this deficiency might be an extensive use of allograft skin which remains the "gold standard" for a temporary coverage of wounds after the excision involving deep skin layers or underlying tissues [7, 8]. A post-mortem skin donation has been the most commonly used source; live donor skin is rarely used [8]. As with any tissue transplants obtained from another individual of the same species, the donor skin is usually called an "allograft" (a homograft as per obsolete classification); tissues transplanted from alternate species are

termed with the prefix "xeno-" ("hetero-" as per obsolete classification). The clinical use of allograft skin stands aloof in a row of transplant issues, since it is based on the understanding of its inevitable rejection that predetermines the role of an allograft skin as a temporary wound cover. Skin allografting reduces the water loss through evaporation, controls protein and fluid losses, prevents the wound surface from drying, and inhibits the microbial proliferation. All these lead to decreased pain sensations and an improved patient's compliance to the conservative therapy and rehabilitation procedures. Thanks to restoring the biological barrier between the wound surface and the environment, the allograft skin reduces a heat loss and alleviates a stress hypermetabolic response to a burn injury [7, 8].

Skin grafting came into clinical practice around 150 years ago. The allograft skin was most often obtained from amputated limbs, and its use seemed the procedure taken for granted at that time. The possibility of using cadaver tissues, despite some fears, also turned into a reality very quickly. The priority of covering a burn wound with cadaver skin belongs to J.H. Girdner. In 1881, he published his experience of using a cadaveric allograft to treat the upper extremity burn in a 10-year child. After 4 days, 3/4 of the graft had taken, but later, an acute inflammation developed in the wound that was described by Girdner as "pseudoerysipelas", and that led to a total necrosis of the newly formed skin [9]. Noteworthy, Medawar, while working in a burn clinic, came closer to discovering the secret of the transplant conflict [10]. After the mechanisms of an inevitable skin allograft rejection had been described, the role of allograft skin was finally defined as a temporary wound cover. Even its temporary adherence often brought success in the struggle for patient's life and health. Great achievements in the

development of skin allografting techniques belong to Russian scientists [11].

We should admit a lowered interest to the use of allograft skin in our country recently. This can be explained by common problems of tissue donation and by the lack of a request from burn surgeons. The concept of a bloodless removal of the eschar from the burn wound (chemical necrolysis) has been widely accepted [12, 13]. In practice, this has led to a nearly complete refrain from early necrectomy in extensive burns in favor of scab drying. However, the significant advances in resuscitation and intensive care, an increased patient survival in the acute period of injury have brought the arousal of the interest to the aggressive surgical approach [13]. So, it also revived the interest to allograft skin. Thus, the review on current trends in the clinical use of donor allograft skin seems rather actual.

Donor skin allografts currently used

Allogenous skin may be used directly after harvesting from a cadaveric donor (Fig. 1). The cells in such a graft maintain about 60% of their metabolic activity compared to the skin from a living donor. When incubated for 18-24 hours at +37° C, they increase their metabolic activity to 95%. Upon their subsequent storage in a liquid medium at +4° C, the metabolic activity gradually decreases, nevertheless, remaining at the acceptable level for 3-5 days [14]. As has been noted, a fresh skin allograft is the "gold standard" of temporary wound covers.

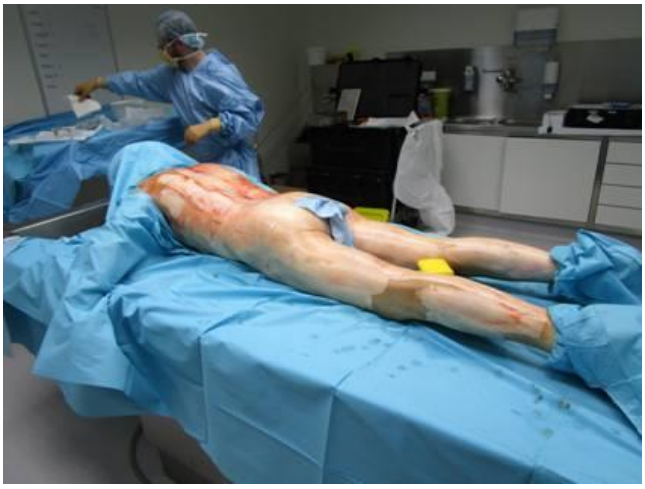


Fig. 1. The procedure of harvesting the skin grafts from a cadaver donor.

It is more resistant to a contamination and displays a better capacity to adhere to the subcutaneous fatty layer after necrectomy when compared to preserved transplants. However, this option entails a high risk of infection transmission [8]. A viable graft is naturally tends to induce a more pronounced immune reaction and rejection [15]. In addition, the fresh allograft transplantation dictates the necessity of donor material to be available on a permanent basis that is hardly feasible to achieve in practice. Unpredictable needs in allograft skin at burn centers, a shortage, or rather, inaccessibility of donor resources, have led to the establishment of skin banks around the world, and all these require a further improvement of preservation methods [8].

One way of the skin preservation is freeze-drying (or lyophylization) [8, 16] (Fig. 2). This process stops the degradation of the biological tissue and practically deprives it of antigenic properties, but, meanwhile, it leads to an epidermal cell destruction and barrier function impairment. Moreover, the freeze-dried skin has a poor adhesion to the wound surface and is less

resistant to microorganisms compared to the fresh or cryopreserved skin [17]. Lyophylization process requires a complex and expensive equipment, which is also a disadvantage of the method. Most often, the lyophilized skin allografts are used as a biological dressing to enhance the wound healing.

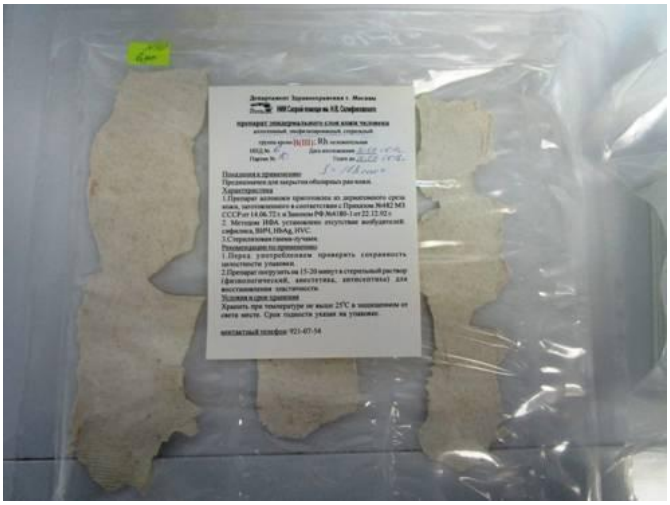


Fig. 2. A lyophilized (freeze-dried) donor skin allograft.

The cryopreservation at a liquid nitrogen temperature, and the preservation in highly concentrated glycerol are the methods most widely used in the world practice. These methods allow the allogenous skin products to be stored for 2-5 years [18, 19]. A review of literature has demonstrated that cryopreservation has been a more prevalent method in the United States, while most European Burn centers prefer using the glycerol-preserved (GP) skin grafts [19]. The main difference is in the viability of the preserved tissue [20]. Cryopreservation provides a certain degree of tissue viability even after a prolonged storage [18]. Advocates of the cryopreservation have noted that cytokines and growth factors entering the wound from the viable cells provide better clinical results [8, 19].

Glycerol keeps the tissue morphology safe, but meanwhile, the cells become irreversibly dehydrated [15]. The glycerol-preserved skin popularity is explained by the low cost of its manufacturing, an easy storage and use [19] (Fig. 3).

Fig. 3. A glycerol-preserved donor skin allograft.

Highly concentrated glycerol dehydrates the skin cells and intercellular matrix by osmosis and diffusion, thus preventing the degradation and decomposition reactions that develop in tissues, including the lysis by proteolytic enzymes and oxygen radicals, and lessens the microbial contamination [21, 22]. GP skin grafts retain their barrier function at a high level. One of the main GP skin advantages is a significant decrease of antigenic properties after its treatment with glycerol [23].

The current trend in using allograft skin is the manufacturing of acellular dermis products (Fig. 4, 5) [24].

Fig. 4. A freeze-dried acellular dermal implant SureDerm derived from donor skin.

Fig. 5. An acellular dermal implant Glyaderm.

The removal of the cellular material considerably reduces the antigenic properties and provides a permanent adherence of the coating to the wound bed with further vascular sprouting and its gradual filling with recipient's own cells [25]. Thanks to native bioactive components in the dermis structure, there is a stimulating effect on angiogenesis and a cell migration [26].

The inherent biological activity makes acellular dermis products different from the generation of synthetic dermal substitutes derived from some of dermis components: collagen, glycosaminoglycans, hyaluronic acid, by using the method of chemical crosslinking. Good mechanical properties of acellular dermis products, and their better resistance to infection than that of synthetic implants, have contributed to a wide use of acellular dermis in the reconstructive surgery of breast and abdominal wall, rhinoplasty, and periodontal surgery [27]. In the long term, decellularized dermal matrices are considered as an option of a framework for creating autologous bio-engineered skin substitutes [4, 27].

Indications for using allograft skin

Treatment of borderline burns

Preserved allograft skin can play the role of a biological dressing to cover superficial skin defects. Its adhesion to the wound surface would bring the pain relief, control the water loss and exudation, lessen the need of frequent and painful dressing changes. While the burn wounds are epithelializing, the allografts slowly separate without a damage to a newly formed epithelium that otherwise could be easily traumatized. Though this method is cost-ineffective for the treatment of limited superficial burns or donor sites, it may be preferable for borderline burns (IIIa degree, according to the Classification adopted by the XXVII All-Union Congress of Surgeons, 1960) when the skin proper regenerative potential is considerably decreased. In this case, the allograft ability to prevent water loss and stimulate epithelialization can contribute to reducing the number of dressings and shortening the hospital stay. This approach has been practiced mainly in pediatric patients. Several publications have demonstrated the advantages of

skin allografts over antibiotics-saturated ointment dressings in the treatment of borderline scalds inflicted with hot liquids [28, 29]. By ensuring a protective effect on the retained skin organelles, and providing optimal conditions for re-epithelialization, an applied skin allograft helps to avoid autografting that is indicated in case when a spontaneous epithelialization has not been completed for more than 3 weeks after the burn injury.

Treatment of deep burns

There are several possibilities of using allograft skin in the treatment of deep burns [2]:

- the application of allograft skin as a temporary wound cover after excision of burn wounds;

- combined skin allo- and autografting;

- the use of allograft skin in combination with cellular and tissue-engineered products.

As already mentioned, the main use of allograft skin is the temporary wound coverage after an early excision of burn eschar in circumstances of lacking autologous skin resources. Virtually, all modern manuals on burn surgical management consider allografting as an integral component for a successful treatment of extensive TBSA burns [2, 6, 13]. Staged restoration of the integument in the affected areas sets the priority for the sites designated for vascular-line access and tracheostomy (periclavicular area, neck, groin), as well as functionally and aesthetically important areas (large joints, hands). These sites are subjected to autografting. Less functionally important areas, and those predicted to have poor results of grafting (the back, a rear surface of the extremities, perineum) are recommended to be covered with allografts. Integument restoration in these areas is postponed to

following stages, when the depth of the injury has been evaluated and the risk of secondary necrosis is lower. The skin allograft adherence and vascular sprouting reliably indicate a sufficient blood perfusion in the wound bed to provide a good adherence of the split-thickness skin autograft. [8].

The most well-known technique of combined skin grafting in our country is a Mowlem Jackson procedure that has been rarely used in recent years [2]. Currently, a more common technique is used that implies the skin allograft application over a widely stretched perforated autografts ("sandwich-grafting" technique). Originally this technique with a mesh allograft was described by Alexander [30] (Fig. 6).

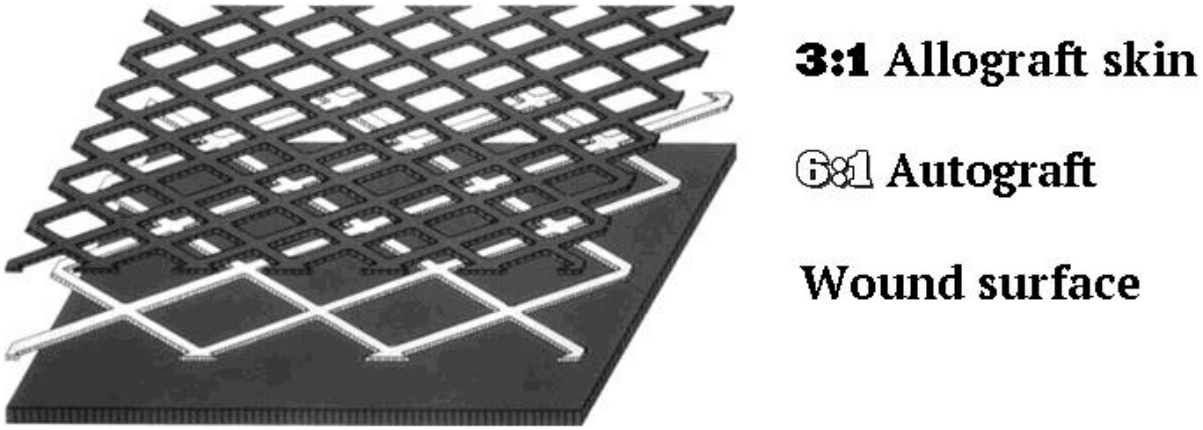
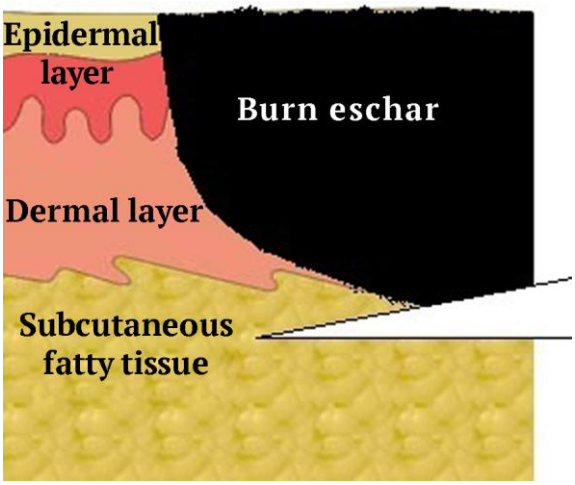


Fig. 6. The schematic presentation of a "sandwich-grafting" technique.

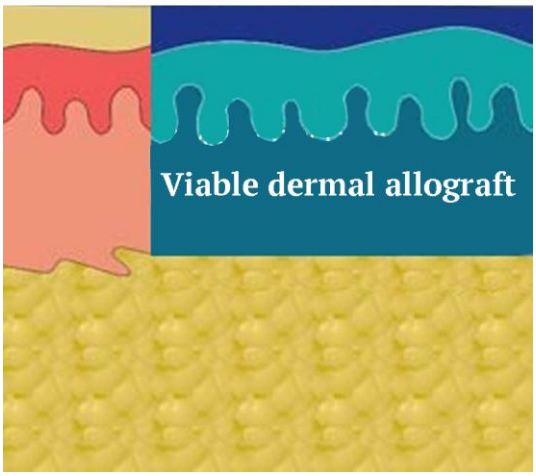
Sheet (non-perforated) allografts provide a more efficient protection of denuded areas of the mesh autograft from drying and microbial contamination. Combined skin grafting remains a valuable option in the treatment of extensive deep burns, but it should be used with caution, as many authors point to a high risk of immune rejection that can reduce the quality and speed of underlying autograft epithelialization [2].

A specific combined technique termed autologous skin "micrografting" has been described by Chinese plastic surgeons [31]. They minced autologous skin into pieces smaller than 1 mm. These micrografts were seeded into the dermis of sheet skin allografts and then applied onto the burn wounds previously subjected to excision. As the autograft epidermal cells proliferated and covered the wound surface, the allograft was gradually separated similar to that described in "sandwich-grafting" technique. This method results in effective skin expansion ratios up to 1:18, but it has been associated with severe pathological scarring, worse than that in case of mesh skin autografts.

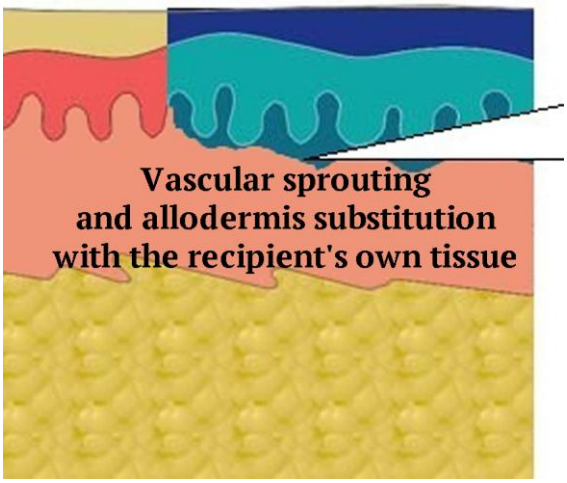
A combined use of allografts and cultured cells of a recipient was proposed by Cuono [32]. A clinical application of multi-layered sheets of cultured autologous keratinocytes for burn treatment was first described as far back as in 1981 [33]. The implementation of this technique was associated with considerable difficulties because many authors noted a low graft survival rate (under 50%), the graft vulnerability and fragility [4, 25]. The lack of the dermis layer has been considered the main drawback of multi-layered keratinocyte sheets as skin substitutes [24]. Cuono's technique involved dermabrasion, i.e. the removal of the epidermal layer containing most of the antigens from the surface of a viable adhered allograft after the vascular sprouting into the dermis (Fig. 7), and further grafting of multi-layered sheets of cultured autokeratinocytes.



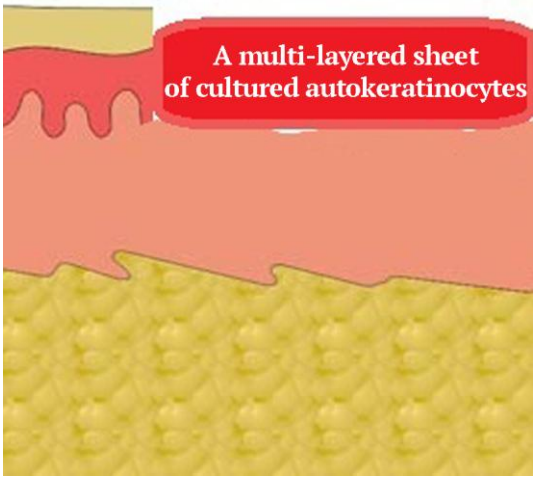
A. Radical excision of nonviable tissue



B. Cover of a postoperative defect with skin allograft.



C. After the vascular sprouting from the recipient bed into the allogenous dermis, the allograft epidermal layer containing most of the antigens should be removed.



D. Epidermal integument is replaced with the multi-layered sheet of autologous keratinocytes that has been cultured by this time.

Fig. 7. A staged reconstruction of integument using Cuono's technique.

The benefit of the technique was the restoration of both the epidermal and dermal layers, and thus, more stable and functionally acceptable skin. In addition, the technique was associated with higher survival rates for the multi-layered keratinocyte sheets. Hickerson obtained promising results in the treatment of severe burns; he assessed the engraftment of the cultured epidermal cells on allogenous dermis to be above 90% with elastic and durable skin formation [34]. Cuono technique, however, has not been widely spread and actually became an intermediate in passing to modern technology of bio-engineered skin substitutes.

The use of allogenous acellular dermis

A combined use of acellular dermal matrix and split-thickness skin allografts was investigated for the treatment of deep burns; the technique implied a two-stage or one-stage grafting [35]. The advantages of using the dermal matrix included better functional and esthetic results of grafting, and a possible application of thinner dermal autografts (less than 0.2 mm) to form superficial donor sites that would heal without pathological scar formation [36, 37].

The use of topical negative pressure therapy systems has been investigated for their potential to accelerate neovascularization in acellular dermal allograft. The results of a multi-center study demonstrated a reduced incidence of infectious complications and improved long-term outcomes of grafting [38].

Encouraging results have been obtained with delayed grafting of human cultured keratinocytes onto acellular dermal matrix taken to the wound bed [39].

The most promising in terms of tissue engineering has been the combination of allogenous extracellular matrix and recipient's cultured cells that represents an equivalent dermal-epidermal skin substitute applicable for a single-stage wound grafting [4]. Technological potential for the creation of an equivalent skin substitute exists already now [40]. And it is supposed to restore both the barrier function, and the typical appearance of normal skin by administration of melanocytes [41]. However, one should note that these studies are still experimental or represent single-case clinical observations. The gain of clinical experience in burn care is impeded by a high cost of bio-engineered products; and the issue becomes crucial when it comes to the treatment of patients with severe burns who do not constitute an exemplary clinical trial model because of unpredictable outcome and a large TBSA affected by the burn. This problem can be solved only by the world's largest medical centers or scientific collaborations, such as, for example, EuroSkinGraft Program operating in Europe since 2000 and uniting the efforts of seven clinics and laboratories from four countries aiming at the development of a bio-engineered skin equivalent substitute.

Potential complications of using allografts

Risk of disease transmission

Allografted skin may be a source of bacterial infection [42]. Currently, donor tissues designated for transplantation should mandatory be subjected to multi-staged microbiological studies prior to its distribution by the tissue bank. Despite the opinion of White [43] who has suggested that cadaver allograft having less than 103/g of microorganisms can be safely used for transplantation, current standards require that allogenous skin should be discarded if the growth of pathogenic bacteria or fungi has been detected

[44]. This is particularly important for the recipients with an immunocompromised status or at a high risk of wound sepsis.

The problem of bacterial contamination can be effectively solved by sterilization [8]. The sterilization with ethylene oxide and gamma irradiation has been the most common sterilization technique in the world practice and can be used for lyophilized or cryopreserved allografts [45].

There have been reports of viral disease transmission via skin allografts. In 1987, Clarke reported the transmission of HIV-1 to a burn patient from HIV-positive donor [46]. Results of donor testing for HIV had not been known by the time of skin grafting.

There have been reports of cytomegalovirus (CMV) transmission to the recipient by cadaveric skin grafting [47]. Nevertheless, the majority of investigators believe that the benefits of using allografts outweigh the risks of CMV-infection [48]. One of the tissue banks in the United States was assessed as an example that demonstrated 63% of tissue donors were seropositive for CMV [49]. The investigators expressed their concern about a possible shortage of skin allograft reserves for burn patients in need should the skin from such donors be discarded. A compromise solution suggested that the decision-making of using allografts from CMV-seropositive donors should be committed to the attending physician of a potential recipient [48].

Graft rejection

Allograft skin contains Langerhans cells capable to express class II antigens on their surface. These antigens induce an immune "host-versus-graft response". It is clinically manifested as an acute inflammatory reaction and can trigger the development of a wound infection. Vascularized viable dermal allografts typically remain intact on the burn wound for 2 to 3 weeks.

In some cases, allografts can survive for up to 67 days due to the immunosuppression inherent of extensive burn injury [50]. Attempts of using pharmacological immunosuppressive agents have been made to prevent an allograft rejection in recipients [51]. Early clinical trials have shown an improvement of allograft and patient survival in children treated with azathioprine and antithymocyte globulin. That protocol was associated with azathioprine-induced neutropenia. However, the improvements in outcome were not confirmed in the course of further studies. Skin allograft survival in patients with extensive full-thickness burns was prolonged by the use of Cyclosporine A [52]. Allograft rejection is generally observed within a few days from the discontinuation of cytostatics therapy. Apparently, this approach aiming at a permanent survival of skin allografts similar to organ transplant survival is currently valuable from the historic point only.

Conclusion

The review of literature has shown evidence-based reasons for allograft skin use in the management of wounds and burns. The main application of allograft skin should be the temporary covering of wounds after necrectomy where autologous tissue resources are depleted. In the setting of unavailable expensive high-tech synthetic and bio-engineered wound dressings, the application of allograft skin remains a saving option for the treatment of patients with extensive burns. The most promising trend here is using the allograft skin to produce decellularized dermal matrices fit for creating tissue-engineered skin substitutes. Obtaining such a "test-tube skin" is the most exciting task of combustiology in the XXI century.

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