Rom J Leg Med [29] 37-44 [2021]
DOI: 10.4323/rjlm.2021.37

THE USE OF CADAVERIC SKIN ALLOGRAFTS IN THE MANAGEMENT OF EXTENSIVE WOUNDS

Liliana Gabriela Popa[1,2], Calin Giurcaneanu[1,2], Mara Madalina Mihai[1,2,3,*], Cristina Beiu[2], Olguta Anca Orzan[1,2], Sivius Negoita[4,5], Marian Burcea[6], Ruxandra Ioana Turlea[7], Catalin Ionel Enachescu[1]

[1]Elias Emergency University Hospital, Department of Dermatology, [2]"Carol Davila" University of Medicine and Pharmacy, Department of Oncologic Dermatology, [3]Research Institute of the University of Bucharest (ICUB), [4]"Elias" Emergency University Hospital, Department of Anaesthesiology and Intensive Care, [5]"Carol Davila" University of Medicine and Pharmacy, Department of Anaesthesiology and Intensive Care, [6]"Carol Davila University of Medicine and Pharmacy, Clinical Hospital for Ophtalmological Emergencies Bucharest, Department of Ophtalmology, [7]"Mina Minovici" National Institute of Legal Medicine, Bucharest, Romania

Abstract: Skin grafting is a major element in the management of extensive wounds. Although the permanent closure of extensive wounds using autologous skin grafts is the gold standard, this scenario is rarely feasible due to the limited availability of autograft skin in these patients. Hence, biological or synthetic skin substitutes are necessary for the temporary coverage of massive wounds. Among these, cadaveric skin allografts remain the first choice due to their numerous advantages. They reduce the loss of water, proteins and electrolytes, improve thermoregulation, reduce pain and lower the risk of wound infection. Furthermore, they improve subsequent autograft take by stimulating epithelization and preparing the wound bed. Prompt excision of massive burn wounds and temporary coverage with allograft skin significantly reduces mortality and shortens hospitalization.

Future research must address the current disadvantages associated with the use of allograft skin, mainly the limited availability, high antigenicity, risk of infection transmission, as well as optimization of the processing and storage techniques.

Keywords: cadaveric, skin, allograft, burn.

INTRODUCTION

The continuity of the integument is crucial for the protection of the body. Therefore, early wound excision or debridement and skin replacement in patients with extensive burns, traumatic cutaneous denudations or exfoliative skin diseases are major determinants for reducing morbidity and improving survival. Skin grafting is the pivotal element in the management of extensive wounds. Although the permanent closure of extensive wounds using autologous skin grafts is the gold standard, this scenario is rarely feasible due to the limited availability of autograft skin in these patients. Hence, biological or synthetic skin substitutes are necessary for the temporary coverage of massive wounds.

Among these, fresh or cryopreserved cadaveric skin allografts represent the best option given their availability, low cost and ability to quickly revascularize. Their content of viable epidermal and dermal cells is of utmost importance. It has been shown that the dermal noncellular constituents of such allografts are passed to the wound bed and the cells release a series of growth factors and cytokines, creating a local environment that favors the growth of keratinocytes and skin renewal [1]. Non-viable allografts such as glycerolized, gamma irradiated, freeze dried or ethylene oxide - treated allografts may also be used. Xenografts, primarily porcine skin grafts are rarely employed for the temporary dressing of extensive wounds as they do not revascularize. As expected, the antigenic incompatibility leads to the rejection of allografts and xenografts.

Skin substitutes, like in vitro cultured epidermal autografts or dermal substitutes consisting of a collagen

*Correspondence to: Mara Madalina Mihai, MD, PhD, Assistant Professor, No.17 Marasti Bd, District 1, Bucharest, Romania, E-mail: mara.mihai@umfcd.ro

and glycosaminoglycans matrix are successfully used for extensive wound coverage, but are rarely the first choice due to their high cost [2]. Another drawback for skin substitutes is their content of either epidermal or dermal components, seldom both. While the first are associated with reduced elasticity and plasticity given the absence of dermal constituents, the later require the growth of a new epidermis over the wound, which takes place over extended periods of time [2]. In addition, skin substitutes are very frail and sensitive to shear stress, therefore the management of wounds covered with skin substitutes is very demanding [3,4]. Bioengineered skin substitutes, composed of a bovine collagen and glycosaminoglycans matrix covered by a silicone sheet that serves as an epidermis have been developed, but they are very expensive and need further research [5].

Another promising product is represented by a suspension of autologous cells (keratinocytes, fibroblasts, melanocytes) that is sprayed over the wounds. The suspension is obtained by performing a dermal-epidermal junction biopsy [2].

Nevertheless, cadaveric allografts remain the top choice for temporary coverage not only of extensive wounds, but also non-healing chronic wounds such as decubitus ulcers, diabetic foot wounds or venous leg ulcers.

HISTORY OF THE USE OF CADAVERIC SKIN ALLOGRAFTS

During the past decades deceased donor skin allografts have been widely used as a temporary dressing for extensive wounds, especially massive burns. In the course of time, the technological advances, the development of skin banking and the clarification of the legislation regarding tissue banking led to great progress in the field [6].

Bert was the first to assert, in 1863, that graft survival is conditioned by neovascularization [7]. Shortly after the description of skin autografting by Reverdin, in 1871, the use of skin allografts was endorsed. In 1874, Thiersch reported the use of partial-thickness grafts for wound coverage in a series of patients. However, these very thin epidermal grafts, referred to as "Thiersch grafts" or "pinch-grafts" only yielded satisfactory results in small wounds. Before long, the importance of the dermal components of skin grafts for their successful use in larger wounds became obvious. In 1886, Thiersch published the manuscript entitled "On skin grafting", laying the foundation for the use of split-thickness skin grafts [7,8].

Although human skin banking started in the early 1900s it was not until 1938 that refrigerated cadaveric skin allografts were used to cover extensive full-thickness burns [8]. However, the high rates of allograft rejection and inadequate methods of preservation represented serious challenges. Research aiming the long term maintenance of human allograft skin viability followed and in 1952, Billingham and Medawar reported successful cryopreservation of skin allografts using glycerol [8]. Cadaveric allograft skin soon became the preferred biologic dressing not only in patients with extensive bruns, but also in those with non-healing skin ulcers, traumatic wounds and even chronic infected wounds owing to its potential to reduce bacterial colonization and proliferation and to stimulate neovascularization [8]. Thus, during the last few decades, numerous skin banks have been founded throughout the world, most of them in the close vicinity of regional burn centers.

Professor Agrippa Ionescu was the first physician to perform skin transplant in an organized hospital setting in Romania, in 1958. The use of skin allografts is regulated by Law No.95/2006 concerning the removal and the transplant of human organs, tissues and cells for therapeutical propose, which is in agreement with the European legislation. Unfortunately, the only skin bank in Romania, founded in "Grigore Alexandrescu" Hospital, Bucharest was closed by the authorities in 2018, after 22 years of activity, due to the lack of infrastructure, human and financial resources.

PRELEVATION AND PREPARATION OF SKIN ALLOGRAFTS

Donor screening

Obtaining the medical history of the donor, performing a detailed skin examination and screening for infections [human immunodeficiency virus (HIV) 1/2, hepatitis B virus (HBV), hepatitis C virus (HCV), human T cell lymphotropic virus (HTLV)-1, syphilis, cytomegalovirus (CMV)] and cutaneous bacterial contamination are mandatory.

Skin retrieval

The interval between the time of death and skin collection, as well as the body storage conditions should be well documented. According to current guidelines, to ensure viability, the cutaneous grafts ought to be removed within 24h postmortem if the donor body is refrigerated during the first 12h of asystole and within 15h after the donor's death if the donor body is not refrigerated

[8]. In addition, skin processing at room temperature (25°C) before hypothermic storage is associated with degradation of the dermis. Therefore, it is advisable that after retrieval the skin be placed immediately into nutrient tissue culture medium maintained at 4°C on wet ice, transported and held at this temperature till packaging and hypothermic storage [8].

The procedure is performed under aseptic conditions, in a sterile operating room. The donor areas are usually the torso, buttocks, and the lower limbs in order not to alter the appearance of the donor's exposed areas in an open coffin. Areas affected by skin diseases, skin cancer, connective tissue disorders, areas covered with tattoos, those that display burn or traumatic injuries or signs of infections are excluded for skin donation [9]. The selected donor areas are shaved, thoroughly disinfected and covered with a fine layer of sterile paraffin oil or another lubricant that reduces resistance and facilitates skin removal. An electric dermatome is then used to obtain split-thickness skin grafts 0.03- 0.045 cm thick and 7.5-10 cm wide [8]. Generally, an average of 0.5 m^2 of skin is collected form one donor. The skin grafts are transported in tissue culture medium [primarily Eagle's Minimal Essential Medium (EMEM), but also Dulbecco's Modified Eagle Medium (DMEM) or RPMI-1640] kept at temperatures of 1-10°C in insulated containers to the skin bank, where they are processed [10]. The addition of antibiotics to the transport medium is controversial, as their action is impaired by the low temperature and this may lead to the development of resistant microorganisms. It has not yet been settled which antibiotics are most effective and less toxic for the autografts' cellular components [8].

Skin samples not exposed to antibiotics obtained from different harvesting areas are sent for microbiological assays, including cultures for aerobic and anaerobic bacteria, yeast, and fungi.

Skin processing and storage

Skin processing is also performed in an aseptic manner. The skin samples ought to be carefully maneuvered in order to reduce tissue deterioration. They are cleansed with antiseptic solutions (0.025% sodium hypochlorite mixed in phosphate buffer saline) that remove the surplus of lubricants and dead skin cells, transferred into sterile containers with nutrient storage medium (especially EMEM with 10% fetal bovine serum or pooled human sera) with or without antibiotics (usually amikacin, amoxicillin and vancomycin) and antifungals (amphotericin B) and refrigerated at 4°C as fresh skin allografts [11,12]. These are the preferred temporary biologic dressing for extensive wounds given their rapid adherence and revascularization. If not used in 5-7 days, refrigerated skin allografts must undergo cryopreservation. However, it has been shown that cellular viability can be maintained for 10 - 14 days at 4°C provided the medium is changed every 3 days [8]. In case the medium cannot be changed at the mentioned rate, the grafts ought to be preserved within 96h of retrieval [13].

Skin allografts that need long term storage are meshed and incubated in a cryoprotectant solution (generally 10-15% glycerol or 10% dimethylsulphoxide) for 30 minutes at 4°C to reduce cryogenic cellular damage [8,11]. Postprocessing skin samples are also sent for microbiological testing. Skin allografts are then packed in thin, flat pouches to ensure uniform freezing, sealed and submitted to a controlled-rate freezing of -1°C/min to -70 - -100°C [8,11]. Afterwards, they are placed in a mechanical freezer (-70 to -100°C) or in vapor-phase (-130°C) or liquid nitrogen (-196°C) [8,9]. This way, 85% of the cellular viability of the skin allografts is maintained [8]. The viability of skin allografts is preserved for 3 - 6 months in mechanical freezers and up to 10 years in liquid nitrogen [8].

Another method of skin preservation is incubation in 85% glycerol. As a consequence, free water is fixed in the intra and extracellular spaces. Glycerolization is preferred by some skin banks given the much lower costs and ease of production, storage and distribution compared to cryopreservation, the possibility to preserve such samples up to 5 years, along with its antibacterial and antiviral effects, as well as the reduced antigenicity of glycerol preserved skin allografts [12,14,15]. However, the later show more pronounced mechanical and structural changes and destruction of skin cells, are more rigid and less expandable than cryopreserved allografts [16,17].

As research on the optimal way to preserve allograft skin continues, new methods have been studied, including the use of highly concentrated propylene glycol [18] or disinfection with peracetic acid and preservation in glycerol [19], but further investigations are needed.

Rewarming of cryopreserved allograft skin

Frozen storage packets are transported on dry ice in insulated containers as skin temperature should not rise above -50°C [8]. Before utilization, warming is carried out over 2 - 4 minutes at a temperature of 10 - 37°C. A rewarming rate of 127 - 470°C /min is recommended in order to minimize cryodamage [8].

CLINICAL USES AND TECHNIQUES

The successful engraftment of extensive wounds is conditioned by an adequate preparation of the wound bed. Necrotic tissue should be promptly excised in order to prevent wound infection, lower the risk of graft rejection, prevent significant scarring and contracture and hasten recovery [2]. In the case of mid dermal wounds, gradual tangential excision is performed down to healthy tissue, which is easily recognized by the presence of diffuse punctate bleeding indicative of a viable dermal plexus [2,7]. In deeper wounds, tangential or fascial excision is required. Apart from the necrotic debris, the granulation tissue must also be removed to prevent infection and increase graft adherence [2]. Once proper debridement and meticulous haemostasis are completed, the allograft is placed on the wound and fixed by suture material, fibrin glue, tissue glue or staples [7].

The use of cadaveric allografts for the temporary closure of extensive wounds has numerous advantages. These allografts are physiological barriers that contain both epidermis and dermis. Therefore, they reduce the loss of water, proteins, electrolytes, as well as heat, preventing wound desiccation, improving thermoregulation and ameliorating the patient's general condition and nutritional status [8,20]. They also reduce pain, lower the risk of wound infection and suppress bacterial proliferation in contaminated wounds [15]. Furthermore, by the transfer of the allograft's dermal elements to the wound bed, they facilitate healing and enhance the function the definitive graft and the quality of the scar [21]. Temporary wound coverage with allografts also reduces later autograft requirement and improves autograft take as it stimulates epithelization and prepares the wound bed [20]. Numerous studies concluded that prompt excision of massive burn wounds and temporary coverage with allograft skin significantly reduces mortality and shortens hospital stay [11,22].

The temporary coverage of extensive full-thickness wounds

In patients with extensive full-thickness wounds, the best results are achieved when skin allografts are applied unmeshed. Fresh allografts are superior for temporary wound closure to cryopreserved grafts as they revascularize faster, adhere better to the wound bed, and tolerate minor bacterial contamination of the wound [23]. Glycerol preserved allografts are less adherent to the wound bed than fresh and cryopreserved skin allografts [7].

Meshing of fresh skin allografts is not recommended for the coverage of full thickness wounds as reepithelialization of the interstices with allogenic epidermis doesn't usually take place [8]. Nevertheless, when wounds cover ≥ 50% of the body, meshed allografts at various expansion rates (3:1, 4:1 or 6:1) may be applied [9].

Shearing of the allograft must be prevented as it impedes graft take and neovascularization [2]. The allografted wound is covered with a non-adherent dressing. The use of negative pressure wound therapy is recommended. It immobilizes the graft, minimizes shearing and also draws out all excessive fluid from under the allograft [2]. Otherwise, the fluid build-up under the allograft prevents its uniform adhesion to the wound bed and may lead to graft failure.

Removal of the allogeneic skin is performed as soon as permanent wound coverage with autologous skin is practicable.

Apart from massive burns, other deep wounds, like pyoderma gangrenosum, a rare disorder usually associated with inflammatory bowel disease or hematologic conditions, that may also arise as a postoperative complication [24] and those encountered in patients with meningococcemia or purpura fulminans have been successfully covered with allograft skin once the patients were able to tolerate surgery [25]. Persistent post-traumatic or surgical wounds are also amenable to allografting. The risk of chronic, non-healing postoperative cutaneous defects is greatly diminished in laparoscopic surgery [26,27].

Deep, long-standing leg ulcers refractory to other treatments represent another indication for allogeneic skin grafting. Although coverage of such leg ulcers with autologous split-thickness grafts is the gold standard, they may not succeed in full thickness ulcers as they only contain superficial parts of the dermis [21]. The dermis does not possess renewal potential [25]. Therefore, the use of allografts or de-epidermized dermis (DED) has proven very helpful as these biomaterials assist the restoration of the dermis. As mentioned previously, their collagen and elastic fibers are passed to the wound bed, creating a scaffold that is subsequently infiltrated by host cells, mainly myofibroblasts that remodel the graft's extracellular matrix (ECM) [26-28]. Capillaries of the wound bed also invade the ECM [21]. Thus, the allograft intimately adheres to the wound bed. Moreover, viable cells within the allograft release growth factors and cytokines that promote healing. In approximately 4 weeks, due

to vascularization and active ECM remodeling, the allograft is replaced by granulation tissue [21].

In patients with deeper wounds with tendon or bone exposure, meshed glycerolized or lyophilized allodermis covered with skin allografts may be used [9].

The "sandwich technique" for the coverage of extensive full-thickness wounds

In patients in whom the coverage of extensive wounds can be achieved by a widely meshed autograft, a "sandwich technique" is commonly used to improve and accelerate healing. This technique, described in 1981 by Alexander *et al.* consists in the application of an unmeshed allograft over the over-expanded autograft, thus ensuring protection of the later against mechanic factors, desiccation and infection. As reepithelization of the interstices by autologous epithelium is completed, separation of the allograft from the wound bed takes place [7]. However, sometimes the allograft causes an inflammatory rejection reaction which impedes reepithelialisation. This may be avoided by the use of less antigenic biologic products, such as lyophilized skin allografts or acellular dermal matrices [8,9].

Temporary coverage of extensive partial-thickness wounds

Several authors advocate the use of meshed or unmeshed cadaveric skin allografts for the temporary coverage of extensive partial-thickness wounds to hasten reepithelialization and shorten hospitalization [29].

Patients with exfoliative dermatoses like Stevens-Johnson syndrome/toxic epidermal necrolysis or staphylococcal scalded skin syndrome greatly benefit from the use of allograft skin for the temporary coverage of their extensive wounds pending spontaneous reepithelialization [30,31].

Predicting and promoting subsequent autologous graft acceptance

Early coverage of the debrided wound bed with an allograft does not only offer protection, but also promotes neovascularization [32]. The integration of the allogeneic skin graft reflects the suitability of the wound bed and the existence of an optimal blood supply that will ensure successful subsequent autografting [33].

The combined use of allogeneic and autologous biomaterials

An interesting approach is the use of allogeneic dermis or an acellular dermal matrix with cultured epidermal autografts or thin autografts [8].

Reports on the use of micrografts of both autologous and allogeneic skin have been published [34]. Autografts smaller than 1 mm are seeded on the dermal surface of large sheets of allograft skin that are consequently applied on the wound. Reepithelization occurs due to the spread of the autologous keratinocytes, while the allograft skin progressively separates from the wound bed. Nevertheless, this micrografting method is associated with important wound contraction [34].

Use of allogenic skin grafts in ophthalmology

Jacques-Louis Reverdin (1842-1929) was the first surgeon to experiment the allograft full thickness skin graft (FTSG) in 1869 [35, 36]. After 1869-1874 at his recommendation the use in ophthalmology for healing of small wounds is very much applied especially in palpebral surgery. While skin graft use in surgery is sporadic, the use in ophthalmology has a lot of benefices. FTSG continue to improve after surgery i.e. in facial nerve palsy and this is to be taken into account before a final forensic evaluation [37]. Even today skin graft in ophthalmology is highly recommendate for surgical treatment of ectropion to allow full closure of the eye lid and further on corneal lesions [38].

Skin graft in ophthalmology may have many other applications such as skin actinic lesions, etc. [39] skin grafts and lens transplantation in ophthalmology is a reparatory domain professional interesting and challenged but also with large social utilities and sustain the progress of modern medicine in improving the quality of life.

Conclusion. The use of periocular FTSG is effective in improving lagophthalmos and periorbital symmetry in patients with FNP

CHALLENGES ASSOCIATED WITH THE USE OF CADAVERIC ALLOGRAFT SKIN

Limited availability and medico-legal issues

The principal issue that restricts the use of cadaveric allograft skin is its limited availability. All over the world, the tissue donor rate does not meet demands and in some countries it is alarmingly low due to lack of resources, logistics problems, but also social and cultural reasons.

Pathologists and forensic pathologists perform sampling for diagnostic purposes during forensic autopsies and this is covered by the law enforcement request. It is a condition sine qua non for a proper autopsy [40].

An important aspect is represented by the organ donation impact on determination of cause of death. Sometimes, there is a problem between organ/tissue donation and forensic processes. Depending on the death circumstances, the forensic pathologist – requested by law enforcement - examines the body and the medical documentation provided by the hospital staff and then consents to donation [52].

Risk of transmission of infectious agents

Transmission of blood borne viruses through allograft skin has been reported. Nowadays, this risk is negligible due to strict adherence to protocols.

Another issue is the risk of contamination of skin allografts with pathogenic bacteria or fungi, which may generate not only wound infection, but also sepsis considering the immunocompromised status of the patients in need of these allografts. As discussed above, measures to minimize the risk of allograft contamination are taken throughout the whole process, from the harvesting, transport, to the processing and storage of skin allografts. Moreover, microbiological tests are run after every phase of the process. If contamination with pathogenic microorganisms is detected at any moment, the allograft ought to be discarded [41]. Nonetheless, according to current guidelines the use of allograft skin that presents a low bioburden of non-pathogenic microorganisms is accepted after a thorough risk assessment [42].

Allograft rejection

Another drawback in the use of cryopreserved allograft skin is its rejection, which generally occurs after 2 - 3 weeks. This is explained by the high antigenicity of such allografts. Their epidermis contains Langerhans cells expressing class II major histocompatibility complex antigens that trigger an immunologic rejection response [8]. Attempts to reduce antigen presentation by allograft exposure to ultraviolet radiation or incubation in glucocorticoids did not prove efficient in preventing rejection. Improved allograft survival in patients with extensive burns was reported with the administration of immunosuppresive agents like azathioprine, antithymocyte globulin, and cyclosporin A, but further studies are needed [8].

Lyophilized skin grafts, on the other hand, do not induce an immunologic reaction and survive longer, but are finally rejected as a result of wound healing [43].

Ethical considerations

Autopsy and forensic autopsy moreover is known to complete the knowledge and to help the truth to prevail. This was declared even from 1594 when the famous aphorism of Girolamo Fabricius Acquapendente known as the father of embryology was expressed at the University of Padua, "Hic locus est ubi mors gaudet succurrere vitae" [44].

Cadaveric transplantation included kidney in 1962, liver in 1966, heart in 1967, heart-lung in 1981, artificial heart in 1982, heart xenotransplantation in 1986, split liver in 1996, and first culture of human embryonic stem cells in 2000.

The primary ethical dilemmas surrounding organ transplantation from cadavers [45] arise from the shortage of available organs [46].

Using access on www.unos.org gives an idea of the extent of the organ shortage (nearly 20 years ago):"106 people are added to the nation's organ transplant waiting list each day--one every 14 minutes", "On average, 68 people receive transplants every day from either a living or deceased donor", "On average, 17 patients die every day while awaiting an organ -- one person every 85 minutes" [47].

The concept of distributive justice rather many ways a person could justify giving an organ to one 30 particular individual over someone else. One distributive justice criteria is equal access: criteria include length of time waiting (i.e. first come, first served) and age (i.e. youngest to oldest). Some argue to have this concept free of medical or social worthiness biases others depriving people who, "have no control over their need," of necessary treatment [48].

A second type of distributive justice criteria is maximum benefit with criteria such as medical need (i.e. the sickest people are prioritised) and best prognosis of a transplant (i.e. giving organs to the person who has the best prognosis -life years gained, stressing out the best medical outcome success probability [49,50], which in turn has counter arguments in not available scenarios for best prognosis in advance, bias and favoritism, and life years criteria is only quantitative giving no equal chances.

Today UNOS [46] encourages in USA transplant centers to consider as moral criteria: 1) medical need; 2) probability of success, and; 3) time on the waiting list 43. Not everyone believes in the need to increase the number of organ transplants because induce the concept of instrumentalization of the person.

The secondary ethical dilemmas surrounding organ transplantation in cadaveric donation [44] arises from donor organs, i.e how to increase the number of donor organs (organ farming or premature declarations of death in order to harvest organs are among the public

highest fears).

No transplantation or skin grating is allowed except from brain death donors (heart beating cadavers). Strategies to increase cadaveric organ donations are: education, mandated choice and a free choice before death, presumed consent (person civic duty *vs*. instrumentalization of the body organs as a social property), incentives (gratitude incentives, memorial plaque, etc. *vs*. payment -altruistic need is morally mandatory), prisoners (death penalty is unlawful in Europe).

A person becomes a cadaveric organ donor after they die and indicating that they would like to donate either in Transplantation Register or in a will or by next of kin approval upon request. Skin grafting for individual use of another person is to be granted by approval on request as in any transplantation activity. Even if the patient is a registered donor the next of kin consent is required. In turn if the deceased is registered in the Transplantation Register this may be considered a last will no matter the next of kin will [51].

According to Romanian law, the consent of the family of a deceased person is mandatory for organ/tissue donation. The rate of organ harvesting is low because of many factors like organizational particularities, restrictive criteria for brain death declaration and, the most important – the mandatory need for relatives approval [53].

An important problem is represented by a high prevalence of comorbidities such as hypertension, diabetes, hepatitis B and C in minority groups. People from racial minorities are disproportionally represented on transplant waiting lists [54].

In conclusion, prompt wound excision or debridement, followed by temporary application of allogeneic skin grafts has proven life-saving in patients with extensive wounds in whom autograft availability is extremely limited. Despite the development of new engineered skin substitutes, the reestablishment of a skin bank in Romania is an urgent need as the use of deceased donor allograft skin as temporary biological wound dressing represents a major element in the successful management of patients with severe burns.
Future research must address the current disadvantages associated with the use of allograft skin, mainly the limited supply, high antigenicity, risk of infection transmission, as well as optimization of the processing and storage techniques.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

This work was supported by a grant of the Ministry of Research, Innovation and Digitization, CNCS/CCCDI – UEFISCDI, project number PN-III-P1-1.1-PD-2019-1225, within PNCDI III.

References

1. See P, Phan TT, Chua JJ, Song C, Tan KC, Lee ST. Our Clinical Experience using Cryopreserved Cadaveric Allograft for the Management of Severe Burns. Cell Tissue Bank. 2001;2(2):113-117.
2. Elseth A, Nunez Lopez O. Wound Grafts. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan, Accessed 2021 Jan 20.
3. Sood R, Roggy D, Zieger M, Balledux J, Chaudhari S, Koumanis DJ, Mir HS, Cohen A, Knipe C, Gabehart K, Coleman JJ. Cultured epithelial autografts for coverage of large burn wounds in eighty-eight patients: the Indiana University experience. J Burn Care Res. 2010;31(4):559-568.
4. Haddad AG, Giatsidis G, Orgill DP, Halvorson EG. Skin Substitutes and Bioscaffolds: Temporary and Permanent Coverage. Clin Plast Surg. 2017;44(3):627-634.
5. Heimbach DM, Warden GD, Luterman A, Jordan MH, Ozobia N, Ryan CM, Voigt DW, Hickerson WL, Saffle JR, DeClement FA, Sheridan RL, Dimick AR. Multicenter postapproval clinical trial of Integra dermal regeneration template for burn treatment. J Burn Care Rehabil. 2003;24(1):42-48.
6. Keswani SM, Mishra MG, Karnik S, Dutta S, Mishra M, Panda S, Varghese R, Virkar T, Upendran V. Skin banking at a regional burns centre-The way forward. Burns. 2018;44(4):870-876.
7. Leon-Villapalos J, Eldardiri M, Dziewulski P. The use of human deceased donor skin allograft in burn care. Cell Tissue Bank. 2010;11(1):99-104.
8. Kagan RJ, Robb EC, Plessinger RT. Human skin banking. Clin Lab Med. 2005;25(3):587-605.
9. Tognetti L, Pianigiani E, Ierardi F, Mariotti G, Perotti R, Di Lonardo A, Rubegni P, Fimiani M. Current insights into skin banking: storage, preservation and clinical importance of skin allografts. Journal of Biorepository Science for Applied Medicine. 2017;5:41-56.
10. Holder IA, Robb E, Kagan R. Antimicrobial mixtures used to store harvested skin: antimicrobial activities tested at refrigerator (4 degrees C) temperatures. J Burn Care Rehabil. 1999;20(6):501-504.
11. Chua A, Song C, Chai A, Chan L, Tan KC. The impact of skin banking and the use of its cadaveric skin allografts for severe burn victims in Singapore. Burns. 2004;30(7):696-700.
12. Germain N, Hatzfeld AS, Pasquesoone L, Danze PM, Guerreschi P, Sendid B, Gaillot O, Marchetti P. How to improve donor skin availability: Pragmatic procedures to minimize the discard rate of cryopreserved allografts in skin banking. Burns. 2020:S0305-4179(20)30463-0.
13. Woll JE, Kasprisin D, editors. Standards for Tissue Banking. McLean, VA: American Association of Tissue Banks; 2001. p. 46–52.
14. Saegeman VS, Ectors NL, Lismont D, Verduyckt B, Verhaegen J. Short- and long-term bacterial inhibiting effect of high concentrations of glycerol used in the preservation of skin allografts. Burns. 2008;34(2):205-211.
15. Cleland H, Wasiak J, Dobson H, Paul M, Pratt G, Paul E, Herson M, Akbarzadeh S. Clinical application and viability of cryopreserved cadaveric skin allografts in severe burn: a retrospective analysis. Burns. 2014;40(1):61-66.
16. Kua EHJ, Goh CQ, Ting Y, Chua A, Song C. Comparing the use of glycerol preserved and cryopreserved allogenic skin for the treatment of severe burns: differences in clinical outcomes and *in vitro* tissue viability. Cell Tissue Bank. 2011;13:269-279.

17. Blome-Eberwein S, Jester A, Kuentscher M, Raff T, Germann G, Pelzer M. Clinical practice of glycerol preserved allograft skin coverage. Burns. 2002;28:10-12.
18. Huang Q, Pegg DE, Kearney JN. Banking of non-viable skin allografts using high concentrations of glycerol or propylene glycol. Cell Tissue Bank. 2004;5:3-21.
19. Lomas RJ, Cruse-Sawyer JE, Simpson C, Ingham E, Bojar R, Kearney JN. Assessment of the biological properties of human split skin allografts disinfected with peracetic acid and preserved in glycerol. Burns. 2003;29(6):515-525.
20. Gore MA, De AS. Deceased donor skin allograft banking: Response and utilization. Indian J Plast Surg. 2010;43(Suppl):S114-120.
21. Mosti G, Mattaliano V, Magliaro A, Picerni P, Bastiani L. Cadaveric Skin Grafts May Greatly Increase the Healing Rate of Recalcitrant Ulcers When Used Both Alone and in Combination With Split-Thickness Skin Grafts. Dermatol Surg. 2020;46(2):169-179.
22. Choi YH, Cho YS, Lee JH, Choi Y, Noh SY, Park S, Sung C, Lim JK, Kim J, Shin JJ, Yang B, Jeong J, Chun H, Kim KJ. Cadaver skin allograft may improve mortality rate for burns involving over 30% of total body surface area: a propensity score analysis of data from four burn centers. Cell Tissue Bank. 2018;19(4):645-651.
23. Robb EC, Bechmann N, Plessinger RT, Boyce ST, Warden GD, Kagan RJ. Storage media and temperature maintain normal anatomy of cadaveric human skin for transplantation to full-thickness skin wounds. J Burn Care Rehabil. 2001;22(6):393-396.
24. Miron A, Giulea C, Tudose I, Petrache D, Giurcaneanu C. Pyoderma gangrenosum, rare parietal complication after colorectal surgery. Chirurgia. 2014;109(2):248-253.
25. Lowery K, Shirley R, Shelley OP, Kaniorou-Larai M, Philp B, Dziewulski P. Purpura fulminans skin loss: surgical management protocols at a regional burns centre. J Plast Reconstr Aesthet Surg. 2008;61(12):1520-1523.
26. Miron A, Giulea C, Nadragea M, Enciu O. The Laparoscopic Approach of Small Bowel Obstruction-The Experience of a Primary Center. Chirurgia. 2016;111(2):126-130.
27. Calu V, Dumitrescu I, Miron A. The role of laparoscopy in the surgical treatment of scleroatrophic cholecystitis. Chirurgia. 2010;105(5):653-656.
28. Zhou H, You C, Wang X, Jin R, Wu P, Li Q, Han C. The progress and challenges for dermal regeneration in tissue engineering. J Biomed Mater Res A. 2017;105(4):1208-1218.
29. Wong AK, Schonmeyer BH, Singh P, Carlson DL, Li S, Mehrara BJ. Histologic analysis of angiogenesis and lymphangiogenesis in acellular human dermis. Plast Reconstr Surg. 2008;121(4):1144-1152.
30. Chauviere MV, Schutter RJ, Steigelman MB, Clark BZ, Grayson JK, Sahar DE. Comparison of AlloDerm and AlloMax tissue incorporation in rats. Ann Plast Surg. 2014;73(3):282-285.
31. Reiffel AJ, Henderson PW, Krijgh DD, Belkin DA, Zheng Y, Bonassar LJ, Stroock AD, Spector JA. Mathematical modeling and frequency gradient analysis of cellular and vascular invasion into integra and strattice: toward optimal design of tissue regeneration scaffolds. Plast Reconstr Surg. 2012;129(1):89-99.
32. Naoum JJ, Roehl KR, Wolf SE, Herndon DN. The use of homograft compared to topical antimicrobial therapy in the treatment of second-degree burns of more than 40% total body surface area. Burns. 2004 Sep;30(6):548-551.
33. Spies M, Sanford AP, Aili Low JF, Wolf SE, Herndon DN. Treatment of extensive toxic epidermal necrolysis in children. Pediatrics. 2001;108(5):1162-1168.
34. Pianigiani E, Ierardi F, Taddeucci P, Perotti R, Biagioli M, Di Simplicio FC, Andreassi A, Fimiani M. Skin allograft in the treatment of toxic epidermal necrolysis (TEN). Dermatol Surg. 2002;28(12):1173-1176.
35. Burd A, Lam PK, Lau H. Allogenic skin: transplant or dressing? Burns. 2002;28(4):358-366.
36. Tenenhaus M, Rennekampff HO. Burn surgery. Clin Plast Surg. 2007;34(4):697-715.
37. Zhang ML, Chang ZD, Wang CY, Fang CH. Microskin grafting in the treatment of extensive burns: a preliminary report. J Trauma. 1988;28(6):804-807.
38. Reverdin H. Jaques-Louis Reverdin (1842-1929). Un chirurgien á l'aube d'une ere nouvelle. Verlag Sauerlander, Aarau, Switzerland, 1971.
39. Reverdin J L. Greffe epidermique-Experience faite dans le service de M. le docteur Guyon, á l'hópital Necker. Bull Soc Imp de Chir de Paris 1869;10:511-515. Reimpreso en: Plast Reconstr Surg 1968; 41:79-82.
40. Maqsood SE, Cascone N, Grixti A, Kannan R, Nduka C, Malhotra R. Functional and aesthetic outcomes of eyelid skin grafting in facial nerve palsy.British Journal of Ophthalmology. 2019;103: 686-691.
41. Klasen H.J. (1981) Skin Grafting in Eyelid Surgery. In: History of Free Skin Grafting. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-642-81653-6_3, ISBN 978-3-642-81655-0, 978-3-642-81653-6.
42. Catherine J. Choi, Alain Bauza, Michael K. Yoon, Rachel K. Sobel,Suzanne K. Freitag. Full-Thickness Skin Graft as an Independent or Adjunctive Technique for Repair of Cicatricial Lower Eyelid Ectropion Secondary to Actinic Skin Changes. Ophthalmic Plast Reconstr Surg. 2015;31(6):474-477.
43. van Diest PJ, Lopes Cardoso NWJ, Niesing J. Cadaveric tissue donation: a pathologist's perspective. Journal of Medical Ethics 2003;29:135-113.
44. Hornicek. AATB standards for tissue banks. 10th edition. McLean, VA: AATB; 2002. p. 112.
45. European Commitee (partial agreement) on organ transplantation (CD-P-TO). 4th edition of the guide to the quality and safety of tissues and cells for human application. 2019. https://www. edqm.eu/en/organs-tissues-and-cells-technical-guides. Accessed 2021 Jan 20
46. Wei LG, Chen CF, Wang CH, Cheng YC, Li CC, Chiu WK, Wang HJ. 500-Gray γ-Irradiation May Increase Adhesion Strength of Lyophilized Cadaveric Split-Thickness Skin Graft to Wound Bed. Ann Plast Surg. 2017;78(3 Suppl 2):S135-S138.
47. Barry Lillie, Silvia Donati. Italy's Ancient Medical Schools: Anatomical Theatres. Wed, 10/29/2014. Accesat in 8.05.2019 [https://www.italymagazine.com/featured-story/italys-ancient-medical-schools-anatomical-theatres].
48. Ethics of Organ Transplantation, Center for Bioethics February 2004, University of Minnesota, accessed February 20th 2021 [https://www.ahc.umn.edu/img/assets/26104/Organ_Transplantation.pdf].
49. Childress JF. The Failure to Give: Reducing Barriers to Organ Donation. Kennedy Institute of Ethics Journal. 2001; 11(1):1-16.
47. United Network for Organ Sharing website. www.unos.org.
50. Kluge EH. Drawing the Ethical Line Between Organ Transplantation and Lifestyle Abuse. Canadian Medical Association Journal. 1994; 150(5):745-746.
51. Williams A. The rationing debate: Rationing health care by age: The case for. British Medical Journal. 1997; 314:820.
52. Ubel PA, Arnold RM, Caplan AL. Rationing failure: Retransplantation of scarce, vital organs in the US. Journal of the American Medical Association. 1993; 270:2469- 2474.
53. van Diest PJ, Lopes Cardoso NWJ, Niesing J. Cadaveric tissue donation: a pathologist's perspective. Journal of Medical Ethics. 2003;29:135-113.
54. Nunnink L, Stobbs N, Wallace-Dixon C, Carpenter B. Does organ donation impact on forensic outcomes? A review of coronial outcomes and criminal trial proceedings. Journal of forensic and legal medicine. 2019;68:101860.
55. Grigoraș I, Blaj M, Florin G, Chelarescu O, Craus C, Neagu R. The rate of organ and tissue donation after brain death: causes of donation failure in a Romanian university city. InTransplantation proceedings 2010; 42(1): 141-143.
56. Bratton, Charles; Chavin, Kenneth; Baliga, Prabhakar Racial disparities in organ donation and why, Current Opinion in Organ Transplantation. 2011;16(2):243-249.