Challenges in the Management of Large Burns

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KEYWORDS

• Large burns • Mortality • Morbidity • Surgical care • Critical care • Palliative care

KEY POINTS

- Large burn injury presents unique challenges for the burn surgeon.
- Early excision and coverage of the large burns improve the survival.
- Alternative skin grafting methods and donor sites are valuable tools for the coverage of large burn wounds.
- Epidermal tissue engineering techniques have not reached the desired clinical potential but may be more efficient when combined with other techniques.
- Palliative care consultation should be considered early in the management of patients with large burns and poor prognosis.

INTRODUCTION

The improvements in critical care and resuscitation increased the survival rates of patients with large burns. However, infections, metabolic derangements, and coverage of these wounds continue to be a challenge. Immunosuppression makes these patients susceptible to invasive burn wound infections and hypermetabolic state increases the nutritional requirements. The best treatment for the burn infections is prevention via hygiene and isolation methods. Supportive care early in the management of these patients is imperative to get the patients ready for a series of surgical procedures for debridement and coverage of the burn wound. Split-thickness skin grafting (STSG) is the traditional coverage method for burn wounds but in case of large wounds may not be possible due to the lack of donor sites. Fortunately, a multitude of skin substitutes have been developed in recent decades to replace, temporarily or permanently, the autologous skin and facilitate the coverage of the large burn wounds. Burn injury is not only a simple wound including the skin, but also a complex cascade of pathophysiologic events that should be addressed with vigilance for optimal outcomes.

BURN PATHOPHYSIOLOGY

The physiologic response to large burns is characterized by poor tissue perfusion due to profound capillary leakage and intravascular volume depletion, coagulopathy, and widespread release of inflammatory mediators.[1] These mediators act on T cells attenuating T-helper (Th)-1 response and enhancing the Th-2 and Th-17 responses.[2,3] This leads to an immunosuppressed state after large burns.[4]

Tumor necrosis factor (TNF)-α is an inflammatory mediator which is secreted primarily by macrophages and Th-1 cells. It is central to the systemic inflammatory response syndrome (SIRS) and sepsis seen in burn injuries.[5] Interleukin (IL)-6 is

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another inflammatory mediator that is elevated in the first week after burn injury.[6] IL-6 activates C-reactive protein.[7] IL-8 also peaks shortly after a burn injury and attracts neutrophils and granulocytes to the burn site.[8] High IL-8 levels correlate with increased mortality in large burns.[9] A similar correlation exists between the levels of granulocyte/macrophage colony-stimulating factor (GM-CSF) and monocyte chemoattractant protein-1 and mortality.[9] The levels of several other inflammatory cytokines are elevated soon after a large burn injury. These cytokines are IL-4, IL-2, IL-5, IL-7, IL-12 and its active form *P*70, IL-13, IL-17, and interferon-c.[5] Enzymes, matrix metalloproteinase (MMP)-8, and MMP-9 are released from neutrophils in response to increased levels of GM-CSF, IL-8, and TNF-α.[10] MMPs increase vascular permeability by breaking down the basement membrane in vessel walls and cause loss of intravascular volume and third spacing seen in burn injuries.[11]

Hypermetabolism

Hypermetabolism is a distinctive feature of systemic response to large burns. It occurs in conjunction with the SIRS as described above. Hypermetabolism increases mortality and may persists for up to 3 years after burn injury.[12] Hypermetabolic changes are seen primarily in the mitochondria of adipocytes. Increased amounts uncoupling protein-1 in mitochondria causes uncoupled mitochondrial respiration that is characterized by inner mitochondrial membrane proton conductance that proceeds without the presence of adenosine triphosphate (ATP) synthase. This derangement in mitochondrial function leads to heat production and shifts the metabolic function of adipose tissue from the storage of energy to the expenditure.[13,14] Skeletal muscle oxygen consumption increases due to increased ATP production.[15] Increase is also seen in ATP-consuming reactions required for protein synthesis, gluconeogenesis, and fatty acid cycling pathways.[16]

Central (hepatic) and peripheral (skeletal muscle) insulin resistance is a part of metabolic response to burn injury. It is probably due to a post-receptor defect involving the glycogen synthesis pathways.[17,18] Insulin resistance leads to hyperglycemia that promotes an aggressive hyperinflammatory response to burn injury.[19,20]

Coagulopathy

Coagulopathy in large burns is characterized by low levels of the anticoagulants: antithrombin, protein C, and protein S.[21] Protein C has potent anti-inflammatory and cytoprotective functions in addition to its anti-factor VIIIa function.[22] Activated form of protein C modulates the inflammatory response,[22] promotes angiogenesis[23] and stimulates reepithelialization.[24] The combined effect is the granulation tissue formation at the base of the wound, reduced inflammatory cell migration, and rapid epithelialization of the wound.[25,26] Inflammatory mediators TNF-α and IL-1 suppress protein C activation and expression, respectively.[27,28] The levels of both TNF-a and IL-1 increase immediately after a burn; therefore, the protein C levels decrease significantly in circulation. Protein C levels also differ significantly between survivors and non-survivors after large burns.[5]

CRITICAL CARE AND RESUSCITATION

Large cutaneous injury with or without concomitant inhalational injury presents several unique challenges to the burn surgeon. Inhalation injury can impact up to one-third of all major burn injuries and significantly increases mortality. Severe inhalation and cutaneous injury can have profound pathophysiologic consequences for the patient. Bronchoscopy should be performed to confirm inhalation injury in high-risk patients and vigorous chest physiotherapy, and ambulation should be initiated early once diagnosis is confirmed.[29] Nebulized N-acetylcysteine, salbutamol, and nebulized heparin can be used reduce the duration of mechanical ventilation after inhalational injury.[30]

Patents must be optimized hemodynamically and from a respiratory standpoint before undergoing operative intervention. High volume resuscitation secondary to capillary leak is often necessary resulting in increased skin turgor, pleural effusions, pulmonary edema, and infrequently, compartment syndrome. Parkland formula,[31] modified Brooke formula,[32] and the Rule of Tens[33] are the formulas used to calculate the amount of fluid needed in the first 24 hours following burn injury. Colloid and other rescue techniques should be used to avoid volume overloading during resuscitation.[34]

Intravenous access in large cutaneous burn patients may be complicated, and clean intravenous line insertion sites are often limited. Both peripheral and central venous insertion lines must be inspected and changed frequently as such patients are at high risk for bloodstream infections.[35] Large burn injuries demonstrate profound hypermetabolism, and early initiation of enteral feeds is essential. Every effort should be made to avoid interrupting feeds, which maybe continued throughout operative interventions. Monitoring of nutritional parameters is important, and

consideration should be given to nutritional adjuncts such as oxandrolone and beta blockers (propranolol) to modulate the hypermetabolic response.[36]

TIMING OF SURGICAL INTERVENTION

After initial stabilization, surgical removal of the devitalized tissues (ie, eschar) down to a healthy well vascularized layer should be carried out early during hospitalization. Early debridement of the necrotic eschar reduces the inflammation and helps to reverse associated hypermetabolism and catabolism,[37] reduces mortality and length of hospital stay, and yields better functional and cosmetic outcomes.[38] It is often necessary in the patient with large burns to plan for serial surgical excisions, limiting the total body surface area (TBSA) excised. Operations should be limited in extent to avoid profound coagulopathy, acidosis, and hypothermia. Once recovered, patients may return quickly to the operating room until the excision is complete.

COVERAGE OF LARGE BURNS

Temporary Coverage

If the burn wound is not ready for coverage several temporary coverage methods can be used. These products help to prepare the wound for skin grafting and provide and additional layer of coverage, therefore increasing the stability of the final scar. There are numerous artificial dermal products in the market today and discussed in detail elsewhere in this volume.

Dehydrated human amniotic/chorion membrane

Sterilized, dehydrated human amnion/chorion membrane is composed of a single layer of epithelial cells, a basement membrane, and an avascular connective tissue matrix. Dehydrated human amniotic/chorion membrane (DHACM) contains growth factors that promote wound healing, including platelet-derived growth factor A and B, basic fibroblastic growth factor, and transforming growth factor beta 1. Amnion is used mainly for ophthalmologic burns.[39] It is available, readily, adherent, transparent (thus allowing wound monitoring), has the potential to reduce the risk of wound infection, and may have an analgesic effect. Disadvantages include difficulty in handling and fast degradation.[40]

Dermal replacement template

Dermal replacement template (DRT) is composed of a cross-linked bovine collagen and glycosaminoglycan dermal layer and a silicone epidermal layer.

Appropriate dressings are used to secure it in place and protect the wound area. The outer dressing can be changed as needed depending on the volume of exudate. Once the template has become vascularized (usually by 14 days), any silicone layer can be removed and an autograft applied.[41]

Acellular dermal matrix

Acellular dermal matrix is an allograft (also called homograft) product created from skin from a nongenetically identical deceased human donor that has been processed to remove the epidermis using a sequential decellularization process.[41] These decellularized matrices fully integrate into the wound bed after application, replacing lost dermal tissue and providing a scaffold into which the recipient's cells can grow and become vascularized, ultimately regenerating into normal skin.

Biodegradable temporizing matrix

Biodegradable Temporizing Matrix (BTM) is a fully synthetic product. It is applied in a two-stage approach. Given the potential protective nature of BTM against infectious complications and its ability to remain in place for longer periods without the need for delamination and application of STSG, BTM might prove to be beneficial in coverage of wound in those with extensively large percentage TBSA burns.[41,42]

Bilayered living cellular construct

The bilayered living cellular construct (BLCC) a dermal part (bovine type I collagen with human neonatal foreskin fibroblasts) and an epidermal part (keratinocytes). The BLCC template serves as a scaffold for neovascular and cellular infiltration from the wound bed. It can be used as a standard two-stage dermal template or as a single stage. In the two-stage procedure, the BLCC scaffold is gradually replaced with the patient's own collagen, forming a neo-dermis. After 2 to 3 weeks, the silicone epidermal layer is removed, and the wound is covered with a thin STSG.[41–43]

Xenografts

Skin xenografts (heterografts) are obtained from an unrelated species and can be used as temporary skin coverage, particularly for large burn wounds. Porcine grafts have been the most commonly used xenograft,[41] however, there's been research into the use of tilapia fish skin as xenograft.[41,43] They have been shown to decrease evaporative water loss, risk of infection, and encourage autologous epidermal growth.[42,43] However, xenografts do not revascularize; therefore, they do not last as long as allografts in the recipient bed.[41]

Cadaveric allograft skin

Cadaveric skin is often used for temporary coverage of large burns. It can provide wound coverage for up to 3 to 4 weeks.[43] When cryopreserved, allograft has an indefinite shelf life.[44] Limiting factors are availability of donors and high costs.[41]

The FDA-approved skin substitutes are summarized in **Table 1**.

Permanent Coverage

STSG is the current gold standard for the coverage of burn wounds. However, STSG is limited by donor skin availability especially in large burns. Moreover, the donor-site wound is associated with pain and additional scarring.[45]

Cultured epidermal autograft (CEA) was first described in 1975 as an alternative method for the coverage of large burns.[46,47] The promise of CEA is to provide large sheaths of skin grafts with minimal donor site requirements. A single full-thickness biopsy measuring 2 cm^2 can be expanded in area up to 10,000 times.[48] For patients with large burns, prompt skin coverage not only reduces the mortality but also is the key for acceptable functional and esthetic outcome.[49] As early excision became the standard of care for deep burns,[50] CEA generated great hopes for prompt reconstruction of the epidermal barrier in patients with large burns and limited donor sites. CEA can also be used to shorten the reepithelialization time of STSG donor sites (average of 7 days) allowing rapid reuse of these sites.[49] However, CEA faces many challenges in clinical application, such as low resistance to infection, long preparation time, high costs, and mechanical fragility.[51–53] The final take of CEA grafts can be as low as 16% because of the great fragility of the cultured keratinocyte sheaths.[49] Cuono method[54] combines the use of CEA with large-meshed STSG (1:6–1:12) for coverage of large burns. With this combined method, success rate can be as high as 85%[48,49,54] (**Fig. 1**). Younger age and low burned TBSA are also correlated with increased rates of CEA take.[48]

Meek's method was developed in 1958[55] and involved mechanical division of the skin graft into small pieces using a MEEK–Wall dermatome, followed by placement of these pieces onto the wound bed, dermal side facing down. Although it allows up to 10-fold skin expansion, this technique never gained widespread acceptance because it is labor-intensive and time-consuming.[56,57] There is a renewed interest in this technique with recent reports of success in patients with large burns.[58] Recent studies reported a graft take between 60% and 90% after an average of 2.21 surgeries.[57]

Other modified skin grafting techniques that have been described to overcome donor site limitations in patients with large burns are (1) Xpansion Micrografting System, (2) fractional skin harvesting, (3) epidermal suction blister grafting, and (4) ReCell technology.[45]

1. Xpansion Micrografting Technique: Based on a mincing device that STSG is passed through yielding 0.8 to 0.8 mm micrografts.

Table 1
FDA-approved skin substitutes used in burn coverage

Biobrane®	Biosynthetic dressing constructed of a silicon film and an embedded nylon fabric
Integra® DRT	Bovine, collagen/glycosaminoglycan dermal replacement
Ez Derm®	Aldehyde cross-linked porcine dermis
Epicel®	Autologous keratinocytes cultured ex vivo
OrCel™	Human dermal cells cultured in bovine collagen. Used for STSG donor sites in burn patients
TransCyte™	Human dermal fibroblasts grown on nylon mesh, combined with a synthetic epidermal layer
TheraSkin®	Cryopreserved split-thickness human skin allograft
AlloDerm®	Native human skin with intact basement membrane and cellular matrix
GraftJacket®	Acellular dermal regenerative tissue matrix
Helicoll (Encol)®	Acellular collagen matrix derived from bovine dermis
Kerecis™	Acellular dermal matrix derived from fish skin
Suprathel®	Synthetic membrane fabricated from a tripolymer of polylactide, trimethylene carbonate, and s-caprolactone

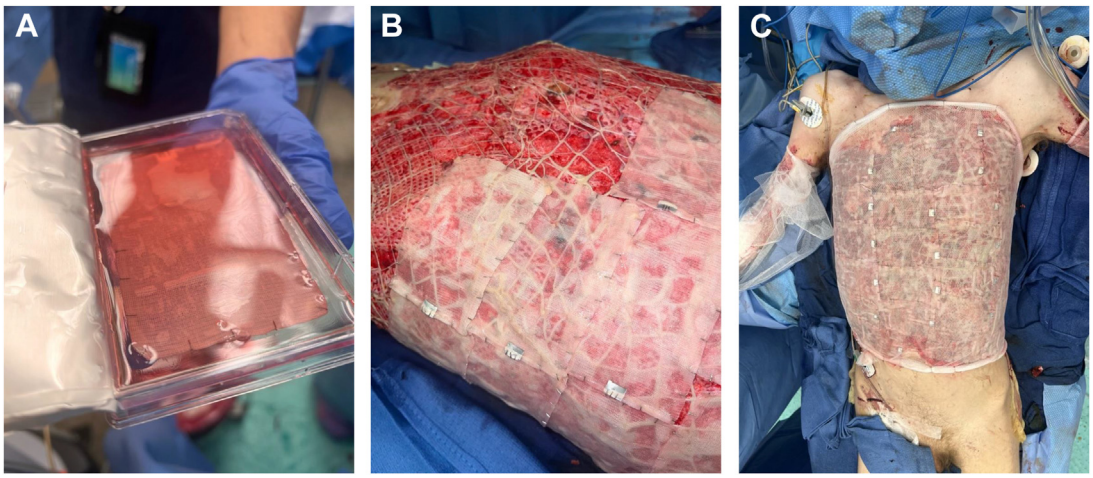

Fig. 1. The application of CEA to a patient with 48% TBSA burns after multiple rounds of cadaver grafting. (*A*) Cultured keratinocyte sheath in culture medium. (*B*) Application of CEA with STSG. (*C*) Final intraoperative result. (*Courtesy of* Francesco M. Egro, MD, Pittsburgh, PA.)

2. Fractional Skin Harvesting: Full-thickness microscopic skin tissue columns are harvested like fractional photothermolysis technique. The epidermis at the donor site heals within 24 hours with minimal scarring.
3. Epidermal Suction Blister Skin Grafting: The technique involves creation of an epidermal blisters using suction, which is then manually harvested from the donor site and transferred to the recipient site. A novel device called CelluTome (Kinetic Concepts, Inc, San Antonio, Texas) is available to harvest STSG using this method.
4. ReCell Technology: This technique involves enzymatic isolation of cells from the donor tissue and immediate autologous replantation to the wound without in vitro culture or expansion. The benefits of this method in terms of healing of burn wounds are controversial.[59]

In addition to the traditional STSG donor sites that might not be available in patients with large burns, soles of the feet, palm, scrotum, and scalp can be used as alternative donor sites for STSG.[60]

PALLIATIVE CARE

The survival of the patients with large burns has improved significantly since the adoption of early excision and grafting along with the advancement of critical care. However, patients with severe comorbidities and advanced age still have a poor prognosis and high mortality.[61] Baux score is a simple method predicting mortality after burn injury. It is calculated as: Percent Mortality = Age + Percent body burned.

Original Baux score was modified to include inhalation injury and recalibrated to reflect modern burn care results.[62,63] Prolonging the treatment of patients with high Baux scores and without a meaningful recovery is considered as "futile treatment."[64,65] Therefore, early involvement of a palliative care team should be considered in this cohort of patients.[64,66]

Palliative care is the ''active holistic care of patients with advanced progressive illness" with a focus on minimizing illness-related discomfort and improving the quality of life for patients and their families.[65] Even though palliative care interventions can reduce health care utilization without increasing mortality for surgical patients, palliative care is still underused in burn patients due to misconceptions around it.[65,66]

Central components of palliative care include reducing the symptoms of disease, fostering communication, providing emotional and spiritual support to patients and families, and matching value-based goals with medical interventions.[66] Predicting survival in patients with large burns can be challenging due to the complex nature of physiologic changes associated with burn. This uncertainty complicates the goals of care/end-of-life care discussions. There is extensive literature regarding end-of-life care in elderly patients in medical intensive care units.[67,68] Burn units have a more heterogenous age distribution, with a larger population of younger patients, and unfortunately similar literature in burn patients is scarce.[69,70] Palliative care pathways, such as the Liverpool Care Pathway, are well established for palliation of patients in other settings but are rarely implemented in the patients with large burns.[71] As the patient

Box 1
Factors increasing the probability of palliative care in burn patients

Age > 50 years

Increasing percentage TBSA

Full-thickness burns

Comorbidities/Elixhauser score >4

Inhalation injury

Frail appearance

Data from Ismail A, Long J, Moiemen N, Wilson Y. End of life decisions and care of the adult burn patient. Burns. 2011;37(2):288-293.

population gets younger, a standardized protocol-based approach to end-of-life care discussions becomes more important. An example protocol for pediatric burn patients was published by Shriner's group.[72] Such protocols include triggers to initiate a palliative care consultation.

The early initiation of goals of care discussion in patients with large burns is appropriate and decreases the uncertainty surrounding the care of these complex patients. If the prognosis is poor, end-of-life care discussions, governed by the medical teams' clinical knowledge, should be initiated. The feelings, beliefs, and values of the patients' and their families should be taken into consideration during this discussion.[65] In general, patients with modified Baux scores between 120 and 150 are the best candidates for palliative care services, given the poor prognosis and unlikely survival. This group of patients might be best served by avoiding unnecessary interventions. The demographics of burn patients who are more likely to receive palliative care are summarized in **Box 1**.[73]

If at any point the decision to withdraw treatment is reached, appropriate comfort care measures should be implemented. A comfortable and dignified death relieves both the patient and family. A clear, standardized, and consistent documentation and communication are crucial during this transition process.[65]

SUMMARY

Early excision and coverage of the large burns improves the survival and prevents infections. However, it is important to understand and treat the complex pathophysiological derangements associated with large burn injury for a successful outcome. Nutrition and infection prevention are two main pillars of the supportive treatment. Skin coverage should be achieved as early as possible. Alternative skin grafting methods and donor sites are valuable tools for this purpose. If the wound cannot be covered soon, temporary dressings and skin substitutes can provide a physiologic environment to facilitate wound healing and can be used as a bridge to definitive coverage. For patients with high Baux scores, palliative care consultation should be considered early in the hospital course. Palliative care is not synonymous with withdrawal of care. On the contrary, it improves the comfort of the patients and families during their often, lengthy hospital stay.

CLINICS CARE POINTS

- Large burns are not merely skin wounds; they trigger a complex pathophysiological response in human body. It is important to treat all aspects of burn injury for a successful outcome.
- Be comfortable with different coverage methods in case of donor site limitations.
- Pay attention to hypothermia and make every effort to minimize blood loss in the operating room.
- Palliative care is not same as withdrawal of care. Identify the patients who may benefit from palliative care early on.

DISCLOSURE

The authors have no disclosures.

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