A Brief History of the Treatment of Burns

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Abstract: Advances in burn care have a long history with accelerated development within the last 50 years. The principal areas of burn treatment include dressings, antimicrobials, fluid resuscitation, burn wound excision, grafting of skin, and skin substitution. This review presents a historical outline of these areas, their current status, and prospects for the future of burn care.

Key Words: burn treatment, burn dressings, infection control, fluid resuscitation, burn surgery

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Treatments of burns have been described since ancient times.5 Burns and their treatments are recognized in cave paintings which are over 3500 years old. Documentation in the Egyptian Ebers papyrus of 1500 BC advocated a 5-day treatment regimen using a mixture of cattle dung, bees wax, ram's horn, barley porridge soaked in resin for topical treatment of burns. In 600 BC, the Chinese treated burn wounds with extracts from tea leaves. Nearly 100 years later, Hippocrates described the use of skin of swine mixed with a resin of bitumen impregnated in bulky dressings which were alternated with warm vinegar soaks augmented with tanning solutions made from oak bark. Celsus used a lotion with wine and myrrh for burns in the first century AD. In 300 AD, Hong Ge described a treatment of topical ointment made of old calcarea blended with plant oil or pig fat cooked with willow bark.2

In the middle of the 16th century, Ambroise Paré treated burns with onions and probably was the first to describe early burn wound excision. In the early 17th century, Guilhelms Fabricius Hildanus discussed the pathophysiology of burns and made unique contributions to the treatment of subsequent cicatrical contractures. In 1797, Edward Kentish described pressure dressings as a means to relieve burn pain and blisters. In 1839, Guillaume Dupuytren reviewed the treatment of 50 burn patients with occlusive dressings and developed a classification of burn depth that remains recognizable today.3 He was also the first to recognize gastric and duodenal ulceration as a complication of severe burns, a concept described in more detail by Curling4 in 1842.

The recognition of the importance of burn surface area and skin grafting by Reverdin clarified both the diagnostic and surgical understanding of burns.5 During and after World War I, consensus was reached that the best management of deep burn wounds included excision, skin grafting, and pain management.

Despite centuries of treatments for burns, many patients still died of shock and infection mainly because the fundamental understanding of the pathophysiological effects of burns was not clear.6 Research inspired by fire disasters, such as the Rialto fire in 1921 and Coconut Grove nightclub fire in 1942, provided the first operational understandings of the pathophysiology of burns.4

Based on the index of mortality, it is evident that our ability to treat burn injuries has improved remarkably since World War II. The 50% lethal area, which is fatal for 50% population, in the immediate postwar era was approximately 40% total body surface area (TBSA) for young adults in the United States. It increased to approximately 80% TBSA by the 1990s.7 According to Bull and Fisher,8 shock, sepsis, and multiorgan failure caused a 50% mortality rate in children with burns covering 50% TBSA between 1942 and 1952. The mortality of children with 80% TBSA or greater burns was only 33% on a large sample study during 1982 to 1996.9 According to a most recent study, a 98% TBSA burn now has a 50% survival rate in burned children.10

Burn treatment is a complex undertaking and involves many components. Elements presented in this brief review include burn dressing, infection control of burn wound, fluid resuscitation, and burn surgeries. Advances in each of these aspects have continued to contribute to survival and functional recovery of burn victims.

Burn Dressings

The application of dressing began in ancient times and included increasingly explicit goals of preventing infection, promoting reepithelialization, avoiding water and heat loss, keeping the wound moist, and decreasing pain.11 A variety of biological, semibiological, and other dressings can be used to cover burn wounds to aid epithelialization and to protect the excised wounds from desiccation, infection, and mechanical trauma.12 Biological dressings, such as allograft skin,13 xenograft (porcine skin),11 and human amnion,14 have been used to cover the wound while reepithelialization occurs. The use of these dressings is associated with problems including availability, collection, storage, transmission of infection, and cost.14

Biobrane is a popular semibiological dressing in the treatment of superficial partial thickness wounds. It is made up of a fenestrated silicone layer bonded to a nylon mesh that has been impregnated with type I porcine collagen. It has been demonstrated to have advantages over conventional topical management in terms of ease of application, reduction in costs, decrease of pain, and time to healing.15 Conventional dressings, such as vaseline gauze or silicone sheets, and synthetic dressings, such as Duoderm, Omniderm, Tegaderm, and hydrocolloids, can be used to cover the wound while reepithelialization takes place.17

A number of silver containing dressings are currently used for burn care. Acticoat is a bilayered polyethylene nanocrystalline silver dressing attached to a soaking coat of polyester that can provide sustained release of silver for up to 7 days.18 Acticoat was substantiated to have better antimicrobial activity and reduce grafting requirements compared with silver sulfadiazine.19,20 Acticoat was also demonstrated to have fewer adverse effects and reduce healing times.21 The easy application and low frequency of dressing change make Acticoat a practical dressing in burn care.

Recent development in dressing and bioengineering technology have introduced the dressings and gels containing naturally occurring glycosaminoglycan and chitin,22–25 with incorporation of growth factors into the gel.26–27 The application of these dressings were reported to prevent early extension of burns,28 express antimicrobial properties,29,30 and promote fibroblast proliferation, angiogenesis and wound healing.31 Lin et al27 investigated the cytotoxicity of an antibiotic-impregnated biodegradable calcium alginate wound dressing and observed no obvious toxic risk of its use as a drug delivery system. Carbon fiber dressings were recently studied and demonstrated to increase the absorptive capacity of the dressing, reduce inflammation and bacterial growth, and promote wound healing.33,34

Infection Control

Sepsis has been the most frequent cause of death after burn injury and contributes to almost 75% to 85% of all burn deaths.35,36 An

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important advancement in burn care that has dramatically reduced mortality is infection control.

**Systemic Antibiotics**

The origin of modern scientific infection control in burn patients began with Leonard Colebrook, a physician, bacteriologist, and colleague of Alexander Fleming. Colebrook proposed that burn wounds became infected with bacteria and that strict infection control practices could prevent infection by reducing transfer of organisms between patients in a specially designed burn unit. Colebrook used a sulfanilamide parent drug, Prontosil, which was first used by Domagk in the chemotherapy of bacterial infections, for the treatment of streptococcal peritonitis in a murine model and reported its lifesaving effects on 38 patients with puerperal fever. Colebrook also studied the use of dressings impregnated with sulfanilamide and penicillin creams for the burn care, and serum and plasma for burn shock resuscitation at the Glasgow Royal Infirmary.

Lyons et al. managing burn patients at Massachusetts General Hospital, found that hemolytic streptococcal infection responded to sulfonamide and an effective blood level of sulfonamide offered the most certain control of systemic infection due to the hemolytic streptococcus. However, in 1943, based on a study with 1500 patients, Meloney concluded that neither local nor systemic sulfonamides were effective at controlling local wound infection, and that inadequate surgical excision predisposed to infection.

Emerging resistance by staphylococci and clostridium to sulfis drugs simulated research on penicillin. The discovery of penicillin by Alexander Fleming, the Scottish biologist, pharmacologist, and botanist, in 1928 was a major breakthrough but its clinical utility was not appreciated until 1940, when Chain and others demonstrated the new drug's lifesaving potential against streptococcus, staphylococci, and clostridium infections in murine and human studies.

Organisms associated with infection in burns included gram-positive, gram-negative, and viral and fungal organisms. Systemic antimicrobials must be thoughtfully considered for burn patients to prevent the emergence of resistant organisms.

Burns infected, caused by most common gram-positive organisms, streptococci, staphylococci, and enterococci, can be treated with penicillinase-resistant penicillins if the organisms are methicillin-sensitive. Staphylococcal infections resistant to penicillinase-resistant penicillins are termed methicillin-resistant Staphylococcus aureus (MRSA) or methicillin-resistant Staphylococcus epidermidis (MRSE). Vancomycin has been considered the antibiotic of choice for infections caused by MRSA and MRSE. Linzold was considered the choice for oral medication of MRSA and MRSE. Most enterococci are susceptible to vancomycin. Vancomycin-resistant enterococci will require treatment with combined medications, such as ampicillin/aminoglycosides, or quinupristin/dalfopristin combination.

The aminoglycosides were historically the antibiotics of choice for gram-negative infections. However, some gram-negative bacteria in burn infections are now resistant to almost all the antibiotic classes and must be treated with the polymixins. Branski concluded that Colistin, or polymyxin E, was a safe and efficacious antimicrobial drug for adult and pediatric burn population without a marked incidence of toxic side effects, but should be used only under close monitoring of renal function.

The 5 classes of systemic antifungal drugs include the polyenes, amphotericin B, azoles, nucleosides (Flucytosine), echinocandins, and allylamines.

**Topical Antimicrobials**

The high susceptibility of burn wounds to infection, coupled with increased antibiotic resistance among pathogenic bacteria and fungi, and the difficulty of systemically administered antibiotics to reach injured tissue, have contributed to the ongoing development and use of topical antimicrobials in the treatment of burns. The aim of topical therapies has changed with the increased understanding of the pathophysiology of burns. In the early 20th century, the goal of topical therapies was to counteract the “toxins” released from burn wounds and to minimize fluid loss. In 1925, Davidson asserted that use of tannic acid in the burn care not only lessened toxemia but also provided analgesia, prevented body fluid loss, limited infection, decreased scar formation, and generated a scaffold for healing. Its use was stopped when it was found to lead to lethal liver necrosis.

Sodium hypochlorite (NaClO), one of the first topical antimicrobials, was discovered in the 18th century by Berthollet and widely used as a disinfectant throughout the 19th century. Its use was hampered by the frequently accompanied irritation and topical reactions, but these side effects were later discovered to be due to variables in quality and chloride in different preparations of the solution. In 1915, Dakin successfully synthesized hypochlorite solutions without irritating contaminants and proposed the concentration of 0.5% NaClO as most effective. During the World War I, Dakin teamed up with the famous French surgeon and Nobel Prize winner Alexis Carrel to develop a protocol for wounds and burns. They specified mechanical cleansing, surgical debridement, and topical application of hypochlorite solution. In 1985, Lineaweaver et al. found that the cellular toxicity of hydrogen peroxide and acetic acid exceeded their bactericidal potency, but concentrations of povidone-iodine and sodium hypochlorite were identified without fibroblast toxicity but with persistent bactericidal activity. Recently, Heggars et al. investigated concentrations of sodium hypochlorite for antibacterial activity and tissue toxicity in vitro and in vivo and found that a modified “Dakin” solution at a concentration of 0.025% NaClO had sufficient bactericidal properties but eliminated detrimental effects on wound healing.

Pruit et al. achieved a remarkable improvement in postburn mortality in 1964, with the use of a topical antimicrobial, mafenide acetate (Sulfamylon) cream, which was effective against Gram-negative burn wound infection. Meanwhile, mafenide acetate was also adapted for treating burns at the Institute of Surgical Research in San Antonio, Tex, by microbiologist Robert Lindberg and surgeon John Moncrief. This antibiotic could penetrate third-degree eschar and was extremely effective against a wide spectrum of pathogens. Because of its ability of deep penetration of burn eschars, mafenide acetate appeared particularly effective in the treatment of full-thickness burns with significant devitalized tissue. It is however a carbonic anhydrase inhibitor and can cause systemic acidosis, compensatory hyperventilation, and pulmonary edema. Therefore the duration and area of mafenide acetate application must be limited to prevent systemic toxicity associated with prolonged or extensive use.

A major milestone in topical burn therapy was the application of silver compounds, which remarkably reduced the incidence of burn wound sepsis and death. Silver-based topical therapies were especially effective in controlling Pseudomonas aeruginosa infections. In 1965, Moyer et al. used 0.5% silver nitrate solution as an effective topical antibacterial agent for the treatment of burn wounds. Simultaneously, Fox et al. developed silver sulfadiazine cream (Silvadene), which has become a mainstay of topical antimicrobial therapy due to its success in controlling infection and minimal side effect profile. Recently, Tredget et al. introduced an aciclocar silver-coated dressing to prevent wound adhesion, limit nosocomial infection, control bacterial growth, and facilitate burn wound care.

**Fluid Resuscitation**

The history of burn resuscitation can be traced back to the treatments and subsequent studies of severely burned cases in large disasters of urban fires at the Rialto Theatre (New Haven, Conn) in 1921 and the Coconut Grove nightclub (Boston, Mass) in 1942, when physicians
noticed that some patients survived the large burns but died from the secondary shock. As burn size approaches 15% to 20% TBSA, hypovolemic shock sets in if no appropriate fluid resuscitation is conducted. In adults with burns approaching 25% to 30% TBSA, damage to cell membranes also occurs in hypovolemic shock, resulting in a decrease in transmembrane potential and the accumulation of intracellular sodium and water. It has been advocated that for maximum benefit, fluid resuscitation should begin as early as 2 hours after burn.

The goal of fluid resuscitation is to prevent hypovolemic shock by maintaining adequate end-organ perfusion. Meticulous attention to details and frequent reassessment is necessary to avoid the dangers of excessive or deficient fluid administration.

Mechanisms that control protein and fluid loss from the vascular space are compromised after severe burns and the subsequent inflammatory reaction. The margination of neutrophils, macrophages, and lymphocytes into these areas is associated with the release of a variety of mediators, including histamine, serotonin, prostaglandins, platelet products, complement components, and members of the kinin family, which affect and disrupt local and systemic vascular permeability. The end result is an immediate shift of intravascular fluid into the interstitial space.

The foundation of current fluid resuscitation began with the studies of Underhill, who found the composition of burn blister fluid was similar to that of plasma and suggested that early burn mortality might be due to loss of fluid rather than toxins. Underhill identified the significance of loss of the liquid and protein components of the blood in the burn area and proposed the concept of thermal injury-induced intravascular fluid deficits in the 1930s and 1940s. Subsequently, he developed a burn edema and introduced an initial formula of infusion therapy in relation to the severity of the injury. At that time, in about 10% to 20% TBSA burns were associated with high rates of mortality. In the 1970s, a 30% TBSA in burns could lead to nearly 100% mortality in older patients.

In 1930, Underhill proposed blood hemoglobin percentage as an index of resuscitation and asserted that resuscitation aimed at preventing hemococoncentration is required for 24 to 36 hours postburn. Intravenous sodium chloride solutions were used, supplemented by oral, rectal, and subdermal solutions. Based on hemococoncentration, Hartkins proposed a formula of fluid resuscitation for burn patients: 100 mL of plasma for each point when the hematocrit exceeds 45. Furthermore, when hematocrit detecting was unavailable, he recommended the “First Aid Method”: 500 mL of plasma for each 10% TBSA burned.

In 1943, Cope et al suggested that the initial dosage of plasma should be determined on the basis of the surface area of the burns. For each 10% TBSA involved, they proposed to give half of the plasma in the first 24 hours. The plasma dosage was adjusted subsequently on the basis of repeated hematocrit and serum protein determinations. Meanwhile, the National Research Council advocated 1000 mL of plasma for each 10 percent burned area over the first 24 hours.

In 1944, Lund and Browder developed diagrams by which physicians could easily and accurately quantify burn surface area. This quantification led to fluid resuscitation strategies based on TBSA burn calculations. Knayser et al advocated a simple “rule of nines” for evaluating the percentage of body surface area burned. In the late 1940s, Cope and Moore were able to quantify the amount of fluid for adequate resuscitation based on the percent of the body surface area burned and described a revised National Research Council formula called the Surface Area Formula in 1947: 75 mL of plasma and 75 mL of isotonic crystalloid solution for 1% TBSA. With one half given in the first 8 hours, and one half in the next 16 hours. Urine output was used as the primary index of resuscitation. Moore went on to develop a formula for estimating the amount of fluid for adequate resuscitation based on the burned percentage of body surface area in 1970.

Multiple subsequent formulas included body weight in the calculations and variations in both the volumes per weight per TBSA and the types of crystalloid or crystalloid-colloid combinations administered. Well-known resuscitation recipes included Evans Formula (colloid 1 mL/kg/TBSA, crystalloid 1 mL/kg/TBSA, and 5% glucose 2000 mL for the first day; one half of these amounts colloid and salt second day), Brooke Formula (colloid, 0.5 mL/kg per TBSA; and crystalloid, 1.5 mL/kg per TBSA, plus 2000 mL glucose for the first day; colloid, 0.25 mL/kg per TBSA; and crystalloid, 0.5 mL/kg per TBSA, plus 2000 mL glucose for the next day), and Modified Brooke Formula (crystalloid, 2 mL/kg per TBSA, one half for the first 8 hours and one half over the next 16 hours).

Colloids used in burn resuscitation have included dextran, albumin, and plasma. The use of colloid solutions in the fluid resuscitation of burns could effectively reduce the edema formation and amount of fluid required. Patients with severe burns, preexisting heart disease, and inhalation injuries may benefit the most from lower-volume resuscitations aided by colloid.

Baxter and Shires postulated that protein administered in the first 24 hours post burn would leak out of the vessels and exacerbate edema. They therefore developed a crystalloid-based formula without colloid, which is now referred to as the Parkland formula and is perhaps the most widely used formula today. The Parkland Formula recommends 4 mL of lactated Ringer solution/kg% TBSA burned during the first 24 hours of resuscitation after burn. Half the volume is given in the first 8 hours postsurgery, with the remaining volume delivered over the subsequent 16 hours.

To date, no single recommendation has been distinguished as the best fluid resuscitation formula for burns. Fluid resuscitation formula is a guide only to assist in estimation of fluid requirements because each patient reacts differently to burn injury and resuscitation. Regardless of the formula or strategy used, the first 24 to 48 hours require frequent adjustments by clinical indicators of the adequacy of resuscitation. Overresuscitation can be a major source of morbidity for burn patients. Fluid overload during the critical early management can result in unnecessary edema, pulmonary dysfunction, and extended ventilator support.

Although the end points for fluid resuscitation are still controversial, the hourly urine output is a well-established parameter for guiding fluid management. The urine output should approach 0.5 mL/kg per hour or approximately 30 to 50 mL/h in most adults and older children (>50 kg), and approximately 1 mL/kg per hour in small children. Yowler and Fratiame suggested that the goal of fluid resuscitation is to maintain urine output in the range of 0.5 to 1 mL/kg per hour for adults and 1 to 1.5 mL/kg per hour in children.

Certain patient populations frequently require higher fluid resuscitation volume. Patients with delayed resuscitation, alcohol abuse, trauma, or inhalation injury may require greater fluid resuscitations than predicted. Patients with inhalation injury sometimes required as much as 30% to 40% higher fluid supplement than calculated by fluid resuscitation formula for adequate resuscitation.

Burn Surgery

Early Excision

In 1510 to 1590 AD, Ambroise Pare described early excision of burn wounds. In 1607, Hildanus also recommended removal of burn eschar to facilitate drainage of serous fluid and allow better medication penetration. Limitations of technique, blood replacement, and perioperative support made excision of large burns impossible. In the 1940s, along with advancements in topical infection control and fluid resuscitation, it was recognized that one of the most effective therapies to reduce mortality in thermal burn injury was the early excision of burn eschar and subsequent skin grafting. Physicians applied pyruvic acid and starch to full thickness burns, followed by grafting as early as 6 days postdebridement. Young, McCorkle, and Salmonstall and Lee subsequently reported extensive experience with surgical excision of full thickness burns in the 1940s.
In 1955, Arzt and Soroff\textsuperscript{100} still suggested that patients should wait until a granulating barrier had formed beneath the eschar, and skin grafting should be performed as soon as possible after eschar separation. In the late 1950s, Jackson et al\textsuperscript{101} advanced the concept of early excision technique in a series of pilot and controlled trials by immediate fascial excision and grafting of small burn areas and eventually covering up to 65% TBSA with autograft and homograft skin. They concluded that excision and grafting of 20% to 30% TBSA could be carried out on the day of injury safely as long as shock was controlled by red cell volume monitoring. In 1964, Walker et al\textsuperscript{102} advocated an early excision, starting postburn day 4, for patients with large burns and immediate coverage with a combination of autograft and cadaver allograft. This technique was not accepted by the majority of surgeons because of controversy over expected outcomes, including mortality, infection, unnecessary blood loss, and total healing time.

It was not until the introduction of tangential excision by Janzekovic\textsuperscript{103–105} in the 1970s that early excision in burns achieved greater acceptance. She reported 2615 patients treating with deep second-degree burns by tangential excision of eschar and the damaged dermis down to bleeding tissues and immediate grafting with autograft 3 to 5 days after burn injury.\textsuperscript{103} Application of the technique was limited to small burns that could be covered by autografted skin.\textsuperscript{106} For the treatment of larger burns, Monaf\textsuperscript{107} was one of the first to advocate the use of tangential excision and grafting in the early 1970s. Burke et al\textsuperscript{108} treated children with burns over 80% TBSA with a combination of tangential excision for the smaller burns and excision to the level of fascia for the larger burns and coverage with split-thickness allografts, achieving a remarkable decrease in both hospital time and mortality. In a randomized prospective study, Engrav et al\textsuperscript{109} reported that early tangential excision and grafting of deep second-degree burns improved mortality and also reduced hospitalization time when compared with conservative treatment.

In a retrospective study, Tompkins et al\textsuperscript{110} reported an improvement in mortality over the course of 1974 to 1984 through the application of prompt eschar excision. Herndon and Parks\textsuperscript{111} implemented an early total excision (within 48–72 hours) to fascia with application of 4:1 expanded autograft and cadaver skin for complete closure in the treatment of large burns in children. The results included a decrease in length of stay but not in mortality. In a randomized prospective trial of 85 patients with third-degree burns greater than 30% TBSA, early excision gained significantly decreased mortality in patients who were 17 to 30 years old without inhalation injury, no different mortality in adult patients older than 30 years of age or with a concomitant inhalation injury, and significantly increased mortality in children when compared with therapy of topical antimicrobial and skin grafting after spontaneous eschar separation.\textsuperscript{110} In 1988, Tompkins et al\textsuperscript{112} also credited the use of prompt eschar excision and grafting for the dramatically decreased mortality for children in severely burned children. A recent meta-analysis found that early excision of burns was beneficial in reducing mortality in patients without inhalational injury.\textsuperscript{113}

### Skin Grafting and Substitutes

The earliest record of skin grafting can trace back to the fifth century AD, when Sushruta, an Indian surgeon, repaired the wounds of noses using reversed skin from forehead and transplanted skin from the buttock.\textsuperscript{114,115} The first documentation of modern skin graft in humans was in 1823, when Carl Burger treated an ulcer using split-thickness skin from the inner thigh. The early success rate of skin grafts was low because of the inefficient harvesting and use of thick grafts.\textsuperscript{115}

In 1869, Reverdin, a Swiss medical student, introduced “pinch grafts,” small circular skin discs, to deal with slowly healing or chronic wounds.\textsuperscript{116} The method was soon popularized in England by George Pollock in the 1870s.\textsuperscript{117,118} Thiersh\textsuperscript{119} advocated the use of “razor flaps” in 1874. Generally, these methods were restricted in the treatment of small ulcerated wounds.

In the 1920s, Blair and Brown discovered that deep islands of hair follicles and epithelial cells could be the basis of healing in skin graft donor sites. Split-thickness skin grafts subsequently became popular in the 1930s. After free hand blades with impeccable control over graft thickness, such as the Blair and Catlin knives,\textsuperscript{120} tools allowing precise thickness control of skin grafts quickly developed.\textsuperscript{121}

Padgett\textsuperscript{122} introduced an adjustable dermograft which allowed the harvest of consistent split-thickness skin grafts. Padgett\textsuperscript{122} also advocated a categorization of split-thickness skin grafts based on thickness. The meshing of grafts were first achieved by Lanz\textsuperscript{123} in 1907, who designed a special dermograft consisting of a series of small knives mounted in parallel to make multiple holes in a skin graft, forming a mesh. Meek\textsuperscript{124} successfully conducted microdermografting using the Meek-Wall microdermatome and prefolded gauzes to expand the graft size as much as nine times the original size. Due to its operational complexity, the Meek microdermatome was substituted by the simpler “mesh dermograft” developed by Tanner et al\textsuperscript{125} in 1964. This device allowed a 3-fold expansion of the harvested graft and other mesh machinery can expand grafts in ratios of 1:1 to 9:1. Recent studies using the modified Meek technique have demonstrated some advantage over mesh grafts when donor sites are limited, especially in extensive burn wounds.\textsuperscript{126–128} Furthermore, recent study by Lyons and Kagan\textsuperscript{129} found that there was great variability in the expected and observed expansion ratios achieved by skin graft meshing devices. Kamolz et al\textsuperscript{130} also demonstrated that the micrografting technique provided more reliable and valid expansion rates, when compared with the skin meshing techniques. They recommend using the micrograft technique when large expansion ratios are required, especially in severe and extensive burns.

The first successful allogeneic skin graft in burn wound coverage was reported by Girnher\textsuperscript{132} in 1881. In 1938, Bettman\textsuperscript{133} reported success in the treatment of children with large full-thickness burn injuries covered by allograft skin. Cadaver allogeneic skin grafts were often used to prepare the granulating wound bed for autografting. In 1954, Jackson\textsuperscript{134} introduced a combined grafting technique, which utilized narrow strips of allograft and autograft in a granulating or excised wound. Walker et al\textsuperscript{102} advocated an early excision and immediate coverage with a combination of autograft and cadaver allograft for patients with large burns. In massively burned patients with limited donor sites, Alexander developed a simple method of applying a widely meshed skin autograft and then covering it with allogeneic skin.\textsuperscript{135}

With the advance of tissue engineering techniques, skin substitution became a prominent wound healing research. In the 1970s, Yannas and Burke developed the first bilayer artificial skin, Integra, which consists of a silastic epidermis and a porous collagen-chondroitin dermis. Burke et al\textsuperscript{136} was also the first to use this artificial skin on patients with 50% to 95% TBSA burn after prompt excision of burn wounds. Heimbach et al\textsuperscript{137} led the first multicenter randomized clinical trial using Integra in 1988. After approval by the Food and Drug Administration in 1996, Integra has been widely used in burns and reconstructive surgery. Tay et al\textsuperscript{138} introduced the use of Biobrane in their burn protocol for superficial to mid-dermal partial thickness burns. Biobrane has a bilaminar structure consisting of an outer silicon membrane and an inner nylon mesh embedded with porcine type 1 collagen. The burn protocol with Biobrane achieved improved clinical results when compared with the historical control group. Other artificial skin substitutes include Apligraf (a bilayered bioengineered skin substitute constructed by cultivating human foreskin-derived neonatal fibroblasts in a bovine type 1 collagen matrix) and Matriderm (a scaffold consisting of a native bovine types 1, 3, and 5 collagen fibre template incorporating elastin hydrolysate).\textsuperscript{139,140}

In 1989, Hainsbrough et al\textsuperscript{141} reported burn wound closure with cultured autologous keratinocytes and fibroblasts attached to a collagen-glycosaminoglycan substrate (composite skin graft [CSS]).
Further study by Boyce substantiated that the use of CSS in extensive burns reduces the requirement for harvesting skin autografts, and that the quality of grafted skin was similar between CSS and skin autograft after 1 year.142 Fang et al143 reviewed the researches using cultured epithelial autografts (CEAs) and the acellular dermal matrices in the treatment of extended burn injuries and concluded that the use of acellular dermal matrices with CEAs is becoming increasingly routine, particularly as a life-saving tool after acute thermal trauma. Cultured skin autografts provide possible material for wound closure for patients with extensive burns, although the hospital cost, length of hospital stay, and number of readmissions for reconstruction of contractures was higher than conventional autografts.144–146

**Summary**

The advancement of burn treatments has been very significant over the last 75 years. The mortality of severely and extensively burns patients has significantly decreased due to the improvements in infection control, early resuscitation, improved surgical approaches and other treatments basing on the better understanding of the burn pathophysiology. Establishment of a standardized, generally accepted, and effective formula of fluid resuscitation of burns still merits further investigation. Limited donor skin and deficiency of eligible skin substitutions in severely burned patients hinders early and effective wound excision and closure, leading to complications and prolonged hospitalizations. Tissue-engineered skin substitutes with all the functions of intact human skin, perhaps combined with mesenchymal stem cells, may offer the best opportunity for better outcomes.147,148 Better understanding and management of the pathophysiology of burn scar contractures and hypertrophic scarring are also important area deserving research.149,150

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