

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Management of Burns

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THE MAJORITY OF BURN INJURIES ARE MINOR AND EITHER DO NOT REQUIRE treatment or can be treated by any caregiver. More severe burns can result in clinically significant morbidity and, unless treated appropriately, can lead to severe scarring. Major burns lead to a profound systemic response that has serious long-term effects on the patient.¹ Failure to properly treat these injuries will lead to rapid development of organ failure and death. Although most major injuries are treated in burn centers, expeditious and appropriate initial treatment will improve outcomes. The goal of this review is to provide basic principles of management that lead to the best outcomes for patients with either small or large burns.

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EPIDEMIOLOGY

Burns are the fourth most common type of trauma worldwide, after traffic injuries, falls, and interpersonal violence.^{2,3} An estimated 11 million people worldwide sought medical care for burns in 2004. The risk of burns tends to increase with lower socioeconomic status, and up to 90% of burns occur in low- or middle-income countries.^{2,3}

The Burn Incidence Fact Sheet of the American Burn Association (ABA) states that in 2016, a total of 486,000 people sought care for burns in the United States.⁴ The majority of burns are small, with 67% occupying less than 10% of total body-surface area, according to the National Burn Repository of the ABA. The ABA reports that 40,000 patients were hospitalized with burns in 2016, and 30,000 of those patients were admitted to the 128 burn centers in the United States.⁴ The mean burn size has been decreasing, especially in high-income countries, but despite these encouraging statistics, large burns still occur. In the United States, the ABA reported 3275 deaths related to burns and smoke inhalation in 2016, with 2745 deaths resulting from residential fires, 310 from vehicle crash-related fires, and 220 from other causes. The estimated total number of deaths per year in all low- and middle-income countries is 180,000.^{1,2,5} Death rates rise with increasing burn size and depth, older age, and smoke inhalation.⁶

In the United States, the prevalence of burns has a bimodal distribution according to age group, with young children (especially toddlers) accounting for 24% of burns and people 20 to 59 years of age accounting for 55%.⁷ Exposure to flame is the most common cause among people older than 5 years of age. Scald burns are more common in children under the age of 5 years. Most burns (75%) occur at home, and 13% occur at work. Approximately 95% of burns are accidental; 2% are related to abuse, and 1% are self-inflicted. Almost all burns are preventable, and simple measures such as installation of smoke detectors have been highly effective.

IMMEDIATE MANAGEMENT

Initial management follows the same principles of care as those for any trauma injury: prioritizing the ABCs (airway, breathing, and circulation) (Table 1).

AIRWAY

The primary airway concern is upper-airway obstruction, and the key decision is whether to place an endotracheal tube. In patients with massive burns, the airway can swell to the point of total obstruction, and early endotracheal intubation is required before the airway is lost.

However, most patients with burns do not require intubation, because their burns are relatively small. A recent study indicated that one third of hospitalized patients with burns were extubated within 1 day after admission.⁸ Patients who require intubation tend to have larger and deeper burns, burns to the face, and clinically significant smoke-inhalation injury. The threshold for intubation should be low for any patient with deep burns occupying more than 30 to 40% of total body-surface area. Smaller burns may be managed without an endotracheal tube, and since it takes several hours for maximal swelling to occur, it is preferable to transfer the patient to

Table 1. Immediate Concerns in Burn Care.

Problem	Comments*
Airway	
Is intubation required to prevent airway obstruction?	Indicators of a requirement for intubation (if in doubt, perform endotracheal intubation): Burn size >40% of TBSA (lower threshold if burns are deeper) Burns to the head and mouth Clinically significant smoke-inhalation injury Delayed transfer to burn center Altered level of consciousness Change in voice or hoarseness
Breathing	
Does the patient have carbon monoxide poisoning?	Indicators of carbon monoxide poisoning: elevated carboxyhemoglobin (arterial blood gas values and pulse oximeter readings are of no value) and persistent metabolic acidosis Administer 100% oxygen until carbon monoxide poisoning is ruled out
Does the patient have smoke-inhalation injury?	Indicators of smoke-inhalation injury: history of exposure to smoke in enclosed space and bronchoscopic evidence of carbonaceous material or injury below vocal cords
Circulation	
Determining burn severity and fluid requirements	Surface-area estimate is based on Rule of Nines or Lund–Browder chart Presence of deeper burns increases fluid requirements Children require more fluid/kg/% of TBSA burned than adults Delayed resuscitation increases fluid requirements Smoke inhalation increases fluid requirements Alcohol intoxication increases fluid requirements
Determining the initial resuscitation volume and rate of administration	Adjust the rate based on urine output, with a target output of approximately 0.5 ml/kg for adults and 1 ml/kg for children weighing <30 kg; urine output above these levels indicates over-resuscitation
Parkland formula	4 ml/kg/% of TBSA burned, with starting rate based on giving half the 24-hr volume in the first 8 hr Example of a 100-kg person with 80% of TBSA burned: $4 \times 100 \times 80 = 32,000$ ml in 24 hr $32,000 \div 2 = 16,000$ ml in first 8 hr Starting rate = $16,000 \div 8 = 2000$ ml/hr Adjust rate up or down for target urine output of 50 ml/hr (0.5 ml/kg/hr)
Brooke formula	2 ml/kg/% of TBSA burned, with starting rate based on giving half the 24-hr volume in the first 8 hr Example of a 100-kg person with 80% of TBSA burned: $2 \times 100 \times 80 = 16,000$ ml in 24 hr $16,000 \div 2 = 8000$ ml in first 8 hr Starting rate = $8000 \div 8 = 1000$ ml/hr Adjust rate up or down for target urine output of 50 ml/hr (0.5 ml/kg/hr)

* TBSA denotes total body-surface area.

the burn center, where the decision about intubation can be made. If there is any doubt, examination of the upper airway with a laryngoscope or bronchoscope is helpful. In a common scenario, a patient receiving supplemental oxygen is burned while smoking a cigarette. Such patients often do not require intubation, since the flash burn typically does not involve the glottis.

BREATHING

Problems with breathing take many forms in patients with burns. Flames consume oxygen, which results in low ambient levels of oxygen and can lead to severe hypoxemia. Another cause of hypoxemia is carbon monoxide; elevated blood levels of carbon monoxide should be considered in patients with prolonged smoke exposure. The affinity of carbon monoxide for hemoglobin is 200 to 250 times the affinity of oxygen for hemoglobin; therefore, in the presence of carbon monoxide, oxygen delivery is substantially reduced.⁹ Measurements of arterial blood gases and pulse oximeter readings are of no value in cases of smoke inhalation, since they do not reveal carbon monoxide levels. Measurement of carboxyhemoglobin is the only accurate test of carbon monoxide levels, and if levels of carboxyhemoglobin are higher than 30 to 40%, the patient has had severe exposure to carbon monoxide. Treatment consists of the administration of 100% oxygen. The half-life of the dissociation of carbon monoxide from hemoglobin decreases from 3 or 4 hours to less than 1 hour in the presence of 100% oxygen. Hyperbaric oxygen further reduces the half-life but is rarely administered in patients with massive burns, since it makes management of other burn-related issues difficult.¹⁰ Routine treatment for cyanide poisoning should be avoided, since cyanide poisoning is rare.

In patients with circumferential chest and abdominal burns, compartment syndromes may develop that require escharotomies (incisions through the burn to relieve pressure), but such syndromes occur after 12 to 18 hours and are preferably treated at the burn center. The acute respiratory distress syndrome occasionally develops in a patient with burns. It should be treated with the use of low tidal volumes (about 6 ml per kilogram of predicted body weight, with positive end-expiratory pressure levels adequate to keep

the airways patent)¹¹; for details, see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Lung damage after smoke-inhalation injury is much more severe when combined with a major body-surface burn.¹² In addition, the presence of smoke-inhalation injury can double mortality, depending on the severity of the burns and the age of the patient.¹² The diagnosis of smoke-inhalation injury requires only two components: prolonged exposure to smoke and bronchoscopic evidence of soot or injury below the vocal cords.¹³ People who are exposed to flash explosions (from propane or butane) are not usually exposed to smoke and generally do not have smoke-inhalation injury. The pathophysiology of smoke-inhalation injury involves smoke particles that settle on bronchiolar mucosa, leading to epithelial-cell death, sloughing, small-airway obstruction, atelectasis, and an increased risk of pneumonia. Treatment of smoke-inhalation injury is similar to treatment of the acute respiratory distress syndrome.

CIRCULATION

Patients with extensive burns require larger resuscitation volumes than patients with any other type of insult. Because initial resuscitation rates are so high, several formulas have been developed, which are based on the total body-surface area that is burned. The Rule of Nines estimates that each arm accounts for 9% of total body-surface area, as does the head, whereas the anterior trunk and the posterior trunk each account for 18%, as does each leg. This rule is fairly inaccurate, since most people do not have the classic body of Atlas (in Greek mythology), and small children have proportionately larger heads and smaller legs than adults. Most burn centers use the Lund–Browder chart, which adjusts for differences on the basis of age. The most important point is that the chart should be used to estimate only the initial fluid rate.¹⁴ All other adjustments should be based on the patient's response to resuscitation.

The best-known formula, the Parkland formula, estimates the rate of fluid resuscitation for the first 24 hours as 4 ml per kilogram of body weight per percent of total body-surface area that is burned, with half the volume of fluids delivered in the first 8 hours. According to the

alternative modified Brooke formula, one may consider dropping that value to 2 ml per kilogram per percent of body-surface area burned, with the lower starting volume used for more superficial burns and the higher volume used for deeper burns. After the initial rate of fluid resuscitation has been determined, fluids should be adjusted on the basis of urine output (with a target urine output of 0.5 ml per kilogram of body weight per hour for adults and 1 ml per kilogram per hour for children weighing <30 kg).

For example, with the Parkland formula, a 100-kg man with deep burns involving 80% of total body-surface area would require 32,000 ml of fluids ($4 \times 100 \times 80$) in 24 hours. Half that volume (16,000 ml) should be given in the first 8 hours (i.e., resuscitation should start at a rate of 2000 ml per hour). The fluid rate should be adjusted on the basis of a target urine output of 50 ml per hour. Patients with deep burns, those with smoke inhalation and associated injuries, patients for whom resuscitation is delayed, small children, and patients with alcohol intoxication require proportionately more fluid. For patients whose urine output meets the target rate (or is just below that rate), the fluid infusion rate should be reduced hourly until a target maintenance rate is reached, based on basal requirements plus evaporative rates at around 24 hours. There have been attempts to use other indicators of the adequacy of resuscitation (central venous pressure, noninvasive monitors, and lactate and hemoglobin values), but they often result in an overestimate of fluid requirements.^{14,15}

The current problem is that clinicians tend to provide too much fluid, leading to what has been called “fluid creep.”¹⁶ Excessive volumes increase the risk of respiratory insufficiency, cardiac failure, and compartment syndromes (involving the trunk and extremities). Fluid creep has been attributed to inattention to urine output, vasodilatation due to opioid use,¹⁷ and increased thoracic pressure that is caused by ventilators and leads to decreased venous return.¹⁸

Balanced isotonic crystalloids have traditionally been used for resuscitation. Many burn centers are now using oncotic fluids (albumin or plasma), since several studies suggest that providing albumin reduces fluid requirements.¹⁹⁻²² High-dose vitamin C (66 mg per kilogram per hour) has also been reported to reduce fluid

needs,²³ but there are questions about whether it works primarily as a diuretic.²⁴

LONG-TERM CARE

A hospital stay for a patient with massive burns is usually long because weeks to months are required to close the wounds. A typical length of stay is approximately 1 day for every percent of the total body-surface area that is burned, although major burns require longer stays.²⁵ During this prolonged inpatient stay, there are three main tasks: close the wound, deal with the hypermetabolic response, and treat the almost inevitable bouts of sepsis and multiple organ dysfunction (Table S2 in the Supplementary Appendix).

ADDRESSING THE HYPERMETABOLIC RESPONSE

A profound hypermetabolic and catabolic response develops in patients with burns covering more than 20% of total body-surface area, leading to muscle wasting and, if untreated, death from multiple organ failure.^{1,26} The foremost strategy for reducing metabolic stress is to expeditiously remove the burned tissue and cover the exposed area with skin or some other form of barrier.²⁷ Patients with the hypermetabolic response have an elevated core temperature (approximately 38°C), so setting the patient's room temperature at around 18°C will reduce the metabolic demand. Minimizing pain and distress also reduces metabolic demand, but eliminating pain is challenging. Likewise, minimizing infection and sepsis reduces metabolic demand but is very difficult to achieve. The use of propranolol to reduce the hypermetabolic effects of catecholamines has received a great deal of study and appears to be beneficial, at least in children.²⁸

Patients with major burns need nutritional support in order to keep up with the high metabolic demand. Placing an enteral feeding tube and starting nutrition as soon as possible, even during the initial resuscitation, is recommended.²⁹ Nasoduodenal feeding tubes are convenient, since feedings can be continued during surgery, with nasogastric tubes used to empty the stomach. Calorie requirements can be calculated with the use of various formulas for resting energy expenditure (e.g., the Harris-Benedict, Toronto,

and Milner formulas) and multiplied by 1.4 to 1.5 (Table S3 in the Supplementary Appendix). Proteins are provided at a rate of 1.5 to 2 g per kilogram per day, and the rate can be adjusted on the basis of nitrogen-balance studies. A large problem is interruption of feedings, but most centers try to make up for deficits by ignoring all but the largest gastric residuals or using volume-based feeding strategies.³⁰

A final strategy is to reduce catabolism and increase muscle mass by providing anabolic agents. Insulin, insulin-like growth factor 1, and growth hormone have all been shown to have a benefit but are rarely used.^{1,26,29,31} Oxandrolone is a testosterone analogue without masculinizing effects that, at a dose of 10 mg twice a day, improves muscle mass and outcomes in patients with burns.³² A simple concept that has gained traction is to promote early mobility and exercise in patients with burns.³³ Endurance and strength are clearly increased with increased movement and exercise.

SEPSIS IN PATIENTS WITH BURNS

Sepsis is a major risk after any large burn because the primary barrier to microbial invasion, the skin, is lost. Sepsis can develop any time after resuscitation, and the risk persists as long as the wound remains open. Unfortunately, antibiotics are ineffective in preventing infection. Instead, their use leads to more resistant organisms. Sepsis is a different problem in patients with burns than in most other patient populations.^{34,35} With burns, there is persistent exposure to microbial products combined with the hypermetabolic response; all patients with burns have persistently elevated temperature, tachycardia, and variable white-cell counts. By definition, all patients with large burns have the systemic inflammatory response syndrome (SIRS)¹³ throughout their inpatient stay, so SIRS alerts are of little value. In addition, the use of central lines, ventilators, and urinary catheters for prolonged periods increases the risk of iatrogenic infections.

In view of these problems, the ABA held a consensus conference to redefine sepsis in patients with burns.¹³ Table S4 in the Supplementary Appendix lists the resulting consensus definitions of burn-related sepsis. Patients must be monitored for signs of sepsis that are unique to burn injuries, such as dropping platelet counts,

feeding intolerance, decreasing urine output, acidosis, and respiratory changes. Early, aggressive treatment with broad-spectrum antibiotics is required, followed by narrowing antibiotic coverage based on culture results. Because of these issues, patients with burns are usually excluded from major sepsis trials. Clearly, there is a need for a “sepsis bundle,” similar to the bundle featured in the current Surviving Sepsis Campaign,³⁶ that focuses on the management of sepsis in patients with burns.

BURN WOUND CARE

The care of burn wounds is based on the depth of injury (Fig. 1). Skin is divided into two components: the epidermis and the dermis. Beneath the dermis is subcutaneous fat, which covers bone, tendon, or fascia. The epidermis, in simple terms, acts as a barrier, keeping water in and preventing the invasion of microorganisms. The basal-cell layer of keratinocytes has the potential for growth and migration. Mixed in with the basal-cell layer are melanocytes with branched extensions, similar to dendrites, that reach 30 to 40 keratinocytes and that deliver melanosomes that are phagocytized by the keratinocytes and placed as a protective layer above the nucleus.³⁷

The dermis does not function as a barrier but instead provides strength, since it is composed primarily of collagen and extracellular matrix proteins. The dermis also contains skin adnexa such as hair follicles, oil glands, and sweat glands that are lined with keratinocytes. In addition, there is a very rich plexus of nerves and vessels coursing through the dermis. The subcutaneous tissue, which is primarily fat, provides padding for the underlying tissues.

Any burn that does not penetrate the epidermis is considered to be a first-degree burn. Since the barrier is intact, the burn is dry and red (Fig. 2A). Minimal treatment (analgesia and moisturizer) or no treatment is required, and healing is very rapid.

A second-degree, or partial-thickness, burn penetrates into but not through the dermis. Because the epidermal barrier is lost, the wound forms a blister or, if uncovered, weeps interstitial fluid (Fig. 2B). Since the dermal plexus of vessels and nerves is intact, the wound will blanch with pressure and the pain will be severe.

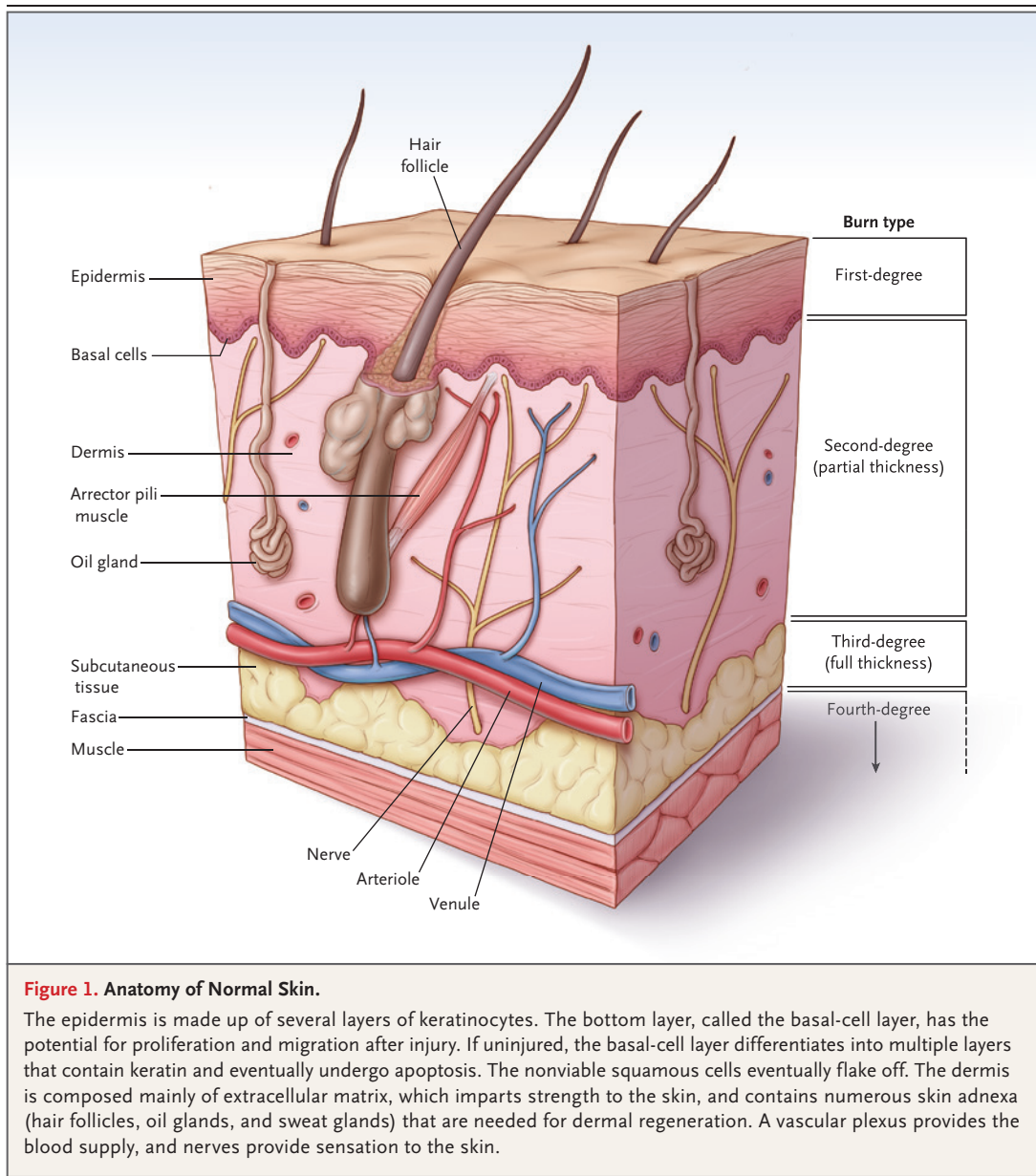


Figure 1. Anatomy of Normal Skin.

The epidermis is made up of several layers of keratinocytes. The bottom layer, called the basal-cell layer, has the potential for proliferation and migration after injury. If uninjured, the basal-cell layer differentiates into multiple layers that contain keratin and eventually undergo apoptosis. The nonviable squamous cells eventually flake off. The dermis is composed mainly of extracellular matrix, which imparts strength to the skin, and contains numerous skin adnexa (hair follicles, oil glands, and sweat glands) that are needed for dermal regeneration. A vascular plexus provides the blood supply, and nerves provide sensation to the skin.

A second-degree burn heals through reepithelialization (Fig. 3). At the wound edge, the basal cells start migrating across the viable wound bed. They are stimulated by loss of cell–cell contact inhibition, release of local growth factors (epidermal growth factor, transforming growth factor α , and keratinocyte growth factors 1 and 2), and contact with wound proteins. Keratinocytes in a moist environment can migrate faster than those in a wound that becomes dry and develops a fibrinous scab. The limit of migration from the

wound edge is only 1 to 2 cm, but in superficial wounds, the keratinocytes in the remnant hair follicles and other skin adnexa migrate onto the surface to reepithelialize the wound. If adnexa are close together, such as in the scalp, reepithelialization is much faster (within 4 to 5 days) than if the adnexa are less densely packed. Elderly patients tend to have fewer hair follicles than younger patients, so reepithelialization can be impaired. The skin is also thinner in older patients, so the consequences of the burn can be

greater. As second-degree burns become deeper, fewer skin adnexa remain; thus, deeper burns require more time to heal.

Any wound that requires more than 2 to 3 weeks to reepithelialize has a high chance of becoming a hypertrophic scar.³⁸ Therefore, as a simple rule, any wound that requires more than 2 to 3 weeks to heal should be considered for excision and skin grafting to reduce the chances of hypertrophic scarring. The goal of treating partial-thickness wounds is to encourage reepithelialization. The wound should be washed with soap and water. Loose skin and blisters should be débrided and a topical ointment applied to maintain a moist environment. If a topical antimicrobial ointment is used, dressings should be changed once or twice per day. Thick blisters on the palms and soles of the feet may be left intact for comfort. Topical ointments such as bacitracin can be used for small wounds, but they should be discontinued within a week, since they will invariably cause a rash. The majority of studies have shown that silver sulfadiazine impairs reepithelialization, so it should be avoided for superficial wounds.³⁹ Most clinicians now use “extended” or “closed” dressings that are designed to adhere to the wound, maintain a moist environment, and fall off when the wound is healed. They are applied after the wound has been cleaned and, as an alternative to daily dressings, may be left in place for 5 to 10 days. Since daily wound care is not required, the need for hospitalization and pain medicines is greatly reduced. Regardless of the dressing, any wound that remains open at 2 weeks should be evaluated by a burn expert to determine whether skin grafting is indicated.

A burn that completely destroys the dermis and enters the fat is considered to be a third-degree, or full-thickness, burn. Since all the vasculature and nerves of the dermis are destroyed, there is no blanching and the burn is much less painful than a second-degree burn. The wounds can be any color and are drier than more superficial burns (Fig. 2C). The dermal adnexa are destroyed, so epithelial migration is limited to basal cells from the wound edges. Therefore, most of the healing results from scar formation and contraction. Small wounds over unimportant areas can contract without problems, but larger burns, especially over important structures, cause

contractures that impair function. Given enough time, contraction can close any wound but leads to profound contractures (Fig. 2D). Fourth-degree burns extend into muscle, bone, or tendon and need to be treated in burn centers, since they may require flaps or amputations.

Excision of the burn and placement of skin grafts is the recommended treatment for sizable third-degree burns or any burn that requires longer than 2 to 3 weeks to heal. In concept, the surgical procedure is simple: excise the burn down to viable tissue, obtain hemostasis, and apply skin grafts harvested from another site. Thicker grafts tend to shrink less than thin grafts.⁴⁰ Small wounds can be covered with full-thickness grafts (harvesting of the entire thickness of skin), but the donor site must be sutured closed, which limits the size of the graft. Split-thickness skin grafts are “shaved” through the dermis of another site. The donor site must reepithelialize within 2 to 3 weeks in order to minimize hypertrophic scarring. For small or medium-size grafts, sheet grafts have the best cosmetic outcome (Fig. 4).⁴¹ A meshing instrument, which cuts holes in skin, is used to expand grafts so that they cover more surface area. Another device, called the Meek’s mesher,⁴² cuts skin into multiple small squares for expansion. The meshed pattern obtained with either device will persist for the life of the patient.

For burns covering more than 60% of total body-surface area, the current philosophy is to excise the burns within the first few days, cover the wounds with as much of the patient’s own, widely meshed skin as possible, and then use skin-banked allografts or dermal substitutes as temporary coverage. In patients undergoing autologous skin grafting, donor skin may be reharvested from the same site multiple times, but 2 to 3 weeks of healing is typically required before the donor site is ready for the harvesting of more autografts. The technology for “growing” skin or using skin substitutes has been available since the early 1980s, but the accessibility of autologous skin composed of an epithelium and a dermis has been limited.⁴³ Cultured epithelial autografts are being used with moderate success but are fragile, since they lack a dermis.⁴⁴ Dermal substitutes are available, but they eventually need to be covered by the patient’s own autografts.⁴⁵⁻⁴⁷ A technique has been developed to harvest epithe-



lial cells and then spray them over the wound,⁴⁸ which may help accelerate healing of meshed skin. Despite little change in the wound-coverage strategy in the past 40 years, many patients with massive wounds survive.

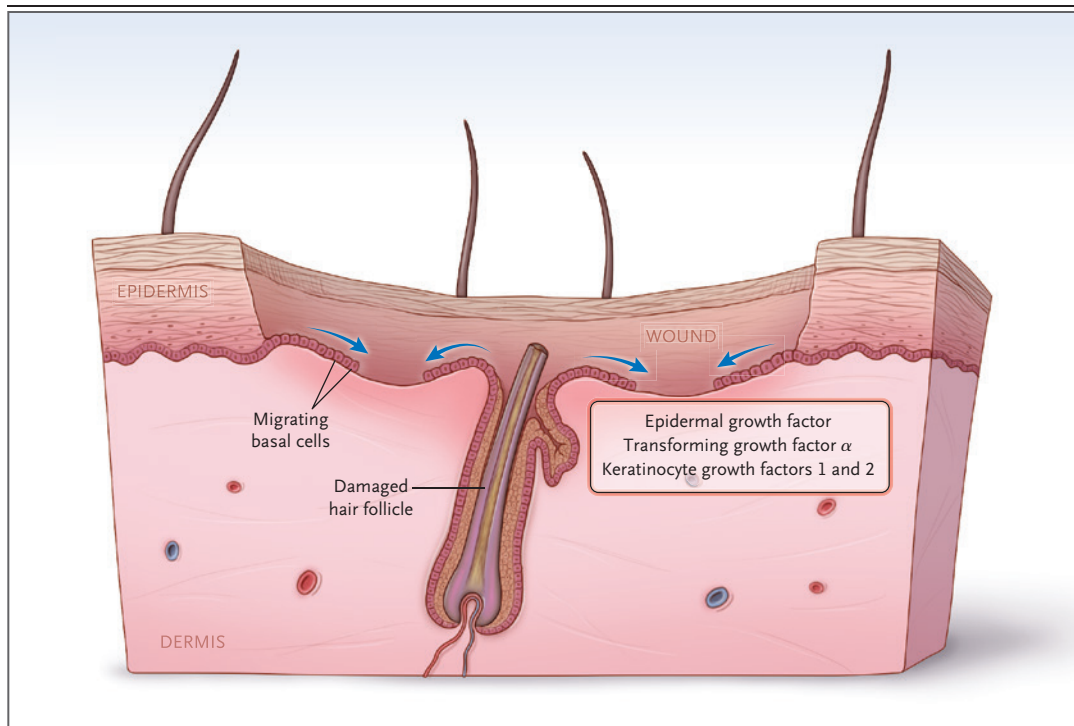
THE FUTURE OF BURN CARE

Since the survival of patients with major burns is relatively common, the current goal of burn

care is functional and cosmetic outcomes that allow the patients to be comfortable and productive in their return to society.⁴⁹ Burn care is a slow process, with the wound changing over a period of months or even years in the case of massive injuries. Although this review covers the physical aspects of burn care, there are severe psychological and emotional hurdles that must be overcome.⁴⁹ Fortunately, support organizations for burn survivors, such as

Figure 2 (facing page). Classification of Burns on the Basis of Depth.

The dry area on the hand shown in Panel A is a first-degree burn. (The moist areas on the fingers are second-degree burns.) A first-degree burn does not course through the epidermis. Since the barrier function of the epidermis is intact, the affected area remains dry but is red and painful. First-degree burns heal rapidly without treatment. Panel B shows a second-degree, or partial-thickness, burn, which has destroyed the epidermis but has not penetrated completely through the dermis. Since the epithelial barrier has been destroyed, the wound weeps or forms a blister. The vascular and neural plexuses remain, so the wound is red, blanches with pressure, and is extremely painful. It will heal through reepithelialization, but if healing takes longer than 2 to 3 weeks, hypertrophic scarring is likely to develop. Panel C shows a third-degree, or full-thickness, burn, which has destroyed both the epidermis and the dermis and has penetrated the subcutaneous fat. Since the dermal vasculature and nerve supply have been destroyed, the affected area no longer blanches and is less sensitive to touch. The wound can be any of several colors: red, yellow, brown, or black. It can heal only by contraction or with skin grafting. A fourth-degree burn (not shown) involves muscle, bone, tendon, or deeper structures. If given enough time, these more severe burns will heal by contraction. However, contraction can lead to severe contractures. The girl shown in Panel D had scald burns that healed through contraction over a period of 16 months, leading to profound contractures. She was treated with surgical releases and skin grafting, with good results.

**Figure 3. Epithelial Healing.**

The epithelial basal cells at the edge of the wound migrate over the viable surface of the wound in response to three stimuli. Loss of cell–cell contact inhibition and growth factors (epidermal growth factor, transforming growth factor α , and keratinocyte growth factors 1 and 2) stimulate migration. In addition, contact with molecules found in the wound (type 1 collagen and fibronectin) stimulates migration. Epithelial migration is faster with a moist wound than with a wound that is allowed to dry. If there are no skin adnexa, epithelial migration stops after 1 to 2 cm, and subsequent healing occurs through contraction. If there are skin adnexa, keratinocytes are stimulated to migrate to the surface and resurface the wound. Areas where the adnexa are dense, such as the scalp, heal relatively fast through reepithelialization and are less likely to have hypertrophic scarring. Areas with less dense adnexa take longer to heal and are more likely to have hypertrophic scarring.



Figure 4. Sheet Skin Grafts and Meshed Grafts on a Patient's Hand and Arm.

Sheet skin grafts, shown on the patient's hand, are not meshed and have a much more natural appearance than meshed grafts, shown on the arm.

There is a need for a viable, autologous, engineered skin consisting of both a dermis and an epidermis that can be rapidly produced to cover a massive burn. Current split-thickness skin grafts lack hair and sweat glands, so novel approaches to regenerating those structures will greatly benefit patients. Another major goal will be to understand the signals produced in an open wound at 2 to 3 weeks that induce hypertrophic scarring. By understanding these signals, one should be able to reduce the most devastating problem for burn survivors — scar formation. Finally, controlling the profound hypermetabolic response will lessen muscle wasting and improve outcomes for patients with burns.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

the Phoenix Society, provide assistance with recovery.

REFERENCES

- Porter C, Tompkins RG, Finnerty CC, Sidossis LS, Suman OE, Herndon DN. The metabolic stress response to burn trauma: current understanding and therapies. *Lancet* 2016;388:1417-26.
- GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;385:117-71.
- Norton R, Kobusingye O. Injuries. *N Engl J Med* 2013;368:1723-30.
- Burn incidence fact sheet. Chicago: American Burn Association (<http://ameriburn.org/who-we-are/media/burn-incidence-fact-sheet/>).
- Peck MD. Epidemiology of burns throughout the world. I. Distribution and risk factors. *Burns* 2011;37:1087-100.
- Taylor SL, Sen S, Greenhalgh DG, Lawless M, Curri T, Palmieri TL. A competing risk analysis for hospital length of stay in patients with burns. *JAMA Surg* 2015;150:450-6.
- National Burn Repository, version 13.0. Chicago: American Burn Association, 2017.
- Romanowski KS, Palmieri TL, Sen S, Greenhalgh DG. More than one third of intubations in patients transferred to burn centers are unnecessary: proposed guidelines for appropriate intubation of the burn patient. *J Burn Care Res* 2016;37(5):e409-e414.
- Rose JJ, Wang L, Xu Q, et al. Carbon monoxide poisoning: pathogenesis, management, and future directions of therapy. *Am J Respir Crit Care Med* 2017;195:596-606.
- Grube BJ, Marvin JA, Heimbach DM. Therapeutic hyperbaric oxygen: help or hindrance in burn patients with carbon monoxide poisoning? *J Burn Care Rehabil* 1988;9:249-52.
- The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301-8.
- Shirani KZ, Pruitt BA Jr, Mason AD Jr. The influence of inhalation injury and pneumonia on burn mortality. *Ann Surg* 1987;205:82-7.
- Greenhalgh DG, Saffle JR, Holmes JH IV, et al. American Burn Association consensus conference to define sepsis and infection in burns. *J Burn Care Res* 2007;28:776-90.
- Cartotto R, Greenhalgh DG, Cancio C. Burn state of the science: fluid resuscitation. *J Burn Care Res* 2017;38(3):e596-e604.
- Paratz JD, Stockton K, Paratz ED, et al. Burn resuscitation — hourly urine output versus alternative endpoints: a systematic review. *Shock* 2014;42:295-306.
- Pruitt BA Jr. Protection from excessive resuscitation: “pushing the pendulum back.” *J Trauma* 2000;49:567-8.
- Sullivan SR, Friedrich JB, Engrav LH, et al. “Opioid creep” is real and may be the cause of “fluid creep.” *Burns* 2004;30:583-90.
- Mackie DP, Spoelder EJ, Paauw RJ, Knape P, Boer C. Mechanical ventilation and fluid retention in burn patients. *J Trauma* 2009;67:1233-8.
- Greenhalgh DG. Burn resuscitation: the results of the ISBI/ABA survey. *Burns* 2010;36:176-82.
- Lawrence A, Faraklas I, Watkins H, et al. Colloid administration normalizes resuscitation ratio and ameliorates “fluid creep.” *J Burn Care Res* 2010;31:40-7.
- Faraklas I, Lam U, Cochran A, Stoddard G, Saffle J. Colloid normalizes resuscitation ratio in pediatric burns. *J Burn Care Res* 2011;32:91-7.
- Navickis RJ, Greenhalgh DG, Wilkes MM. Albumin in burn shock resuscitation: a meta-analysis of controlled clinical trials. *J Burn Care Res* 2016;37(3):e268-e278.
- Tanaka H, Matsuda T, Miyagantani Y, Yukioka T, Matsuda H, Shimazaki S. Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration: a randomized, prospective study. *Arch Surg* 2000;135:326-31.
- Lin J, Falwell S, Greenhalgh D, Palmieri T, Sen S. High-dose ascorbic acid for burn shock resuscitation may not improve outcomes. *J Burn Care Res* 2018;39:708-12.
- Taylor SL, Sen S, Greenhalgh DG, Lawless M, Curri T, Palmieri TL. Not all patients meet the 1 day per percent burn rule: a simple method for predicting hospital length of stay in patients with burn. *Burns* 2017;43:282-9.
- Williams FN, Jeschke MG, Chinkes

- DL, Suman OE, Branski LK, Herndon DN. Modulation of the hypermetabolic response to trauma: temperature, nutrition, and drugs. *J Am Coll Surg* 2009;208:489-502.
27. Hart DW, Wolf SE, Chinkes DL, et al. Effects of early excision and aggressive enteral feeding on hypermetabolism, catabolism, and sepsis after severe burn. *J Trauma* 2003;54:755-61.
28. Herndon DN, Hart DW, Wolf SE, Chinkes DL, Wolfe RR. Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med* 2001;345:1223-9.
29. Abdullahi A, Jeschke MG. Nutrition and anabolic pharmacotherapies in the care of burn patients. *Nutr Clin Pract* 2014;29:621-30.
30. McClave SA, Saad MA, Esterle M, et al. Volume-based feeding in the critically ill patient. *JPEN J Parenter Enteral Nutr* 2015;39:707-12.
31. Auger C, Samadi O, Jeschke MG. The biochemical alterations underlying post-burn hypermetabolism. *Biochim Biophys Acta Mol Basis Dis* 2017;1863:2633-44.
32. Wolf SE, Thomas SJ, Dasu MR, et al. Improved net protein balance, lean mass, and gene expression changes with oxandrolone treatment in the severely burned. *Ann Surg* 2003;237:801-10.
33. Porter C, Hardee JP, Herndon DN, Suman OE. The role of exercise in the rehabilitation of patients with severe burns. *Exerc Sport Sci Rev* 2015;43:34-40.
34. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:801-10.
35. Greenhalgh DG. Sepsis in the burn patient: a different problem than sepsis in the general population. *Burns Trauma* 2017;5:23.
36. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med* 2017;45:486-552.
37. Greenhalgh DG. A primer on pigmentation. *J Burn Care Res* 2015;36:247-57.
38. Deitch EA, Wheelahan TM, Rose MP, Clothier J, Cotter J. Hypertrophic burn scars: analysis of variables. *J Trauma* 1983;23:895-8.
39. Rashaan ZM, Krijnen P, Klamer RR, Schipper IB, Dekkers OM, Breederveld RS. Nonsilver treatment vs. silver sulfadiazine in treatment of partial-thickness burn wounds in children: a systematic review and meta-analysis. *Wound Repair Regen* 2014;22:473-82.
40. Schwanholt C, Greenhalgh DG, Warden GD. A comparison of full-thickness versus split-thickness autografts for the coverage of deep palm burns in the very young pediatric patient. *J Burn Care Rehabil* 1993;14:29-33.
41. Archer SB, Henke A, Greenhalgh DG, Warden GD. The use of sheet autografts to cover extensive burns in patients. *J Burn Care Rehabil* 1998;19:33-8.
42. Kreis RW, Mackie DP, Vloemans AW, Hermans RP, Hoekstra MJ. Widely expanded postage stamp skin grafts using a modified Meek technique in combination with an allograft overlay. *Burns* 1993;19:142-5.
43. Singer AJ, Boyce ST. Burn wound healing and tissue engineering. *J Burn Care Res* 2017;38(3):e605-e613.
44. Sood R, Roggy D, Zieger M, et al. Cultured epithelial autografts for coverage of large burn wounds in eighty-eight patients: the Indiana University experience. *J Burn Care Res* 2010;31:559-68.
45. Singh M, Nuutila K, Collins KC, Huang A. Evolution of skin grafting for treatment of burns: Reverdin pinch grafting to Tanner mesh grafting and beyond. *Burns* 2017;43:1149-54.
46. Parcels AL, Karcich J, Granick MS, Marano MA. The use of fetal bovine dermal scaffold (PriMatrix) in the management of full-thickness hand burns. *Eplasty* 2014;14:e36.
47. Li A, Dearman BL, Crompton KE, Moore TG, Greenwood JE. Evaluation of a novel biodegradable polymer for the generation of a dermal matrix. *J Burn Care Res* 2009;30:717-28.
48. Holmes IV JH, Molnar JA, Carter JE, et al. A comparative study of ReCell device and autologous split-thickness meshed skin graft in the treatment of acute burn injuries. *J Burn Care Res* 2018;39:694-702.
49. Pereira C, Murphy K, Herndon D. Outcome measures in burn care: is mortality dead? *Burns* 2004;30:761-71.

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