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Advances in the treatment of burn patients

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Introduction

Over the last two decades burn mortality rates have declined (*Table I*) due to the development of new treatment modalities. The advances that have led to decreased mortality rates in burn patients have evolved from ongoing research of new therapies that improve long-term outcome. In 1952, a 50 per cent total body surface area burn victimized nearly one-half of young patients under 17 years of age, currently the majority of children survive this size burn and a 98 per cent total body surface area burn kills only half the young people who receive it[1]. An improved understanding of burn pathophysiology has contributed to improvements in fluid resuscitation, infection control, support of the hypermetabolic response to trauma, nutritional support, early closure of the burn wound and timely rehabilitation. These advances have all contributed to the improved long-term survival of severely burned patients.

Pathophysiology

Thermal injury and chemical injury can cause coagulation necrosis of the skin and underlying subcutaneous tissues. The tissue surrounding the central zone of coagulation has a moderate degree of vascular injury that causes a decrease in tissue perfusion. This zone of stasis can progress to a partial-thickness or a full-thickness injury due to the release of local mediators, such as arachidonic acid, oxidants and cytokines produced by the burn wound. These mediators cause arteriolar and venular dilatation followed by platelet aggregation that causes vascular stasis. Thromboxane A_2 (TXA_2) is found in high concentrations in the burn wound and is thought to contribute to the decreased blood flow in the zone of stasis. TXA_2 increases platelet aggregation and neutrophil migration in the wound microcirculation. TXA_2 inhibitors applied locally have been shown to improve blood flow in the zone of ischaemia[2]. Increased local vascular permeability may also be attenuated by the use of antioxidants, particularly xanthine oxidase inhibitors, which indicates that an ischaemic-reperfusion injury occurs[3].

Many local and systemic physiological alterations are caused by the release of cytokines from the burn wound. The cytokines are involved in haemodynamic changes, tissue inflammation, wound healing, immune defenses, hypermetabolism and catabolism. The major cytokines that have so far been found to be involved in burn injury are tumour necrosis factor (TNF), interleukin 1 (IL-1), IL-2, IL-4,

Table I. Burn mortality rates (LD_{50})

	Age groups (yr)			
	0–14	*15–44*	*45–64*	*>65*
1942–52 Bull and Fisher	49% TBSA	46% TBSA	27% TBSA	10% TBSA
2807 patients	1366 patients	967 patients	330 patients	144 patients
1967–70 Bull	64% TBSA	56% TBSA	40% TBSA	17% TBSA
1917 patients	962 patients	565 patients	246 patients	144 patients
1975–79 Curreri and Abston	98% TBSA	70% TBSA	46% TBSA	19% TBSA
1508 patients	1056 patients	301 patients	120 patients	30 patients
1980–95 SBI/UTMB*	98% TBSA	70% TBSA	46% TBSA	19% TBSA
2169 patients	1526 patients	453 patients	127 patients	63 patients

*Shriners Burns Institute and University of Texas Medical Branch.

IL-6, IL-8, IL-12 and interferon gamma[4] (IFN-γ). TNF is associated with neutrophil sequestration. Neutrophils are central mediators of the microvascular injury responsible for the extension of burn size in the zone of stasis. Antibodies that inhibit neutrophil adherence have been shown to improve the circulation in the zone of stasis[5]. Cytokines not only have a direct action but they also activate other classes of inflammatory mediators potentiating their actions. As inflammation progresses, local and systemic mediators cause alterations in the hypothalamic control of temperature and metabolism. Burn wound colonization and gut bacterial translocation produce circulating endotoxin that is a potent activator of primed macrophages and neutrophils that release large amounts of oxidants, arachidonic acid metabolites and proteases, causing further local and systemic inflammation and tissue damage. The cytokines potentiate the process which can contribute to the progression of organ failure in severely burned patients. Modulation of the inflammatory response is an active field of research, which has tremendous potential to benefit burn patients.

Fluid resuscitation

An accurate clinical assessment of the extent and depth of the burn injury is the first step in effective resuscitation. Determination of the presence or absence of smoke inhalation injury and an examination for concomitant trauma are also vital during the initial clinical assessment. Smoke inhalation injury is suspected if the patient presents with clinical features such as facial burns, carbonaceous sputum or a history of injury in a closed space. Smoke inhalation injury can also be assumed if carboxyhaemoglobin levels are elevated immediately postburn and can be diagnosed with the aid of fiber optic bronchoscopy and/or xenon-133 ventilation-perfusion scintigraphy[6]. Delays in resuscitation can increase the amount of fluid required for adequate resuscitation by 30 per cent, and patients with smoke inhalation injury require up to a third more fluid during their acute resuscitation then those with similar size burns without smoke injury[7].

The goal of fluid resuscitation is to support the patient through the initial 24–48 h of hypovolaemia due to the sequestration of fluid resulting from the burn injury. Multiple resuscitation formulae have been used with success during the initial 48 h (*Table II*). Crystalloid, in particular lactated Ringers, is the most common resuscitation fluid utilized. The Parkland formula was developed from a retrospective study that showed that the majority of patients required lactated Ringer's solution in the amount of 4 ml/kg/per cent body surface area burned[8]. One-half of the calculated fluid requirement is given in the first 8 h and the remaining half given over the next 16 h.

Weight-based formulae uniformly overload children. Several resuscitation formulae for children have been proposed. As in adults most are based on the weight of the patient. However, surface area and weight relationships are not linear in growing children. Weight-based formulae underresuscitate injuries in children. A formula based on body surface area is more effective in the resuscitation of paediatric patients. At the Shriners Burns Institute in Galveston, fluid is administered at 5000 ml/m^2 body surface area burn plus 2000 ml/m^2 total body surface area for maintenance, with half the volume infused in the first 8 h and the remainder infused over the next 16 h postburn.

All formulae are only guidelines to fluid replacement and the adequacy of resuscitation must be constantly monitored. A urine output of 0.5–1.0 ml/kg/h is a good clinical indicator of vital organ perfusion. However, in patients with severe burns, the use of urinary output and vital signs may lead to a suboptimal resuscitation[9]. For these patients, invasive cardiorespiratory monitoring may be indicated to optimize fluid therapy. Even with maintenance of cardiac output, elevated levels of TXA_2 and vasopressin may result in hypoperfusion, GI ileus, mucosal cell apoptosis or, at worst, ischaemic GI lesions[11] (*Figure 1*). In our models the decrease in mesenteric blood flow postburn is associated with bacterial translocation to mesenteric lymph nodes and systemically to distant organs[12] (*Figures 2* and *3*). Future additions to resuscitation programmes will include agents that control the vasospastic mediators of decreased mesenteric blood flow, such as thromboxane antagonists and vasopressin antagonists. These have been effective in animal models (*Figures 4* and *5*). Future advances will also include effective monitoring and optimization of cerebral blood flow.

Table II. Formulae for estimating adult burn patient fluid resuscitation

Crystalloid formulae			
Modified Brooke		Lactated Ringer's	2 ml/kg/% burn
Parkland		Lactated Ringer's	2 ml/kg/% burn
Colloid formulae			
	Crystalloid	*Colloid*	*DSW*
Brooke	Lactated Ringer's 1.5 ml/kg/% burn	0.5 ml/kg	2000 ml
Evans	Normal saline 1.0 ml/kg/% burn	1.0 ml/kg/% burn	2000 ml
Slater	Lactated Ringer's 2 l/24 h	Fresh frozen plasma 75 ml/kg/24 h	
Hypertonic saline formulae			
Hypertonic Saline Solution (Monafo)		Fluid contains 250 mEq Na/l vol. to maintain urine output at 30 ml/h	
Modified Hypertonic Saline Solution (Warden)		Lactated Ringer's + 50 mEq $NaHCO_3$ (180 mEq Na/l) for 8 h to maintain urine output at 30–50 ml/h	
Dextran Formula (Demling)		Dextran 40 in saline – 2 ml/kg/h × 8 h Lactated Ringer's vol. to maintain urine output at 30 ml/h Fresh frozen plasma – 0.5 ml/kg/h × 18 h beginning 8 h postburn	

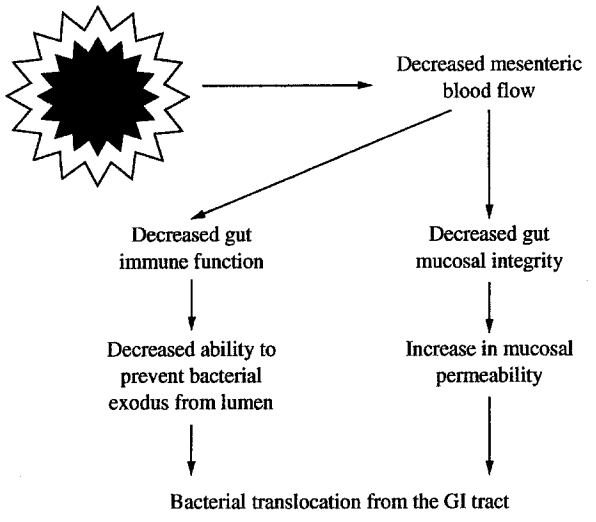

Figure 1.

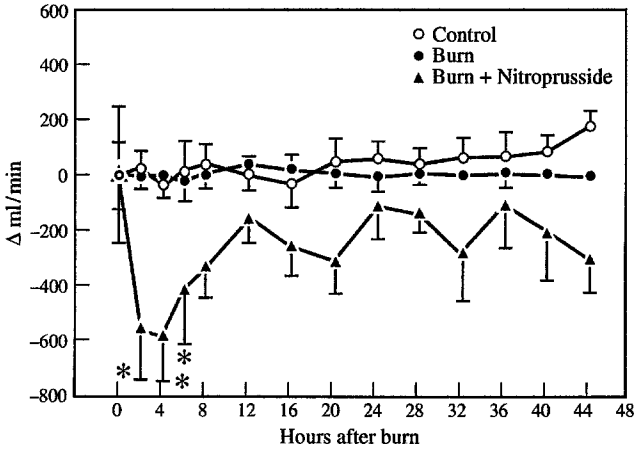

Figure 2. Mesenteric blood flow following burn injury. *$P < 0.05$ Significant from the baseline (Dunnett's test).

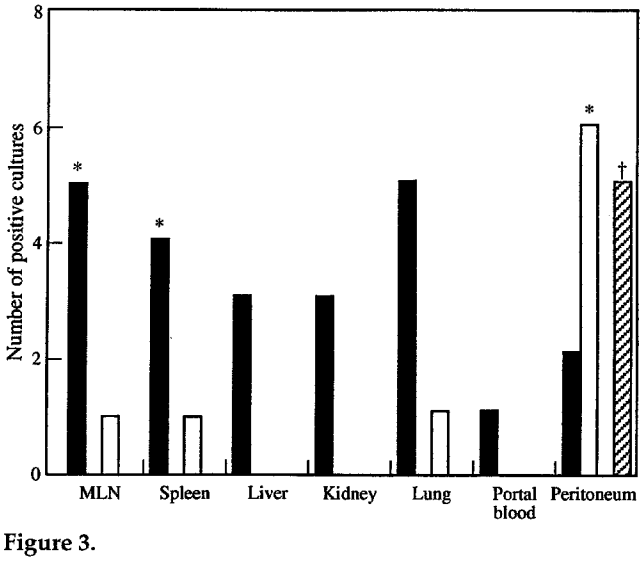

Figure 3.

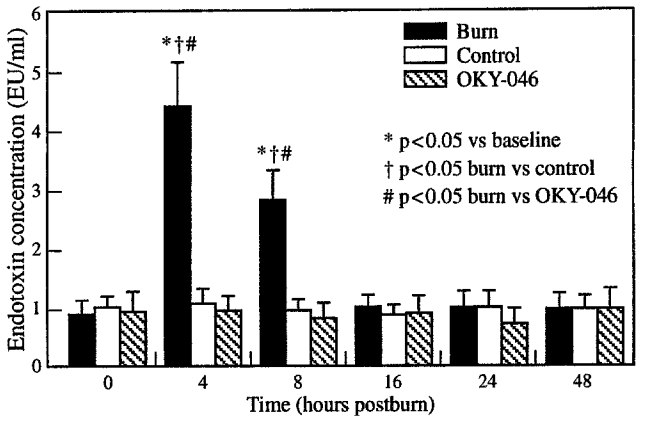

Figure 4. Endotoxin levels in the superior mesenteric vein of burn, control and OKY-046 groups. *$P < 0.05$ vs. baseline; †$P < 0.05$ burn vs. control; #$P < 0.05$ burn vs. OKY-046.

Infection control

Topical antimicrobial agents are used to limit bacterial proliferation and fungal colonization in the burn wound. The three most commonly used topical antimicrobials are silver sulfadiazine (Silvadene), mafenide acetate (Sulfamylon) and 0.5 per cent silver nitrate solution. Nystatin can be added to silvadene, reducing the incidence of invasive candidal growth on burn wounds[13]. Perioperative broad-spectrum intravenous antibiotics and antibiotics specific for identified wound cultures or lung infections are routinely used. Unfortunately, multiply resistant bacteria have developed to all known antibiotics, including vancomycin-resistant Enterococcus, totally resistant Pseudomonas and Serratia. The cost of developing new drugs is so great that pharmaceutical development has slowed. Current research is focussing on reversal of the profound suppression of immune function in burn patients. The helper cell suppressor cell active in burns is similar to that found in immunosuppressed organ transplant patients. Recent studies have shown a relationship of decreased cellular cytotoxicity postburn to increased production of IL-4 and IL-10 (*Figure 6*). Administration of immunopotentiators such as IL-12 can reverse

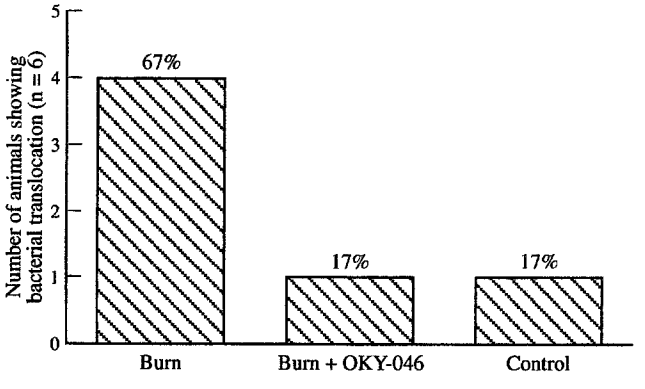

Figure 5. Incidence of bacterial translocation.

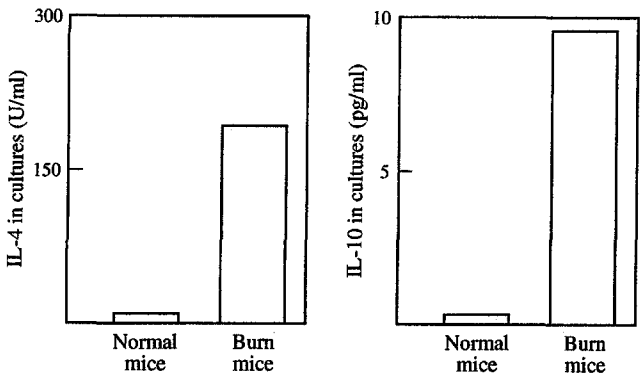

Figure 6. IL-4 and IL-10 production in cultures of splenic T cells from thermally injured mice. Splenic T cells from mice 25 days after thermal injury were cultured in vitro at a cell density of 5×10^6 cells/ml for 48 h at 37°C. Culture fluids were assayed for IL-4 in CTLL-2 cells and for IL-10 by ELISA technique.

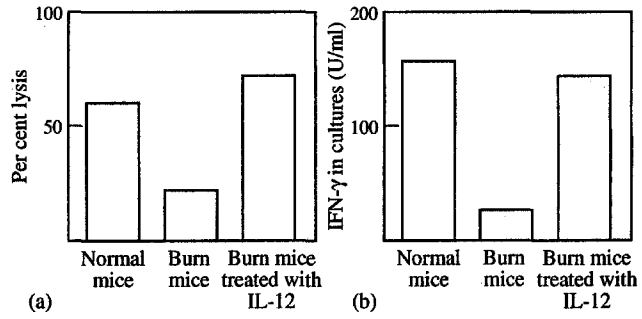

Figure 7. The generation of CTL and production of IFN-γ from splenic T cells of thermally injured mice treated with or without IL-12. Thermally injured mice were treated i.p. with IL-12 (800 U/mouse) every other day for 24 days beginning just after thermal injury. **a**, Splenic T cells were obtained from normal mice, thermally injured mice or IL-12-treated thermally injured mice all of which were immunized with allogeneic spleen cells. Cytotoxicity of these cells were tested in the ^{51}Cr-release assay. **b**, Splenic T cells from thermally injured mice treated with or without IL-12 were stimulated with SEA (0.02 μg/ml) for IFN induction. Culture fluids harvested 72 h after cultivation were assayed for IFN-γ activity.

immunosuppressant cytokine patterns (*Table III*) and markedly improve postburn mortality and improve resistance to subsequent bacterial challenge (*Figure 7*).

Metabolic response

The degree of metabolic changes experienced by burn patients is directly releated to the extent of injury. The decrease in cardiac output and metabolic rate initially experienced is called the 'ebb phase'[14]. Once fluid resuscitation is completed the cardiac output returns to normal and then achieves above normal levels with a simultaneous increase in resting energy expenditure (REE). Severe burn injury can drive the metabolic rate to twice normal. This hypermetabolic response can be blunted to 40–60 per cent above normal if the patient is wrapped in bulky dressings and kept warm with external radiant heating devices. A true upward central temperature reset occurs between days 5 and 15 postburn to a core temperature of 38.5°C and the temperature remains elevated for up to 2 months in major injuries regardless of the timing of wound closure. This is due to direct stimulation of the hypothalamus by inflammatory mediators and cytokines that increase the thermoregulatory set point and alter endocrine function.

In large burn injuries, cortisol, glucagon and catecholamines are all markedly elevated. Cortisol is strongly catabolic and is associated with negative nitrogen and calcium balance and loss of tissue protein and bone mineral. It also stimulates gluconeogenesis, increases proteolysis and sensitizes adipocytes to the action of lipolytic hormones. Catecholamines increase the rate of glycogenolysis, hepatic gluconeogenesis, promotes lipolysis and peripheral insulin resistance. Although burn patients have elevated blood glucose levels, their insulin levels are not depressed but rather they are elevated. This hyperglycaemia is the result of serum glucagon levels that are increased disproportionately to serum insulin levels. However, primarily the elevated serum glucose levels reflect a six-fold increase in the rate of glucose flow (gluconeogenesis), not a lower rate of glucose utilization[15]. The elevated levels of glucagon seen following burn injury are critical for maintaining an adequate rate of glucose production to meet the patient's energy requirements, particularly for accelerated wound healing.

Glucose is an important energy source in burn patients. When glucose cannot be adequately supplied, the result is excessive protein catabolism. Common treatment has been to provide burn patients with as much glucose as they can tolerate, however, studies by Wolfe and colleagues have shown that burn patients have difficulty metabolizing glucose when the rate of infusion exceeds 4 mg/kg/min[11]. Further, a randomized study of maximally tolerated enteral feedings versus TPN maximally tolerated calories to meet one to four times REE showed the TPN-treated patients to have an increased mortality and decreased immune function[16] (*Tables III* and *IV*).

High concentrations of free amino acids result from a significant increase in muscle protein catabolism in severe burn injury. Hyperaminoacidaemia will stimulate protein synthesis in normal

Table III. Patient characteristics

	Age	*% TBSA burned*	*% Third-degree burn*	*Mortality (%)*
TPN ($n = 17$)	34±3	69±3	40±6	76
No TPN ($n = 23$)	35±3	76±3	41±6	57

Data are means±SE.

Table IV. Formulae for estimating adult burn patient fluid resuscitation

	OKT4/OKT8	
	PBD 0–5 h	*PBD 6–10 h*
TPN ($n = 17$)	1.07±0.35	0.82±0.34*
No TPN ($n = 23$)	1.7±0.23	1.24±0.23*

Data are means±SE.
*$P < 0.05$, compared to normal (2.24±0.42).

individuals. Hyperaminoacidaemia does not prevent protein catabolism from proceeding at a higher rate than protein anabolism. In burns this is partly due to decreased growth hormone (GH) and insulin-like growth factor I (IGF-I) levels following burn injury[17]. There is a increase in amino acid and protein recycling to allow for the synthesis of collagen for wound healing and of antibodies for resisting infection.

Recombinant growth hormone is a potent anabolic agent that has been shown to improve nitrogen balance and increase muscle mass in hypercatabolic burn patients. The anabolic action of GH appears to be mediated by an increase in protein synthesis, while IGF-I decreases protein degradation. Since the effects of GH and IGF-I are complementary, both may promote net protein synthesis by independent mechanisms.

Administration of 2 mg/kg/day recombinant growth hormone to massively burned children has been shown to accelerate skin graft donor site wound healing, allowing wounds to be closed earlier, shortening hospital stay by 28–33 per cent[18]. Recombinant GH has also been shown to accelerate donor site healing time by 2–3 days[16]. This increase in wound healing is possibly due to the three-fold increase in IGF-1 concentrations. Growth hormone enhances wound healing by stimulating hepatic and local production of IGF-1 to increase circulating and wound site levels. The hypothesis is that IGF-1 receptor complex stimulates cell mitosis and increases synthesis of laminin type IV and VII collagen and cytokeratin 14[19]. All of these important components of skin are three- to eight-fold increased in randomized studies in which 0.2 μg/kg/day of growth hormone was compared to placebo administered to massive burns.

Although catabolic hormone levels are increased with exogenous administration of GH, there is still an upregulation of protein synthesis[20]. GH improves protein synthesis in muscle as well as improving wound healing in the treatment of severely burned patients.

Postburn hypermetabolism is also characterized by an increase in heart rate and oxygen consumption. Beta blocking agents such as propranolol can lower the heart rate of a burn patient. Propranolol can also reduce left ventricular work index and rate pressure product[21]. Although large doses of propranolol will stop the heart in a normal individual, burn patients have markedly elevated levels of catecholamines and the administration of propranolol (0.5 mg/kg/day) in a child with a 60 per cent burn will cause only a 20 per cent decrease in heart rate[17].

Nutrition

Patients with severe burns (>40 per cent of total body surface area) have metabolic rates that are 100–150 per cent above their basal rate. These patients have increased energy and protein requirements that must be satisfied in order to prevent impaired wound healing, cellular dysfunction and decreased resistance to infection. Early enteral feedings, within the first 24 h postburn, have been shown to decrease the production of catabolic hormones, improve nitrogen balance, maintain gut mucosal integrity, lower the incidence of diarrhoea and decrease hospital stay. Total parental nutrition (TPN) in burn patients has been associated with metabolic and immunological complications[22] and its use is limited to supporting patients with severe gastrointestinal dysfunction.

Currently the exact nutrient requirements of burn patients are not clear, although it is accepted that maintenance of energy requirements and replacement of large protein losses are vital. Enteral tube feedings that are optimal would consist of 20 per cent of the calories as protein, 30 per cent as fat and 50 per cent as carbohydrate. A number of formulae have been developed for both adults and children (*Tables V* and *VI*). The role of dietary additions such

Table V. Commonly utilized formulae for adult burned patients

Curreri	Age 16–59 yr	Basal (approx. 25 kcal/kg + 40 kcal/% burn)
	Age >60 yr	Basal (approx. 20 kcal/kg + 65 kcal/% burn)
Modified Harris–Benedict	All ages	Calculated or measured RMR × M where M ranges from 1.3 to 2.0
Long's Modified Harris–Benedict		
Males: BMR = (66.47 + 13.75W + 5.0H − 6.76A) × (activity factor) × (injury factor)		
Females: BMR = (55.10 = 9.56W + 1.85H − 4.68A) × (activity factor) × (injury factor)		
Activity factor:	Confined to bed	1.2
	Out of bed	1.3
Injury factor:	Severe thermal burn	2.10
	Skeletal trauma	1.35
	Major sepsis	1.60
	Minor operation	1.20

Table VI. Formulae for determining energy needs for paediatric burned patients

	Age	*Daily requirements*
Galveston infant	0–12 months	2100 kcal/m² + 1000 kcal/m² burn
Revised child	1–11 yr	1800 kcal/m² + 1300 kcal/m² burn
Adolescent male (kcal/m²)	12 yr and above	1500 kcal/m² + 1500 burn
Curreri, junior	0–1	BMR + 15 kcal/% burn
	1–3	BMR + 25 kcal/% burn
	4–15	BMR + 40 kcal/% burn

Children's Hospital Center, Akron, Ohio
Normal requirements for height–age (RDA) + added needs for burn hypermetabolism:

Weight (kg)	*kcal/% burn*
0–9	15
10–13	20
14–18 (burns >40%)	20
14 (all other burns)	30

as glutamine, arginine, vitamine C, vitamin E, fish oil and minerals are currently under investigation but all appear promising.

Wound healing

An aggressive approach to burn wound excision is the standard of care today. Early excision and wound closure in large burns (>30 per cent TBSA) in young adults and children has been shown to reduce mortality[23]. However, all surgical excision must be tailored to the individual circumstance.

Once the burn wound is excised rapid wound closure is essential. In small burns wound closure can be obtained with autologous skin. With massive burns, greater than 50 per cent total body surface area, skin graft donor sites are limited and complete closure after total excision is achieved by a combination of autograft and allograft or synthetic wound coverings. In large wounds where cosmesis is not a concern, autograft can be meshed 4:1 and overlaid with unexpanded meshed cadaver skin (*Figure 8*) with cadaver skin alone used for areas for which there are no donor sites. The use of cadaver skin in large burns is clearly life saving. The potential for transmission of hepatitis, CMV or HIV has unrealistically frightened many. Alternatives to cadaver skin have been synthetic covers such as Biobrane or potato peels. One currently available cover, dermagraft-TC, performs as well as cadaver skin. Dermagraft is essentially Biobrane populated with neonatal fibroblasts which secrete structural support proteins and cytokines prior to being inactivated. Repeat grafting is required in large burns by sequential harvesting of limited donor sites until the entire burn wound is closed with autologous skin.

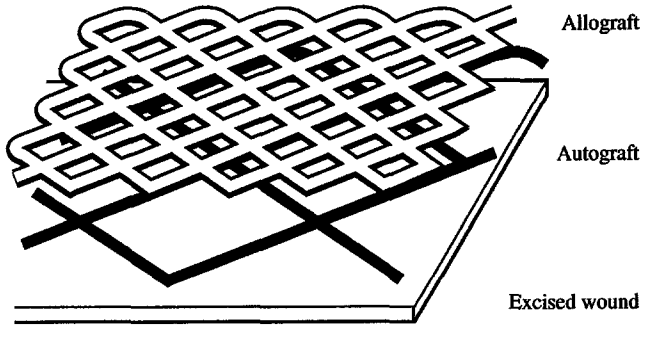

Figure 8.

Another technique to achieve total wound closure in massive burns is the use of cultured epidermal keratinocytes. The use of cultured epidermal autograft has been disappointing, however, due to exorbitant cost and tenuous long-term skin cover. Initially cultured skin has an 80–90 per cent take. A repeated problem that has been observed, however, is that large bullae result due to minimal shear forces, even 6 months after application. The fluid in these bullae were found to have elevated thromboxane and prostaglandin levels as compared to normal burn blister fluid. The elevated levels of thromboxane represent an inflammatory process that might explain the ongoing graft loss of cultured skin over time[24]. This inflammatory response prevents secure adhesion of the cultured epidermis to the wound interface even months after application. This greatly limits the long-term clinical usefulness. A bilaminar skin substitute of collagen mesh or allodermis providing a neodermis that could be covered with cultural autograft would be beneficial to patients with extensive burns and improve the quality of their outcome. Two dermal replacements are currently available, Integra, which is a bilaminate of collagen and chondroitin sulfate with a silastic cover, and Alloderm, which is de-epithelialized pathogen-free cadaver skin.

Once complete closure of the burn wound is achieved the treatment emphasis shifts from wound management to rehabilitation. Burn scars are kept moist with emollients to prevent dry scaly regions that are prone to breakdown and infection. Better control of burn scar can be obtained by applying pressure garments to healed skin grafts as well as deep second-degree burns. The routine use of pressure garments appears to reorient collagen so that scars are smoother, flatter and mature more rapidly. Pressure garments and plastic moulds for the

face and neck have been found to reduce the incidence of scar contracture. Early splinting in combination with pressure garments also reduces the formation of joint contractures that limit rehabilitation.

Advances in manipulation of scarring will only come with a further understanding of cell-to-cell signals that promote fibroblast hyperplasia and hypertrophic scarring. Until that time consistent scar control and patient rehabilitation is dependent upon a well-developed treatment plan utilizing the complete burn team approach. This includes a coordinated plan involving surgeons, operative nurses, therapists, psychologists, and the families of burned patients providing physical and emotional recovery from traumatic burn injury.

Inhalation injury

The most mortal, as yet uncovered, challenge in burns is the carnage caused by smoke inhalation injury resulting in progressive respiratory distress (*Figure 9*). There are glimmers of hope however. A

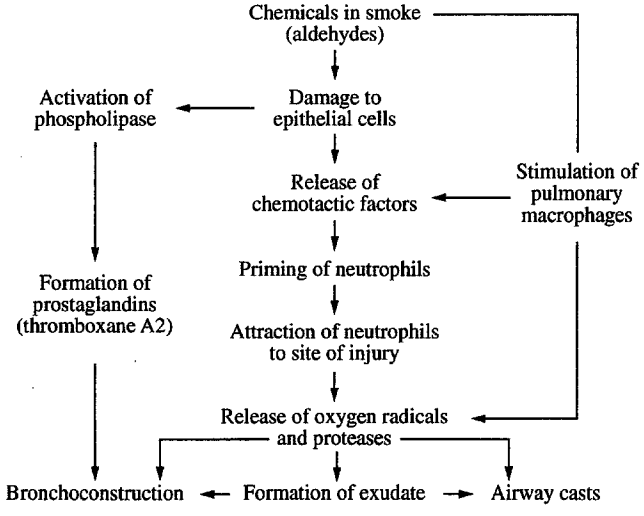

Figure 9. Tracheobronchial damage.

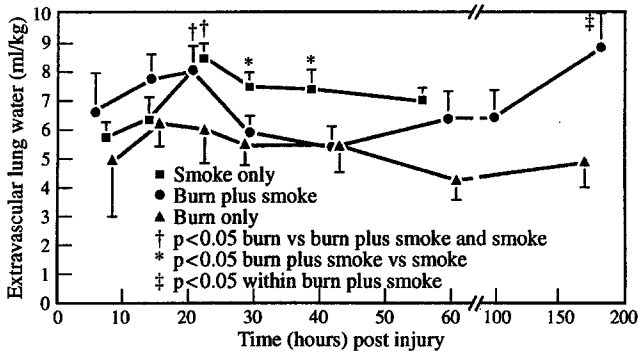

Figure 10.

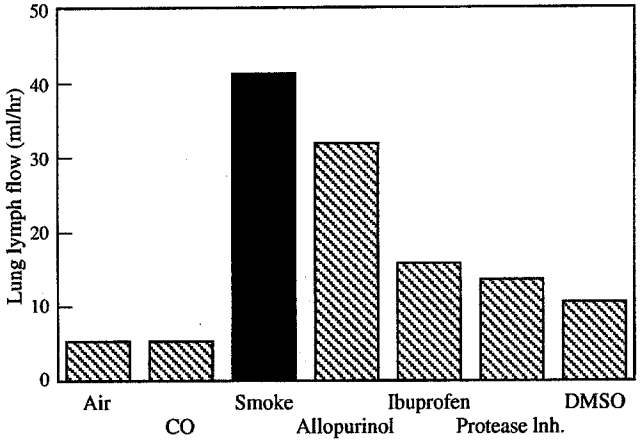

Figure 11. Modulation of lung lymph flow following inhalation injury.

series of animal experiments have clearly established many pathophysiological features of the response to inhalation injury[25,26]. Pulmonary oedema, secondary to increased microvascular permeability, develops 48 h after injury, resulting in an endstage lung showing areas of atelectasis and flooded pulmonary parenchyma[27] (*Figure 10*). Pulmonary macrophages are activated with smoke inhalation and recruit large numbers of polymorphonuclear leucocytes to the lung. These polymorphonuclear leucocytes are markedly increased in the lung microvasculature at 24–48 h postinjury[23]. The production of proteases and oxygen free radicals parallel the appearance of polymorphonuclear leucocytes in the lung and cause an increase in microvascular fluid formation, and increase in lung lymph flow and lung water appearance[25]. Simple therapies based on these findings have been tested and have resulted in great decreases in permeability oedema caused by smoke[28,29] (*Figure 11*).

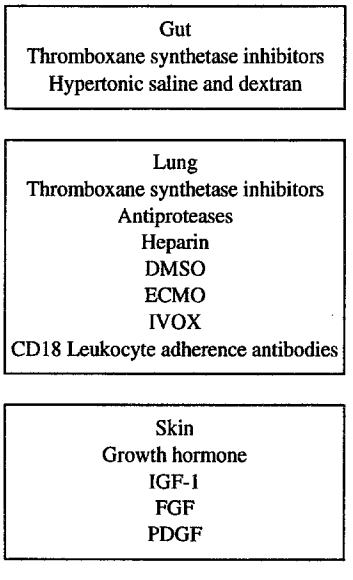

Figure 12. Initial burn wound.

Randomized prospective studies using anti-adherence antibodies to polymorphonuclear leucocytes are currently underway in an attempt to decrease pulmonary oedema after lung injury.

Conclusion

Advances in the understanding of burn pathophysiology have led to improvements in the clinical problems of thermally injured patients (*Figure 12*). Burn trauma continues to have a large socioeconomic impact on health care and advances in this field have contributed to other areas of critical care. Continued studies in fluid resuscitation, infection control, support of the hypermetabolic response, nutritional support, wound healing and scar control are vital to lead burn care into the twenty-first century.

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