Advances in burn critical care

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Background: **Management of burn patients requires a complex interaction of surgical, medical, critical care, and rehabilitation approaches. Severe burn patients are some of the most challenging critically ill patients who may have multiple-system organ failure with life-threatening complications.**

Objective: **To review and highlight some of the recent advances in burn critical care. We focused on some of the new treatment modalities in the management of respiratory complications, advances in burn resuscitation, management of the metabolic response to burns, and recent ideas in burn immunotherapy.**

Data Source: **A search of the MEDLINE database and manual review of published articles and abstracts from national and international meetings.**

Data Syntheses and Conclusions: **The respiratory management of burn patients includes strategies to minimize iatrogenic injury with low tidal volume ventilation, to improve ventilation/perfusion mismatch, and to diagnosis pneumonia. Many aspects of burn resuscitation remain controversial, and the best form of fluid resuscitation has yet to be identified. Recent research in the metabolic response to thermal injury has identified many potentially beneficial treatments. Although immunomodulation therapy is promising, currently most of these treatments are not clinically viable, and further clinical and translational research is warranted. (Crit Care Med 2006; 34[Suppl.]: S239–S244)**

KEY WORDS: burn; critical care; inflammation; signal transduction; mitogen-activated protein kinase (MAPK); adrenergic receptors; immunotherapy

Treating patients with burn injuries requires a complex, multidimensional approach. Burn patients may have extensive damage to skin, which may require multiple surgical interventions, burn wound management, physical and occupational therapy, and scar management. In the last decade, there have been major advances in this aspect of burn care, which includes early excision and grafting with autologous or allogeneic skin or biosynthetic dermal substitutes (1). Although this approach has decreased morbidity and mortality, burn patients continue to face many serious complications. Thermal insult may induce a major disturbance in the homeostatic mechanisms, with severe disturbance in hemodynamic, respiratory, and metabolic pathways (2). Potential postburn complications are severe systemic inflammatory response syndrome, sepsis, acute respiratory distress syndrome, multiple-system organ failure, and death. Addition of inhalation injury may double the mortality rate and act as a synergistic insult on the pulmonary system (3). Physicians treating burn patients face complex critical care issues. The present article will be a brief report on some of the new advances in burn critical care. Rather than being all inclusive, we focused on four critical care issues: new approaches in management of respiratory complications, advances in the resuscitation strategies, complex management of the metabolic response to burns including nutritional support, and recent ideas and approaches in immunotherapy.

AIRWAY MANAGEMENT AND VENTILATORY STRATEGIES

Most severely burn-injured patients are intubated early for airway management and respiratory support. Pulmonary insufficiency and failure in severely burned patients is multifactorial. The pathogenesis can be differentiated into direct pulmonary and upper airway inhalation injury and indirect or secondary acute lung injury due to activation of the systemic inflammatory response. There is also secondary delayed pulmonary injury due to sepsis and pneumonia. In addition, ventilator-associated lung injury has been described as an important iatrogenic factor contributing to the secondary accentuation of pulmonary injury (4). The reduced pulmonary compliance and chest wall rigidity of burn patients can lead to aggressive ventilatory management and high airway pressures, exacerbating acute lung injury. Institution of low tidal volume ventilation, allowing permissive hypercapnia, was shown to reduce the development of ventilator-associated lung injury and significantly improve outcomes (4). In addition, use of alternate ventilation strategies such as high-frequency oscillatory ventilation and high-frequency percussive ventilation may be beneficial in selected burn patients (5). Although there are limited comparative data regarding these two strategies, it seems that high-frequency percussive ventilation is especially useful in inhalation injuries (6). Extracorporeal membrane oxygenation is described by some authors as an ultimate salvage option in the pediatric population (7). For adult patients, extracorporeal membrane oxygenation is to be considered when patients face respiratory death from inhalation injury (8).

Adjunct therapies such as inhaled nitric oxide have gained momentum in treating hypoxic vasoconstriction in burn patients, improving ventilation/perfusion mismatches and thereby tissue oxygenation (9, 10). In an animal model of inhalation injury, aerosolized heparin attenuated cellular infiltrates, lung edema, congestion, and cast formation and improved oxygenation (11). In a study of 90 consecutive burn pediatric patients who had inhalation injury, there was a signif-

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icant decrease in reintubation rates, in the prevalence of atelectasis, and in mortality for patients treated with the regimen of aerosolized heparin and N-acetylcysteine when compared with controls (12).

Although most recent studies demonstrate improved outcomes with early tracheostomy, controversy still exists on the general "optimal" tracheostomy technique and timing (13). A retrospective study of pediatric burn patients demonstrated that early tracheostomy was safe, provided a secure airway, and improved the ventilatory management of patients (14); but there was no significant change in oxygenation, minute ventilation, or pH after tracheostomy. In a retrospective review of adult patients with severe burn injury, there were no differences in ventilatory support, length of stay, prevalence of pneumonia, or survival (15); however, patients with tracheostomy had a significantly shorter time to extubation. Although there is controversy regarding improved pneumonia rate and mortality, most researchers agree that tracheostomy offers some advantages in terms of patient comfort and security. Regarding the preferred tracheostomy technique, recent studies demonstrate that percutaneous tracheostomy may be safe in burn patients (16, 17). Addition of fiberoptic assistance may avoid rare but serious complications (18). The enthusiasm for percutaneous tracheostomy should be tempered in patients with severe facial and neck burns or upper airway edema because loss of airway in these patients may be associated with significant complications.

Pneumonia. Pneumonia is still one of the most common infectious complications in severe burn patients. Ventilator-associated pneumonia is very common in burn patients, and similar to other critically ill patients, it is associated with increased risk of fatal outcome (19, 20). Several factors prime burn victims for increased susceptibility for pneumonia: relative immunosuppression, dysfunctional ciliary movement in inhalational injuries leading to impaired secretory clearance, pulmonary inflammatory activation with acute lung injury, and increased leakage of nutrient-rich plasma into lung parenchyma. Due to severe underlying inflammatory pulmonary pathology, accurate clinical diagnosis of ventilator-associated pneumonia can be very difficult in burn patients. The recent emergence of multi–drug-resistant bacterial pathogens has mandated a more accurate diagnosis of infectious complications such as pneumonia. The National Infection Surveillance System uses physiologic data, laboratory evaluation, and radiographic data to define pneumonia. Recognizing the difficult diagnosis of ventilator-associated pneumonia in the injured patients (21), many investigators have demonstrated the improved sensitivity and specificity by including quantitative cultures obtained via bronchoalveolar lavage (22, 23). In a retrospective review of adult burn patients, the use of bronchoalveolar lavage eliminated the unnecessary antibiotic treatment of 21% of patients and was associated with a lower rate of ventilator-associated pneumonia (24).

RESUSCITATION

Burn trauma leads to a combination of hypovolemic and distributive shock on the basis of generalized microvascular injury and interstitial third-spacing through collagen and matrix degeneration. Burn injury is marked by dynamic and ongoing fluid shifts, which have led to the development of fluid resuscitation formulas based on percentage of total body surface area burn and weight. Fluid resuscitation based on the Parkland burn formula is extensively used in burn centers and has helped minimize the occurrence of burn shock (25). However, a recent survey of 28 burn centers found that in 58% of patients, actual fluid resuscitation exceeded the 4 mL/kg recommended by Baxter and Shires (26). Over-resuscitation has been shown to correlate directly with increasing intraabdominal pressure and the development of abdominal compartment syndrome (27). Apart from the well-described extremity compartment syndrome, orbital compartment syndrome requiring canthotomy in patients receiving supranormal resuscitation was recently described (28). The current high-volume fluid regimens have shifted postburn resuscitation complications from renal failure to pulmonary edema, with increased requirement for ventilatory support, the need for fasciotomies in unburned limbs, and the occurrence of the abdominal compartment syndrome (29). The increased use of sedative and analgesic medication may have contributed to increased fluid volumes given to burn patients. In essence, the pendulum may have swung from insufficient resuscitation to excessive volume loading.

Crystalloid solutions, such as lactated Ringers solution and normal saline, are still first-line fluid replacements in burn resuscitation. Due to reduced intravascular fluid retention, large volumes have to be infused, which accentuate tissue edema, and the development of tissue edema can lead to worsening outcomes (30). Hypertonic saline (HTS) resuscitation (7.5% NaCl) has been promoted for its efficient intravascular volume resuscitation, rapid restoration of blood pressure and cardiac output with improved cerebral perfusion, and potential for expanding circulating volume by reabsorption of fluid from the interstitial space (31). More recently, HTS has been studied as a fluid with significant modulation of systemic inflammatory response secondary to reperfusion injury, which may be beneficial in patients with shock (32, 33). In animal models of trauma and burn, use of HTS resuscitation has been associated with decreased edema and improved organ perfusion and outcomes (34–36). Data on the effectiveness of HTS to prevent organ damage in the clinical setting are inconsistent (37). Some of the studies in burn patients have demonstrated that HTS may have decreased the fluid load, tissue edema, and complications such as abdominal compartment syndrome (38–40). But others have noted no benefit in fluid requirement and potential increase risk of renal failure (41). It seems that the benefit of HTS is seen in early resuscitation (42), and some researchers have recommended stopping HTS infusion when serum sodium concentration exceeds 160 mEq/L (29, 43). Currently, HTS is not routinely used in burn patients, and further research is required to better define potential benefits, the timing, and the optimal volume.

Theoretically, the use of colloids in resuscitation of hypovolemic patients may be associated with preservation of plasma osmotic pressure, more efficient plasma volume expansion, and decreased tissue and pulmonary edema. However, clinical studies have not demonstrated a significant improvement in patient outcomes with colloid resuscitation (31, 44, 45). In burn patients, treatment with albumin did not improve outcomes (44).

A prospective randomized study demonstrated that a restrictive strategy of red-cell transfusion (hemoglobin concentration maintained at 7.0–9.0 g/dL) may be superior to a liberal transfusion strategy (hemoglobin concentration maintained at 10.0–12.0 g/dL) in critically ill

patients, with the possible exception of patients with acute myocardial infarction and unstable angina (46). A recent multiple-center cohort analysis found an increased mortality in burn patients associated with blood transfusions (47). Therefore, there is a push to decrease blood transfusion in burn patients. Recombinant human erythropoietin has been shown to be useful in treatment of chronic anemia and, theoretically, may decrease the need for blood transfusion in the ICU. However, in a prospective, double-blind, randomized study of 40 severely burned patients, recombinant human erythropoietin did not prevent the development of postburn anemia or decrease transfusion requirements (48). Interestingly, a recent animal study demonstrated that recombinant human erythropoietin improved healing of burn wound through increased epithelial proliferation, maturation of the extracellular matrix, and angiogenesis (49). Currently, most centers do not use erythropoietin in treatment of burn patients, and further clinical study is required before routine clinical use.

METABOLIC RESPONSE

During the flow phase postburn, there is an impressive hyperdynamic response. For pediatric patient with >40% total body surface area burn, the resting metabolic rate is increased in the ranges between 160% and 200% (50). This global hypermetabolism is associated with tachycardia, fever, muscle protein catabolism, and derangement in hepatic protein synthesis (51, 52). This response may be associated with significant complications such as immunodeficiency, impaired wound healing, sepsis, loss of lean body and muscle mass, cardiac ischemia, and potential death. Primary treatment modalities include avoidance of infectious complications such as sepsis and early excision of full-thickness burns, which is associated with attenuation of hypermetabolism (52–54). Several other approaches have been used to attenuate the burn-induced hypermetabolism (54). This article will focus on early nutritional support and modulation of hormonal/endocrine response.

Nutritional Support

The use of early enteral feeding in burn patients may attenuate catabolic response after thermal injury (55). Because there is significant increase in energy expenditure after burns, high-calorie nutritional support was thought to decrease muscle catabolism. However, aggressive high-calorie feeding with a combination of enteral and parenteral nutrition was associated with increased mortality (56). Increasing enteral feeding beyond the body energy expenditure, 20–40% above the resting energy expenditure, does not improve lean body mass and is associated with complications such as fatty liver (51). Most authors recommend adequate calorie intake via enteral feeding and avoidance of overfeeding (54).

High carbohydrate diets compared with high fat diets may improve the net balance of skeletal muscle protein (57). Increased endogenous insulin may contribute to improved muscle metabolism. In a study of six adult patients with >40% total body surface area burn, treatment with insulin and metformin were associated with improved muscle kinetic (58). However, high carbohydrate diet may be associated with elevated glucose, which may be detrimental in critically ill patients. In a study of 58 pediatric burn patients, there was a significant association between poor glucose control and complications such as increased bacteremia, reduced skin graft take, and increased mortality (59). In another study, tight glucose control in severe burn patients seemed to be safe and associated with decreased risk of infection and improved survival (60). Therefore, aggressive monitoring and treatment of hyperglycemia is recommended.

Similar to all critically ill patients, adequate protein intake is required. Because there is an increased oxidation rate of amino acids in burn patients, the protein requirement is increased to 1.5–2.0 g/kg per day in treatment of severely burned patients (54).

Modulation of Hormonal and Endocrine Response

Burn injury is associated with increased levels of catecholamines and catabolic hormones. Therefore, it is logical to assume blockade of catecholamine response or use of anabolic steroids may attenuate hypermetabolism or blunt catabolic response after burn injury. In this review, we will focus on beta-adrenergic receptor blockade and oxandrolone.

Beta-Adrenergic Receptor Blockade. There has been a recent increased enthusiasm for use of beta-blockers in treatment of surgical patients. In elective noncardiac operations, perioperative treatment with beta-blockers has been associated with reduced mortality and prevalence of cardiovascular complications (61, 62). In burn patients, beta-blockers can blunt the catecholamine effect by attenuating hypermetabolism, decreasing oxygen demand and resting energy expenditure, and decreasing heart rate and cardiac oxygen demand (54). Beta-blockers may also attenuate catecholamine-induced muscle catabolism and lipolysis (63, 64). Moreover, there are data to suggest that beta-blockers can modify catecholamine-mediated defect in lymphocyte activation and improve immune response with decreased infectious complications (65). Various studies have demonstrated the potential beneficial effect of beta-blockers in burn patients. Administration of propranolol (nonselective beta-antagonist) to burned children reduces the release of free fatty acids from adipose tissue and decreases hepatic triacylglycerol storage and fat accumulation (66, 67). In a randomized study of 25 children with severe burns, treatment with propranolol attenuated hypermetabolism and reversed muscle protein catabolism (68). In a retrospective study of adult burn patients, use of beta-blockers was associated with decreased mortality, wound infection rate, and wound healing time (69). Although these data strongly support the use of beta-blockers in burn patients, there are no large randomized studies looking at mortality and wound healing in burn patients. Nevertheless, many burn units use beta-blockers such as propranolol or metoprolol as the most effective catabolic treatment in burn patients.

Oxandrolone. Oxandrolone is an analog of testosterone, which is an anabolic hormone. It has been used to treat muscle wasting in various disease processes such as acquired immune deficiency syndrome (70). In a study of 14 severely burned children, oxandrolone improved muscle protein metabolism through enhanced protein synthesis efficiency (71). In adult burn patients, oxandrolone significantly decreased weight loss and net nitrogen loss and increased donor site wound healing compared with placebo controls (72). In a prospective randomized study of 81 patients, 10 mg of oxandrolone every 12 hrs was associated with decreased hospital stay (73). Although there was no hepatic insufficiency, a significant increase in hepatic transami-

nases was observed. The authors recommended monitoring liver function tests in patients treated with oxandrolone. Enthusiasm to use oxandrolone should also be tempered by the findings of potential increase in ventilatory days; in a study of trauma patients, oxandrolone was associated with increased ventilatory days (74). The authors suggested that oxandrolone may enhance collagen deposition in acute respiratory distress. Overall, it seems that oxandrolone may be beneficial in patients with large body surface area burns.

IMMUNOTHERAPY

Severe dermal burns are known to induce systemic inflammatory response syndrome, which is correlated with a high risk of end-organ failure (5, 75). Also severe burn injury is associated with increased risk of infection, sepsis, and immunosuppression (76, 77). Therefore, many investigators have studied the benefit of immune modulation in severely burned patients.

Immunonutrition. The immune-enhancing diets/agents include arginine, glutamine, omega-3 fatty acids, and antioxidants such as ascorbic acid (vitamin C) and α-tocopherol (vitamin E). Multiple studies looking at a combination diet of these agents have failed to demonstrate a benefit in critically ill patients (78, 79). The controversy regarding the use of immune-enhancing diets is ongoing, with many studies showing benefit and others showing no improvement in outcomes. For instance, whereas many previous studies support the use of glutamine supplementation, a recent study demonstrated that addition of glutamine to the enteral feed did not improve outcomes (80). Also, although many studies in burned animal models show improvement with a specific immune supplementation, there are no human studies to investigate the response in a clinical setting. As an example, in burned rats, supplementation with omega-3 fatty acids improved protein metabolism and attenuated muscle breakdown (81), but no large human trial has confirmed these finding in burned patients. Most researchers agree that an indiscriminate use of a combination formula immunonutrition diet in critically ill patients is not beneficial (78, 82). Therefore, a more selective approach is proposed, and there is a need for more clinical studies.

Use of high doses of ascorbic acid in experimental burn-injured sheep was associated with decreased edema and fluid requirement (83). In a randomized trial of critically ill surgical patients, a combination of ascorbic acid and α-tocopherol reduced the prevalence of organ failure and ICU length of stay (84). Early use of high-dose antioxidant therapy in the injured patients seems to be beneficial; however, further clinical trials are required to confirm this potential effect and better define the timing and the required dose (85, 86).

Recombinant Human Activated Protein C. Recombinant activated protein C (activated drotrecogin alfa) is the first agent approved by the Food and Drug Administration for treatment of severe sepsis. The Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial demonstrated a statistically significant relative risk reduction of 28-day mortality (87). *Post hoc* analyses of 532 possible surgical patients in the PROWESS trial demonstrated a favorable benefit/risk profile in surgical patients (88, 89). Increased risk of bleeding was similar to the medical patients, and there was no fatal bleeding in the surgical cohort. Twenty-four patients in this group were defined as having a skin surgical procedure within 30 days before the study. There was a 12-hr waiting period after an operation before starting the treatment. Other exclusion criteria for PROWESS were pregnancy, recent cerebrovascular accident, intracranial pathology, active bleeding, or anticipated need for surgery within the ensuing 96-hr period. It should also be noted that because 90% of the drug is eliminated within 2 hrs after discontinuation of infusion, stopping the treatment should rapidly stop drotrecogin alfa–induced bleeding (88). Although there are no published trials specifically in burn patients, based on available information, burn patients with severe sepsis who lack the exclusion criteria should be considered for recombinant activated protein C.

Topical Immunomodulation. Thermal injury induces dermal inflammatory and pro-apoptotic signaling. In the absence of inhalation injury, the burn wound is the inflammatory source triggering systemic inflammatory response via liberation of a plethora of potentially deleterious proinflammatory mediators and attraction/activation of neutrophils (90–92). Studies using rodent models of thermal injury have demonstrated that controlling the source of inflammation at the dermis may attenuate systemic inflammatory response and acute lung injury (93, 94). In these studies, topical application of p38-mitogen–activated protein kinase inhibitor to the burn wound decreased dermal inflammation, postburn skin apoptosis, systemic inflammatory response, and secondary pulmonary complications. Topical inflammatory modulation in severe burns is attractive because it can be readily used in patients who are already receiving topical antimicrobial agents, and it may avoid some of the systemic complications. However, currently there are no clinically approved topical immunomodulators for burn patients.

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