Research Article

ISSN 2689-1085

Journal of Pediatrics & Neonatology

Update in the Management of Burns in Children 2024

Ana María Navío Serrano[1,2*]

[1]*Specialist in Emergency Medicine as well as Critical Medicine, Spain.*

[2]*Member of AAEM, EuSEM, ALACEM.*

[*]Correspondence:
Ana María Navío Serrano, Specialist in Emergency Medicine as well as Critical Medicine, Spain.

Received: 04 Nov 2024; **Accepted:** 20 Dec 2024; **Published:** 29 Dec 2024

Citation: Ana María Navío Serrano.Update in the Management of Burns in Children 2024. J Pediatr Neonatal. 2024; 6(2): 1-9.

ABSTRACT

Findings of publications on burn´s management from a 2012 study in The Lancet showed that a burn size of more than 60% total body surface area burned (an increase from 40% a decade ago) is associated with risks and mortality. Similar data have been obtained in adults and elderly people who have been severely burned. Here is an update on recent and future developments in burn care in children.

Keywords

Pediatric burns, Burn management 2024, Advances in burn care, Burn injury treatment in children, Pediatric wound care.

Introduction

Major burn injury can be classified according to cause and depth of the burns. Every year more than half a million burn injuries happen in the USA [1]. Most of these injuries are not severe, although about 50 000 patients with burns still need admission and treatment at a burn centre or burn hospital. Because the effects of burns are disabling, substantial the specialty has grown in full swing which has greatly improved outcomes of patients with burns [2-4]. And that´s the main reason why specialised burn centres have shown up, and also, advances in resuscitation, protocols to follow up and specialised critical care, improved coverage of wounds and treatment of infections, better treatments for inhalation injury, and the burn-induced hypermetabolic response [4,5].

Another major advance are the currently initiatives by burn care providers to hold consensus conferences and implement specific definitions of disease processes in patients who have been severely burned, which will allow appropriate multicentre trials [6].

All these changes have substantially improved morbidity and mortality after burn injury. A recent study in The Lancet showed that the burn size associated with increased risk of mortality at a specialised centre increased from 40% total body surface area (TBSA) burned to more than 60% TBSA burned in the past decade or so [5].

The pathophysiological response to burn injury and the mortality of patients with burns are proportional to the extent of burn, following a sigmoid dose-response way, and these responses are not an all or none phenomenon beginning at 60%. The cutoff for these pathophysiological responses is around 30% TBSA burned in children (aged 0–18 years), 20% in adults (aged 18–65 years), and about 15% in elderly people (older than 65 years). Nevertheless, severe burns still damage almost every organ in the body, resulting in deep disable complications or even death [2,5-7]. Each year, almost 4000 cases of burns result in death from complications related to thermal injury [2,8,9]. The cause of deaths after suffering a burn can happen immediately after the injury or weeks later as a result of infection or sepsis, multisystem organ failure, or hypermetabolic catabolic responses [5,10].

In the last decade, the cause of death has thoroughly changed [10]. The major cause of death in patients who had been severely burned and admitted to a burn centre, ten years ago was anoxic brain injury, followed by sepsis and multiple organ failure. Nowadays, the major cause of death in burned paediatric patients is sepsis followed by multiple organ failure and anoxic brain injury [10]. This change in the cause of death needs a review of the basic understanding and treatment approaches to improve post-burn morbidity and mortality. Patient outcome and survival are directly related to the quality of the complex care that burn patients receive.

We can define three stages:

1. Initial care at the scene, pre-hospital care, and the early hospital phase: adequate and timely response, the best hospital

is not the nearest but the best prepared for treating these burns, resuscitation, and admission to a burn centre, escharotomies or fasciotomies, resuscitation, and treatment of inhalation injury.

2. After hospital phase: wound care including burn surgeries, infection control, maintenance of organ function, and attenuation of hyper metabolism.
3. Long-term phase: persistent hypermetabolism, reconstruction, and rehabilitation.

There are the standard and novel treatments in these topics:

Burn shock and resuscitation

The American Burn Association recommendations on the management of a patient with burns starts after emergency medical response teams are called and the patient is transported to a burn centre. The stabilization of the patient is primordial.

The uselessness in adults or elderly patients with burns is usually determined by the sum of age (years), burn size (%), and the presence or absence of inhalation injury (±17), with values of greater or equal to 140–150 being indicative of futility [11], but focusing on paediatric care there is no futility in children except in very rare instances. TBSA full-thickness burn. Once the decision to treat is made, the initial management and therapeutic goal is preservation of limbs and prevention of organ failure, which begins with well-established recognition of injury severity, first-care protocols, and surgical interventions. We need an accurate resuscitation [2,4,12-14].

The most frequent used formula is the Parkland Formula [13], which provides the total volume of crystalloid to be given over the first 24 h (4 mL/kg bodyweight/% TBSA burned) [12,14]. Although, recent data suggest that the Parkland Formula provides non correct estimates of fluid requirements in patients with large and deeper burns, inhalation injury, delays in resuscitation, alcohol or drug use, and electrical injury, resulting in inadequate and inappropriate resuscitation [12,15]. The catastrophic events associated with under-resuscitation include multiple organ failure and death. Over-resuscitation induces a fluid creep with its complications such as pulmonary oedema, pleural effusions, pericardial effusions, abdominal compartment syndrome, extremity compartment syndrome, and con version of burns to deeper wounds [12,13,16,17]. And over hydration in patients with burns increases the risk of acute respiratory distress syndrome, pneumonia, blood stream infections, multiple organ failure, and death [18].

The known endpoints of urine output (0·5–1 mL/kg bodyweight/h), mean arterial pressure (>65 mm Hg), normal base excess, and lactate concentrations are not always accurate and can be misleading [13,15,18]. No better physiological markers exist that enable adequate resuscitation, and so, these parameters remain the gold standard. New tools to improve and individualise resuscitation include use of thermal dilution catheters (PiCCO, Philips, UK) and computer-assessed closed the resuscitation [14,19-21]. There are not been fully established in clinical attendance.

Crystalloids have been compared with colloids or other means of resuscitation. So far, no large prospective randomised trial has been done to establish whether crystalloids are better than colloids in resuscitation but most burn surgeons use crystalloids (eg, Ringer's lactate) and add colloids (eg, albumin) [13,22]. Fresh frozen plasma, which is used in patients with trauma, is not given to patients with burns because experimental and clinical trials offer the efficacy of the fluid have not been done in children patients. Hypertonic saline showed some promise in small studies of patients with burns [2], but it does not improve outcome in patients with traumatic brain injury [23,24]. Resuscitation has profoundly evolved over the past two decades and will continue to do so.

We should keep an accurate oxygenation and treatment of inhalation injury. A marked proportion of fire-related deaths are not attributable to burn injury, but to the toxic effects of airborne combustion byproducts [15,25-27]. Recent studies suggest that between 20% and 30% of all severe burns are associated with inhalation injury and that between 25% and 50% of patients die if they need ventilator support for more than 1 week after burn [2,4,26]. Inhalation injury increases mortality 15,26,28 and in most cases, needs endotracheal intubation, which increases the incidence of pneumonia. Early detection of bronchopulmonary injury is crucial to improve survival. Clinical signs of inhalation injury are quite different vary [15,26], but when the patient has been exposed to smoke in an enclosed area and has physical findings of burns on the face, singed nasal vibrissae, bronchorrhea, sooty sputum, and wheezing or rales. The best practice to diagnose inhalation injury is bronchoscopy with the inhalation injury scale of Endorf and colleagues [25]. Patients with inhalation injury should not be intubated, nor be treated with prophylactic antibiotics. Standard care protocols for inhalation injury include bronchodilators (salbutamol), nebulised heparin, nebulised acetylcysteine, and for extreme mucosal oedema, racemic adrenaline [15,26]. The corticosteroid treatment in several animal and clinical studies, mortality increased with corticosteroid treatment, and bronchopneumonia was associated with more extensive abscess formation [2]. So that, the use of corticosteroids is contraindicated. Clinical conclusions in a recent trial confirmed findings from previous trials, showing that patients with inhalation injury have increased mortality and need longer intensive-care unit stays, hospitalisations, and time on ventilation. This trial was unique in that the investigators identified the effect of inhalation injury on genomic expression in peripheral blood leucocytes. The results showed that inhalation injury was associated with only subtle alterations in 169 probe sets corresponding to 115 genes, which encode proteins known to participate in cell cycle and transcriptional control. This finding was confirmed in a study in 2007,29 which showed that inhalation injury was not associated with major inflammatory changes, but with minimum distinct changes indicative of a slight immunosuppressive effect. However, we need more studies on this topic.

Burn wound closure establishes length of hospital stay, risk of infection, and ultimately survival, whereas failure to get the wounds closed results in death. Treatment strategies for superficial wounds

must be differentiated from treatment plans for deeper wounds. The most important factor in the improvement of patient outcome has been the implementation of early excision and grafting of burn wounds, which was first described by Jankovic in the 1970s [30]. If the source of stress and inflammation is removed early, surgical blood loss is reduced and survival is markedly improved [31-33]. The gold standard is to cover these wounds with autografts, either as a sheet or meshed skin with or without coverage of allograft (cadaver skin), or synthetic materials. Several new strategies will come in no longer future.

Partial-Thickness Burns

Partial-thickness burns can be superficial or deep burns

Superficial wounds usually heal between 7 and 14 days, whereas complete reepithelialisation of deep dermal burns can take up to 4–6 weeks, with scarring often resulting from the loss of dermis. A large variety of topical creams and agents are available for treatment, and many are silver based for anti-infective effects. Recent studies support the use of synthetic and biosynthetic membranes Biobrane (USA) established in 1982, and Suprathel (Germany) [34,35]. These membranes decrease the number of dressing changes, and the amount of pain drugs associated with these dressing changes. Several studies of Biobrane its efficacy for superficial burns [36,38]. Suprathel is a synthetic copolymer containing more than 70% DL-lactide. Findings from prospective randomised clinical studies of partial-thickness burns and split-thickness donor sites have shown that Suprathel is associated with less pain than other commercially available membranes, although wound healing times and long-term scar qualities are similar between this synthetic membrane and other membranes [34].

A novel approach to burn wound coverage is the use of biological membranes. Human amniotic membrane has a long history of use as a wound dressing but is a temporary wound covering, not as a skin transplant. Some of the benefits of amnion are that it is thin, pliable, adhesive, but not prone to sticking, and easily removed. In a recent prospective study of burns in children by Branski and colleagues [39], amnion showed outstanding wound healing properties and produced excellent long-term cosmetic results. The most interesting point of amniotic membrane is that it contains stem cells, which can be applied in various ways to create new treatment approaches. These approaches will be further investigated in prospective clinical trials.

Bioengineered approaches have also been tested for use in patients with partial-thickness burns. include keratinocyte-fibrin sealant sprays, fibrin sealant-containing growth factors, and cell suspensions. Full-thickness deep burns are treated by excision and coverage with autograft. As already mentioned, if complete autografting is not possible because the burn is large, allograft or other dermal or epidermal substitutions are needed. The oldest and best studied dermal substitute is Integra (Integra Life Sciences Corporation, Plainsboro, NJ, USA), which was developed by a team led by surgeon John Burke from the Massachusetts General Hospital (Boston, MA, USA) and by scientist Ionnas Yannas from the Massachusetts Institute of Technology (Cambridge, MA, USA) [40,41]. Integra is composed of bovine collagen and glycosaminoglycans, which allow fibrovascular ingrowth. And it is an effective method for burn surgeons and results in excellent cosmetic and functional outcomes [39,42]. Another dermal analogue available for the treatment of full-thickness burns is Alloderm (Life Cell Corporation, Branchburg, NJ, USA). Alloderm consists of cadaveric dermis devoid of cells and epithelial element. Dermal analogue is used in a similar way to other dermal analogues, and it has produced favourable results [43].

After the potential of dermal substitutes was recognised, the trend became to produce epithelial skin substitutes with or without a dermis. Cultured epithelial autografts became a surgical option in the management of patients with massive injuries involving more than 90% TBSA burned. Cultured epithelial autografts are created in vitro from autologous keratinocytes and as the name suggests, consist of keratinocytes. The promise of this technique has not been fully realised because of costs and the low quality of the neo-skin [44]. A possible improvement over cultured epithelial auto grafts is ReCell (Avita Medical, Royston, UK). This spray contains autologous keratinocytes, melanocytes, fibroblasts, and Langerhans cells that are harvested from a split-thickness biopsy. ReCell is sprayed onto the wound, which is usually grafted with widely meshed autograft. Positive findings from small animal studies and clinical trials need to be confirmed in larger randomised multicentre trials [45,46]. This ReCell trial is in progress and results are expected by 2014.

Another very promising bioengineered approach is the combination of autologous keratinocytes and Integra, known as cultured skin substitute. Boyce and col leagues first described this method in the 1990s [47-50]. The healing and take were very good, but cultured skin substitute had several issues: spotty pigmentation, a long production time, and high overall costs. Many researchers consider these matrices to be the best substitute for acellular human dermal matrices in the future [51,52]. Three acellular porcine dermal matrices are on the market: Permacol (Covidien, Ireland), Strattice (Kinetic Concepts, Kidlington, UK), and Xenoderm (Healthpoint Biotherapeutics, Fort Worth, TX, USA). The efficacy of these dermal matrices needs to be proven in clinical trials.

Stem cells represent a new hope in the management of burns. These cells play an important roll in wound healing, both locally and systemically, and several of the mechanisms underlying their actions in wound healing have been described. In human beings, stem cells can be found in adipose tissue, bone marrow, umbilical blood, and the blastocyst mass of embryos [53,54]. Stem cells can be used to regenerate dermis and expedite re-epithelialisation and would allow them to be transplanted with relative ease [55,56]. Stem cells present in the bone marrow migrate to tissues affected by injury and help the healing and regeneration process [54]. Embryonic human stem cells can be differentiated into keratinocytes in vitro and stratified into an epithelium that resembles human epidermis [57]. This graft can then be applied to open wounds on patients with burns as a temporary skin substitute while autograft or other permanent coverage means become available.

Facial Transplantation

There´s no evidence that standard treatment for severe facial burns offer improvements in function or scar outcome. These patients frequently become socially isolated, and many suffer from psychological disorders and phobias [58,59]. These patients usually need multiple reconstructive procedures under conditions in which minimal normal tissue (secondary to burns in other areas) is available. Facial transplantation in such patients can offer the possibility of improved quality of life. Following the lead of a surgical team in Amiens, France, in 2005 several groups in Europe, China, and the USA have successfully done composite tissue allotransplantation [60,61]. This transplantation of donor facial tissue allows for the best possible functional and aesthetic outcome. Antirejection drug regimens for solid organ transplantation are well established [58,59]. And this new treatment has unique psychological and ethical challenges that need to be addressed by a burn team [62]. Once the large challenges posed by facial transplantation are overcome, this will become a promising treatment for patients with serious facial burns [63].

Hypermetabolism

The hypermetabolic response is associated with severe alterations in glucose, lipid, and amino acid metabolism [3,7,64,65]. Hypermetabolism leads to severe catabolism and a protein breakdown in muscles and organs, leading to multiple organ dysfunction. So that, hypermetabolism, organ function, and survival, seem to be close.

The burn-induced hypermetabolic response that happens in an early phase (48 h after burn) and flow phase (>96–144 h after burn) is profound, extremely complex, and most likely induced by stress and inflammation [3,7,64,65]. and it has to do with increases in catecholamines, glucocorticoids, glucagon, and dopamine secretion [66-73]. Therefore, coagulation and complement cascades and cytokines, endotoxin, neutrophil-adherence complexes, reactive oxygen species, and nitric oxide can modulate the hypermetabolic response [74].

The hypermetabolic response seem to prolonged hypermetabolism with changes in glucose, lipid, and amino acid metabolism [7,64]. Recent studies show that burn-induced hypermetabolism seems to last a much longer time, as seen by a 3 year increase in energy requirements, catecholamines, urine cortisol, and serum cytokines, and impairment in glucose metabolism and insulin sensitivity [7,64,75]. These results underscore the importance of long-term follow-up and treatment of individuals with serious burns.

The hypermetabolic response involves glucose metabolism with insulin resistance and hyperglycaemia and lipid metabolism with increased lipolysis [76-83]. At first, the glucose level increases and so the lactate [84,85]. Hyperglycaemia in patients with burns is associated with increased frequency of infections, sepsis, incidence of pneumonia, catabolism, hypermetabolism, and most importantly, mortality [76-79,86,87]. Fatty liver is very common after burn injury and is associated with an increase in clinical morbidities and metabolic alterations. Findings from pathology analyses and spectroscopy studies have shown that children with burns have a three times to five times increase in hepatic triglycerides and it is associated with infection, sepsis, and poor outcome [80,88-92].

Treatment of The Hypermetabolic Response

Treatment options include pharmacological and non-pharmacological strategies [3].

The goal of nutritional support is to provide an adequate energy supply and the nutrients necessary to maintain organ function and survival [93]. Early adequate enteral nutrition relieves catabolism and improves outcomes but overfeeding in the form of excess calories or protein, or both, is in relation with hyperglycaemia, carbon dioxide retention, fatty infiltration of organs, and azotaemia The energy requirements of patients with burns are estimated with equations that incorporate body mass, age, and se which are based on patient-specific factors, caloric requirements can still be greatly overestimated, increasing the risk of overfeeding [96,97]. The adapted Toronto equation seems to be the best formula to calculate resting energy expenditure [98]. An adequate nutrition is essential and should be initiated within 12 h after injury [99].

Supplementation of single amino acids, especially alanine and glutamine, is controversial. After burn injury, glutamine is quickly depleted from serum and muscle [100,101]. However, this depletion happens mainly intracellularly, and effective delivery of glutamine to the cells is very difficult, but it seems to diminish the incidence of infection, length of hospital stay, and mortality [100,101]. A multicentre trial (REDOX; NCT00133978) is addressing this question, and the results are expected in the next 4–5 years; but the first data shows that, in critically ill patients, glutamine has no benefit in terms of outcomes [102]. And dietary components that have gained more recent attention are vitamins, micronutrients, and trace elements [103]. Replacement of vitamins reduces morbidity in patients with severe burns [104-110].

Non-Pharmacological Strategies

Early excision and grafting has substantially reduced basal energy expenditure, mortality, and costs [2,31-33111]. The early excision of burn wounds diminishes burn-induced inflammatory and stress responses, and in turn decreases hypermetabolism.

Providing patients with burns with physical therapy is a very important intervention that can ameliorate metabolic disruptions and prevent contractures of the burn wound. Progressive resistance exercises have been shown to promote muscle protein synthesis, increase body mass, strengthen muscles, and build endurance resistance exercises are safe for burned children who do not have exercise-related hyperpyrexia [96,97,112,113].

Outcome Measures

The goal of intensive burn care is to keep the patient alive, an outcome that is dependent on coverage of burn wounds, maintenance of organ function, control of infection and sepsis, and alleviation of hyper metabolism. The ability to predict patient outcomes, identify patients at risk, or even individualise patient

care is highly desirable. However, there are not predictors that would allow for any such identification Serum concentrations of interleukin 6, interleukin 8, granulocyte colony-stimulating factor, monocyte chemoattractant protein-1, C-reactive protein, glucose, insulin, blood urea nitrogen, creatinine, and bilirubin were higher in patients who did not survive. The patients also had a heightened hypermetabolic response accompanied by a greater frequency of sepsis and organ dysfunction [114-145]. These findings will enable the development of models that can predict patient outcome and treatments to improve patient outcomes. Another study on predicting burns mortality was done at the time; however, it focused on spline modelling [146]. Findings from this study showed that mortality could be reliably predicted by the combination of information about protein abundance with clinical covariates in a multi variate adaptive regression splines classifier. Finally, exciting results are expected from the Inflammation and the Host Response to Injury Collaborative Research programme by Glue Grant. More than 500 patients with burns have been enrolled in this study, and the genomic and proteomic changes in patients with various outcomes and morbidities are being analysed. Preliminary data suggest that patients who die from burns have a distinct genomic profile compared with survivors. Similarly, patients with sepsis, pneumonia, multiple organ failure, and non-healing wounds all have a different genomic signature, suggesting that the genome plays a central part in the determination of outcome of an individual. The results of this huge trial will be published over the next 3–4 years and could lead to novel treatment avenues for patients with severe burns. A substantial effort is underway to identify genomic and proteomic predictors of good and poor outcome. Such predictors will be indispensable for the development of individualised medicine, and we believe that the future of burn care is closely linked to understanding of these patient trajectories. Nevertheless, survival after burn injury depends on implementation of fundamental aspects of burn care including wound coverage, infection control, and reduction of the hypermetabolic response.

Conclusions

Burn injury triggers pathophysiological responses associated with harmful outcomes. New treatment strategies, like early excision and grafting, early and adequate nutrition, relieve of the hypermetabolic response, treatment of hyperglycaemia, and the catecholamine surge with use of β blockers, improved ventilation strategies, and exercise make better survival and outcomes in patients with severe burns, but we need big multicentre trials with protocolised care will improve morbidity and mortality after burn injury. Burn care providers cope with new challenges, mostly about quality of life and long-term outcomes in these patients. Recently, a system was developed by researchers from Shriners Hospital in Boston (MA, USA) to assess and quantify several details of functional recovery in convalescent patients with burns. This system sets up a previous trajectory of various functional indices to be identified, which ultimately enables researchers to identify changes needed to the rehabilitation programme. In summary, it is becoming more apparent that a burn is not over once burn wounds are healed, and that profound pathophysiological responses persist for a substantially longer time than previously thought [7,64]. Let's make a change in how we treat burns is needed.

References

1. WHO. The injury chart book: a graphical overview of the global burden of injuries. World Health Organization. 2002.
2. Herndon DN. Total burn care. Saunders Elsevier. 2007.
3. Herndon DN, Tompkins RG. Support of the metabolic response to burn injury. Lancet. 2004; 363: 1895-1902.
4. Jeschke MG, Kamolz L, Sjoeberg F, et al. Handbook of burns. Springer. 2012.
5. Kraft R, Herndon DN, Al-Mousawi AM, et al. Burn size and survival probability in paediatric patients in modern burn care: a prospective observational cohort study. Lancet. 2012; 379: 1013-1021.
6. Greenhalgh DG, Saffle JR, Holmes JH, et al. American Burn Association consensus conference to define sepsis and infection in burns. J Burn Care Res. 2007; 28: 776-790.
7. Jeschke MG, Chinkes DL, Finnerty CC, et al. Pathophysiologic response to severe burn injury. Ann Surg. 2008; 248: 387-401.
8. Peck MD. Epidemiology of burns throughout the world. Part I: Distribution and risk factors. Burns. 2011; 37: 1087-1100.
9. Peck MD. Epidemiology of burns throughout the World. Part II: intentional burns in adults. Burns. 2012; 38: 630-637.
10. Williams FN, Herndon DN, Hawkins HK, et al. The leading causes of death after burn injury in a single pediatric burn center. Crit Care. 2009; 13: 183.
11. Roberts G, Lloyd M, Parker M, et al. The Baux score is dead. Long live the Baux score: a 27-year retrospective cohort study of mortality at a regional burns service. J Trauma Acute Care Surg. 2012; 72: 251-256.
12. Greenhalgh DG. Burn resuscitation. J Burn Care Res. 2007; 28: 555-565.
13. Greenhalgh DG. Burn resuscitation: the results of the ISBI/ABA survey. Burns. 2010; 36: 176-182.
14. Kraft R, Herndon DN, Branski LK, et al. Optimized fluid management improves outcomes of pediatric burn patients. J Surg Res. 2013; 181: 121-128.
15. Latenser BA. Critical care of the burn patient: the first 48 hours. Crit Care Med. 2009; 37: 2819-2826.
16. Pruitt BA Jr. Protection from excessive resuscitation: "pushing he pendulum back". J Trauma. 2000; 49: 567-568.
17. Saffle JI. The phenomenon of "fluid creep" in acute burn resuscitation. J Burn Care Res. 2007; 28: 382-395.
18. Klein MB, Hayden D, Elson C, et al. The association between fluid administration and outcome following major burn: a multicenter study. Ann Surg. 2007; 245: 622-628.
19. Branski LK, Herndon DN, Byrd JF, et al. Transpulmonary thermodilution for hemodynamic measurements in severely burned children. Crit Care. 2011; 15: 118.

20. Salinas J, Chung KK, Mann EA, et al. Computerized decision support system improves fluid resuscitation following severe burns: an original study. Crit Care Med. 2011; 39: 2031-2038.
21. Salinas J, Drew G, Gallagher J, et al. Closed-loop and decision-assist resuscitation of burn patients. J Trauma. 2008; 64: 321-332.
22. Faraklas I, Lam U, Cochran A, et al. Colloid normalizes resuscitation ratio in pediatric burns. J Burn Care Res. 2011; 32: 91-97.
23. Belba MK, Petrela EY, Belba GP. Comparison of hypertonic vs isotonic fluids during resuscitation of severely burned patients. Am J Emerg Med. 2009; 27: 1091-1096.
24. Bulger EM, May S, Brasel KJ, et al. Out-of-hospital hypertonic resuscitation following severe traumatic brain injury: a randomized controlled trial. JAMA. 2010; 304: 1455-1464.
25. Endorf FW, Gamelli RL. Inhalation injury, pulmonary perturbations, and fluid resuscitation. J Burn Care Res. 2007; 28: 80-83.
26. Palmieri TL, Warner P, Mlcak RP, et al. Inhalation injury in children: a 10 year experience at Shriners Hospitals for Children. J Burn Care Res. 2009; 30: 206-208.
27. Sheridan RL, Hess D. Inhaled nitric oxide in inhalation injury. J Burn Care Res. 2009; 30: 162-164.
28. Erdman AR. Is hydroxocobalamin safe and effective for smoke inhalation? Searching for guidance in the haze. Ann Emerg Med. 2007; 49: 814-816.
29. Finnerty CC, Herndon DN, Jeschke MG. Inhalation injury in severely burned children does not augment the systemic inflammatory response. Crit Care. 2007; 11: 22.
30. Janzekovic Z. Early surgical treatment of the burned surface. Panminerva Med. 1972; 14: 228-232.
31. Desai MH, Herndon DN, Broemeling L, et al. Early burn wound excision significantly reduces blood loss. Ann Surg. 1990; 211: 753-759.
32. Herndon DN, Barrow RE, Rutan RL, et al. A comparison of conservative versus early excision. Therapies in severely burned patients. Ann Surg. 1989; 209: 547-552.
33. Herndon DN, Parks DH. Comparison of serial debridement and autografting and early massive excision with cadaver skin overlay in the treatment of large burns in children. J Trauma. 1986; 26: 149-152.
34. Rahmanian Schwarz A, Beiderwieden A, Willkomm LM, et al. A clinical evaluation of Biobrane(®) and Suprathel(®) in acute burns and reconstructive surgery. Burns. 2011; 37: 1343-1348.
35. Wood F, Martin L, Lewis D, et al. A prospective randomised clinical pilot study to compare the effectiveness of Biobrane® synthetic wound dressing, with or without autologous cell suspension, to the local standard treatment regimen in paediatric scald injuries. Burns. 2012; 38: 830-839.
36. Lesher AP, Curry RH, Evans J, et al. Effectiveness of Biobrane for treatment of partial-thickness burns in children. J Pediatr Surg. 2011; 46: 1759-1763.
37. Pham C, Greenwood J, Cleland H, et al. Bioengineered skin substitutes for the management of burns: a systematic review. Burns. 2007; 33: 946-957.
38. Barret JP, Dziewulski P, Ramzy PI, et al. Biobrane versus 1% silver sulfadiazine in second-degree pediatric burns. Plast Reconstr Surg. 2000; 105: 62-65.
39. Branski LK, Herndon DN, Celis MM, et al. Amnion in the treatment of pediatric partial-thickness facial burns. Burns. 2008; 34: 393-399.
40. Burke JF, Yannas IV, Quinby WC Jr, et al. Successful use of a physiologically acceptable artificial skin in the treatment of extensive burn injury. Ann Surg. 1981; 194: 413-428.
41. Yannas IV, Burke JF, Orgill DP, et al. Wound tissue can u
42. Heimbach DM, Warden GD, Luterman A, et al. Multicenter postapproval clinical trial of Integra dermal regeneration template for burn treatment. J Burn Care Rehabil. 2003; 24: 42-48.
43. Wainwright DJ, Bury SB. Acellular dermal matrix in the management of the burn patient. Aesthet Surg J. 2011; 31: 13-23.
44. Wood FM, Kolybaba ML, Allen P. The use of cultured epithelial autograft in the treatment of major burn injuries: a critical review of the literature. Burns. 2006; 32: 395-401.
45. Gravante G, Di Fede MC, Araco A, et al. A randomized trial comparing ReCell system of epidermal cells delivery versus classic skin grafts for the treatment of deep partial thickness burns. Burns. 2007; 33: 966-972.
46. Wood FM, Giles N, Stevenson A, et al. Characterisation of the cell suspension harvested from the dermal epidermal junction using a ReCell kit. Burns. 2012; 38: 44-51.
47. Boyce ST. Skin substitutes from cultured cells and collagen-GAG polymers. Med Biol Eng Comput. 1998; 36: 791-800.
48. Boyce ST, Kagan RJ, Meyer NA, et al. Cultured skin substitutes combined with Integra Artificial Skin to replace native skin autograft and allograft for the closure of excised full-thickness burns. J Burn Care Rehabil. 1999; 20: 453-461.
49. Drago H, Marín GH, Sturla F, et al. The next generation of burns treatment: intelligent films and matrix, controlled enzymatic debridement, and adult stem cells. Transplant Proc. 2010; 42: 345-349.
50. Ge L, Sun L, Chen J, et al. The viability change of pigskin in vitro. Burns. 2010; 36: 533-538
51. Branski LK, Gauglitz GG, Herndon DN, et al. A review of gene and stem cell therapy in cutaneous wound healing. Burns. 2009; 35: 171-180.
52. Wu Y, Zhao RC, Tredget EE. Concise review: bone marrow-derived stem/progenitor cells in cutaneous repair and regeneration. Stem Cells. 2010; 28: 905-915.
53. Kita K, Gauglitz GG, Phan TT, et al. Isolation and characterization of mesenchymal stem cells from the sub-amniotic human umbilical cord lining membrane. Stem Cells Dev. 2010; 19: 491-502.

54. Trojahn Kølle SF, Oliveri RS, Glovinski PV, et al. Importance of mesenchymal stem cells in autologous fat grafting: a systematic review of existing studies. J Plast Surg Hand Surg. 2012; 46: 59-68.
55. Guenou H, Nissan X, Larcher F, et al. Human embryonic stem-cell derivatives for full reconstruction of the pluristratified epidermis: a preclinical study. Lancet. 2009; 374: 1745-1753.
56. Pomahac B, Nowinski D, Diaz-Siso JR, et al. Face transplantation. Curr Probl Surg. 2011; 48: 293-357.
57. Pomahac B, Pribaz J, Eriksson E, et al. Three patients with full facial transplantation. N Engl J Med. 2012; 366: 715-722.
58. Devauchelle B, Badet L, Lengelé B, et al. First human face allograft: early report. Lancet. 2006; 368: 203-209.
59. Petruzzo P, Testelin S, Kanitakis J, et al. First human face transplantation: 5 years outcomes. Transplantation. 2012; 93: 236-240.
60. Soni CV, Barker JH, Pushpakumar SB, et al. Psychosocial considerations in facial transplantation. Burns. 2010; 36: 959-964.
61. Pushpakumar SB, Barker JH, Soni CV, et al. Clinical considerations in face transplantation. Burns. 2010; 36: 951-958.
62. Jeschke MG, Gauglitz GG, Kulp GA, et al. Long-term persistance of the pathophysiologic response to severe burn injury. PLoS One. 2011; 6: 21245.
63. McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. Crit Care Clin. 2001; 17: 107-124.
64. Coombes EJ, Batstone GF. Urine cortisol levels after burn injury. Burns. 1982; 8: 333-337.
65. Goodall M, Stone C, Haynes BW Jr. Urinary output of adrenaline and noradrenaline in severe thermal burns. Ann Surg. 1957; 145: 479-487.
66. Hart DW, Wolf SE, Chinkes DL, et al. Determinants of skeletal muscle catabolism after severe burn. Ann Surg. 2000; 232: 455-465.
67. Jeschke MG, Klein D, Herndon DN. Insulin treatment improves the systemic inflammatory reaction to severe trauma. Ann Surg. 2004; 239: 553-560.
68. Mlcak RP, Jeschke MG, Barrow RE, et al. The influence of age and gender on resting energy expenditure in severely burned children. Ann Surg. 2006; 244: 121-130.
69. Norbury WB, Herndon DN. Modulation of the hypermetabolic response after burn injury. Saunders Elsevier. 2007: 420-433.
70. Przkora R, Barrow RE, Jeschke MG, et al. Body composition changes with time in pediatric burn patients. J Trauma. 2006; 60: 968-971.
71. Przkora R, Herndon DN, Suman OE, et al. Beneficial effects of extended growth hormone treatment after hospital discharge in pediatric burn patients. Ann Surg. 2006; 243: 796-801.
72. Sheridan RL. A great constitutional disturbance. N Engl J Med. 2001; 345: 1271-1272.
73. Gauglitz GG, Herndon DN, Kulp GA, et al. Abnormal insulin sensitivity persists up to three years in pediatric patients post-burn. J Clin Endocrinol Metab. 2009; 94: 1656-1664.
74. Gore DC, Chinkes D, Heggers J, et al. Association of hyperglycemia with increased mortality after severe burn injury. J Trauma. 2001; 51: 540-544.
75. Gore DC, Chinkes DL, Hart DW, et al. Hyperglycemia exacerbates muscle protein catabolism in burn-injured patients. Crit Care Med. 2002; 30: 2438-2442.
76. Hemmila MR, Taddonio MA, Arbabi S, et al. Intensive insulin therapy is associated with reduced infectious complications in burn patients. Surgery. 2008; 144: 629-635.
77. Jeschke MG, Kulp GA, Kraft R, et al. Intensive insulin therapy in severely burned pediatric patients: a prospective randomized trial. Am J Respir Crit Care Med. 2010; 182: 351-359.
78. Barret JP, Jeschke MG, Herndon DN. Fatty infiltration of the liver in severely burned pediatric patients: autopsy findings and clinical implications. J Trauma. 2001; 51: 736-739.
79. Barrow RE, Wolfe RR, Dasu MR, et al. The use of beta-adrenergic blockade in preventing trauma-induced hepatomegaly. Ann Surg. 2006; 243: 115-120.
80. Martini WZ, Irtun O, Chinkes DL, et al. Alteration of hepatic fatty acid metabolism after burn injury in pigs. JPEN J Parenter Enteral Nutr. 2001; 25: 310-316.
81. Morio B, Irtun O, Herndon DN, et al. Propranolol decreases splanchnic triacylglycerol storage in burn patients receiving a high-carbohydrate diet. Ann Surg. 2002; 236: 218-225.
82. Gore DC, Ferrando A, Barnett J, et al. Influence of glucose kinetics on plasma lactate concentration and energy expenditure in severely burned patients. J Trauma. 2000; 49: 673-677.
83. Wolfe RR, Miller HI, Spitzer JJ. Glucose and lactate kinetics in burn shock. Am J Physiol. 1977; 232: 415-418.
84. Jeschke MG, Klein D, Thasler WE, et al. Insulin decreases inflammatory signal transcription factor expression in primary human liver cells after LPS challenge. Mol Med. 2008; 14: 11-19.
85. Pham TN, Warren AJ, Phan HH, et al. Impact of tight glycemic control in severely burned children. J Trauma. 2005; 59: 1148-1154.
86. Randle PJ, Garland PB, Hales CN, et al. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet. 1963; 1: 785-789.
87. Barrow RE, Hawkins HK, Aarsland A, et al. Identification of factors contributing to hepatomegaly in severely burned children. Shock. 2005; 24: 523-528.
88. Jeschke MG. The hepatic response to thermal injury: is the liver important for postburn outcomes? Mol Med. 2009; 15: 337-351.
89. Cree MG, Newcomer BR, Herndon DN, et al. PPAR-alpha agonism improves whole body and muscle mitochondrial fat oxidation, but does not alter intracellular fat concentrations in burn trauma children in a randomized controlled trial. Nutr Metab (Lond). 2007; 4: 9.

90. Cree MG, Newcomer BR, Katsanos CS, et al. Intramuscular and liver triglycerides are increased in the elderly. J Clin Endocrinol Metab. 2004; 89: 3864-3871.

91. Mochizuki H, Trocki O, Dominioni L, et al. Mechanism of prevention of postburn hypermetabolism and catabolism by early enteral feeding. Ann Surg. 1984; 200: 297-310.

92. Williams FN, Jeschke MG, Chinkes DL, et al. Modulation of the hypermetabolic response to trauma: temperature, nutrition, and drugs. J Am Coll Surg. 2009; 208: 489-502.

93. Saffle JR, Graves C. Nutritional support of the burned patient. Saunders Elsevier. 2007: 398-419.

94. Gore DC, Rutan RL, Hildreth M, et al. Comparison of resting energy expenditures and caloric intake in children with severe burns. J Burn Care Rehabil. 1990; 11: 400-404.

95. Suman OE, Mlcak RP, Chinkes DL, et al. Resting energy expenditure in severely burned children: analysis of agreement between indirect calorimetry and prediction equations using the Bland-Altman method. Burns. 2006; 32: 335-342.

96. Royall D, Fairholm L, Peters WJ, et al. Continuous measurement of energy expenditure in ventilated burn patients: an analysis. Crit Care Med. 1994; 22: 399-406.

97. Gore DC, Chinkes D, Sanford A, et al. Influence of fever on the hypermetabolic response in burn-injured children. Arch Surg. 2003; 138: 169-174.

98. Wischmeyer PE. The glutamine story: where are we now? Curr Opin Crit Care. 2006; 12: 142-148.

99. Wischmeyer PE, Lynch J, Liedel J, et al. Glutamine administration reduces Gram-negative bacteremia in severely burned patients: a prospective, randomized, double-blind trial versus isonitrogenous control. Crit Care Med. 2001; 29: 2075-2080.

100. Heyland D, Muscedere J, Wischmeyer PE, et al. A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med. 2013; 368: 1489-1497.

101. Gamliel Z, De Biasse MA, Demling RH. Essential microminerals and their response to burn injury. J Burn Care Rehabil. 1996; 17: 264-272.

102. Berger MM. Can oxidative damage be treated nutritionally? Clin Nutr. 2005; 24: 172-183.

103. Berger MM. Antioxidant micronutrients in major trauma and burns: evidence and practice. Nutr Clin Pract. 2006; 21: 438-449.

104. Berger MM, Baines M, Raffoul W, et al. Trace element supplementation after major burns modulates antioxidant status and clinical course by way of increased tissue trace element concentrations. Am J Clin Nutr. 2007; 85: 1293-1300.

105. Berger MM, Binnert C, Chiolero RL, et al. Trace element supplementation after major burns increases burned skin trace element concentrations and modulates local protein metabolism but not whole-body substrate metabolism. Am J Clin Nutr. 2007; 85: 1301-1306.

106. Berger MM, Eggimann P, Heyland DK, et al. Reduction of nosocomial pneumonia after major burns by trace element supplementation: aggregation of two randomised trials. Crit Care. 2006; 10: 153.

107. Berger MM, Shenkin A. Vitamins and trace elements: practical aspects of supplementation. Nutrition. 2006; 22: 952-955.

108. Berger MM, Shenkin A. Trace element requirements in critically ill burned patients. J Trace Elem Med Biol. 2007; 21: 44-48.

109. Solomon JR. Early surgical excision and grafting of burns including tangential excision. Prog Pediatr Surg. 1981; 14: 133-149.

110. Wilmore DW, Mason AD, Johnson DW, et al. Effect of ambient temperature on heat production and heat loss in burn patients. J Appl Physiol. 1975; 38: 593-597.

111. Suman OE, Spies RJ, Celis MM, et al. Effects of a 12-wk resistance exercise program on skeletal muscle strength in children with burn injuries. J Appl Physiol. 2001; 91: 1168-1175.

112. Herndon DN, Hawkins HK, Nguyen TT, et al. Characterization of growth hormone enhanced donor site healing in patients with large cutaneous burns. Ann Surg. 1995; 221: 649-656.

113. Jeschke MG, Herndon DN, Wolf SE, et al. Recombinant human growth hormone alters acute phase reactant proteins, cytokine expression, and liver morphology in burned rats. J Surg Res. 1999; 83: 122-129.

114. Jeschke MG, Chrysopoulo MT, Herndon DN, et al. Increased expression of insulin-like growth factor-I in serum and liver after recombinant human growth hormone administration in thermally injured rats. J Surg Res. 1999; 85: 171-177.

115. Branski LK, Herndon DN, Barrow RE, et al. Randomized controlled trial to determine the efficacy of long-term growth hormone treatment in severely burned children. Ann Surg. 2009; 250: 514-523.

116. Aili Low JF, Barrow RE, Mittendorfer B, et al. The effect of short-term growth hormone treatment on growth and energy expenditure in burned children. Burns. 2001; 27: 447-452.

117. Takala J, Ruokonen E, Webster NR, et al. Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med. 1999; 341: 785-792.

118. Demling R. Growth hormone therapy in critically ill patients. N Engl J Med. 1999; 341: 837-839.

119. Ramirez RJ, Wolf SE, Barrow RE, et al. Growth hormone treatment in pediatric burns: a safe therapeutic approach. Ann Surg. 1998; 228: 439-448.

120. Herndon DN, Ramzy PI, DebRoy MA, et al. Muscle protein catabolism after severe burn: effects of IGF-1/IGFBP-3 treatment. Ann Surg. 1999; 229: 713-720.

121. Cioffi WG, Gore DC, Rue LW, et al. Insulin-like growth factor-1 lowers protein oxidation in patients with thermal injury. Ann Surg. 1994; 220: 310-316.

122. Jeschke MG, Barrow RE, Herndon DN. Insulinlike growth factor I plus insulinlike growth factor binding protein 3 attenuates the proinflammatory acute phase response in severely burned children. Ann Surg. 2000; 231: 246-252.

123. Hart DW, Wolf SE, Ramzy PI, et al. Anabolic effects of oxandrolone after severe burn. Ann Surg. 2001; 233: 556-564.

124. Demling RH, DeSanti L. Oxandrolone induced lean mass gain during recovery from severe burns is maintained after discontinuation of the anabolic steroid. Burns. 2003; 29: 793-797.

125. Demling RH, Seigne P. Metabolic management of patients with severe burns. World J Surg. 2000; 24: 673-680.

126. Wolf SE, Edelman LS, Kemalyan N, et al. Effects of oxandrolone on outcome measures in the severely burned: a multicenter prospective randomized double-blind trial. J Burn Care Res. 2006; 27: 131-139.

127. Jeschke MG, Finnerty CC, Suman OE, et al. The effect of oxandrolone on the endocrinologic, inflammatory, and hypermetabolic responses during the acute phase postburn. Ann Surg. 2007; 246: 351-360.

128. Porro LJ, Herndon DN, Rodriguez NA, et al. Five-year outcomes after oxandrolone administration in severely burned children: a randomized clinical trial of safety and efficacy. J Am Coll Surg. 2012; 214: 489-502.

129. Przkora R, Herndon DN, Suman OE. The effects of oxandrolone and exercise on muscle mass and function in children with severe burns. Pediatrics. 2007; 119: 109-116.

130. Jeschke MG, Norbury WB, Finnerty CC, et al. Propranolol does not increase inflammation, sepsis, or infectious episodes in severely burned children. J Trauma. 2007; 62: 676-681.

131. Herndon DN, Hart DW, Wolf SE, et al. Reversal of catabolism by beta-blockade after severe burns. N Engl J Med. 2001; 345: 1223-1229.

132. Brooks NC, Song J, Boehning D, et al. Propranolol improves impaired hepatic phosphatidylinositol 3-kinase/akt signaling after burn injury. Mol Med. 2012; 18: 707-711.

133. Herndon DN, Rodriguez NA, Diaz EC, et al. Long-term propranolol use in severely burned pediatric patients: a randomized controlled study. Ann Surg. 2012; 256: 402-411.

134. Jeschke MG, Kraft R, Emdad F, et al. Glucose control in severely thermally injured pediatric patients: what glucose range should be the target? Ann Surg. 2010; 252: 521-527.

135. Pierre EJ, Barrow RE, Hawkins HK, et al. Effects of insulin on wound healing. J Trauma. 1998; 44: 342-345.

136. Klein D, Schubert T, Horch RE, et al. Insulin treatment improves hepatic morphology and function through modulation of hepatic signals after severe trauma. Ann Surg. 2004; 240: 340-349.

137. Ferrando AA, Chinkes DL, Wolf SE, et al. A submaximal dose of insulin promotes net skeletal muscle protein synthesis in patients with severe burns. Ann Surg. 1999; 229: 11-18.

138. Finfer S, Liu B, Chittock DR, et al. Hypoglycemia and risk of death in critically ill patients. N Engl J Med. 2012; 367: 1108-1118.

139. Moon RJ, Bascombe LA, Holt RI. The addition of metformin in type 1 diabetes improves insulin sensitivity, diabetic control, body composition and patient well-being. Diabetes Obes Metab. 2007; 9: 143-145.

140. Gore DC, Wolf SE, Herndon DN, et al. Metformin blunts stress-induced hyperglycemia after thermal injury. J Trauma. 2003; 54: 555-561.

141. Gore DC, Wolf SE, Sanford A, et al. Influence of metformin on glucose intolerance and muscle catabolism following severe burn injury. Ann Surg. 2005; 241: 334-342.

142. Mecott GA, Herndon DN, Kulp GA, et al. The use of exenatide in severely burned pediatric patients. Crit Care. 2010; 14: 153.

143. Jeschke MG, Gauglitz GG, Finnerty CC, et al. Survivors versus nonsurvivors postburn: differences in inflammatory and hypermetabolic trajectories. Ann Surg. 2014; 259: 814-823.

144. Finnerty CC, Qian WJ, Kaushal A, et al. Determination of burn patient outcome by large scale quantitative discovery proteomics. Crit Care Med. 2013; 41: 1421-1434.

145. Finnerty CC, Ju H, Spratt H, et al. Proteomics improves the prediction of burns mortality: results from regression spline modeling. Clin Transl Sci. 2012; 5: 243-249.

146. Ryan CM, Schneider JC, Kazis LE, et al. Benchmarks for multidimensional recovery after burn injury in young adults: The development, validation, and testing of the American Burn Association/Shriners Hospitals for Children Young Adult Burn Outcome Questionnaire. J Burn Care Res. 2013; 34: 121-142.