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Variables Influencing the Differential Host Response to Burns in Pediatric and Adult Patients

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Abstract

Burn injury is a significant source of morbidity and mortality in the pediatric population. Although 40,000 pediatric patients in the United States are admitted to the hospital with burn wounds annually, significant differences exist in the management and treatment of these patients, even among highly specialized burn centers. Some aspects of pediatric burn research, such as metabolic changes and nutritional support following burn injury have been studied extensively; however, in many aspects of burn care, pediatric research lags behind the study of adult populations. This review compares and contrasts a wide array of physiologic and immune responses between children and adults after burn injury. Such a review elucidates where robust research has been conducted, where adult research is applicable to pediatric patients, and where additional pediatric burn research needs to be conducted.

Keywords

pediatric burn; thermal injury; immunology; critical care

1. INTRODUCTION

Burn injury affects patients of all ages, but children (particularly young children) are affected disproportionately[1]. Some aspects of patient care differ significantly between adults and children based on differences in anatomy, physiology, and response to burn injury. Research of pediatric burn populations has increased significantly in the last several decades,

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but is still overshadowed by the amount of existing adult burn research. In some instances, it is appropriate to treat these patient populations similarly based on their underlying response; however, it is not uncommon for burn literature performed in adult populations to be applied to pediatric patients without considering potential physiologic differences.

It is the purpose of this review to gather many of the known differences between pediatric and adult burned patients across several aspects of care, emphasizing immunology and critical care physiology. The topic is vast and efforts have been made to succinctly establish the responses of children to burn injury before comparing and contrasting this with available information in the adult population, allowing for a broad overview from which to begin learning about a child's response to burn injury.

2. PATIENT CHARACTERISTICS

2.1 Epidemiology of Burns

One million children suffer burn injuries annually[2]. Thankfully, both hospitalization and mortality rates are decreasing due to a combination of prevention and advancements in care, but burn injury still remains the fourth leading cause of death of children in the United States[3]. The makeup of the pediatric burned population differs significantly from adults. The most common mechanism of injury in children is scald injury, followed by contact injury[4], whereas in adults, flame burn injuries are most common[5]. Flame burns are more likely to be deeper and inflict concordant inhalation injury, which results in fundamentally different management algorithms.

Among pediatric admissions, half of injuries occur in patients younger than four years of age[1]. While teenagers can be similar in body habitus and physiology to adults (interestingly, the most common mechanism for burns in adolescents is flame injury, as in adults), the same cannot be said for the majority of younger pediatric burn patients, necessitating completely different management in some respects. Regarding location of injury, two-thirds of pediatric burns take place at home[3,6], compared to half of adult burns (due to a significant proportion of injury at the workplace) [5]. Rates of intentional burn injury (abuse and self-harm) are also significantly higher in children (up to 20%) compared to adults (2%) [7,8].

Adults are more likely than children to have pre-existing medical conditions, which contributes to an overall higher mortality (4%) [9]. Comparatively, pediatric burn mortality is 0.9–2% [3,10], and overall mortality in this population has decreased by 50% in the twenty-first century[1]. High-volume pediatric burn centers (>200 pediatric burn admissions per year) have the lowest mortality and early transfer to these institutions shortens hospital stay[11,12]. Interestingly, burn center volume does not correlate with improved outcomes in adult burn patients, indicating that pediatric patients have unique responses to burn injury that benefit from treatment by specialists with an understanding of their pathophysiology[11].

Some epidemiologic commonalities exist between children and adult burn patients. Extremities are the most common region of the body involved regardless of age[13]. Males are more likely to suffer burn injury compared to females[6]. Burn care overall is becoming more centralized and more protocolized. The epidemiologic differences of these populations

reflect the need to treat them as distinct groups. The following discussion of anatomy will continue to highlight these differences.

2.2. Biologic Response to Burn Injury

2.2.1 Anatomic Differences—

Pediatric patients exhibit significant anatomic and physiologic differences compared to adults, which lessen as the child develops. These differences call for special considerations in pediatric groups, particularly for neonates and young children.

Anatomic Differences: Children have thinner skin with fewer dermal appendages which affects both their local tissue response to burns as well as consideration for skin grafting[14]. Because of this, they have an increased risk of deeper burns compared to adults[4]. Children have a higher body-surface-area-to-mass ratio, which predisposes them to hypothermia and results in higher relative fluid requirements per percent burn[14].

Children are also proportionally different: the '*rule of 9s*' is used to estimate burn wound size in adults, whereas in children, the Lund and Browder Chart is used (Figure 1). This dynamic chart allows for more accurate quantification of burns based on changes in development as children age. Young children have larger relative head sizes and smaller relative leg sizes. As in adults, however, the palm of the patient's hand still represents approximately 1% total body surface area (TBSA) burn size[4].

Concerning the pediatric airway, the smaller relative diameter, shorter trachea, anteriorly displaced pharynx, and larger tonsils result in an airway which is predisposed to obstruction secondary to edema (Figure 2) [4,15]. Children are also at greater risk for bronchospasm compared to adults after suffering inhalation injury[16]. Lung development in children occurs throughout the first eight years of life, so burn injury to the respiratory system in young children affects development[4]. The external anatomic differences are visually apparent, but the physiologic differences in response to burn injury between children and adults are just as profound.

2.2.2 Physiologic Differences

Initial Response: The initial physiologic response after a burn injury is similar between children and adults. Burn injury results in coagulation at the site of the burn, along with vasoconstriction and capillary thrombosis adjacent to the burned tissue[17]. Histamine is released from mast cells, which increases membrane and vascular permeability, while serotonin and thromboxane A2 are released systemically, acting to increase pulmonary vascular resistance and enact mesenteric vasoconstriction, respectively[2]. The tissue adjacent to the area of necrosis is threatened, and may convert to a deeper burn wound, particularly in the setting of hypotension, hypoxia, and infection[18].

The systemic effects of burn injury occur at approximately 30% TBSA involvement[18]. With respect to their cardiovascular system, infants have limited ability to modulate contractility and are unable to significantly increase their stroke volume[4]. They experience increased capillary permeability, reduced myocardial contractility, and selective vasoconstriction, while their respiratory system is subject to bronchoconstriction[18]. Relative blood volume is

increased in children. Children are also more likely to experience hyponatremia, particularly if they are less than one year of age due to urinary sodium losses because of a relative inability to concentrate urine[14,17]. Young children have less glycogen stores and therefore require supplemental dextrose as part of fluid administration. Children react differently to treatment plans and interventions and require different management systems for optimal outcomes during recovery.

Differences in Metabolism: Wolf et al. provides an extensive review of the physiology of patients during the initial hypermetabolic response to burn injury[2]. These changes include increases in energy expenditure, stroke volume, temperature, and heart rate fueled by protein and fat breakdown. Macroendocrine hormones are released systemically in large burns and include catecholamines, cortisol, and glucagon. This results in proteolysis, lipolysis, gluconeogenesis, and glycogenolysis, leading to a loss of lean body mass and body fat[19,20]. Catecholamines increase gluconeogenesis, glycogenolysis, lipolysis, acute phase reactant production, thermogenesis, and heart rate[21]. Catecholamines also, along with the systemic release of IL-1β and IL-6, increase the temperature set point in pediatric and adult patients through action on the hypothalamus[21]. Cortisol production leads to an increase in glucose mobilization and utilization, which results in hyperglycemia. Muscle tissue can decrease by 50% through breakdown of protein. Peripheral lipolysis leads to increased deposition of fat in the liver. The negative nitrogen balance which exists in burn patients is a combination of protein storage breakdown and decreased synthesis. This loss of muscle mass which particularly affects children can hinder rehabilitation efforts following acute resuscitation[22]. A review by Chan et al. focuses on additional differences between children and adults after burn injury, including limited relative energy reserves and a higher minute volume in children compared to adult patients[21]. Adults, on the other hand, have a relative delay in collagen synthesis which can manifest as delayed wound healing or impaired wound contraction, and their skin has decreased tensile strength compared to children[21].

Additional information regarding the hypermetabolic state and nutritional demands in pediatric and adult burn patients have previously been extensively reported and are beyond the scope of this review.

Alterations in Bone Formation: Reduced bone formation also occurs in patients and persists chronically, which leads to increased fracture risk following discharge[23]. These changes are multifactorial, and are influenced in part by glucocorticoids, inflammatory cytokines, hypoparathyroidism, and pervasive vitamin D deficiency, which is of special concern for pediatric burn patients suffering from suppressed osteoblast differentiation[24–26].

2.2.3 Growth and Development—Growth and development in children after burn injury are inherently different than in fully developed adults. In a problem unique to children, severe burn injury leads to growth arrest which can persist up to three years[27]. Alterations in energy and protein metabolism have been studied to the point where therapeutic interventions have been widely introduced into practice. The testosterone-analogue oxandrolone is associated with an increase in lean body mass and bone mineral density in pediatric patients with large burns[28]. Oxandrolone combined with propranolol shortens the period of growth arrest by 3 months in burned children[29]. Long-term use of

oxandrolone results in further increases in bone mineral content, bone density, and a greater height velocity which is more efficacious compared to short-term use[30].

With regards to spinal development, contractures can develop following significant full thickness burns to the trunk which lead to spinal deformities in growing children who may require operative intervention[31]. Growth and developmental changes in pediatric burn patients have been extensively evaluated, and the existence of multiple therapeutic interventions which are starting to generate long-term data is indicative of the depth of understanding with which other aspects of pediatric burn research should be conducted.

2.2.4 Acute and Chronic Immune Response to Pediatric Burn Injury—Burn injury results in changes in the host immune milieu and generates a durable inflammatory response as a result of the incipient tissue damage generated by thermal, chemical, or electrical injury[32]. While there remains a relative paucity of information in the pediatric population, investigations into the differences in host response in younger patients does demonstrate several key differences in both acute and chronic immunologic changes as a response to burn injury[32,33].

Local inflammatory response to burn injury: Burn injury results in compromise of the body's first line of host defense, its protective skin barrier. The result of this local barrier disruption leads to increased susceptibility to infectious microbes and imbalances in thermoregulation and metabolic homeostasis[34]. Local capillary damage, as well as local and systemic vasodilation, leads to tissue edema (with its associated detrimental effects on wound healing) as well as significant insensible fluid losses[34]. Local tissue damage increases permeability to invasion by infectious microbes, increasing susceptibility to host infection, which can be further compounded by alterations in production of antimicrobial proteins and peptides (APPs)[35].

Local tissue damage caused by burn injury generates a cascade of pro- and anti-inflammatory signaling, alterations in the local immune milieu, and longer-term transcriptomic changes in both the adaptive and innate immune systems which can persist for years after the initial insult[36,37]. The disruption of this first line of defense also results in an inherent reliance on cellular immune defense mechanisms to protect against invasive pathogens. We will review what is known regarding the local and systemic inflammatory response in pediatric burn patients, how these responses contribute to wound healing, as well as the acute, chronic, and pathologic immune changes that can be seen in this population.

Acute host immune response to burn injury: Following burn injury, protein degradation and catabolism are exacerbated by a systemic inflammatory response syndrome (SIRS). This pro-inflammatory environment is eventually attenuated by a compensatory anti-inflammatory response syndrome (CARS)[38]. The interplay between the pro- and anti-inflammatory responses in burn patients affects morbidity and mortality in the acute setting, and an imbalance in the two processes contributes to higher rates of sepsis, multisystem organ failure, and death (reviewed in: [38]). Elevated levels of IL-10 have been associated with increased rates of sepsis and death[39]. Conversely, an increase in pro-inflammatory cytokine production (i.e., IL-6, IL-8, IL-1β, and IFN-γ) is associated with worsening renal and

hepatic function in burned children, and has been associated with an increase in mortality in rodents[40]. Cytokine levels have also been analyzed as biomarkers for identification of burn patients at risk for poor outcome, with significant derangements of IL-8 associated with increased incidences of multisystem organ failure, sepsis, and mortality[41].

Disruptions in homeostasis in these children continue as they heal their burn wounds and become well enough for hospital discharge. The effects of excessive inflammation or inflammatory suppression, measured by overall cytokine production, has been studied in pediatric patients with varying burn sizes up to two months after burn injury[42]. Jeschke et al. measured seventeen serum cytokines associated with the inflammatory response in burned children, and found that all were significantly changed, particularly G-CSF, IL-6, IL-8, MCP-1, and MIB-1β[42]. The significant perturbations in cytokine expression months after injury suggest a component of persistent immune dysregulation and dysfunction which could ultimately result in a state of relative immunosuppression, potentially increasing susceptibility to infections and sepsis even after the initial hospitalization.

Acute adaptations in innate immunity after burn injury: In adult burn patients, most innate immune effector cells, including neutrophils, monocytes, macrophages, mast cells, and dendritic cells (DCs) are significantly dysregulated after burn injury[43]. An overall reduction of DCs has been found in adult burn patients with persistent DC depletion in septic burn patients[44]. Mast cells localize to areas of burn injury and release histamine, heparin, chymase, cathepsin G, and hydroxypeptiase A which promote wound healing[43]. The ability of monocytes to perform phagocytosis is disrupted following burn injury[45]. Macrophage hyperactivity following burns is associated with a pro-inflammatory state which disrupts immunologic homeostasis and predisposes patients to sepsis[46]. Neutrophils normally migrate to injured tissue and perform integral tasks for wound healing; however, in patients with burn injuries, neutrophils become less able to perform chemotaxis, phagocytosis, and generate reactive oxygen species[43]. Natural Killer (NK) cell function is compromised with effects proportional to burn size[32]. NK cells are particularly helpful in defending against viral infections; however, this ability may be lessened following burn injury[47]. Impaired NK cell capability persists at least 40 days following injury, indicating that immunologic changes in this patient population can become chronically deranged[48]. The data presented in this section is overwhelmingly representative of adult patients, revealing a need for increased immunologic research into pediatric-specific innate immune responses.

Adaptive immune response: Th1 vs Th2 phenotypes following burn injury: T helper type 1 (Th1) cells are CD4+ T cells which are overall pro-inflammatory and produce TNF-α, IFN-γ, IL-2, as well as other cytokines which regulate the cellular immune response[49]. This pathway primes the body to defend itself against pathogens, which is useful as the barrier function provided by the skin is compromised in burn patients. T helper type 2 (Th2) cells produce IL-4 and IL-10 and facilitate the humoral immune response[50]. This pathway dampens the inflammatory response through changes in cytokine production, macrophage suppression, and limiting of lymphocyte differentiation[51]. This decreases the inflammatory environment promoted by Th1 cells and promotes the development of a more durable

humoral response to infection. Burns may favor a Th1 response immediately following injury; however, the body rapidly adapts to a Th2-phenotypic response. This switch in phenotype increases susceptibility to sepsis[52]. It is unknown how long it takes for the anti-inflammatory response to normalize in burned pediatric patients. The re-establishment of homeostasis may be more gradual across this population than previously suspected. It is also possible that sub-segments of pediatric burn patients exist, with some patients experiencing more rapid recovery and others experiencing persistent immunosuppression. This could result in increased susceptibility to infection long after hospital discharge. More research is needed in this area to develop understanding of this issue.

Other immune cell responses: Cytotoxic T-cell activity is suppressed acutely following burn injury, with subsequent recovery and increased activity two weeks following insult[53]. This interplay between increased cytotoxic T-cell activity and Th2 cells dampening the inflammatory response is part of the complex balance between the pro- and anti-inflammatory states that exist following burn injury. Regulatory T cells become unregulated following burn trauma, which may lead to overall suppression of T cells and subsequent immunosuppression[54]. B cell immunoglobulin production can also be depressed following burn insult in the pediatric population[55].

The inflammatory cascade and subsequent alterations in the immune system of these patients represents a potential avenue for therapy. Murine studies have looked at propranolol and insulin in an attempt to attenuate derangements in homeostasis and rebalance the pro- and anti-inflammatory systems with promising results[56,57]. Differences in these patient populations and the long-term prevalence of indolent infections have not yet been adequately studied.

Hypertrophic burn scars: Burn scars complicate the long-term outcomes of many burn patients[58]. They can lead to perceived disfigurement and interfere with joint mobility, resulting in chronic contractures. Inflammation plays a key role in initial wound healing which can result in scarring. Finnerty et al. reviewed the foundation of wound healing, which occurs through inflammation, proliferation, and remodeling (Figure 3) [58]. During the inflammatory phase, fibrin clot establishes a scaffold while cytokines (i.e., PDGF, TGF-β, EGF, and IGF-1) recruit cells to the site of injury. During proliferation, fibroblasts first produce collagen and synthesize the eventual extracellular matrix, followed by differentiation into myofibroblasts which lead to wound contraction. In remodeling, the extracellular matrix is degraded and type III collagen is modified into type I collagen. Hypertrophic scars arise from excess dermal collagen accumulation, as well as aberrant alignment of collagen bundles[59]. Pathologic scars are more likely to form in the presence of inflammation, or if wound healing is delayed[60]. This is particularly important in a pediatric population that is still growing, especially given the complex interplay between scar appearance, pruritus, and effects on social normalization and school reintegration.

3. HOSPITALIZATION

3.1 Initial Treatment

3.1.1 Early Resuscitation—Resuscitation of acutely burned children sets the stage for their remaining hospitalization. Palmieri at al. reviewed principles of resuscitation in pediatric burn victims, which involves maintaining adequate organ perfusion while limiting excess fluid administration and pathologic edema[4]. General resuscitation of burned children differs from adults in airway management, fluid resuscitation, and choice of pharmacologic treatment[4]. Concerning airway management, endotracheal tube sizing is determined by the size child's nares, small finger diameter, or the formula *tube size = 4 + (age in years/4)* [61]. Surgical cricothyrotomy is contraindicated in children due to increased risk of stricture compared to adults. Children swallow air while crying and frequently require nasogastric tube placement[4].

Fluid resuscitation is enacted when children have greater than approximately 15% TBSA burns, as opposed to the threshold of 20% TBSA burns seen in most adult burn protocols[4]. Two commonly accepted formulas for initial fluid resuscitation in children include the Parkland formula[62]:

$$Volume\ (mL) = 4 \times weight\ (kg) \times \%TBSA\ burn$$

And the Galveston formula[2]:

$$Volume\ (mL) = 5000mL/m^2\ TBSA\ burn + 2000mL/m^2\ TBSA + albumin\ and\ D5W\ as\ needed.$$

Modern resuscitation requirements are tailored to the individual burn patient through assessment of end organ perfusion, regardless of age. Overestimation of burn size occurs in up to 60% of pediatric patients in varying stages of development[63]. This increases the likelihood of over-resuscitation and fluid creep, increasing risk of pulmonary complications and abdominal compartment syndrome[64]. Factors which increase the amount of required resuscitation include inhalation injury, deeper burns, and delay in resuscitation[17]. Delay in care is also associated with increased length of stay, complications, renal failure, and mortality[2,65].

Resuscitative fluids in children should be titrated to urine output as a marker of end-organ perfusion, which is similar to adults. The urine output goal is approximately 0.5–1 mL/kg/hr, which is an update from the prior practice of 1–2 mL/kg/hr[2,17,66]. Other methods for assessment of adequate resuscitation are not as commonly utilized. Lactated Ringer's solution is an acceptable resuscitative fluid in all burned patients; however, infants may develop hypoglycemia during administration due to limited relative glycogen stores, necessitating a concomitant dextrose infusion for calories[4]. Colloids were shown in a randomized controlled trial in pediatric burns to decrease crystalloid infusion amount, fluid creep, and hospital length of stay[67], however, other studies are equivocal, and the discussion of appropriate incorporation of colloids into resuscitation algorithms is ongoing within in the burn community[68]. Other methods of volume-reducing resuscitation have been largely

abandoned with respect to acute burns in children: dextran due to coagulopathy, plasma due to disease transmission, and hypertonic saline due to possible increases in mortality and renal failure[69,70]. Multiple studies have compared different resuscitation formulas and variations with hypertonic saline or colloids with varying results, so it is difficult to develop a standardized method of resuscitation. Resuscitation is now understood as a dynamic and individualized process in which fluid administration is titrated based on evidence of end-organ perfusion in the pediatric burn patient.

3.1.2 Inhalation injury—Although occurring less frequently than in the adult burn population, inhalation injury remains prevalent in the pediatric burn population with an incidence of approximately 30%[71]. Inhalation injury is a major predictor of morbidity and mortality in pediatric patients. While the mainstays of treatment for inhalation injury are similar, key physiologic and anatomic distinctions in children require special consideration.

As in adults, early management of inhalation injury in children begins with a thorough airway assessment and confirmation of a secure airway. Ensuring a stable airway is of particular importance in infants and toddlers as these patients are particularly vulnerable to airway compromise secondary to the edema precipitated by inhalation injury. Their comparatively shorter mandibles, prominent tongues, and larger adenoids, as well as shorter, narrower airways, contribute to more rapid airway obstruction and increased resistance to airflow following inhalation injury (reviewed in: [72]). Coupled with depressant medications administered for sedation and analgesia, these factors place children at a uniquely elevated risk of rapid airway collapse. A lower threshold for early intubation should be therefore be considered in pediatric patients presenting with significant facial burns or classical physical examination findings suggestive of inhalation injury, which include singed nares, soot in the airway, stridor, hoarseness, dysphonia, wheezing, or dyspnea[73]. It is important to avoid uncuffed endotracheal tubes in children to prevent air leaks, which is an update from prior practice[74].

Additionally, given the developmental and physical limitations that may hinder a pediatric patient from escaping from a burn source, special care must be taken to assess for potential cyanide or carbon monoxide toxicity, which can be seen in up to 5% of all pediatric inhalation injuries and requires prompt attention[75]. Aggressive pulmonary hygiene, secretion management, bronchodilation, and prevention of cast formation with nebulized heparin and N-acetylcysteine, as in adults, remain important adjuncts in managing the resulting mucosal edema, sloughing, and increased secretion burden[76].

Given increased rates of oxygen consumption and carbon dioxide production in infants and young children, along with increased susceptibility to developing pulmonary edema, tailoring of mechanical ventilation to allow for adequate gas exchange while minimizing ventilator-associated lung injury is a primary concern and often mandates higher respiratory rates compared to adults[77]. Beyond these basic principles, however, there remains no consensus on an optimal ventilation strategy for this age group even though a variety of strategies have been described, including conventional pressure and volume-controlled ventilatory modes, high-frequency oscillatory ventilation, and high tidal volume ventilation

strategies (reviewed in: [72]). Limited sample sizes and the retrospective nature of the existing literature underscores the need for more rigorous investigation in this domain.

3.1.3 Abdominal Compartment Syndrome—Patients undergoing resuscitation receive massive amounts of fluid in short time intervals. The subsequent leakage of fluid into the interstitium and resulting edema places the patient at risk of developing intra-abdominal hypertension that can progress to secondary abdominal compartment syndrome[4,78]. The volume of resuscitation which increases risk of abdominal compartment syndrome is 250mL/kg in the first day after burn injury, which is known as the Ivy Index[79]. A systematic review of burned adults and children observed the prevalence of intra-abdominal hypertension to be 65–75%, while the prevalence of abdominal compartment syndrome was 4–16%[80]. Increased abdominal pressures lead to physiologic changes, including compression of the cardiopulmonary system via the diaphragm and reduced venous return through external compression. Renal perfusion is decreased which lowers urine output; similarly, mesenteric flow is decreased[81,82]. Systemic inflammation during this time also can exacerbate injury[82].

Intra-abdominal hypertension: Abdominal hypertension is defined as pressure within the abdominal cavity >12mmHg and is commonly measured with bladder pressures. Airway peak pressures can also be monitored. This diagnosis is associated with increased risk of kidney injury[82]. If intra-abdominal hypertension is diagnosed, steps such as escharotomy, paralysis, diuresis, and drain placement can be attempted in an attempt to halt progression to compartment syndrome[81]. Prior to laparotomy, percutaneous drain placement is recommended, particularly in children[83].

Abdominal compartment syndrome: Abdominal compartment syndrome is defined as intra-abdominal pressures >20mmHg with evidence of end organ dysfunction. Children are more susceptible to the development of abdominal compartment syndrome in part due to their relatively smaller abdominal cavity[84]. Abdominal compartment syndrome is associated with increased mortality[82]. If non-surgical treatments fail, definitive treatment of abdominal compartment syndrome is laparotomy, in which a functional fascial release allows decompression. If decompressive laparotomy is performed, the goal should be closure as soon as appropriate; a study of adults and children showed 100% survival for patients closed within two days[85]. Mortality due to abdominal compartment syndrome in burn injury is 40–100% and is similar between children and adults[86,87].

Associated complications include extremity compartment syndrome, pulmonary edema, and decreased perfusion of burn wounds through fluid creep[64]. Overall, abdominal compartment syndrome has not been studied enough in children to determine differences in parameters compared to adults. The available literature consists largely of case reports. It is possible that abdominal compartment syndrome occurs at a lower set point in children compared to adults, but this needs to be studied at a larger scale to determine how best to manage these patients[84].

3.1.4 Escharotomy—Circumferential eschar secondary to burn injury is non-pliable and affects nerves and circulation in the extremities, as well as ventilation in the thorax[88].

Surgical release of eschar can lead to improvements in circulation and prevention of development of compartment syndrome. Escharotomies involve longitudinal incisions on lateral and medial aspects of extremities and digits, with a slightly more varied pattern across the thorax[89]. Crossing joint spaces in the extremities allows for adequate decompression. Children have different fat distribution compared to adults, so staying in the proper plane can be challenging[4].

Following recovery from burn injuries, many children may require scar revision of their escharotomy sites. Escharotomies are, by necessity, full thickness injuries, but subsequent operative debridement in children may not require excision to subcutaneous fat, leading to an uneven appearance with differential healing. This process is also occurring in the setting of continued limb growth in pediatric patients[89]. As scar formation in children with burns has been strongly linked to social anxiety and negative self-image, it is important to be deliberate with the decision to perform an escharotomy, with care taken to minimize the number of incisions needed to effectively decompress the affected compartment[89]. Alternative methods include enzymatic debridement that is gaining popularity in the United States but is actively undergoing clinical trials and will not be covered in this review.

3.2 Critical Care Topics

3.2.1 Sepsis—Infection is the leading cause of morbidity and mortality in children and adults with large burns following the initial resuscitative period[90]. Adults are likely more susceptible to mortality from burn sepsis compared to children (50–84% compared to 55%) [91]. Dysregulation in the immune response of the burn patient renders them susceptible to infection. The most common type of infection in pediatric patients is urinary tract infection, followed by pneumonia, burn wound infection, and central catheter infection[92]. Risk factors include burn depth, inhalation injury, indwelling devices, and TBSA burn size[93,94]. Identification of infection and sepsis is particularly challenging in burned patients in the setting of an active systemic inflammatory response. The American Burn Association held a Consensus Conference to define sepsis and infection, and differentiated between child and adult parameters given their state of development and differing physiology based on age[95].

Physiologically, adult and pediatric patients respond to sepsis differently. Pediatric patient mortality is related to a low cardiac output leading to inadequate oxygen delivery[96]. Adults, on the other hand, develop decreased systemic vascular resistance with myocardial dysfunction, along with an inability to perform efficient oxygen extraction[96]. Most cases of sepsis in non-healed patients are related to burn wounds[97]. Early burn sepsis is typically caused by gram-positive bacteria, whereas late burn sepsis during hospitalization is caused by gram-negative bacterial and fungal infections[98]. If the burn wound is identified as the infectious source, then treatment involves excision[97]. Topical and enteral/parenteral antibiotics are also administered. Once a source is identified, it is important to de-escalate antibiotics therapy with a goal of decreasing rates of antibiotic resistance. As a child has many decades still to live, antibiotic stewardship is of particular importance. If vasopressor medications are required due to septic shock, then epinephrine is preferred in pediatric patients, which differs from norepinephrine recommended for adults[96].

3.2.2 Multi-organ Dysfunction—Organ system dysfunction is a major source of morbidity during the hospitalization of the pediatric burn patient. Failure of multiple organ systems significantly increases risk of mortality[99]. These patients require careful assessment and multi-disciplinary management. The most common type of organ failure in pediatric burn patients is respiratory failure, followed by cardiac, hepatic, and renal failure[99]. Multisystem organ failure occurs in one in five pediatric burn patients in the ICU, and is correlated with increasing burn size, age, full-thickness burns, and inhalation injury. These patients suffer from an increased number of surgeries and major infections, longer lengths of stay, and higher rates of sepsis and mortality (41% vs 2%) [99]. Sepsis is nearly always associated with multisystem organ failure[100]. However, compared to adults, children have a lower mortality rate after developing multisystem organ failure, in part due to pre-existing comorbidities in adult patients[101]. Studies in adults differ with respect to incidence of failure by organ system, but generally were similar in that respiratory failure was most common overall[100,102].

Extracorporeal membrane oxygenation (ECMO) is a process that allows for externalized oxygenation of blood in the event of cardiopulmonary failure. Pooling various studies, the ECMO survival rate for pediatric burn patients is 52–77%[103,104] whereas adult burn patient survival on ECMO was lower overall at 28–52%[105,106].

3.2.3 Acute Kidney Injury—Pediatric patients are susceptible to acute kidney injury (AKI) at varying points in their hospitalization. Under-resuscitation can lead to pre-renal kidney failure. Drug-induced intrinsic kidney injury can also occur. Renal perfusion can be affected by blood loss, operations, or septic shock. Kidneys can also become injured secondary to rhabdomyolysis. Regardless of the etiology, acute kidney injury offers important principles in the care of the burned pediatric patient.

The incidence of AKI in pediatric burns admitted to the intensive care unit is 30–50% compared to 21–40% in adults, with risk factors including %TBSA burn, multiple surgical operations, sepsis, compartment syndrome, and increased ICU and hospital lengths of stay[107–109]. Mortality of burned children with AKI is increased six-fold compared to children without AKI, but is still half the mortality rate of adults with AKI[107,110,111].

Incidence of kidney injury over time is bimodal, with early kidney largely associated with resuscitation and volume status, and late kidney injury occurring as a result of sepsis[112]. During sepsis, bacteria cause cytokine release which leads to endothelial damage and vasoplegia with resulting hypotension, which inflicts injury on renal tubules and vasculature[112]. Interestingly, late kidney injury in children is associated with increased mortality, whereas in adults, prognosis for early renal failure is worse than late renal failure[107,113].

3.2.4 Blood Products—Blood products and burn patients are inexorably linked. Tangential excision and skin grafting causes significant blood loss despite meticulous attempts at hemostasis, and patients with major burns often receive greater than one blood volume worth of transfusions during their hospitalization[114]. Blood loss in pediatric burn operations is estimated at 3% per %TBSA excised and 2% per %TBSA grafted[115] compared

to 9% per %TBSA excised and grafted in adults[116]. Blood loss due to surgery is coupled with baseline anemia in the setting of critical illness, along with wounds, iron deficiency, hemodilution, and coagulopathy[117].

Now that stewardship of blood products is at the forefront of research and hospital policy, it is pertinent to examine distinctions between pediatric and adult burns. In 1999, the TRICC Trial showed an effective restrictive transfusion strategy in the ICU, but excluded burn patients[118]. Voigt et al. performed a prospective randomized control trial in pediatric burns looking at a restrictive transfusion goal of 7mg/dL (prior standard 10mg/dL), and found that patients received 50% less blood in the OR and 25% outside of the OR with comparable outcomes[119]. The Transfusion Requirement in Burn Care Evaluation (TRIBE) trial also looked at a restrictive strategy in burn patients, with the restrictive group receiving one-third less blood transfusions with similar mortality, organ dysfunction, and infectious complications[114]. This restrictive strategy also decreased ventilator days and ICU days[120]. The use of whole blood in pediatric burns will soon become more widely studied as use of whole blood in trauma scenarios is regaining popularity.

4. CONCLUSION

Pediatric burn victims are a unique population with physiology that differs from adults. Advances in the study of hypermetabolism led to pharmacologic treatment in children that improved their quality of care. Research into the pediatric response to burn injury is critical to the understanding of the mechanisms involved in pediatric burns. This is followed by the development of tailored interventions specific to this population which allow for improved recovery. Impressive advancements have been made in reducing pediatric burn mortality. It is now time to take the next steps in the progression of research in pediatric burns.

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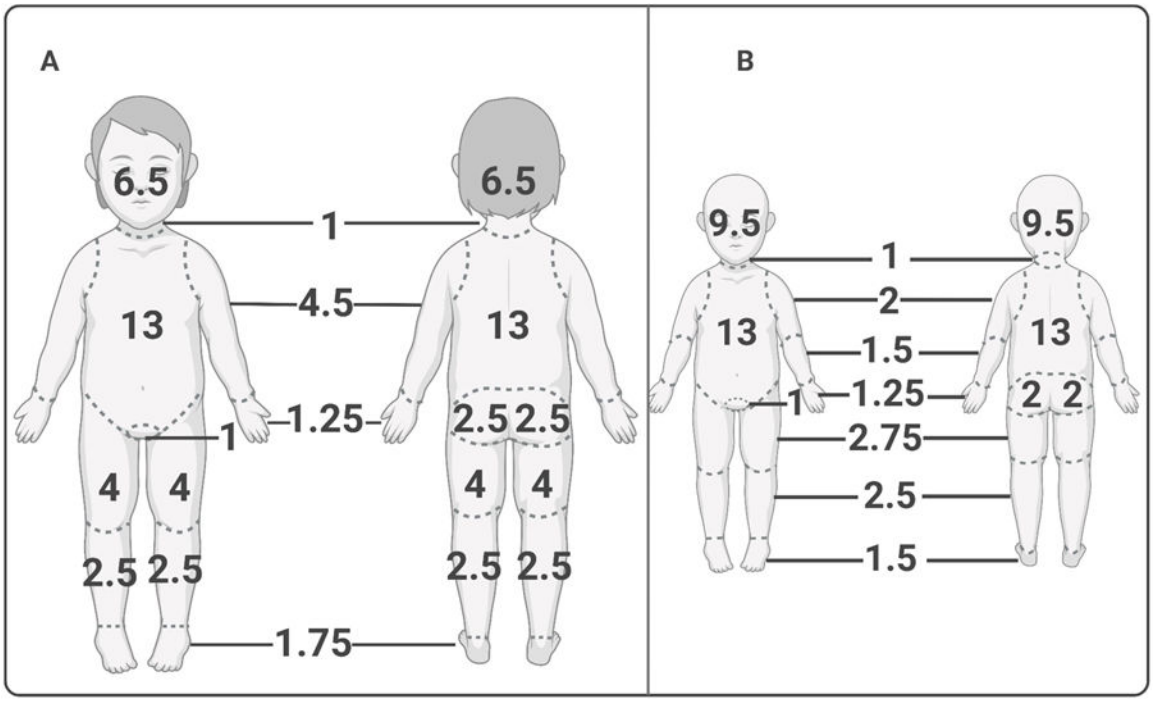

Figure 1.

Lund and Browder burn estimation chart for child (A) and infant (B). Developmental differences in body proportion preclude the use of the traditional “rule of 9’s” used to estimate total body surface area (TBSA) percentages, as in adults. The Lund and Browder chart reflects the increased head to body ratio seen in young children (A) and especially infants (B), as well as their smaller relative limb sizes. Despite these differences in body part proportions, the hand still represents approximately 1% TBSA in both children and infants. Created with biorender.com.

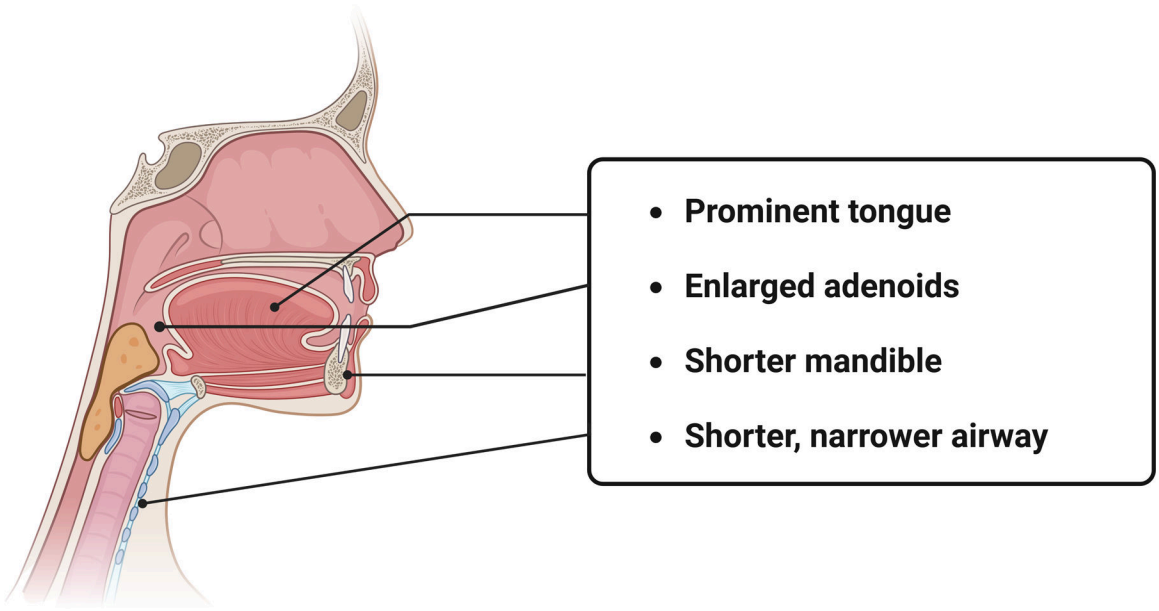

Figure 2.

Anatomy of the pediatric airway. Special consideration should be taken in assessment and securing of the pediatric airway, as several anatomic distinctions predispose this population to more rapid airway compromise. The upper airway is characterized by a shorter mandible length, a more prominent tongue as well as proportionally larger tonsils and adenoids. In cases of inhalation injury, the resulting edema can lead to rapid airway obstruction and collapse. The naturally shorter, narrower airway seen in this age group additionally contributes to increased airway resistance. Created with biorender.com.

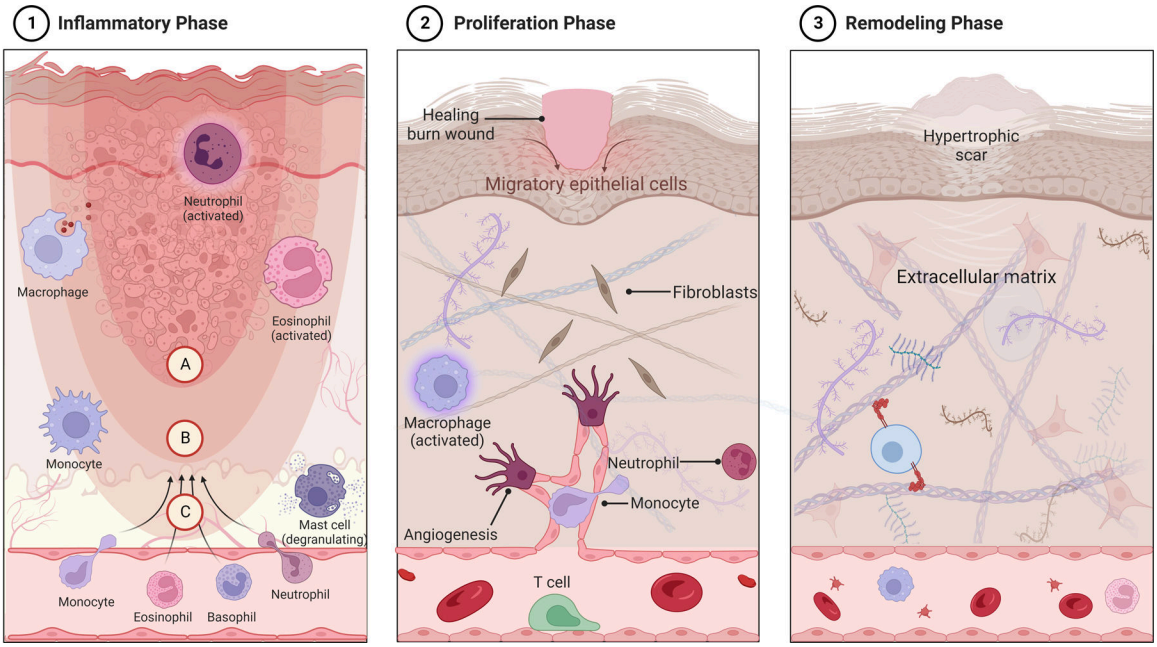

Figure 3.

Immune response to burn injury and phases of healing. Burns, similar to other wounds, undergo three major phases of healing: the acute inflammatory phase (1), the proliferation phase (2), and the remodeling, or maturation phase (3). The inciting burn injury results in coagulation necrosis of the epidermis and underlying tissues, depending on burn depth, leading to degeneration of extracellular proteins and cell lysis (1). This is most prominent in the coagulation zone of injury (A), where irreversible tissue damage occurs. The zone of stasis (B), characterized by reduced tissue perfusion, remains potentially salvageable with assurance of adequate resuscitation and tissue perfusion, whereas the hyperemic zone (C) is characterized by increased tissue perfusion with increased vasodilation and capillary leak, contributing to tissue edema. Mast cells, neutrophils and monocytes are some of the first immune cells to migrate to the site of burn injury, followed by macrophages as initial neutrophil numbers decline (1). The initial cellular innate response triggers increased pro-inflammatory signaling, and their phagocytic activity helps with clearance of denatured proteins, dead tissue and toxins. The proliferative phase begins within hours of initial burn injury, with migration of keratinocytes from surrounding skin appendages. Growth and angiogenic factors released by responding immune cells trigger fibroblast activation and neovascularization within the dermis (2). In the final phase, or remodeling phase, increased collagen and elastin deposition strengthens the extracellular matrix, which is remodeled into scar tissue (3). Fibroblasts obtain a myofibroblast phenotype that contributes to scar contraction. In cases of prolonged wound healing (i.e., deep partial or full thickness burns allowed to heal by secondary intention), and in cases of excess dermal collagen accumulation, hypertrophic scars may develop (3). Created with biorender.com.