

## Trauma, Sepsis, Innate, Adaptive Immunity and Inflammation

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### ABSTRACT

**Introduction:** This review paper covered, trauma, sepsis, innate, adaptive immunity and inflammation along with anxiety, and depression that occurs both in women with asthma, traumatic children and adult patients.

**Materials and Methods:** This is a review article. Areas covered include immune function changes, which can lead to both trauma and pro-inflammatory activation known as systemic inflammation response syndrome (SIRS) related to sepsis.

**Results:** Stress management in trauma is based upon the notion that stress causes an immune imbalance in susceptible individuals.

**Conclusion:** Various topics covered were the neuroimmune system, oxidative stress, inflammation, and adaptive immunity, the role of NF-kappa B related to inflammation, cytokines, procalcitonin related to sepsis.

### KEYWORDS

Trauma; Sepsis; Innate; Adaptive Immunity; Inflammation.

### INTRODUCTION

#### Trauma

Moog et al addressed the hypothesis that intergenerational transmission may begin during intrauterine life via the effect of maternal childhood trauma exposure on placental-fetal stress physiology, specifically placental corticotrophin-releasing hormone pCRH. Maternal childhood trauma (CT+) was significantly associated with pCRH production [1].

#### Renal Trauma

Blunt childhood renal trauma with pre-existing renal abnormalities was reviewed by Dahlstrom [2]. The injuries may appear to be disproportionate in relation to the severity of the trauma history, and recognition of both the underlying disease process as well as the manifestations of acute trauma is important [2]. This author stated that the kidneys are the most commonly injured genitourinary organ in children following blunt abdominal trauma. In conclusion, recognition of both the underlying disease process as well as the manifes-

tations of acute trauma is important; therefore, the author presented a pictorial essay of traumatized kidneys in children with pre-existing renal abnormalities.

A recent study by Mahajan et al compared the test characteristics of clinician suspicion with a derived clinical prediction rule to identify children at risk of intra-abdominal injuries [3]. The higher specificity of clinician suspicion, however, did not translate into clinical practice, as clinicians frequently obtained abdominal CT scans in patients they considered very low risk. If validated, this prediction rule can assist in clinical decision-making around abdominal CT use in children with blunt torso trauma [3].

A toddler with a closed head injury six days prior to admission, recently diagnosed with post-concussive syndrome to the emergency department with complaint of uncontrollable shaking of the head and extremities [4]. Wu et al presented this case, accompanied by a video of the patient, to help the emergency physician recognize this rare and often misdiag-

nosed syndrome [4]. A recent study developed by Connelly et al for simple clinical tool to predict the risk of developing VTE in pediatric trauma patients based on a model created using a large national database and was internally validated [5]. The clinical tool required external validation and provided an initial step toward the development of the specific VTE protocols for pediatric trauma patients.

### Impact of trauma on neutrophil function

Hazel dine discussed the emerging role of the neutrophil, the first line of defense against microbial challenge in the initiation and propagation of trauma and the inflammatory response [6].

The author discussed the consequence of traumatic injury and immune dysregulation, where an initial increase in immune activity is followed by a period of immune depression, the latter leaving hospitalized trauma patients at an increased risk of nosocomial infections.

Trauma-induced changes in neutrophil biology are linked to the development of post-traumatic complications as multiple organ failure and the acute respiratory distress syndrome. This is an area of research within the field of trauma immunology that is gaining considerable interest. Manipulation of neutrophil function is a means by which to potentially improve patient outcomes. Hietbrink et al discussed polymorph nuclear phagocytes as the main effector-cells of the innate immune system that are involved in organ failure, controlled by cytokines, complement and specific tissue signals [7].

Tsukamoto et al described the pathophysiological approach for MOF after trauma studied so far and also introduced the prospects of this issue for the future [8].

Following major trauma, IL-6 release correlates with injury severity, complications, and mortality

Interleukin-10 (IL-10) can markedly inhibit lymphocyte and phagocytic functions, essential for an adequate immune response [8]. In this early study by Neidhardt, patients who died from injury or developed posttraumatic complications and had elevated IL-10 levels in comparison with injured patients with an uneventful posttraumatic course [9]. Trauma causes an enhanced release of IL-10 and increase IL-10 levels are significantly related to posttraumatic complications.

A significant increase of both IL-6 and IL-10 concentrations was found by Stensballe with a significant correlation between the Injury Severity Score and the levels of both IL-6 and IL-10 at all sampling points [10]. Serum concentrations of IL-6 and IL-10 were significantly higher in patients not surviving 30 days.

### IL-6, obesity and trauma

There is a relationship between obesity and trauma. Among children admitted after trauma, increased BMI percentile is associated with increased risk of death and potentially preventable complications. These findings by Witt et al suggest

that obese children may require different management than nonobese counterparts to prevent complications [11].

Peters et al considered the possibility that systemic inflammation, which arises in subgroups of obese and older patients, increases the severity of asthma [12].

Pati provided a state of the science review regarding cellular therapies in trauma and critical care, and to provide a foundation from which the potential of this emerging field can be harnessed to mitigate outcomes in critically ill trauma patients [13]. A study by Tulloch et al was reported in the Journal of Intensive Care Medicine [14]. All adult patients who triggered a Code Sepsis in the emergency department (ED) were included. Hospital mortality and hospital loss of stay of sepsis are similar to those reported in other observational studies. This study confirmed a decline in the mortality of sepsis predicted by earlier longitudinal studies [14]. This was a prospective observational study conducted at a university-affiliated urban teaching hospital and level-1 trauma and burn center. All adult patients who triggered a Code Sepsis in the emergency department (ED) between January 2010 and December 2011 were included. One hundred eighty four patients presented with a verified sepsis syndrome and triggered a Code Sepsis in the ED during the studied time period [14]. The decline in mortality was most likely due to the initiation of the Code.

A study by Oral et al reviewed adverse childhood experiences (ACEs) related to short- and long-term negative physical and mental health consequences among children and adults. Studies of the last three decades on ACEs and traumatic stress have emphasized their impact and the importance of preventing and addressing trauma across all service systems utilizing universal systemic approaches [15].

### Sepsis

Scott et al stated SIRS with proven infection is referred to as sepsis. SIRS vital signs are common among medical pediatric patients presenting to an ED, and critical illness is rare [16]. The majority of patients with SIRS vital signs were discharged without IV therapy and without readmission. However, SIRS vital sign criteria did not identify the majority of patients with mortality or need for critical care. Singer reviewed The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [17]. These updated definitions and clinical criteria should replace previous definitions, offer greater consistency for epidemiologic studies and clinical trials, and facilitate earlier recognition and more timely management of patients with sepsis or at risk of developing sepsis [17].

Prediction models for neonatal health care-associated sepsis was studied by Verstraete [18]. The author stated prediction models should be considered as guidance rather than an absolute indicator because they all have limited diagnostic accuracy. Lethargy and pallor and/or mottling for all neonates as

well as apnea and/or bradycardia and poor peripheral perfusion for very low birth weight neonates are the most powerful clinical signs. However, the clinical context of the neonate should always be considered.

Optimal amikacin dosing regimens for the empirical treatment of Gram-negative bacterial sepsis in pediatric patients with burn injuries was studied by Yu [19]. This study aimed to develop optimal amikacin dosing regimens for the empirical treatment of Gram-negative bacterial sepsis in pediatric patients with burn injuries. A pharmacodynamics (PD) target in which the peak concentration ( $C_{max}$ ) is  $\geq 8$  times the minimum inhibitory concentration (MIC) ( $C_{max}/MIC \geq 8$ ) is reflective of optimal bactericidal activity and has been used to predict clinical outcomes. Amikacin pharmacokinetics are altered in patients with burn injuries, including a significant increase in clearance and volume of distribution. In simulations, increased doses led to improved PD target attainment rates. In simulations, increased doses ( $\geq 25$  mg/kg) led to improved a pharmacodynamic target attainment rates. Further clinical evaluation of this proposed dosing regimen is warranted to assess clinical and microbiological outcomes in pediatric patients with burn wound sepsis [19].

Children ages 2-17 years presenting to the PICU or ED with sepsis or for procedural sedation to the ED were enrolled by Mickiewicz [20] who stated the first steps in goal-directed therapy for sepsis are early diagnosis followed by appropriate triage. These steps are usually left to the physician's judgment, as there is no accepted biomarker available. He aimed to determine biomarker phenotypes that differentiate children with sepsis who require intensive care from those who do not. The study was a prospective, observational nested cohort study at two pediatric intensive care units (PICUs) and one pediatric emergency department (ED). Children ages 2-17 years presenting to the PICU or ED with sepsis or presenting for procedural sedation to the ED were enrolled. He used the judgment of regional pediatric ED and PICU attending physicians as the standard to determine triage location (PICU or ED). This study performed metabolic and inflammatory protein mediator profiling with serum and plasma samples followed by multivariate statistical analysis combining metabolic and protein mediator profiling improved the model differentiating PICU sepsis from ED sepsis with accuracy of 0.87. Separation of PICU sepsis or ED sepsis from ED controls was even more accurate [20].

### Procalcitonin

Septic children aged between 28 days and 14 years were divided into sepsis (SG;  $n = 46$ ) and septic shock (SSG;  $n = 41$ ) groups. CRP and procalcitonin (PCT) were measured at admission. At T0, there was a higher frequency of SSG with PCT  $>10$  compared to SG [SSG: 30  $>$  SG: 14 (30.4%); Procalcitonin was

significantly higher for SSG patients with higher PCT than SG patients. PCT was better than CRP for diagnosing sepsis and septic shock [21].

Zhou et al investigated the diagnostic value of the IL-8 in neonatal sepsis and an important cause of morbidity and mortality [22]. Eight studies in 548 neonates were evaluated. IL-8 had a moderate accuracy for the diagnosis of neonatal sepsis and IL-8 is a helpful biomarker for early diagnosis, but one should combine the results with clinical symptoms, laboratory and microbial results [22].

Sepsis is a major cause of morbidity and mortality. Without specific antisepsis therapies, management relies on infection control and organ support. Reidel stated it is necessary to not only recognize the importance of critical clinical awareness and thorough physical patient examination, but to understand traditional microbiological methods to facilitate an early diagnosis and goal-directed therapy in patients suspected of sepsis [23]. He stated sepsis and severe sepsis cause significant morbidity and mortality among populations worldwide; the rapid diagnosis poses a considerable challenge to physicians in acute care settings. An ideal biomarker should allow, with high diagnostic accuracy, for an early and rapid recognition of sepsis. Mat-Nor et al recruited consecutively adult patients with SIRS admitted to an intensive care unit and divided them into sepsis and noninfectious SIRS based on clinical assessment with or without positive cultures [24]. Future studies should include clinical indices, for example, SOFA score, for prognostic evaluation of biomarkers [24].

In surgical intensive care unit (SICU) patients, it is difficult to distinguish bacterial sepsis from other causes of SIRS and biomarkers have proven useful to identify the presence of bacterial infection. In this paper by Carr et al the combination of alpha 2 macroglobulin and procalcitonin discriminated bacterial sepsis from other SIRS among SICU patients with suspected sepsis [25].

Shiferaw showed that procalcitonin is a more accurate diagnostic parameter for sepsis and a predictor of mortality [26]. Procalcitonin is a more reliable marker than other biomarkers including C-reactive protein, Interleukins and lactate levels. The patient's immune surveillance could fail to eliminate the pathogen, allowing it to spread and there is a pro-inflammatory mediator release with, inappropriate activation. 27. Serum procalcitonin levels are elevated in patients with bacterial infections [27].

This recent review article by Frieri discussed chronic rhinosinusitis, epidemiology, pathogenesis, innate adaptive immunology, nuclear factor-kappa B related to inflammation, sepsis, complement, reactive oxygen species, asthma, sinusitis, elderly pathogenesis, oxidative stress, depression, seasonal variation, and other topics related to trauma and stress [28].

A literature search was conducted from several articles, prospective studies, recent reviews and earlier reports [28]. A synergistic relationship develops between activation of the innate immune system and the loss of organ barrier functions. Asthma and sepsis, a common condition encountered in hospital environments remains an important cause of death at intensive care units. This earlier article by Frieri reviewed current concepts of airway inflammation with a special emphasis on the epithelium, and airway remodelling [29]. Future therapeutic strategies may involve these targets and a synergistic approach in preventing remodeling in selected asthmatic patients [29].

With the increase in the global prevalence of obesity, there is a parallel rise in the proportion of obese patients admitted to the ICU's, referred for major surgery or requiring long-term non-invasive ventilation (NIV) at home for chronic respiratory failure. Ducharme et al addressed other aspects of care of obese patients, including antibiotic dosing and catheter-related infections [30].

Obstructive sleep apnea is associated with rhinitis and asthma and is highly prevalent in the general population worldwide, especially in its mild form [31]. Clinical manifestations correlate poorly with disease severity measured by the apnea-hypopnea index (AHI), which complicates diagnosis. Full polysomnography might be more appropriate to assess suspected mild cases because limited ambulatory diagnostic systems are least accurate in mild disease. Treatment options in mild obstructive sleep apnea includes continuous positive airway pressure (CPAP) and oral appliance therapy, in addition to positional therapy and weight reduction.

Although a small number of asthmatics have severe disease, and it accounts for the majority of morbidity related to the illness. Severe asthma comprises a heterogeneous group of phenotypes. Targeted treatments for these phenotypes represent a major advancement in the management of severe asthma [32]. Omalizumab, improves asthma control in patients with a predominant allergic phenotype. Monoclonal antibodies targeted to interleukin 4 $\alpha$  and interleukin 5 have shown substantial benefit in patients with the eosinophilic asthma phenotype; so too have monoclonal antibodies targeted to interleukin 13 in patients with a type 2 allergic phenotype.32Triverdi et al discussed bronchial thermoplasty, a new technique to decrease airway smooth muscle mass, improves symptoms and reduces exacerbations in patients with severe uncontrolled asthma and also in chronic airflow obstruction phenotype [33].

Korevaar discussed eosinophilic airway inflammation is associated with increased corticosteroid responsiveness in asthma, but direct airway sampling methods are invasive or laborious. Mini-

mally invasive markers for airway eosinophilia could present an alternative method, but estimates of their accuracy vary [34].

Raedler et al discussed early life influences are crucial for the development of distinct childhood asthma phenotypes, Besides genetics, epigenetics and environmental factors have an effect on innate and adaptive immune regulatory networks. Crucial determining factors for complex immune regulation and barrier function include family history of atopy, respiratory infections, microbiome, and nutrition [35].

### Neuroendocrine Immunology

Frieri et al reviewed concepts of neuroendocrine immunology, dysregulation, stress, and treatment of allergic and autoimmune diseases. Neuroendocrine hormones triggered during stress may lead to immune dysregulation resulting in atopic, autoimmune diseases or decreased host defense [36].

The stress response and induction of a dysregulation of cytokine balance can trigger the hypothalamic-pituitary-adrenal axis and sympathetic nervous system that contains chiefly adrenergic fibers and tends to depress secretion, decrease the tone and contractility of smooth muscle, and increase heart rate [37].

The stress response and induction of a dysregulation of cytokine balance can trigger the hypothalamic-pituitary-adrenal axis and sympathetic nervous system [37]. The sympathetic nervous system is the part of the autonomic nervous system that contains chiefly adrenergic fibers and tends to depress secretion, decrease the tone and contractility of smooth muscle, and increase heart rate. The sympathetic nervous system and the parasympathetic nervous system constitute the autonomic nervous system The multiple roles of Th2 cells in maintaining allergic inflammation and altering the balance between Th1 and Th2 responses are important mechanisms for allergic inflammation, and can also relate to stress [37]. Mast cells are important in allergic diseases and asthma, but they also have a role in trauma and neuroinflammation and contribute to end-organ damage after trauma related to complement activation [37].

Sun et al reviewed substance P at the neuro-immune crosstalk in the modulation of inflammation, asthma and antimicrobial host defense [38].

It modulates a variety of inflammatory processes, including asthma, trauma, systemic inflammatory response syndrome or sepsis [38].

### Oxidative Stress

Oxidative stress occurs in asthma as a result of inflammation but also from environmental exposure to air pollution which can occur in children [39]. The specific localization of antioxidants in the lung suggests the important role of oxidative stress, and therapeutic interventions that decrease exposure to the

environment [39].

### Pediatric Stress

A recent paper by Ramirez et al reviewed evidence-based parent programs to support children hospitalized after a traumatic injury using qualitative methods in evaluation and intervention and completed a formative research study in 2012 to develop a new program of psychological first aid and held focus groups [40]. A recent pilot study by Biffi assessed the complexity of need and difficulty with obtaining services at the time of transition from inpatient to outpatient care for pediatric rehabilitation [41]. Current developments on the implementation of trauma informed care in a variety of service systems call for the surveillance of trauma, resiliency and health impact.

This article by Oral et al reviewed childhood adversity and traumatic toxic stress and presented epidemiologic data on the prevalence of adverse childhood experiences and their physical and mental health impacts, and discussed intervention modalities for prevention [42].

Schonfeld provided practical suggestions on how to identify common adjustment difficulties in children in the aftermath of a disaster and to promote effective coping strategies as well as any associated bereavement and secondary stressors [43]. This information can serve as a guide to pediatricians as they offer anticipatory guidance to families or consultation to schools, child care centers for mental health.

### Posttraumatic Stress Disorder

Arcaya examined associations between PTSD symptoms and self-reported post disaster asthma attacks [44]. A 1-point increase in the IES-R avoidance score, which corresponded to one standard deviation change in this sample, was associated with double the odds of reporting an asthma attack or episode since a hurricane

### Multiple Organ Failure

Cellular stress is increased in adipose tissue of obese individuals. However, the relation between cellular stress and weight regain is unclear. Roumans observed increased adipose tissue cellular stress of participants regaining weight compared to participants maintaining weight loss [45]. These present findings indicate that the risk for weight regain is related to expression changes of distinct sets of stress-related genes during the first four weeks after returning to energy balance, and during dietary intervention. Further research is required to investigate the mechanistic significance of these findings and find targets for preventing weight regain

Arslan stated a large proportion of splenic injuries recover with conservative therapy and some of the advantages of conservative therapy includes short hospitalization time, less need for blood transfusion, and less morbidity and mortality [46].

### Innate and Adaptive Immunity

Altered innate and adaptive immunity, tissue remodeling, and/or effects of microorganisms may play a role in the development of chronic rhinosinusitis (CRS) with nasal polyps (CRSwNPs) and its pathophysiology [47].

A down-regulation of epithelial innate immunity by maladaptive T helper cell type 2 (Th2) tissue inflammation was reviewed by Hamilos and established in patients with recalcitrant CRSwNPs. Maladaptive Th2 inflammation in the sinuses might negatively affect innate immunity in sinus mucosa by down-regulating Toll-like receptor 9 expression and a defect in innate immunity most commonly found in patients with refractory CRS is a decrease in lactoferrin levels in sinus secretions [48].

Foreman reviewed the adaptive immune responses that characterize *Staphylococcus aureus* biofilm-associated CRS, the relative contributions of staphylococcal superantigens, and *S. aureus* biofilms in the inflammatory makeup of this disease has been documented. *S. aureus* biofilms are associated with eosinophilic inflammation, across the spectrum of CRS, on the back of a Th2 skewing of the host's adaptive immune response, elevated eosinophilic cationic protein, and IL-5 [49]. Madeo reviewed bacterial biofilms in CRS, *S. aureus* biofilms, and exotoxins that act as superantigens have been implicated in playing an important pathological role in the incidence, maintenance, and ongoing burden of CRS. A better understanding of the interplay between bacterial factors, host factors, and the environment will facilitate better management of this disease [50].

Adaptive humoral immune responses in the airways are mediated by B cells and plasma cells that express highly evolved and specific receptors and produce immunoglobulins of most isotypes. A recent review by Kato et al discussed the generation, differentiation, signaling, activation, and recruitment pathways of B cells and plasma cells, with special emphasis on unique characteristics of subsets of these cells functioning within the respiratory system [51]. Antigen exposure in the upper or lower airways can also drive expansion of B-lineage cells in the airway mucosal tissue and lead to the formation of inducible lymphoid follicles or aggregates that can mediate local immunity or disease, generation, differentiation, signaling, activation, and recruitment pathways of B cells and plasma cells, with special emphasis on unique characteristics of subsets of these cells functioning within the respiratory system [51].

### CONCLUSION

The take home message of this paper is that stress, management related to asthma, trauma, sepsis, inflammation, anxiety, and depression can occur both in women with asthma, traumatic children and adult patients. Immune function

changes can lead to both trauma and pro-inflammatory activation known as SIRS related to sepsis. Stress management in trauma is based upon the notion that stress causes an immune imbalance in susceptible individuals. The neuroimmune system is important as well as oxidative stress, inflammation, innate immunity, the role of NF-kappa B related to inflammation, cytokines, and procalcitonin related to sepsis.

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