

# Biomarkers, Trauma, and Sepsis in Pediatrics: A Review

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## Abstract

**Context:** There is a logical connection with biomarkers, trauma, and sepsis. This review paper provides new information and clinical practice implications. Biomarkers are very important especially in pediatrics. Procalcitonin and other biomarkers are helpful in identifying neonatal sepsis, defense mechanisms of the immune system. Pediatric trauma and sepsis is very important both in infants and in children. Stress management both in trauma is based upon the notion that stress causes an immune imbalance in susceptible individuals.

**Evidence Acquisition:** Data sources included studies indexed in PubMed, a meta-analysis, predictive values, research strategies, and quality assessments. A recent paper by one of the authors stated marked increase in serum procalcitonin during the course of a septic process often indicates an exacerbation of the illness, and a decreasing level is a sign of improvement. A review of epidemiologic studies on pediatric soccer patients was also addressed. Keywords for searching included biomarkers, immunity, trauma, and sepsis.

**Results:** Of 50 reviewed articles, 34 eligible articles were selected including biomarkers, predictive values for procalcitonin, identifying children at risk for intra-abdominal injuries, blunt trauma, and epidemiology, a meta-analysis. Of neonatal associated sepsis, the NF-kappa B pathway by inflammatory stimuli in human neutrophils, predictive value of gelsolin for the outcomes of preterm neonates, a meta-analysis interleukin-8 for neonatal sepsis diagnosis.

**Conclusions:** Biomarkers are very important especially in pediatrics. Procalcitonin and other biomarkers are helpful in identifying neonatal sepsis, defense mechanisms, and physiological functions of the immune system. Pediatric trauma and sepsis is very important both in infants and in children. Various topics were covered such as biomarkers, trauma, sepsis, inflammation, innate immunity, role of neutrophils and IL-8, reactive oxygen species, neonatal hypoxia, NF-kappa B related to inflammation. These topics are clearly linked and are very important for pediatricians, pulmonologists, and immunologists in academic centers and in practice.

**Keywords:** Biomarkers, Immunity, Trauma, Sepsis

## 1. Context

Biomarkers are very important especially in pediatrics. Procalcitonin and other biomarkers are helpful in identifying neonatal sepsis, defense mechanisms of the immune system. Pediatric trauma and sepsis is very important both in infants and in children. Stress management both in trauma is based upon the notion that stress causes an immune imbalance in susceptible individuals. The aim of this review article is to understand pediatric biomarkers, trauma, sepsis, activation of the immune system, loss of barrier functions, genetics, physical agents and mediators related to trauma and sepsis in children. These factors are clearly linked. Sepsis is a common hospital condition and an important cause of death in the pediatric intensive care units.

## 2. Evidence Acquisition

Data sources included studies indexed in PubMed, a meta-analysis, predictive values, research strategies, and quality assessments. A recent paper by one of the authors

stated marked increase in serum procalcitonin during the course of a septic process often indicates an exacerbation of the illness, and a decreasing level is a sign of improvement. A review of epidemiologic studies on pediatric soccer patients was also addressed. Keywords for searching included biomarkers, immunity, trauma, and sepsis. The qualitative results from searching in international databases are presented here.

## 3. Results

### 3.1. Biomarkers

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 (1). This review covered sepsis and the systemic immune response, cytokines and procalcitonin, innate immunity and reactive oxygen species related to sepsis

and the impact on neutrophil function (1). Procalcitonin has been proved to be superior biomarker in terms of diagnosing sepsis, predicting clinical outcome and the use of procalcitonin should be considered within the context of the clinical workup including patient history, physical examination and other laboratory findings. Integrating use of procalcitonin into pediatric practice in the early golden hours of sepsis diagnosis and antibiotic stewardship program would be beneficial (1).

Early diagnosis of neonatal sepsis followed by appropriate treatment decreases mortality and morbidity in infants. The aim of this study was to assess the role of procalcitonin (PCT) as a marker in the early diagnosis of neonatal sepsis where 35 neonates with early onset sepsis were included in the study (2). Another 35 healthy neonates with no clinical or biological data of infection were included as a control group. Subjects were subjected to a thorough history taking and routine laboratory investigations. Serum PCT and C-reactive protein (CRP) levels were determined by enzyme-linked immunosorbent assay (ELISA). Mean levels of PCT and CRP in neonates with sepsis were significantly higher than in the control group ( $P = 0.0001$ ) (2). There was a moderate, but significant, positive correlation between PCT and C-reactive protein and an insignificant correlation between procalcitonin and total leukocytic count among the neonates with sepsis. In addition, procalcitonin had high sensitivity, specificity, a high positive predictive value, and a high negative predictive value. Procalcitonin showed higher sensitivity when compared to CRP. Procalcitonin is a sensitive, independent, and useful biomarker in comparison to CRP in early diagnosis of neonatal sepsis (2).

Dynamics of procalcitonin level was studied in 75 pediatric patients in whom on background of polychemotherapy conduction for oncological disease bacteremia and neutropenia have occurred. Determination of procalcitonin level as a rapidly reacting biomarker of generalized infectious process permits to establish its progression, to conduct early diagnosis, to perform timely and adequate treatment measures (3).

A study aimed to determine serum adrenomedullin levels and compare them with levels of C-reactive protein (CRP) and procalcitonin (PCT). Cancer patients aged 0 - 18 years who experienced febrile neutropenia attacks were included in the study (4). Adrenomedullin, CRP, and PCT were analyzed at admission, day 3, and days 7 - 10 later. Fifty episodes of febrile neutropenia that developed in 37 patients were analyzed in this study. The mean age of the patients was  $7.5 \pm 4.7$  (1 - 18) years. Patients had leukemia (73%), solid tumors (19%), and lymphoma (8%). The percentages of the patients in the clinically documented infection (CDI), fever of unknown origin (FUO), sepsis, and microbiological documented infection (MDI) categories were 34%, 34%, 20%, and 12%. During the study period, four patients were lost. In the MDI group, adrenomedullin levels on day 3 were significantly higher than those in the CDI and FUO groups. PCT levels were significantly higher

in the sepsis group than those in the CDI group at admission, day 3, and days 7 - 10. In the sepsis group, PCT levels on days 7 - 10 days were significantly higher than those in the sepsis group (4). PCT values from the deceased patients on days 7 - 10 were significantly higher than those from patients who survived. CRP levels did not differ significantly among the febrile neutropenia groups. First, in his study, adrenomedullin was used as a biomarker in the febrile neutropenia episodes of children with cancer. Among adrenomedullin, CRP, and PCT, procalcitonin demonstrates the highest correlation with the severity of infection (4).

The correct diagnosis of neonatal sepsis is a relevant problem because sepsis is one of the most important causes of neonatal morbidity, mortality, and prolonged hospital stay (5). Calprotectin is an antimicrobial, calcium and zinc binding heterocomplex protein that could be used as a nonspecific marker for activation of granulocytes and mononuclear phagocytes. Calprotectin has been proposed for the diagnosis of inflammatory conditions (5). The aim of this study evaluated serum calprotectin as a biomarker for neonatal sepsis diagnosis in 41, 20 females, 21 male infants who underwent blood culture due to suspected sepsis were enrolled in the study. Serum calprotectin was measured by a commercial ELISA. Eight neonates showed sepsis with positive culture and 33 showed suspected sepsis. The optimal cut-off for calprotectin is 2.2  $\mu\text{g/mL}$  with a sensitivity of 62.5% and a specificity of 69.7%. Thus, calprotectin may be considered a promising early, sensitive, specific marker of sepsis thanks to the importance of calprotectin in defense mechanisms and physiological functions of the immune system (5).

The primary pathophysiological trigger for elevated level of procalcitonin is infection. Investigations identified procalcitonin as part of the complex pro-inflammatory response of the innate immune system (6). A marked increase in serum procalcitonin often indicates an exacerbation of the illness, and a decreasing level is a sign of improvement.

With sepsis, there is an increase in CALC-1 gene expression which causes a release of procalcitonin and, more importantly, their levels persist for relatively long periods of time and correlate with sepsis severity and mortality (6).

It has shown that it induces pro-inflammatory like effects on leukocytes (increased the expression of surface markers on neutrophils and lymphocytes), increases leukocyte-derived cytokines and also augments nitric oxide (increases level correlates with severity of inflammation (7). Advance researches that are designed in clarifying the role of procalcitonin in sepsis would aid in better understanding the pathogenesis of sepsis. The procalcitonin test is relatively new, but its utilization is increasing. Multiple studies have shown that it has promise in helping to evaluate the risk of developing sepsis.

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 PCT were measured at admission (T0) and 12 hours later (T12 hour). PCT results were classed

as: 0.5 ng/mL = sepsis unlikely;  $\geq 0.5$  to  $< 2$  = sepsis possible;  $\geq 2$  to  $< 10$  = systemic inflammation;  $\geq 10$  = septic shock. At T0, there was a higher frequency of SSG with PCT  $> 10$  compared to SG, SSG: 30 (73.1%)  $>$  SG: 14 (30.4%); P significantly higher for SSG patients with higher PCT than SG patients. CRP levels were not statistically different for groups and time points. PCT was better than CRP for diagnosing sepsis and septic shock, mainly at admission, and is related to disease severity (8).

### 3.2. Trauma

The types of splenic traumas, accompanying injuries management, and results in children in 90 patients treated for splenic injuries as a result of blunt abdominal trauma between 2005 - 2012 were evaluated (9). Age, sex, hospitalization time, mechanisms of traumas, accompanying injuries and management methods were recorded. Causes of trauma were falls from height, pedestrian traffic accidents, passenger traffic accidents, bicycle accidents and falling objects from height (9). Splenic injury alone was observed in 57 patients and other organ injuries together with splenic injury in 33 patients. Splenectomy was performed in six patients due to hemodynamic instability and small intestine repair due to small intestine injury in one patient. None of these patients died from their injuries. The authors stated a large proportion of splenic injuries recover with conservative therapy and some of the advantages of conservative therapy include short hospitalization time, less need for blood transfusion, and less morbidity and mortality. Falls from height and traffic accidents are important factors in etiology. The possibility of other organ injuries together with splenic injuries should be considered (9).

Blunt renal trauma in children with pre-existing renal abnormalities was reviewed (10). The authors stated though the retroperitoneal location affords the kidneys some protection from the forces experienced in blunt abdominal trauma, the kidneys are at greater risk of injury when a disease process exposes them from their normal shielded location (10). The injuries may appear to be disproportionate in relation to the severity of the trauma history, confusing the imaging findings and recognition of both the underlying disease process as well as the manifestations of acute trauma is important (10).

Improved resource utilization in the diagnosis of pediatric abdominal injury has been described. Sufficient evidence has become available to radically change the management of pediatric abdominal injury, which is being incorporated into new evidence-based management algorithms (11).

Records of trauma patients age 0 year to 17 years (2005 - 2013) who presented to a pediatric level 1 trauma center were retrospectively reviewed and data collected included demographics, computed tomographic scan findings, need for an intervention secondary to bleeding (blood transfusion, angio-embolization, or operation), and ad-

mission hematocrit (12). An admission hematocrit of 35% or less provided reliable screening because of its low false negative rate and high specificity for identifying patients at an increased risk of bleeding after injury. Thus, a mission hematocrit could be widely implemented to identify patients who may need a transfusion with low expense and minimal harm for pediatric patients and may be able to alter the entire course of their trauma resuscitation (12).

A recent planned sub analysis study compared the test characteristics of clinician suspicion with a derived clinical prediction rule to identify children at risk of intra-abdominal injuries undergoing acute intervention following blunt torso trauma (13). Clinicians documented their suspicion for the presence of intra-abdominal injuries needing acute intervention. The derived clinical prediction rule had a significantly higher sensitivity, but lower specificity, than clinician suspicion for identifying children with intra-abdominal injuries undergoing acute intervention. 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. This prediction rule can assist in clinical decision-making around abdominal CT use in children with blunt torso trauma if validated (13).

The prevalence of non-iatrogenic pediatric venous injuries was discussed related to options in management of traumatic venous injury mortality from venous injury in pediatric trauma (14). The authors provided the practicing clinician with a summary of the published literature and to develop an evidence-based guide to the diagnosis and management of traumatic venous injuries in children (14).

Although rare, the incidence of venous thromboembolism (VTE) in pediatric trauma patients is increasing, and the consequences of VTE in children are significant. Studies have demonstrated increasing VTE risk in older pediatric trauma patients and improved VTE rates with institutional interventions. While national evidence-based guidelines for VTE screening and prevention are in place for adults, none exist for pediatric patients (15).

A recent study developed a 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. Authors developed a 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 it was internally validated. The clinical tool requires external validation but provides an initial step toward the development of the specific VTE protocols for pediatric trauma patients (15).

### 3.3. Epidemiology of Trauma

Epidemiology data is important. A prospective descriptive epidemiological study on soccer injuries over 2 seasons in children aged 7 to 12 years was reported (16). Children showed a relatively high proportion of fractures and bone stress and of injuries to the upper limbs. The study provides

an evidence base for injury incidence rates and injury characteristics in children's soccer and these data are the basis to develop an age-specific injury-prevention program (16).

An epidemiology and outcomes of pediatric burns was evaluated which contained data from January 1974 until August 2010. Patient age, cause of burn, total body surface area (TBSA), depth of burn, and patient outcomes were collected. Demographics were compared with regional census data. Mortality was significantly correlated with inhalation injury, size of burn, and history of abuse. Over 35 years in North Texas, the median burn size and incidence of pediatric burn admissions decreased and the, length of stay and mortality have also decreased (17).

Pediatric traumatic amputations are capable of causing permanent physical and psychological sequel. Few epidemiologic reports exist for guidance of prevention strategies. The objective of this study was to review the recent trends in pediatric traumatic amputations using a national databank (18).

Young children sustain more finger amputations from a caught between objects mechanism, whereas adolescents sustain serious amputations such as firearms-related and motor vehicle-related injuries. Lawnmower-related amputations continue to most significantly affect younger children despite increased public awareness. Improved prevention strategies targeting age and mechanism-related trends are necessary to prevent these costly and debilitating injuries (18).

### 3.4. Inflammation, Innate Immunity, and Trauma

Immunologic abnormalities can provoke multiple organ failure in severely injured patients and can manifest in two forms, which follow a biphasic pattern (19). The first phase, in addition to the injury by trauma, organ damage is caused by the immune system during a systemic inflammatory response. In the second phase the patient is more susceptible for sepsis due to host defense failure or immune paralysis (19). The innate immune system is an immune monitor and has a very prominent role in organ failure after trauma. Polymorphonuclear phagocytes and monocytes are the main effector-cells of the innate immune system that are involved in organ failure and are controlled by cytokines, chemokines, complement factors, and specific tissue signals (19).

An earlier review discussed some basic aspects of complement biology, addressed the clinical effects of hereditary complement deficiencies and the role of complement related to host cell entry, pathogenesis of infectious diseases, and apoptosis (20).

### 3.5. Role of Neutrophils

Major torso trauma can prime and activate polymorphonuclear neutrophils (PMNs) within 3 to 6 hours after injury and post injury priming of PMNs may create an early vulnerable window during which a second event (e.g., a secondary operation or delayed hemorrhage) ac-

tivates exuberant PMN cytotoxic superoxide anion  $O_2^-$  release, rendering the injured patient at high risk for multiple organ failure (21).

The impact of trauma on neutrophil function was evaluated by Hazeldine 22 with trauma-induced changes in neutrophil biology linked to the development of such post-traumatic complications as multiple organ failure and acute respiratory distress syndrome, an area of research within the field of trauma immunology that is gaining considerable interest is the manipulation of neutrophil function as a means by which to potentially improve patient outcome (22).

Neutrophils play an essential role in the body's innate immune response to infection (23).

### 3.6. NF-kappa B, Inflammation and Trauma

Activated neutrophils can upregulate many genes, in particular those encoding cytokines and chemokines, and to subsequently release the corresponding proteins. Many of these genes depend on the activation of transcription factors, such as NF-kappa B, for inducible expression (23). NF-kappaB activation may underlie the action of proinflammatory stimuli towards human neutrophil gene expression and, and adds a new facet to our understanding of neutrophil biology (24). Systemic inflammation subsequent to poly trauma can be connected to neutrophil (PMN) dysregulation characterized by reduced NF-kB-translocation and cytokine expression. NF-kB-activation as well as its downstream regulation of IL-8-expression in PMN can follow major trauma (24). NFkB- translocation was significantly increased on admission, reduced within 6 hours, while it increased in the survivors group. A significant increase in NF-kB-activity and IL-8-expression was found after 24 hours in survivors that was subsequently reduced in both groups. A concomitant initial increase in transcriptional NF-kB-activity and IL-8 mRNA expression was observed in the early posttraumatic period which preceded the down-regulation of the innate immune system (25).

Severe trauma can lead to immediate hyper inflammatory responses with neutrophil activation, continuous pro inflammatory interleukin secretion related to IL-6, that can induce upregulation of further major anti-inflammatory cytokines mediators, such as IL-10 markedly inhibiting lymphocyte and phagocytic functions, which are essential for an adequate immune response to invading microbes (26).

The majority of trauma victims end-up being managed at least initially, in the emergency department (E.D) of health care facilities. This makes the E.D of any hospital a critical area in terms of assessment of quality of care (27). The initial management of these patients is often challenging, and experienced personnel, the utilization of high technology imaging modalities for accurate diagnosis, timely and appropriate resuscitation measures, frequent monitoring of response and timely consultation with the appropriate specialty is important. The

high death rate in this prior study is multifactorial (27). First, is the deficiency of trained man power in trauma management; secondly, the systemic deficiencies such as the lack of a trauma system, pre hospital care and intensive care facilities, are independent contributory factors. The factors responsible for late presentation at the definitive care center are multiple and justify the fact that, the public needs to be aware of the fact high seed and high velocity trauma of today's world is beyond the comprehension of alternative practitioners (27).

### 3.7. Sepsis

A prospective, observational nested cohort study at two pediatric intensive care units (PICUs)

and one pediatric emergency department (ED) was conducted (28). Children ages 2-17 years presenting to the PICU or ED with sepsis or presenting for procedural sedation to the ED were enrolled (28). The authors used the judgment of regional pediatric ED and PICU attending physicians as the standard to determine triage location (PICU or ED), and performed metabolic and inflammatory protein mediator profiling with serum and plasma samples, collected upon presentation, followed by multivariate statistical analysis. Ninety-four PICU sepsis, 81 ED sepsis, and 63 ED control patients were included (28). Metabolomic profiling revealed clear separation of groups, differentiating PICU sepsis from ED sepsis with accuracy of 0.89, area under the receiver operating characteristic curve and a predictive ability of 0.60. Protein mediator profiling also showed clear separation of the groups, differentiating PICU sepsis from ED sepsis with accuracy of 0.78. Combining metabolomic 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. Pre specified age subgroups (2 - 5 years old and 6 - 17 years old) improved model accuracy minimally. Seventeen metabolites or protein mediators accounted for separation of PICU sepsis and ED sepsis with 95% confidence (28). In children ages 2 - 17 years, combining metabolomic and inflammatory protein mediator profiling early after presentation may differentiate children with sepsis requiring care in a PICU from children with or without sepsis safely cared for outside a PICU. This may aid in making triage decisions, particularly in an ED without pediatric expertise. This finding requires validation in an independent cohort (28).

Prediction models for neonatal health care-associated sepsis were reviewed (29). The systematic search revealed nine articles with 12 prediction models representing 1295 suspected and 434 laboratory-confirmed sepsis episodes. Models exhibit moderate-good methodologic quality, large pretest probability range, and insufficient diagnostic accuracy. Random effects meta-analysis showed that lethargy, pallor or mottling, total parenteral nutrition, lipid infusion, and postnatal corticosteroids were predictive for health care-associated bloodstream infection. The

paper 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 and the clinical context of the neonate should always be considered (29).

Optimal amikacin dosing regimens for the empirical treatment of Gram-negative bacterial sepsis in pediatric patients with burn injuries were developed (30). Amikacin pharmacokinetics are altered in patients with burn injuries, including a significant increase in clearance and the volume of distribution. In simulations, increased doses lead to improved PD 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.

### 3.8. Systemic Inflammation Response Syndrome and Sepsis

Injury due to trauma can induce immune function changes, which can lead to both pro inflammatory activation known as systemic inflammation response syndrome (SIRS) and an anti-inflammatory reaction with immunosuppression or compensatory anti-inflammatory response syndrome (CARS). SIRS with proven infection is referred to as sepsis, however clinically it is often difficult to isolate the microbial inoculum, making the differential diagnosis between SIRS and sepsis difficult (31). This differential diagnosis is crucial for further therapeutic decisions: as is an antimicrobial therapy and aggressive search for a septic focus with all its side-effects necessary or is a focused symptomatic therapy of the SIRS the adequate treatment concept? In multiple traumas, both syndromes can develop simultaneously, recently described as mixed antagonist response syndrome (MARS) (32).

SIRS vital signs are common among medical pediatric patients presenting to an ED, and critical illness is rare. The majority of patients with SIRS vital signs were discharged without IV therapy and without readmission. Patients with SIRS vital signs had a statistically significant increased risk of critical care requirement, ED IV treatment, ED laboratory tests, admission, and readmission. SIRS vital sign criteria did not identify the majority of patients with mortality or need for critical care. SIRS vital signs had low sensitivity for critical illness, making it poorly suited for use in isolation in this setting as a test to detect children requiring sepsis resuscitation (33).

### 3.9. Sepsis and Plasma Gelsolin

Levels in premature infants at 72 hours and were significantly lower in patients with respiratory distress syndrome and in patients who were administered surfactant therapy and in patients who developed sepsis. Plasma gelsolin levels at 28 days were significantly lower in pa-

tients who developed broncho pulmonary dysplasia and retinopathy of prematurity. Low plasma gelsolin levels in the first postnatal month may be associated with poor outcomes in premature infants (34).

### 3.10. Sepsis and Interleukin 8

A systematic review and meta-analysis to investigate the diagnostic value of the IL-8 in neonatal sepsis that is a life-threatening disorder and an important cause of morbidity and mortality in neonates was conducted (35). Eight studies in 548 neonates were evaluated. Meta-analysis showed IL-8 had a moderate accuracy for the diagnosis of neonatal sepsis and IL-8 is a helpful biomarker for early diagnosis. However, the authors stated that one should combine the results with clinical symptoms and signs, laboratory and microbial results (35).

### 3.11. Reactive Oxygen Species, NFκB Band Newborn Hypoxia

A review on hypoxia inducible factor (HIF) signaling and experimental persistent pulmonary hypertension of the newborn was conducted (36). Mitochondrial reactive oxygen species (ROS) levels and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) activity are increased in an animal model of persistent pulmonary hypertension of the newborn (PPHN). These events can trigger hypoxia inducible factor (HIF) signaling in response to hypoxia and complex physiological and biochemical processes facilitate the fetal to newborn transition, and abnormal lung development and or vascular dysfunction may disrupt these events (36).

Increased HIF signaling in PPHN is triggered by stretch, via mechanisms involving mitochondrial ROS and NFκB. Hypoxia substantially amplifies HIF activity in PPHN vascular cells. Targeting these molecules may attenuate and reverse pulmonary vascular remodeling associated with PPHN (36). This study identified components of the HIF signaling pathway that may contribute to the pathogenesis of PPHN and further studies are warranted in vivo and in vitro to investigate the mechanisms involved to improve current detection and treatment strategies for babies with PPHN (36).

### 3.12. Reactive Oxygen Species and Quinones

Quinones are electron and proton carriers that play a primary role in the aerobic metabolism of virtually every cell in nature. They undergo highly regulated redox reactions in the mitochondria, Golgi apparatus, plasma membrane, and endoplasmic reticulum. Important consequences of these electron transfer reactions are the production of and protection against reactive oxygen species (ROS) (37).

A review of the literature revealed an inflammatory response and an increased production of ROS to be common immune responses to nanomaterial use. The mecha-

nisms by which the inflammatory response and ROS production occur was also discussed (38).

## 4. Conclusions

This paper provided new information and clinical practice implications. Biomarkers are very important especially in pediatrics and these were covered. Procalcitonin and other biomarkers are helpful in identifying neonatal sepsis, defense mechanisms, and physiological functions of the immune system. Pediatric trauma and sepsis is very important both in infants and in children. Stress management both in trauma is based upon the notion that stress causes an immune imbalance in susceptible individuals. Various topics were covered such as biomarkers, trauma, sepsis, inflammation, innate immunity, role of neutrophils and IL-8, reactive oxygen species, neonatal hypoxia, NF-kappa B related to inflammation. These topics are very important for pediatricians, pulmonologists and immunologists in academic centers and in practice.

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