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Review Article

Trauma, Sepsis, Shock and Biomarkers

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Abstract

Background: This original contribution included trauma, sepsis, shock, inflammation, innate immunity, neutrophils, IL-8, reactive oxygen species, neonatal hypoxia, NF-kappa B, procalcitonin, intestinal fatty acid binding protein.

Objective: The purpose of this article is to understand trauma, sepsis, shock, the procalcitonin, biomarker and the synergistic relationship between the activation of the innate immune system, loss of organ barrier functions.

Discussion: Data was obtained from several reports, retrospective, descriptive cohort prospective studies, gene cluster and expression analysis listed in the papers and in references. Many complex factors such as genetics, physical agents, and mediators are involved in the development of organ failure in trauma. These factors are clearly linked and can lead to susceptibility of patients to posttraumatic organ failure. Sepsis is a common condition encountered in hospital environments and remains an important cause of death in the intensive care units. Procalcitonin was mentioned in this review as related to sepsis and infections.

Conclusions: Trauma and sepsis, shock and biomarkers are very important both in adults, infants and children. Various topics were covered such as trauma, sepsis, shock inflammation, innate immunity, role of neutrophils and IL-8, reactive oxygen species, neonatal hypoxia, the role of NF kappa B related to inflammation. Procalcitoninas helpful in identifying adult and neonatal sepsis, defense mechanisms and physiological functions of the immune system.

Keywords: Trauma; Sepsis; Shock; Reactive oxygen species; Biomarkers

Introduction

Trauma and sepsis in adults

A leading cause of death related to trauma occurs both in the military and in civilians [1]. Medical advances in this area have improved the overall morbidity and mortality but therapeutic interventions are necessary to improve patient outcomes. Both barriers in the translation of cell therapies, manufacturing, clinical trial design challenges and lack of funding are important needed areas. The objective of this review provided a state of the science related to regarding cellular therapies in trauma, critical care and provided a foundation to improve outcomes in critically ill adult trauma patients [1].

In a study, data was collected by a structured chart review and provided a detailed up-to-date description of both the epidemiology and microbiology related to sepsis syndromes [2]. This study was a prospective observational study conducted at a university-affiliated urban teaching level-1 trauma and burn center [2]. All adult patients were evaluated over one year in the emergency department. Patients with an unspecified infection source and those without an isolated pathogen had the highest inpatient mortality. Hospital mortality and length of stays in sepsis were similar to those reported in other observational studies. This study confirmed a decline in sepsis mortality as shown by earlier longitudinal studies and according to the authors should lead to a resurgence of epidemiological research related US. Sepsis syndromes [2].

A retrospective analysis of charts and trauma register data of adult blunt trauma victims, admitted without abdominal pain or alterations in the abdominal physical examination, but were subsequently diagnosed with intra-abdominal injuries, in a period of 2 years assessed the severity and treatment of "occult" intra-abdominal injuries in blunt trauma victims. Severe "occult" intra-abdominal injuries, requiring specific treatment, may be present in adult blunt trauma patients [3].

Blast wave-induced TBI is one of the most common injuries to military personnel [4].

Diffuse axonal injury is regarded as a signature wound of mild TBI and blast loads may also cause synaptic injury that may result in temporary disconnect of the neural circuitry and transient loss in neuronal communication wherein neuronal synapses are stretched and sheared [4].

Pediatric trauma

Pediatric trauma patients with blunt splenic injuries are very important to be properly managed. Types of splenic traumas, accompanying injuries, management and results in children due to blunt abdominal trauma were assessed over 7 years [5]. Age, sex, time of hospitalization, mechanisms of trauma due to injuries and management methods were recorded. Causes of trauma were falls were evaluated [5] Splenic injury alone was observed in 63.3% and other organ injuries together with splenic injury in 36.7%. Splenectomy was performed in 6.6% from hemodynamic instability and small intestine repair due to small intestine injury was only in one patient. None of any of these patients died from their injuries. The authors

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stated a large proportion of splenic injuries recover with conservative therapy and advantages of conservative therapy includes a short hospitalization time, less requirement for blood transfusion, and less morbidity and mortality. The authors felt falls from height and traffic accidents are important etiologic factors but the possibility of other organ injuries along with splenic injuries should be considered [5].

Blunt renal trauma in children with pre-existing renal abnormalities was reviewed [6]. The location affords the kidneys some protection from forces that occur with blunt abdominal trauma, but they are at greater risk of injury when a disease process exposes them from their normal shielded area [6]. The authors of this article stated that injuries may appear to be disproportionate related to the severity of the trauma history, and recognition of both the underlying disease process and the manifestations of acute trauma is important [6].

Improved resource utilization in the diagnosis of pediatric abdominal injury has been recently described and non-operative management of pediatric blunt abdominal injury has significantly changed but operative management of certain pancreatic injuries may have more favorable outcomes than management of non-operative cases [7]. The authors stated that stable patients spend less time in the hospital, after discharge return to school, and are allowed lower hemoglobin levels prior to transfusion. Intensive care units are reserved for patients with recent or ongoing bleeding, unstable previous patients, or children with concomitant injuries requiring intensive care [7]. Thus, there is sufficient evidence available to radically change the management of pediatric abdominal injury, which is being incorporated into new evidence-based management [7].

A recent paper stated that admission hematocrit predicts the transfusion requirement in blunt trauma pediatric patients [8]. Records of trauma patient's age 0 year to 17 years of age over 8 years who presented to a pediatric Level 1 trauma center were retrospectively reviewed. Data collected included demographics, findings from CT scans, and the requirement for intervention secondary to bleeding [8]. An admission hematocrit of 35% or less provided a reliable screening test because of its low false negative rate and high specificity for identifying patients at an increased risk of injury due to bleeding. Thus, a mission hematocrit could be widely used to identify pediatric patients who may need a transfusion with low expense and minimal harm and may be able to alter the entire course of their trauma [8].

Emergency department identification and evaluation of childhood radiographs with intra-abdominal injuries who require acute intervention is known to be a challenge.

A recent study compared a clinician's suspicion with a derived clinical prediction rule to identify children at risk of intra-abdominal injuries undergoing acute intervention after blunt torso trauma as a planned subanalysis of a prospective, multicenter observational study in children (<18 years old) with blunt torso trauma done in 20 pediatric emergency departments [9]. Clinicians documented intra-abdominal injuries requiring acute intervention. The derived clinical prediction had a significantly higher sensitivity, but lower specificity, than clinician suspicion for identifying children with intra-abdominal injuries However, the higher specificity of clinician suspicion, did not translate into clinical practice, since clinicians frequently obtain abdominal CT scans in very low risk patients they consider. The authors stated "if validated, this prediction can assist in clinical decision-making around abdominal CT use in children with blunt torso trauma [9].

A recent retrospective study developed a simple clinical tool to predict the risk of developing Venous Thromboembolism (VTE) in pediatric trauma patients based on a model created using a large national database that was internally validated [10]. The clinical tool required external validation and provided an initial step toward the development of the specific VTE protocols for pediatric trauma patients [10]. These 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.

Trauma and inflammation

Immune dysfunction can lead to multiple organ failure in severely injured patients. Trauma can result in the induction of a systemic inflammatory response or SIRS by significant increases in circulating cytokines implicated in multiple-organ dysfunction syndrome and increased mortality. The innate immune system has a very prominent role in organ failure after trauma. Alarm signals provoke an inflammatory reaction and can be secreted by healthy cells or released by necrotic cells, which are present after injury is sustained [11]. Alarmins are proinflammatory and induce the activation of various immune cells during infection and tissue damage.

Polymorphonuclear phagocytes are key effector cells related to the innate immune system and other immune cells are the main effector-cells of the innate immune system involved in organ failure and are controlled by cytokines, chemokines, complement factors and specific tissue signals [11]. Immunologic abnormalities can lead to multiple organ failure in severely injured patients and can manifests in two different forms [11].

Many immune cells play a central role in early innate immune systemic responses after trauma and inducing inflammation after injury contributing to end-organ damage after trauma related to complement activation. Complement is a collection of many proteins involved in the protection against micro-organisms but can lead to tissue damage through immune complexes. 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 [12]. Multiple organ failure following trauma is still a leading cause of late post-injury death and morbidity and excessive systemic inflammation following trauma can lead to the development of multiple organ failure. The inflammatory response is a host-defense response; however this response canturn around to cause deterioration to host depending on exo- and endogenic factors. This review described the pathophysiological approach for multiple organ failure following trauma and introduced the prospects of this topic for the future [13].

Neutrophils in trauma

Activated Polymorphonuclear Neutrophils (PMNs) can be primed after major torso trauma. and post injury priming of PMNs can lead to second event related to a secondary operation or delayed hemorrhage that activates exuberant PMN cytotoxic superoxide anion O_2- release, leaving the injured patient at high risk for multiple

organ failure [14]. Release of O_2- is markedly enhanced when PMNs that have been activated previously or "primed" by inflammatory mediators after trauma. These authors hypothesized that PMN priming occurs as an integral part of the early inflammatory response to trauma.

The impact of trauma on neutrophil function was evaluated by Hazeldine and others [15]. These authors discussed the role of the neutrophil and the first line of defense against microbes in initiation and propagation of the inflammatory traumatic response. They also reviewed recent studies investigating the impact of trauma on neutrophil function and discussed how alterations in neutrophil biology are evaluated as potential biomarkers to predict the outcome of hospitalized trauma patients [15]. They also discussed 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 interest related to the manipulation of neutrophil function to potentially improve patient outcomes [15]. Neutrophils are important in the body's innate immune response to infection. To protect the host, these cells possess an impressive array of microbicidal weapons that can attack an invading pathogen, including a variety of toxic oxygen radical species and proteolytic enzymes [15].

As discussed earlier, one of the regulatory mechanisms in controlling neutrophil responses is priming. Through the action of these priming agents, activation and subsequent responses of the cell can be regulated in order that a continuum of activation states is achieved. In this review, the authors described key features of the priming response related to host defense, disease pathogenesis and focused on the unique role of reactive oxygen species as priming agents [16].

NF-kappa B, inflammation in trauma

Activated neutrophils are able to up regulate gene expression encoding cytokines and chemokines, and to subsequently release corresponding proteins and many of these genes depend on the activation of transcription factors, as NF-kB for inducible expression [17]. The authors stated neutrophil proinflammatory stimuli promoted the accumulation of Ikappa B-alpha mRNA transcripts, leading to re-expression of the Ikappa B-alpha protein. NF-kB activation may underlie the action of proinflammatory stimuli towards human neutrophil gene expression and adds a new facet to our understanding of neutrophil biology [17]. Systemic inflammation related to poly trauma can be associated to MN) dysregulation due to reduced NF-kB-translocation and cytokine expression. NF-kB-activation and its down-stream regulation of IL-8-expression in PMN can follow major trauma [18]. In this study, it was found that NFkB-translocation was significantly increased on admission and reduced within 6 hours, but it increased in the survivors group. In addition, a second significant increase in NF-kB-activity and IL-8-expression was found after 24 hours in survivors and subsequently reduced in both groups. The authors stated thus, a concomitant initial increase in transcriptional NF-kB-activity and IL-8 mRNA expression was noted in the early posttraumatic period which preceded the down-regulation of the innate immune system [18].

Severe trauma can lead to immediate hyperinflammatory responses with neutrophil activation, continuous proinflammatory interleukin secretion related to IL-6, inducing up regulation of further major anti-inflammatory cytokines mediators, such as IL-10 that can markedly inhibits lymphocyte and phagocytic functions, which are essential for an adequate immune response to invading microbes [19]. Thus, .trauma causes an enhanced release of IL-10 dependent on injury severity. Increased IL-10 levels are significantly related to posttraumatic complications and may be involved in their pathogenesis [19].

The initial management of these patients is often challenging, requiring precise interpretation of symptoms and signs by specialized 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 [20]. The high death rate in this prior study is multifactorial. First, is the deficiency of trained man power in trauma management; secondly, the systemic deficiencies such as the lack of a trauma system, prehospital care and intensive care facilities, are independent contributory factors. The factors responsible for late presentation at the definitive care center are multiple; cumulatively they justify the fact that, the public need to be aware of the fact high seed and high velocity trauma of today's world, is beyond the comprehension of alternative practitioners [20].

Intestinal fatty acid binding protein

This study assessed intestinal damage using the intestinal Fatty Acid Binding Protein (iFABP) biomarker in trauma patients during the first days of hospital admission and also involved risk factors [21]. Plasma iFABP levels were obtained from adult multiple trauma patients at a trauma scene by the Helicopter EMS at arrival at the Emergency Department and the following days 1,3,5,7,10 and 14 after trauma and this was related to severity injury and hemodynamic measures [21]. Plasma iFABP concentrations revealed the highest levels immediately after trauma at time points via the Helicopter EMS and Emergency Department. Non-survivors demonstrated higher iFABP levels at the Emergency Department compared with survivors. iFABP values at the Emergency Department correlated with injury severity scores. Patients suffering from abdominal trauma demonstrated significantly higher iFABP concentrations in comparison with patients with other types of trauma or healthy controls [21]. Patients with low hemoglobin also had significantly higher iFABP concentrations in comparison with patients with normal hemoglobin or in healthy controls. Thus, according to the authors "plasma iFABP levels, indicative of intestinal injury are increased immediately after trauma in patients with abdominal trauma, low mean arterial pressure or low hemoglobin are related to the severity of the trauma". Multiorgan dysfunction syndrome or sepsis in trauma patients, strategies to prevent intestinal damage after trauma could be of benefit for these patients [21].

Sepsis

Systemic inflammation response syndrome and sepsis

Sepsis and SIRS (systemic inflammatory response syndrome) belong to a severe disease complex characterized by infection and/or a whole-body inflammatory state. SIRS and sepsis are two different entities of the same disease complex both leading to multiorgan dysfunction and eventually death of the patient. Causes for SIRS and sepsis could be manifold since SIRS can develop as sterile

complication of severe trauma, extensive burns, shock, or severe local inflammation [22]. SIRS with proven infection is referred to as sepsis, however clinically it is often difficult to isolate microbes making the differential diagnosis between SIRS and sepsis difficult [22].

This differential diagnosis is crucial for further therapeutic decisions: 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? [22].

In multiple trauma situations, both syndromes can develop together, recently described as mixed antagonist response syndrome [23]. Mast cells play a role in early innate immune systemic responses after trauma and in inducing inflammation after injury contributing to end-organ damage after trauma related to complement activation [24]. In multiple trauma situations, both syndromes can develop together, recently described as Mixed Antagonist Response Syndrome (MARS) [24]. Early postoperative sepsis seems to be characterized by a primary MARS. Sepsis severity was positively correlated with a disproportionate elevation of the anti-inflammatory response relative to the pro-inflammatory response, a pattern reminiscent of TLR-driven responses [25]. Measurement of serum inflammatory and suppressive activities may help to differentiate patients with SIRS, CARS or MARS and to select the appropriate immunotherapy [25].

A disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13 or known as ADAMTS-13 seems to be associated with a poor septic prognosis [26]. ADAMTS-13 has also been observed in severe sepsis and is associated with poor survival and deficiency on in-hospital mortality in pediatric patients with severe sepsis can occur.ADAMTS-13 deficiency might also play a role in sepsis-induced thrombocytopenia. Decreased ADAMTS-13 has also been reported in disseminated intravascular coagulation due to severe sepsis. The aims of this study in 178 patients were to evaluate ADAMTS-13 levels in patients with septic syndromes or noninfectious SIRS and determine their association with morbidity and mortality [26]. Patients were admitted to the medical ICU with septic syndromes or noninfectious SIRS. The authors found that patients with septic syndromes showed significantly lower levels of ADAMTS-13 compared with those with noninfectious SIRS and those with severe sepsis or septic shock presented lower levels than those of patients with sepsis. Patients who died had significantly lower levels of ADAMTS-13 compared with survivors; both in the whole population and among the septic patients and logistic regression analysis showed that decreased Thus, ADAMTS-13 levels were associated with a significantly increased risk of in ICU care unit mortality [26]. Adenosine is able to exert anti-inflammatory and tissue-protective effects during systemic inflammation. Tissue-protective effects might limit organ damage; however its anti-inflammatory properties may induce immunoparalysis and impede bacterial clearance [26].

The common 34C>T is a gene polymorphism in AMPD1 deficiency and a loss-of-function variant of AMPD1 (rs17602729) is associated with increased adenosine formation, but effects on immune function and outcome in sepsis patients are unknown [27]. In this study, the effects of the presence of the 34C>T variant on sepsis susceptibility, immune function, multi-organ dysfunction, and mortality in septic patients were evaluated. Patients with community acquired and ventilator-associated pneumonia and control patients without infection were studied [27].

The presence of the AMPD1 34C>T variant was associated with higher infection susceptibility to community acquired pneumonia but not to ventilator-associated pneumonia. More pronounced immunoparalysis in these patients mediated by the anti-inflammatory effects of adenosine may account for these findings [27].

This study evaluated a Perfusion Index (PI) to predict vasopressor requirement during early resuscitation in 36 severe septic patients. All patients with clinically suspected severe sepsis were defined by the criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [28]. Twenty-one patients required vasopressors. Perfusion variables included PI, arterial lactate level, central venous oxygen saturation, the difference between central venous carbon dioxide and arterial carbon dioxide pressures before resuscitation and at 6hours. Other perfusion variables failed to predict vasopressor requirements in severe septic patients. The authors of this paper concluded that PI and arterial lactate level are good predictors of vasopressor requirements during early resuscitation in severe septic patients. However, further studies are warranted to investigate whether monitoring PI during resuscitation improves the outcome of patients with septic shock [28].

Targeting sirtuins may provide a new class of inflammation and immune regulators and sirtuins could improve outcome in chronic inflammatory diseases and in the extreme stress response of sepsis. The sirtuin family consists of seven NAD^+ dependent enzymes that affect regulatory protein networks by primarily catalyzing the deacetylation of key lysine residues in regulatory proteins [29]. This paper evaluated the therapeutic potential of the STAC SRT3025 in two preclinical models of severe infection, the murine Cecal Ligation and Puncture (CLP) model to induce peritonitis and intra-tracheal installation of Streptococcus pneumoniae to induce severe bacterial pneumonia [29]. Enzymatic activity of SIRT1 can be enhanced by small molecule activators known as SIRT1 Activator Compounds (STACs). The authors stated that SRT3025 provided significant survival benefits over vehicle control in both the peritonitis and pneumococcal pneumonia models when given with appropriate antimicrobial agents. Thus, pharmacologic activation of SIRT1 modulates the innate host response and could represent a novel therapy for severe infection [29].

This retrospective descriptive cohort study of all visits to the emergency department of a tertiary academic free-standing pediatric hospital over 1 year evaluated the prevalence, test characteristics, and severity of illness of pediatric patients with SIRS, vital signs among pediatric emergency department visits [30]. SIRS vital signs are common among medical pediatric patients presenting to an emergency department, and critical illness is rare [30]. The presence of vital signs were related to the pediatric SIRS definitions and specific vital sign pairs comprising SIRS were evaluated as predictors such as temperature-heart rate, temperature respiratory rate, and temperature-corrected heart rate. A formula was used to correct heart rate for degree of temperature elevation. 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, Emergency department IV treatment, emergency department laboratory tests,

admission, and readmission. However, 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, thus, poorly suited for use in isolation in this setting as a test to detect children requiring sepsis resuscitation [30].

Management of sepsis relies on effective resuscitation with fluids and vasopressors, appropriate adequate antimicrobial therapy, and organ support [31]. This article focused on key hemodynamic signs of sepsis and discussed the potential safety risks associated with the management of each of them, including optimizing arterial pressure, cardiac output and oxygen delivery [31]. Patients with septic shock are heterogeneous, and it is difficult to provide therapeutic recommendations that are safe and effective for all. According to the authors, a personalized medicine approach should be used with treatment decisions carefully considered and the risks and benefits of each intervention balanced in each individual patient [31].

A systematic analysis of sepsis gene expression studies including both adult and pediatric cohorts was studied using clustering methods to partition samples according to gene expression levels, and compared expression cluster labels to clinical diagnoses [32]. This paper quantified the strength of cluster formation based on expression data from different tissue sources using average silhouette widths as a measure of cluster cohesiveness. Whole blood was used as the source tissue in 15 studies whole blood samples yielded greater specificity for the diagnosis of sepsis than data from leukocyte isolates. Whole blood derived data also yielded more cohesive clusters (median silhouette widths for whole blood and leukocyte isolates. These results support the use of whole blood to derive gene expression data in sepsis studies investigating novel diagnostics and discovery of subtypes. This strategy has a number of practical advantages, and the resulting data also have potential utility in developing molecular classifications of sepsis syndromes [32].

Dysregulation of the inflammatory response related to infection leads to sepsis mortality [33]. Inflammation can be critical for host defense, but can also lead to tissue damage, multiple organ failure and mortality. Peroxisome proliferator-activated receptor γ or (PPARγ) can possibly have therapeutic utility. These authors characterized the role of PPARγ in sepsis and evaluated severity of clinical signs, survival rates, cytokines leukocyte influx, and bacterial clearance in a murine model. They showed aPPARγ agonist rosiglitazone, a member of the thiazolidinedione class of drugs as an insulin sensitizer binds to the PPAR receptors in fat cells and improved clinical status and mortality. Rosiglitazone has anti-inflammatory effects in addition to its effect on insulin resistance. NF-κB, a signaling molecule, and stimulates the inflammatory pathways. The authors showed it increased IL-10 production, decreased TNF-α and IL-6 levels, and peritoneal neutrophil accumulation 24h after a cecal ligation and puncture in the murine model. They also noted increased bacterial killing in animals treated with rosiglitazone and correlation with increased generation of reactive oxygen species. PMNs incubated with LPS or E. coli and rosiglitazone increased peritoneal Neutrophil Extracellular Trap (NET)-mediated bacterial killing, an effect reversed by aPPARγ antagonist [33]. Rosiglitazone also enhanced the release of histones by PMNs, a surrogate marker of NET formation, modulated the inflammatory response and increased bacterial clearance through PPARγ activation and NET formation, combining immunomodulatory and host-dependent anti-bacterial effects. The authors stated this, warrants further study as a potential therapeutic agent in sepsis [33].

Neutrophils in sepsis

Neutrophil CD64 (nCD64) expression has been reported to be a promising marker of bacterial infections and sepsis [34].The aim of this meta-analysis was to assess the accuracy of nCD64 expression in the diagnosis of sepsis in critically ill adult patients [34]. The authors systematically searched multiple literatures and reference lists of identified primary studies [34]. Studies were included if they included nCD64 expression accuracy for sepsis diagnosis in adult patients that provided sufficient information to construct a 2×2 contingency table [34]. A total of 8 studies comprising 1986 patients fulfilled the inclusion criteria for the final analysis. On the basis of their meta-analysis, nCD64 expression was a helpful marker for early sepsis diagnosis for critically ill patients. The authors stated that results should not be used alone to diagnose sepsis, but should be interpreted in combination with medical history, physical examination, and other test results [34].

Neonatal sepsis

Therapeutic strategies by combining increased bacterial elimination via improving the innate immunity and decreasing the inflammatory injury could be worthwhile sepsis. There is significant variability in the criteria used by investigators to substantiate the diagnosis of neonatal sepsis. Increased nCD64 expression could also be useful in diagnosis of neonatal sepsis [35]. This study evaluated the diagnostic efficacy of nCD64 expression as an early indicator of neonatal sepsis in 60 neonates in which 24 were culture positive and 36 were culture negative, with suspected sepsis along with 30 controls [35]. The expression of CD64 was studied using flow cytometry both on neutrophils and monocytes. Sick neonates had significantly higher mean and median nCD64 expression compared with controls. Monocyte CD64 values did not differ significantly among the groups. Both mean and median monocyte/neutrophil CD64 ratios were significantly lower in the former group and culture-positive neonates had significantly higher mean and median nCD64 values but significantly lower mean and median monocyte/neutrophil CD64 ratios than clinically indistinguishable culture-negative neonates and both groups were significantly different to these indices from normal controls [35]. Thus, enhanced nCD64 reported as the monocyte/neutrophil median CD64 ratio is a highly sensitive marker of culture-positive neonatal sepsis; it identifies a separate group among culture-negative sick neonates and may be useful to guide antibiotic administration especially in these neonates [35]. A systematic review and meta-analysis to investigate the diagnostic value of the IL-8 in neonatal sepsis an important cause of morbidity and mortality in neonates was conducted [36]. 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 [36].

The gold standard for diagnosing bloodstream infections is blood culture, but can be time-consuming. These authors reviewed systematically prediction models for Healthcare-Associated Blood

Stream Infection (HABSI) in neonates, identified superior models, and pooled clinical predictors [37]. The systematic search included 9 articles with 12 prediction models that listed 1295 suspected and 434 laboratory-confirmed sepsis episodes. Models exhibit moderate-good methodologic quality, large pretest probability range, and insufficient diagnostic accuracy. A meta-analysis of random effects showed that lethargy, pallor/mottling, total parenteral nutrition, lipid infusion, and postnatal corticosteroids were predictive for HABSI [37]. Neonates with low-gestational-age by post hoc analysis demonstrated that apnea/bradycardia, lethargy, pallor/mottling, and poor peripheral perfusion were predictive for HABSI. Some limitations included clinical and statistical heterogeneity. These authors stated that lethargy and pallor and/or mottling for all neonates, apnea, 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 [37].

A prospective, observational nested cohort study at two Pediatric Intensive Care Units (PICUs) and one pediatric Emergency Department (ED) was performed in children ages 2-17 years that presented to the PICU or ED with sepsis for procedural sedation to the ED along with controls [38]. The authors performed metabolic and inflammatory protein mediator profiling with serum and plasma drawn on presentation, followed by analysis of multivariate statistics. Metabolomic profiling revealed clear separation of groups, differentiating PICU sepsis from ED sepsis and protein mediator profiling also showed clear separation of the groups. Combining metabolomic and protein mediator profiling improved the model differentiating PICU sepsis from ED sepsis and separation of PICU sepsis or ED sepsis from ED controls was even more accurate [38]. In children ages 2-17 years, combining metabolomic and inflammatory protein mediator profiling in the early period may differentiate children with sepsis requiring care in a PICU from children with or without sepsis in an outside PICU. The authors stated "this may aid in making triage decisions, especially in an ED without pediatric expertise, however this finding requires validation in an independent cohort' since sepsis is one of the most important causes of neonatal morbidity, mortality, and prolonged hospital stay [38].

The aim of this prospective, observational nested cohort study was to evaluate serum calprotectin for neonatal sepsis as a biomarker. Eight neonates had sepsis with a positive culture and 33 had suspected sepsis. Thus, calprotectin may be considered a promising early, sensitive, specific marker for sepsis and it is important in defense mechanisms and immune physiological functions [39].

Newborn hypoxia and reactive oxygen species

A review on Hypoxia Inducible Factor (HIF) signaling and experimental persistent pulmonary hypertension of the newborn animals was conducted [40]. 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 lead to Hypoxia Inducible Factor (HIF) signaling in response to hypoxia with complex physiological and biochemical processes facilitating the fetus to newborn transition, abnormal lung development and/or vascular dysfunction that can disrupt these events [40].

Increased signaling by HIF in PPHN can be triggered by stretch, through mechanisms involving mitochondrial ROS and NFkB. Hypoxia substantially amplifies HIF activity in PPHN vascular cells targeting these signaling molecules may attenuate and reverse pulmonary vascular remodeling associated with PPHN [40]. The authors stated 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 therapeutic strategies for babies with PPHN [40].

Quinones and reactive oxygen species

Quinones are electron proton carriers that are important in the aerobic metabolism of mostly every cell in nature [41]. They lead to 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) [41]. Quinones have been extensively studied for their cytotoxic and cellular protective properties and they have been especially useful in rational drug design.

Nanomaterials, substances are used in medical diagnosis and treatment every day. A review of the literature revealed an inflammatory response and an increased production of ROS to be common immune responses to nanomaterial use and the mechanisms by which the inflammatory response and ROS production occurs was discussed [42]. This paper also investigated the successful treatments made with nanoparticles and some general health effects.

Severe sepsis and septic shock remains a leading cause of mortality and morbidity in children.

Pediatric septic shock

There is ongoing uncertainty regarding the optimal treatment pathways however the initial management of sepsis is crucial. This article by the authors was designed to be an informal and personal review of recent developments in pediatric sepsis over the past 3 years the surviving sepsis campaign recommendations focus on early identification of severe sepsis and septic shock, prompt administration of IV antibiotics with haemodynamic resuscitation and then ongoing supportive care [43].

Septic shock remains an important cause of death and disability in children. Optimal care requires early recognition and treatment. Critically ill children with septic shock treated in a children's hospital ED who received antibiotics in ≤1 hour were significantly more severely ill than those treated later, but they did not have increased risk of new or progressive multiple system organ dysfunction syndrome or death [44].

Procalcitonin biomarker related to sepsis

A recent paper by one of the authors stated marked increase in serum procalcitonin during a septic process often indicates exacerbation of the illness with a decreased sign of improvement [45]. Immune surveillance in the patient could fail to eliminate the pathogen, and could spread with a pro-inflammatory release and inappropriate activation [45].

This recent review showed that procalcitonin is a more accurate

diagnostic parameter for sepsis and a better predictor of mortality [46]. Procalcitonin is a more reliable marker than other biomarkers including C-reactive protein, Interleukins and lactate levels. Procalcitonin has been proved to be superior biomarker; however its use still has to be interpreted in the context of clinical presentation [46]. Further study on the role of procalcitonin is needed for more effective and targeted approach in sepsis. 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 [47].

Procalcitonin is useful for the diagnosis of sepsis a value [greater than or equal to] 7ng/ml obtained at the time of admission to the ICU is a predictor of short-term mortality and thus may allow the identification of those septic patients at increased mortality risk, and help improve their treatment [48].

Procalcitonin is synthesized by a large number of tissues and organs in response to the invasion by pathogenic microorganisms and it is useful as a marker to improve the diagnosis of bacterial infections and guide antibiotic therapy [49]. Procalcitonin also correlates with the extent and severity of infection, and it can be used for a prognostic marker [49].

Delay in initiation and the diagnosis of antibiotics have been reported to increase mortality in critically ill patients [50]. These authors stated procalcitonin has emerged as the most studied and promising sepsis biomarker. Many studies have demonstrated that serum procalcitonin levels are increased in patients with sepsis, and the high levels of procalcitonin correlate with the outcome of the disease and can be used for differential diagnosis, prognosis, and follow-up of critically ill patients [50].

This paper stated an ideal biomarker should have high diagnostic accuracy for early and rapid recognition of sepsis and procalcitonin meets many of these requirements [51]. Serum procalcitonin levels have been noted to increase with the increase in the severity of sepsis and rising procalcitonin levels might be used as an indicator that an infectious process is not under control [51]. The author stated procalcitonin provides important information in early stages of sepsis and during antimicrobial therapy and it can be useful for antimicrobial stewardship leading to significant reduction of unnecessary antimicrobial therapy [51]. This paper also stated this information is intended to provide an additional area for clinicians and microbiologists to understand better the physiology and diagnosis using procalcitonin for sepsis and other infectious diseases.

Early diagnosis of neonatal sepsis is important and appropriate treatment is known to decreases mortality and morbidity in infants. The aim of this paper was to evaluate procalcitonin as a marker in the early diagnosis of neonatal sepsis. Thirty eight neonates with early onset sepsis were admitted to the neonatal ICUs in Egypt over one year in late summer [52]. Another 35 healthy neonates with no clinical or biological evidence of infection were included as a control group. A complete history and routine laboratory investigations were performed. Serum procalcitonin and C-reactive protein levels were performed using a enzyme-linked immunosorbent assay. The mean levels of procalcitonin and C-reactive protein levels in septic neonates were significantly higher than in the controls [52]. There was also a moderate, but significant, positive correlation between procalcitonin and C-reactive protein but an insignificant correlation between procalcitonin and total leukocytic counts in the neonates with sepsis. The authors stated procalcitonin had a high sensitivity, specificity, and a high positive predictive value, and a high negative predictive value. Thus, procalcitonin had a higher sensitivity when compared to C-reactive protein and it is a sensitive, independent, and useful biomarker in comparison to C-reactive protein in the early diagnosis of neonatal sepsis [52].

This paper stated that defining sepsis is often difficult and even more challenging is differentiating infection-induced from non-infection-induced SIRS and multiple organ dysfunctions [53]. Biomarkers are often used, and one of the most frequently investigated one is procalcitonin. Substantial improvements in outcomes have occurred due to early stabilization of vital functions through adequate supportive therapy and antibiotic treatment. This intervention has been applied on a large scale in daily practice with a strong pathophysiological rationale but weak evidence as supported in clinical trials. The purpose of this review was to give an overview on the pathophysiology of sepsis, biomarker interpretation and their potential use in assisting in future adjunctive sepsis therapies [53].

Procalcitonin has been known to be a sensitive inflammatory biomarker marker in non-neutropenic patients. The aim of this study was to determine and compare procalcitonin with other inflammatory biomarkers markers in immune suppressed children with hematological malignancies; and to evaluate the predictive value of these mediators in distinguishing between both bacterial and non-bacterial infection [54]. According to their results the procalcitonin concentration increased rapidly in those patients with microbial infection and the response was quickly detectable with the onset of fever due to microbial infections. The authors stated procalcitonin is a specific and sensitive marker of microbial infection in patients with neutropenic fever. The markers, C-reactive protein, interleukin-6 and NO_2/NO_3 may not help to identify infections and to distinguish the cause of infection in neutropenic febrile children with acute lymphoblastic leukaemia [54].

Serum procalcitonin levels also rapidly increase in patients with bacterial disease that is invasive. Procalcitonin levels increase more quickly than C-reactive protein levels and a rapid decrease in the procalcitonin level is supporting evidence that the bacterial infection source responds to clinical management [55]. In patients with community-acquired bacterial pneumonia, sequential procalcitonin levels are also useful as a guide to shorter courses of antimicrobial treatments. According to this author with use of emerging multiplex real-time polymerase chain reactions for the detection of viral and bacterial respiratory pathogens, it should be possible to assess critically whether an elevated serum procalcitonin level is a valid biomarker for invasive bacterial infection [55].

Conclusion

Trauma and sepsis, shock and biomarkers are very important both in adults, infants and 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 trauma, sepsis, shock inflammation, innate immunity, role of neutrophils and

IL-8, reactive oxygen species, neonatal hypoxia, the role of NF-kappa B related to inflammation. Procalcitonin and other biomarkers are helpful in identifying adult and neonatal sepsis, defense mechanisms and physiological functions of the immune system..These topics are very important for pediatricians, pulmonologists, intensivists and immunologists in academic centers and in practice.

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