



Review Article

Trauma-Induced Systemic Inflammatory Response: A Comprehensive Review

M Mileković^{1*}, A Ristić², LB Grošelj², I Rović¹, D Šijan¹, Ž Uskoković¹, K Petrović¹

¹University Clinical Centre of Serbia, Belgrade, Serbia

²University of Belgrade - Faculty of Medicine, Serbia

*Correspondence author: Marija Milenkovic, University Clinical Centre of Serbia, Belgrade, Serbia; Email: marija.milenkovic@med.bg.ac.rs

Citation: Milenkovic M, et al. Trauma-Induced Systemic Inflammatory Response: A Comprehensive Review. J Surg Res Prac. 2023;4(3):1-5.

<https://doi.org/10.46889/JSRP.2023.4301>

Received Date: 30-08-2023

Accepted Date: 20-09-2023

Published Date: 27-09-2023



Copyright: © 2023 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CCBY) license (<https://creativecommons.org/licenses/by/4.0/>).

Abstract

Trauma is a noteworthy contributor to death and disability in adults. Its impact can extend to multiple organ systems via complex physiological reactions. This article comprehensively examines the physiological responses that transpire following trauma. It begins with the initial immune and inflammatory responses and advances to the possibility of sepsis and multi-organ dysfunction syndrome (MODS). The article delves into the roles of the innate and adaptive immune systems, the Systemic Inflammatory Response Syndrome (SIRS), and the various stages of sepsis. It emphasizes the importance of early detection and treatment, showcasing the benefit of the Injury Severity Score (ISS) to assess trauma severity and the Sequential Organ Failure Assessment (SOFA) scores to estimate sepsis severity. While acknowledging progress in understanding and identifying trauma-related conditions, the article emphasizes the importance of providing timely and accurate treatment to improve patient's recovery.

Keywords: Trauma; Physiological Responses; Immune System; Inflammatory Responses; Sepsis; Multi-Organ Dysfunction Syndrome (MODS); Systemic Inflammatory Response Syndrome (SIRS); Injury Severity Score (ISS); Sequential Organ Failure Assessment (SOFA); Early Detection and Treatment

Introduction

Trauma refers to harm inflicted on the body by external forces. Despite progress in treatment for trauma patients, it remains the primary cause of death and disability in adults [1,2]. Trauma encompasses a range of injuries, from single wounds to complex damage affecting multiple organ systems [3]. Therefore, it can be classified as severe or polytrauma. Severe trauma refers to damage to one organ or system that may result in death, while polytrauma correlates to injury

of two or more organs or systems that may lead to death [4]. The Berlin definition outlines criteria for identifying polytrauma, which includes injuries in at least two body areas with physiological indicators like low blood pressure, altered consciousness, acidosis, or age (70 years or older) [5]. The severity of an injury is typically assessed using the Injury Severity Score (ISS), estimated from data in the Abbreviated Injury Scale (AIS). Utilization of the above is vital in a multidisciplinary team approach while obeying the established protocol to provide adequate care.

Epidemiology and Impact

Trauma is a leading cause of death, especially for young adults (18-29 years), with over 5.8 million deaths annually. Obesity and health issues worsen outcomes. Hemorrhage, MODS and cardiac arrest are common causes. Preventable deaths include extubation, surgical failure, overlooked injuries and catheter complications. Fast treatment is crucial in the first few hours (the "golden hour") to prevent most deaths [3].

Pathophysiological Processes

Apprehending the fundamental pathophysiological processes in managing traumatized patients is essential for minimizing the risk of severe health damage. This is especially consequential given trauma's significant impact on mortality and disability rates. As such, the forthcoming chapters will cover the various segments of the body's defense system in trauma.

Immune System and Inflammatory Responses

Following a trauma, the body undergoes a sequence of interactions to minimize tissue damage. Pathogens produce PAMPs, or DAMPs, expressed on damaged host cells due to infection, chemical, physical, or thermal trauma injury and hypoperfusion. Responses to DAMPs benefit from eliminating damaged cells and initiating the process of tissue repair [7]. The innate immune system utilizes cellular receptors and soluble molecules in the blood to recognize PAMPs and DAMPs. These molecules trigger the inflammatory response by stimulating the innate immune system via receptors similar to Toll-like receptors located on the cells of the natural immune system [7,8]. Our skin and mucous membranes shield us from harmful microorganisms. When compromised, specialized cells assemble antimicrobial substances and activate the body's defenses [7]. When there is a DAMP-TLR interaction, the immune system responds by releasing inflammatory mediators like cytokines. This attracts immune cells like neutrophils and monocytes to the site of infection or injury. If proinflammatory defense pathways dominate, it can increase the risk of sepsis and organ failure [9,10].

The immune system interacts with other bodily systems, like the nervous and endocrine systems-physical trauma and distress cause the CNS to release neurotransmitters that suppress the immune response. The parasympathetic system also suppresses cytokine release [9]. Trauma can impair the blood vessel's endothelium and trigger platelet aggregation, leading to the coagulation cascade activation and by-products in fibrin formation and hemostasis. This pathway underlies trauma-induced coagulopathy [11].

Innate Immune System

The innate immune system identifies microorganisms or damaged host cells and triggers an inflammatory response and Toll-like receptors play an essential role. The skin and mucous membranes operate as barriers and their disturbance can increase the risk of infection. Antimicrobial substances are released and a cascade involving immune cells and the complement system releases proinflammatory and anti-inflammatory mediators. Over-drive of proinflammatory pathways can lead to persistent inflammation, increasing the chance of sepsis and organ failure. Trauma can subdue the immune response by discharging neurotransmitters and vasoconstriction, initiating the coagulation cascade and leading to coagulopathy [12].

Adaptive Immune System

The non-specific immune system also activates the adaptive immune system that comprises T and B lymphocytes. Activation occurs through the created IFN- γ molecules, which influence dendritic cells and macrophages to express costimulators that bind to naive T-lymphocytes and cause their activation. Likewise, IL-12, IL-1 and IL-6 cytokines stimulate the proliferation and differentiation of naive T-lymphocytes into effector cells that additionally activate B lymphocytes [12].

Inflammation

Inflammation is a tissue response to infection or damage. It causes redness, swelling and pain. The initial reaction is meant to immobilize the injury site, whereas it can lead to dysfunction and coagulopathy if it is not proportional. An exaggerated response can cause immunosuppression and secondary infections [13].

The Systemic Inflammatory Response Syndrome

SIRS is a response to multiple harmful factors with suspected or proven infection. It is defined as symptoms including fever, heart rate increase, breathing rate increase and abnormal white blood cell count. Two of these symptoms indicate sepsis. The goal is to diagnose and treat sepsis early to decrease mortality [14,15]. During inflammation, there is an inequality between free radicals and the body's antioxidant defense. Glutathione, thyroedoxin and selenium are vital antioxidants that can diminish inflammation when introduced via parenteral nutrition. SIRS was withdrawn from the definition of sepsis by the Third International Consensus for Sepsis and Septic Shock (Sepsis-3) due to restricted accuracy in clinical practice [17].

Sepsis

The second modern definition of sepsis aimed to diagnose patients quickly. It showed sepsis as a clinical syndrome, graded by severity. This definition included parameters to aid diagnosis but had low specificity. It helped with early diagnosis and treatment [14].

Sepsis is defined as a Systemic Inflammatory Response to Infection (SIRS) with two or more of the following parameters: temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, heart rate $>90/\text{min}$, respiratory rate $>20/\text{min}$ or $\text{PaCO}_2 <32 \text{ mmHg}$, white blood cell count $>12,000/\mu\text{L}$ or $<4000/\mu\text{L}$ or $>10\%$ immature forms as of 1991. Sepsis-2/2001 added parameters for sepsis detection and organ dysfunction, including significant edema/positive fluid balance, hyperglycemia without diabetes, C-reactive protein 2x beyond average, procalcitonin 2x above normal, arterial hypotension, mixed venous saturation $>70\%$, arterial hypoxemia, acute oliguria with creatinine increase $\geq 0.5 \text{ mg/dL}$, coagulation abnormalities, thrombocytopenia, ileus, hyperbilirubinemia, hyperlactatemia and reduced capillary refill [18]. The severity of organ dysfunction in sepsis is measured by the SOFA score, which must increase by at least 2 points to confirm the diagnosis.

SOFA Score

The SOFA score assesses organ dysfunction in ICU patients using specific parameters. A change of 2 or more points indicates dysfunction, with a sharp increase indicating severe dysfunction and a 10% mortality rate. Parameters evaluate respiratory, cardiovascular, coagulation, renal, metabolism and central nervous systems. The qSOFA score simplifies assessment based on low blood pressure, high respiratory rate and altered mental status [19].

Pathophysiology of Sepsis

Sepsis ensues when the release of proinflammatory mediators in response to trauma. It is considered a malignant intravascular inflammation as it is unregulated and self-perpetuating [20]. Roger Bone presented five stages of the septic cascade that overlap.

An early response called Compensatory Anti-Inflammatory Response Syndrome (CARS) aims to establish a balance in the immune system. This is led by mediators IL-4 and IL-10. The predominance of proinflammatory cytokines can lead to Systemic Inflammatory Response Syndrome (SIRS), which can progress to endothelial dysfunction and coagulopathy. In cases where CARS is predominant over SIRS, there may be a relative immunosuppression, making the organism more susceptible to secondary infections, eventually leading to Multiorgan Dysfunction Syndrome (MODS) [15]. Inflammation provokes organ dysfunction via various mechanisms, such as tissue ischemia, proinflammatory mediators, apoptosis, microcirculatory further endothelial lesions and mitochondrial dysfunction. Cell death can also be induced through apoptosis. When immune cells are activated, their programmed cell death can be delayed, leading to extended inflammation and weakened immunity against invading microorganisms. Excessive autophagy can worsen tissue damage [15,26,20].

Organ-Specific Effects of Sepsis

The damage to both endothelial and parenchymal cells during sepsis leads to dysfunction in multiple organ systems, resulting in the term Multiple Organ Dysfunction Syndrome (MODS).

Hypotension of the cardiovascular system is driven by vasodilation from inflammatory mediators, possibly by means of nitric oxide. Fluid can also shift between compartments due to endothelial permeability and vascular resistance changes. The heart's capacity decreases due to inhibitory substances. Decreases in functional capillaries and hypoperfusion in the splanchnic system are noted due to the centralization of blood flow [20,21]. Damage to the endothelium in the pulmonary circulation during sepsis impairs circulation and advances the permeability of small blood vessels, inducing pulmonary edema. A ventilation-perfusion mismatch occurs, leading to hypoxemia, progressing to Acute Respiratory Distress Syndrome (ARDS) [22].

Further, the gastrointestinal system suffers from hypoxia, leading to inadequate function of intestinal cells and disrupted barrier role of the intestinal epithelium, prolonging inflammation. Kidneys will be affected by acute renal insufficiency, likely that damage occurs due to a toxic effect on tubulocytes caused by cytokines released from acute tubular necrosis, along with inflammation caused by activated neutrophils [20]. Sepsis can affect the central nervous system, causing encephalopathy due to altered metabolism and signaling from inflammatory mediators, as the hematoencephalic barrier becomes compromised [20,22].

Conclusion

Traumatic injuries induced by external forces usually result in disability or death in adults, frequently due to traffic collisions. Researchers worldwide have investigated this topic considerably. Its impact is additionally complicated by a many-sided physiological response that involves various body systems, from the immune response to coagulation pathways. The body's immune system responds to initial injury using cells and substances. After, the body goes through an inflammatory response. This is pursued by an anti-inflammatory reaction that returns the body to a normal state. When the body generates an inflammation response, it becomes additionally susceptible to infection, potentially leading to sepsis. Scientists have been working to specify sepsis for decades, with the latest international definition established in 2016 as a dangerous infection response that can cause organ dysfunction. Furthermore, the SOFA score interprets it and dictates the most appropriate next steps in treatment. If contrary, it can potentially advance to MODS, impacting multiple organs and resulting in a 50% mortality rate. Despite advancements in defining conditions like sepsis, we can conclude that the stakes remain high, with poor outcomes often hinging on swift and valid diagnosis and treatment. Therefore, it is essential to comprehend the nuances of these pathophysiology processes and, with it, the optimal and punctual therapy provision to traumatized patients.

Conflict of Interest

The authors have no conflict of interest to declare.

References

- Butcher N, Balogh ZJ. The definition of polytrauma: the need for international consensus. *Injury*. 2009;40:S12-22.
- Mathers C, Loncar D, Projections of global mortality and disease burden from 2002 to 2030. *PLoS Med*. 2006;3(11):e442.
- Ali R, Richard D Z. Initial management of trauma in adults. [Last accessed on: September 15, 2023]
https://www.uptodate.com/contents/initial-management-of-trauma-in-adults?search=trauma&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1
- Butcher NE, Enninghorst N, Sisak K, Balogh ZJ. The definition of polytrauma: variable interrater versus intrarater agreement—a prospective international study among trauma surgeons. *J Trauma and Acute Care Surg*. 2013;74(3):884-9.
- Pape HC, Lefering R, Butcher N, Peitzman A, Leenen L, Marzi I, et al. The definition of polytrauma revisited: An international consensus process and proposal of the new 'Berlin definition'. *J Trauma Acute Care Surg*. 2014;77(5):780-6.
- Palmer CS, Gabbe BJ, Cameron PA. Defining major trauma using the 2008 Abbreviated Injury Scale. *Injury*. 2016;47(1):109-15.
- Shiv P, Abbas A, Lichtman A, Pillai S. Cellular and molecular immunology E-book. Elsevier Health Sciences. 2014.
- Pape HC, Moore EE, McKinley T, Sauaia A. Pathophysiology in patients with polytrauma. *Injury*. 2022;53(7):2400-12.
- Richard B Johnston, Jr MD. An overview of the innate immune system. [Last accessed on: September 15, 2023]
https://www.uptodate.com/contents/an-overview-of-the-innate-immune-system?search=innate%20immune%20system%20trauma&source=search_result&selectedTitle=1~150&usage_type=display_rank=1
- Chakraborty S, Karasu E, Huber-Lang M. Complement after trauma: suturing innate and adaptive immunity. *Frontiers Immunol*. 2018;9:2050.
- Camire RM. Blood coagulation factor X: Molecular biology, inherited disease and engineered therapeutics. *J Thrombosis Thrombolysis*. 2021;52(2):383-90.
- Shiv P, Abas AK, Liktman EH, Ramić Z, Mostarica-Stojković M, Popadić D, et al. Osnovna imunologija: funkcionisanje i poremećaji imunskog sistema. 2006.
- Balk RA. Systemic Inflammatory Response Syndrome (SIRS) Where did it come from and is it still relevant today? *Virulence*. 2014;5(1):20-6.
- Dimić N, Đurić M, Nenadić I, Boboš M, Bojić S, Vukotić T, et al. Development of the definition of sepsis. *Srpski medicinski časopis Lekarske komore*. 2023;4(1):75-81.
- Chakraborty RK, Burns B. Systemic inflammatory response syndrome. 2019.
- Bosmann M, Ward PA. The inflammatory response in sepsis. *Trends Immunol*. 2013;34(3):129-36.
- Jaramillo-Bustamante JC, Piñeres-Olave BE, González-Dambrauskas S. SIRS or not SIRS: Is that the infection? A critical review of the sepsis definition criteria. *Boletín médico del Hospital Infantil de México*. 2020;77(6):293-302.

18. Boehm D, Menke H. Sepsis in burns-lessons learnt from developments in the management of septic shock. *Medicina*. 2021;58(1):26.
19. Singer M, Deutschman CS, Seymour CW. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):801-10.
20. Neviere R. Pathophysiology of sepsis. 2013. UpToDate, Waltham (MA).
21. Dolmatova EV, Wang K, Mandavilli R, Griendling KK. The effects of sepsis on endothelium and clinical implications. *Cardiovascular Res*. 2021;117(1):60-73.
22. Ghosh S, Latimer RD, Gray BM, Harwood RJ, Oduro A. Endotoxin-induced organ injury. *Critical care medicine*. 1993;21(2):S19-24.

Journal of Surgery Research and Practice



Publish your work in this journal

Journal of Surgery Research and Practice is an international, peer-reviewed, open access journal publishing original research, reports, editorials, reviews and commentaries. All aspects of surgery health maintenance, preventative measures and disease treatment interventions are addressed within the journal. Medical surgeons and other researchers are invited to submit their work in the journal. The manuscript submission system is online and journal follows a fair peer-review practices.

Submit your manuscript here: <https://athenaeumpub.com/submit-manuscript/>