Review

https://doi.org/10.23934/2223-9022-2023-12-1-92-98

Pathogenetic Mechanisms of Organ Dysfunction in Severe Concomitant Trauma

G.V. Bulava✉

Clinical Immunology Laboratory
N.V. Sklifosovsky Research Institute for Emergency Medicine
3 Bolshaya Sukharevskaya Sq., Moscow, 129090, Russian Federation

✉ **Contacts:** Galina V. Bulava, Doctor of Medical Sciences, Scientific Consultant, Clinical Immunology Laboratory, N.V. Sklifosovsky Research Institute for Emergency Medicine. Email: gbulava@mail

ABSTRACT Severe concomitant trauma has been a major demographic and medical problem for many years, being the cause of high mortality of the able-bodied population. The simultaneous formation of an array of destroyed tissues triggers a systemic inflammatory reaction, which, against the background of traumatic and hemorrhagic shock, leads to an imbalance in immune reactivity and predisposes to the development of septic complications. The review presents the basic concepts of post-traumatic reactions and violations of the balance of cellular and humoral immune mechanisms leading to the development of complications.

Keywords: severe concomitant trauma, acute blood loss, systemic inflammatory reaction, cytokines, traumatic brain injury, microbiome

For citation Bulava GV. Pathogenetic Mechanisms of Organ Dysfunction in Severe Concomitant Trauma. *Russian Sklifosovsky Journal of Emergency Medical Care.* 2023;12(1):92–98. https://doi.org/10.23934/2223-9022-2023-12-1-92-98 (in Russ.)

Conflict of interest Author declare lack of the conflicts of interests

Acknowledgments, sponsorship The study has no sponsorship

Affiliations

Galina V. Bulava	Doctor of Medical Sciences, Scientific Consultant, Clinical Immunology Laboratory, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0002-1244-2135, gbulava@mail.ru

ATP – adenosine triphosphate
DNA – deoxyribonucleic acid
IL – interleukin
HIV/AIDS – Human Immunodeficiency Virus/ Acquired immunodeficiency syndrome
miRNA – microribonucleic acid
mtDNA – mitochondrial DNA
NP – neutrophil
PSA – polysaccharide A
SIRS – systemic inflammatory response syndrome
TBI – traumatic brain injury
TNF–α - tumor necrosis factor α
T-reg – regulatory T-lymphocytes

Severe injury is one of the leading causes of death worldwide. According to the World Health Organization, injuries account for 10% of deaths and 16% of disability worldwide—significantly more than malaria, tuberculosis, and HIV/AIDS combined [1]. The proportion of deaths caused by injuries continues to rise, and according to relatively recent projections, by 2020 road traffic accidents alone should have become the fifth leading cause of death and disability [2].

This review presents the basic concepts of the post-traumatic reaction and describes some of the innate immune events that occur in the early stages after a severe concomitant injury (polytrauma), as well as disorders of immune defense mechanisms leading to the development of septic complications.

The systemic response to severe trauma involves interactions between the immune, endocrine, nervous, and coagulation-lysis systems, exacerbating the initial injury caused by hypoperfusion (shock) and reperfusion. The endothelium, activated by exposure to inflammatory cytokines, becomes more porous, allowing mediators of tissue injury to gain access to the extracellular space. Violation of macro- (such as skin) and micro-barriers (such as cell membranes) causes immediate activation of innate immunity. The subsequent complex response aimed at limiting further damage and stimulating healing is also the main provoking factor in the development of complications and death after injury [3–6].

In the early stages after injury, the cause of victims' death is severe damage to several vital organs, hypoxia and hypovolemia as a result of massive blood loss, and head trauma with damage to brain structures. At the same time, uncontrolled bleeding is the main cause of death. The first hour after a serious injury with massive bleeding is, of course, the most crucial period in the provision of life-saving care [7, 8]. Hemorrhagic shock leads to tissue

hypoperfusion and physiological changes that eventually lead to organ dysfunction and death. Therefore, measures to combat damage should be primarily aimed at stopping massive bleeding [9]. Despite differences in massive hemorrhage protocols, most of them recommend the use of erythrocyte concentrate, fresh frozen plasma in a 1:1 ratio, then platelets and cryoprecipitate [10]. But, it is known that as a result of storage, normal, smooth, easily deformable and curving disc-shaped erythrocytes, which easily pass through microvessels, change to spheroechinocytes - spherical cells with protrusions that are rigid and more likely to adhere to the capillary endothelium [11, 12]. Microparticles released during storage — fragments of the cell membrane and hemoglobin of submicron size — are the damage components that stimulate inflammation, absorb nitric oxide which regulates many processes in the body, including relaxation of vascular smooth muscles. As a result, there is no vasodilation and no increase in blood flow [13]. It should be noted that in recent years there has been a renewed interest in replenishing acute blood loss with whole blood. It has been shown that the transfusion of whole blood, rather than its components, facilitated better survival in adult patients with injuries compared with patients in whom blood loss was replenished with blood components [14].

However, stopping the bleeding and restoring blood pressure is no guarantee that the danger has passed. The cause of death in two-thirds of patients who die after a serious injury is not bleeding, but the consequences of a systemic inflammatory response caused by trauma, which includes an acute, non-specific immune response, subsequently associated, paradoxically, with a decrease in resistance to infection, leading to sepsis and further activation of the destructive inflammatory response [3]. Infection, ischemia/reperfusion, or surgery can further enhance the pro-inflammatory immune response, which is defined as systemic inflammatory response syndrome (SIRS). With an imbalance in the mechanisms that regulate inflammation activity, tissues in organs not affected by the initial injury can be damaged and destroyed, followed by the development of multiple organ dysfunction and septic complications, which correlate with high mortality in later periods after injury [15–17].

SIRS begins within 13 minutes after a major injury and is an inflammatory response to blood loss and tissue damage rather than infection. The systemic response results from the release of endogenous factors called damage-associated molecular patterns (DAMPs) [18, 19]. They are secreted by activated immune cells such as neutrophils and tissue macrophages [20–23]. When local barriers are destroyed, endogenous DAMP molecules are perceived by the complement and coagulation systems and induce the activation of immune cells, which leads to an instant cellular immune response. Ideally, a balanced pro-inflammatory and anti-inflammatory response leads to a rapid clearance of cellular "garbage" and the induction of effective tissue repair and regeneration [24]. However, this balance is often impaired, which leads to the development of early (aseptic) or late (septic) multiple organ dysfunction.

Peptides and mitochondrial DNA (mtDNA), which are released when cells and tissues are damaged or dead, elicit a particularly strong immune response. To date, most research on mitochondria has focused on their role as cellular organelles responsible for energy production, protein synthesis, catabolism, and cell death [25, 26]. However, recent studies have shown that mitochondrial components from cells damaged as a result of trauma are a key factor for the development of SIRS under aseptic conditions [27, 28].

Examples of well-known immune response stimulators include DNA, high mobility group box1 proteins, and heat shock proteins [29]. Of greatest interest was mtDNA, a molecule capable of stimulating an immune response through interaction with the toll-like receptor TLR9 and inflammasomes [27, 29]. In recent years, a lot of scientific literature has appeared showing that mtDNA is not just released during critical illness, but is an independent predictor of death in critically ill patients, and contributes to the inflammatory response observed in sepsis [30]. Therefore, it is highly likely that the determination of mtDNA concentration may be used as a predictor of the severity of the disease or the development of septic complications and mortality in severely affected patients. A group of authors [32] found out that a significant increase in the level of mtDNA in the blood plasma in patients with severe polytrauma occurred during the first 24 hours. Moreover, statistically significant differences in the plasma levels of mtDNA both in patients with bronchopulmonary infectious complications developed later and in those who did not have such complications were detected already in the first 12 hours. This allowed the authors to recommend the measurement of mtDNA on the first day after injury to predict the development of infectious complications.

Changes in the immune response after multiple trauma, post-traumatic sepsis and surgery are recognized as physiological responses of the body to the restoration of homeostasis. The severity of these immunological changes correlates with the degree of tissue damage, as well as with the severity of bleeding and ischemia [8, 32]. The main regulatory and integral components of this immune response are cytokines. It appears that their balance

or imbalance partially controls the clinical course in patients with severe trauma. An overproduction of either pro-inflammatory or anti-inflammatory cytokines can lead to organ dysfunction. Major pro-inflammatory cytokines involved in the response to trauma and surgery include tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-β), IL-6, and IL-8 [33]. These cytokines, predominantly produced by monocytes and macrophages, mediate a variety of often overlapping effects, and their action may be additive. TNF-α and IL-1β are early regulators of the immune response and both induce the release of secondary cytokines such as IL-6 and IL-8.

The functioning of the immune system is built on the principle of feedback which is necessary to restore homeostasis. SIRS is associated with a compensatory anti-inflammatory response characterized by increased levels of anti-inflammatory cytokines (eg, IL-10) and transforming growth factor beta (TGF-β) and cytokine antagonists (eg, IL-1-Ra) [34]. Other important anti-inflammatory mediators are soluble TNF receptors and an IL-1 receptor antagonist, which interfere with the effects of TNF-α and IL-1β [35]. Depending on the balance of pro- and anti-inflammatory factors, the response may return to baseline or progress to persistent hyperactive inflammation, immunosuppression, and catabolism syndrome with an increased risk of multiple organ dysfunction and sepsis [36]. The risk of developing an enhanced and unstabilizable inflammatory response increases with age – with a comparable severity of injury [37]. Older adults have a significantly worse prognosis after injury, regardless of the nature or severity of the trauma, even after adjusting for comorbidities [38].

The most severe dysfunction of several parts of the immune system in patients with multiple injuries manifests itself in the first two days after injury. However, even on day 5, the immune system is still not fully functional and cytokine imbalance persists. Due to discovered correlation between IL-6 and IL-8 levels and the development of post-traumatic infectious complications, their monitoring can help identify patients susceptible to infection in the first two days of hospitalization. The authors believe that the most useful prognostic parameters are the level of IL-6 on the first day after injury and the level of C-reactive protein on the second day [33].

Paradoxically, the excessive non-specific immune response in SIRS is accompanied by suppression of the body's ability to create defenses against invading pathogens. The result is an increased susceptibility to infection, with invading microbes further stimulating immune cells with their pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide, for example. A vicious circle ensues as SIRS leads to inflammation and immunoparalysis, which in turn result in sepsis with further increased inflammation and risk of multiple organ dysfunction. The inflammatory response also includes rapid activation of the complement system, but initial activation is followed by consumption and subsequent imbalance of components of the complement cascade [39], which is one of many factors that reduce the body's ability to defend itself against microorganisms.

One cannot ignore the important role of platelet factors in the activation of the immune response. Platelets under the influence of injury release pro-inflammatory mediators that stimulate the immune system, thereby contributing to SIRS. Activation of the immune system increases platelet activity, creating a self-sustaining cycle [40]. Platelets form leukocyte-platelet aggregates, which are powerful activators of immune cells and cause damage to endothelial cells [41]. Platelets [42] and neutrophils (NP) [43] are also major sources of microvesicles and exosomes that express surface markers and may contain various molecules (including cytokines, miRNAs, metabolites, and lipids) [44] that enhance SIRS. Humoral elements of the pathways of the coagulation-lytic and complementary systems act together to initiate an inflammatory response, while C3a, C5a complement components and fibrin are known to be chemoattractants of neutrophilic cells [24]. Activated NPs release proteases (including elastase) and reactive oxygen species, which is accompanied by damage to healthy tissues. This process exacerbates inflammation and leads to the development of localized organ damage, similar to that in acute respiratory distress syndrome [45]. It was shown that neutrophils release their DNA as part of the extracellular network to trap and destroy pathogens [46]. However, this anti-infective function of the neutrophil networks is to some extent canceled out by the histones present in these networks, which act as shock absorbers initiating further inflammation. It is important to note that although neutrophils are initially activated as a result of SIRS, their bactericidal function is markedly impaired at a later time [47, 48].

Over the past decade, it has been shown that the kinetics and amplitude of acute inflammatory reactions are also regulated by non-protein effectors, including lipid mediators such as protectins, maresins, resolvins, and miRNAs [49].

It should be noted that the combination of multiple injuries of the anatomical regions of the body with traumatic brain injury (TBI) significantly affects the development of infectious complications in the victims and the outcome. Damage to the membranes and structures of the brain is accompanied by the death of meningeal cells, damage to neurons, and activation of glial cells, such as microglia and astrocytes, which, by releasing

cytokines (for example, IL-1β and IL-6), recruit neutrophils and blood monocytes - macrophages to the damaged area, resulting in an inflammatory reaction in the brain [50, 51]. Moreover, extensive and stable secretion of cytokines can last up to several years.

The interaction between the brain and the nervous system is bidirectional: the injured brain exacerbates both SIRS and immune deficiency via parasympathetic and sympathetic pathways, respectively [52]. In addition, human models of traumatic brain injury (TBI) and experimental models have shown that the complement system is an early mediator of post-traumatic neuroinflammation and secondary neuronal damage, which ultimately leads to behavioral, emotional, and cognitive problems [53, 54]. The multifactorial development of edema, an increase in intracranial pressure, and a decrease in cerebral perfusion pressure and blood flow form a vicious circle that exacerbates hypoxic conditions disrupting the energy supply (ATP) in the brain. These intracerebral changes often lead to additional damage to the white and gray matter [55]; and nervous regulation impairment is accompanied by the development of dysfunction of many organs.

It should be noted that dysfunction of the intestinal barrier was recognized as one of the consequences of TBI [56]. Severe TBI was shown to induce structural changes in the intestinal villi and epithelium with disruption of the intestinal barrier, shift of the gut microbiome towards the pathobiome, and changes in the composition of local immune cells [56–58]. In addition, TBI was proved to activate the gut-brain axis and increase gut permeability [59]. The exact mechanism by which TBI alters intestinal permeability is still under investigation. However, one of the noteworthy results of an experimental study is that after TBI, intracellular adhesion molecules (ICAM-1) 1 accumulate in the intestine, the production of TNF-α, IL-6 and other cytokines is activated [60], which leads to an acute inflammatory response.

Perhaps one of the most important functions of the gut microbiota is to provide constant stimulation of the gut immune system, which contributes to the reduction of the inflammatory state in healthy individuals. The well-known human commensal microorganism Bacteroides fragilis produces polysaccharide A (PSA). The impact of PSA on the intestine leads to the production of regulatory T-lymphocytes (T-reg), an increase in the production of anti-inflammatory IL-10 and a decrease in the excretion of pro-inflammatory factors such as TNF-α, IL-17 and IL-23 [61].

The microbiome, which is described by a fairly stable phylogenetic composition and a relative abundance of bacterial taxa, changes significantly in the first 72 hours after injury. This rapid change in the gut microbiota represents a critical event that can affect outcomes after severe injury and induce an immunosuppressive state [62, 63]. Dysbacteriosis creates a disequilibrium and induces a pro-inflammatory phenotype. The pathophysiology underlying this immunomodulation remains complex and is the subject of ongoing research. It is likely that both aspects of the innate and adaptive immune systems are involved [61]. The combination of polytrauma with TBI significantly aggravates the course of the post-traumatic period, including due to endotoxicosis, which develops as a result of impaired intestinal permeability and accompanying dysbacteriosis [64]. Given that gut microbes protect against transiently invading pathogens by providing a tonic stimulation of the innate immune system through toll-like receptor signaling [65, 66], and the fact that the composition of the microbiome in those who died after severe concomitant injury differed significantly from that of the survivors [67], attempts to influence the composition of the microflora, accelerate its recovery and thereby reduce mortality are legitimate. It was shown that treatment with probiotics, prebiotics and synbiotics reduces systemic inflammation by maintaining the intestinal microbiota, decreases the incidence of postoperative infectious complications and pneumonia associated with mechanical ventilation. In critically ill patients in the intensive care unit, such treatment significantly lowered the number of septic complications and contributed to the modulation of immunity [68].

In conclusion, we would like to note that the management of patients with severe injuries is one of the biggest problems of modern medicine. The combination of blood-derived biochemical markers with other clinical, physical and radiological diagnostic methods may serve to improve the prediction of early clinical trends after severe concomitant injury. It is critical to reliably monitor the immune response in real time and space before any therapeutic immunomodulation can be effectively performed. Because innate and adaptive immune responses can differ significantly with age, comorbidities, and other pre-existing conditions, this should be taken into account when evaluating detectable disorders. Furthermore, in the era of precision medicine, big data-based judgment in complex trauma situations such as TBI and polytrauma can be feasible with the help of bioinformatics tools such as topological data analysis. These strategies could improve the phenotyping of injury patterns, accurate diagnosis, and treatment planning [69].

REFERENCES

1. World Health Organization. Global Health Estimates: *Life expectancy and leading causes of death and disability. Deaths by cause, age and sex*. Available at: http://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html [Accessed Feb 21, 2023]
2. World Health Organization. *Violence and injuries: the facts*. Geneva, Switzerland: World Health Organization; 2010.
3. Lord JM, Midwinter MJ, Chen YF, Belli A, Brohi K, Kovacs EJ, et al. The systemic immune response to trauma: an overview of pathophysiology and treatment. *Lancet*. 2014;384(9952):1455–1465. PMID: 25390327 https://doi.org/10.1016/S0140-6736(14)60687-5
4. Sauaia A, Moore FA, Moore EE. Postinjury inflammation and organ dysfunction. *Crit Care Clin*. 2017;33(1):167–191. PMID: 27894496 https://doi.org/10.1016/j.ccc.2016.08.006
5. Gabbe BJ, Simpson PM, Cameron PA, Ponsford J, Lyons RA, Collie A, et al. Long-term health status and trajectories of seriously injured patients: a population-based longitudinal study. *PLoS Med*. 2017;14(7):e1002322. PMID: 28678814 https://doi.org/10.1371/journal.pmed.1002322 eCollection 2017 Jul.
6. Callcut RA, Wakam G, Conroy AS, Kornblith LZ, Howard BM, Campion EM, et al. Discovering the truth about life after discharge: Long-term trauma-related mortality. *J Trauma Acute Care Surg*. 2016;80(2):210–217. PMID: 26606176 https://doi.org/10.1097/TA.0000000000000930
7. Tonglet ML, Greiffenstein P, Pitance F, Degesves S. Massive bleeding following severe blunt trauma: the first minutes that can change everything. *Acta Chir Belg*. 2016;116(1):11–15. PMID: 27385134 https://doi.org/10.1080/00015458.2015.1136488
8. Vargas M, García A, Caicedo Y, Parra MW, Ordoñez CA. Vargas M, et al. Damage control in the intensive care unit: what should the intensive care physician know and do? *Colomb Med (Cali)*. 2021;52(2):e4174810. PMID: 34908625 https://doi.org/10.25100/cm.v52i2.4810
9. Tien HC, Spencer F, Tremblay LN, Rizoli SB, Brenneman FD. Preventable deaths from hemorrhage at a level I Canadian trauma center. *J Trauma*. 2007;62(1):142–146. PMID: 17215745 https://doi.org/10.1097/01.ta.0000251558.38388.47
10. Schäfer N, Driessen A, Fröhlich M, Stürmer EK, Maegele M; TACTIC partners. Diversity in clinical management and protocols for the management of major bleeding of trauma patients across European level 1 Trauma Centres. *Scand J Trauma Resusc Emerg Med*. 2015;23:74. PMID: 26428070 https://doi.org/10.1186/s13049-015-0147-6
11. Chin-Yee IH, Gray-Statchuk L, Milkovich S, Ellis CG. Transfusion of stored red blood cells adhere in the rat microvasculature. *Transfusion*. 2009;49(11):2304–2310. PMID: 19624601 https://doi.org/10.1111/j.1537-2995.2009.02315.x
12. D'Alessandro A, Liumbruno G, Grazzini G, Zolla L. Red blood cell storage: the story so far. *Blood Transfusion*. 2010;8(2):82–88. PMID: 20383300 https://doi.org/10.2450/2009.0122-09
13. Jy W, Ricci M, Shariatmadar S, Gomez-Marin O, Horstman LH, Ahn YS. Microparticles in stored red blood cells as potential mediators of transfusion complications. *Transfusion*. 2011;51(4):886–893. PMID: 21496051 https://doi.org/10.1111/j.1537-2995.2011.03099.x
14. Curry N, Brohi K. Surgery in Traumatic Injury and Perioperative Considerations. *Semin Thromb Hemost*. 2020;46(1):73–82. PMID: 31563126 https://doi.org/10.1055/s-0039-1697932
15. Lenz A, Franklin GA, Cheadle WG. Systemic inflammation after trauma. *Injury*. 2007;38(12):1336-1345. PMID: 18048040 https://doi.org/10.1016/j.injury.2007.10.003
16. Agadzhanyan VV (ed.) *Politravma. Septicheskie oslozhneniya*. Novosibirsk: Nauka; 2005. (In Russ.).
17. Wafaisade AP, Lefering RMD, Bouillon BMD, Sakka SGMD, Thamm OCMD, Paffrath TMD, et al.; Trauma Registry of the German Society for Trauma Surgery. Epidemiology and risk factors of sepsis after multiple trauma: An analysis of 29,829 patients from the Trauma Registry of the German Society for Trauma Surgery. *Crit Care Med*. 2011;39(4):621–628. PMID: 21242798 https://doi.org/10.1097/CCM.0b013e318206d3df
18. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature*. 2010;464(7285):104–107. PMID: 20203610 https://doi.org/10.1038/nature08780
19. Pugin J. How tissue injury alarms the immune system and causes a systemic inflammatory response syndrome. *Ann Intensive Care*. 2012;2(1):27. PMID: 22788849 https://doi.org/10.1186/2110-5820-2-27
20. Manson J, Thiemermann C, Brohi K. Trauma alarmins as activators of damage-induced inflammation. *Brit J Surg*. 2012;99(Suppl 1):12–20. PMID: 22441851 https://doi.org/0.1002/bjs.7717
21. Liew PX, Kubes P. The Neutrophil's Role During Health and Disease. *Physiol Rev*. 2019;99(2):1223–1248. PMID: 30758246 https://doi.org/10.1152/physrev.00012.2018
22. Rosales C. Neutrophils at the crossroads of innate and adaptive immunity. *J Leukoc Biol*. 2020;108(1):377–396. PMID: 32202340 https://doi.org/10.1002/JLB.4MIR0220-574RR
23. Arango Duque G, Descoteaux A. Macrophage cytokines: involvement in immunity and infectious diseases. *Front Immunol*. 2014;5:491. PMID: 25339958 https://doi.org/10.3389/fimmu.2014.00491 eCollection 2014.
24. Huber-Lang M, Lambris JD, Ward PA. Innate immune responses to trauma. *Nat Immunol*. 2018;19(4):327–341. PMID: 29507356 https://doi.org/10.1038/s41590-018-0064-8
25. Nunnari J, Suomalainen A. Mitochondria: in sickness and in health. *Cell*. 2012;148(6):1145–1159. PMID: 22424226 https://doi.org/10.1016/j.cell.2012.02.035
26. Galluzzi L, Kepp O, Trojel-Hansen C, Kroemer G. Mitochondrial control of cellular life, stress, and death. *Circulation Research*. 2012;111(9):1198–1207. PMID: 23065343 https://doi.org/10.1161/CIRCRESAHA.112.268946
27. West AP, Shadel GS. Mitochondrial DNA in innate immune responses and inflammatory pathology. *Nat Revs Immunol*. 2017;17(6):363–375. PMID: 28393922 https://doi.org/10.1038/nri.2017.21
28. Nakahira K, Hisata S, Choi AM. The Roles of Mitochondrial Damage-Associated Molecular Patterns in Diseases. *Antioxid Redox Signal*. 2015;23(17):1329–1350. PMID: 26067258 https://doi.org/10.1089/ars.2015.6407
29. Boyapati RK, Rossi AG, Satsangi J, Ho GT. Gut mucosal DAMPs in IBD: from mechanisms to therapeutic implications. *Mucosal Immunol*. 2016;9(3):567–582. PMID: 26931062 https://doi.org/10.1038/mi.2016.14
30. Krychtiuk KA, Ruhittel S, Hohensinner PJ, Koller L, Kaun C, Lenz M, et al. Mitochondrial DNA and Toll-Like Receptor-9 Are Associated with Mortality in Critically Ill Patients. *Crit Care Med*. 2015;43(12):2633–2641. PMID: 26448617 https://doi.org/10.1097/CCM.0000000000001311
31. Nakahira K, Kyung SY, Rogers AJ, Gazourian L, Youn S, Massaro AF, et al. Circulating mitochondrial DNA in patients in the ICU as a marker of mortality: derivation and validation. *PLoS Med*. 2013;10(12):e1001577. PMID: 24391478 https://doi.org/10.1371/journal.pmed.1001577
32. Khubutia MS, Shabanov AK, Skulachev MV, Bulava GV, Savchenko IM, Grebenchikov OA, et al. Mitochondrial and Nuclear DNA in Patients with Severe Polytrauma. *General Reanimatology*. 2013;9(6):24. https://doi.org/10.15360/1813-9779-2013-6-24
33. Gołąbek-Dropiewska K, Pawłowska J, Witkowski J, Lasek J, Marks W, Stasiak M, et al. Analysis of selected pro- and anti-inflammatory cytokines in patients with multiple injuries in the early period after trauma. *Cent Eur J Immunol*. 2018;43(1):42–49. PMID: 29731691 https://doi.org/10.5114/ceji.2018.74872
34. Xiao W, Mindrinos MN, Seok J, Cuschieri J, Cuenca AG, Gao H, et al. A genomic storm in critically injured humans. *J Exp Med*. 2011;208(13):2581–2590. PMID: 22110166 https://doi.org/10.1084/jem.20111354
35. Hildebrand F, Pape HC, Krettek C. Die Bedeutung der Zytokine in der posttraumatischen Entzündungsreaktion [The importance of cytokines in the posttraumatic inflammatory reaction]. *Unfallchirurg*. 2005;108(10):793–794, 796–803. PMID: 16175346 https://doi.org/10.1007/s00113-005-1005-1

36. Gentile LF, Cuenca AG, Efron PA, Ang D, Bihorac A, McKinley BA, et al. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. *J Trauma Acute Care Surg*. 2012;72(6):1491–1501. PMID: 22695412 https://doi.org/0.1097/TA.0b013e318256e000
37. Duggal NA, Upton J, Phillips AC, Sapey E, Lord JM. An age-related numerical and functional deficit in CD19(+) CD24(hi) CD38(hi) B cells is associated with an increase in systemic autoimmunity. *Aging Cell*. 2013;12(5):873–881. PMID: 23755918 https://doi.org/10.1111/acel.12114
38. Bruijns SR, Guly HR, Bouamra O, Lecky F, Lee WA. The value of traditional vital signs, shock index, and age-based markers in predicting trauma mortality. *J Trauma Acute Care Surg*. 2013;74(6):1432–1437. PMID: 23694869 https://doi.org/10.1097/TA.0b013e31829246c7
39. Burk AM, Martin M, Flierl MA, Rittirsch D, Helm M, Lampl L, et al. Early complementopathy after multiple injuries in humans. *Shock*. 2012;37(4):348–354. PMID: 22258234 https://doi.org/10.1097/SHK.0b013e3182471795
40. Jenne CN, Urrutia R, Kubes P. Platelets: bridging hemostasis, inflammation, and immunity. *Int J Lab Hematol*. 2013;35(3):254–261. PMID: 23590652 https://doi.org/10.1111/ijlh.12084
41. van Gils JM, Zwaginga JJ, Hordijk PL. Molecular and functional interactions among monocytes, platelets, and endothelial cells and their relevance for cardiovascular diseases. *J Leukoc Biol*. 2009;85(2):195–204. PMID: 18948548 https://doi.org/10.1189/jlb.0708400
42. Laffont B, Corduan A, Ple H, Duchez AC, Cloutier N, Boilard E, et al. Activated platelets can deliver mRNA regulatory Ago2 microRNA complexes to endothelial cells via microparticles. *Blood*. 2013;122(2):253–261. PMID: 23652806 https://doi.org/10.1182/blood-2013-03-492801
43. Timar CI, Lorincz AM, Csepanyi-Komi R, Valyi-Nagy A, Nagy G, Buzas EI, et al. Antibacterial effect of microvesicles released from human neutrophilic granulocytes. *Blood*. 2013;121(3):510–518. PMID: 23144171 https://doi.org/10.1182/blood-2012-05-431114
44. Cocucci E, Racchetti G, Meldolesi J. Shedding microvesicles: artefacts no more. *Trends Cell Biol*. 2009;19(2):43–51. PMID: 19144520 https://doi.org/10.1016/j.tcb.2008.11.003
45. Leonard JM, Zhang CX, Lu L, Hoofnagle MH, Fuchs A, Clemens RA, et al. Extrathoracic multiple trauma dysregulates neutrophil function and exacerbates pneumonia-induced lung injury. *J Trauma Acute Care Surg*. 2021;90(6):924–934. PMID: 34016916 https://doi.org/10.1097/TA.0000000000003147
46. Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y, Weiss DS, et al. Neutrophil extracellular traps kill bacteria. *Science*. 2004;303(5663):1532–1535. PMID: 15001782 https://doi.org/10.1126/science.1092385
47. Hietbrink F, Koenderman L, Althuizen M, Leenen LP. Modulation of the innate immune response after trauma visualised by a change in functional PMN phenotype. *Injury*. 2009;40(8):851–855. PMID: 19339006 https://doi.org/10.1016/j.injury.2008.11.002
48. Groeneveld KM, Koenderman L, Warren BL, Jol S, Leenen LPH, Hietbrink F. Early decreased neutrophil responsiveness is related to late onset sepsis in multitrauma patients: An international cohort study. *PLoS One.* 2017;12(6):e0180145. PMID: 28665985 https://doi.org/10.1371/journal.pone.0180145 eCollection 2017.
49. Serhan CN, Chiang N. Resolution phase lipid mediators of inflammation: agonists of resolution. *Curr Opin Pharmacol.* 2013;13(4):632–640. PMID: 23747022 https://doi.org/ 10.1016/j.coph.2013.05.012
50. McKee CA, Lukens JR. Emerging roles for the immune system in traumatic brain injury. *Front Immunol*. 2016;7:556. PMID: 27994591 https://doi.org/10.3389/fimmu.2016.00556 eCollection 2016.
51. Liu MH, Tian J, Su YP, Wang T, Xiang Q, Wen L. Cervical sympathetic block regulates early systemic inflammatory response in severe trauma patients. *Med Sci Monitor*. 2013;19:194–201. PMID: 23492458 https://doi.org/10.12659/MSM.883833
52. Hall S, Kumaria A, Belli A. The role of vagus nerve overactivity in the increased incidence of pneumonia following traumatic brain injury. *Br J Neurosurg*. 2014;28(2):181–186. PMID: 24024980 https://doi.org/10.3109/02688697.2013.835373
53. Bellander BM, Singhrao SK, Ohlsson M, Mattsson P, Svensson M. Complement activation in the human brain after traumatic head injury. *J Neurotrauma*. 2001;18(12):1295–1311. PMID: 11780861 https://doi.org/10.1089/08977150152725605
54. Braun M, Vaibhav K, Saad NM, Fatima S, Vender JR, Baban B, et al. White matter damage after traumatic brain injury: A role for damage associated molecular patterns. *Biochim Biophys Acta Mol Basis Dis*. 2017; 1863(10 Pt B):2614–2626. PMID: 28533056 https://doi.org/10.1016/j.bbadis.2017.05.020
55. Kharrazian D. Traumatic Brain Injury and the Effect on the Brain-Gut Axis. *Altern Ther Health Med*. 2015;21(Suppl 3):28–32. PMID: 26348611
56. Patterson TT, Nicholson S, Wallace D, Hawryluk GWJ, Grandhi R. Complex Feed-Forward and Feedback Mechanisms Underlie the Relationship Between Traumatic Brain Injury and the Gut-Microbiota-Brain Axis. *Shock*. 2019;52(3):318–325. PMID: 30335675 https://doi.org/10.1097/SHK.0000000000001278
57. Sundman MH, Chen NK, Subbian V, Chou YH. The bidirectional gut-brain-microbiota axis as a potential nexus between traumatic brain injury, inflammation, and disease. *Brain Behav Immun*. 2017;66:31–44. PMID: 28526435 https://doi.org/10.1016/j.bbi.2017.05.009
58. Alverdy JC. Microbiome Medicine: This Changes Everything. *J Am Coll Surg*. 2018;226(5):719–729. PMID: 29505823 https://doi.org/10.1016/j.jamcollsurg.2018.02.004
59. Patel JJ, Rosenthal MD, Miller KR, Martindale RG. The gut in trauma. *Curr Opin Crit Care*. 2016;22(4):339–346. PMID: 27314259 https://doi.org/10.1097/MCC.0000000000000331
60. Hang CH, Shi JX, Li JS, Li WQ, Yin HX. Up-regulation of intestinal nuclear factor kappa B and intercellular adhesion molecule-1 following traumatic brain injury in rats. *World J Gastroenterol*. 2005;11(8):1149–1154. PMID: 15754395 https://doi.org/10.3748/wjg.v11.i8.1149
61. Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. *Nat Rev Immunol*. 2009;9(5):313–323. PMID: 19343057 https://doi.org/10.1038/nri2515
62. Howard BM, Kornblith LZ, Christie SA, Conroy AS, Nelson MF, Campion EM, et al. Characterizing the gut microbiome in trauma: significant changes in microbial diversity occur early after severe injury. *Trauma Surg Acute Care Open*. 2017;2(1):e000108. PMID: 29766103 https://doi.org/10.1136/tsaco-2017-000108 eCollection 2017.
63. Shimizu K, Ojima M, Ogura H. Gut Microbiota and Probiotics/Synbiotics for Modulation of Immunity in Critically Ill Patients. *Nutrients*. 2021;13(7):2439. PMID: 34371948 https://doi.org/10.3390/nu13072439
64. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Ann Gastroenterol*. 2015;28(2):203–209. PMID: 25830558
65. Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, Edberg S, Medzhitov R. Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. *Cell*. 2004;118(2):229–241. PMID: 15260992 https://doi.org/10.1016/j.cell.2004.07.002
66. Ivanov II, Honda K Intestinal commensal microbes as immune modulators. *Cell Host Microbe*. 2012;12(4):496–508. PMID: 23084918 https://doi.org/10.1016/j.chom.2012.09.009
67. Burmeister DM, Johnson TR, Lai Z, Scroggins SR, DeRosa M, Jonas RB, et al. The gut microbiome distinguishes mortality in trauma patients upon admission to the emergency department. *J Trauma Acute Care Surg*. 2020;88(5):579–587. PMID: 32039976 https://doi.org/10.1097/TA.0000000000002612
68. Nielson JL, Paquette J, Liu AW, Guandique CF, Tovar CA, Inoue T, et al. Topological data analysis for discovery in preclinical spinal cord injury and traumatic brain injury. *Nat Commun*. 2015;6:8581. PMID: 26466022 https://doi.org/10.1038/ncomms9581

Received on 10.03.2022

Review completed on 30.11.2022

Accepted on 27.12.2022