Review paper DOI: 10.5114/ceji.2015.52835

Current views on the mechanisms of immune responses to trauma and infection

ANETA MAŁGORZATA BINKOWSKA[1,2], GRZEGORZ MICHALAK[1], ROBERT SŁOTWIŃSKI[3,4]

[1]Department of Emergency Medicine, Medical University of Warsaw, Warsaw, Poland
[2]Department of Disaster Medicine, Medical University of Warsaw, Warsaw, Poland
[3]Department of Immunology, Biochemistry, and Nutrition, Medical University of Warsaw, Warsaw, Poland
[4]Department of Surgical Research and Transplantology, Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland

Abstract

According to the World Health Organization, post-traumatic mortality rates are still very high and show an increasing tendency. Disorders of innate immune response that may increase the risk of serious complications play a key role in the immunological system response to trauma and infection. The mechanism of these disorders is multifactorial and is still poorly understood. The changing concepts of systemic inflammatory response syndrome (SIRS) and compensatory anti-inflammatory response syndrome (CARS) early inflammatory response, presented in this work, have been extended to genetic studies. Overexpression of genes and increased production of immune response mediators are among the main causes of multiple organ dysfunction syndrome (MODS). Changes in gene expression detected early after injury precede the occurrence of subsequent complications with a typical clinical picture. Rapid depletion of energy resources leads to immunosuppression and persistent inflammation and immune suppression catabolism syndrome (PICS). Early diagnosis of immune disorders and appropriate nutritional therapy can significantly reduce the incidence of complications, length of hospital stay, and mortality. The study presents the development of knowledge and current views explaining the mechanisms of the immune response to trauma and infection.

Key words: *sepsis, SIRS, CARS, PICS, MODS, innate immune response.*

(Centr Eur J Immunol 2015; 40 (2): 206-216)

Introduction

According to the World Health Organization, injuries are still a major cause of severe disability and death. There are approximately 3-9 million injuries recorded annually in developed countries. It is predicted that in 2020 they will be a major cause of death. According to statistical data, within an hour in the world around 2000 people sustain traffic injuries, including 148 deaths [1-3]. The number of deaths due to injuries has doubled in the last 30 years in Poland and other European countries. The most common cause of death due to injury is damage to the head, chest, and abdomen and associated haemorrhages. Injuries more frequently affect men than women and individuals aged 20-60 years [4-6]. As shown by statistical studies, in 2008 in Poland there were 49,054 traffic accidents, in which 92% of people were injured and 8% died. This was a significant increase in the number of accidents compared to the study conducted in 1985, which recorded 36,100 accidents with a slightly higher mortality (10%) [7]. Overall, in Poland approximately 3 million people are injured annually. Of these, 300,000 require hospitalisation and 30,000 die. The post-traumatic mortality rate in our country is 75/100,000 people a year, which is much higher than in Western Europe or the United States. In Poland, traumatic disability affects approximately 25% of hospitalised patients, and thus 100% more than in the USA and Western Europe [8, 9].

Severe infections (sepsis) and multiple organ failure (multiple organ dysfunction syndrome – MODS) are among the most severe traumatic complications burdened with high mortality [2, 9, 10]. According to the scarce data from intensive care units (ICU), in Poland injuries are still a major cause of severe infections [11, 12]. According to these analyses, severe infections are diagnosed in 50,000 patients a year, including 16% of patients hospitalised in ICUs, approximately half of which die. The largest group are surgical patients (58.9%), and the most common complications are respiratory (88.7%) and cardiovascular failure (82.2%). This is confirmed by studies from other centres elsewhere in the world. Sepsis caused by various factors is the cause of death of every fourth patient [11, 13]. In the United States, 750,000 new cases of sepsis are recorded each year, of which 210,000 die [14]. In turn, in

Correspondence: Aneta Małgorzata Binkowska, MA, Department of Emergency Medicine, Medical University of Warsaw, Warsaw, Poland, e-mail: aneta@caltha.pl

Canada there are about 30,000 cases of sepsis recorded each year, and 35% of these patients die [15]. In summary, 40% of ICU patients are admitted because of sepsis, or they develop its symptoms in a short period of time; of these, 36.7% are patients from the emergency room [11]. As demonstrated by the study conducted in the United States, severe infections are now the cause of more mortalities than stroke, lung cancer, and breast cancer combined [14]. Studies in Polish ICUs showed that severe sepsis is the leading cause of death in 30-60% of patients [16].

An immune response to trauma

As shown in a previous study conducted by E. Faist [17] in a group of 433 young patients with multiple traffic injuries, mortality in the course of multiple organ failure (MOF) was 56%. It was found that 42% of patients died of MOF following concomitant infection. The authors of this study emphasised that in order to improve the results of treatment in these patients, the proper functioning of the respiratory and circulatory systems should be ensured as soon as possible (preferably still at the scene). The results of this study indicated a significant proportion of infections as one of the causes of MOF. The resulting disorders of the immune response after trauma are primarily associated with increased production of inflammatory response mediators (e.g. cytokines) and the dysfunction of gut-associated lymphoid tissue (GALT). According to this hypothesis, translocation of microorganisms from the intestine into the lymphatic system and the peripheral blood occurs due to extensive trauma and ischaemia of intestinal mucosa. This process increases the risk of MOF, mainly respiratory failure [18]. Bone *et al.* introduced the concept of systemic inflammatory response syndrome (SIRS) (Fig. 1) [19, 20].

According to this theory, the immune response to tissue injury and associated infection starts at the site of the injury and is related to the production of pro- and anti-inflammatory mediators, primarily by cells of the innate immune response (e.g. neutrophils). This part of the immune response is directed at restoring the homeostasis, and may be considered as an early physiological inflammatory reaction. The local inflammatory response and the associated immune response is a favourable phenomenon in the process of wound healing. It is known, however, that persistent infection in the wound or the existence of any additional source of infection (e.g. in the respiratory tract) increases the local and systemic immune disorders, which can lead to sepsis and multiorgan failure. According to this concept, exacerbation of immune disorders through increased activation of the immune system can lead to "immune paralysis" syndrome (CHAOS), which increases the number of complications and mortality [19, 21]. An important element of this hypothesis was the attempt to link immune disorders with clinical signs of disease severity. The authors stressed the importance of apoptosis of the immune system cells (macrophages, neutrophils, lymphocytes), which may exacerbate immunosuppression and is an important element of response to injury/infection, and they indicated the importance of mediators involved in the inflammatory response. A better understanding of the impact of pathological response of SIRS/CARS type (compensatory anti-inflammatory response syndrome) on the occurrence of MODS was hindered by poorly understood cooperation mechanisms of immune cells involved in direct organ damage and the influence of other effects (e.g. the size of the injury, previous comorbidity, type of infection) [18]. Attempts to simplify the classical molecular model have had an adverse impact on the diagnostics and have given a better understanding of the immune response to injury and infection. The above-presented concept of immune disorders has not been widely adopted by clinicians because of the complicated course of SIRS/CARS response and difficulties in the interpretation of the results of immunological studies in severely ill patients with infections. Nevertheless, a simple clinical model of SIRS, sepsis, and severe sepsis diagnostics has been introduced (Table 1) [22, 23].

A lack of conviction of clinicians to perform immunological tests among the most seriously ill patients had a significant impact on reducing early molecular diagnostics in the ICU, although numerous studies have indicated that the immune dysfunction observed in these patients preceded the occurrence of organ complications [24]. Thus, a routinely applied scheme of SIRS, sepsis, and severe sepsis diagnosis still does not include the evaluation of selected immunity parameters (e.g. testing the levels of cytokines, chemokines, or alarmins) that could give information about the dynamics of the immune response to trauma and infection, and potential complications. This scheme does not include immune disorders caused by injury and infection, which are a direct cause of multiple organ failure. It is known that the mechanism of these disorders is multifactorial. The diagnosis of sepsis in the initial stage can be difficult. Clinical signs of MODS usually occur late, and routine laboratory diagnostics markers (e.g. levels of CRP, PCT, lactates, D-dimers, albumins) are still of little help in the early diagnosis of threatening complications. The increase in the concentration of these indicators is most often observed at the onset of clinical symptoms. As numerous studies have shown, the levels of immune mediators of pro- and anti-inflammatory responses are significantly elevated in patients with MODS and usually precede the occurrence of clinical symptoms by dozens of hours. This phenomenon has been termed "immunological diagnostic window" (Fig. 2) [24-26].

Previous studies have highlighted the disorders of cellular immunity and immunosuppression associated with trauma, stressing the importance of cytokines (IL-2, IL-13, TGF-β), prostaglandins, thymus hormones, complement, NK cells, and granulocytes [27]. The relationship has been

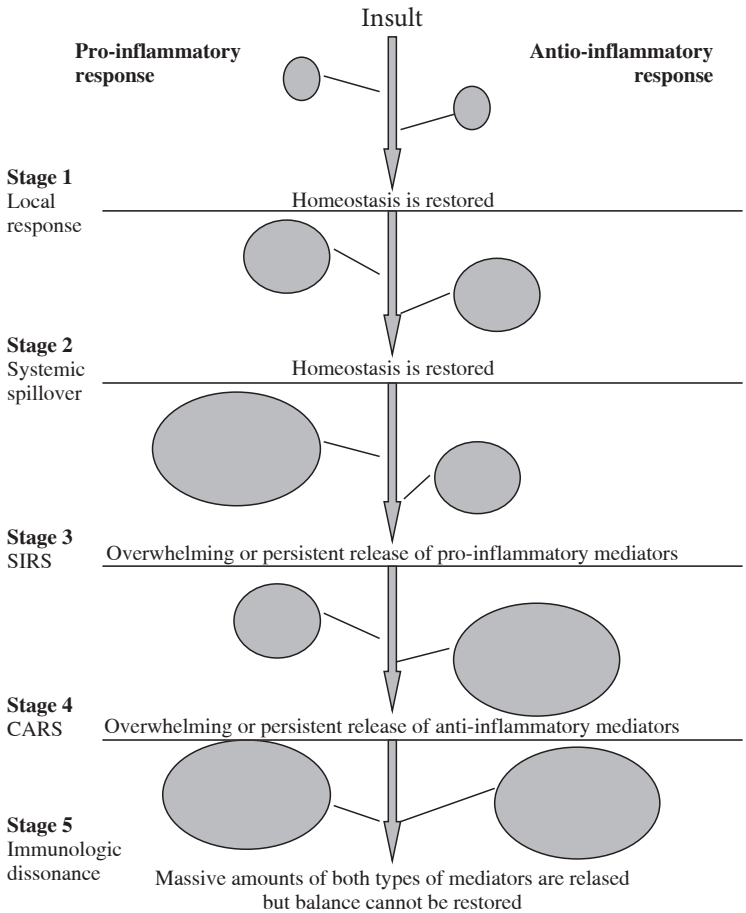

Fig. 1. The hypothetical model of pro-inflammatory (SIRS) and anti-inflammatory response (CARS) to trauma and infection, which can lead to multiple organ failure (according to Bone *et al.*) [19].

found between the severity of SIRS/CARS and MOF and impaired apoptosis of cells involved in pro- and anti-inflammatory response (mainly neutrophils), which increases the production of cytokines and free radicals. It has been suggested that uncontrolled immune response to trauma or infection can lead to the induction of self-destruction of tissues and organ dysfunction distant from the site of injury (e.g. in the lungs). It was necessary to modulate immune cell function in order to improve the resistance in severely ill patients. This concept has survived to this day. The proposed treatment with antibodies neutralising the action of mediators of the inflammatory response (anti-TNF-α, anti-endotoxin, IL-1antagonist, NO inhibitor, eicosanoids) [28], thymus hormones [29], indomethacin [30], thymopentin in combination with indomethacin [31], stimulation of IL-2 production by lymphocytes [32, 33], and regulation of macrophage activity (including blocking the migration of macrophages) [34]. In addition, modulation of the immune response was attempted by endotoxin removal (hemofiltration) or the blocking action of the complement system activity and neutralisation of active oxygen species [10, 35]. As demonstrated by numerous clinical studies, these methods have not caused a significant decrease in mortality in the most severely ill patients [10]. Although preliminary experimental results were promising, they have not been confirmed in randomised clinical trials. Some of these failures resulted from improper use of animal models or from difficulties in precise classification of clinically septic patients. Additionally, there was no correlation between the inflammatory response and the severity of the clinical status of a heterogeneous group of septic patients. It should be assumed that the more precise linking of the inflammatory response with the severity of the disease could be helpful to give a better understanding of the contribution of immune disorders in severe infections. It has been found that the immune response in sepsis is one of the causes of multiple organ failure, but changes in the inflammatory response do not always correlate with the clinical status of the patient. Probably, monitoring changes in immunity during treatment could provide an

Table 1. Clinical diagnosis of SIRS, sepsis and severe sepsis [22]

SIRS	Sepsis	Severe sepsis
Body temperature < 36°C or > 38°C	SIRS + suspected or confirmed infection	Sepsis + organ dysfunction(s)
		Oliguria
HR > 90/min		Acute alteration of mental status
Respiratory rate > 20/min or		Acute respiratory distress
Hyperventilation $PaCO_2$ < 32 mmHg		Circulation dysfunction(s)
WBC <4000 or > 12000/mm^3		Hypotension or hypoperfusion
Immature granulocytes > 10%		Requirement of inotropic or vasopressor agents

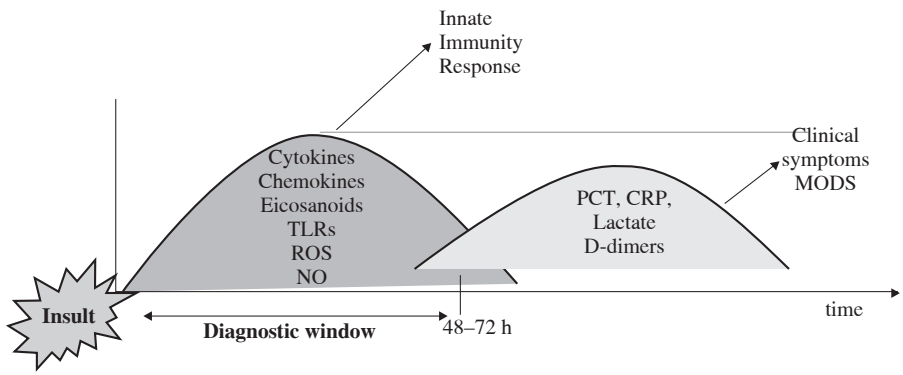

Fig. 2. Cascade inflammatory response to trauma and infection, including immunological indicators and "diagnostic window"

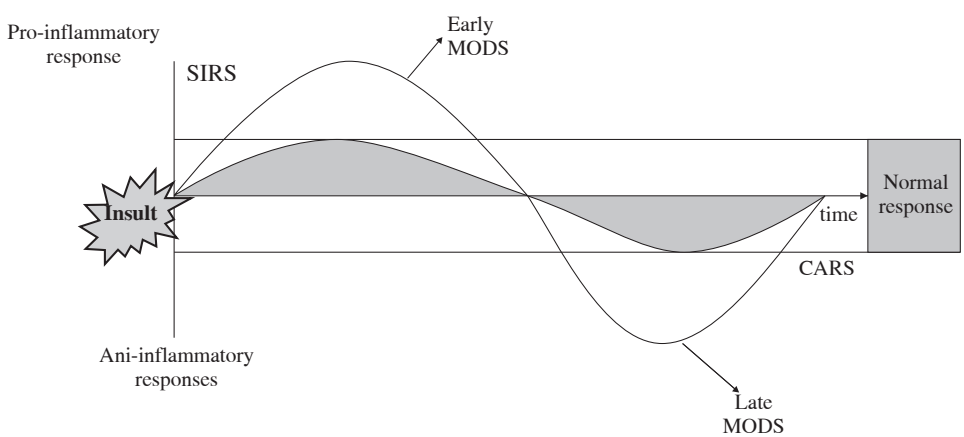

Fig. 3. Dynamics of changes in SIRS and CARS response to trauma and infection, including the physiological and pathological reactions (according to Moore *et al.*) [36]

answer to the question of to what extent a given immunological indicator can be used in practice as an early marker of impending organ failure.

A division into early and late multiple organ failure has been introduced, depending on the dynamics of changes in the inflammatory response [36]. Early organ failure was caused by pathological immune disorders occurring during the SIRS response, while late organ failure was caused by pathologic response of the CARS type (Fig. 3). A concept of physiological SIRS and CARS response was also presented, which may develop in patients with extensive trauma and does not lead to severe septic complications and multiple organ failure [36]. An unquestionable problem of this research was the determination of specific numerical values for inflammatory response markers that allow clinicians to distinguish early physio-

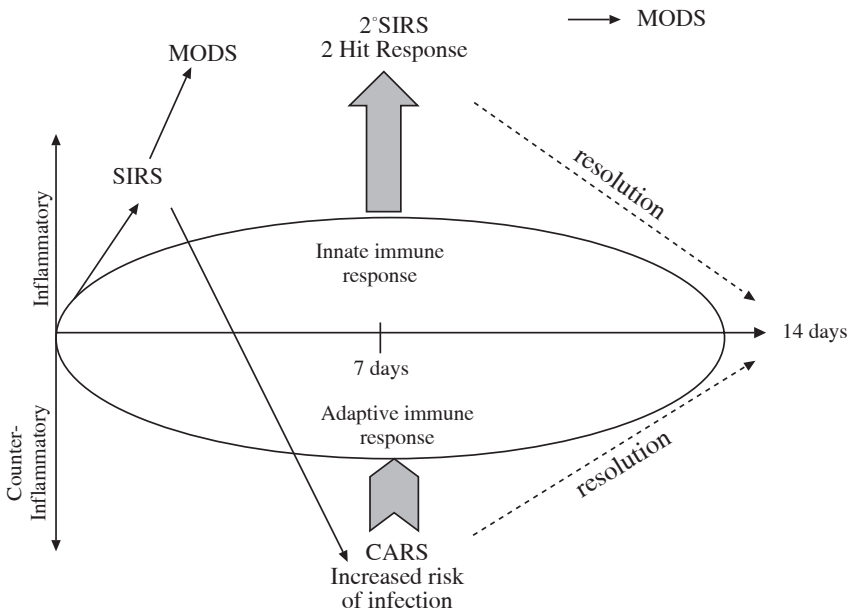

Fig. 4. Changes in the inflammatory response to trauma and infection, including the parallel course of SIRS and CARS response (according to Murphy *et al.*) [37]

logical SIRS reaction from pathological response. Similar problems were related to CARS, in which the increased production of IL-4 was assumed to be an "early" indicator of immunosuppression [28].

According to a newer concept developed by Murphy *et al*. [37] (Fig. 4), CARS occurs in parallel SIRS-compensating response, mainly associated with increased production of anti-inflammatory cytokines (e.g. IL-4, IL-10) and the development of immunosuppression.

According to these authors, an additional factor (e.g. infection, re-injury) may be the cause of another SIRS type reaction (second hit SIRS), and a pathological increase in this response can lead to MODS. Thus, a new element of this scheme is made up of parallel reactions of SIRS and CARS and disorders of the innate and acquired immune response, which increase the risk of severe septic complications. Despite the simplification, the scheme presented indicates a complex mechanism of immune disorders that occur as a result of severe trauma and infection. According to the hypothesis of the authors, the largest immune disorders, as a result of extensive trauma, occur during the first seven days after injury, and then physiological "extinction" of inflammatory response should occur after fourteen days from the uncomplicated trauma. A certain novelty was the introduction of the second hit concept of SIRS response, which can also lead to MODS. In addition, the key role of the immune response self-adaptation to trauma was stressed. This scheme did not include the important parameters of innate antimicrobial response, particularly the participation of Toll-like receptors (TLR2, TLR4), although the authors of this study pointed out the significant role of these receptors in response to trauma and infection. In patients after injury with infection, increased expression was emphasised of TLRs located on macrophages and neutrophils, as a defence mechanism enhancing the innate immune response. Lack of increased expression of TLRs favoured the occurrence of severe infection [37].

Undoubtedly, discrimination between normal and pathological inflammatory response is a difficult element of diagnosis [38, 39]. According to the current concept of the inflammatory response to trauma and infection concomitant to SIRS, in which the cells of the innate immune response are primarily involved, CARS inflammatory response develops, which may lead to immunosuppression. This part of the immune response involves adaptive immune cells including lymphocytes producing anti-inflammatory cytokines, immunosuppressive T_{Reg} cells ($CD4^+/CD25^+$), and antigen-presenting dendritic cells [40]. More recent studies have confirmed that CARS can lead to a reduction in the severity of SIRS proinflammatory response in order to achieve balance, but in some patients it led to increased immunosuppression [41]. It should be assumed that the adoption of the hypothesis of a parallel course of SIRS and CARS was another factor that hindered the designation of appropriate immunological markers that would allow the differentiation of physiological reaction and pathologic post-traumatic response.

It should be recalled that based on an extensive review of the literature, the control of the dynamics of inflammatory response in severe infection, on the basis of selected SIRS and CARS parameters (e.g. TNF-α, IL-1,

IL-6), has repeatedly been proposed [10]. The authors have also suggested other prognostic factors, including genetic predisposition, the type and source of infection, and the degree of multiple organ failure, and formulated on this basis a classification system for sepsis (PIRO scoring system – ***P****redisposition, the* ***I****nsult infection, the* ***R****esponse of the host system and* ***O****rgan dysfunction*) (Table 2) [10, 42]. This system attempted to link the assessment of selected genetic, immunological, and bacteriological markers with clinical signs of infection.

The most recent studies, conducted in the Netherlands, Portugal, and the United States on a large group of patients (about 3,500), compared the PIRO system with the scales routinely applied in the evaluation of the severity of the patients' status (APACHE – Acute Physiology and Chronic Health Evaluation, SOFA – Sequential Organ Failure Assessment, MEDS – Mortality in Emergency Department Sepsis). Based on these studies, it was found that this system had a higher prognostic value in the assessment of severity of infection, MODS and mortality risk. Moreover, it was found that the point value in this system correlated with clinical symptoms [43-45].

The next scheme (Fig. 5), which illustrates the dynamics of pro- and anti-inflammatory response to trauma and

Table 2. Classification of sepsis based on the PIRO system [42]

Diagnostics	**P**	**I**	**R**	**O**
	Predisposition	**Infection**	**Response**	**Organ failure**
Clinical	Age Comorbidity General condition Cause of trauma/infection (degree and severity)	Susceptibility to infection Site of infection Pathogen identification Source of infection (hospital or non-hospital) Extent of the infection	SIRS Other clinical signs of sepsis shock CRP	Organ failure according to the scale: MODS, SOFA, LODS, PEMOD, PELOD
Molecular	Genetics (Polymorphism TLR, TNF, IL-1, CD14)	Gene transcript profiles Analysis of microbial products (LPS, mannan, bacterial DNA) Assessment of virulence factors	Biomarkers Non-specific markers of inflammation (e.g. PCT, IL-6) or markers of immune disorders (e.g. HLA-DR)	Monitoring of cell-mediated immunity (abnormal apoptosis, mitochondrial and endothelial damage and activation of adhesion molecules, cell hypoxia)

MODS – multiple organ dysfunction syndrome, SOFA – sequential organ failure assessment, LODS – logistic organ dysfunction system, PEMOD – paediatric multiple organ dysfunction, PELOD – paediatric logistic organ dysfunction

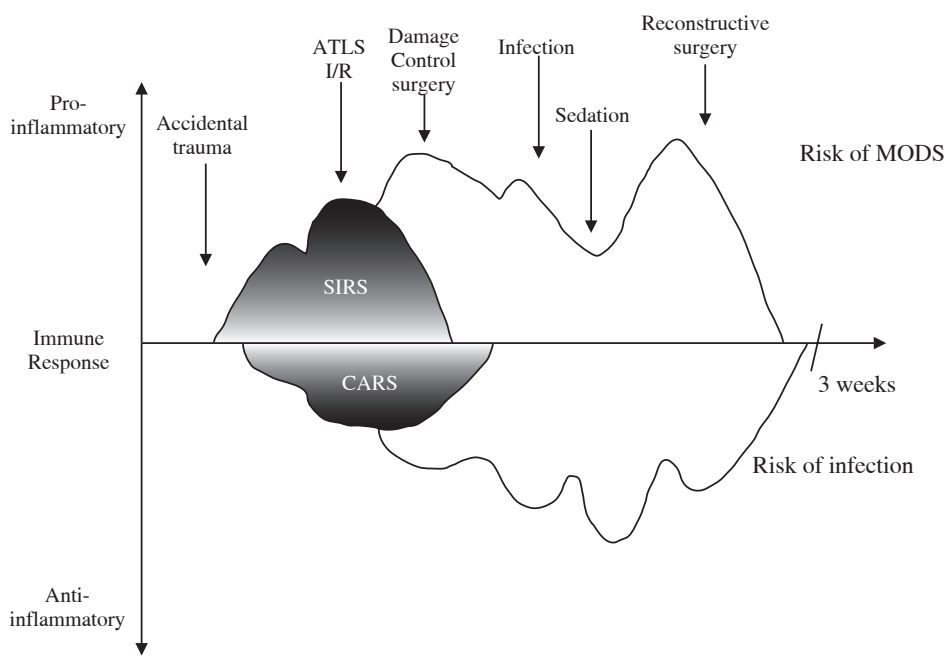

Fig. 5. An example of changes in the pro- and anti-inflammatory response to injury and infection (according to Brochner *et al*.) [46]

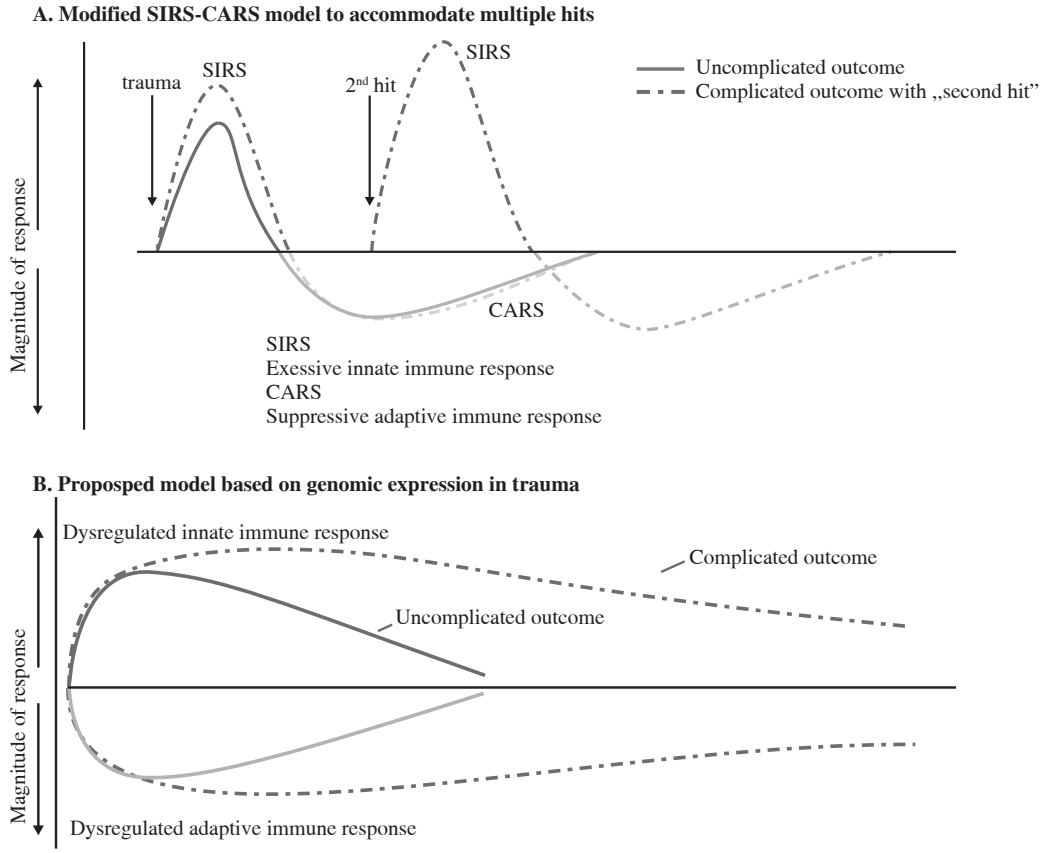

Fig. 6. Dynamics of changes in SIRS and CARS response in trauma patients based on genetic studies (according to Xiao *et al*.) [47]

infection, emphasised the influence of other factors on the inflammatory SIRS response (mechanism of injury, ischaemia, reperfusion, medical procedures, ATLS – *Advanced Trauma Life Support*, type of surgery, anaesthesia, additional infection, and possible reoperation) [46].

These factors also affect the variability of CARS response. According to these authors, the presented scheme should be reflected in the treatment of post-traumatic patients, which should be supported by monitoring the levels of IL-6 in peripheral blood, coagulation markers, lactates, changes in pH, temperature, and diuresis. In the first hours of the occurrence of trauma, life-saving treatments should be primarily implemented (e.g. chest drainage). The authors of this study emphasise that every surgical procedure may be another stimulus that increases the immune disorders, therefore, subsequent re-operations should be performed only after normalisation of the indicators examined [46].

In the latest studies, the concept of SIRS and CARS has been complemented with genetic studies. The results of these studies have shown that the concept of the so-called second hit SIRS response to trauma and infection is unlikely (Fig. 6A) [47]. In turn, based on the expression of genes (mediators of the immune response), it was confirmed that SIRS and CARS occur simultaneously (Fig. 6B).

The concept presented covers a fairly wide range of genetic studies. The following genes have been studied: TLRs (except for TLR3 and TLR7), haptoglobins, collagenases, cytokines (IL-1Ra, IL-4, IL-6, IL-8, IL-10) expressed in T and B cells, leukocytes, neutrophils, and genes encoding proteins responsible for apoptosis [47]. Attention has been drawn to the dynamics of the selected signalling pathways activation or their suppression in conjunction with the degree of the severity of multiple organ failure. The authors introduced the term „gene storm" stemming from the involvement of virtually all genes in response to external and internal stimuli. It was found that the trauma can induce the production of various inflammatory mediators and activate the receptor protein genes involved in the recognition of molecular patterns of microorganisms (PRR), suppressing at the same time receptor genes responsible for antigen presentation, proliferation of T cells, apoptosis, receptor function or activity of NK cells. "Gene storm" is a highly coordinated and repeatable response, so that the immune system undergoes rapid

adaptive changes in response to trauma. In this work, it was found that the quantitative and not qualitative changes in genes' expression are the cause of post-traumatic complications. In patients without complications, silencing of gene transcription occurs within 7-14 days, whereas gene activation in patients with complications lasts significantly longer (over 28 days) [47].

Thus, the previous concepts assuming that SIRS is short term and transient were wrong. The expression of genes involved in the immune response can be prolonged in severely ill patients after the injury, resulting in the production of immature bone marrow cells (MDSCs – myeloid derived suppressor cells), which exhibit a potent immunosuppressive action and do not differentiate into the cells of the early immune response [48]. The main mediators of myeloid cell activation include cytokines and prostaglandins, which are involved in both pro- and anti-inflammatory response [47, 48]. Appropriate myeloid stem cells with the ability of self-renewal differentiate successively into CMP cells (common myeloid progenitor) and MDSCs, which are important in the formation of early immune response cells (granulocytes, macrophages, dendritic cells). Trauma excessively increases the production of MDSCs, the result of which is that the immature cells cannot activate subsequent immune response pathways [48].

It is known that in severely ill patients after trauma, treated long-term in the ICU, the cells of the immune response to injury and infection that produce nitric oxide (NO), reactive oxygen species (ROS), and other mediators of immunosuppressive action consume large amounts of energy (e.g. arginine). Rapid depletion of energy resources may give rise to so-called persistent inflammation and immune suppression syndrome catabolism (PICS) (Fig. 7) [49].

There is a need to change the therapeutic approach directed at balancing the multi-level defects of immune response and reducing protein catabolism, which in turn requires appropriate monitoring of immunity changes. A wider introduction of testing the concentrations of selected cytokines of pro- and anti-inflammatory action (IL-6, IL-10, IL-1Ra, or sTNFRI) to the routine diagnostics of

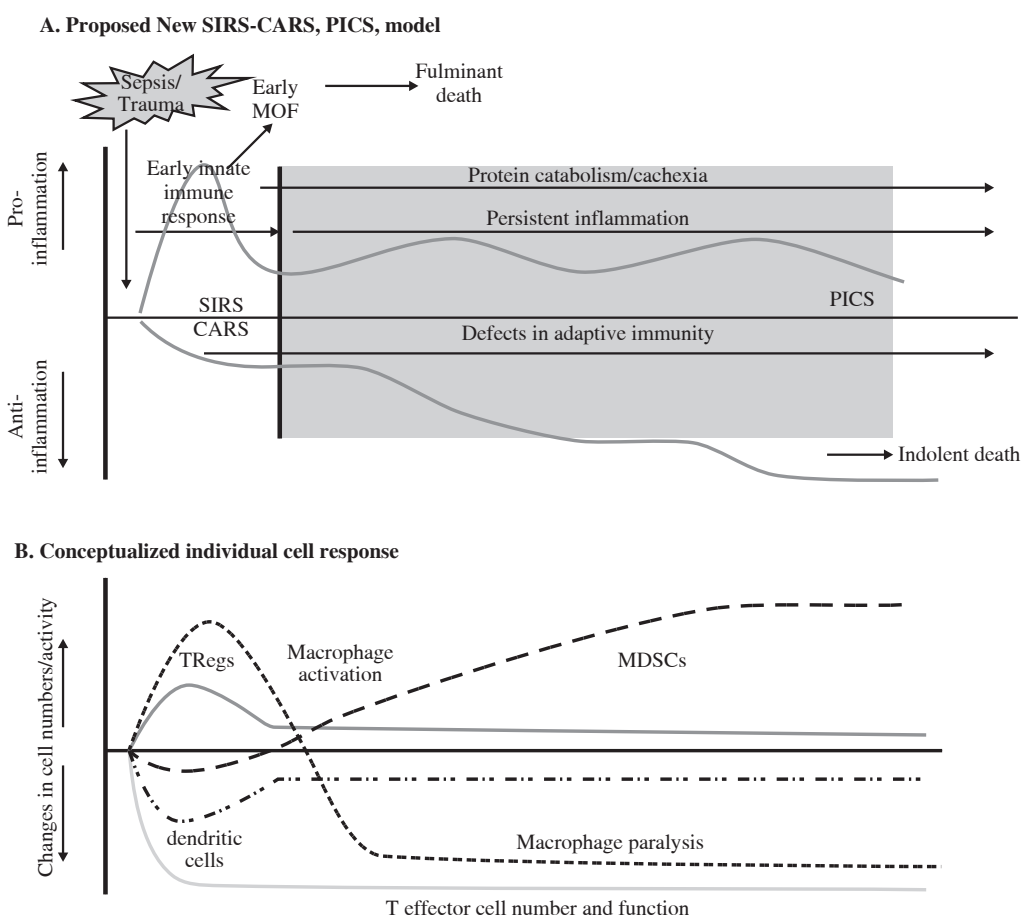

Fig. 7. A new concept of the immune response to trauma and infection, involving PICS and disorders of cell-mediated immunity (according to Gentile *et al*.) [49]

inflammatory response to trauma and infection raises some hopes. These indicators give earlier information about the pathological changes in the innate immune response to injury and infection, and their concentration can be routinely assayed using a simple ELISA [49]. On the other hand, the routine use of flow cytometry allows rapid evaluation of disorders of cell-mediated immunity, including the examination of the current activity of monocytes involved in the later stage of the immune response to trauma and infection (analysis of HLA-DR or CD80/CD86 expression in $CD14^+$ cells) [50]. More advanced techniques enable evaluation of the expression of selected genes in the MDSC responsible for persistent immunosuppression, but this part of diagnostics is still in the experimental phase [51].

An important element in the treatment of these patients is the need to rapidly provide energy substances required for the proper functioning of the immune cells in a suitable nutritional therapy. This applies in particular to patients with PICS requiring longer treatment in the ICU [47, 48]. These patients are diagnosed with difficult to balance catabolism, exacerbating malnutrition, impaired wound healing, and recurrent infections. PICS is characterised by simple parameters assessing the nutritional status: ICU stay > 10 days, weight loss >10% during hospitalisation, or BMI < 18%, CRP level > 150 mg/dl, total lymphocyte count (TLC) < 0.8×10^9/l, albumin <3.0 g/dl, prealbumin < 10 mg/dl, retinol binding protein (RBP) < 10 mg/dl [49]. The authors emphasise that the clinical image is accompanied by chronic inflammation, increasing immunosuppression with macrophage function paralysis, and a decreased count and activity of lymphocytes. This group of patients usually requires long-term treatment in the ICU and is subject to the highest risk of secondary complications (respiratory failure, traumatic coagulopathy syndrome, hypothermia, hypocalcaemia, acidosis, infection) and death [49, 52]. Previous therapy attempts using antibodies, factors stimulating the activity of immune cells, or immunomodulatory preparations did not yield any significant breakthrough in reducing the high mortality of patients with severe sepsis treated in the ICU. Some hope for improving the results of treatment is associated with a more accurate assessment of nutritional status and with the wider introduction of new immunomodulatory preparations, e.g. an appropriate nutritional treatment of immunonutrition type – agents blocking immune response by affecting the TLRs (e.g. Eritoran) [53, 54]. The clinical usefulness of novel survival biomarkers and severity of infection has also been tested (e.g. Endocan) [55]. Patients in metabolic stress after major trauma, surgery, or sepsis often require supply of a modified diet composition enriched with specific immune-modulating nutrients such as glutamine, arginine, omega-3 fatty acids, or nucleotides (Impact, Reconvan, Intestamin) [54-58]. Opinions on the use of immunonutrition in severely ill patients with post-traumatic sepsis, treated in the ICU, are still controversial. As recent studies have shown, the use of glutamine in patients with multiple organ failure may increase mortality [59, 60]. Characteristic in these studies are very high doses of glutamine (0.35 g/kg bw/d *i.v.* + 30 g/d enterally) that may exacerbate organ failure (according to ESPEN, glutamine dose should not exceed 0.5 g/kg bw/d). It should be emphasised that these studies were performed in a heterogeneous group of patients, which could also have influenced the obtained results.

Summary

In conclusion, one of the important factors that increase mortality in posttraumatic patients is pathological pro- and anti-inflammatory response occurring in the first hours after extensive trauma with massive infection, which is still difficult to control and to discriminate from physiological immune response. Interpretation of the results of studies is hindered by the parallel course of SIRS and CARS response, and the significant heterogeneity of the patient groups investigated. Complementing the SIRS and CARS concept with genetic research partly explains this problem. As demonstrated by the most recent studies, during the so-called gene storm, which occurs immediately after the injury and infection, a large number of genes are induced, which are ultimately responsible for the production of many inflammatory response mediators and the expression of receptors involved in the recognition of molecular patterns associated with pathogens. In parallel, the expression of genes responsible for the proper presentation of antigens, lymphocyte proliferation, and apoptosis is decreasing. These are primarily qualitative rather than quantitative changes in the expression of genes that are one of the causes of severe post-traumatic complications. Prolonged activation of genes is another factor that increases the risk of complications. Changes in gene expression detected early after injury precede the occurrence of later complications with a typical clinical picture. Furthermore, rapid depletion of energy resources increases the immunosuppression, burdened with the highest mortality rate. Early diagnosis of PICS and appropriate treatment, nutritional therapy in particular, can reduce the length of stay of patients in the ICU and decrease mortality.

This work was supported by grant no. NN 401 103340
The authors declare no conflict of interest.

References

1. Boyle MJ, Smith EC, Archer F (2008): Is mechanism of injury alone a useful predictor of major trauma? Injury, Int. J. Care Injured 39: 986-992.
2. Soreide K (2009): Epidemiology of major trauma. Br J Surg 96: 697-698.

3. Peden M, Scurfield R, Sleet D, et al. (2004): World report on road traffic injury prevention. WHO Geneva.
4. Aldrian S, Koenig F, Weninger P, et al. (2007): Characteristics of polytrauma patients between 1992 and 2002: What is changing?, Injury, Int J Care Injured 38: 1059-1064.
5. Brongel L, Lasek J, Karski J, et al. (2009): Multicenter study of optimal management strategy in severe multiple trauma. Pol Przegl Chir 81: 518-525.
6. Laupland KB, Svenson LW, Grant V, et al. (2010): Long-term mortality outcome of victims of major trauma. Injury, Int J Care Injured 41: 69-72.
7. www.policja.pl/palm/pol/71/statystyki.html (accessed 5 June 2011).
8. Karwan K, Michalak G, Gałązkowski R (2013): Organizacja ratunkowego leczenie chorych po urazach z mnogimi i wielonarządowymi obrażeniami ciała w warunkach szpitalnych. OPM 12: 28-31.
9. Probst, C, Pape HC, Hildebrand F, et al. (2009): 30 years of polytrauma care: Ananalysis of the change in strategies and results of 4849 cases treated at a single institution. Injury, Int J Care Injured 40: 77-83.
10. Riedemann NC, Guo RF, Ward PA (2003): The enigma of sepsis. J Clin Invest 112: 460-467.
11. Glapiński A, Jaszczuk E, Gaszyński W (2008): Severe sepsis in Intensive Care Unit of M. Kopernik Memorial Regional Specialized Hospital in Lodz from 2001through 2004. Sepsis 1: 5-11.
12. Kübler A, Durek G, Zamirowska A, et al. (2004): Severe sepsis in Poland – results of internet surveillance of 1043 cases. Med Sci Monit 10: CR635-641.
13. Gierek D, Kuczera M, Dąbek J, Piłat D, et al. (2011): Analiza leczenia chorych z ciężką sepsą w Oddziale Anestezjologii i Intensywnej Terapii Górnośląskiego Centrum Medycznego. Anestezjol Inten Terap 43: 22-28.
14. Angus DC, Linde-Zwirble WT, Lidicker J, et al. (2001): Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 29: 1303-1310.
15. Husak L, Marcuzzi A, Herring J, et al. (2010): National Analysis of Sepsis Hospitalizations and Factors Contributing to Sepsis In-Hospital Mortality in Canada. Healthcare Quarterly 13 (Suppl): 35-41.
16. Kübler A, Mayzner-Zawadzka E, Durek G, et al. (2006): Results of severe sepsis treatment program using recombinant human activated protein Cin Poland. Med Sci Monit 12: CR107-112.
17. Faist E, Baue AE, Dittmer H, Heberer G (1983): Multiple organ failure in polytrauma patients. J Trauma 23: 775-787.
18. Fukushima R, Gianotti L, Alexander JW, Pyles T (1992): The degree of bacterial translocation is a determinant factor for mortality after burn injury and is improved by prostaglandin analogs. Ann Surg 216: 438-445.
19. Bone RC (1996): Immunologic dissonance: A continuing evolution in our understanding of the Systemic Inflammatory Response Syndrome (SIRS) and the Multiple Organ Dysfunction Syndrome (MODS). Ann Intern Med 125: 680-687.
20. Bone RC (1996): Toward a theory regarding the pathogenesis of the systemic inflammatory response syndrome: What we do and do not know about cytokine regulation. Crit Care Med 24: 163-172.
21. Bone RC (1996): Sir Isaac Newton, sepsis, SIRS, and CARS. Crit Care Med 24: 1125-1128.
22. Bone RC, Balk RA, Cerra FB, Delinger RP (1992): Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovation Therapies in Sepsis. Chest 101: 1644-1655.
23. Bone RC, Grodzin CJ, Balk RA (1997): Sepsis: A New Hypothesis for pathogenesis of the disease process. Chest 112: 235-243.
24. Gogos CA, Drosou E, Bassaris HP, Skoutelis A (2000): Pro-versus anti-inflammatory cytokine profile in patients with severe sepsis: a marker for prognosis and future therapeutic options. J Infect Dis 181: 176-180.
25. Tseng CC, Fang WF, Leung SY et al. (2014): Impact of serum biomarkers and clinical factors on intensive care unit mortality and 6-month outcome in relatively healthy patients with severe pneumonia and acute respiratory distress syndrome. Dis Markers 2014: Article ID 804654, 9 pages, 2014. doi:10.1155/2014/804654.
26. Ingels C, Derese I, Wouters PJ, Van den Berghe G et al. (2015): Soluble rage and the reage ligands HMGB1 and S100A12 in critical illnes: impact of glycemic control with insulin and relation with clinical outcome. Shock 43: 109-116.
27. Napolitano LM, Faist E, Wichman MW, Coimbra R (1999): Immune Dysfunction in trauma. Surg Clin North Am 79: 1385-1416.
28. Faist E, Ertel W, Cohnert T, et al. (1990): Immunoprotective effects of cyclooxygenase inhibition in patients with major surgical trauma. J Trauma 30: 8-18.
29. Faist E, Ertel W, Salmen B, et al. (1988): The immune-enhancing effect of perioperative thymopentin administration in elderly patients undergoing major surgery. Arch Surg 123: 1449-1453.
30. Faist E, Kupper TS, Baker CC, et al. (1986): Depression of cellular immunity after major injury. Its association with posttraumatic complications and its reversal with immunomodulation agents. Arch Surg 121: 1000-1005.
31. Faist E, Markewitz A, Fuchs D, et al. (1991): Immunomodulatory therapy with thymopentin and indomethacin: Successful restoration of interleukin-2 synthesis in patients undergoing major surgery. Ann Surg 214: 264-274.
32. Faist E, Mewes A, Baker CC, et al. (1987): Prostaglandin E2 (PGE2)-dependent suppression of interleukin alpha (IL-2) production in patients with major trauma. J Trauma 27: 837-848.
33. Faist E, Schinkel C, Zimmer S, et al. (1993): Inadequate interleukin-2 synthesis and interleukin-2 messenger expressionfollowing thermal and mechanical trauma in human is caused by defectivetransmembrane signalling. J Trauma 34: 846-854.
34. Calandra T, Echtenacher B, Le Roy D, et al. (2000): Protection from septic shock by neutralization of macrophage migration inhibitory factor. Nat Med 6: 164-170.
35. Czermak BJ, Sarma V, Pierson CL, et al. (1999): Protective effects of C5a blockade in sepsis. Nat Med 5: 788-792.
36. Moore FA, Sauala A, Moore EE, et al. (1996): Postinjury Mulitple Organ Failure: A Bimodal Phenomenon. J Trauma 40: 501-512.
37. Murphy TJ, Paterson HM, Mannick JA, Lederer JA (2004): Injury, sepsis, and regulation of Toll-like receptor responses. J Leukoc Biol 75: 400-407.
38. Lenz A, Franklin GA, Cheadle WG (2007): Systemic inflammation after trauma. Injury, Int J Care Injured 38: 1336-1345.
39. Hoover L, Bochocchio GV, Grant V, et al. (2006): Systemic Inflammatory Response Syndrome and Nosocomial Infection in Trauma. J Trauma 61: 310-317.

40. Adib-Conquy M, Cavaillon JM (2009): Compensatory anti-inflammatory response syndrome. Thromb Haemost 101: 36-47.
41. Tschoeke SK, Ertel W (2009): Immunoparalysis after multiple trauma. Injury, Int J Care Injured 38: 1346-57.
42. 2001 SCCM/ESICM/ACCP/ATS/SIS (2003): International Sepsis Definition Conference. Intensive Care Med 29: 530-538.
43. Howell MD, Talmor D, Schuetz P, et al. (2011): Proof of principle: The predisposition, infection, response, organ failure sepsis staging system. Crit Care Med 39: 322-327.
44. Granja C, Póvoa P, Lobo C, et al. (2013): The Predisposition, Infection, Response and Organ Failure (Piro) Sepsis Classification System: Results of Hospital Mortality Using a Novel Concept and Methodological Approach. PLoS One 8: e53885.
45. de Groot B, Lameijer J, de Deckere ERJT, Vis A (2014): The prognostic performance of the predisposition, infection, response and organ failure (PIRO) classification in high-risk and low-risk emergency department sepsis populations: comparison with clinical judgement and sepsis category. Emerg Med J 31: 292-300.
46. Brochner AC, Toft P (2009): Pathophysiology of the systemic inflammatory response after major accidental trauma. Scand J Trauma Resusc Emerg Med 17 p43 doi:10.1186/1757-7241-17-43.
47. Xiao W, Mindrinos MN, Seok J, et al. (2011): A genomic storm in critically injured humans. J Exp Med 208: 2581-2590.
48. Cuenca AG, Delano MJ, Kelly-Scumpia KM, et al. (2011): A paradoxical role for myeloid-derived suppressor cells in sepsis and trauma. Mol Med 17: 281-292.
49. Gentile LF, Cuenca AG, Philip A, et al. (2012): Persistent inflammation and immunosuppression: A common syndrome and new horizon for surgical intensive care. J Trauma Acute Care Surg 72: 1491-1501.
50. Venet F, Tissot S, Debard AL, et al. (2007): Decreased monocyte human leukocyte antigen-DR expression after severe burn injury: Correlation with severity and secondary septic shock. Crit Care Med 35: 1910–1917.
51. Kotz KT, Xiao W, Miller-Graziano C, et al. (2010): Clinical microfluidics for neutrophil genomics and proteomics. Nat Med 16: 1042-1047.
52. Lier H, Böttiger BW, Hinkelbein J, et al. (2011): Coagulation management in multiple trauma: a systemic review. Intensive Care Med 37: 572-582.
53. Korff S, Loughran P, Cai C, et al. (2013): Eritoran attenuates tissue damage and inflammation in hemorrhagic shock/trauma. J Surg Res 184: E17-25.
54. Słotwiński R, Słotwińska S, Kędziora S, Bałan BJ (2011): Innate Immunity Signaling Pathways: Links between Immunonutrition and Responses to Sepsis. Arch Immunol Ther Exp 59: 139-150.
55. Mihajlovic DM, Lendak DF, Brkic SV, et al. (2014): Endocan is useful biomarker of survival and severity in sepsis.; Microvasc Res 93: 92-97.
56. Huschak G, zur Nieden K, Hoell T, et al. (2005): Olive oil based nutrition in multiple trauma patients: a pilot study. Intensive Care Med 31: 1202-1208.
57. Pérez-Bárcena J, Crespí C, Regueiro V, et al. (2010): Lack of effect of glutamine administration to boost the innate immune system response in trauma patients in the intensive care unit. Crit Care 14: R233 doi: 10.1186/cc9388.
58. Slotwinski R, Olszewski WL, Slotkowski M, et al. (2007): Can the Interleukin-1 Receptor Antagonist (IL-1ra) Be a Marker of Anti-Inflamatory Response to Enternal Immunonutrition In Malnourished Patients after Pancreaticoduodenectomy; JOP J Pancreas 8: 759-769.
59. Heyland DK, Elke G, Cook D, et al. (2014): Glutamine and Antioxidants in the Critically Ill Patient: A Post Hoc Analysis of a Large-Scale Randomized Trial. JPEN J Parenter Enteral Nutr 20 (10): 1-9.
60. Heyland D, Muscedere J, Wischmeyer PE, et al. (2013): A randomizes trial of glutamine and antioxidants in critically ill patients. N Engl J Med 386: 1489-1497.