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The role of the immune system in the development of sepsis after burns

El papel del sistema inmunitario en el desarrollo de la sepsis después de las quemaduras

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Abstract.
Burns are a destructive form of trauma that remain a major cause of morbidity and mortality worldwide; despite the improvements in medical care, burns often leave lifelong physical and emotional sequelae. Likewise, infectious complications, including sepsis and septic shock are common in patients with moderate to severe burn injuries. In this regard, sepsis is a life-threatening disturbance produced by a dysregulated reaction to infections, which can cause serious complications and lead to death. Therefore, the study of pathophysiological mechanisms related to development of sepsis is pivotal. In this article, we perform a comprehensive description of immune processes associated with burn injury, particularly the mechanisms involved in the development of sepsis after burns. In addition, we provide relevant information about immune mediators potentially useful as biomarkers of sepsis

Resumen.
Las quemaduras son una forma destructiva de trauma que sigue siendo una de las principales causas de morbilidad y mortalidad en todo el mundo; a pesar de las mejoras en la atención médica, las quemaduras a menudo dejan las secuencias físicas y emocionales de por vida. Del mismo modo, las complicaciones infecciosas, como la sepsis y el shock séptico, son frecuentes en pacientes con lesiones por quemaduras de moderadas a graves. En este sentido, la sepsis es una alteración potencialmente mortal producida por una reacción desregulada a las infecciones, que puede causar complicaciones graves y llevar a la muerte. Por lo tanto, el estudio de los mecanismos fisiopatológicos relacionados con el desarrollo de la sepsis es fundamental. En este artículo, realizamos una descripción completa de los procesos inmunológicos asociados con la lesión por quemaduras, particularmente los mecanismos involucrados en el desarrollo de la sepsis después de las quemaduras. Además, proporcionamos información relevante sobre mediadores inmunes potencialmente útiles como biomarcadores de sepsis

Introduction

Burns are considered among the most devastating injuries that can undergo a person, especially in childhood. Since burns are a significant cause of disability and death[1]; moreover, in survivors, there are often lifelong physical complications and emotional sequelae[2,3].

According to the International Society of Burn Injuries, a burn is an injury to the skin and/or other organic tissue mainly caused by thermal or other acute trauma. Burns occur when some or all of the cells of the skin or other tissues are injured or destroyed by flames (flame burns), hot liquids (scalds), or hot solids (contact burns). In addition, injuries to the skin or other organic tissues due to radiation, radioactivity, electricity, friction or contact with chemicals are also identified as burns[1].

Burns injury is highly variable in terms of the severity, the affected tissue, and resultant complications. In this respect, depending on variables such as mechanism of injury, the burn location, size and depth, the burned patient may experience a high number of dangerous conditions including electrolytes imbalance, shock, and respiratory failure[4]. In addition, it should be noted that skin plays an indispensable first line of defense against microorganisms, which its disruption leaves patients greatly susceptible to invasion by pathogens that may lead to sepsis[5].

Regarding this, sepsis is a life-threatening condition considered as a strong public-health concern, since a recent study demonstrated that mortality in patients with sepsis after burns was 34.4%[6], which may be increased due to lack of suitable medical care[7]. Sepsis is defined as a dysregulated inflammatory response associated with infection on the basis of either microbiologic cultures or strong clinical evidence of the presence of an infection[8–10]. Accumulated experimental and clinical evidences indicate that burns injury can alter function of immune system, predisposing the patients to infections and sepsis[11]. However, despite numerous studies focused in understanding the relationship between function of immune system and development of sepsis, the mechanisms responsible for initiating and controlling burn-induced immunosuppression have not been completely understood[12].

This article describes the current understanding of the pathophysiology of burns, particularly the immune mechanisms involved in the development of sepsis after burn injury; in addition we offer an overview of immune mediators potentially useful as biomarkers of sepsis.

Molecular bases of sepsis in burn injury

Burns produce diverse complications of varied severity, such as edema, cutaneous barrier breakdown, hypovolemic shock, and a hypermetabolic response, which may lead to an organic dysregulation and giving rise to greater susceptibility to infection and eventually sepsis[13]. Once the sepsis is established, several mechanisms of immune response become activated, and the duration of the infection is dependent on the type of microorganism involved. However, many severe drawbacks, such as septic shock, massive organ dysfunction, and even death, are results of burn injury and sepsis[14–16].

Therefore, in order to clear the pathophysiology of sepsis, it is necessary the knowledge of the anatomical, physiological, cellular, and molecular alterations caused by burns.

In this regard, burn injury induces a plethora of local and circulating mediators that are produced in the blood or released by cells after thermal injury. These mediators play important roles in the pathogenesis of edema and the cardiovascular abnormalities of burn injury. The increased vascular permeability post-burn is mediated by histamine and numerous vasoactive substances, including serotonin, bradykinin, prostaglandins, leukotrienes, and platelet activating factor[5]. In addition, hypermetabolism is mediated by hormones such as catecholamines, glucagon, and particularly cortisol. Many mediators alter vascular permeability directly or indirectly by increasing the microvascular hydrostatic pressure and surface area via the arteriolar vasodilation superimposed on an already altered membrane[4]. The exact mechanism(s) of mediator-induced injury is/are of considerable clinical importance, as this understanding would allow for the

development of pharmacologic modulation of burn edema and shock by mediator inhibition.

Likewise, after a burn injury, several processes, such as hemostasis and inflammation, neovascularization, fibroplasia, contraction, retraction, and coagulation, are initiated. The initial stage involves heat-induced protein denaturation, inflammation, ischemia-induced injury, and cell death, which cause burns of diverse depth. At the molecular level, free radicals such as superoxide, hydroxyl, hydrogen peroxide, nitric oxide, nitroperoxide, alkylperoxyl, and lipid radicals are present after severe burns[17]. Both intravascular stimulation and complement activation of neutrophils lead to the production of these free radicals that can react with DNA, leading to important functional and structural changes. In addition, damage to cell membranes induces a cascade of inflammatory molecules that increases cell-to-cell permeability[18]. The main risk after burn injury comprises a subsequent infection because of several reasons, including tissue damage and exposure to pathogenic bacteria or the host immunosuppressive state (Figure 1A). Bacterial toxins along with cytokines may give rise to endothelial-cell damage. The organism's pathophysiological response to burn injury is to release proinflammatory substances that may lead to different clinical stages, according to the body-surface area injured; for instance, septic shock is a severe response to an infection characterized by hypotension, fever, tissue hypoperfusion, lactic acidosis, and organ dysfunction. All of these events are mediated by a plethora of molecules that may serve as signals of and responses to survival. Furthermore, experimental observations have demonstrated that there is significant loss of gastrointestinal physical-barrier function after burn injury, which is due to physical disruption of its mucosa; there is intestinal- bacteria overgrowth, systemic translocation, and suppression of the immune defense[19].

An additional feature is the important increase in several markers such as plasma catecholamines, cortisol, and growing numbers of inflammatory cells, which results in complete body catabolism, elevated resting-energy expenditure, and the dysfunction of several organs[20]. The anti-inflammatory response and immunosuppression following burn injury are characterized by the production and release of cytokines and monocyte/macrophage dysfunction, which may lead to sepsis[21]. These alterations directly modify the immune response in the organism; hence, knowledge on the latter is important

Innate immunity activity and sepsis

The most important determinants of the first immune response comprise the innate receptor families, such as NOD-Like Receptors (NLR), C-type Lectin Receptors (CLR), Toll-Like Receptors (TLR), and RIG-1-Like Receptors (RLR). These proteins are expressed by immune cells, mainly the Antigenic Presenting Cells (APC), and their primary function is to detect microbial molecules, generally known as Pathogenic Associated Molecular Patterns (PAMP), which indicate the presence of extra- or intracellular pathogens. In response to this activity, innate receptors induce cytokine expression and release, inflammation induction, and even cell death. The impairment of the innate immune system, by PAMP Recognizing Receptors (PPR), is one of the initial events observed after burn injury[22]. PAMP include molecules that are present on the cell surface or that are highly associated with organisms but that are not present in the host. In addition, PRR are also able to detect Damage Associated Molecular Patterns (DAMP); however, DAMP are the result of host-cell destruction and the release of internal molecules. Failure of the mechanism of control of DAMP can lead to inflammation and sepsis. Several stimuli such as PAMP can induce immune cells to secrete DAMP via various non-classical pathways, indicating that there is cross-talk between DAMP and PAMP in the regulation of the innate immune system. The most studied DAMP in inflammatory diseases are High-Mobility Group Box 1 (HMGB1), Heat Shock Proteins (HSP), Adenosine TriPhosphate (ATP), DNA, and uric acid[23]. Both DAMP and PAMP induce inflammation in tissue adjacent to the injury site. After detection of molecules, APC become more active and begin the process of pathogen phagocytosis and engulfment. This process eventually results in antigen processing and presentation (mainly peptides) derived from the microorganism's lysis. Antigen presentation by Major Histocompatibility

Complex (MHC) molecules leads to the activation of a more precise immune response in which the development of specialized cells is the main purpose[24]. The interaction between APC and regulatory T cells activates the cellular and humoral responses.

During sepsis, dysregulated responses among immunity cells lead to unpredicted, destructive patient outcomes such as elevated heart rate, high fevers, and flushed skin. At the cellular level, dendritic cells and monocyte-macrophage cells play a key role in modulating this innate immune response. The activated phagocytic cells release proinflammatory mediators such as chemokines, cytokines, nitric oxide, lipid mediators, and oxygen radicals[25] that contribute to the deregulation of the immune system, as well as to the development of the Systemic Inflammatory Response Syndrome (SIRS), the reason for its giving rise to greater susceptibility to sepsis (Figure 1A). In addition, complement factors are released as part of the inflammatory reaction to infection during sepsis. In some models, high plasma levels of proteins C3a and C5a can be detected, indicative of activation of the complement system[26], which react with each other to opsonize pathogens and induce a series of responses to face the infection (opsonization, pathogen lysis, and coordination of inflammatory events)[27]. Finally, sepsis has been associated with a variety of alterations in pro- and anticoagulant mechanisms. In this respect, it has been shown that infection produces diverse responses that can lead to coagulation[28]. Actually, many of the innate immune responses that fight infection may also lead to coagulation. Furthermore, infection may range from subtle activation of coagulation to fulminant, disseminated intravascular coagulation. On the other hand, it should be noted that coagulation in many cases limits dissemination of the infectious agent.

Adaptive immunity mechanisms and sepsis

On the other hand, the presence of increasing levels of certain immunoglobulins indicates that an infectious process is occurring. In addition, activation of cells and the detection of signaling molecules such as interleukins or chemokines are evidence of adaptive immune response. Activation of T-cell and B-cell response leads to a series of molecular, cellular, and physiological events to confront the infectious process. It is important to consider that a burn injury may be only superficial or it may expose a considerable internal surface; in any case, a burn injury is a clear opportunity for pathogens to establish themselves in the host. Moreover, the patient's health status, age, and First Aid care are also important factors that play a role in the late immune response. During the adaptive response, B cells become key players in order to produce Immunoglobulins (Ig) against pathogens. These proteins (also known as antibodies) aid in exacerbating the phagocytosis and lysis of microorganisms, neutralize toxic proteins, and increasing the inflammatory activity of granulocytic cells. At the same time, other cells, such as the regulatory T lymphocytes (CD4+CD25+ regulatory, gamma delta, and NK T cells) participate in the control of immune responses. Widespread lymphocyte apoptosis is observed in animal models of sepsis and in patients with sepsis; in fact, lymphopenia is a hallmark of sepsis. In addition, lymphocyte anergy has been also described in patients with burns or major trauma, associated with a high mortality rate and associated septic complications[25].

Immune mediators as biomarkers of sepsis associated to burns injury

As described in previous sections, immune responses evoked by sepsis are transmitted by an assortment of molecules, which have been proposed as biomarkers of sepsis. Thus, the measurement of these molecular complexes in serum or tissue may represent an index of sepsis progression. In this regard, the most common markers are cytokines, procalcitonin (ProCT), and C-reactive protein (CRP).

Diverse studies have suggested that levels of serum cytokines, such as Tumor Necrosis Factor alpha (TNF-α), basic Fibroblast Growth Factor (bFGF), and Interleukin-6 (IL-6), IL-8, or IL-10 are related to the immune response triggered by infections and by the intensive damage associated to burns[29,30].

For example, the plasma levels of IL6 are increased in burned patients with sepsis, compared to non-septic and healthy subjects, which suggests that this cytokine could play a role in the pathogenesis of sepsis in these patients[31]. Furthermore, another study revealed significant differences in serum IL-6 values among patients who survived or died, or among patients with a total body-surface area of >50% or <50% from the burn injury[32]. Likewise, it has been shown that the levels of IL-8 in burn patients increase significantly[33] and a positive correlation between IL-10 levels and the development of sepsis has been suggested[31]. In addition, the levels of TNF-α, a central regulator of inflammation, were found elevated in non-survivor patients in contrast to patients who survived[34,35].

In a similar way, ProCT has been suggested as a marker of infection[36] and its levels in serum increases in sepsis cases[37–39]. In this regard, serum ProCT levels are undetectable in physiological condition; however, those levels increases up >100 ng/ml in severe infections. On the other hand, the function of CRP in acute inflammation is not completely clear; however, it is known that the levels of CRP significantly increase during this process than the levels of other markers[40]. In addition, the levels of CRP in serum reach >10 mg/dL in burned patients, which suggest that it could be an appropriate marker for early analysis after burning and that the combination of CRP and ProCT could facilitate opportune detection of infection in sepsis patients[41].

Potential new markers

Recent researches are focused in the search for novel markers that provide greater efficacy in the detection of early sepsis in burned patients. In this respect, the short form of soluble CD14 (sCD14-ST) seems to exhibit improved specificity and sensitivity in the diagnosis of sepsis than biomarkers such as IL-6, CRP, and ProCT[42,43]. Likewise, it has been shown increases in levels of Intercelular Adhesion Molecule 1 (ICAM-1) during inflammation. In addition, the highest levels of ICAM-1 appear to correlate with best outcomes in septic children[44]. In a similar way, animal models of burn sepsis and analyses of burned patients have demonstrated that some Heat Shock Proteins (HSP), particularly HSP27, HSP60, and HSP70, and HSP90 are up-regulated in sepsis cases, suggesting their possible usefulness as biomarkers[45–47]. On the other hand, plasma Granzyme A (GZMA) levels were shown decreased in septic burned patients with respect to non-septic burned patients and healthy individuals. Moreover, plasma GZMA was significantly higher in survivor than in non-survivor patients, which strongly suggests that GZMA could exert as biomarker of severity of sepsis[48]. Finally, animal models of experimental sepsis have revealed increased levels of Monocyte chemo-attractant protein 1 (MCP-1) in lung and liver, suggesting a role a pro-inflammatory mediator in this condition[49]. This notion is supported by a study that demonstrated significant differences in plasma levels of MCP-1 between survivors and early death patients with sepsis[50]; therefore, MCP-1 could be a promising biomarker.

Conclusion

Burn injury is a devastating condition that often causes severe disability, as well as lifelong physical and emotional sequelae; in addition, burned patients frequently develop severe infections that lead to sepsis. In this regard, although the relationship between function of immune system and development of sepsis is not completely understood, diverse studies have provide information about a variety of pathophysiological processes that take place after burn injury. This has permitted to identify key immune mediators that participate in the dysregulated inflammatory response associated to sepsis. Concerning this, increasing clinical and experimental evidences have suggested that burn injury may disturb levels of cytokines and other molecules related to immune response, such as IL-6, IL-8, IL-10, TNFα, ProCT, CRP, ICAM-1, sCD14-ST, HSP27, HSP60, HSP70, HSP90, GZMA, and MCP-1. Since dysregulation of these molecules may predispose the patients to develop severe infections and sepsis, measurements of their levels may be useful to early detection of sepsis and predicting non-favorable clinical outcomes.

References

1. Peck MD. Epidemiology of burns throughout the world. Part I: Distribution and risk factors. Burns 2011; 37:1087–1100.
2. Mock C, Peck M, Krug E, Haberal M. Confronting the global burden of burns: A WHO plan and a challenge. Burns 2009; 35:615–617.
3. Dissanaike S, Rahimi M. Epidemiology of burn injuries: Highlighting cultural and sociodemographic aspects. International Review of Psychiatry 2009; 21:505–511.
4. Evers LH, Bhavsar D, Mailänder P. The biology of burn injury. Experimental Dermatology 2010; 19:777–783.
5. Keck M, Herndon DH, Kamolz LP, Frey M, Jeschke MG. Pathophysiology of burnsDas Verbrennungstrauma: Die Pathophysiologie. Wiener Medizinische Wochenschrift 2009; 159:327–336.
6. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, *et al.* Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*. Critical Care Medicine 2006; 34:1589–1596.
7. Sen S, Greenhalgh D, Palmieri T. Review of burn research for the year 2011. Journal of Burn Care and Research 2013; 33:577–586.
8. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, *et al.* 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Medicine 2003; 31:1250–1256.
9. Dellinger P, Levy M, Rhodes A, Annane D, Gerlach H, Opal S, *et al.* Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012. Crit Care Med 2013; 41:580–637.
10. Wynn J, Cornell TT, Wong HR, Shanley TP, Wheeler DS. The host response to sepsis and developmental impact. Pediatrics 2010; 125:1031–1041.
11. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. New England Journal of Medicine 2003; 348:138–150.
12. Fazal N. T Cell Suppression in Burn and Septic Injuries. In: Immunosuppression - Role in Health and Diseases. In Tech; 2012. p. 161–190
13. Muñoz B, Suárez-Sánchez R, Hernández-Hernández O, Franco-Cendejas R, Cortés H, Magaña JJ. From traditional biochemical signals to molecular markers for detection of sepsis after burn injuries. Burns 2019; 45:16–31.
14. Baron P, Traber LD, Traber DL, Nguyen T, Hollyoak M, Heggers JP, *et al.* Gut Failure and Translocation Following Burn and Sepsis. Journal of Surgical Research 1994; 57:197–204. Published online: 1994.
15. Baskin T, Rosenthal A, Pruitt B. Acute Bacterial Endocarditis: A Silent Source of Sepsis in the Burn Patient. Annals of Surgery 1976; 184:618–621.
16. Fitzwater J, Purdue GF, Hunt JL, O'keefe GE. The risk factors and time course of sepsis and organ dysfunction after burn trauma. Journal of Trauma 2003; 52:959–966.
17. Singh V, Devgan L, Bhat S, Milner SM. The pathogenesis of burn wound conversion. Annals of Plastic Surgery 2007; 59:109–115.
18. Bratu LM, Rogobete AF, Sandesc D, Bedreag OH, Tanasescu S, Nitu R, *et al.* The Use of Redox Expression and Associated Molecular Damage to Evaluate the Inflammatory Response in Critically Ill Patient with Severe Burn. Biochemical Genetics 2016; 54:753–768.
19. Orman MA, Ierapetritou MG, Berthiaume F, Androulakis IP. The dynamics of the early inflammatory response in double-hit burn and sepsis animal models. Cytokine 2011; 56:494–502.
20. Williams FN, Herndon DN, Jeschke MG. The Hypermetabolic Response to Burn Injury and Interventions to Modify this Response. Clinics in Plastic Surgery 2009; 36:583–596.
21. Church D, Elsayed S, Reid O, Winston B, Lindsay R. Burn Wound Infections. Clinical Microbiology Reviews 2006; 19:403 LP – 434.
22. Barber RC, Chang LYE, Arnoldo BD, Purdue GF, Hunt JL, Horton JW, *et al.* Innate immunity SNPs are associated with risk for severe sepsis after burn injury. Clinical Medicine and Research 2006; 4:250–255.
23. Kang J-W, Kim S-J, Cho H-I, Lee S-M. DAMPs activating innate immune responses in sepsis. Ageing Research Reviews 2015; 24:54–65.
24. Schneider DF, Glenn CH, Faunce DE. Innate Lymphocyte Subsets and Their Immunoregulatory Roles in Burn Injury and Sepsis. Journal of Burn Care & Research 2007; 28:365–379.
25. De Pablo R, Monserrat J, Prieto A, Alvarez-Mon M. Role of Circulating Lymphocytes in Patients with Sepsis. BioMed Research International 2014; 2014.

26. Wiersinga WJ, Leopold SJ, Cranendonk DR, van der Poll T. Host innate immune responses to sepsis. Virulence 2014; 5:36–44.
27. Markiewski MM, DeAngelis RA, Lambris JD. Complexity of complement activation in sepsis. Journal of Cellular and Molecular Medicine 2008; 12:2245–2254.
28. Esmon CT, Xu J, Lupu F. Innate immunity and coagulation. Journal of Thrombosis and Haemostasis 2011; 9:182–188.
29. Vandijck DM, Brusselaers N, Blot SI. Inflammatory markers in patients with severe burn injury: What is the best indicator of sepsis? Burns 2007; 33:939–940.
30. Rousseau A-F, Layios N. Serum Markers of Sepsis in Burn Patients: It Takes More to Convince! Critical Care Medicine 2015; 43.
31. Pileri D, Accardo Palombo A, D'Amelio L, D'Arpa N, Amato G, Masellis A, *et al.* Concentrations of cytokines IL-6 and IL-10 in plasma of burn patients: their relationship to sepsis and outcome. Annals of burns and fire disasters 2008; 21:182–185.
32. Yeh FL, Lin WL, Shen HD, Fang RH. Changes in circulating levels of interleukin 6 in burned patients. Burns 1999; 25:131–136.
33. Kraft R, Herndon DN, Finnerty CC, Cox RA, Song J, Jeschke MG. Predictive Value of IL-8 for Sepsis and Severe Infections After Burn Injury: A Clinical Study. Shock 2015; 43.
34. Zhang B, Huang YH, Chen Y, Yang Y, Hao ZL, Xie SL. Plasma tumor necrosis factor-α, its soluble receptors and interleukin-1β levels in critically burned patients. Burns 1998; 24:599–603.
35. Yeh FL, Lin WL, Shen HD, Fang RH. Changes in serum tumour necrosis factor-α in burned patients. Burns 1997; 23:6–10.
36. Mokline A, Garsallah L, Rahmani I, Jerbi K, Oueslati H, Tlaili S, *et al.* Procalcitonin: a diagnostic and prognostic biomarker of sepsis in burned patients. Annals of burns and fire disasters 2015; 28:116–120.
37. Mann EA, Wood GL, Wade CE. Use of procalcitonin for the detection of sepsis in the critically ill burn patient: A systematic review of the literature. Burns 2011; 37:549–558.
38. Neely AN, Fowler LA, Kagan RJ, Warden GD. Procalcitonin in Pediatric Burn Patients: An Early Indicator of Sepsis? Journal of Burn Care and Rehabilitation 2004; 25:76–80.
39. Becker KL, Snider R, Nylen ES. Procalcitonin in sepsis and systemic inflammation: a harmful biomarker and a therapeutic target. British Journal of Pharmacology 2010;
40. Faix JD. Biomarkers of sepsis. Critical Reviews in Clinical Laboratory Sciences 2013; 50:23–36.
41. Yang Y, Xie J, Guo F, Longhini F, Gao Z, Huang Y, *et al.* Combination of C-reactive protein, procalcitonin and sepsis-related organ failure score for the diagnosis of sepsis in critical patients. Annals of Intensive Care 2016; 6:51.
42. Madenci ÖÇ, Yakupoğlu S, Benzonana N, Yücel N, Akbaba D, Kaptanağası AO. Evaluation of soluble CD14 subtype (presepsin) in burn sepsis. Burns 2014; 40:664–669.
43. Zou Q, Wen W, Zhang X-C. Presepsin as a novel sepsis biomarker. World journal of emergency medicine 2014; 5:16–19.
44. Hildebrand F, Pape H-C, Harwood P, Müller K, Hoevel P, Pütz C, *et al.* Role of adhesion molecule ICAM in the pathogenesis of polymicrobial sepsis. Experimental and Toxicologic Pathology 2005; 56:281–290.
45. Duan X, Berthiaume F, Yarmush D, Yarmush ML. Proteomic analysis of altered protein expression in skeletal muscle of rats in a hypermetabolic state induced by burn sepsis. Biochemical Journal 2006; 397:149 LP – 158.
46. Hashiguchi N, Ogura H, Tanaka H, Koh T, Nakamori Y, Noborio M, *et al.* Enhanced Expression of Heat Shock Proteins in Activated Polymorphonuclear Leukocytes in Patients with Sepsis. Journal of Trauma and Acute Care Surgery 2001; 51.
47. McConnell KW, Fox AC, Clark AT, Chang N-YN, Dominguez JA, Farris AB, *et al.* The Role of Heat Shock Protein 70 in Mediating Age-Dependent Mortality in Sepsis. The Journal of Immunology 2011; 186:3718–3725.
48. Accardo-Palumbo A, D'Amelio L, Pileri D, D'Arpa N, Mogavero R, Amato G, *et al.* Reduction of plasma granzyme A correlates with severity of sepsis in burn patients. Burns 2010; 36:811–818.
49. Ramnath RD, Ng SW, Guglielmotti A, Bhatia M. Role of MCP-1 in endotoxemia and sepsis. International Immunopharmacology 2008; 8:810–818.
50. Hong T-H, Chang C-H, Ko W-J, Lin C-F, Liu H-H, Chow L-P, *et al.* Biomarkers of early sepsis may be correlated with outcome. Journal of Translational Medicine 2014; 12:146.