# We are IntechOpen,
# the world's leading publisher of
# Open Access books
# Built by scientists, for scientists

## 6,900
Open access books available

## 186,000
International  authors and editors

## 200M
Downloads

## 154
Countries delivered to

Our authors are among the

## TOP 1%
most cited scientists

## 12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
**BOOK CITATION INDEX**
INDEXED

**WEB OF SCIENCE**™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

# Interested in publishing with us?
# Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

# Early Detection of Sepsis, MOF and Outcome Prediction in Severely Traumatized Patients

Zeljko Lausevic and Mirjana Lausevic

Additional information is available at the end of the chapter

## 1. Introduction

Trauma is the most common cause of death in developed countries among the population under 40 and the fourth overall cause of death in the general population. In the USA 4.6% of all deaths per year are due to accidental injuries. The hospital expenses for injured patients are higher compared to the expenses for patients hospitalized due to other causes.[1] Injury-induced anergy is one of the key factors contributing to trauma victims' high susceptibility to sepsis. Patients are mostly young and it is therefore essential to be able to predict as accurately as possible the development of septic complications so that the appropriate treatment could be provided. Multiple organ failure (MOF) is the leading cause of late death following trauma.[2] The term defines an "all-or-nothing" event and represents only the extreme points of a continuous dynamic process of organ function deterioration. Nowadays the concept of MOF could be revisited as a transient state of metabolic shutdown analogous to hibernation. Avoiding the detrimental effects of inappropriate and counter-adaptive iatrogenic interventions is an important cornerstone of therapeutic management.[3] Severity of injury, late or inadequate resuscitation, inadequate surgical intervention, persistent inflammatory focus, previous organ damage, chronic disease and age over 65 may affect the presentation and the outcome of MOF. Studies demonstrate that the degree of an initial injury is important in determining the patient's susceptibility to post-traumatic complications, but the issue of secondary surgical procedures acting as additional inflammatory insults (second hit) and a genetic predisposition are suspected to be responsible for different outcomes.[4] These factors can explain why some patients develop serious post-traumatic complications and others do not, despite the same injury severity scores. It is still not possible to identify the risk group when efficient intervention could be undertaken. There is a tight correlation between the cytokin plasma level, the development of MOF and the mortality rate.[5] Immunological system plays a major role in an inflammatory response to trauma, which leads to the negative outcome without a direct connection to the severity of trauma or quality of the initial treatment.

The development of immunomonitoring would help in the selection of patients at risk of post-traumatic complications and, thereby, the choice of the most appropriate treatment protocols for severely injured patients.[6]

Trauma triggers a complex cascade of post-traumatic events that are important when predicting the outcome in the first few days after the trauma.[7] Mediators play an important role in the development of the systemic inflammatory response syndrome (SIRS), multiple organ dysfunction (MODS) and multiple organ failure (MOF), the last two associated with high mortality.  In critically injured patients who underwent resuscitation early, non-infective SIRS develops.  A severe trauma can provoke  serious SIRS, although mild SIRS can be useful and helpful in patient recovery.  The objectives of the therapy should be pointed towards modulating early SIRS. [8,9]

Interleukin 6 (IL-6) plasma level could be the marker of cytokine's cascade activity and might show the severity of  injury. In patients with an obscure sepsis syndrome, IL-6 plasma levels are well correlated to the later sepsis development and consecutive mortality.[10,11,12] The experiments in vitro showed that human monocytes produce interleukin 10 (IL-10) after lipopolysacharide stimulation, later compared to the production of the tumor necrosis factor (TNF)-α, IL-1, IL-6, or IL-8. The presence of anti IL-10 blocking antibodies in the cell culture results in production increase of these cytokines, implicating on the regulatory function of IL-10. IL-10 plasma levels are significantly increased in critically injured patients, especially in patients with sepsis, suggesting that this cytokine is an important inflammation mediator.[13,14]

Infection is identified as the essence of the major cause of multiple organ dysfunction in critically injured patients. [15,16] The course of patophysiological events, especially in the early post-traumatic period, is very important in predicting the outcome.[17,18]

The objectives of the study were to:

1. determine blood levels of C reactive protein (CRP), immunoreactive phospholypase $A_2$ group II (PLA$_2$-II), IL-6 and IL-10 concentration as quantifiable parameters of the outcome for critically injured patients;
2. evaluate prognostic values of the Simplified Acute Physiology Score (SAPS II), Injury Severity Score (ISS) score values and multiple organ failure (MOF) signs;
3. construct early predictive models for the outcome prediction.

## 2. Material and methods

A prospective 65- subject- study was performed  at the Intesive Care Unit (ICU) of the Clinical Center of Serbia. The atients met the following criteria: ISS > 18, aged 16-65 , admittance in the first 24 hours after the trauma, survival longer than 48  hours. Patients with the leading neurosurgical trauma were excluded.

Mediators of inflammation were determined in all patients within the first 24 hours, on the second, third, seventh and tenth day of hospitalization. CRP concentration was determined

by immunonephelometry on «Behring» laser nephelometer (normal value <9 mg/mL). Phospholipase $A_2$-II concentration was determined with enzyme-linked immunoadsorbent assay (ELISA), Boehringer Mannheim GmbH, Germany. Interleukin concentration was determined with Immunotech test based on «sandwich» enzyme immunodetermination. The reference range for IL-6 was 0 - 8 pg/mL and for IL-10 0 - 10 pg/mL.

We applied the MOF  score, in which the presence of organic damages is defined by the presence of one or more characteristics.[19,20] Lung dysfunction is defined as mandatory mechanical ventilation, for at least 72 hours, $PO_2/FiO_2 < 37,3$ kPa, positive end expiratory pressure greater than 8 cm $H_2O$, ARDS verified using X-ray, or respiratory frequence $\leq$ 5/min or $\geq$ 49/min. Liver insufficiency is defined as bilirubinaemya >51 μmol/L, at least for 48 hours; heart insufficiency is defined as cardiac index <3,0  L x $min^{-1}$ x $m^{-2}$, mandatory use of inotropic drugs, heart frequency $\leq$ 54/min, the presence of ventricular tachycardia and/or fibrilation, mean arterial pressure $\leq$ 49 mm Hg or pH $\leq$ 7,24; renal insufficiency is defined as blood level of serum creatinine >177 μmol/ L; haemathologic insufficiency is thrombocytopenia (<20000 cells/$mm^3$) or leucocytopenia (<1000 cells/ $mm^3$). All these analyses were conducted daily. The worst value was taken into account when defining the presence of organic  insufficiency (the presence of only one of these listed meant the presence of insufficiency).

The criteria for defining the presence of the SIRS were: body temperature >38 or <36 °C, heart frequency greater than 90 bpm, tachypnea (>20 respiration per minute at room temperature or $PaCO_2$ <4.3 Kpa), WBC >12000 cells/$mm^3$ or < 4000 cells/$mm^3$, or presence of more than 10% immature neutrofils (bands). [21]

Simplified Acute Physiology Score (SAPS II) is made out of 17 variables: 12 of them are physiological, age, type of treatment (urgent surgery, planned surgery or non-operative treatment) and three variables are connected to the existence  of chronic commorbidities, such as AIDS, metastatic cancer or hematologic malignancy. Each  of these variables  was given a certain number of points ranging from 0 to 3 (for body temperature) or from 0 to 26 (for the Glasgow Comma Scale). For 12 physiologic variables we took the worst values (with the highest number of points) during the first 24 hours after admission in ICU.[22]

*ISS*  was calculated in a standard manner, by squaring the highest individual values for three body regions in the first 24 hours: ISS = $AIS^2$ + $AIS^2$ + $AIS^2$. [23,24]

The $Chi^2$ test  was used for estimating the difference of frequency for categories that behaved according to the nominal scale. The  differences between numerical charactistics were tested using the t-test.  The Mann Whitney U test or Wilcoxon's test of pairs were used if the distribution was significantly different from normal. Each variable was assessed individually with the univariate analysis as a resulting variable for survival. The parameters that were found to be statistically significant predictors with the univariate analysis were included in the multivariate model. The logistic regression coefficient was used to  analyse the correlation between the daily average CRP, IL-6, IL-10 and PLA2-II concentrations and mortality. Values p<0.05 or p<0,01 were considered significant.

## 3. The results

Sixty five patients (52 male and 13 female), average age 47.13 ± 15.03 years, were included in this study. This can be explained by a greater exposure of men to trauma. There is a significant age difference among groups with MOF and without MOF (t= - 2.058, p=0.044) and survived and deceased patients group (t = - 3.26; p= 0.002). The most frequent was blunt trauma (51 patient, 78.1%), 14 patients (21.9%) had open wounds. Fourty three (66.1%) patients underwent surgical intervention, while 22 (33.9%) patients were treated non-operatively. The overall hospital stay was 23.85 ± 5.94 days, ranging from two days (which is a minimal entry criterion for this study) to 131 days. The overall mortality rate was 50.76% (33 died, 32 survived).  After a severe trauma MOF developed in 36 patients, while 29 were with no MOF signs. The mortality rate in the group of patients with MOF was 75%. Concerning the outcome, there is a significant difference between the groups with and without MOF (Pearson –20,571 (b), p=,000).

The average CRP daily values, in both survived and deceased patients, are shown in the Table 1. There was a significant difference, with the highest value for the seventh day of hospitalization (Mann – Whitney U test). The level of correlation of serum concentrations and the survival rate is very high for the third and seventh day of hospitalization, and it is significant for the first ($R_1$), second ($R_2$) and tenth day ($R_{10}$) of hospital stay ($R_3$ = 0,4355, $R_7$ = 0,5460, $R_1$= 0,3246, $R_2$ = 0,3610, $R_{10}$ = 0,3517). The average IL-6 values for each day of the two observed groups are shown in Table 1. There is a highly significant difference in IL-6 average values between the two observed groups for the four initial days of hospitalization, especially in the first three days. There is also a significant correlation between serum concentration and the overall survival, especially in two starting days ($R_1$ = 0,4278, $R_2$ = 0,4338), but with remaining significance for the third and seventh day, ($R_3$ = 0,4018, $R_7$ = 0,3082 ). There is a highly significant difference for the IL-10 concentration for the first three days and also for the tenth day of hospitalization. But, there is a high degree of correlation for the serum concentration of this cytokine and the negative outcome for the second day of hospitalization ($R_2$ = 0,2491).

We also compared average $PLA_2$ group II serum concentrations in the two observed groups, in the same manner and at the same time as described previously.

There is a substantial difference in average $PLA_2$ II levels in the first four measurments related to the outcome. There is a strong correlation between its values and the outcome, especially for the measurments conducted on the first, second, third and seventh day ($R_1$ = 0,3188, $R_2$ = 0,2766, $R_3$ = 0,2911, $R_7$ = 0,2977).

There is a significant difference in the number of positive SIRS characteristics for the day 1, 4. and 5 between the observed groups. There is also a huge statistically significant correlation between the SIRS charactersistics and the survival rate for the first, second, fourth and fifth day of hospitalization (Table 2).

| Days | | CRP | IL-10 | IL-6 | PLA$_2$ |
|---|---|---|---|---|---|
| 1. | S | 129,83±13,44** | 144,90±46,30** | 256,59±75,34** | 42,69±8,61 |
| | D | 212,83±18,29 | 285,96±64,28 | 804,33±96,62 | 120,68±19,94 |
| 2. | S | 148,66±14,40** | 64,95±14,31** | 189,69±57,71** | 57,42±11,90 |
| | D | 256,03±22,00 | 244,20±64,02 | 655,41±86,82 | 126,25±18,39 |
| 3. | S | 141,99±14,59** | 47,31±13,56** | 106,81±26,87** | 51,48±9,49 |
| | D | 257,28±18,27 | 161,50±53,28 | 437,18±79,55 | 119,80±19,62 |
| 7. | S | 127,57±13,41** | 34,75±14,93** | 72,75±19,96** | 41,75±9,00 |
| | D | 274,20±18,53 | 153,50±53,57 | 373,14±109,0 | 125,87±27,88 |
| 10. | S | 163,71±25,69** | 32,14±15,09 | 96,57±44,42 | 78,79±21,28 |
| | D | 275,38±26,33 | 86,83±45,69 | 151,66±44,76 | 109,48±32,45 |

C-reactive protein - CRP in mg/l
interleukin (IL) 6 (pg/mL)
IL-10 (pg/mL)
phospholipase A$_2$ (PLA$_2$ in ng/L)
survived (S) ,deceased (D)
\*  p<0,05
\*\*p<0,01

**Table 1.** Average C-reactive protein, interleukin 6, interleukin 10 and phospholipase A$_2$ in survived (S) and deceased (D) patients following severe trauma (Mann Whitney U test).

| days | SIRS1 | SIRS2 | SIRS3 | SIRS4 | SIRS5 | SIRS6 | SIRS7 |
|---|---|---|---|---|---|---|---|
| S | 2,31±0,06 | 2,31±0,09 | 2,13±0,12 | 2,04±0,10 | 1,85±0,15 | 2,25±0,13 | 2,30±0,15 |
| D | 2,71±0,03 | 2,56±0,08 | 2,54±0,10 | 2,62±0,13 | 2,87±0,12 | 2,70±0,16 | 2,76±0,18 |
| p | <0,01 | >0,05 | >0,05 | <0,01 | <0,01 | >0,05 | >0,05 |
| pR | <0,01 | <0,01 | <0,05 | <0,01 | <0,01 | >0,05 | >0,05 |

p – derived from t-test
pR – derived from logistic regression coefficient

**Table 2.** Number of positive systemic inflammatory response (SIRS) variables per hospital days in survived (S) and deceased (D)patients

SAPS II values in both groups are higly different ( t = - 5.805; p<0.000), Table 3. The degree of correlation shows a considerable significance for the method of logistic regression (R = 0.4811; p<0.000). The prognostic power of this score considering the outcome is 78.13% in our series.

The anatomic score model for injury severity, ISS, in the group of survivors (27,62 ± 5,31 SD) and the group of deceased are highly different (t= - 4.103; p<0.0001), Table 3. Its predictive power in our series was 75%. The method of logistic regression shows a highly significant correlation between the severity of the injury (ISS) and the survival rate (R = 0.3627).

|   | ISS | SAPS2 |
|---|---|---|
| S | 27,62±5,09 (SD) | 31,39±9,24 (SD) |
| D | 33,34±6,01 (SD) | 47,31±11,8 (SD) |
| R | 0,3627 | 0.4811 |
| p | <0,01 | <0,01 |

R- logistic regression coefficient
p - derived from t-test

**Table 3.** The Injury Severity Score (ISS) and Simplified Acute Physiology Score (SAPS II) values in survived (S) and deceased (D) patients

The mutual effect of all significant variables obtained by the univariate analysis is examined by the multivariate logistic regression model, estimating that the most important predictors of the outcome were the values of SAPS II and the CRP values for day 2 (CRP 2), mutually combined. This model shows the predictive power of 88.50% (Table 4).

|   | B | S.E. | Wald | sign | $R^2$ |
|---|---|---|---|---|---|
| **SAPS II** | 0,122 | 0,035 | 12.316 | 0,0001*** | 0,341 |
| **CRP 2** | 0,008 | 0,003 | 5.083 | 0,024* | 0,410 |
| **Const.** | -6.179 | 1.461 | 17.896 | 0,0001 | Ø |

**Table 4.** Multivariate logistic regression model 1

$$Y = -6.179 + 0,122 \times SAPS\ II + 0,008 \times CRP\ 2$$

The second model includes CRP values for the second day of hospitalization, the numbers of positive SIRS criteria for the day 1 (SIRS.1) and the values of SAPS II score. This model shows the predicitve power of 80.70% (Table 5).

|   | B | S.E. | Wald | s | R |
|---|---|---|---|---|---|
| **SIRS-1** | 1,9609 | 0,8401 | 5,4486 | 0,0196 | 0,2095 |
| **SAPS II** | 0,1306 | 0,0451 | 8,2631 | 0,0040 | 0,2833 |
| **CRP 2** | 0,0066 | 0,0035 | 3,5060 | 0,0611 | 0,1384 |
| **Const.** | -11,4242 | 3,3775 | 11,4410 | 0,0007 | Ø |

**Table 5.** Multivariate logistic regression model 2

$$Y = -11,4242 + 1,96 \times SIRS1 + 0,13 \times SAPS\ II + 0,007 \times CRP\ 2$$

The same significance has the predicitve model that takes into account the MOF development and the CRP values for the second day, again in mutual combination (Table 6).

|   | B | S.E. | Wald | s | R |
|---|---|---|---|---|---|
| **MOF** | 2,6426 | 0,9643 | 7,5103 | 0,0061 | 0,3178 |
| **CRP 2** | 0,0132 | 0,0053 | 6,1129 | 0,0134 | 0,2746 |
| **Const.** | -3,9805 | 1,3985 | 8,1014 | 0,0044 | Ø |

**Table 6.** Multivariate logistic regression model 3

$$Y = -3,98 + 2,64 \times MOF + 0,013 \times CRP$$

## 4. Discussion

The mortality rate is higher in the group of patients with a greater number of positive SIRS criteria. SIRS duration can play an important role. In other words, persistent SIRS probably assumes a high risk level. [25,26,27] The number of SIRS characteristics during the several initial days of hospitalization (for days 1 and 3) and SIRS duration are significantly related to the outcome. In our study the number of SIRS characteristcs is a better outcome predictor, than the SIRS duration. Three or more positive SIRS characteristics for the first and second day in our series are associated with a high risk of intrahospital death. Nowadays, the development of resuscitation and reanimation has decreased the mortality rate. One decade ago, a similar approach to sepsis included an early goal – directed therapy. The properly timed application of enteral nutrition, prevention of nosocomial infection, decubitus, mechanical ventilation, or haemodialysis, have a greater significance than previously thought.[28,29]

The predictive significance of physiological scoring systems is mostly expressed as «daily risk». We used the simple acute physiological score, second version, because of its simplicity of taking and calculating, and positive criticism.[22] The values of this score ranged from 17 to 75, with the average value of 39 points. There is a highly significant difference between the two groups related to the outcome. The overall predicting accuracy of intrahospital mortality in our series is very good (near 80%), greater than the ISS. SAPS II, using the method of multivariate logistic regression, entered as one of the most important variables into the model of regression for the outcome prediction. We feel that this data shows the usefulness of the physiological scoring systems application in the assessment of the patient's response to trauma and in outcome predicting. The best accuracy is obtained when combining physiological and anatomical scores, with the determination of specific inflammation markers, which is the recommendation of many researchers.[30,31]

The peak of IL-6 serum levels is related to surgical trauma, with the surgical procedure duration and blood loss.[43] Stratification of injured patients according to injury severity and the outcome, takes into account the cytokine status. [11,33] According to cytokine serum levels, patients are divided into four groups, with prognostic significance. The number of patients with the worst prognostic group, the third (over 250 pg/L) and the fourth (over 500 pg/L) in our series is very high (over 45%); there is a highly significant difference among the patients related to the outcome (p=0.0000). In deceased patients high levels persists in the form of plateau and decrease minimally (in case of death). Significantly high values for the first and second day are found, but the majority indicate that the window is closed after three days, meaning that values after that period have no predictive power.

Clinical IL-10 application was disappointing and its administration immediately after the trauma or surgical intervention didn't improve the survival rate. Also, this cytokine failed to decrease the level of other proinflammatory cytokines (TNF, IL-1, IL-8) in serum and fail in

blocking the neutrophil accumulation in the lungs.[36] The IL-10 administration increase mice mortality during endotoxaemia, while blocking IL-10 activity decreased mortality in the Klebsiella and Candida infected mice.[34] In patients with an inevitable negative outcome (extensive combustions, critically injured patients), IL-10 serum levels are the highest. On the other hand, in patients with clinical signs of ARDS, the low IL-10 levels in the bronchalveolar lavage are associated with the increased mortality. These results pose a question when it would be the problem to have too little or too much IL-10; in other words, when IL-10 can be taken as a relevant marker or a mediator. The ratio of IL-6 to IL-10 may be a predictive factor in SIRS.[33] In our study we partially confirmed the disappointing overwhelming reports on a possible protective role of IL-10 in human sepsis.[34] The kinetics of its concentration is very similar to the IL-6 kinetics and appears to be more realistic in describing the illness severity and the outcome, than in playing a protective role in critically injured patients. Based upon our results, IL-10 kinetics and its high serum levels in the groups with the poorer outcome are not in favor of its protective role as a cytokine, but it can be used as a good predictor of injury course and the outcome for some group of patients.[14, 37,38]

A signifficant correlation between non-pancreatic PLA$_2$ levels and the development of respiratory insufficiency and hypotension in sepsis was found.[39] There is an obvious increase in non-pancreatic PLA$_2$ levels in relation to mortality. There are several contradictory results on the correlation of this enzyme plasma concentration with some diseases, their course and the outcome. It was found in patients with multiple trauma that PLA$_2$ group II might be considered as an important predictor of injury severity the outcome, and it was shown in several studies that its concentrations and kinetics are well correlated to the course and the outcome of septic syndrome.[40] On the other hand, the role of PLA$_2$ II in different conditions (multiple injuries, acute pancreatitis, sepsis) was studied and it was shown that in case of critical injuries (ISS average value was 41) the PLA$_2$ levels correlate well to the illness severity and the outcome.[41,42] In our series, average PLA$_2$ II values for each day have been compared to the septic syndrome and multiorganic insufficiency development and the outcome. The highest signifficance exists in average serum concentrations on the second and third day, related to the outcome. On the seventh day there is a peak value in patients with a negative outcome, while serum levels on the 10th and 14th day decreased. We created three models concerning the outcome. Al the models included CRP values for the second day of hospitalization. In the first model SAPS II values were added. Because of the availability of the needed data and the fact that it can be calculated on the second day of the hospitalization, this is the model we would like to emphasize. The second model includes the number of SIRS characteristics on the first day, SAPS II values and CRP values on second day of hospitalization. The third model that points out the probability of intrahospital death, except the CRP value for the second day, takes into account the presence of MOF (MOF present – 1; MOF absent – 0). Although the accuracy of this model is very high, the calculating of MOF score can be very complicated, and the MOF presence itself is a serious prognostic sign that decreases the predictive power of this model. We think that the utilization of these models in our practice would be very interesting and would test its value in the best way.

## 5. Conclusion

In our study the number of positive SIRS characteristics is related to the outcome. SAPS II values are significantly different in the survived and deceased groups. ISS enables very good quantification of the patients' injuries and represents a precise outcome predictor. It is possible to predict the outcome based on CRP kinetics from Day 1 to Day 10. IL-6 kinetics in the first seven days, before the clear appearance of clinical symptoms, can point to the possible outcome. A high average IL-10 serum level in the initial 24 hours after the injury, the second and the third day announce a negative course and injury outcome. PLA2 in our series reflects the injury severity and systemic response, and its average daily concentrations with high probability can divide patients into groups of the survived and the deceased. It is possible to create predictive models based on our results considering the outcome. The most important parameters are SAPS II values and CRP values on  day 2 combined.

## Author details

Zeljko Lausevic*
*Emergency Center, Clinical Center of Serbia, Serbia*
*School of Medicine, University of Belgrade, Belgrade, Serbia*

Mirjana Lausevic
*Clinic of Nephrology, Clinical Center of Serbia, Serbia*
*School of Medicine, University of Belgrade, Belgrade, Serbia*

## 6. References

[1]  Wilson C.W, Grande M.C and Hoyt B.D. (2007) Trauma, Emergency Resuscitation, Perioperative Anesthesia and Surgical Management.  Informa Healthcare USA

[2]  Waydhas C, Nast-Kolb D, Trupka A, et al. Posttraumatic inflammatory response, secondary operations, and late multiple organ failure. *J Trauma.* 1996; 40(4):624-31

[3]  Mongardon N,  Dyson A, Singer M. Is MOF an outcome parameter or a transient, adaptive state in critical illness? Curr Opin Crit Care. 2009 October; 15(5): 431–436.

[4]  Moore FA, Sauaia A, et al. Postinjury multiple organ failure: a bimodal phenomenon. *J Trauma.* 1996; 40(4):501-12

[5]   Hildebrand F, Pape HC, Krettek C. The importance of cytokines in the posttraumatic inflammatory reaction. Unfallchirurg. 2005; 108(10): 793-803

[6]  Vincent JL. Prevention and Therapy of Multiple Organ Failure. World J. Surg. 1996;20(4): 465-70

[7]  Sauaia A, Moore FA, Moore EE, Norris JM, Lezotte DC, Hamman RF. Multiple  organ failure can be predicted as early as 12 hours after injury. The Journal of Trauma Injury, Infection, and Critical Care 1998; 45(2):291-303

---

* Corresponding Author

[8]  Bone RC. Toward a theory regarding the pathogenesis of the systemic inflammatory response syndrome: What we know and do not know about cytokine regulation. *Crit Care Med* 1996; 24(1):162-72

[9]  Ogawa M. Systemic Inflammatory Response Syndrome - A Concept for Avoiding Organ Dysfunction Induced by a "Second Attack". *Surgery Today* 1998; 28(7):679-81

[10] Frink M, Van Griensven M, Kobbe P, Brin T, Zeckey C, Vaske B, Krettek C, Hildebrand F. IL-6 predicts organ dysfunction and mortality in patients with multiple injuries. Scand J Trauma Resusc Emerg Med. 2009; 17: 49.

[11] Pileri D, Accardo Palomb A,  D'Amelio L, Conte C. Concentrations of Cytokines Il-6 and Il-10 in Plasma of Burn Patients: Their Relationship to Sepsis and Outcome. Ann Burns Fire Disasters. 2008 ; 21(4): 182–185.

[12] Borden EC, Chin P. Interleukin-6: a cytokine with potential diagnostic and therapeutic roles. J Lab Clin Med. 1994; 123 (6):824-9

[13] A. Marchant, J.L. Vincent, M.Goldman. The protective role of interleukin-10 in sepsis; Yearbook of intensive care and emergency medicine 1994; 42-47

[14] Remick D.G., Gard S.J., Newcomb D.E., et al: Exogenous interleukin-10 fails to decrease the mortality or morbidity of sepsis. Crit. Care Med. 1998; 26:895-904

[15] Nasraway SA. Sepsis research: We must change course. Crit Care Med 1999; 27:427-30

[16] Cohen NH. Reduced mortality from septic shock – Lessons for the future. Crit Care Med 1998; 26:1956-8

[17] Guirao X, Lowry SF. Biologic control of injury and inflammation: Much more than too little or too late. World J Surgery. 1996; 20(4):437-46

[18] Keel M, Trentz O. Pathophysiology of polytrauma. Injury. 2005; 36(6): 691-709

[19] Vincent JL, Moreno R, Takala J, et al. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. Intensive Care Med 1996; 22:707-710.

[20] Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med 1995; 23:1638-1652.

[21] Members of the American College of Chest Physicians / Society of Critical Care Medicine Consensus Conference Committee: American College of Chest Physicians/Society of Critical Care. Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsys. Crit Care Med 1992; 20:864-74

[22] Auriant I et al. Simplified acute physiology Score II for measuring severity of illness in intermediate care units. Crit Care Med 1998; 26:1368-1372.

[23] Champion HR, Sacco WJ, Lepper RL, et al: An anatomic index of injury severity. J Trauma 20:197, 1980

[24] Champion HR, Copes WS, Sacco WJ, et al: Improved predictions from a severity characterization of trauma (ASCOT) over trauma and injury severity score (TRISS): Results of an independent evaluation. J Trauma 40:42, 1996

[25] Marshal J: Both the disposition and the means of cure: "Severe SIRS," "sterile shock," and the ongoing challenge of description. Crit-Care-Med. 1997 Nov; 25(11): 1765-6

[26] Rixen D. et al.: "Sepsis/SIRS," physiologis slassification, severity stratification, relation to cytokine elaboration and outcome prediction in posttrauma critical illness. The Journal of Trauma: Injury, Infection, and Critical Care 1996; 4:581-598.

[27] Michio Ogawa. Systemic Inflammatory Response Syndrome - A Concept for Avoiding Organ Dysfunction Induced by a "Second Attack". Surgery Today 1998; 28:679-681.

[28] Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med;36(1):296-327

[29] Cannon CM, for the Multicenter Severe S, Septic Shock Collaborative G. The GENESIS Project (GENeralisation of Early Sepsis Interventions): A Mulzicenter Quality Improvement Collaborative. Acad Emerg Med. 2010;17(11);1258

[30] Gorra AS, Clark DE, Mullins RM. Using Hospital Outcomes to Predict 30-Day Mortality Among Injured Patients Insured by Medicare.Arch Surg. 2011;146(2):195-200.

[31] Jack E. Zimmerman, MD et al.: Severity stratification and outcome prediction for multisystem organ failure and dysfunction. World J. Surg 1996; 20:401-405.

[32] Marecaux G, Pinsky MR, Dupont E, Kahn RJ, Vincent JL. Blood lactate levels are better prognostic indicators than TNF and IL-6 levels in patients with septic shock. Intensive Care Med. 1996. May 22:5 404-8

[33] Miyaoka K, Iwase M, Suzuki R, et al. Clinical evaluation of circulating interleukin-6 and interleukin-10 levels after surgery-induced inflammation J Surg Res. 2005;125 (2): 144-50

[34] Osuchowski F.M, Welch K, Siddiqui J, Remick D.G. Circulating Cytokine/Inhibitor Profiles Reshape the Understanding of the SIRS/CARS Continuum in Sepsis and Predict Mortality. The Journal of Immunology 2006 ; 177(3) 1967-1974.

[35] Parsons PE. Interleukin-10: The ambiguity in sepsis continues. Crit Care Med 1998; 26:818-9

[36] Parsons PE, Moss M, Vannice JL, et al: Circulating IL-1ra and IL-10 levels are increased but do not predict the development of acute respiratory distress syndrome in at-risk patients. Am J Respir Crit Care Med. 1997; 155:1469-73

[37] Gomes-Jimenes J, Martin MC, Sauri R, et al. Interleukin-10 and the monocytic/macrophage-induced inflammatory response in septic shock. Journal of Infectious Diseases 1995;711:472-5

[38] Donnelly SC, Strieter RM, Reid PT, et al: The association between mortality rates and decreased concentrations of IL-10 and IL-1ra in the lung fluids of patients with the adult respiratory distress syndrome. Ann Intern Med 1996; 125: 191-6

[39] Vadas P, Pruzanski W, Stefanski E, et al. Pathogenesis of hipotension in septic shock: correlation of circulating phospholipase A2 levels with circulatory collapse. Crit. Care Med. 1988;16(1): 1-7

[40] Waydhas C, Nast-Kolb D, Duswald KH, Lehnert P, Schweiberer L. Prognostic Value of Serum Phospholipase A in the Multitraumatized Patient. Klin Wochenschr 1989; 67(3):203-6.

[41] Buchler M, Deller A, Malfertheiner P, et al. Serum Phospholipase A2 in Intensive Care Patients with Peritonitis, Multiple Injury, and Necrotizing Pancreatitis. Klin Wochenschr 1989; 67(3):217-2

[42] Juha M. Grönroos, MD, et al. Group II phospholipase A$_2$ in serum in critically ill surgical patients. *Crit Care Med* 1994; 22:956-960.

[43] Giannoudis-PV, Smith-MR, Evans-RT, Bellamy-MC, Guillou-PJ: Serum CRP and IL-6 levels after trauma. Not predictive of septic complications in 31 patients. Acta-Orthop-Scand. 1998 Apr; 69(2): 184-8