

Minerva Anestesiologica

=====

Title: Injury-induced immunosuppression: we are finally on the right track?

Paper code: Minerva Anestesiol-11632

Submission Date: 2016-08-05 16:27:22

Article Type: Editorial

Files:

1): Reply letter to comments on the manuscript

Version: 2

File format: application/msword

2): Manuscript

Version: 4

Description: manuscript

File format: application/msword

PEER REVIEW COPY
MINERVA ANESTESIOLOGICA

TO:

Editor in Chief of Minerva Anestesiologica

Modena, 3 October, 2016

Dear Dr Cavaliere,

As kindly requested we shortened the text by about 150 words (around 15%), simplified some concepts and revised grammar and bibliography.

We thank you again for the opportunity given

Yours Sincerely,

Dr. Massimo Girardis

Address for Correspondence:

Massimo Girardis

Cattedra di Anestesia e Rianimazione 1

Azienda Ospedaliera Universitaria di Modena

L.go del Pozzo, 71, 41100 Modena, ITALY

Tel: +39-059-4224896

Fax: + 39-059-4224899

e-mail: girardis.massimo@unimo.it

PEER REVIEW COPY
MINERVA ANESTESIOLOGICA

Injury-induced immunosuppression: we are finally on the right track?

Stefano Busani, Andrea Cossarizza* and Massimo Girardis

Intensive Care Unit and *Chair of Pathology and Immunology, University of Modena and
Reggio Emilia, Modena, Italy

In critically ill patients multiple stress events such as infection, trauma, surgery and burn may

lead to dysregulation of the immune response with an excessive pro-inflammatory phase

and/or a prolonged and profound dysfunction in **immune response**. This latter, called immune-

paralysis, predisposes patient to secondary life-threatening infections and seems to be crucial

for long-term outcomes in patients surviving to first hit [1]. Moreover, due to impairment in the

innate and adaptive immunity, antibiotic therapy alone may result ineffective in

immunosuppressed patients. Therefore, early detection of immune dysfunction and **its** support

by specific strategies may be the key for improving survival [2, 3].

In the last years the awareness of the pivotal role of immunity in acute illnesses **has** led to

significant advances in the identification of biomarkers **useful for the assessment of the**

immune system competence in critically ill patients. In the current issue of Minerva

Anestesiologica, Rouget et al. [4] provided a detailed and exhaustive review of **these bio-**

markers. The authors focused on immature granulocytes, quantitative and qualitative

alterations in dendritic cells, monocytes human leucocytes antigen DR, anti-inflammatory

interleukins and the recent concept of leucocyte reprogramming [5]. **The** role of the possible

markers of immunosuppression expressed by B and/or T lymphocytes **has** been **also** reviewed

Eliminato: led

Eliminato: , for instance,

Eliminato: basic immunological mechanisms.

Eliminato: phase

Eliminato: the

Eliminato: these

Eliminato: the

Eliminato: the

Eliminato: of the immune response

Eliminato: the patients'

Eliminato: Unfortunately, in critically ill patients, for many

Formattato: Rientro: Sinistro: 0 cm

Eliminato: fine evaluation of immune competence and the reasons for its variability remained mostly unexplored. Recently, the

Eliminato: able to suggest whether

Eliminato: patient is in a pro-inflammatory state or in a phase of immunoparalysis. ¶

Eliminato: .

Eliminato: bio-markers that may be useful for the assessment of the competence of the immune system in critically ill patients.

Eliminato: Moreover, the

Eliminato: have

in detail, along with a novel transcriptomic view that **would allow** the identification of genes that are up or down-regulated during a stressing insult.

Eliminato: allows

Eliminato: those

In addition to molecules and cells **described** by Rouget et al. [4], further bio-markers may be helpful for identifying an hypo-reactive state of the immune system. A low plasma concentration of the different isotypes of endogenous immunoglobulins at the onset and throughout the course of sepsis has been associated to an increased risk of mortality in septic patients [6, 7]. Due to the pleiotropic effects of immunoglobulins in the inflammatory-immune

Eliminato: Beside

Eliminato: identified

response, the reasons and the true meaning of this association are still debated. However, several mechanisms by which immunoglobulins may exert anti-apoptotic effects of different immune cells populations **have been identified in preclinical models**. Therefore, a decreased immunoglobulin plasma levels could facilitate a boost of apoptosis that has been recognized as an important cause of major immune dysfunction during late phases of sepsis [8, 9]. Remaining on apoptosis, **caspase 1** is a key component of inflammasomes that trigger a potent pro-inflammatory response, ultimately inducing a type of cell death defined "pyroptosis" [10, 11]. In

Eliminato: of the host

Eliminato: preclinical models identified

Eliminato: .

Eliminato: the expression of caspase 1 on monocytes may be also considered an interesting biomarker. Caspase

Eliminato: Therefore, caspase 1 expression,

Eliminato: a

Eliminato: specific markers,

Eliminato: be

Eliminato: a spy of cellular "pyroptosis" and, thus, of the hypo-reactivity state

Eliminato: the

Eliminato: . ¶

Eliminato:

Eliminato: . MAIT cells are

Eliminato: and are restricted by the evolutionarily conserved major histocompatibility complex related molecule.

Eliminato: reported

Eliminato: . In fact, Grimaldi et al.

Eliminato: recently showed that patients with persistent MAIT cells depletion display a higher incidence of infections acquired in intensive care unit.

Eliminato: host's

Eliminato: pathophysiological and clinical

Eliminato: not only during

Eliminato: , but also after surgery,

Eliminato: and

Eliminato: more

addition to **its role as marker of an excessive** pro-inflammatory **condition, persisting high level of caspase 1** could **be** also considered **an early indicator** of immune system **hypo-reactivity**. A further potential marker of immune dysfunction might be **mucosal-associated invariant T (MAIT) cells**, a population of T lymphocytes that express a semi-invariant T cell receptor. An important role of MAIT cells in the early stages of bacterial infections has been **postulated** [12] **and a recent study showed that critically ill patients with persistent MAIT cells depletion display a high susceptibility to develop hospital acquired infections** [13].

A proper evaluation of hyper or under-activation of the **host** immune system may provide a better comprehension of **the pathobiology** changes occurring **in sepsis, as well as in other conditions such as** trauma, burn **and surgery**, and may **finally** guide to a tailored therapeutic

Eliminato: suppressing

approach [14]. For instance, the traditional strategy aimed to suppress the immune system by inhibition of inflammatory mediators could be helpful in patients with an overwhelming pro-

Eliminato: case of

Eliminato: severely

Formattato: Rientro: Sinistro: 0,01 cm

inflammatory state, but may be harmful in patients with a suppressed immune response [15].

The review by Rouget et al. [4] provides a straightforward analysis on the rationale for use and

Eliminato: gives a proper understanding of possible biomarkers underlying complex immune dysfunction that could become essentials for those who interact daily with critically ill patients.

the feasibility of measuring immune-competence at the bedside. Unfortunately, most of the biomarkers described requires sophisticated techniques such as flow cytometry, immunohistochemistry, cytokine ELISA arrays or RNA analysis for gene expression. Despite many of these procedures are complex and have a high cost, we believe that the evaluation of the immune response is today mandatory for a proper management of septic patients. To this aim, official guidelines or consensus conferences are urgently needed to provide clinicians with a sort of "immunoscope" to monitor critically-ill patients and treat them. The future in which specific therapies will be tailored on a sound evaluation of patient pathobiology could be around the corner.

Eliminato: Unfortunately, measuring most of the reported biomarkers requires sophisticated techniques such as flow cytometry, immunohistochemistry, cytokine ELISA arrays or RNA analysis for gene expression. Such procedures are rather complex, have a high cost and may be difficult to use in hospitals with low economic resources. However, we believe that at least the cheapest and more accessible, routinely usable biomarkers should be urgently transferred to the clinical practice. To do this, it would be necessary to draw up an official document based on scientific evidence and on expert opinions that provided to all clinicians, including those who do not work in third-level care facilities, the basis to implement an easily accessible "immunoscope" with the standard treatment of critically ill patients. The purpose of this new tool would be to identify earlier and with greater accuracy the host response to the insult, thus allowing the clinicians to titrate the appropriate immune therapy. The future in which specific therapies will be tailored on a sound evaluation of patients' pathobiology could be around the corner.¶

REFERENCES

1. Pop-Vicas A, Opal SM. The clinical impact of multidrug-resistant gram-negative bacilli in the management of septic shock. *Virulence* 2014;5(1):206-12.

2. Venet F, Lukaszewicz AC, Payen D, Hotchkiss R, Monneret G. Monitoring the immune response in sepsis: a rational approach to administration of immunoadjuvant therapies. *Curr Opin Immunol* 2013;25(4):477-83.

3. Delano MJ, Ward PA. Sepsis-induced immune dysfunction: can immune therapies reduce mortality? *J Clin Invest* 2016;126(1):23-31.

4. Rouget C, Girardot T, Textoris J, Monneret G, Rimmelé T, Venet f. Biological markers of injury-induced immunosuppression. *Minerva Anestesiol* 2016; [epub ahead of print].

5. Shalova IN, Lim JY, Chittezhath M, Zinkernagel AS, Beasley F, Hernandez Jimenez E, et al., Human monocytes undergo functional re-programming during sepsis mediated by hypoxia-inducible factor-1alpha. *Immunity* 2015;42(3):484-98.

6. Bermejo-Martin JF, Rodriguez-Fernandez A, Herran-Monge R, Andaluz-Sieda D, Muriel-Bombin A, Merino P, et al., Immunoglobulins IgG1, IgM and IgA: a synergistic team influencing survival in sepsis. *J Intern Med* 2014;276(4):404-12.

7. Justel M, Socias L, Almansa R, Ramirez P, Gallegos MC, Fernandez V, et al., IgM levels in plasma predict outcome in severe pandemic influenza. *J Clin Virol* 2013;58(3):564-7.

8. Busani S, Damiani E, Cavazzuti I, Donati A, Girardis M. Intravenous immunoglobulin in septic shock: review of the mechanisms of action and meta-analysis of the clinical effectiveness. *Minerva Anestesiol* 2016;82(5):559-72.

Eliminato: ... [1]

Formattato ... [1]

Eliminato: |

Eliminato: . and S.M.

Formattato ... [2]

Formattato ... [3]

Formattato ... [4]

Formattato ... [5]

Eliminato: |

Formattato ... [6]

Eliminato: |

Formattato ... [7]

Eliminato: p.

Formattato ... [8]

Eliminato: 2. . Venet, F., et al.,

Formattato ... [9]

Eliminato: |

Formattato ... [10]

Eliminato: |

Formattato ... [11]

Eliminato: p.

Formattato ... [12]

Eliminato: 3. .

Formattato ... [13]

Eliminato: M.J. and P.A.

Formattato ... [14]

Eliminato: |

Formattato ... [15]

Eliminato: |

Formattato ... [16]

Eliminato: p.

Formattato ... [17]

Formattato ... [18]

Eliminato: 4. .

Formattato ... [19]

Eliminato: |

Formattato ... [20]

Eliminato: ., et al.,

Formattato ... [21]

Eliminato: |

Formattato ... [22]

Eliminato: |

Formattato ... [23]

Eliminato: 5. . Shalova, I.N.,

Formattato ... [24]

Eliminato: |

Formattato ... [25]

Eliminato: |

Formattato ... [26]

Eliminato: p.

Formattato ... [27]

Eliminato: 6. . Bermejo

Formattato ... [28]

Formattato ... [29]

Formattato ... [30]

Formattato ... [31]

Formattato ... [32]

Formattato ... [33]

Formattato ... [34]

Formattato ... [35]

9. Leentjens J, Kox M, van der Hoeven JG, Netea MG, Pickkers P. Immunotherapy for the adjunctive treatment of sepsis: from immunosuppression to immunostimulation. Time for a paradigm change? *Am J Respir Crit Care Med* 2013;187(12):1287-93.

10. Kepp O, Galluzzi L, Zitvogel L, Kroemer G. Pyroptosis - a cell death modality of its kind? *Eur J Immunol* 2010;40(3):627-30.

11. Wallach D, Kang TB, Dillon CP, Green DR. Programmed necrosis in inflammation: Toward identification of the effector molecules. *Science* 2016;352(6281):aaf2154.

12. Le Bourhis L, Guerri L, Dusseaux M, Martin E, Soudais C, Lantz O. Mucosal-associated invariant T cells: unconventional development and function. *Trends Immunol* 2011;32(5):212-8.

13. Grimaldi D, Le Bourhis L, Sauneuf B, Dechartres A, Rousseau C, Quaaaz F, et al., Specific MAIT cell behaviour among innate-like T lymphocytes in critically ill patients with severe infections. *Intensive Care Med* 2014;40(2):192-201.

14. Hamers L, Kox M, Pickkers P. Sepsis-induced immunoparalysis: mechanisms, markers, and treatment options. *Minerva Anestesiol* 2015;81(4):426-39.

15. Boomer JS, To K, Chang KC, Takasu G, Osborne DF, Walton AH, et al., Immunosuppression in patients who die of sepsis and multiple organ failure. *JAMA* 2011;306(23):2594-605.

Corresponding Author: Massimo Girardis, Via del Pozzo 71, Policlinico di Modena, 41124 Modena, Italy. E-mail: girardis.massimo@unimore.it

Conflicts of interest: The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Eliminato: []
 Formattato: []
 Eliminato: []
 Formattato: [381]
 Formattato: [39]
 Eliminato: []
 Formattato: [40]
 Eliminato: []
 Formattato: [41]
 Eliminato: p.
 Formattato: [42]
 Eliminato: 10.
 Formattato: [43]
 Eliminato: []
 Formattato: [44]
 Eliminato: , et al.,
 Formattato: [45]
 Eliminato: []
 Formattato: [46]
 Eliminato: []
 Formattato: [47]
 Eliminato: p.
 Formattato: [48]
 Eliminato: 11.
 Formattato: [49]
 Eliminato: []
 Formattato: [50]
 Eliminato: , et al.,
 Formattato: [51]
 Eliminato: []
 Formattato: [52]
 Eliminato: []
 Formattato: [53]
 Eliminato: p.
 Formattato: [54]
 Eliminato: 12.
 Formattato: [55]
 Eliminato: , L., et al.,
 Formattato: [56]
 Eliminato: []
 Formattato: [57]
 Eliminato: []
 Formattato: [58]
 Eliminato: p.
 Formattato: [59]
 Eliminato: 13.
 Formattato: [60]
 Eliminato: []
 Formattato: [61]
 Eliminato: []
 Formattato: [62]
 Eliminato: []
 Formattato: [63]
 Eliminato: []
 Formattato: [64]
 Formattato: [65]
 Formattato: [66]
 Formattato: [67]
 Formattato: Page 7 of 16 [68]
 Formattato: [69]

Pagina 5: [1] Formattato	Massimo Girardis	09/10/2016 16.30.00
Giustificato, Rientro: Sinistro: 0,63 cm		
Pagina 5: [2] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [3] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [4] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [5] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [6] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [7] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Non Grassetto, Evidenziato		
Pagina 5: [7] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [8] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [9] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [9] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Non Corsivo, Evidenziato		
Pagina 5: [9] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [10] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [11] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Non Grassetto, Evidenziato		
Pagina 5: [12] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [13] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [14] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [15] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [16] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Non Grassetto, Evidenziato		
Pagina 5: [16] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [17] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [18] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [19] Formattato	Massimo Girardis	09/10/2016 16.30.00

Tipo di carattere: Candara, Evidenziato

Pagina 5: [20] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [21] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [22] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [23] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [24] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [25] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [26] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Non Grassetto, Evidenziato		
Pagina 5: [26] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [27] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [28] Eliminato	Massimo Girardis	09/10/2016 16.30.00
6. Bermejo-Martin, J.F.,		
Pagina 5: [29] Formattato	Massimo Girardis	09/10/2016 16.30.00
Normale, Giustificato, Rientro: Sinistro: 0,63 cm, Nessun controllo righe isolate, Non regolare lo spazio tra testo asiatico e in alfabeto latino, Non regolare lo spazio tra testo asiatico e caratteri numerici		
Pagina 5: [30] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Inglese (U.S.A.), Evidenziato		
Pagina 5: [30] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [31] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [32] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Non Grassetto, Evidenziato		
Pagina 5: [33] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [33] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 5: [34] Formattato	Massimo Girardis	09/10/2016 16.30.00
Giustificato, Rientro: Sinistro: 0,63 cm		
Pagina 5: [35] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Italiano (Italia), Evidenziato		
Pagina 5: [36] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Italiano (Italia), Evidenziato		
Pagina 6: [37] Formattato	Massimo Girardis	09/10/2016 16.30.00

Tipo di carattere: Candara, Evidenziato

Pagina 6: [38] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Evidenziato

Pagina 6: [39] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Evidenziato

Pagina 6: [39] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Non Corsivo, Evidenziato

Pagina 6: [39] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Evidenziato

Pagina 6: [40] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Evidenziato

Pagina 6: [41] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Non Grassetto, Evidenziato

Pagina 6: [41] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Evidenziato

Pagina 6: [42] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Evidenziato

Pagina 6: [43] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Evidenziato

Pagina 6: [44] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Evidenziato

Pagina 6: [45] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Evidenziato

Pagina 6: [46] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Evidenziato

Pagina 6: [47] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Non Grassetto, Evidenziato

Pagina 6: [47] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Evidenziato

Pagina 6: [48] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Evidenziato

Pagina 6: [49] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Evidenziato

Pagina 6: [50] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Evidenziato

Pagina 6: [51] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Evidenziato

Pagina 6: [52] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Evidenziato

Pagina 6: [53] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Non Grassetto, Evidenziato

Pagina 6: [53] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Evidenziato

Pagina 6: [54] Formattato Massimo Girardis 09/10/2016 16.30.00

Tipo di carattere: Candara, Evidenziato

Pagina 6: [55] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 6: [56] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 6: [57] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 6: [58] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Non Grassetto, Evidenziato		
Pagina 6: [58] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 6: [59] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 6: [60] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 6: [61] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 6: [62] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 6: [63] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 6: [64] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Non Grassetto, Evidenziato		
Pagina 6: [64] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 6: [65] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 6: [66] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 6: [67] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 6: [68] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 6: [69] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		
Pagina 6: [70] Formattato	Massimo Girardis	09/10/2016 16.30.00
Tipo di carattere: Candara, Evidenziato		

Injury-induced immunosuppression: we are finally on the right track?

Stefano Busani, Andrea Cossarizza* and Massimo Girardis

Intensive Care Unit and *Chair of Pathology and Immunology, University of Modena and
Reggio Emilia, Modena, Italy

In critically ill patients multiple stress events such as infection, trauma, surgery and burn may lead to dysregulation of the immune response with an excessive pro-inflammatory phase and/or a prolonged and profound dysfunction in immune response. This latter, called immune-paralysis, predisposes patient to secondary life-threatening infections and seems to be crucial for long-term outcomes in patients surviving to first hit [1]. Moreover, due to impairment in the innate and adaptive immunity, antibiotic therapy alone may result ineffective in immunosuppressed patients. Therefore, early detection of immune dysfunction and its support by specific strategies may be the key for improving survival [2, 3].

In the last years the awareness of the pivotal role of immunity in acute illnesses has led to significant advances in the identification of biomarkers useful for the assessment of the immune system competence in critically ill patients. In the current issue of *Minerva Anestesiologica*, Rouget et al. [4] provided a detailed and exhaustive review of these biomarkers. The authors focused on immature granulocytes, quantitative and qualitative alterations in dendritic cells, monocytes human leucocytes antigen DR, anti-inflammatory interleukins and the recent concept of leucocyte reprogramming [5]. The role of the possible markers of immunosuppression expressed by B and/or T lymphocytes has been also reviewed in detail, along with a novel transcriptomic view that would allow the identification of genes that are up or down-regulated during a stressing insult.

In addition to molecules and cells described by Rouget et al. [4], further bio-markers may be helpful for identifying an hypo-reactive state of the immune system. A low plasma concentration of the different isotypes of endogenous immunoglobulins at the onset and throughout the course of sepsis has been associated to an increased risk of mortality in septic patients [6, 7]. Due to the pleiotropic effects of immunoglobulins in the inflammatory-immune response, the reasons and the true meaning of this association are still debated. However, several mechanisms by which immunoglobulins may exert anti-apoptotic effects of different immune cells populations have been identified in preclinical models. Therefore, a decreased immunoglobulin plasma levels could facilitate a boost of apoptosis that has been recognized as an important cause of major immune dysfunction during late phases of sepsis [8, 9]. Remaining on apoptosis, caspase 1 is a key component of inflammasomes that trigger a potent pro-inflammatory response, ultimately inducing a type of cell death defined “pyroptosis” [10, 11]. In addition to its role as marker of an excessive pro-inflammatory condition, persisting high level of caspase 1 could be also considered an early indicator of immune system hypo-reactivity. A further potential marker of immune dysfunction might be mucosal-associated invariant T (MAIT) cells, a population of T lymphocytes that express a semi-invariant T cell receptor. An important role of MAIT cells in the early stages of bacterial infections has been postulated [12] and a recent study showed that critically ill patients with persistent MAIT cells depletion display a high susceptibility to develop hospital acquired infections [13].

A proper evaluation of hyper or under-activation of the host immune system may provide a better comprehension of the pathobiology changes occurring in sepsis as well as in other conditions such as trauma, burn and surgery, and may finally guide to a tailored therapeutic approach [14]. For instance, the traditional strategy aimed to suppress the immune system by

inhibition of inflammatory mediators could be helpful in patients with an overwhelming pro-inflammatory state, but may be harmful in patients with a suppressed immune response [15].

The review by Rouget et al. [4] provides a straightforward analysis on the rationale for use and the feasibility of measuring immune-competence at the bedside. Unfortunately, most of the biomarkers described requires sophisticated techniques such as flow cytometry, immunohistochemistry, cytokine ELISA arrays or RNA analysis for gene expression. Despite many of these procedures are complex and have a high cost, we believe that the evaluation of the immune response is today mandatory for a proper management of septic patients. To this aim, official guidelines or consensus conferences are urgently needed to provide clinicians with a sort of "immunoscope" to monitor critically-ill patients and treat them. The future in which specific therapies will be tailored on a sound evaluation of patient pathobiology could be around the corner.

PEER REVIEW COPY
MINERVA ANESTESIOLOGICA

REFERENCES

1. Pop-Vicas A, Opal SM. The clinical impact of multidrug-resistant gram-negative bacilli in the management of septic shock. *Virulence* 2014;5(1):206-12.
2. Venet F, Lukaszewicz AC, Payen D, Hotchkiss R, Monneret G. Monitoring the immune response in sepsis: a rational approach to administration of immunoadjuvant therapies. *Curr Opin Immunol* 2013;25(4):477-83.
3. Delano MJ, Ward PA. Sepsis-induced immune dysfunction: can immune therapies reduce mortality? *J Clin Invest* 2016;126(1):23-31.
4. Rouget C, Girardot T, Textoris J, Monneret G, Rimmelé T, Venet f. Biological markers of injury-induced immunosuppression. *Minerva Anesthesiol* 2016; [epub ahead of print].
5. Shalova IN, Lim JY, Chittechath M, Zinkernagel AS, Beasley F, Hernandez-Jimenez E, et al., Human monocytes undergo functional re-programming during sepsis mediated by hypoxia-inducible factor-1alpha. *Immunity* 2015;42(3):484-98.
6. Bermejo-Martin JF, Rodriguez-Fernandez A, Herran-Monge R, Andaluz-Ojeda D, Muriel-Bombin A, Merino P, et al., Immunoglobulins IgG1, IgM and IgA: a synergistic team influencing survival in sepsis. *J Intern Med* 2014;276(4):404-12.
7. Justel M, Socias L, Almansa R, Ramirez P, Gallegos MC, Fernandez V, et al., IgM levels in plasma predict outcome in severe pandemic influenza. *J Clin Virol* 2013;58(3):564-7.
8. Busani S, Damiani E, Cavazzuti I, Donati A, Girardis M. Intravenous immunoglobulin in septic shock: review of the mechanisms of action and meta-analysis of the clinical effectiveness. *Minerva Anesthesiol* 2016;82(5):559-72.

9. Leentjens J, Kox M, van der Hoeven JG, Netea MG, Pickkers P. Immunotherapy for the adjunctive treatment of sepsis: from immunosuppression to immunostimulation. Time for a paradigm change? *Am J Respir Crit Care Med* 2013;187(12):1287-93.
10. Kepp O, Galluzzi L, Zitvogel L, Kroemer G. Pyroptosis - a cell death modality of its kind? *Eur J Immunol* 2010;40(3):627-30.
11. Wallach D, Kang TB, Dillon CP, Green DR. Programmed necrosis in inflammation: Toward identification of the effector molecules. *Science* 2016;352(6281):aaf2154.
12. Le Bourhis L, Guerri L, Dusseaux M, Martin E, Soudais C, Lantz O. Mucosal-associated invariant T cells: unconventional development and function. *Trends Immunol* 2011;32(5):212-8.
13. Grimaldi D, Le Bourhis L, Sauneuf B, Dechartres A, Rousseau C, Ouaz F, et al., Specific MAIT cell behaviour among innate-like T lymphocytes in critically ill patients with severe infections. *Intensive Care Med* 2014;40(2):192-201.
14. Hamers L, Kox M, Pickkers P. Sepsis-induced immunoparalysis: mechanisms, markers, and treatment options. *Minerva Anestesiol* 2015;81(4):426-39.
15. Boomer JS, To K, Chang KC, Takasu O, Osborne DF, Walton, AH, et al., Immunosuppression in patients who die of sepsis and multiple organ failure. *JAMA* 2011;306(23):2594-605.

Corresponding Author: Massimo Girardis, Via del Pozzo 71, Policlinico di Modena, 41124 Modena, Italy. E-mail: girardis.massimo@unimore.it

Conflicts of interest: The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.