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Immunoparalysis in Septic Shock Patients

Giorgio Berlot and Silvia Passero

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Abstract

In the recent years, it has become clear that septic shock is characterized by the simultaneous production of inflammatory and anti-inflammatory mediators; the primary role of the latter is to counterbalance the former, thus limiting the severity of their systemic effects. However, in a number of patients, the anti-inflammatory substances can cause a downregulation in both the innate and adaptive immune capabilities, leading a second phase characterized to secondary infections caused by opportunist germs and the reactivation of latent viruses, muscle wasting; altogether, these abnormalities set the stage for a chronic critical condition. This condition, whose identification is relatively recent, is called immunoparalysis. Unfortunately, the current approach to septic shock is focused much more on the inflammatory phase than in the ensuing immunoparalysis, whose diagnosis can be challenging. In this chapter, the role played by both classes of mediators, the monitoring of the immune system, and the possible current and not yet available therapeutic strategies of immunoparalysis are reviewed and discussed.

Keywords: septic shock, compensatory anti-inflammatory reaction syndrome, immunoparalysis, immunomonitoring

1. Introduction

The classical clinical manifestations of septic shock (SS) include fever, tachycardia, arterial hypotension, and abnormalities of the white blood cell count (WBC) associated with a wide range of organ dysfunction carrying a substantial risk of death [1]; the current approach, issued under the auspices of the Surviving Sepsis Campaign on the basis of clinical trials fulfilling the evidence-based medicine (EBM) criteria, includes the rapid administration of wide-spectrum antibiotics, the maintenance of a proper perfusion pressure via the administration of fluids and/or to vasopressors, the drainage of septic foci, etc. [2]. Overall, it appears that

both the description and the therapies apply to acutely ill patients suffering from an infection-induced overwhelming reaction determined by a huge number of pro-inflammatory mediators produced and released by the innate immunity system. However, more than 20 years ago, Bone [3] hypothesized that this early hyperinflammatory phase could be accompanied by a compensatory anti-inflammatory response (CARS) aiming to limit the tissue damage. In the last decade, the concept of CARS has changed from a time-limited and somehow beneficial mechanism to a harmful reaction, potentially leading to a condition of marked reduction of the immune capabilities known as immunoparalysis [4–6]. Clinically, this condition is marked by recurrent and/or unresolving infections caused by germs with relatively low virulence; the reactivation of silent virus such as *cytomegalovirus* (CMV), Epstein-Barr virus (EBV), and herpesvirus (HV); a persisting low-grade inflammation; nutrition-resistant hypercatabolism; and muscle wasting [7, 8] (**Table 1**). The immunoparalysis characterizes also the clinical course of the chronic critically ill patients, namely, subjects who survived the initial insult (i.e., septic shock due to pneumonia, peritonitis, etc.) but fails to recover enough to be weaned from the mechanical ventilation and discharged from the intensive care unit (ICU) [9]. Moreover it should be noted that factors other than pathophysiological mechanisms can reduce the immune response, including the administration of steroids and norepinephrine [1, 10]. The aims of this chapter are (1) to review the main mechanism determining a SS, (2) to describe the transition from an easily recognizable hyperinflammatory condition to a less straightforward diagnosable one featured by a downregulation of the immune capabilities, (3) to provide some monitoring tools of the immune function, and, finally, (4) to identify some possible therapeutic approaches.

Variable	Uncontrolled inflammatory response	Immunoparalysis
Clinical phenotype	Fever, arterial hypotension, elevated cardiac output, rapidly evolving MODS, community or surgical infections	Altered mental status, normo-/hypothermia, slow-evolving MODS, health care- or hospital-acquired infections
Patients population	Young, middle-aged	Elderly, fragile
Comorbidities	Often absent Low Charlson's index	Often present High Charlson's index
Germs characteristics	Virulent, toxin releasing	Low virulence, opportunistic Latent virus reactivation
Laboratory findings	↑↑ or ↓ neutrophil count, ↑ blood lactate levels	↓ lymphocyte
Nutritional status	Normal	Sarcopenia/cachexia Muscle wasting
Clinical course	Resolution of sepsis Immuno restoration Early deaths	Protracted ICU LOS Chronic critical disease Late deaths

LOS, length of stay.

Table 1. Different clinical presentations of sepsis-induced immunological alterations.

2. Pathophysiology of septic shock: a classical overview

2.1. The inflammatory response

Since the late 1970s, it has become clear that the clinical and biochemical manifestations of sepsis and its related complications are not caused directly by invading germ(s) but rather by the host's response to the infection. The innate immune response largely accounts for the above described signs and symptoms. The presence of microorganism-derived substances collectively known as pathogen-associated molecular pattern (PAMP) which include endotoxin, capsular antigens, elements derived from the cell wall, flagellins, and other substances derived from the bacterial lysis determines the rapid activation of genes encoding for an extremely elevated (and still partially unknown) mediators able to trigger a strong inflammatory reaction, including the tumor necrosis factor- α (TNF), a number of interleukins (IL), the platelet-activating factor (PAF), etc. (**Table 2**). It is worthwhile to recall that (a) the list of mediators is incomplete because new elements are added on a weekly or at maximum monthly basis, (b) the rise of blood levels of inflammatory mediators is a matter of minutes since it represents the first line of defense to contrast the deleterious effects of PAMP and DAMPS, and (c) for this reason, the innate response is highly similar among all species of mammals [6].

Independently from their biochemical structure, the term inflammasome lumps together all these heterogeneous mediators that are characterized by (a) the presence of many positive and negative feedback loops, determining an array that can be better conceived as a network

Cytokine	Source	Effects	Interactions	Antagonists
TNF	Innate and adaptive immune system	Activation of immune cells Fever cachexia, apoptosis	Activation of downstream inflammatory mediators	Soluble TNF receptors Anti-TNF ab
IL-1	"	Fever, pro-coagulation Hematopoiesis	"	IL-1 receptor antagonists
IL-6	"	Activation of T and B lymphocytes Fever	Inhibits the release of TNF and IL-1 Promotes anti-inflammatory response	IL-6 receptor antagonists
IL-12	Monocyte, macrophages, neutrophils, dendritic cells	Activation of adaptive response	Promotes IFN- γ production	Unknown
IFN- γ	NKT cells CD 8 T cell	Antiviral action Potentially reverse immunoparalysis	Released in response to TNF, IL-12, and IL-18	Unknown

TNF, tumor necrosis factor; IL, interleukin; IFN, interferon.

Table 2. Some relevant pro-inflammatory mediators.

and not a cascade, thus making understandable the therapeutic failure demonstrated in many trials in which septic patients were treated with substances aimed to block a single mediator via monoclonal or chimeric specific antibodies (Ab) such as anti-TNF α Ab or with the administration of circulating antagonists (ra) (i.e., soluble IL1-ra and TNF TNF α -ra) directed to block the receptors present on the cell surface; (b) the pleiotropic and paracrine effects, accounting for the multiple effects exerted in different organs; (c) the interference with the mitochondria causing a disturbance of the O₂ uptake and consumption by the tissues; and (d) the interaction with other biological systems including the complement system and the coagulative cascade. Notably, the very same mediators are produced in noninfectious conditions, including trauma, low-flow states, surgery, burns, etc.; in these circumstances the trigger is represented by an intracellular substance derived from the injured tissues (DAMP, damage-associated molecular patterns). The endothelium is massively involved in this reaction causing a microvascular plugging and the abnormal production of nitric oxide (NO) which exert a profound vasodilation [11, 12].

From an evolutionary perspective, it is likely that these mediators have been developed and maintained, aiming to contain the initial inoculum and to destroy the responsible organisms. This explains why in most cases an infection does not cause a SS: actually, the latter occurs only when the pro-inflammatory mediators exert their effects at a systemic level, thus determining the clinical phenotype of SS and the almost unavoidable presence of the simultaneous dysfunction of different organs and systems even not directly involved by the infection (MODS).

2.2. The compensatory reaction

The secretion of inflammasome is accompanied by the production of other substances aimed to limit their action at a local level and, at the same time, to prevent their systemic spread (**Table 3**). As stated above for the inflammatory mediators, their list is incomplete for the very same reasons. Actually, it was hypothesized that during the initial phase (almost), only pro-inflammatory mediators were produced and that these conditions subsided due to the action of the CARS-associated mediators. Despite its popularity, it became clear that this scheme represents an oversimplification as (a) both classes of substances are produced since the initial phase of sepsis albeit in different rates; (b) the action of anti-inflammatory mediators is responsible for the late-onset immunoparalysis; and finally (c) a low-level production of pro-inflammatory substances can be maintained even during the advanced stages of sepsis leading to malnutrition, protein waste, and reduced adaptive immunity. Overall, the sepsis-associated immunoparalysis resembles the normal aging process of the immune system (immunosenescence) that is characterized by the overall downregulation of both the innate and adaptive immunity functions. This appears particularly relevant as the ever-increasing age of septic patients exposes them to both conditions.

Put shortly, it appears that the mediators implicated in the CARS can represent a double-edged sword, as they both can exert (a) a beneficial role when they determine the restoration of the immune condition existing prior to the sepsis (immune restoration) and (b) can trigger a life-threatening condition when their excess production and/or duration of action causes the shutdown of the immune response [13, 14].

Cytokine	Source	Effects	Interactions
IL-10	Innate and adaptive immune system	Immunosuppression Inhibition of antigen presentation and phagocytosis	Suppression of the production of inflammatory mediators
TGF- β	Macrophages Smooth muscle cells	Immunosuppression	"
IL-4	Mast cells T _H 2 T cells Basophils Eosinophils	Promotes T _H 2 T-cell differentiation	Induces the production of IL-10

TGF, transforming growth factor.

Table 3. Some relevant anti-inflammatory mediators.

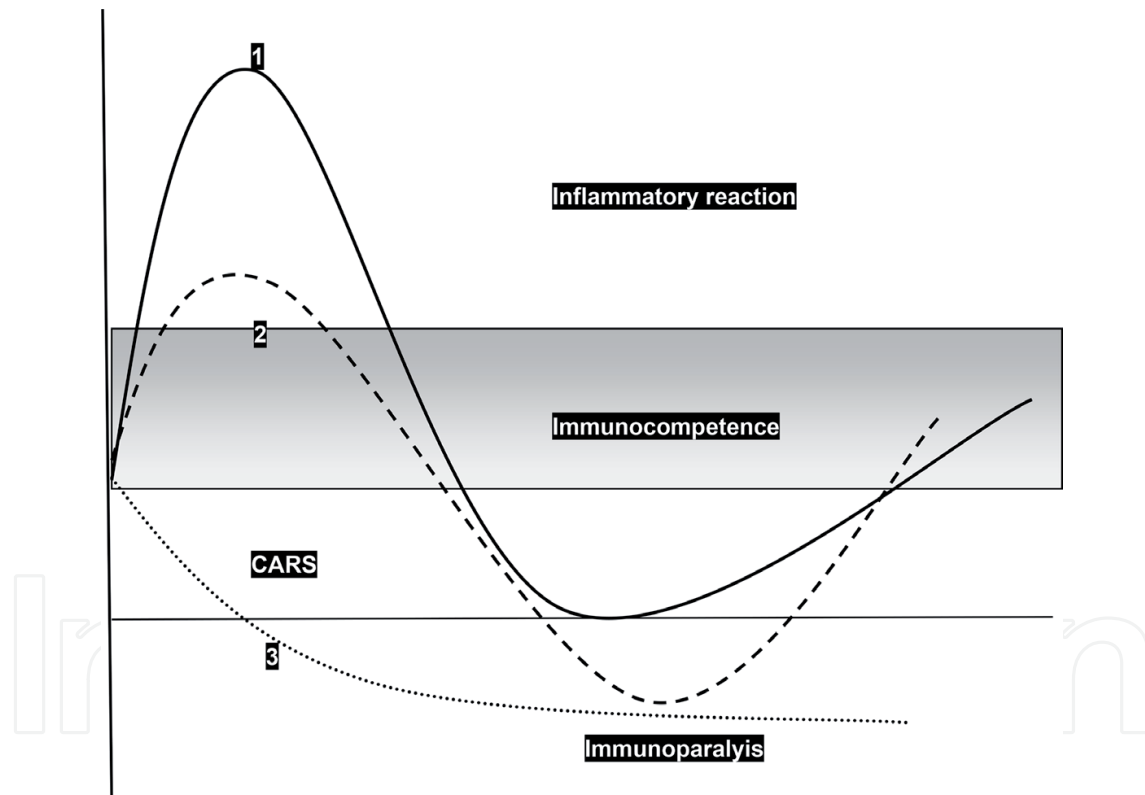


Figure 1. Possible clinical trajectories of patients with sepsis shock. Line 1, intense hyperinflammatory reaction followed by CARS and the return to the baseline immune state. Line 2, weak hyperinflammatory reaction followed by immunoparalysis and immune restoration. Line 3, immunoparalysis not preceded by a hyperinflammatory reaction.

In conclusion, (at least) three clinical trajectories can be hypothesized (**Figure 1**): the first includes patients with an intense hyperinflammatory reaction that subsides once the CARS is well established and the immune function is restored; in the second the initial phase is shorter and weaker, and the CARS determines a short-lived immunoparalysis preceding the return

toward the baseline immune function; and in the third one, the CARS prevails and causes the loss of the immune capabilities.

3. The determinants of immunoparalysis

Only recently it became clear that the CARS does not represent only a physiologic counterbalance to the inflammatory response to PAMP and DAMP but that it can determine a critical condition in and by itself [13, 15].

Actually, different experimental and clinical studies indicate that the advanced stage of sepsis and SS is characterized by a reduction of both the innate and adaptive immune responses (**Table 4**). Extensive evidence supports this model, even if large inter-patient differences exist. First, monocytes present a reduced expression of membrane HLA-DR in association to either a decreased secretion of inflammatory mediators when stimulated or a diminished antigen presentation. Second, different membrane-bound receptors able to potentiate the immune response, including IL-2 α , IL-7R α , CD86, etc., are reduced. Third, the production of immunosuppressant substances, such and programmed death 1 (PD1) and its ligand (PD-L1), is increased in antigen-presenting cells, thus inhibiting the activation of T lymphocytes. Fourth, there is an increased appearance of immunosuppressive T-cell subpopulations, such as myeloid-derived suppressor cell and CD4⁺ and CD25⁺ T-regulatory cells (T_{reg}), which suppress adaptive immunity. These appear to be particularly relevant, as Treg (a) actively produce anti-inflammatory cytokines including TGF- β and IL-10, (b) downregulate the secretion of pro-inflammatory mediators, (c)

Factors involved	Marker
Monocyte deactivation	↓ mHLA-DR expression ↓ TNF- α production
Tissue macrophage dysfunction	Presently none
Negative regulatory mediators	↑ PD-(L)1 expression ↑ CTL-4, BTLA expression ↑ LAG-3 and TIM-3 expression
Receptors downregulation	↓ IL-7 receptor
Apoptosis	↑ FAS ↓ lymphocytes
Suppression of immune cells	↑ CD-4, CD-25 ↑ myeloid-derived suppressor cells
Anti-inflammatory cytokines	↑ IL-10, IL-13, IL-4, IL1 receptor antagonists, TGF- β ↑ IL-10/TNF- α

mHLA-DR, human leukocyte antigen on the monocyte surface; PD-(L1), programmed death ligand; CTLA-4, cytotoxic lymphocyte antigen 4; BTLA, B and T lymphocyte attenuator; LAG-3, lymphocyte activation gene 3; TIM-3, T lymphocyte immunoglobulin protein 3; sFAS, soluble FAS ligand; TGF- β , transforming growth factor- β .

Table 4. Factors of immunosuppression.

Mechanisms	Effect
Endotoxin tolerance	↑ Anti-inflammatory mediators, ↓ pro-inflammatory mediators ↓ Antigen presentation
Apoptosis	↓ Immune cell number Immune cell number anergy
Energy failure	Immune cell anergy Apoptosis
Epigenetic regulation	↓ Pro-inflammatory mediators

Table 5. Mechanisms of immunoparalysis.

neutralize cytotoxic T cells, and (d) deactivate the monocytes. Fourth, immune cells present an increased apoptosis, and their loss is not replaced enough by the production of new ones. Finally, the phagocytosis of apoptotic cells by fixed and circulating macrophages leads to a switch of the latter to the M2 phenotype, whose feature is an increased production of the anti-inflammatory substances IL-10 and IL-1ra. Put briefly, all these mechanisms exert their action via relatively few common pathways, which include the increased apoptosis determining the reduction of immune cells, the loss of antigen presentation, the blunted response to PAMP, and the reduction of energy production caused by the impairment of the glucose metabolism (Table 5) [16, 17]. All these reactions are driven by epigenetic changes causing in different time frames the activation or deactivation of genes involved in the immune response, and the resulting phenotype is an intense inflammatory response or, conversely, an immunoparalysis.

4. The diagnosis of immunoparalysis

The recognition of sepsis-induced immunoparalysis is not straightforward because the clinical manifestations associated with the switch from the hyperinflammatory state to CARS and the full-blown depression of the immune capabilities are not so protean as the symptoms of SS [18]. Moreover, the SSC guidelines focus almost exclusively on the former and pay much less attention, if any, to the latter. From a practical and clinical point view, some issues appear particularly relevant.

4.1. Timing of onset

The transition from the hyperinflammatory phase to immunoparalysis can be challenging to identify and to monitor at the bedside and represents a kind of no man's land in the clinical course of patients which survived from the initial phase of SS.

The onset is highly variable. Actually, although the secretion of immunomodulatory substances can occur relatively early, their clinical consequences present wide variations. Some authors [19] observed a substantial difference of mHLA-DR starting from 3 to 7 days in a small group of surgical septic patients, and other authors demonstrated that significant decrease of

the CD14/HLA-DR and of heat-shock proteins (HSP) 70 and 90 was present already within 24 hours from the onset of sepsis [5]; in both studies, these alterations were more marked in patients who developed SS later on. More recently, Morris et al. [20] in association with raised percentage of regulatory T cells (T_{reg}) were predictive for infections occurring between 3 and 9 days after ICU admission, and a similar timing has been demonstrated also in another study in which the mortality rate of secondary infection was ~14% [17]. On the basis of these findings, it is reasonable to hypothesize that (a) a combination of cellular and soluble factors able to blunt the immune response is present since the very initial phase of sepsis; (b) their effects on the clinical course, namely, the appearance of secondary infections and/or viral reactivation, can occur within the initial 10 days from the admission; and (c) these are associated with a substantial mortality of patients surviving the initial insult.

4.2. Monitoring of the immune function

In ICU patients, every organ system is monitored to allow a change in the treatment tailored on the variation observed. An ideal monitoring system should be accurate, cheap, and not labor-intensive, and the information gathered should be readily if not continuously available. Since it has become clear that the immune system in sepsis undergoes modifications not reflected by the commonly measured biological variables such as the arterial pressure, the heart rate, the urinary output, etc., different investigations aimed to identify one or more markers of changes of its functions whose follow-up could be valuable to modify the therapy according to its changes: as an example, the occurrence of immunoparalysis contraindicates the administration of steroids whose use is recommended by the SSC guidelines.

Several monitoring systems exploring both legs of the immune response have been developed so far, based on the repeated assessments of the cells involved, their response to different

Function	Cell	Marker	Outcome	Lab technique	Runaround (h)
Innate immunity	Neutrophils	↑ Immature forms	Death Secondary infections	FC. Hematology analyzer	1.5
	Monocytes	↓ HLA-DR	Death Secondary infections	FC, IHC, PCR	1.5
Adaptive immunity	All lymphocytes	Lymphopenia	Death Secondary infections	FC. Hematology analyzer	0.5
	White blood cells	NTL	Death Secondary infections	FC. Hematology analyzer	0.5
Both	Lymphocytes	Viral reactivation	Death	PCR	12

FC, flow cytometry; IHC, immunohistochemistry; PCR, polymerase chain reaction; NTL, neutrophil/lymphocyte ratio.

Table 6. Some currently available indicators of immune function.

challenges, and the measurement of the blood concentrations of soluble mediators involved in the different clinical frames [14, 15, 21, 22]. It could be useful to describe separately those currently available and those which will be used likely in the next future. Most of the former (**Table 6**) can be obtained cheaply and on a daily basis; among all, the neutrophil-to-lymphocyte ratio has been indicated as the less costly and more rapidly available monitoring tool [23, 24]. Other advanced, expensive, and not yet widely available monitoring tools take advantage of more sophisticated lab techniques (**Table 7**) requiring lab expertise and financial resources putting them at risk of not being used outside the research center. Another dynamic approach, which shares the very same limitations of the previously described advanced techniques, consists in challenging the immune cells with substances able to trigger their activation, including LPS, other PAMP, and phytohemagglutinin; actually, a number of investigators demonstrated that a blunted response to the stimulation is associated with an increased rate of severe infectious complications in different patient populations [25–27].

Independently from the systems used, it should be clear that the monitoring of the immune response in septic as well in other clinical conditions (a) is based on the time variations of a panel of indicators and not on a single one and (b) due to their direct and indirect costs,

Function	Cell	Marker	Outcome	Lab technique	Runaround (h)
Innate immunity	Monocytes	↓ sCD127	Death, secondary infections	FC, PCR, IHC, ELISA	5
		Endotoxin tolerance	Not clear	Cell culture, ELISA, FC, IHC	72
		↑ PD-L1	Secondary infections	FC, IHC	1.5
		IL10/TNF ratio	Death	ELISA	5
	Dendritic cells	↓ Count	Death, secondary infections	FC	1.5
Adaptive immunity	All lymphocytes	↑ CTLA 4, BTLA	Not clear	FC, IHC	1.5
		↑ PD	Death	FC, IHC	1.5
		CD 127	Death, secondary infections	FC, IHC	1.5
	T cells	Proliferation	Death, secondary infections MODS	Cell culture + FC	72
	T _{reg}	↑ T _{reg}	Death	FC	1.5
Both	Transcriptomic	CD 74, CX3CR1	Not clear	PCR, microarray	72

FC, flow cytometry; IHC, immunohistochemistry; PCR, polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay.

Table 7. Some promising, yet not currently available, markers of immunoparalysis.

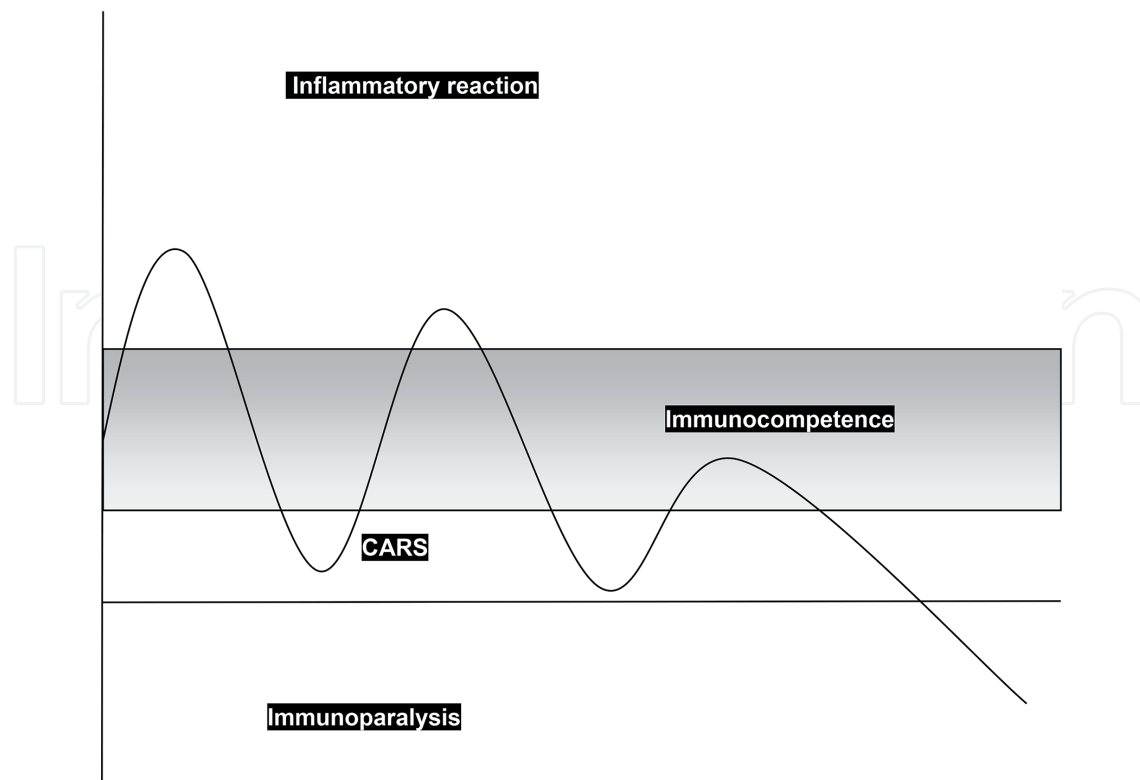


Figure 2. The multiple hits phenomenon ultimately leading to the exhaustion of the immune response.

it should be limited to the subjects at risk; as an example, it is worthwhile to monitor the immune function in patients undergoing multiple abdominal surgical procedures for suture dehiscence but not in another one safely recovering after peritonitis.

4.3. The identification of patients at risk of immunoparalysis

Even with the exclusion of clinical conditions and/or treatments known to cause an immunoparalysis (i.e., solid and hematologic cancers, autoimmune disorders), etc., this circumstance can occur in virtually all ICU patients; however, different studies identified some predisposing factors that should be considered particularly relevant, including septic shock, advanced age, health care-associated infections, elevated Charlson's score indicating a substantial underlying fragility, comorbidities, prolonged hospital and ICU length of stay, and multiple surgical procedures [17, 28, 29]. The latter, which are associated with the repeated activation of the inflammatory and anti-inflammatory responses, according to the multiple hits model, ultimately lead to the exhaustion of the immune response [30] (Figure 2).

5. The treatment of immunoparalysis

In the last decade, a number of drugs have been developed to restore a normal immune function in patients with solid or hematologic tumors on the basis of many investigations

demonstrating the tumor cells are able to suppress in many different ways the host's immune response against themselves. Independently from the substance use and the molecular target, these innovative treatments have been demonstrated to be effective but somehow difficult to handle, as they are associated with a number of side effects ranging from mild to life-threatening [31]. As several similarities exist between tumor- and sepsis-induced blunting of the immune response [32], it is likely that in the next future the immune-boosting treatments will be developed to treat the latter, aiming to develop a precision medicine also in ICU patients [33] (**Table 8**).

Presently, according to the SSC guidelines [2], the immune-targeted approaches are limited to the administration of steroids in not fluid and catecholamine-responding SS, whereas the use of intravenous immunoglobulins (IvIg) is discouraged. Actually, this latter position is questionable as a number of trials performed in several thousands of patients demonstrated that (a) the administration of IvIg is associated with the reduction of mortality in different subsets of SS patients; (b) among the different preparations available, the only ones containing supra-normal concentrations of IgM and IgA appears more effective, and (c) the improvement of survival is time-dependent, as a ~6% increase of mortality has been observed for every day of delay in the administration [34].

Besides steroids and IvIg, other treatments aimed to modulate the immune response include blood purification (BPT) techniques and a number of substances able to boost it.

Cells/factors involved	Alterations	Possible therapies
Myeloid cells	↑ Immature neutrophils	GM-CSF
	↑ Tolerant dendritic cells	Toll-like receptor antagonists
	↑ Myeloid-derived suppressor cells	FTL3L
	↓ Monocyte HLA-DR expression	TNF
Lymphocytes	↓ Cytokine production	Anti-PD1 ab
	Altered metabolism	Anti-PDL 1 ab
	↓ Proliferation	Anti CTLA4, TIM3, LAG3 ab
	↑ Immune checkpoint inhibitors	
	Malfunction of NKT cells	
	↑ T _{reg} and B _{reg} cells	
↑ Systemic cytokine release	↑ CD 155 expression	
	↑ IL-10	GM-CSF
	↑ PGE 2	TLR agonists
	↑ TGFβ	FT3L TNF

GMC-SF, granulocyte-macrophage colony-stimulating factor; FTL3L, FMS-related tyrosine kinase 3 ligand; PD, programmed death; PDL1, programmed cell death ligand 1; CTL4, cytotoxic T-cell protein 4; TIM3, T-cell immunoglobulin mucin receptor 3; T_{reg}, B_{reg}, regulatory T and B cells; TGFβ, transforming growth factor-β; PGE, prostaglandin E2.

Table 8. Immunosuppressive pathways shared by cancer and sepsis.

5.1. Blood purification techniques

Since the 1980s, a number of extracorporeal techniques have been developed aiming to remove the “toxic” mediators responsible for the clinical manifestations of SS.

Independently from their principle of functioning (see later), the BPT consists in an extracorporeal circuit where the patient’s blood flows till enters in the depurative device; once the latter is passed, the blood returns to the patient. According to the principle used, the BPT can be subdivided into (a) blood processing or (b) plasma processing techniques. In the former, the whole blood is depurated via a number techniques, which differ in terms of type and surface of the membranes used, their permeability to the high molecular weight of the septic mediators, etc., whereas in the latter the plasma is separated from the blood, processed in a cartridge, and reinfused downstream. The mediators can be eliminated through the membranes or adsorbed over it. In both cases, the neutralizing capabilities are time-limited. A detailed description of the BPT is beyond the aim of this chapter, but some considerations are necessary. First, there are no studies clearly demonstrating the superiority of one of them, even if some meta-analysis indicates that the those using the adsorption are more effective; (b) they can remove also antibiotics, nutrients, vitamins, hormones, etc.; (c) they require anticoagulation; and, most importantly; and (d) they are not selective and thus remove pro- as well as anti-inflammatory mediators [35].

5.2. Immune-boosting agents

Different substances have been used or likely will be used in the next future (**Table 9**) to enhance the depressed immune function in septic and non-septic critically ill patients, including [36, 37]:

- **Interferon- γ (IFN- γ)** is a cytokine produced by helper T cell and an activator of monocytes. Different case series and case report performed in a limited number of patients demonstrated that its administration was associated with an increased HLA-DR expression; however, presently there are no RCT fulfilling the EBM criteria demonstrating a beneficial effect on the outcome of patients with SS.
- **Granulocyte-macrophage colony-stimulating factor (GMC-SF)** stimulates the production of neutrophils from the bone marrow. Even if prophylactic use in neutropenic patients did not demonstrate any beneficial effect, a number of investigations demonstrated that its administration was associated with an improved outcome especially in patients with a decreased HLA-DR expression.
- **Interleukin-7 (IL-7)** is a cytokine released by bone marrow and thymus cells that prompts the growth and the differentiation of T cells. This substance is considered an immune-boosting agent in patients with cancer and multifocal leukoencephalopathy and in septic patients suffering from immunoparalysis.
- **Programmed death inhibitors (PD1i)** are proteins whose effect is to block the programmed death of immune cells, which appears to be a critical factor for the progression of cancer.

	Treatment	Effect	Pro	Against
Available	IvIg	Antibacterial action ↓ TNF and other pro-inflammatory mediators	Many small RCT demonstrated their efficacy	No EBM-validated Heterogeneity of patients treated High costs
	Blood purification techniques	Removal of mediators	Many small RCT demonstrated their efficacy	Not selective Heterogeneity of techniques (i.e., HVHV vs. plasma adsorption) Heterogeneity of patients treated Need of anticoagulation Not selective
Not yet available	Interferon- γ	Enhanced production of pro-inflammatory mediators	Some small RCT and case reports demonstrated its efficacy	Possible septic shock-like Systemic inflammatory reactions
	GMC-SF	Enhanced production of immune cells	"	Possible septic shock-like Systemic inflammatory reactions
	IL-7	Enhanced production of pro-inflammatory mediators	"	Possible septic shock-like Systemic inflammatory reactions
	Immune checkpoint inhibitors	Reduced apoptosis	"	Potentially severe and life-threatening side effects High costs No RCT available

Table 9. Possible immunomodulating treatments in septic shock.

This approach is new as it aims to increase the immune response to the cancer cells without interfering with their metabolism. Due to their mechanism of action, their administration could determine a potentially life-threatening inflammatory reaction caused by the sudden release of mediators determining a "cytokine storm"; although their use is not codified yet in critically ill septic patients, in a recent RCT, the restoration of the immune response in the absence of a hyperinflammatory reaction was demonstrated in some SS patients given a novel PD1i at different doses [38].

6. Conclusions

Independently from its source, septic shock can be considered a double-step process: the initial phase is characterized by an intense inflammatory response that is counterbalanced

by the production of several anti-inflammatory substances aiming to restore the immunity pre-sepsis steady state. However, in many cases this compensatory mechanism prevails and not only extinguishes the initial response but determines a condition of immunoparalysis that dominates the clinical course and influences the outcome. Unfortunately, the current approach is mainly directed against the initial inflammatory phase although some techniques of monitoring of the immune function are currently developed and others are being studied. The same concepts apply to treatments directed to potentiate the immune capabilities, but in this case the goal appears to be still far.

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