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REVIEW

Adjuvant therapies and sepsis from multidrug resistant bacteria: a narrative review

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Abstract

Sepsis represents one of the major health problem due to the high mortality rate and elevated health care costs. An important role in the genesis and the mechanisms sustaining sepsis has been found in the release of pro-inflammatory mediators. They are able to induce hemodynamic instability, end-organ dysfunction, and coagulation abnormalities. The host immune response involves a first extreme response to infective process that leads to tissue damage, organ failure and endothelial dysfunction. It was recently described the existence of a contrasting process, that is directed to restore homeostasis and it's related with the release of anti-inflammatory mediators. The treatment of sepsis and septic shock could therefore benefit from the association of source control and antibiotic therapy with the use of drugs and other techniques, that act by modulating the cytokine storm. This approach is referred to an adjuvant therapy. The goal of this narrative review is to examine the various adjuvant therapies in the treatment of sepsis and septic shock.

Keywords

Blood purification; Vitamin C; Thymosin; IVIg; GM-CSF; Interferon gamma

1. Introduction

Sepsis has been defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. The mortality caused by sepsis continues to increase, affecting specially patients treated in intensive care units (ICUs) due to the increased prevalence of multidrug resistant (MDR) gram-negative bacilli. In particular, an increased frequency of MDR Gram-negative pathogens, such as MDR Acinetobacter baumannii (MDR-AB) and Klebsiella pneumoniae carbapenemase-producing (KPC-Kp), have been observed among critically ICU patients and these ones are frequently responsible of sepsis or septic shock. The infection from MDR is characterized by greater morbidity and mortality compared with the one infected by susceptible pathogens [2–5]. Septic shock (SS) represents a subset of sepsis that is associated with cardiovascular and metabolic anomalies. Today its mortality rate is greater than 40% [3, 4]. The identification of the patient with SS is based on the presence of certain or suspected infection, haemodynamic alteration or persistent hypotension despite an infusion of vasoactive amines, and an increase in lactate blood level >2 mmol/L despite adequate fluid resuscitation. The beginning of the syndrome is played from both the host and the infectious agent. Sepsis frequently presents a clinical and a biochemical course. First of all, there is a phase in which the mediators of infection, Pathogen Associated Molecular Patterns and Damage-associated molecular patterns (PAMPs and DAMPs) trigger the proinflammatory response with the release into the circulation of proinflammatory cytokines (IL-1, TNF, and IL-17). These cytokines have an important role into the suffering of the different organs, with an increase in the Sequential Organ Failure Assessment (SOFA) score, and/or in the development of shock. A possible second phase could be present in some patients, where the anti-inflammatory mediators (IL-10) do not determine the resolution of the infection, but create a persistent state of immune dysfunction and/or immunosuppression (Fig. 1) [5, 6]. Multidrug resistant bacteria, are largely indolent organisms that infecting the immunocompromised, critically-ill patient: protracted hospitalization in ICUs, long-term residence in nursing homes, oncologic diseases, neonatal diseases of prematurity, burns, organ transplant, or chronic hemodialysis are the main causes of death. Because of the antibiotic-resistance, we urgently need to find a new way to enhance the immune response and control the inflammatory reaction. Because MDR are more and more emerging, the adjuvant therapies may represent a valid supportive therapy to antibiotics for the treatment of severe infections caused by these microorganisms. Sepsis and SS treatment due to MDR bacteria, could therefore benefit

from the association of the use of antibiotics, even if with limited activity, and adjuvants that act by modulating the cytokine storm [7] (Fig. 2). The goal of this narrative review is to examine the various adjuvant therapies in the treatment of sepsis and SS due to multidrug resistant bacteria infection.

2. Blood purification technique

Several clinicians agree that the use of extracorporeal blood purification techniques can be useful in the treatment of sepsis, although large randomized controlled trials are missing. These techniques facilitate the non-specific removal of inflammatory mediators, anti-inflammatory or toxins, and may restore immunological haemostasis. The use of blood purification systems in septic patient is supported by five theories: (a) the cytokine peak concentration hypothesis which was published by Ronco [8]. He describes that the peak cytokine concentration should be regulated in the first proinflammatory phase. (b) The threshold immunomodulation hypothesis described by Honoré [9]. The author described that the extraction of mediators from the blood also leads to their reduction in the tissue. When the mediators concentration fall down a specific threshold value the biochemical processes related to them can be interrupted. (c) The mediator transport hypothesis, published by Di Carlo [10]. The authors describe that they obtain an optimum removal of inflammatory mediators by applying high volume hemofiltration. (d) The cellular level theory of Peng [11]. The author showed a positive influence on the cellular activity after the application of blood purification techniques in septic patients. (e) The cytokinetic model theory is proposed by Rimmelé and Kellum [12], who describe that the blood purification systems can bring back the cytokine gradients at the center of the infection/inflammation. The cells usually move along a concentration gradient and so, after the cytokine gradient restoration, the leukocytes migrate towards the inflammation center.

The 2021 SSC Guidelines issued a weak recommendation against the use of polymyxin B haemoperfusion therapy. They did not identify new evidence on other modalities such as haemofiltration, combined haemoperfusion and haemofiltration or plasma exchange. Accordingly, no recommendation regarding the use of these modalities is made. This is unchanged from the 2016 guidelines. On the other side the panel concludes that the analysis of new data has emerged, but it was not sufficient to reconsider the recommendation at this stage [32].

One of the first techniques used was high-flow hemodiafiltration (HVHF). The IVOIRE (high volume in intensive care) randomized controlled clinical trial demonstrated that there is no difference in term of mortality between patients treated with the high volume (70 mL/kg/h) and standard volume (35 mL/kg/h). They are patients affected by acute kidney injury (AKI) and septic shock (SS) from gram negative bacteria. Moreover, there wasn't an improvement in hemodynamic parameters, morbidity and ICU length of stay [13].

The cascade hemofiltration system was developed to perform high HVHF (120 mL/kg/h) without the side effects of normal HVHF. The system is based on the use of two hemofilters. The blood passes first thought a conventional membrane (cutoff in the range of 30–40 kDa), then this ultrafiltrate passes through a second membrane with a lower cutoff (15 kDa). Finally, the blood is reinjected into the bloodstream. The aim of this technique is that the high and medium molecular weight molecules are retained by the second membrane, avoiding therefore the drawbacks of normal HVHF. However, clinical trials have shown that cascade hemofiltration used to perform HVHF is safe in patients with septic shock, but the catecholamines use during the first 28 days was not reduced [14].

Another promising aspect was the marketing of membranes defined as high cut-off cartridge (HCO), which present a cut-off value very close to albumin's molecular weight (60 Kda).

The pilot study on HCO was published by Morgera. The authors demonstrated reductions in Acute Physiology and Chronic Health Disease Classification System II (APACHE II) and Multiple Organ Dysfunction Score (MODS) in patients treated with HCO membranes compared to standard high-flux membranes [15]. A prospective multicenter study was conducted, later, on 38 patients suffering from SS and AKI and in therapy with CVVHD with high cuff-off membranes (HCO-CVVHD). The authors demonstrated that the treatment with HCO-CVVHD is correlated with an improvement of SOFA score. This effect was evident at the start of the blood purification therapy and correlated with a significant reduction in circulating inflammatory cytochines (IL-6 and TNF-α) [16]. The data published by Chelazzi on patients with sepsis from MDR Gram Negative bacteria treated with high cut-off membranes hemodialysis are also very interesting. The authors conclude that in patients with SS from gram-negative infection and AKI may be useful the HCO-CVVHD in terms of reduced days of vasopressor infusion and mechanical ventilation (MV). They conclude, also, that other studies with similar highly selective patient populations are necessary in order to support these data [17].

The *in vitro* study published by Malard compares the adsorbing capacity of a membrane usable in hemodialysis and continuous hemodiafiltration (OXiris®), and two cartridges with hemoadsorbent properties (CytoSorb®, and Toraymyxin®). The author showed that although Toraymyxin is effective in removing of endotoxins, it's not able to remove inflammatory mediators. Cytosorb is able, instead to remove a wide range of inflammatory mediators but not the endotoxins. OXiris, on the other hand, has adsorbent properties similar to Toraymyxin for endotoxins and it is also able to remove inflammatory mediators [18].

The fiber column immobilized with polymyxin B (Toraymyxin®) is the most widely used as circulating endotoxin removal technique [19, 20]. The results of Euphas trials and other studies are ambiguous, especially on the mortality rate [21, 22]. Several randomized controlled trials comparing the adsorption of polymyxin B with other treatments have revealed opposing results. It's been suggested that Toraymyxin® should have a positive effect only in subgroups of patient, like severe patients with gram negative and gram positive infection and with endotoxin activity levels between 0.6 and 0.9, or those with a specific genetic characteristic [23, 24]. Alteco® LPS presents similar characteristics in terms of endotoxin adsorption. Some

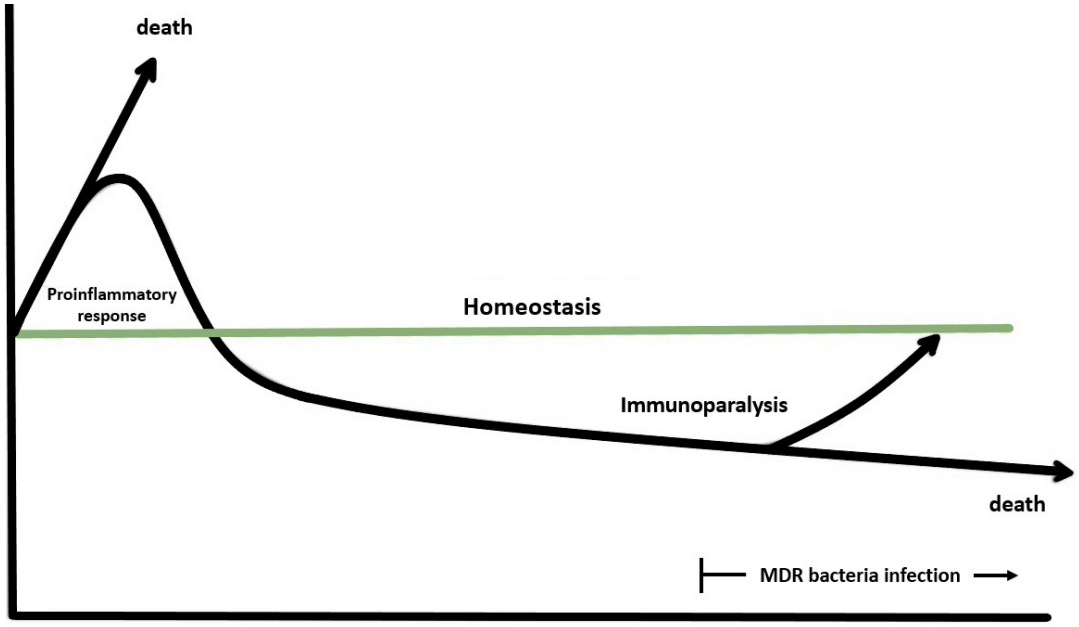

FIGURE 1. Sepsis and immune-dysfunction. Abscissa axis: time; Ordinate axis: immune system; MDR: multidrug resistant.

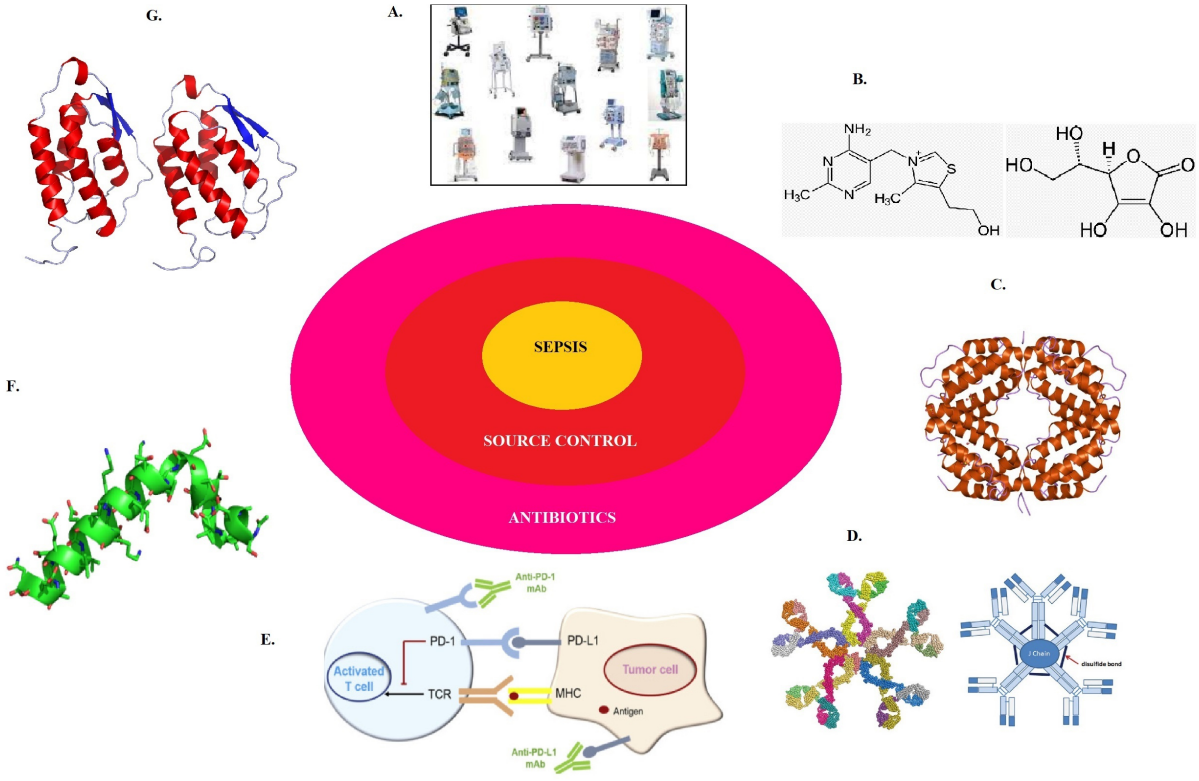

FIGURE 2. Adjuvant therapies and sepsis. A. Blood purification technique; B: Vitamin C and Thiamine; C: Interferon; D: IgM enriched immunoglobulins; E: PD-1/PD-L pathway; F: Thymosin α-1; G: Granulocyte-macrophage colony-stimulating factor.

clinical cases have shown a decrease in endotoxin levels and a hemodynamic improvement in patient recovered in ICU [25–27]. However, this study (ASSET multicentre RCT study) was stopped early because of the recruitment problems [28]. Finally, there is more evidence on the AN69-ST Oxiris membrane that can be used both in hemodialysis and in haemofiltration.

Turani demonstrated that in 60 patients treated with Oxiris there was an improvement in cardio-renal and respiratory parameters as well as a reduction in blood levels of cytokines (IL-6, IL-10), procalcitonin and endotoxin [29]. 6% of the patients enrolled had a Gram-negative bacterial infection, while 35% a Gram-positive infection; 5% had a fungal infection [29]. The experience of two French centers have demonstrated that continuous renal replacement therapy with Oxiris® is able to determinate an increase in survival compared to non-treated patients with the same severity score (SAPS II). In addition, both hemodynamics and blood levels of lactate improved in particular in subjects with intra-abdominal infection or infections with gram negative bacteria [30]. Finally, Broman's first double-blind randomized crossover clinical trial was recently published [31]. The study enrolled patients with septic shock from different germs (*E. Coli ESBL, Klebsiella Oxytoca, Pseudomonas aeruginosa*). The authors at last say that Continuous Renal Replacement Therapy (CRRT) treatment with an Oxiris filter is able to determinate a reduction of circulating endotoxin and cytokine levels. This reduction shows an association with a hemodynamic improvement as well as a reduction in circulating lactic acid. The Surviving Sepsis Campaign (SSC) Guidelines published in 2021 suggested using either continuous or intermittent renal replacement therapy in adults with sepsis or SS and AKI who require renal replacement therapy.

3. Vitamin C and Thiamine

During last thirty years about one hundred clinical trials, have been conducted in order to evaluate drugs and other therapeutic option available to treat patients with sepsis and SS [33, 34]. Vitamin C and thiamine are soluble vitamins that are fundamental to human, in fact their shortage may determinate severe symptoms [35]. Patients in SS show vitamin C and thiamine depletion, which can further aggravate the clinical condition. Intravenous thiamine (vitamin B1) and vitamin C nowadays are strongly considered as a new frontier for sepsis therapeutic approach.

The panel of SSC issued a weak recommendation against the use of vitamin C in patients with sepsis and septic shock [32].

A 2016 retrospective before-after study from Marik *et al.* [36] consecutively enrolled 94 patients admitted during six months because of severe sepsis or SS associated with procalcitonin (PCT) level $\geq$2 ng/mL. 47 patients were allocated in the study group and were treated with intravenous vitamin C, hydrocortisone, as well as intravenous thiamine. Data extracted from their analysis highlighted promising results: the mean length of vasopressor use was higher in control group then in treatment group ($p < 0.001$); the SOFA score was lower in the treatment group compared to control group after 72 hours of treatment ($p < 0.001$). None of the patients in the treatment group developed new organ failure (as reflected by an increase in their SOFA score) requiring an escalation of therapy.

Also Masood *et al.* [37] (2019) adopted a protocol study similar to the previous one. The authors develop a cross-sectional study in order to analyze the effect vitamin C, hydrocortisone, and thiamine in patients with septic shock. The outcomes were length of vasopressor support, mortality, and the length of ICU stay. The authors demonstrated a suspension of vasopressors in all the subjects treated, and also a reduction in term of mortality in the group treated with Vitamin C, hydrocortisone, and thiamine. In 2019 Mitchell conducted a retrospective study on sepsis and SS patients comparing the effect of treatment with Vitamin C, thiamine, and hydrocortisone *vs.* hydrocortisone alone in terms of mortality, length of stay in hospital, ICU length of stay, SOFA score variation and weaning time form vasopressor [38]. The authors didn't demonstrate any difference in mortality rate, but only a reduction of ICU length of stay in patients treated with Vitamin C *vs.* patient treated only with hydrocortisone. Actually, a double-blind randomized placebo-controlled trial designed to evaluate the effects of early combination therapy with intravenous vitamin C and thiamine on recovery from organ failure in patients suffering from septic shock is ongoing [39]. Moreover, another trial published in 2020 examined the effects of vitamin C, hydrocortisone, and thiamine combination therapy on vasopressor requirements compared with hydrocortisone monotherapy in patients with SS. The authors demonstrated that this association did not significantly improve the duration of time alive and free of vasopressor administration over 7 days, suggesting so that treatment with intravenous vitamin C, hydrocortisone, and thiamine does not lead to a more rapid resolution of SS compared with intravenous hydrocortisone alone [40]. In another randomized, placebo-controlled trial, the authors evaluated the effect of vitamin C (at a dose of 50 mg per kilogram of body weight) *vs.* matched placebo administered every 6 hours for up to 96 hours in adults who had been in the ICU for no longer than 24 hours, who had proven or suspected infection as the main diagnosis, and who were receiving a vasopressor. They conclude that in adults with sepsis receiving vasopressor therapy in the ICU, those who received intravenous vitamin C had a higher risk of death or persistent organ dysfunction at 28 days than those who received placebo [41].

A recent trial was published on Journal of the American Medical Association with the aim of demonstrate if a combination of vitamin C, thiamine, and hydrocortisone every 6 hours increases ventilator- and vasopressor-free days compared with placebo in patients with sepsis. Among critically ill patients with sepsis, treatment with vitamin C, thiamine, and hydrocortisone, compared with placebo, did not significantly increase ventilator- and vasopressor-free days within 30 days. However, the trial was terminated early for administrative reasons and the author conclude that it may have been underpowered to detect a clinically important difference [42].

The results of ongoing RCTs may influence the quality of evidence and future updates of the SSC guidelines [32].

4. IgM enriched immunoglobulin

Intravenous immunoglobulins are immunomodulatory agents with a complex mechanism. They play their role in modulating immune system, both the innate system then the adaptive one. Many immunoregulatory mechanisms, not yet fully demonstrated, have been hypothesized to explain their beneficial effect. These factors cooperate synergistically and exert a potentially beneficial effect in patients with severe inflammatory disease.

It has recently been demonstrated that a small fraction of glycosylated IgG has anti-inflammatory effect and also that the removal of that glycosylated portion eliminates this function at the same level as non-glycosylated immunoglobulins. Furthermore, experimental data supported the hypothesis that there is a specific macrophage receptor capable of recognizing glycosylated IgG linked to the Fc fragment, participating on that anti-inflammatory activity.

The SSC guidelines published in 2021 suggest avoiding the routine use of IV immunoglobulins in patients with sepsis and septic shock. In particular, the panel has declared that the balance between positive and negative effects of IVIg remains uncertain, while the cost is very high and it could reduce its feasibility in countries with low- and middle-income economies [32].

Several experimental trials have demonstrated that polyvalent intravenous immunoglobulins can enhance opsonization, inhibit the aspecific activation of complement, preserve from the endotoxin release induced by antibiotic activity as well as neutralize both endotoxin and a large amount of superantigens [43]. In virtue of this, and of their extensive anti-infective and immunoregulatory properties, intravenous polyclonal immunoglobulins have been proposed as an adjunct therapy in the course of sepsis and SS. In particular, these drugs act differently in function on the specific clinical situation; during sepsis, their acts on restoring the balance between the host's immune response and the pathogen's virulence factors.

Monovalent intravenous immunoglobulin preparations are a blood derivative obtained from a large number of healthy donors, thus offering a wide spectrum of antibodies capable of counteracting and opsonizing a variety of microbial antigens and multiple epitopes. IgG and complement proteins are the major classes of opsonins, which contribute to elimination of bacteria. Only one product, Pentaglobin® (Biotest, Germany) is enriched in IgM. This preparation contains in one milliliter of solution, 50 mg of proteins distributed as follows: 38 mg of IgG, 6 mg of IgM and 6 mg of IgA. In contrast, non-enriched formulations usually are constituted by 96% IgG. In this way, Pentaglobin® is very similar to human plasma, because it contains all three classes of immunoglobulins. It has clearly been highlighted that the preparations enriched in IgM are superior to polyvalent immunoglobulins, containing exclusively IgG, probably also because IgM is the first defense of immune system and contain elevated titers of antibodies and opsonins. This class of immunoglobulins has a pentameric structure, which gives it a greater efficacy in neutralizing toxins and in the agglutination of bacteria in comparison with that of class G immunoglobulins. The enriched preparation also contains IgA, antibodies that have a strong anti-inflammatory activity on monocytes, and on the monuclear cells of the peripheral blood [44–46].

For Pentaglobin, a neutralizing effect has been demonstrated against endotoxin precisely through the binding with the IgM component [47, 48]. Intravenous immunoglobulin preparations, especially those enriched in IgM, contain antibodies against the lipopolysaccharides of Escherichia Coli, Pseudomonas Aeruginosa and Klebsiella spp [49].

Literature data seem to suggest that patients affected by Gram-negative infection related SS are able to benefit from enriched IgM intravenous immunoglobulin therapy [50].

The IVIg usage in patients with sepsis is very appealing not only because of their effect on bacteria and toxin elimination, but also because a reduction of circulating IgG and IgM was demonstrated in non-survivors patients. Busani demonstrated in its meta-analysis that the therapy of IVIg in adult patients with severe sepsis and SS seems to be connected with a reduction in the mortality [51]. The mechanisms of action are still not completely understood, but several studies show Ig supplementation should have a role in modulating host response to infection. The assessment of plasma Ig levels has been suggested in order to recognize patients at higher mortality risk. It's important to underline that more studies on the association between endogenous Ig variations and sepsis are needed.

The German Sepsis Society (DSG) analyzed the use of IgM enriched immunoglobulins (ivIgGAM) *vs.* IgM non-enriched immunoglobulins (ivIgG) for adjuvant therapy of sepsis. They are evaluated two metanalysis from the year 2007 and published in the same volume of Crit Care Med. The first metanalysis included 27 trials on the use of immunoglobulins, with level evidence Ia, and gave a recommendation level C for the use of ivgGAM. The second metanalysis (evidence level Ia) employed a different trial quality evaluation methodology and produced different results, and gave a recommendation level B for IvGg. Despite this two metanalysis, the DSG are not in agreement about the use of ivIgGAM because the study is not adequately powered and transparently presented, while it agrees about not using ivIgG, as demonstrated by the SBITS study [52, 53].

The retrospective study published by Cavazzuti showed that SS patients treated early (24 hours after the diagnosis) with 250 mg/kg/day of IgM over 3 days presented a reduction in 30-day mortality rate in comparison to those who received IgM [54].

Rossmann published recently a study comparing the effect of polyclonal standard IgG (Intraglobin) and IgM-enriched preparations (Pentaglobin) in terms of opsonization and effective protection against multi-resistant nosocomial pathogens. He demonstrated that preparation containing IgM showed an enhanced killing activity against Gram-negative bacteria in comparison to pure IgG solution [55]. Unpublished clinical data suggest a beneficial effect also at the microvascular level of application of the method of near infrared spectroscopy with vascular occlusion test level of thenar eminence of the hand.

Nowadays the use of monoclonal, as well as polyclonal IVIg in septic patients, has been studied in more than 42 RCTs and several meta-analyses. A recent meta-analysis of 2019 [56] demonstrated pentaglobin is able to reduce the mortality of septic patients as well as the days of mechanical ventilation

but not the length of stay in the ICU. The author concluded that the evidence was low for both results.

4.1 Thymosin α-1

Thymosin α-1 (Tα-1) is a peptide that derives from thymus and it's just used for Hepatitis B and C, melanoma and hepatocellular cancer treatment [57, 58]. The therapeutic role of thymosin α-1 is based on its immunomodulating properties, in particular the enhancement T-lymphocyte function [59].

A relatively recent systematic review of randomized controlled trials showed a decrease 28 days mortality, as well as a reduction in APACHE II Score, both Tα-1 1.6 mg once daily and 1.6 mg twice daily. Tα-1 increased the level of IL-10 and reduced the level of TNF-α among sepsis patients. However, the quality of evidence supporting the effectiveness is low considering the small sample sizes and inadequate adherence to standardized reporting guidelines for RCTs among the included studies [60]. Ulinastatin (UTI) is an acidic glycoprotein (molecular weight 30 kDa) and Kunitz-type serine protease inhibitor composed of 143 amino acid residues and includes two Kunitz-type domains. The treatment based on the association of Tα-1 and UTI seems to enhance the survival rate for patients affected by carbapenem-resistant bacteria infection in a trial published in 2008 [61]. The sample examined this study was relatively small and all the size of the group examined was not statistically correct. A recent meta-analysis was conducted to verify the efficacy of immunomodulatory therapy that combines UTI and Tα-1 in sepsis patients. Six trials were included in the meta-analysis. Data coming from 465 assigned to UTI + Tα-1 treatments *vs.* 450 to placebo, showed that, compared with placebo, the use of UTI plus Tα-1 was associated with significantly decreases in 28-day all-cause mortality as well as duration of mechanical ventilation. The authors conclude that larger, long-term randomized controlled trials are necessary to support these beneficial data. The panel of expert of SSC doesn't consider Tα-1 and UTI into the guidelines [62].

4.2 Immunomodulation

The most important area of intervention in septic patient is on Immunity modulation.

For a precision medicine approach, a stratified immune biomarker research is needed. Such biomarkers would need to accurately monitor the individual patient's immune response (hyperinflammation or immune deficiency) and their measurement would need to be reproducible over time in order to be able to predict patients at high risk of adverse outcomes such as secondary infection, progression to septic shock, and death.

From the perspective of clinical trial design, one potential reason for the failures was the lack of a stratified approach in delivering the immunomodulatory therapy.

Although around 180 sepsis biomarkers have been reported in the literature, 44 currently monocyte HLA-DR and cytokine, released by *ex-vivo* Immune cell, are the only immune biomarkers that have been used to guide immune adjuvant therapy in clinical trials [63].

Sepsis is characterised by dysregulated immune response, the intensity of which is dependent on multiple factors specific to the pathogen and host. Immunosuppression occurs early on in its course. If sepsis progresses, many patients may enter into a period of protracted immuneparalysis, resulting in increased mortality. Adjuvant immune therapy to restore immune homeostasis either by reducing inflammation or by stimulating the innate and adaptive immune responses is an attractive therapeutic option, which may improve outcome and ease the burden of antimicrobial resistance. Sepsis clearly alters the innate and adaptive immune responses for sustained periods of time after clinical recovery, with immune suppression, chronic inflammation, and persistence of bacterial representing such alterations [3].

However, before this can become a clinical reality, we must recognise that sepsis is a heterogeneous syndrome. The challenge in developing effective adjuvant immune-modulating therapies is to better characterise this heterogeneity by not only defining disease-specific cohorts but also identifying subphenotypes who might benefit from specific interventions [63]. If we can identify these treatable traits, we may be able to deliver targeted, personalised immune therapy, guided by the bedside measurement of immune biomarkers.

In 2021 Amit Pant *et al.* [64] presented recent advancements in nanotechnology-based solutions for sepsis diagnosis and management. Development of nanosensors based on electrochemical, immunological or magnetic principals provide highly sensitive, selective and rapid detection of sepsis biomarkers. Nanoparticle-based drug delivery of antibiotics in sepsis models have shown promising results in combating drug resistance.

4.3 Granulocyte-macrophage colony-stimulating factor (GM-SCF)

A biomarker of sepsis-related immunosuppression, also connected with reduced survival and increasing frequency of nosocomial infection and MDR infection at 28 days, seems to be low level of monocytic HLA-DR surface expression [63]. Although the initial problem related to the inter-test/laboratory variability, which has been solved with the design of a new system that allows the standardized quantitative measurement of cell surface antigens, this marker is often used during clinical trials investigating the use of GM-CSF therapy in order to guide immunotherapy [65].

It has been demonstrated that Granulocyte-macrophage colony-stimulating factor, a cytokine with growth factor properties produced by Th-1 and B-cells could enhance mHLA-DR expression and endotoxin-related pro-inflammatory cytokine secretion in *ex vivo* experiment [66, 67]. Furthermore, it might promote migration of neutrophils, enhance their adhesion and intensify antimicrobial response [68]. Granulocyte-macrophage colony-stimulating factor has been included in many randomized controlled trials, one of these including the determination of HLA-DR expression. In this trial, patients with monocyte HLA-DR with a value minor then 8000 AB/C were randomized to receive or 4 mg/kg/day of Granulocyte-macrophage colony-stimulating factor or placebo for five consecutive days. Granulocyte-macrophage colony-stimulating factor was after administered for more 3 days at a dose of 8 mcg/kg/day if

monocyte HLA-DR value was 415,000 AB/C or 4 mcg/kg/day if monocyte HLA-DR value was minor then 15,000 AB/C. The authors demonstrated that the mHLA-DR expression in patients treated with Granulocyte-macrophage colony-stimulating factor was normalized (instead of what happened in placebo group of patients) and it was supplemented by the increment of pro-infiammatory cytokine release (IL-6, TNF-I) and the reduction of monocytic antiinflammatory cytokines (IL-10). In addition, examining T-cell numbers and T-cell cytokines after stimulation with mitogens and recall antigens we found that both CD4+ and CD8+ T-cells augmented suggestively under Granulocyte-macrophage colony-stimulating factory administration [36]. Because of the hypothetic risk of worsening sepsis-induced immune suppression by the application of GM-CSF therapy at the wrong moment, we have to subscript the necessity of using immune therapy according to the immune biomarkers values, in order to improve the therapeutic strategies. A study involving GM-CSF treatment in septic patients also exposed other benefits as well as reduced time of mechanical ventilation, intrahospital and ICU stay. Furthermore, it has also been shown that GM-CSF decreases the progression of atherosclerosis and moderate lug remodeling in pulmonary fibrosis [69–71].

In addition, there are various trials presenting benefits of GM-CSF therapy even for children. GM-CSF would facilitate immune recovery, prevent nosocomial infection and increase the number of monocytes presenting HLA-DR on the surface [72]. In a recent RCT the hypothesis that GM-CSF improves neutrophil phagocytosis in critically ill patients in whom phagocytosis is known to be impaired was tested. The authors conclude that GM-CSF did not improve mean neutrophil phagocytosis on the second day, but it was safe and appeared to increase the proportion of patients with adequate phagocytosis. The study suggests proof of principle for a pharmacological effect on neutrophil function in a subset of critically ill patients [73]. Now there is no evidence of short-term survival benefit from GM-CSF treatment. GM-CSF represents a promising immunoadjuvant therapy in patients with sepsis, although larger randomized controlled trials are still necessary to confirm these initial results [74]. We are waiting for the publication of The GRID trial (French multicentre clinical trial) that have evaluated this therapeutic approach in patients with SS [75].

4.4 PD-1/PD-L pathway

Due to its anti-apoptotic effect and the suppression of negative regulatory molecules, PD-1/PD-L pathway might offer a worthy approach in sepsis treatment. This pathway is based on programmed Cell Death Protein 1 and Programmed Cell Death Ligand 1 and Ligand 2 [76]. The expression of PD-1 on T-cells is increased in septic patients and it represents a stimulus for IL-10 secretion, apoptosis and the inhibition of cell proliferation. Patients with high levels of PD-1 related molecules frequently show harmful outcomes in terms of mortality and nosocomial infections. At the moment, we have interesting results in murine trials showing that the break of programmed Cell Death Protein 1/Programmed Cell Death Ligand 1 pathway leads to increment survival. Furthermore, antibodies anti PD-1 and anti PD-L could favorite a T-cells reinstatement in different types of cancer with limited adverse effects occurring after long-term administration [77]. These encouraging results lay the foundations to upcoming studies investigating the role of the antibodies in humans.

4.5 Interferon

Interferon-γ (IFN-γ) is a cytokine produced by Th1 cells. It's one of the major activator of monocytes. It's able to increase their antigen-presentation capability and their phagocytic skills [74]. The use of IFN-γ in patients with severe infection has only been reported in clinical cases. INF-γ was used to treat nine patients with sepsis for their reduced monocytic HLA-DR expression. The administration of INF-γ was sub-cutaneaous 100 mcg/day on two or three consecutive days based on the percentage of growth of monocytes. It was well tolerated and it immediately enhance the representation monocytic HLA-DR in all the patients [78]. Nine patients were treated with INF-γ: 8 patients healed from sepsis shortly after therapy with INF-γ; 1 died without sepsis resolution and 2 relapsed at a later stage after the discontinuation of the therapy. No one randomized controlled trials have tested IFN-γ therapy in patients in the ICU. So it's not possible to consider its treatment into guidelines.

Another category of patients who have benefited from the use of INF-γ are the immunocompromised ones with severe fungal infections, low absolute lymphocyte count and low monocyte HLA-DR [79]. Expert propose IFN-γ as a therapeutic alternative for treating non-resolving fungal infections in immunosuppressed patients with haematological cancers [79].

5. Conclusions

Despite our developments in understanding the pathogenesis of this sepsis and SS, innovative therapeutic strategies to break the problem of sepsis or at least to reduce its incidence often keep on being elusive. Therefore, the main chance we have to fight the problem is represented by the early diagnosis and therapy. Trying to find a different solution for the spreading problem, the attention has been focused on the development of innovative immune-modulatory therapy.

Further studies certainly need to confirm current findings and to strengthen actual data, in order to update and standardize this new emerging approach for evaluate end-point that have a clinical value like mortality, length of stay and re-admission in ICU.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

VP, CA, MCP—Conceptualization; VP, GSM, AP, MCP, FM, MS, VI, FB—Writing-review and editing; FC, PS, MBP, AB, MDP—Supervision.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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