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Endogenous immunoglobulins and sepsis: New perspectives for guiding replacement therapies

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ABSTRACT

The recently emerging concept of immunosuppression developing in the field of severe sepsis generated the need to measure circulating immunoglobulins as part of the necessary tests to evaluate immunocompetence status in patients suffering from this condition. Serum concentrations can be used as a surrogate marker of the final outcome and as a biomarker to explore the need for supplementation of the host with intravenous immunoglobulin preparations. Available evidence from recent clinical studies pinpoints the main observations. The first is that circulating IgM is a phenomenon associated with progression from severe sepsis to septic shock. Deficient kinetics of circulating IgM during the first 7 days following the start of vasopressors is linked with unfavourable outcome. The second is the development of immunoscores using low levels of IgM, IgG_1 and IgA. These immunoscores can predict 28-day mortality with an odds ratio ranging between 3 and 5. Novel techniques for evaluating patient's immune status are shedding new light on the development of modern therapeutics where immunoglobulin replacement may be part of a personalised therapeutic approach.

1. Introduction

Severe sepsis results as a failure of the immune system to contain an infection. In this case, the literature describes several potential sequences of immunological events in patients with sepsis: those with predominant pro-inflammatory responses usually found when sepsis develops in a young, otherwise healthy individual; those with predominant anti-inflammatory responses usually developing in immunosuppressed individuals; those with fluctuating pro- and anti-inflammatory responses usually developing in healthy individuals where the infection source is not adequately controlled; and those starting with concomitant pro- and anti-inflammatory responses followed by an impairment of immunocompetence status, which is the typical sequence of events in the majority of patients [1]. Anti-inflammation is characterised by failure of the immune system to respond adequately to a bacterial stimulus. At that time course, lymphopenia predominates, part of which involves B-lymphocytes and the subsequent capacity for adequate production of immunoglobulins [2] (Fig. 1).

Recognition of the existence of immunosuppression as a major event in severe sepsis generated the concept that stimulation of the immune response and/or replacement of key immunological factors may be a promising therapeutic strategy. Treatment with immunoglobulins may be part of that strategy. Although administration regimens consisting of immunoglobulins of the IgG class failed to improve outcomes [3,4], a recent meta-analysis has shown a considerable decrease in the relative risk of death due to severe sepsis both in paediatric and adult populations with the administration of regimens enriched with immunoglobulins of the IgM subclass [polyclonal IgG, IgM and IgA (IgGAM); Pentaglobin®] [5]. This developed the need to recognise those patients who have functional deficiency of IgM. Measurement of circulating levels of immunoglobulins in the blood of patients may be a biomarker to distinguish patients with severe sepsis who might benefit from IgGAM treatment. Several studies have been published over the last 2 years monitoring the changes of circulating immunoglobulin subclasses in severe sepsis and the relationship with final outcome.

2. Circulating immunoglobulins as biomarkers in sepsis

Measurement of immunoglobulins in serum or plasma in severe sepsis has appeared in the medical literature since 2009. They include a total of seven publications [6–12], most of them

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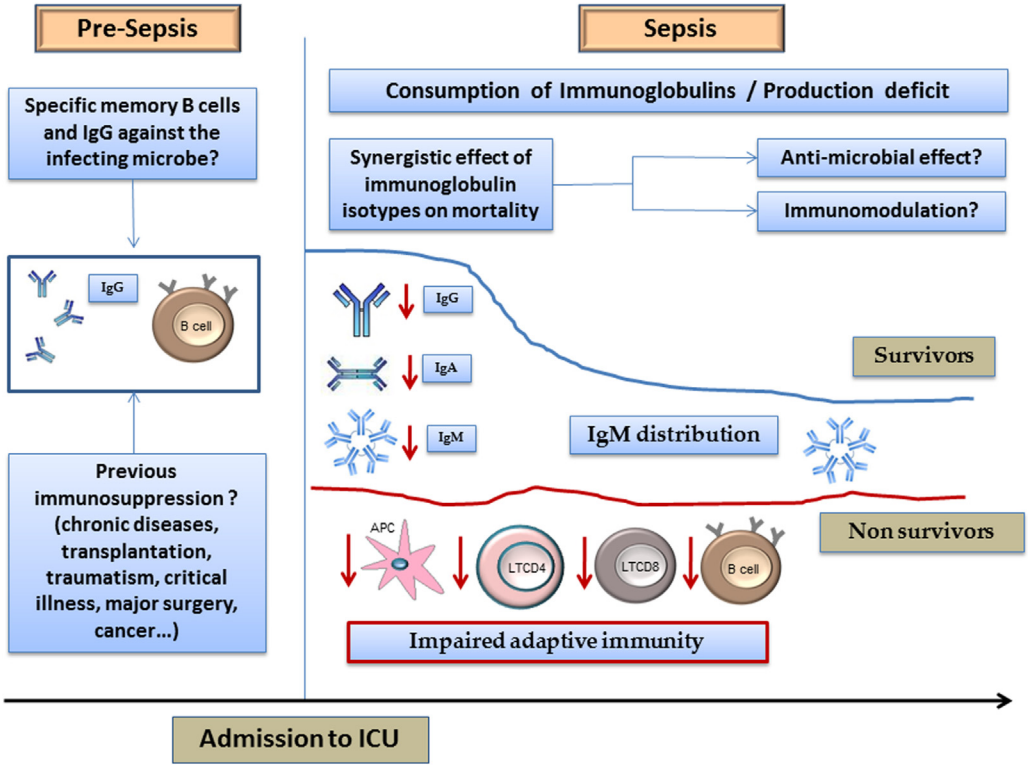

Fig. 1. Major factors and events influencing the role of endogenous immunoglobulins in sepsis. Absence/presence of previous memory responses of B-cells and IgG against the infecting microbe could influence infection control. In addition, the presence of a previous status of immunodeficiency could impair immunoglobulin production affecting their levels in blood. When sepsis is already established, the three major immunoglobulin isotypes show a synergistic beneficial effect on the risk of mortality, with non-survivors showing lowers levels of immunoglobulins. A maintained distribution of IgM along time translates into improved outcomes. Beneficial effects of endogenous immunoglobulins include potential antimicrobial and immunomodulatory activities. During sepsis, immunoglobulin consumption is thought to occur (due to formation of immune complexes with microbial antigens or oxidation products, or unspecific binding to leucocyte receptors). The presence of quantitative and functional depression of the adaptive immunity observed in severe sepsis (which is more acute in non-survivors) could in turn impair production of specific antibodies against the infecting microbe and preclude maintaining adequate immunoglobulin levels along the disease course. APC, antigen-presenting cell; ICU, intensive care unit. Red colour corresponds to non-survivors. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

appearing in the last 2 years [8–12]. These publications refer to studies of measurements of immunoglobulins levels in severe sepsis and septic shock or in severe pneumonia and to studies of the kinetics of IgM in sepsis.

2.1. Immunoglobulin levels in severe sepsis and septic shock

The first small study enrolled 21 patients with septic shock; 16 had hypogammaglobulinaemia. These patients could be classified into those with selectively low IgG, those with selectively low IgM and those with combined low IgG and IgM. Of the 21 patients, 6 (28.5%) died [6]. In the next study on 62 septic shock patients, circulating IgG, IgA and IgM were measured on Days 1–2, 3–4 and 5–7 of the course of septic shock. IgG and IgM were below the levels of healthy controls particularly on Days 1–2 and Days 3–4; a similar decrease was not found for IgA. During the start of septic shock, 61% of patients had low IgG, 40% of patients had low IgM and 4% of patients had low IgA [7]. Shankar-Hari et al. have recently reviewed the available evidence on the association between endogenous IgG levels and outcome in patients with severe sepsis or septic shock [13]. This meta-analysis found that the prevalence of IgG hypogammaglobulinaemia on the day of sepsis diagnosis was as high as 70% in heterogeneous sepsis cohorts reporting different lower limits of normality for IgG. None the less, based upon the results of this review, a single subnormal measurement of IgG on the day of sepsis diagnosis would not be useful to identify a subgroup of patients with a higher risk of death.

In our view, the answer could be in considering immunoglobulin isotypes not as isolated entities but in evaluating their prognostic ability in combination. In a recent multicentre prospective study from nine hospitals in Spain, IgG, IgA and IgM were measured in 172 patients at the time of diagnosis of severe sepsis or septic shock [8]. In that study, categorical variables were used to develop immunoscores predictive of final outcome. A cut-off of the measured level of each immunoglobulin was identified based on the impact of individual immunoglobulin isotypes and subclasses on mean survival time, and each patient was classified as of low or high level for each immunoglobulin according to this cut-off. The cut-offs were 300 mg/dL for IgG_1, 35 mg/dL for IgM and 150 mg/dL for IgA. Admission concentrations below each of these cut-offs were predictive of unfavourable outcome. The first interesting finding was that these cut-offs were well below the range of hypogammaglobulinaemia for IgG and IgM. As a consequence, the concept of hypogammaglobulinaemia defined as 'subnormal levels of immunoglobulins' appears to be no use in sepsis, where real biological cut-offs influencing patient outcomes are needed. When these cut-offs were combined using logistic regression analysis, it was found that three immunoscores were significantly associated with unfavourable outcome: (i) all three IgG_1, IgM and IgA below the cut-offs [odds ratio (OR) = 5.27]; (ii) both IgG_1 and IgM below the cut-offs (OR = 3.10); and (iii) both IgG_1 and IgA below the cut-offs (OR = 4.10) [8]. The prevalence of patients with previous immunosuppression was 20% in this cohort. As a consequence, the presence of this condition in patients with sepsis should be taken into account in the design of clinical trials with intravenous immunoglobulin (IVIg), since these patients should potentially constitute a priority regarding treatment indication. Our group is working in developing new immunoscores based on

immunoglobulin levels, and new data are emerging supporting the synergy of total IgG, IgA and IgM regarding mortality prediction in severe sepsis.

2.2. Kinetics of IgM in sepsis

The largest study conducted so far on the kinetics of IgM in sepsis is that from the Hellenic Sepsis Study Group (http://www.sepsis.gr) enrolling 332 critically ill patients from 27 study sites; 41 were classified as sterile systemic inflammatory response syndrome (SIRS) due to acute pancreatitis, 100 as uncomplicated sepsis, 113 as severe sepsis and 78 as septic shock using internationally well accepted definitions; in addition, 35 healthy controls were studied. Circulating IgM was measured within the first 24 h from diagnosis and were significantly higher in controls, patients with SIRS and patients with severe sepsis than in patients with septic shock. Surprisingly, circulating IgM in uncomplicated sepsis did not differ from septic shock. Measurements were repeated for 83 patients who worsened. A decrease of IgM was found only in the case of transition from severe sepsis into septic shock. Finally, serum IgM was measured at presentation of septic shock and for another 6 consecutive days in 30 patients. The time of initiation of administration of vasopressors was the start point for measurements. The area under the curve of IgM over the entire time of follow-up (7 days) was measured separately for survivors and non-survivors. It was considered that this area represented the body distribution of IgM. The area was significantly larger in survivors than in non-survivors both when censoring was done on Day 28 and on the day of hospital discharge [11].

A salient feature of this study was the isolation of peripheral blood mononuclear cells from patients and their stimulation with the lymphocyte agonist phytohaemagglutinin for the production of IgM. Low IgM production was a common characteristic of all stages of sepsis compared with healthy controls and it was more pronounced in severe sepsis and septic shock. These findings, in conjunction with the reported kinetics of circulating IgM, led to the hypothesis that suppression of B-lymphocytes supervenes in severe sepsis and septic shock. However, serum IgM remains at high levels in severe sepsis and it is consumed upon worsening into septic shock. Survival is probably linked with the ability of the host to maintain adequate body distribution of IgM [11]. IgM plays an important role in the clearance of oxidation-specific epitopes and, as a consequence, may provide a generalised protective response against the consequences of oxidative stress produced in the context of critical illness [14].

It should be underscored that the primary endpoint of all of the above studies was the association between endogenous immunoglobulin levels and mortality. This is in contrast with current trials on the administration of IVIg in severe infections such as community-acquired pneumonia that consider softer endpoints such as days of mechanical ventilation, days of hospitalisation and days in the intensive care unit (ICU) [15].

3. Commentary

Acquired knowledge over the last years has shown that early measurements of circulating immunoglobulins may be used as a surrogate marker of unfavourable outcome in severe sepsis as well as the need for replacement of immunoglobulins to reverse the course of the patient. The concept is based on the assumption that lack of immunoglobulins renders a critically ill patient prone to unfavourable outcome. This concept is further supported by a recently published prospective study on 90 critically ill patients admitted without infection to the ICU; those with admission levels of IgM of <58 mg/dL had an unfavourable outcome [12].

The developed immunoscores of severe sepsis linking admission levels of low IgG_1, low IgA and low IgM with unfavourable outcome generate the hypothesis that early administration of a regimen containing all three classes of immunoglobulins, such as IgGAM, may be effective. This hypothesis is compatible with evidence from a retrospective analysis of 129 patients with septic shock who were treated with IgGAM; survival benefit was associated with early start of treatment within the first 23 h [16].

Finally, endogenous immunoglobulins should not be considered as isolated elements of the immune system. Profound alterations in both innate and adaptive arms of the immune response are observed in cases of severe sepsis [17]. Real-time PCR and emerging technologies such as droplet digital PCR or next-generation sequencing [18] could help to obtain a wider picture of the patient's immune status. At the same time, it is necessary to know more about the biological effects of immunoglobulins in sepsis, i.e. antimicrobial or immunomodulatory [19]; evaluating the influence on patient outcome of previous specific IgG antibodies against the infecting microbe, or identifying the inflammatory targets modulated by IgM are two examples. Integrating immunoglobulin levels with this complementary information could help to better understand the role of the former in sepsis.

Despite the need for randomised controlled trials, the above accumulating evidence clearly opens new perspectives for the use of circulating immunoglobulins as a surrogate market to define the best candidates for treatment with intravenous IgGAM. Considerations commented in these article could help to clarify the role of endogenous immunoglobulins in sepsis as well as to improve the results of trials employing IVIg for the treatment of sepsis.

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