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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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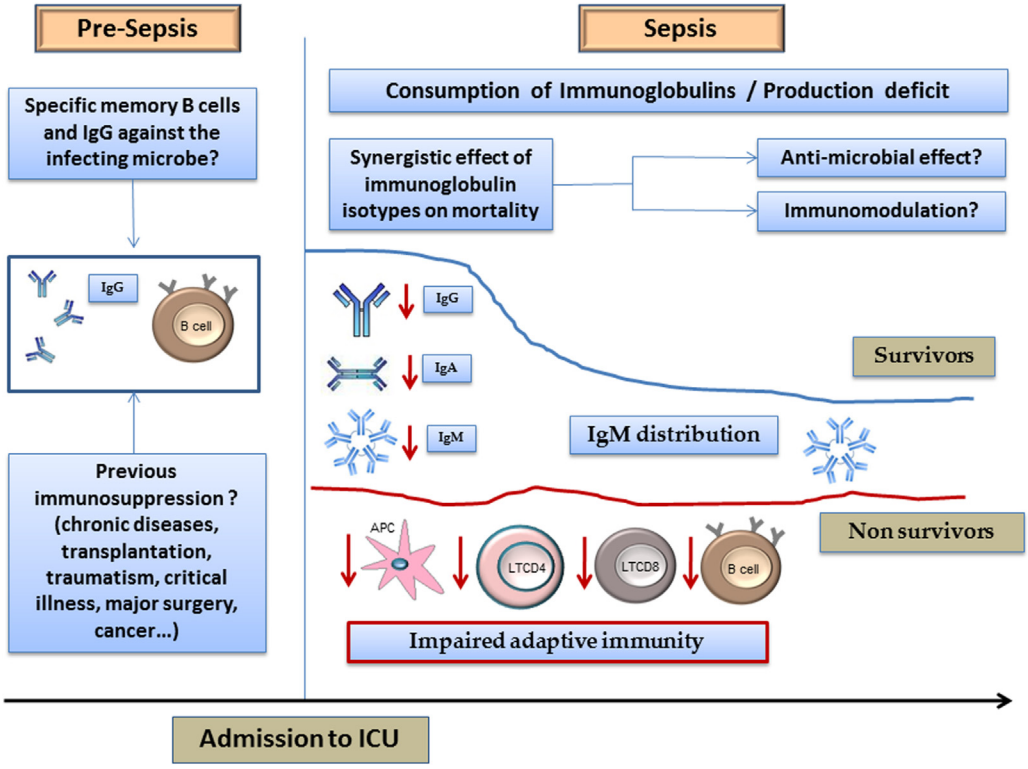

Fig. 1. Major factors and events influencing the role of endogenous immunoglobulins in sepsis. Absence/presence of previous memory responses of B-cells and IgG against the infecting microbe could influence infection control. In addition, the presence of a previous status of immunodeficiency could impair 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