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FULL PAPER

A Position Paper on IgM-Enriched Intravenous Immunoglobulin Adjunctive Therapy in Severe Acute Bacterial Infections: The TO-PIRO SCORE Proposal

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SUMMARY

IgM-enriched immunoglobulins (IgM) may be useful in patients with severe acute bacterial infections. The evidence for the administration of IgM is not extensive and a definitive consensus has never been reached on its best use in patients with acute infections as well as in critically ill patients. However, the official indication in several countries, including Italy, is quite wide and mainly refers to supportive treatment of patients with acute severe bacterial infections.
A multidisciplinary meeting of Italian Experts in Infectious Diseases, Anesthesia and Critical Care, Pneumology, Microbiology and Oncohaematology aimed to produce a statement on the best practical methodological score that could improve the use of IgM in patients with different infections, variable severity of disease and etiology. The Expert Panel reviewed the literature and the available guidelines, discussed the experience and eventually proposed to adapt the PIRO score to the practical methodological needs of a simple tool that could guide the administration of IgM.

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INTRODUCTION

In recent years, it has become clear that inflammatory response and innate/adaptive immune response play a major role in the outcome of septic patients, with real difficulties in defining the most appropriate supportive treatment, particularly in patients with septic shock or persisting/relapsing infections (Busani *et al*., 2016; Levy *et al*., 2003). Septic shock is a life-threatening condition characterized by severe hypotension and abnormalities in cellular metabolism with very high mortality despite the appropriate therapy (Singer *et al*., 2016). Among the multiple immunological effects, a significant decrease of serum level of IgM has been reported during septic shock, specifically in those cases progressing from severe sepsis into septic shock, with lower IgM levels among non-survivors (Giamarellos-Bourboulis *et al*., 2013). The combined presence of low levels of endogenous immunoglobulins IgG1, IgM and IgA in plasma was also associated with reduced survival in patients affected by severe sepsis or septic shock (Bermejo-Martin *et al*., 2014). In this context, there is a rational to discuss the use of adjunctive therapies, in addition to appropriate antimicrobials and cardiovascular support, such as the administration of intravenous immunoglobulins and, specifically, IgM-enriched immunoglobulins (IgM).
Since the official indication in several countries, including Italy, is the supportive treatment of patients with acute severe bacterial infections, it was felt that a simple tool could be helpful in guiding the administration of IgM. The aim of this multidisciplinary consensus was to develop a score for the identification of patients with bacterial infection who may best benefit by an early administration of IgM.

Key words:
PIRO, IgM-enriched immunoglobulins, critically ill patients, TO-PIRO, sepsis.

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METHODS

Position Paper Procedure

The process was managed by a multidisciplinary panel, including specialists in Anesthesiology and Critical Care, Infectious Diseases, Pulmonology, Hematology and Clinical Microbiology highly experienced in research and in the clinical management of patients with sepsis. A multistep process, with review of evidence, panel discussion and proposal of a clinical score or practical tool to support the IgM administration was adopted.

The process was conducted in May 2018 and the opinions of the experts about IgM use in severe bacterial infections were discussed according to the literature and existing guidelines. The Experts were then invited to share their opinions based on their clinical experiences. Thereafter, a critical discussion and a comprehensive review of the literature was promoted. A general consensus was considered achieved if the level of agreement was ≥75%.

After extensive discussion amongst the experts, the PIRO concept was proposed as a practical tool to support the evidence for IgM-IG administration. In 2001, the International Sepsis Definitions Conference proposed a new, sophisticated, but more conceptual way of looking at sepsis syndrome: predisposition, infection (or insult), response and organ dysfunction score, also called "PIRO." The PIRO concept of classification scheme for sepsis includes predisposing condition, nature and extent of insult, nature and magnitude of host response, pattern and degree of organ dysfunction (Levy *et al*., 2003). As opposed to the usual staging, based mainly on the severity of organ dysfunctions (i.e., sepsis) and metabolic involvement (i.e., septic shock), the PIRO concept takes into account many important aspects of the management of patients with infections, closely related to their risk of mortality (Rello *et al*., 2009; Cardoso *et al*., 2013; Chen *et al*., 2013). The panel decided to use the PIRO as a supportive tool for the identification of patients to be treated with IgM.

REVIEW OF THE EVIDENCE

Sepsis and septic shock

The effects of IgM have been investigated in different settings and in different populations, especially in Surgery and Intensive Care Units (ICUs). A Cochrane review on 43 studies evaluated the effects of IgM as adjunctive therapy in patients with bacterial sepsis or septic shock based on mortality, bacteriological failures and duration of stay in hospital. Unfortunately, clinical heterogeneity prevented a pooled analysis of polyclonal and monoclonal intravenous immunoglobulins (IVIG) and the reaching of a global statistical significance. Moreover, a significant reduction of mortality in adults with sepsis compared to placebo or no intervention was observed in a subgroup analysis of 10 polyclonal IVIG trials and seven trials on IgM preparation (RR 0.81), but not in trials at low risk. The authors concluded that polyclonal IVIG reduced mortality among adults with sepsis, but the evidence for IgM preparation is still insufficient to support a robust conclusion of benefit, even if the mortality reduction was about 20% (Alejandria *et al*., 2013). The results of this review confirmed those reported by the metanalysis from Kreymann et al (Kreymann *et al*., 2007). A more recent retrospective study evaluated the efficacy of early therapy with IgM (administered within 24 hours after shock onset) on 30-day mortality rate in ICU patients with septic shock. As many as 92 out of 168 (54.8%) patients included in the study received IgM therapy. The results showed a 21.1% reduction of the 30-day mortality rate in the group treated with IgM compared to the control group ($p<0.05$). Early adjunctive therapy with IgM can be associated with a survival benefit in patients with septic shock (Cavazzuti *et al*., 2014). Finally, the meta-analysis of 18 randomized clinical trials by Busani et al. evaluated the clinical effectiveness of immunoglobulins use in adult septic patients. According to this review, the administration of IgM may reduce the mortality risk of septic patients (odds ratio 0.50), in spite of the bias of these studies (low quality, heterogeneous dosing regimens and type of Ig preparations, different control interventions) (Busani *et al*., 2016).

A recent phase II trial (CIGMA trial) evaluated the safety and efficacy of a new product (i.e., trimodulin) containing a higher proportion (23%) of IgM than the standard preparation (12%) as adjunctive therapy in patients with severe community acquired pneumonia (sCAP). Although the primary end-point (i.e., significant reduction of ventilator free days) was not achieved, the study confirmed the safety of the product and indicated a potential improvement in survival of patients with low IgM and/or elevated reactive protein C plasma levels at enrollment (Welte T *et al*., 2018). A phase III trial aimed at evaluating the effects of trimodulin on mortality of patients with sCAP is underway.

Timing of administration

An important issue is the appropriate timing of IgM administration. Overwhelming septic shock caused by *Neisseria meningitidis* and *Streptococcus pneumoniae* is a specific phenotype of hyperacute sepsis, occurring in young and healthy people, whose associated mortality has remained unchanged even after remarkable improvements in patient identification and timely antibiotic therapy in many countries in the last decades (Giraud *et al*., 1991). Berlot *et al.* retrospectively evaluated the relationship between the timing of administration of IgM enriched immunoglobulins and the outcome of 129 adult ICU patients with severe sepsis and septic shock. The results demonstrated that the timing of IVIG administration is essential, with a linear relationship in terms of survival (survivors were treated significantly earlier than non-survivors: 23 vs 63 hours, $p<.05$) and an increase of mortality risk by 0.7% for each hour of delay. The authors concluded that the efficacy of IgM is time-dependent and is higher in the early phases of severe sepsis and/or septic shock (Berlot *et al*., 2012). These data were further confirmed in a larger population of similar patients, including for the subgroup of patients with septic shock by MDR pathogens (*Berlot et al*., 2018).

A specific topic related to the timing of administration is the kinetics of circulating IgM during the different stages of sepsis and its relationship with final outcome, which was the objective of the prospective multicenter study performed by Giamarellos *et al*. on 332 critically ill patients (83 of whom progressed to more severe stages of sepsis; 30 patients with severe sepsis progressed to shock and IgM was monitored daily for seven consecutive days). IgM levels decreased in septic shock compared to patients with systemic inflammatory response syndrome (SIRS) and patients with severe sepsis, but only when patients deteriorated from severe sepsis to septic shock. Moreover, the production of IgM in peripheral blood mononuclear cells was significantly lower during sepsis compared with healthy controls (Giamarellos-Bourboulis *et al*., 2013). These results may clearly indicate an important role of IgM levels on the patients' outcome.

Severe Infections by Multi-drug resistant bacteria (MDR)

Patients with sepsis and septic shock by opportunistic MDR bacteria are at very high risk of death despite adequate antibiotic therapy. This seems to be caused by the severe dysfunction of the immune system (i.e., im-

mune-paralysis) occurring in many patients after sepsis, trauma or extensive surgery. In this context, IgM may have a therapeutic role as supportive immune-therapy. The available data demonstrate a positive effect of IgM on the mortality rate of patients with MDR infections (Berlot *et al*., 2018). A recently published retrospective study analyzed the risk factors for 30-day mortality and the impact of sepsis management in 94 patients with septic shock caused by MDR bacteria admitted to the ICU of Modena University Hospital during a 6-year period. Among all the therapeutic interventions applied to patients during the ICU stay, only the administration of IgM was significantly associated with survival. The multivariate adjusted analysis showed that an active cancer and *Acinetobacter baumannii* infections were related to an increased risk of 30-day mortality and that IgM had a protective role (Busani *et al*., 2017). A retrospective analysis of a large prospective multicenter cohort study evaluated the outcomes (28-day mortality rate, mortality by MDR pathogens) of 100 ICU patients with microbiologically confirmed severe infections by MDR pathogens after adjunctive treatment with IgM versus a control group (n=100 matched for stage of sepsis, source of infection, appropriateness of antimicrobials and co-morbidities). Mortality was significantly reduced in the group treated with IgM (odds ratio 0.46; p=0.011); mortality in patients infected by MDR Gram-negative bacteria was also higher in comparators respect to the group treated with IgM-IG (62.5% vs. 38.5%, respectively; p=0.008) (Giamarellos-Bourboulis *et al*., 2016).

BENEFIT OF IGM USE IN CLINICAL PRACTICE: THE TO-PIRO SCORE

The administration of intravenous immunoglobulins (IVIG) represents a possible additional supportive treatment for the management of acute severe bacterial infections, even though a general consensus based on scientific evidence is still lacking. A meta-analysis of 15 trials on 1,492 adult patients with sepsis or septic shock showed that IVIG had a significant effect on mortality (relative reduction of the risk of death - RR: 0.79, p≤.0003), with a trend in favor of immunoglobulin preparations enriched with IgA and IgM (RR=0.66 versus 0.85 of preparations with IgG only) (Kreymann KG *et al*., 2007). Although the results of further metanalysis confirmed the possible beneficial effects of the use of IVIG in septic patients (Busani *et al*., 2016), the last edition of the Surviving Sepsis Campaign Guidelines did not find clear evidence to support its administration (Rodhes *et al*., 2017). The major issues raised were the high heterogeneity of available studies in terms of patient populations, type and dose of IVIG used, age (children or adults), underlying infections and selection of control groups. Indeed, the use of IVIG in patients with sepsis and/or specific infections such as necrotizing fasciitis or meningitis was only advised by other evidenced-based guidelines (Sartelli *et al*., 2014; Wilkins *et al*., 2017), widely used in many countries.

The high heterogeneity of immune-inflammatory response makes it implausible that a single supportive therapy might be effective in all patient populations with sepsis. Therefore, it is crucial to identify patient phenotypes that can receive special advantage from each specific adjunctive therapy, especially with the widely approved indications of IgM. Many papers have been published over the last 30 years on the use of IgM, mainly on IgM preparation, in the treatment of the sepsis syndrome (Kakoullis *et al*., 2018) but the evidence of clinical benefit is still inconclusive (Rodhes A *et al*., 2017). The practical question is when and how to administer IgM in the supportive treatment of acute severe bacterial infections, a complex and challenging clinical phenotype.

A specific TO-PIRO score was proposed and discussed with a multi-step review process: literature evidences, pathophysiological reasoning and personal clinical experience. The role of clinical, microbiological and biochemical parameters on the efficacy of IgM were evaluated and the following criteria were considered for the development of TO-PIRO score (*Table 1*):

1) The predisposition (**P**) components of PIRO were: cancer, MDR pathogens or candida colonization, neutropenia, immunosuppressive therapy (steroids, monoclonal antibodies, mycophenolate, cyclosporine), allogenic stem cell transplant, splenectomy;

Table 1 - *Evaluation criteria of the TO-PIRO score.*

Items	*Criteria*	*Score*
Predisposition	• Uncontrolled cancer	1
	• Colonization by MDR bacteria and/or candida	1
	• Neutropenia or immunosuppressive drugs (monoclonal/steroids/micophenolate/cyclosporin) or allogenic stem cell transplant or splenectomy	2
Insult	• Necrotizing fasciitis, invasive meningococcal/ pneumococcal diseases, *Streptococcus pyogenes*; CA-MRSA	5
	• MDR infections or nosocomial infections	2
	• Secondary/tertiary peritonitis	2
Response	• Leucocytes < 600/ul	2
	• IgM < 60 mg/dl	2
	• PCT > 10 ng/l and CRP >20 mg/dl	1
	• PCT > 100 ng/l or endotoxin > 0.6 or IL-6>1000 pg/ml or adrenomedullin > 4 nm/l *or* presepsin 1400 ng/l	2
	• Disseminated intravascular coagulation	1
Organ	• Septic shock	3
	• Sepsis with ≥ 1 organ failure	2
	• Infection without sepsis	1

CA-MRSA, methicillin-resistant *Staphylococcus aureus*; CRP, C-reactive protein; IgM, immunoglobulins M; IL, interleukin; MDR, multi-drug resistant; PCT, procalcitonin.

Table 2 - *TO-PIRO score: recommendations for use and timing of administration of IgM according to the TO-PIRO categories.*

TO-PIRO SCORE	*Recommendation*	*Timing*
TO-PIRO ≤ 5	The use of IgM may be beneficial according to clinical scenario	–
TO-PIRO > 5-10	The use of IgM is suggested: evidence suggest a potential benefit in these patients	Administered within 24h from clinical presentation
TO-PIRO >10	Use of IgM is strongly recommended: evidence showed a low mortality rate associated to the use of IgM	As soon as possible and within 6 h

IgM, immunoglobulins M.

2) Insults (**I**) components were: necrotizing fasciitis, invasive meningococcal or pneumococcal disease; *Streptococcus pyogenes* infections; community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA), MDR or nosocomial infections; complicated intra-abdominal infections;
3) Response (**R**) components were: leucocyte count <600/ul; serum IgM <60 mg/dl; procalcitonin (PCT) >10 ng/l and, C-reactive protein (CRP) >20 mg/dl; PCT >100 ng/l or endotoxin >0.6 or interleukin (IL)-6 >1000 pg/ml or adrenomedullin >4 nm/l or presepsin >1400 ng/l, disseminated intravascular coagulation (DIC);
4) Organ failure (**O**) components were: septic shock, sepsis with more than 2 organ failures, infection without any sign or symptoms related to sepsis.

The Consensus assigned a score ranging from 1 to 5 (1 = not relevant; 5 = very important) to each criterion of the TO-PIRO score (*Table 2*). After the first proposal, the TO-PIRO score was further discussed and then further modified and validated in a plenary session the day after the Consensus meeting.

According to the result of the TO-PIRO score, the Expert Panel identified three levels of support: IgM administration considered, recommended or strongly recommended (*Table 2*). A TO-PIRO score ≤5 indicates an uncertain benefit from the use of IgM: individual assessment should be performed according to guidelines. A TO-PIRO score in the range of 6-10 suggests a potential benefit of IgM, initiated after antibiotic therapy and within 24 hours after identification of infection. Finally, when the TO-PIRO score is ≥10, the use of IgM is strongly recommended within 6 hours after identification because the therapy may significantly decrease the mortality risk.

CONCLUSION AND FUTURE PERSPECTIVES

This Consensus aimed, through a multi-step multidisciplinary process, systematic literature review and discussion of personal experience, to propose a practical score to be used for showing a benefit from IgM administration; for this purpose, the TO-PIRO score, based on the PIRO concept, was proposed. The selection of the TO-PIRO criteria resulted from an extensive review of published experiences on the use of IgM in terms of pre-existing diseases, type of infection, inflammatory/immune response profile and severity of sepsis. Similarly, the selection of the relative weight of each criterion for score calculation was based on literature analysis and on personal experiences. The TO-PIRO score has limitations and should be considered as a useful guide to practically translate the official indications of IgM. Its efficacy in the identification of patients who may benefit from IgM therapy should be urgently confirmed by large databases and by application in daily clinical practice.

In conclusion, several aspects of the role of IgM therapy were reviewed, evaluated and addressed. While waiting for future large prospective trials clarifying the role of Ig therapy in sepsis (Kakoullis L et al., 2018), the experts concluded that IgM administration may greatly benefit from a simple practical tool to guide its use in severe bacterial infections. The TO-PIRO score may be useful to appropriately identify patients who may best benefit from IgM treatment.

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Conflicts of interest

The funding organization(s) played no role in the study design, in the collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the report for publication.

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