

## **Adjuvant therapy in septic neonates with immunoglobulin preparations containing Ig isotypes in addition to IgG: A critical review of current literature.**

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### **Abstract**

**Preterm VLBW neonates are extremely susceptible to sepsis and its consequences in terms of morbidity and mortality. This susceptibility to sepsis is related either to the immaturity of their immune system either to the exposure to invasive NICU maneuvers. The paucity of immunoglobulins contributes to the high risk of systemic infection. Very recent data on critical septic adults demonstrated that IgM enriched immunoglobulins reduce mortality. Available data about the role of IgM enriched immunoglobulins as adjuvant therapy in neonatal sepsis are still conflicting especially on VLBW infants that are the class of neonate more susceptible to infection. We provide a critical review on current literature.**

**Keywords:** IgM enriched immunoglobulins, Newborn, Passive immunotherapy, Prematurity, VLBW, Sepsis.

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### **Introduction**

Neonatal sepsis is still an important cause of mortality and morbidity for preterm and Very Low Birth Weight (VLBW) infants [1-3]. A number of constituents of the immune system gain its complete function only long time after birth [4]. Because of this important immunodeficiency, newborn is particularly exposed to the risk of serious infections. Preterm and VLBW infants are at high risk of infections because of immaturity of their immune system, reduced levels and activity of immunoglobulins and complement, invasive practices in NICU [5-7]. The newborn also present an inadequate inflammatory response that explains the lack of clinical signs of localization, which frequently makes difficult to identify a systemic infection [8]. In these setting intravenous immunoglobulins as supplementary therapy could represent an important support to these immature immunary functions. Recent literature about the use of standard immunoglobulins (S-IVIG) in addition to standard antibiotic therapy in neonates with infection evidenced no effect on death in neonates [3]. IgM-enriched immunoglobulins showed positive results in adult patients with sepsis. After more than twenty years since the first study on this passive immunotherapy as adjunctive treatment in neonatal sepsis was published available data are still controversial.

In the following paragraphs, we provide a brief digression on immunological determiners of infection susceptibility in newborn and a critical analysis of current literature on the role of immunoglobulins in neonatal sepsis.

### **Infection Susceptibility in the Newborn**

Important features differentiate the mechanisms of neonatal immunity respect to the adult one. These differences explain the increased susceptibility and severity of infections in neonatal period and the absence of early clinical marks of alert, which can delay the diagnostic suspect, and the introduction of an appropriate therapy. For example, the immaturity of the skin barrier acts a critical role in the preterm infection vulnerability because represent an insufficient barrier against pathogens and despite a fast maturation its function is still impaired long after birth. Applying 80% humidity in incubator is a crucial step to face the loss of transepidermic water experienced by very preterm newborn but this strategy may favor colonization of the skin and bacterial and fungal growth [9]. Respiratory and gastrointestinal mucosal are immature as well; microorganisms that access through nasogastric and endotracheal cannulas may colonize these areas and may increase intestinal permeability and favor translocation of microorganism in bloodstream [10-12]. Secretory class A immunoglobulin, mucins and defensins, have an important role in the mucosal defense

but in newborn their levels are low. Intestinal peristalsis, absorptive capacity and intraepithelial lymphocytes are compromised as well [13].

Also, innate immunity in the neonatal period is immature. Neutrophils and monocytes present inadequate chemotactic activity and random migration but their phagocytosis and microbicidal activity are comparable to adult ones [4,14,15]. The production of cytokines, such as IL-6 and TNF- $\alpha$ , is reduced, causing a compromised febrile response [16,17]. The absolute number of NK cells in fetal blood is lower and they have a decreased response to signaling [18]. The APC (antigen presenting cells), have a decreased function that could clarify the reduction of T-mediated response in neonatal period [19-22]. Regarding non-specific humoral factors, the lower the gestational age is the lower is serum concentration. In fetal life the production of complement proteins starts from the 5th-6th month [2,14]. The transplacental transport has not been reported [4,23-25]. All fractions show low concentration correlated to the low gestational age for deficient synthesis. The activation of the classical pathway is impaired due to deficit of the opsonizing immunoglobulins while the alternative pathways try to compensate this deficit [14]. In preterm neonates either the classical either the alternative pathway are impaired. The complement deficit together with an impaired phagocytic activity increases the susceptibility regards sepsis especially from extracellular pathogens [19]. Expression of complement receptors on neutrophils is similar in term and preterm neonates but reduced expression of CR3 on neutrophils in preterm neonates has been reported [26,27]. The fetal thymus in utero initiates its lymphoid activity after the sixth week of gestation with an intense lymphopoiesis besides antigenic stimulation [28]. The production of T lymphocytes enhances during the second trimester, achieving normal values within the 30-32 week of gestation. However, T lymphocytes are functionally inadequate: CD4+ T cells generate clonal expansion, but are not completely competent for helper function and the cytotoxic activity is low [8]. B-lymphocytes are present in fetal bone marrow, blood, liver and spleen before the 12th week of gestation. Fetal IgG can be detected in blood although the most of IgG circulating in fetus are of maternal origin. From the 12th week of gestation starts the active placental transfer of maternal IgG to the fetus. Only IgG across the placenta thanks to the low molecular weight and the ligation to specific receptors on chorionic villi. This active transport of maternal IgG across placenta increases after 32 weeks of gestation and allows reaching in term neonate's level of IgG equal or even higher than the adults. In neonates born preterm consequently, the antibody levels are much lower the lower the gestational age is, in particular if they born before 32 weeks of gestation, contributing to the high susceptibility to infection of such neonates [14].

After birth in at term neonates, most of immunoglobulins are maternal IgG, whose concentration decreases for

physiological catabolism and whose specificity is related to mother antigen exposure. Infant antibody production begins around the 3rd month of life and IgG increase to adult levels at 4-6 years of age. IgA are not synthesized in fetal life, therefore at birth mucous membranes are totally devoid of such antibodies; as compensatory mechanism colostrum is enriched of secretory IgA [14].

### **Role of Immunoglobulins in the Treatment of Neonatal Sepsis**

Given the immaturity of humoral defense in the newborn, the use of immunoglobulins as adjuvant treatment in sepsis could represent an appealing strategy, especially in VLBW and preterm infants; however current literature still provide controversial evidence. A 2010 Cochrane review included ten studies undertaken in 8 countries for a total of 378 neonates enrolled. It evidenced a reduction in mortality in neonates with suspected and subsequently proven infection treated with IVIG [22,29].

In 2011 the INIS study, an international, placebo-controlled, multi-centerrandomized trial on 3493 infants compared the adding of standard immunoglobulins (S-IVIG) to antibiotic therapy in neonates with suspected infection to the antibiotic treatment alone [30]. It evidenced no effect on death or major disability at the age of 2 years in neonates treated with S-IVIG [30]. However, in this study some important limits are evident: a single dose of S-IVIG was given at an average age of 8 days for suspected sepsis but the primary endpoint was set at 2 years of corrected age. The trials lasted 11 years, a time interval in which, according to Vermont Oxford Network, the global rate of late onset sepsis decreased significantly. There was heterogeneity of the enrolment for clinical sepsis by physicians in very different operating contexts. Another main critical point is the exact timing of single S-IVIG supplementation in relation to sepsis onset that it is not clear. While the average admission length was 64 days and 28% of cases had two or more sepsis episodes, where immunoglobulins were administered just one time! That might have been represented a significant confounder for outcomes set both at discharge and at 2 years of corrected age considering the serum half-life of exogenous immunoglobulins. Finally, the authors do not explain why they did not consider IgM enriched IVIG (IgM-IVIG) for their investigation that have a stronger biological rationale and might have been a better choice to test in this contest [31]. Despite these limits, given the preponderant weight of this study, the 2013 and 2015 Cochrane update on passive immunotherapy for neonatal sepsis conclude not recommending the use of sIVIG [32].

### **IGM-Enriched Immunoglobulins as Adjuvant Therapy in Sepsis**

The use of Pentaglobin, an IgM/IgA-enriched, chemically modified IVIG preparation, as adjuvant treatment in sepsis has a stronger rational than S-IVIG: in vitro essay showed that thanks to the pentameric structure IgM-IVIG

presents higher antimicrobial and opsonization activity, an improved activation of complement and contain an elevated titer of antibody IgM, IgA, IgG against both Gram- and Gram+ organism [33].

The mode of action of polyvalent immunoglobulin is complex, including neutralization of toxins and modulation of complement activation and cytokine formation toward an anti-inflammatory profile. In an *E. coli*-model of pig sepsis, *in vitro* experiments showed a higher binding affinity for IgM and IgA to LPS than for IgG and LPS-induced formation of IL-6 was significantly attenuated by Pentaglobin in an *in vitro* whole blood model. Also IL-1 $\beta$ , the key inflammation molecule, was decreased [34].

A recent *in vitro* study also evidenced an increased protective efficacy against some bacterial strains, such as *Staphylococcus aureus*, of preparations with IgM Ig, probably due to antibodies directed against cell wall carbohydrates [35].

*In vivo* studies showed that this therapy enhances oxidative burst, decreases endothelial damage and liver and spleen colonization in models with Gram-bacteremia [36]. This passive immunotherapy showed encouraging results in adult human patients with sepsis: an important reduction in mortality and in severity illness score (APACHE score), an improvement of the survival in surgical ICU patients [37,38] and a decrease of procalcitonin levels and days with fever in patients with post-surgical infections [39]. IgM-IVIG presents a promising adjuvant therapy also economically, as demonstrated by a recent cost-effectiveness analysis [40]. The 2013 Cochrane update reviewed seven studies (n=528) showing a significant mortality reduction in treated septic patients compared to placebo or to no intervention [relative risk (RR) 0.81; 95% confidence interval (CI) 0.70-0.93 and RR 0.66; 95% CI 0.51-0.85, respectively] [41].

The potential role of IgM enriched IVIG in the treatment of infections is also demonstrated by some new studies on the use of BT086, a predominantly IgM IVIG solution (23% of all immunoglobulins are IgM). Shmygalev et al recently evidenced that the IgM-enriched IVIG has the potential to improve host defense in a rabbit model of endotoxemia and systemic sepsis [42]. The CIGMA study, a multicenter, randomized, placebo-controlled, double-blind, phase II study has the aim to determine the efficacy and safety of BT086, an IgM-enriched immunoglobulin preparation, as an adjunctive treatment in mechanically-ventilated patients with severe community-acquired pneumonia. The results of this study will give an overview of the efficacy of IgM enriched IVIG in the treatment of severe acquired infection in the adult population [43].

Newer evidences in adults have recently been published. Bermejo-Martin et al. [44] showed that low levels of endogenous IgG1, IgM and IgA relate to decreased survival in patients with severe sepsis suggesting the synergistic effect of different isotype of immunoglobulins

to be protective against sepsis. Giamarellos-Bourboulis et al. [45] in a prospective study showed that IgM decreased when patients deteriorated from severe sepsis to septic shock, the distribution of IgM over time was significantly greater for survivors than for non survivors and production of IgM by peripheral blood mononuclear cells was significantly lower at all stages of sepsis compared with healthy controls. Recently, in 2016 a retrospective study showed in 100 adults that IgM-IVIG added to antimicrobial treatment for septic shock caused by multidrug-resistant Gram-negative bacteria are associated to reduction of 28 days mortality [46]. These interesting and new results suggest a new direction for treatment of critical septic patients where the Ig replacement may be part of a personalized therapeutic approach [47].

The role of IgM-IVIG in neonates is still unclear: Haque et al. [48] compared the use of S-IVIG and IgM-IVIG finding a significant reduction of mortality in the group treated with IgM-IVIG respect to the group treated with S-IVIG and controls with a more rapid normalization of laboratory parameters in IgM-IVIG group. In a preceding study the same authors evidenced a decrease of mortality in neonates (GA 28-37 weeks) with suspected sepsis treated with IgM-IVIG versus placebo [49]. Erdem et al. [50] reached a negative result, but their study presented an underpowered cohort (n=40). The same negative result was published by Akdag et al. [51] in a small trial inducing the 2015 Cochrane review by Ohlsson et al. [52] not to recommend IgM-IVIG as routine adjuvant therapy in neonatal sepsis and to discourage further studies. We underline that in the study of Akdag et al. [51] although it is a prospective, controlled study, the sample size was calculated on the incidence of mortality for NEC (that is approximately zero among term infants), both premature and term neonates were enrolled with proven or suspected sepsis, the cohort enrolled was underpowered (70%), while positive blood culture was confirmed only in 37% of controls and 45% of neonates treated with IgM-IVIG.

Our group published a recent study on IgM-IVIG as supplementary therapy in addition to antibiotic treatment in VLBW neonates with late onset sepsis with positive blood culture [53]. Our population was composed of 79 VLBW, 40 patients received IgM-IVIG in association to antibiotics and 39 received antibiotic treatment alone. The population was homogeneous for birth weight, gestational age and SNAP II score (risk of mortality score). IgM-IVIG treated infants had a significantly lower short-term mortality than the control group (OR 0.16; 95% CI: 0.3-0.7, p=0.005). In a subgroup analysis of sepsis by *Candida* spp. were found fewer short term deaths in the immunoglobulin treated group: 10% of deaths in treated group versus 53% in the untreated one (OR 0.1; 95% CI: 0.01-0.97, p=0.047). Our study in a selected restricted population, showed a significant reduction of short-term mortality in VLBW infants with proven sepsis according recent adults study and the earliest neonatal studies on

the topic [46]. Our most frequent pathogen was candida; IgM-IVIG proved to be effective against fungi and this new evidenced is likely related to the action of antibodies against disseminated candidiasis, in effect, antibody opsonization is critical to Candida phagocytosing and killing by neutrophils and monocytes [54]. Short-term mortality has been considered as primary outcome because serum half-life of exogenous IgG and IgM is respectively around two weeks and one week with a wide range of IgG and IgM kinetics in the healthy VLBW and ELBW infants [55]; consequently, the benefit of this type of treatment cannot be evaluated in a long period. Also, mortality at discharge is influenced by many other variables [3]. We provide a homogeneous patient population of very low birth weight neonates and certainly affected by systemic infection, differently from Akdag et al. [51] where the demonstrated short-term benefit has a strong biological rationale. The retrospective character of our approach is an obvious and significant limitation. Another key point of our study according to Berlot et al. [56] and Cavazzuti et al. [57] is the timing of IgM-IVIG supplementation that is associated to reduction of mortality when Ig are administered in the first 24 h of sepsis onset (each 24 h of delay is associated with increased mortality of 2.8%) as we did, together with the beginning of antibiotics, differently from INIS study in which it is not clear when the antibiotic therapy and IgG were started after the diagnosis of sepsis.

Recently Abbasoglu et al. [58] in 2014 published a similar study on the role of IgM-enriched immunoglobulins in culture proven septic preterm VLBW neonates. In this study 63 neonates with culture proven sepsis were evaluated, 31 infants treated with antibiotics alone and 32 treated with antibiotics plus IgM-IVIG immunoglobulins. The study revealed that mortality in the treated group was almost the half than the control one [58,59]. Nevertheless, the authors concluded that adjuvant IgM-enriched IVIG treatment had no supplementary advantage in neonatal sepsis, especially in Gram-positive cases, because the statistical analysis did not meet the set threshold for statistical significance. In a post hoc analysis for the setting described, we found that the study power is only 35%, with a minimum of 97 patients for each group to reach power of 80% and  $\alpha$  error=0.05 for the same mortality reduction. The author achieved a drastic conclusion considering that it is drawn from a retrospective underpowered study.

## Conclusion

Given the enormous levels of morbidity and mortality caused by neonatal sepsis, IgM-enriched immunoglobulins may represent a successful therapy for neonatal sepsis in an era of rampaging resistance to antibiotics. Current recommendations on neonate advice against this strategy, irrespectively of patient age or immunoglobulin preparation based on relatively small number of papers that have either a small power and weak design or disputable primary outcomes. On the other hand, very recent data on critical septic adults seems to drive to the opposite conclusion.

The only way to solve this enigma is a properly designed prospective trial where IgM-IVIG could be consistently used if needed in a well-individualized population throughout the NICU admission to appropriately evaluate its effect on mortality at discharge

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