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# Immunoglobulins in the Prevention and Treatment of Neonatal Sepsis

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<http://dx.doi.org/10.5772/54538>

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## 1. Introduction

It is a daily challenge and the most common clinical practise to rule out possible bacterial infection in the ill neonate and especially in the preterm infant. Approximately half of all newborn infants admitted to the neonatal ward carry a diagnosis of “rule-out sepsis”, and diagnosis is often difficult as symptoms and signs of bacterial infection are subtle and nonspecific (1). The incidence of infection is higher in the neonatal period than at any other time of life, and factors that determine this increased susceptibility to bacterial infection include on the one hand the immaturity of the immune system with poor humoral responses to organisms (IgG and A), relatively poor neutrophil responses and complement activity, impaired macrophage function, and relatively poor T cell function, and on the other hand the exposure to microorganism from the maternal genital tract by ascending infections via the amniotic fluid or transplacental haematogenous spread. Additionally peripartum factors like trauma to skin or vessels during parturition or exposure to invasive obstetric procedures as well as portals of colonization and subsequent invasion (umbilicus, mucosal surfaces, eye, skin especially in very preterm infants) contribute to this increased risk for bacterial infection (2). Among extremely low birth weight infants at least 65% had one or more infections during their hospitalization in a National Institute of Child Health and Human Development Neonatal Research Network study including 6093 infants with follow-up at 18 to 22 months of corrected gestational age. Compared with uninfected infants infected infants were significantly more likely to have adverse neurodevelopmental outcomes at follow-up, including cerebral palsy (range of significant odds ratios [ORs], 1.4-1.7), low Bayley Scales of Infant Development II scores on the mental development index (ORs, 1.3-1.6) and psychomotor development index (ORs, 1.5-2.4), and vision impairment (ORs, 1.3-2.2). Infection in the neonatal period was also associated with impaired head growth, a known predictor of poor neurodevelopmental outcome (3). Reasons for the greater susceptibility to infection of preterm infants also include invasive procedures during

their stay at the NICU, prolonged artificial ventilation, intravenous feeding and antibiotic pressures. (2). The incidence is estimated to range from 1 to 5-8.1 per 1000 live births (2,4). The proportion of child deaths that occurs in the neonatal period (38% in the year 2000) is increasing, and the Millennium Development Goal for child survival cannot be met without substantial reductions in neonatal mortality. Every year an estimated 4 million babies die in the first four weeks of life (the neonatal period), and, globally, the main direct causes of neonatal death are estimated to be preterm birth (28%), severe infections (26%), and asphyxia (23%) (5).

## 2. Pathophysiology of neonatal sepsis

The immune system of the neonate is immature in both humoral and cell mediated defense with prematurity further increasing the physiological inadequacies of the immune system. Sepsis spreads easily to the various organ systems in the neonates and thus, often presents as a multiorgan dysfunctions syndrome. Infection initiates a complex immune process, which includes antigen detection, T-cell activation and proliferation, and release of cytokines. Cytokines are low molecular mass proteins, which mediate cell growth, inflammation, immunity, differentiation, migration and repair. They regulate the amplitude and the duration of the inflammatory response and include interleukins-6 and -8, interferons- $\gamma$ , colony-stimulating factors, tumour necrosis factor- $\alpha$  and others. However in the setting of overwhelming sepsis as a result to the microbial insult, these cytokines give rise to what is described as the systemic inflammatory response syndrome, where the much of the damage paradoxically results from the host defences (e.g. cytokines) analogous to a chain reaction themselves. The neutrophil functions: adhesion, diapedesis, phagocytosis and degranulation are also of prime importance in the host defence mechanisms against bacterial and fungal pathogens. The proteolytic enzymes released by the neutrophils are also damaging to the host tissue. Thus, immunoglobulins and neutrophils are responsible for both host defence and damage in the setting of overwhelming neonatal sepsis (6).

In 2005, definitions for paediatric infection, systemic inflammatory response syndrome, sepsis, severe sepsis, septic shock, and organ dysfunction were published that included term neonates of 0 to 7 days and newborns of 1 to 4 weeks of age (7). But one has to question why there are no criteria for the definition of sepsis and septic shock in preterm infants? The challenge of diagnosis of sepsis in the preterm infants is strongly associated with the immaturity of organ systems and transitional physiology. Suggested modifications of these definitions have recently been published (8) but still have to be proven in clinical trials (9).

## 3. Immunoglobulins and the innate immune response

Humoral immunity of the human newborn is provided primarily by maternal immunoglobulin G (IgG) transferred transplacentally, beginning at 8 to 10 weeks of gestation and accelerating during the last trimester. In a study to evaluate the role of maternally acquired antibody to native type III polysaccharide of group B *Streptococcus* as a determinant of susceptibility for infant systemic infection the authors found a significant

correlation with maternal antibody levels in 111 acutely ill infants (10). These data extended earlier observations suggesting the correlation between low levels of type-specific antibody in serum and risk for systemic infection in neonates. Premature infants, compared to full-term infants, have lower levels of IgG at birth that further decreases during the first few weeks of life (11). The relative deficiency of humoral immunity in premature newborns might contribute to the inverse correlation of birth weight and rate of neonatal sepsis, with an 86-fold increased rate of sepsis in newborns of birth weight 600 to 999 grams compared to newborns of birth weight of more than 2500 grams (11). Ballou et al. (12) measured plasma immunoglobulin concentrations of premature infants of birth weight less than 1500 g longitudinally from birth to 10 months chronological age. During the first week of life plasma IgG levels correlated well with gestational age. At the age of three months mean plasma IgG levels were 60 mg/dl in infants of 25 to 28 weeks gestational age and 104 mg/dl in those of 29 to 32 weeks. Most infants remained hypogammaglobulinaemic at six months with 64% and 62%, respectively, of the infants having plasma IgG levels below 200 mg/dl. Plasma IgM concentrations were low in both groups during the first week of life (7.6 and 9.1 mg/dl, respectively) and rose to 41.8 and 34.7 mg/dl, respectively, by eight to ten months of life. IgA concentrations were comparable for both groups during the first week of life (1.2 and 0.6 mg/dl, respectively). After discharge Ballou et al. (12) followed 43 preterm infants until ten months chronological age and observed a significantly higher incidence of infections compared to 41 term infants ( $p = 0.04$ ). In another study the level of maternal antibody required to protect neonates against early-onset disease caused by group-B streptococci (GBS) type Ia was estimated (15). Levels of maternal serum IgG GBS Ia antibodies of 45 neonates with early onset disease case caused by GBS Ia and 319 control subjects (neonates colonized by GBS Ia but without early-onset disease) born at  $\geq 34$  weeks gestation were compared. The probability of developing infection declined with increasing maternal levels of IgG GBS Ia antibody ( $P < .03$ ). Neonates whose mothers had levels of IgG GBS Ia antibody  $\geq 5$  mg/mL had an 88% lower risk (95% confidence interval, 7%–98%) of developing type-specific early-onset disease, compared with those whose mothers had levels  $< 0.5$  mg/mL (13).

Yang et al. (14) studied the mechanism of bacterial opsonization by intravenous immune globulin (IVIG) complement consumption and polymorphonuclear leukocyte membrane receptor mediated phagocytosis of *Staphylococcus epidermidis*, *Klebsiella pneumoniae*, and groups A and B streptococci. IGIV alone did not consume complement and showed no opsonic activity by itself for these organisms. When these bacteria were preopsonized in intravenous immune globulin, significant amounts of complement were consumed (44%–94%) and the uptake and killing of bacteria occurred. An important finding was the fact that in vitro opsonic activity of IGIV for these organisms was significantly correlated with the amount of complement consumed by the IVIG – opsonised bacteria. The in vivo protective efficacy of IVIG also appeared to be directly associated with its ability to activate and consume complement. The higher the titers of the IVIG preparation are (higher than 200 units:ml) the more opsonic activity has been shown towards slime-producing *S. epidermidis* (15). Administered as a prophylactic agent to low-birth weight (lower than 1700 g) preterm neonates immediately after birth revealed significantly higher specific IgG in blood sera

compared to controls with an effect even lasting ten days after the last infusion. These results suggest that specific IgG titers might be well indicative of its opsonic activity against slime-producing *S. epidermidis* and might protect against bacteraemia.

The complement-inhibitory activity of different IVIG preparations was assessed in vitro by measurement of the blocking of C1q-, C4-, and C3 deposition on solid-phase aggregated rabbit IgG by enzyme-linked immunosorbent assay (16). Results showed that IgM enrichment of IVIG preparations enhances their effect to prevent the inflammatory effects of complement activation. No IgG preparation negatively affected in vitro phagocytosis of *Escherichia coli* by human granulocytes.

The mechanisms and effects of IVIGs are summarized in table 1 according to the description of Ballow (17).

<ul style="list-style-type: none"><li>• Fc receptor blockade of reticulo-endothelial cell system and mononuclear phagocytes<ul style="list-style-type: none"><li>• Competitive interaction of IVIG with anti-platelet antibodies for FC receptor</li><li>• Soluble Fcγ receptors compete with membrane Fc receptors of the reticulo-endothelial system</li></ul></li><li>• Modulation of Fc receptor expression or affinity</li><li>• Immunomodulation<ul style="list-style-type: none"><li>• Enhancement of T cell suppressor function</li><li>• Inhibit B cell function and/or antigen-processing cells via Fc receptor</li></ul></li><li>• Restoration of idiotype-antiidiotypic network</li><li>• Modify complement-dependent immune damage to tissue and cells</li><li>• Inhibit cytokine/interleukin production/action</li><li>• “Neutralize” toxin superantigen</li><li>• Soluble CD4 and CD8, soluble HLA Class II molecules that modulate antigen processing and/or T cell activation</li></ul>
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**Table 1.** Mechanisms of action of intravenous immune globulins (17)

Similar to most immunoglobins, the transplacental transport of IgG from the mother to fetus begins around 32 weeks of gestational age and increases until term. Premature infants born prior to 32 weeks gestation have profound IgG deficiencies. The major function of IgG in host defense is to opsonize bacteria and neutralize viruses. Levels of postnatal IgG are often low due to insufficient production by the immature neonatal immune system and catabolism of maternal IgG. Opsonic activity is also type-specific; therefore humoral immunity transferred to the neonate will be insufficient if the mother does not have immunity to the specific pathogen (18).

4. Immunoglobulins in neonates

Immunotherapy was a common method of treatment of infectious diseases in the preantibiotic era with serotherapy being a popular approach to serious infections by use of antisera from large animals. This administration unfortunately was associated with the risk



of anaphylaxis and serum sickness. Further on immune globulins obtained from pooled human plasma were used, but antibodies provided by these preparations always represented those common to the donor population, and intravenous injection of early human IgG preparations was complicated by severe allergic reactions (19). The next step was the purification of human immune globulins, and, currently there are multiple formulations of safe, pooled, human immunoglobulins for the intravenous use.

The mortality rate of the preterm infants with septicaemia decreased from 44% in the infants receiving only antibiotics to 8% in the infants treated by IVIG together with the same antibiotic following administration of IVIG to preterm neonates (0.3 g/day in neonates below 1000 g; 0.5 g/day in neonates over 1000 g for 6 consecutive days). The IVIG preparation was well-tolerated by all newborns, and no adverse events were observed by monitoring blood gas analysis, clinical examination, monitoring of respiration, pulse and body temperature. Follow-up at an average age of 2.5 years showed no evidence of harmful effects of IVIG treatment in the neonatal period (20).

Cates et al. (21) evaluated the formation of specific and functional antibody in preterm infants born weighing less than 1500 g (mean 1088 g) and less than 32 weeks of gestational age (mean 28.8 weeks). In the presence of complement, the strain of coagulase negative staphylococcus used was opsonized by IgG antibody, and the strain of *Escherichia coli* by IgM. Geometric mean plasma levels of tetanus and diphtheria IgG antibody fell from birth to 4 months chronological age, but rose significantly by 9 months (approximately 2 months after the third dose of diphtheria, tetanus, pertussis vaccine). However, at 9 months they remained lower than the respective geometric mean levels in 9-month-old term infants. The preterm infants' mean plasma IgG staphylococcal opsonic activity fell from birth to 2.5 months, but by 9 months was comparable to that of term infants of the same age. Mean IgM opsonic activity for *Escherichia coli* was very low at birth in both preterm and term infants. It rose with chronological age, correlating with the rise in total IgM by 9 months the mean preterm and term infants' levels of IgM opsonic activity for *E. coli* were comparable.

Sasidharan (22) studied serially IgG levels postnatally in 42 infants of very low birth weight with gestational ages ranging from 23 to 31 weeks (mean birth weight 971 g). Eighteen infants (43%) had IgG levels of less than 100 mg/dl by a mean postnatal age of 71 days. The lowest level was found in a 700g infant with 22 mg/dl. In sixteen cases having cord blood IgG levels determined mean IgG values was 414 mg/dl. This had dropped to a mean of 140 mg/dl by 57 days. As expected, the lowest IgG levels postnatally were a reflection of the degree of prematurity and the length of postnatal age.

To prove the significance of low serum IgG and complement proteins in very low birth neonates Lassiter et al (23) measured serum IgG, C3, C4 and Factor B weekly by rate nephelometry in 15 neonates who developed proven nosocomial bacterial or candidal sepsis and 27 neonates who did not develop sepsis. In the first and second week of life the serum IgG of infected neonates was significantly lower (mean 295 and 270 mg/dl compared to 440 and 473 mg/dl, respectively). If the IgG was less than 350 mg/dl in the first week or less than 230 mg/dl in the second week, the relative risk of acquiring sepsis was greater than or equal to 5 (CI 95% 1.7 to 11.2).

Amato et al. (24) investigated serial IgG and IgM serum levels during the neonatal period in two groups of non-septic, preterm infants treated prophylactic with IVIG. Twenty-two very low birth weight infants (mean gestational age 31.8 weeks and mean birth weight 1265 g with a range of 1001 - 1500g) and 12 extremely low birth weight infants < 1000g (mean gestational age 28.6 weeks and mean birth weight 910g) received at random three standard doses of IVIG (0.5 g/kg/day) or IVIGAM (IgM enriched preparation) (5 ml/kg/day). IgG and IgM concentrations were assayed by rate nephelometry before treatment and at day 3, 5, 7, 14 and 28 of life. At any time IgG levels were higher in the IVIG very low birth weight group and no difference was observed in the extremely low birth weight group. IgM levels were higher at day 3 and 5 in the IVIGAM very low birth weight group and until day 7 in the extremely low birth weight group. The authors concluded that their findings indicate a wide range of IgG and IgM kinetics in the healthy premature infant.

Supplementation of the preterm serum with either intravenous immunoglobulin or IgM-enriched immunoglobulin did not change the results of phagocytosis rates (percentage of neutrophils phagocytosing group B streptococci in vitro in infants < 32 weeks of gestation and adult controls) significantly (25).

In a rat model marked neutropenia, complete depletion of the neutrophil storage pool, and death within 48 hours were observed in newborn rats intrapulmonically inoculated with type III group B streptococci (26). Intraperitoneal administration of 225 mg of IVIG immediately after intrapulmonic inoculation of GBS significantly lessened the degree of neutropenia and prevented depletion of the neutrophil storage pool and death. No effect of IVIG on neutrophil production was observed in vitro or in vivo in normal neonatal rats injected with IVIG. IVIG, however, markedly hastened release of neutrophils from the reserves into the blood and hastened the arrival of neutrophils at the site of the bacterial injection. Specific antibody to GBS, as opposed to a nonspecific IgG effect, appeared to be responsible for the improvements in neutrophils kinetics and for survival of the animals.

In animal experiments following administration of IVIGAM endotoxemia was induced by intraperitoneal inoculation of a sublethal dose of *Escherichia coli* and subsequent intravenous administration of an antimicrobial agent (27). Prophylactic administration of IVIGAM was found to significantly attenuate the antibiotic-induced increase in endotoxin activity as compared to the albumin control group. These experimental results suggested that in endotoxaemia the polyclonal immunoglobulin preparation had a prophylactic protective effect on the acute phase responses and reduced the cardiodepressant effects of *Escherichia coli* septicaemia.

The pharmacokinetics and safety of IVIG were examined in thirty neonates with suspected sepsis who were randomly assigned either to a treatment (receiving either 250, or 500, or 1,000 mg/kg of IVIG plus antibiotics) or control (antibiotics alone) group (28). The 500 mg/kg dose produced a rise in total IgG for greater than 8 and in group B streptococcus type-specific IgG for greater than 4-14 days. The type-specific antibody elevation varied with the amount of pathogen-specific antibody and dose of IVIG. Pharmacokinetic analysis suggested a biphasic elimination curve and a terminal elimination half-life of 24.2 days. No toxicity was observed (28).

Prophylactic IVIG at a dose of 0.5 g/kg/day was given prospectively in 28 healthy preterm infants with a mean gestational age of 29.4 weeks and weight of 1,387g when they were 3-10 days old (29). Urine samples of the neonates were obtained for analysis on days 1, 2 and 3 following IVIG administration as well as 1 day before; and urinary nitrite levels were  $2.77 \pm 1.66$   $\mu\text{mol}/\text{mmol}$  creatinine before IVIG administration;  $4.33 \pm 3.88$   $\mu\text{mol}/\text{mmol}$  creatinine on the 1st;  $3.77 \pm 2.73$   $\mu\text{mol}/\text{mmol}$  creatinine on the 2nd, and  $3.64 \pm 3.28$   $\mu\text{mol}/\text{mmol}$  creatinine on the 3rd day. The increase of urinary nitrite levels was significant between before and after IVIG administration, thereafter levels did not differ significantly, suggesting that endogenous NO formation might play an important role in both the therapeutic and adverse effects of IVIG (29).

## 5. Use of immunoglobulins in the treatment of neonatal sepsis

Polyvalent immunoglobulin preparations are widely used as adjunctive therapy for sepsis or septic shock, but their efficacy is still a matter of debate. In 2007 Kreymann et al. (30) conducted a systematic review summarizing data on adults and neonates separately. In neonates, 12 trials (31-42) involving 710 patients were published. The estimate of the pooled effect on mortality was  $\text{RR} = 0.56$  (95% CI 0.42– 0.74,  $p < .0001$ ). Five studies (32,35,37,39,41) involving 352 patients were performed with the IgGAM preparation. The range of the cumulative dose of IgG was 0.57– 0.76 g/kg birth weight plus 0.09–0.12 g/kg birth weight IgA and 0.09–0.12 g/kg birth weight IgM. In this subgroup, the estimate of the pooled effect was  $\text{RR} = 0.50$  (95% CI 0.34–0.73), equivalent to a 50% relative reduction in mortality ( $p < .0003$ ). The study effects were comparable, and the test of heterogeneity was not significant. The study of El Nawawy (32) reported a significant reduction of mortality, the other four a positive trend (35,37,39,41). Polyvalent immunoglobulin preparations containing only IgG were evaluated in seven trials (31,33,34,36,38,40,42) involving 358 patients. The cumulative dose of IgG was 0.5–3 g/kg birth weight. The estimate of the pooled effect for this subgroup was  $\text{RR} = 0.63$  (95% CI 0.42– 0.96), equivalent to a 37% relative reduction in mortality ( $p < .03$ ). The test of heterogeneity was not significant. One study (38) reported a significant reduction in mortality, three studies reported a positive trend (31,33,42), and two studies (34,40) showed no effect. One trial (36) showed a duplication of mortality; one neonate died in the control group and two in the treatment group. Comparing the two treatment modalities, a small and insignificant difference in favour of IgGAM was observed ( $z = 0.80$ ,  $p \leq .42$ ). Kreymann et al. (30) found a negative correlation with the severity of illness (as measured by the mortality of the control groups) in neonates; however, this held true only when the results reported by Chen (36) were included: In this study, an exceptionally low mortality in the control group was observed (1 of 28, respectively, 3.6%), which was doubled in the treatment group (2 of 28, respectively, 7.1%). If these results were omitted, the correlation lost significance. Additionally the authors found no correlation with the dosage of immunoglobulins administered.

In adults and children, Kreymann et al. (30) found a strong trend in favour of IgGAM over IgG preparations with a 34% and 15% reduction of the risk to die, respectively, compared to an even higher 50% and 37% relative reduction of mortality in neonates, respectively. In



neonates and especially preterm infants, therapy with polyclonal immunoglobulins should be understood much more as a substitutional therapy than as an adjunctive therapy as for adults or older children (43). Comparing the two treatment modalities (IgGAM vs. IgG) in neonates, Kreymann et al. (30) only found a slight difference without statistical significance. A major limitation of this meta-analysis is the inclusion of the study of El Nawawy (32), who originally included infants of 1 to 24 months of age hospitalized at a pediatric intensive care unit, of which 50 were proven septic patients. This study strongly influenced study results favouring immunoglobulin therapy.

Ohlsson and Lacy (44) recently reviewed IVIG for suspected or subsequently proven infection in neonates including randomized or quasi-randomized controlled trials comparing IVIG treatment to placebo or no intervention in newborn infants below 28 days of age. They found 10 studies meeting their inclusion criteria that differed to the above mentioned analysis (30) by additional including the small study of Christensen et al. (45) and a new study by Ahmend et al. (46) and not including the studies by El Nawawy (32), Gökalp (38), and Gunes (31). The results showed a statistically significant reduction in mortality in cases of proven and also of suspected infection with a NNT of 10 infants (95% CI; 6, 33) to avoid one death.

IVIG preparations with high concentrations of antibodies to bacteria that are commonly isolated from neonates in specific local settings or geographical areas may be more effective in reducing adverse outcomes (44). However, the use of antistaphylococcal immunoglobulins to prevent staphylococcal infection in very low birth weight infants has recently been reviewed and is currently not recommended (47).

A very recent study published by the International Neonatal Immunotherapy Study (INIS) Collaborative group enrolled 3493 infants with birth weight less than 1500g receiving antibiotics for suspected or proven serious infection and randomly assigned them to receive two infusions of either IgG immune globulin (at a dose of 500 mg per kilogram of body weight) or matching placebo 48 hours apart (48). The researchers found no significant between-group difference in the rates of death or major disability at the age of two years (39 and 39%, respectively). Similarly, there were no significant differences in the rates of secondary outcomes including the incidence of subsequent sepsis episodes. In the 2-years follow-up of the study participants there were no differences in the rates of major or non-major disability or of adverse events. Thus, IgG IVIG was not found to be helpful in diminishing the risk of major complications or adverse outcomes in neonates with suspected or proven sepsis. The duration of hospital stay also did not differ between groups (48).

The clinical efficacy of IgM-enriched IVIG (currently there is only one preparation available, Pentaglobin®) has been reviewed by Norrby-Teglund et al. (49) for both adult and paediatric/neonatal patients. The authors concluded that patients most likely to benefit are Gram-negative septic shock patients. Therefore it is important to emphasize that selection of study patients as well as microbiological aetiology are of high relevance affecting the efficacy of IVIG.

## 6. Use of immunoglobulins in the prevention of neonatal sepsis

There have been published a lot of studies and reviews on the preventive use of IVIG in preterm infants and I herewith report ("pars pro toto") two multicenter randomized, double-blind, placebo-controlled trial published early in the New England Journal of Medicine (50,51) with divergent results and the latest Cochrane Review (52).

Baker et al. (50) included 588 infants with a birth weight of 500 - 1750 g and age of 3 - 7 days from six centres in the U.S. between 1987 and 1988. The trial was randomized, double-blind, placebo-controlled with 287 infants having received 500 mg/kg of IVIG at enrolment (age 3 to 7 days), one week later, and then every 14 days until a total of five infusions had been given or until hospital discharge, whichever came first, and 297 controls having received an equal volume of a sterile solution of 5 % albumin and 0.9 % sodium chloride. Outcomes included proven infection - clinical findings of sepsis and at least one of the following: a positive blood culture of either bacteria or fungi (the isolation of a pathogen from a normally sterile other body site or urine obtained by suprapubic or bladder catheterization, or the isolation of virus from an infant with clinical deterioration), necrotizing enterocolitis stage II or III, intraventricular haemorrhage grade 1 to 4, bronchopulmonary dysplasia, death, and total days in hospital. There were 50 episodes of sepsis among 287 infants (17.4%) in the IVIG group and 75 episodes of sepsis among 297 infants (25.3%) in the placebo group. The cumulative relative risk reduction was 0.7 (CI 95% 0.5-0.9).

In a prospective, multicenter, two-phase controlled trial, Fanaroff et al. (51) stratified 2416 infants according to birth weight (501 to 1000 g and 1001 to 1500 g) and randomly assigned to an IVIG (n = 1204) or a control group (n = 1212). Control infants were given placebo infusions during phase 1 of the study (n = 623) but were not given any infusions during phase 2 (n = 589). Infants weighing 501 to 1000 g at birth were given 900 mg of immune globulin per kilogram of body weight, and infants weighing 1001 to 1500 g at birth were given a dose of 700 mg per kilogram. The immune globulin infusions were repeated every 14 days until the infants weighed 1800 g, were transferred to another center, died, or were sent home from the hospital. Nosocomial infections of the blood, meninges, or urinary tract occurred in 439 of the 2416 infants (18.2 %): 208 (17.3 %) in the immune globulin group and 231 (19.1%) in the control group (relative risk, 0.91; CI 95% 0.77 to 1.08). Septicemia occurred in 15.5% of the immune globulin recipients and 17.2% of the controls. The predominant organisms included gram-positive cocci (53%), gram-negative bacilli (22.4%), and candida species (16%). Adverse reactions were rarely observed during the infusions. Immune globulin therapy had no effect on respiratory distress syndrome, bronchopulmonary dysplasia, intracranial hemorrhage, the duration of hospitalization, or mortality. The incidence of necrotizing enterocolitis was 12% in the immune globulin group and 9.5% in the control group. Thus, the authors concluded that the prophylactic use of IVIG failed to reduce the incidence of hospital-acquired infections in very-low-birth-weight infants (51).

The prophylactic administration of intravenous immunoglobulins (IVIG) to prevent nosocomial infections has been studied in >5,000 neonates from 19 studies enrolled in randomised controlled trials (52). The results of these meta-analyses showed a statistically

significant reduction in sepsis (number needed to treat – NNT - 36) and/or any serious infection (NNT 31), but no reduction in mortality from infection. The reviewers concluded that IVIG administration resulted in a 3% reduction in sepsis and a 4% reduction in any serious infection of one or more episodes. Nevertheless it was not associated with reductions in other important outcomes including necrotizing enterocolitis intraventricular haemorrhage, or length of hospital stay. Most importantly, IVIG administration did not have any significant effect on mortality from any cause or from infections. There were no adverse events observed to be associated with prophylactic use of IVIG. From a clinical perspective a 3-4% reduction in nosocomial infections without a reduction in mortality or other important clinical outcomes might be of marginal importance and has to be outweighed by the costs and the values assigned to the clinical outcomes (52). This Cochrane review ends with the statement that there is no justification for further randomized trials testing the efficacy of previously studied IVIG preparations to reduce nosocomial infections in preterm and/or low birth weight infants. In contrast, these results should encourage basic scientists and clinicians to pursue other avenues to prevent nosocomial infections (52).

## 7. Conclusions

There is a rational to use of IVIG in either adjunctive treatment neonatal sepsis or in the prevention by low immunoglobulin levels associated with the immature innate immune system of preterm infants. Studies so far revealed a benefit for IgM enriched IVIG in the use as adjunctive sepsis treatment by an overall significantly reduced mortality rate. Prophylactic use of IVIG resulted in marginally reduced rates of nosocomial infections, and other non-invasive approaches like use of lactoferrin (53) and/or probiotics (54) seem to be more promising in the prevention of nosocomial infections in very low birth weight infants.

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## 8. References

- [1] Escobar GJ. The neonatal “sepsis work-up”: personal reflections on the development of an evidence-based approach toward newborn infections in a managed care organization. *Pediatrics* 1999;103:360–733.
- [2] Issacs D, Moxon ER. Handbook of neonatal infections, a practical guide. WB Saunders, London, Edinburgh, New York, Philadelphia, Sydney, Tokio 1999, pp1-13
- [3] Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, Higgins RD; National Institute of Child Health and Human Development Neonatal Research

- Network. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. *JAMA* 2004;292:2357-2365.
- [4] Gerdes JS. Diagnosis and management of bacterial infections in the neonate. *Pediatr Clin North Am* 2004;51:939-959
  - [5] Lawn JE, Cousens S, Zupan J; Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: when? Where? Why? *Lancet* 2005;365:891-900.
  - [6] Shaw CK, Thapalia A, Shaw P, Malla K. Intravenous immunoglobulins and haematopoietic growth factors in the prevention and treatment of neonatal sepsis: ground reality or glorified myths? *Int J Clin Pract* 2007;61:482-487
  - [7] Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005;6:2-8.
  - [8] Wynn JL, Wong HR. Pathophysiology and treatment of septic shock in neonates. *Clin Perinatol* 2010;37:439-479
  - [9] Hofer N, Zacharias E, Müller W, Resch B. Performance of the definitions of the systemic inflammatory response syndrome and sepsis in neonates. *J Perinat Med* 2012 Jun 14;0(0):1-4. doi: 10.1515/jpm-2011-0308.
  - [10] Baker CJ, Edwards MD, Kasper DL. Role of Antibody to Native Type III Polysaccharide of Group B Streptococcus in Infant Infection. *Pediatrics* 1981;68:544-549
  - [11] Jenson HB, Pollock BH. Meta-analyses of the Effectiveness of Intravenous Immune Globulin for Prevention and Treatment of Neonatal Sepsis. *Pediatrics* 1997;99: e2 doi: 10.1542/peds.99.2.e2
  - [12] Ballou M, Cates KL, Rowe JC, Goetz C, Desbonnet C. Development of the immune system in very low birth weight (less than 1500 g) premature infants: concentrations of plasma immunoglobulins and patterns of infections. *Pediatr Res* 1986;20:899-904.
  - [13] Lin FYC, Philips III JB, Azimi PH, Weisman LE, Clark P, Rhoads GG, Regan J, Concepcion NF, Frasch CE, Troendle J, Brenner RA, Gray BM, Bhushan, Fitzgerald G, Moye P, Clemens JD. Level of maternal antibody required to protect neonates against early-onset disease caused by group b streptococcus type Ia: a multicenter, seroepidemiology study. *J Infect Dis* 2001;184:1022-1028
  - [14] Yang KD, Bathras JM, Shigeoka AO, James J, Pincus SH, Hill HR. Mechanisms of bacterial opsonization by immune globulin intravenous: correlation of complement consumption with opsonic activity and protective efficacy. *J Infect Dis* 1989;159:701-707
  - [15] Lamari F. Determination of slime-producing *S. epidermidis* specific antibodies in human immunoglobulin preparations and blood sera by an enzyme immunoassay. Correlation of antibody titers with opsonic activity and application to preterm neonates. *J Pharm Biomed Ana* 2000;23:363-374
  - [16] Rieben R, Roos A, Muizert Y, Tinguely C, Gerritsen AF, Daha MR. Immunoglobulin M-Enriched Human Intravenous Immunoglobulin Prevents Complement Activation In Vitro and In Vivo in a Rat Model of Acute Inflammation. *Blood* 1999 93: 942-951
  - [17] Ballou M. Mechanisms of action of intravenous immune serum globulin therapy. *Pediatr Infect Dis J* 1994;13:806-811

- [18] Melvan JN, Bagby GJ, Welsh DA, Nelson S, Zhang P. Neonatal Sepsis and Neutrophil Insufficiencies. *Int Rev Immunol*. 2010; 29: 315–348
- [19] Kliegman RM, Clapp DW. Rational principles for immunoglobulin prophylaxis and therapy of neonatal infections. *Clin Perinatol* 1991;18:303-324.
- [20] von Muralt G, Sidiropoulos D. Prenatal and postnatal prophylaxis of infections in preterm neonates. *Pediatr Infect Dis J* 1988;7(5 Suppl):S72-78.
- [21] Cates KL, Goetz C, Rosenberg N, Pantschenko A, Rowe JC, Ballow M. Longitudinal development of specific and functional antibody in very low birth weight premature infants. *Pediatr Res* 1988;23:14-22.
- [22] Sasidharan P. Postnatal IgG levels in very-low-birth-weight infants. Preliminary observations. *Clin Pediatr (Phila)* 1988;27:271-274.
- [23] Lassiter HA, Tanner JE, Cost KM, Steger S, Vogel RL. Diminished IgG, but not complement C3 or C4 or factor B, precedes nosocomial bacterial sepsis in very low birth weight neonates. *Pediatr Infect Dis J* 1991;10:663-668.
- [24] Amato M, Hüppi P, Imbach P, Llanto A, Bürgi W. Serial IgG and IgM serum levels after infusion of different Ig-preparations (IgG or IgM-enriched) in preterm infants. *Pediatr Allergy Immunol*. 1993 Nov;4(4):217-20.
- [25] Bialek R, Bartmann P. Is there an effect of immunoglobulins and G-CSF on neutrophil phagocytic activity in preterm infants? *Infection* 1998;26:375-378.
- [26] Redd H, Christensen RD, Fischer GW. Circulating and storage neutrophils in septic neonatal rats treated with immune globulin. *J Infect Dis*. 1988;157:705-712.
- [27] Oesser S, Schulze C, Seifert J. Protective capacity of a IgM/IgA-enriched polyclonal immunoglobulin-G preparation in endotoxemia. *Res Exp Med (Berl)* 1999;198:325-339.
- [28] Weisman LE, Fischer GW, Marinelli P, Hemming VG, Pierce JR, Golden SM, Peck CC. Pharmacokinetics of intravenous immunoglobulin in neonates. *Vox Sang* 1989;57:243-248.
- [29] Özkan H, Uzuner N, Ören H, Çabuk N, Islekel H. Urinary nitrite excretion after prophylactic intravenous immunoglobulin in premature infants. *Biol Neonate* 2000;77:101-104
- [30] Kreymann KG, de Heer G, Nierhaus A, Kluge S. Use of polyclonal immunoglobulins as adjunctive therapy for sepsis or septic shock. *Crit Care Med* 2007;35:2677-2685
- [31] Gunes T, Koklu E, Buyukkayhan D, Kurtoglu S, Karakukcu M, Patiroglu T. Exchange transfusion or intravenous immunoglobulin therapy as an adjunct to antibiotics for neonatal sepsis in developing countries: A pilot study. *Ann Trop Paediatr* 2006; 26:39–42
- [32] El Nawawy A, El Kinany H, Hamdy El-Sayed M, Boshra N. Intravenous polyclonal immunoglobulin administration to sepsis syndrome patients: A prospective study in a pediatric intensive care unit. *J Trop Pediatr* 2005; 51:271–278
- [33] Weisman LE, Stoll BJ, Kueser TJ, Rubio TT, Frank CG, Heiman HS, Subramanian KN, Hankins CT, Anthony BF, Cruess DF, et al. Intravenous immune globulin therapy for early- onset sepsis in premature neonates. *J Pediatr* 1992; 121:434–443



- [34] Shenoi A, Nagesh NK, Maiya PP, Bhat SR, Subba Rao SD. Multicenter randomized placebo controlled trial of therapy with intravenous immunoglobulin in decreasing mortality due to neonatal sepsis. *Indian Pediatr* 1999; 36:1113–1118
- [35] Samantha S, Jalalu MP, Hegde RK, et al: Role of IgM enriched intravenous immunoglobulin as an adjuvant to antibiotics in neonatal sepsis. *Karnataka Pediatr J* 1997; 1:1–6
- [36] Chen JY: Intravenous immunoglobulin in the treatment of full-term and premature newborns with sepsis. *J Formos Med Assoc* 1996; 95:839–844
- [37] Seitz RC, Tureson M, Grosse R, et al: Infusion of immunoglobulins for therapy of neonatal sepsis. *Z Geburtshilfe Perinatol* 1995; 199:288
- [38] Gökalp AS, Toksoy HB, Turkey S, Bakici MZ, Kaya R. Intravenous immunoglobulin in the treatment of *Salmonella typhimurium* infections in preterm neonates. *Clin Pediatr (Phila)* 1994; 33:349–352
- [39] Erdem G, Yurdakok M, Tekinalp G, Ersoy F. The use of IgM-enriched intravenous immunoglobulin for the treatment of neonatal sepsis in preterm infants. *Turk J Pediatr* 1993; 35: 277–281
- [40] Mancilla-Ramirez J, Gonzalez-Yunes R, Castellanos-Cruz C, García-Roca P, Santos-Preciado JI. Intravenous immunoglobulin in the treatment of neonatal septicemia. *Bol Med Hosp Infant Mex* 1992; 49:4–11
- [41] Haque KN, Zaidi MH, Bahakim H: IgMenriched intravenous immunoglobulin therapy in neonatal sepsis. *Am J Dis Child* 1988; 142:1293–1296
- [42] Sidiropoulos D, Böhme U, von Muralt G, Morell A, Barandun S. Substitution of immunoglobulins for the treatment of neonatal sepsis. *Schweiz Med Wochenschr* 1981; 111:1649–1655
- [43] Bell SG: Immunomodulation, part III: Intravenous immunoglobulin. *Neonatal Netw* 2006; 25:213–221
- [44] Ohlsson A, Lacy J. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. *Cochrane Database of Systematic Reviews* 2010, Issue 3. Art. No.: CD001239. DOI: 10.1002/14651858.CD001239.pub3.
- [45] Christensen RD, Brown MS, Hall DC, Lassiter HA, Hill HR. Effect of neutrophil kinetics and serum opsonic capacity of intravenous administration of immune globulin to neonates with clinical signs of early-onset sepsis. *Journal of Pediatrics* 1991;118: 606–614.
- [46] Ahmed SS, Chowdhury MAK, Hoque MM, Begum D, Ahmed ASMNU. Role of intravenous immunoglobulin (IVIG) as an adjuvant in the treatment of neonatal sepsis in preterm babies. *Journal of Bangladesh College of Physicians and Surgeons* 2006;24:97–104.
- [47] Shah PS, Kaufman DA. Antistaphylococcal immunoglobulins to prevent staphylococcal infection in very low birth weight infants. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: 10.1002/14651858.CD006449.pub2]
- [48] INIS Collaborative Group. Brocklehurst P, Farrell B, King A, Juszczak E, Darlow B, Haque K, Salt A, Stenson B, Tarnow-Mordi W. Treatment of neonatal sepsis with intravenous immune globulin *N Engl J Med* 2011;365:1201-1211.

- [49] Norrby-Teglund A, Haque KN, L. Hammarström L. Intravenous polyclonal IgM-enriched immunoglobulin therapy in sepsis: a review of clinical efficacy in relation to microbiological aetiology and severity of sepsis. *Journal of Internal Medicine* 2006; 260: 509–516
- [50] Baker CJ, Melish ME, Hall RT, et al. Intravenous immune globulin for the prevention of nosocomial infection in low-birth-weight neonates. *New Engl JMed* 1992;327:213–219.
- [51] Fanaroff AA, Korones SB, Wright LL, Wright EC, Poland RL, Bauer CB, Tyson JE, Philips JB 3rd, Edwards W, Lucey JF, et al. A controlled trial of intravenous immune globulin to reduce nosocomial infections in very-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. *New Engl J Med* 1994;330(11):107-13.
- [52] Ohlsson A, Lacy JB. Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants. *Cochrane Database Syst Rev* 2004;(1):CD000361
- [53] Manzoni P, Rinaldi M, Cattani S, Pugni L, Romeo MG, Messner H, Stolfi I, Decembrino L, Laforgia N, Vagnarelli F, Memo L, Bordignon L, Saia OS, Maule M, Gallo E, Mostert M, Magnani C, Quercia M, Bollani L, Pedicino R, Renzullo L, Betta P, Mosca F, Ferrari F, Magaldi R, Stronati M, Farina D; Italian Task Force for the Study and Prevention of Neonatal Fungal Infections, Italian Society of Neonatology. Bovine lactoferrin supplementation for prevention of late-onset sepsis in very low-birth-weight neonates: a randomized trial. *JAMA* 2009;302:1421-1428.
- [54] Alfaleh K, Anabrees J, Bassler D, Al-Kharfi T. Probiotics for prevention of necrotizing enterocolitis in preterm infants. *Cochrane Database Syst Rev* 2011 Mar 16;(3):CD005496.