Immuno-modulation in neonatal sepsis: intravenous immunoglobulin therapy in the prevention and treatment of neonatal sepsis: Is the answer, ‘Yes’, ‘No’, or ‘Don’t know’?

Neonatal sepsis remains a major cause of mortality and morbidity in the newborn both in developing and the developed world. This is despite the advances in perinatal and neonatal care and use of very potent antibiotics. This lack of success is in part due to the delayed recognition that disturbed immune homeostasis is a major factor for mortality and morbidity. Unless modalities, which restore immune homeostasis, are used in conjunction with anti-microbials we are unlikely to reduce the unacceptably high mortality and morbidity in neonatal sepsis. Though there are a number of immuno-modulatory therapies available, this paper reviews the evidence on the use of Intravenous Immunoglobulin therapy in the prevention and treatment of neonatal sepsis. This review concludes that whilst there is insufficient evidence for routine use of standard polyvalent Intravenous Immunoglobulin (ivIgG) to prevent neonatal sepsis, there is compelling evidence that the use of ivIgG as an adjunct would be a beneficial addition to standard treatment of neonatal sepsis. Evidence also suggests that IgM-enriched (ivIgGMA) immunoglobulin may be superior to standard polyvalent ivIgG particularly in Gram-negative infection. Thus, should ivIgG or ivIgGMA be used to prevent neonatal sepsis? The answer is ‘don’t know’ and to the question should ivIgG or ivIgGMA be used in the treatment of neonatal sepsis the answer is ‘yes’.

Sepsis and septic shock remain the most common cause of death in neonates and children in the world. 1.6 million neonates die every year from infection. Though most of these infections and deaths occur in the developing countries; neonatal sepsis remains a major cause of admission to neonatal intensive care units and mortality in the developed world.

This review will address the issue of immuno-modulation with intravenous immunoglobulin (IVIG) in neonatal sepsis.

In neonates, maternal antibody (IgG) transfer starts around thirty weeks of gestation to reach maternal levels at term. IgM is not trans-placentally transferred. Hence the preterm infant is antibody deficient. Moreover, physiologically the rate of catabolism of maternally acquired antibodies exceeds neonatal de novo production. This immune deficient state is worsened in sepsis.

In the healthy state there is a balance or homeostasis within the immune system ensured by mutual interaction between its components. Severe bacterial infection induces the patho-physiological conditions leading to: a) generalised inflammatory response (hyper inflammation), b) Immune paralysis and c) anti-inflammatory response. Generalised inflammatory response results in activation of granulocytes, macrophages, monocytes and endothelial cells along with increased synthesis of pro-inflammatory cytokines, followed by the release of anti-inflammatory cytokines.

Immune paralysis causes dysregulation of other systems such as the complement, coagulation and the Kallikrein–kinin systems leading to multi-organ dysfunction and failure. Thus, the aim of treatment in severe infection is to kill the pathogens with antibiotics, control the haemodynamic impairment and organ dysfunction. Along with this providing immunotherapy to restore immune homeostasis is proving to be an important causal approach to modulate and affect the inflammatory process.

Recently, the International Sepsis Campaign published evidence-based guidelines for the treatment of sepsis and septic shock. They indicated therapeutic modalities which are effective and which are not. With respect to immunoglobulin therapy the guidelines were silent except for stating that in paediatrics polyclonal ivIgG therapy has been reported to reduce mortality rates in sepsis and are a promising therapeutic tool but asserted that there is insufficient evidence to suggest a robust conclusion of benefit. Recently however, El-Nawawy et al. have...
shown significant reduction in mortality, length of stay in intensive care and complications in infants and children admitted to paediatric intensive care unit with sepsis syndrome treated with IVIG.

Cochrane review\(^5\) suggested that IVIG lowers mortality in severe sepsis in adults. It pointed out that ivIgGMA products being more effective (RR 0.48) than mainly ivIgG containing products (RR 0.73). This review suggested that in children and neonates with sepsis, whilst there was a trend towards reduced mortality with the use of IVIG. The number of patients studied was small and quality of some of the studies was poor, hence they suggested that better quality studies with larger number of patients should be done before any firm conclusions could be drawn. Though IVIG was first used in neonatal sepsis over a quarter of a century many clinicians still view IVIG therapy as either experimental or not ‘evidence-based’! Hence this review.

**Background**

Current understanding for the management of severe sepsis and septic shock is that it requires therapeutic interventions that act at many different levels in the patho-physiological cascade of sepsis. The primary objective of immuno-modulation is to reestablish the immunological homeostasis. In pre-clinical trials immuno-therapy with monoclonal antibodies against LPS or TNF-\(\alpha\), IL-1 receptor antagonists, soluble TNF receptors and platelet aggregation factor inhibitor proved effective but the results of clinical trials have been disappointing.

Intravenous immunoglobulin has been used to treat and prevent neonatal sepsis since 1980’s but its use still remains controversial.

IVIG is not a generic drug. Commercial IVIG preparations (see below) differ in their antibody titer profile depending on the donor pool used. Most manufacturers use a donor pool between 1000 to 100,000 donors. The greater the donor pool the greater antibody spectrum is likely. Preparations differ with regard to their method of manufacture for example in the methods used for purification i.e. alcohol, heat, pH modification, chemical ultra-filtration and diafiltration and exchange chromatography or a mixture of treatments for virus inactivation and viral elimination. Thus each IVIG preparation differs from another plus there may be significant batch-to-batch variability in the same product.

IVIG preparations used in various clinical trials have been either only ivIgG or ivIgGMA. This is an important distinction and must be taken into account when reviewing literature. Similarly, great care should be taken to differentiate between studies where IVIG has been used for prevention or treatment and studies that mainly address adults against those, which address children and newborn infants.

**Manufacturing process**

As stated above IVIG is not a generic drug and each preparation may have subtle differences. It is important to know the properties of ideal IVIG. These have been defined by the World Health Organisation and the European Medicines agency (http://www.emea.eu.int). The main objective during the manufacturing process is to maintain the immunoglobulin molecule in its native form with a minimum aggregates, and other impurities, whilst not causing fragmentation or loss of activity. All commercially available IVIG preparations are prepared from pooled human plasma using a modification of cold-ethanol fractionation together with one or more methods to ensure intravenous tolerance and viral reduction. Exchange chromatography is the most modern method for protein purification.

World Health Organisation has set minimum standards required of commercially available IVIG preparations. They include that the minimal plasma donor pool of at least 1000. The preparation must contain more than 90% intact IgG and as small an amount of IgA as possible. The product should be free from fragments and aggregates and be modified as little as possible biochemically. The product should also contain all subclasses in naturally occurring proportions and its antibody spectrum should be known.

**Composition of IVIG**

IVIG is prepared from plasma from between 1000 to 100,000 donors thus the end product contain an array of variable regions of antibodies and a spectrum of antibodies against pathogens that are present in healthy individuals. Despite differing manufacturing processes most present generation IVIG products have near physiological distribution of IgG sub-classes plus antibodies of the IgM and IgA isotypes. Commercially available polyclonal ivIgG preparations contain over 96% IgG, containing a broad spectrum of opsonic and neutralizing antibodies, directed against a variety of organisms.\(^8\) Another commercially available product has been enriched with IgM (38 g/L IgG, 6g/L IgM, 6g/L IgA) to give the preparation a more ‘physiological’ composition. It is thought that the pentameric structure of IgM provides superior opsonic and neutralizing ability against bacterial toxins. Since IVIG is a blood product manufacturing processes require viral reduction procedures, which are usually undertaken by using heat, alcohol, pH modification, chemicals, ultra-filtration, diafiltration and exchange chromatography or a mixture of these. No cases of viral transmission have been reported using current generation of IVIG.

**Mechanism of action of IVIG**

The exact mode of action of IVIG is not clearly understood. IVIG once infused is immediately and complete-
Table 1. Possible mechanisms of action of intravenous immunoglobulin in sepsis.

Offering broad spectrum of antibodies.
Neutralisation and clearance of Endotoxins, exotoxins and superfantigens.
Help killing the organism by increasing opsonisation.
Increase macrophage surveillance.
Increase number and activity of PMN’s.
Increase in opsonisation and phagocytosis.
Inhibition of release of pro-inflammatory cytokines and stimulation of the release of their antagonists.
Improve chemotaxis.
Complement mediated killing of pathogens.
Scavenging of activated complement factor C3b and C4b.
Regain Immunological balance.
Reduction in bacterial cell adherence.
Modulation of pro and anti-inflammatory cytokines.

IVIG also limits tissue
IVIG modulates the release
In neonates Clapp
Viral transmission has not been reported
have shown significant reduc-
analed
sion of adhesion molecules.
anti-inflammatory cytokines, chemokines and expres-
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which it does this is not clearly understood but possible mechanisms of action are shown in Table
1. In our own unpublished work we have found reduced
ery bio-available in the recipient’s circulation. It is distrib-
uted relatively rapidly between plasma and extra-vas-
cular fluid. Infused IVIG has a half-life of about 7 to 14
days in the newborn infant.
Anti-inflammatory effects of IVIG depend both on the
variable and the Fc region of the infused antibodies in
the preparation used. IVIG has the ability to neutralize
bacterial toxins, modulate the production of pro and
anti-inflammatory cytokines, chemokines and expres-
sion of adhesion molecules.13-15 IVIG also limits tissue
damage triggered by activated complement factors and
alter the inflammatory potential soluble immune com-
plex. It is thought that the major anti-inflammatory
action of IVIG is through its ability to modulate
cytokines and cytokine antagonists in addition to scav-
enging active complement.14 IVIG modulates the release
of cytokines and other mediators; modifies IL-6 pro-
duction in cord blood of premature infants16 though the
method by which it does this is not clearly understood but possible mechanisms of action are shown in Table
1. In our own unpublished work we have found reduced
serum IL-6 and IL-8 levels in babies with infection treat-
ed with ivIgGMA compared to controls.

Dosage and safety of IVIG
All the published studies using IVIG vary in the dosage
and therapeutic schedule used. There is no consensus on
the optimal dosage or duration of IVIG therapy in
neonatal sepsis. It is not clear whether one should attain
a certain (physiological) plasma level of immuno-
globulin for prolonged period or to “spike” the immune
system with intermittent bolus therapy. Some recent
studies in adults have suggested the need to achieve
normal serum levels (8 g/L) of IgG to reduce the num-
ber of bacterial infections.6,17 In neonates Clapp et al.38
also suggested keeping serum IgG levels between 700
and 800 mg/dL but in our experience19 an IgG level of
400 mg/dL and an IgM level above 20 mg/dL is suffi-
cient. Higher IgG levels have been found to inhibit the
functions of the immune system; inhibiting maturation
and function of dendritic cells, blocking the reticulo-
endothelial system and the proliferation of T lympho-
cytes whilst accentuating the production the production
of pro-inflammatory cytokines.20,21

Over the years IVIG has been proven to have a very
good safety profile with adverse reaction rates well
below 5%. In adult’s headaches, aseptic meningitis,
chills, nausea and fatigue have been reported whilst in
the newborn minor self-limiting haemolysis has been
reported.9 Viral transmission has not been reported
using modern generation IVIG.

Use of IVIG in the prevention and treatment of
neonatal infection
This has been subject to a number of meta-analyses
and systemic reviews6,22-25 thus a very brief review will
be presented here.

Prevention of infection
Nosocomial infections continue to be a significant
cause of mortality and morbidity among preterm and
low birth weight infants. A number of meta-analyses
and systemic reviews24,22-25 have shown significant reduc-
tion in frequency of infections, mortality and morbidi-
ty. The most recent Cochrane systemic review24 analysed
nineteen studies involving approximately 5000 preterm
and or low birth weight babies. They found a statisti-
cally significant reduction (p = 0.02) in the rate of sep-
sis. {RR 0.85 (95% CI–0.74-0.98)} but the number to
treat (NNT) was high at 33. There was also a statisti-
cally significant reduction in any, one or more serious
infection {RR 0.82 (95% CI–0.74-0.92)} and NNT was
25. There was no reduction in mortality from infection
or reduction in the incidence of NEC, BPD, or length of
stay. No adverse effects of IVIG were reported from any
of the studies.

These authors concluded that IVIG administration
resulted in 3% reduction in sepsis and a 4% reduction
in one or more episode of serious infection. They went
on to say that as the incidence of infection was low (in
developed countries) this reduction in the rate of sep-
sis did not justify the routine use of ivlgG prophylaxis.
We agree with the authors that the decision to use IVIG
prophylactically should depend on the costs and values
assigned to the clinical outcomes. We therefore feel
that individual judgment and decisions need to be made
depending on the circumstances whether to use IVIG for
prevention of infection/sepsis or not.
Treatment of infection

Similar to the prevention studies, treatment studies have also been subject to a number of meta-analyses and systemic reviews, which have all shown significant reduction in mortality from infection in neonatal sepsis. The most recent is a Cochrane systematic review of nine studies involving 553 neonates with suspected infection. Of the six studies (n = 318) which reported mortality showed statistically significant reduction in infants with suspected sepsis given IVIG (RR 0.63 [95% CI – 0.40–1.00]). Treatment with IVIG in seven trials (n=262) of cases of subsequently proven infection resulted in a statistically significant reduction in mortality following IVIG therapy (RR 0.55 [95% CI – 0.31–0.98], NNT 11).

Two reports using ivIgGMA in the treatment of neonatal sepsis showed statistically significant reduction in mortality from 16% to 3.3% (p = 0.002). A recent unpublished review has demonstrated significant reduction in mortality in patients with sepsis and septic shock treated with ivlgGMA (RR 0.35 [95% CI – 0.23–0.54]).

Whilst it is recognised that the number of studies are few and the total number of patients studied small but all the studies reviewed clearly show that the use of ivlgG and ivlgGMA reduces mortality from neonatal sepsis significantly and the number to treat is small. Thus, IVIG as adjuvant therapy offers a significant advantage over conventional therapy in sepsis and septic shock in general and ivlgGMA offers a particular advantage in gram-negative sepsis.

Conclusions

Sepsis is a pathogen initiated but a cytokine-mediated condition in which immune homeostasis is disturbed. Since so many factors are involved in the cascade and process of sepsis there cannot be a magic bullet for treatment. Once this is accepted then if we are to succeed in improving the outcome from neonatal sepsis we will need not only to kill the pathogen but also modulate the immune system to regain immune homeostasis. Based on the evidence presented above immunomodulation with IntraVenous Immunoglobulin in the management of neonatal sepsis is worthy of serious consideration.

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References


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