**SPECIAL COLLABORATION**

# Appropriate indicated use for IVIG in neonatal infections

## Uso indicado y apropiado de la inmunoglobulina G intravenosa para el tratamiento de infecciones neonatales

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**ABSTRACT**

Infection is a leading cause of mortality and morbidity in the newborn and preterm neonates due to immuno-incompetence in these patients. Administration of intravenous immunoglobulin (IVIG) provides immunoglobulin G (IgG) that can protect the body from infection. In theory, morbidity and mortality due to infections in newborns and preterm infants could be reduced by the administration of IVIG. Two meta-analyses were evaluated comparing IVIG to treat various infection *versus* conventional treatments. The results showed that IVIG is not effective as an adjunctive treatment for suspected or proven infections in neonates.

**Key words:** intravenous immunoglobulin; newborn; preterm neonates; infection; meta-analyses.

**RESUMEN**

La infección es la causa principal de la mortalidad y de la morbilidad entre los recién nacidos y los neonatos prematuros debido a la incompetencia inmunológica de estos pacientes. El suministro de inmunoglobulina por vía intravenosa brinda la inmunoglobulina G que protege al cuerpo humano de las infecciones. En términos teóricos, la morbilidad y la mortalidad por infecciones en recién nacidos y en bebés prematuros, podrían reducirse si se administra inmunoglobulina G intravenosa. Se evaluaron dos meta-análisis que comparaban el uso de la inmunoglobulina G

intravenosa para tratar diversas infecciones con los tratamientos convencionales. Los resultados demostraron que dicha inmunoglobulina no es eficaz como tratamiento adyuvante para combatir sospechas de infección o infecciones comprobadas en los recién nacidos.

**Palabras clave:** inmunoglobulina intravenosa; recién nacido; neonatos prematuros; infección; meta-análisis.

## INTRODUCTION

Neonatal systemic infection is a major cause of morbidity and mortality in the world.[1] In particular, the preterm neonates are at high risk because their organs and tissues are not fully developed. Symptoms may be subtle and clinical signs may be non-specific. Common signs and symptoms of infection are tachypnea, apnea or other respiratory distress, which may lead quickly result in permanent neurological impairment or death.[2]

Approximately 10-20 % of very low birth weight (< 1 500 mg) infants suffer from proven infection and 10-20 % die from infection despite antimicrobial treatment during their neonatal period.[3] The exact causes of infection in neonates are not well understood. It is hypothesized that the B-lymphocytes are produced shortly before 12th week of gestation. As a result, maternal IgG are actively translocated into the fetal bloodstream via the placenta.[4] Endogenous immunoglobulin synthesis does not begin until 24 weeks of life: thus, young infants rely on in-utero maternally acquired immunoglobulins for protection against systemic infection.[5] Premature interruption of transplacental IgG transfer contributes to weakened defense capacity of the fetus during gestational-age.[6] Since maternal IgG are generally cleared from the neonatal circulation after birth, it has been proposed the use of intravenous immunoglobulins (IVIG) to prevent and treat neonatal sepsis.[7]

The objective of this article is to evaluate two meta-analyses in order to know if IVIG is effective as an adjunctive treatment for suspected or proven infections in neonates.

### PHARMACOLOGIC TREATMENT

#### Antimicrobial

*Coagulase-negative staphylococci* are the prevalent organisms followed by E. coli and multidrug resistant Gram-negative organisms including Klebsiella, Pseudomonas and fungi.[8] Misuse or inappropriate use or broad-spectrum antimicrobial therapy could result in super-infections and multi-drug resistance.[8] This is becoming a clinical and financial burden in China.

## IVIG

IVIG is a therapeutic preparation that mainly includes human IgG collected from a large number of healthy donors that is commonly used for replacement therapy in patients with primary or secondary antibody deficiencies. IgG is a type of antibody, which be created and released by plasma B-cells and consists of approximately 75 % of serum antibodies in humans IgG.[9] They can bind to pathogens such as viruses, bacteria, and fungi. In theory, the contribution from IgG is to protect the body from infection. The mechanism of actions for IgG is unclear but it is thought to:

- Mediate the binding of pathogens causes the immobilization of pathogens.
- Coating of pathogen surfaces allows their recognition and ingestion by phagocytic immune cells.
- Activates the classical pathway of the complement systems.
- Binds and neutralizes toxins associated with type II and type III hypersensitivity reactions.

In clinical studies,[10] it has been shown that polyvalent IVIG can provide opsonic activity, activate complement, promote antibody-dependent cytotoxicity and improve neutrophilic chemo-luminescence. So theoretically IVIG are being evaluated as an adjunctive treatment for suspected or proven infection, to reduce morbidity and mortality.

As indicated in chart, the key difference among three countries is the definition of secondary immunodeficiency. The Chinese guidelines include infection and neonatal sepsis as secondary immunodeficiency.[11] However the international definition of secondary immunodeficiencies[5,8] due to leukemia, lymphomas, various tumors, chemotherapy, other immunosuppressive therapy and human immunodeficiency virus infection is accepted by many countries. Perhaps, the Chinese indications for secondary immunodeficiency should be re-examined through evidence-based medicine.

**Chart 1.** Approved indications for IVIG

| FDA (USA) | HEATH (Canada) | CFDA (China) |
|---|---|---|
| • **Replacement therapy** Primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age or older.<br>• **Maintenance therapy** To improve muscle strength and disability in adult patients with Multifocal motor neuropathy [MMN]. | • Idiopathic thrombocytopenic purpura<br>• Kawasaki disease<br>• Guillain-Barré syndrome, includes Miller-Fisher syndrome<br>• Primary immunodeficiency<br>• Secondary immunodeficiency | • Primary immunodeficiency<br>• Secondary immunodeficiency: neonatal sepsis, serious infection<br>• Autoimmune diseases: Kawasaki, Idiopathic thrombocytopenic purpura |

## EVIDENCE-BASED REVIEW

A systematic review included randomized controlled trials (RCT) or quasi-RCT to evaluate the use of IVIG for children with pneumonia in China.[10] This study was one of the references in China Food and Drug Administration (CFDA) product package insert. The study compared IVIG plus conventional treatment such as antimicrobial use versus conventional treatment. The study did not conduct a thorough literature to include all databases. The sample size for the systematic review was over 3 602 children. The investigators used clinical surrogate markers such as rales, fever, and cough to diagnose pneumonia. The clinical outcome measures were length of hospital stay, and resolution of the surrogate symptoms. The results showed the mean difference for fever was -1.73 (-2.06, -1.39), for rales -2.09 (-2.34,-1.83), cough -1.85 (-2.17,-1.53), length of hospital stay -2.53 (-2.86,-2.21). The investigators stated that the results showed that IVIG used, as an adjunctive therapy is more effective than conventional treatments for children with severe pneumonia. However, there are many limitations to the systematic review. First, the population cannot be applied to neonate since it was studied in children. There was no indication of attempt to prove that there was no selection bias in the studies. Also, none of the study mentioned about allocation concealment. Most importantly, the study did not examine clinical outcome measures such as death cause, death from infections, complication of infections, or follow-up after patients were discharged from hospital.

The second systematic review is a Cochrane Review,[12] which included all RCT, and quasi-RCT evaluating the use of IVIG with conventional treatment *versus* conventional treatment alone in proven or suspected infections in neonates. The Cochrane review was very cleared with their literature search using all possible databases. The review included over 3973 neonates. The studies defined neonates as newborns < 28 days old. Suspected infection was defined as having clinical signs and symptoms (temperature instability, feeding intolerance, prolonged jaundice) consistent without culture. Proven infection was defined as clinical signs and symptoms consistent with

infection in association with isolation of a causative organism (bacteria or fungi) from the blood, cerebrospinal fluid culture, urine culture or a normally sterile site such as liver, spleen, or lung.

The strengths of the Cochrane review are:

1. Large sample size.

2. Most studies disclosed allocation concealment.

3. The primary outcomes are clinical outcome measures such as death, complications and length of hospital stay.

4. There was a follow-up on death and complications after patients were discharged.

5. The population is applicable to neonates.

The results from Cochrane review show that IVIG is not effective as an adjunctive treatment of suspected or proven infections in neonates. As for the other systematic review, the patient population studies do not applied to neonates. Therefore, clinicians should take caution when interpreting results from this review and attempt to apply to their practice.

## CONFLICTS OF INTEREST

The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript.

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