INPLASY

Efficacy and Safety of Intravenous Immunoglobulin in the Treatment of Neonatal Sepsis: An Updated Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 March 2025 and was last updated on 20 March 2025.

INTRODUCTION

Review question / Objective Neonatal sepsis is a severe condition with high mortality and morbidity. The use of intravenous immunoglobulin (IVIG) as adjunctive therapy to antibiotics remains controversial. This meta-analysis aimed to assess the efficacy and safety of IVIG in treating neonatal sepsis.

Condition being studied Neonatal sepsis is a life-threatening condition characterized by systemic inflammation and multiorgan dysfunction in response to infection [1]. It is classified as early-onset sepsis (EOS) if it occurs within the first 72 hours of life and late-onset sepsis (LOS) if it occurs after 72 hours of life [2]. The incidence of neonatal sepsis varies from 1 to 170 cases per 1,000 live births, with higher rates in low- and middle-income countries [3]. A study from the Burden of Antibiotic Resistance in Neonates from Developing Societies (BARNARDS) project reported mortality rates of 0.83 per 1,000 neonate-days in Low- and middle-income countries (LMICs) [4]. Despite advances in neonatal care, sepsis remains a leading cause of morbidity and mortality among neonates worldwide.

The pathophysiology of neonatal sepsis involves a complex interplay between the immature immune system of the neonate and the invading pathogen [5]. Neonates have a reduced ability to mount an effective immune response due to a variety of factors, including decreased production of immunoglobulins, complement proteins, and cytokines; reduced phagocytic activity of neutrophils and macrophages; and impaired T-cell function [6]. These deficiencies in the neonatal immune system predispose them to severe infections and sepsis.

The mainstay of treatment for neonatal sepsis is prompt initiation of empiric broad-spectrum antibiotics [7]. However, the use of antibiotics alone may not be sufficient to control the systemic inflammatory response and prevent organ dysfunction in severe cases of sepsis. Intravenous immunoglobulin (IVIG) has been proposed as an adjunctive therapy to enhance the immune response and improve outcomes in neonates with

sepsis [8]. IVIG consists of pooled immunoglobulins from healthy donors and has demonstrated immunomodulatory and anti-inflammatory properties [9]. Despite these potential benefits, the efficacy and safety of IVIG in neonatal sepsis remain controversial, with conflicting evidence from previous studies [10,11].

Previous meta-analyses on this topic have provided valuable insights but are limited by outdated data and insufficient analysis of specific subgroups of neonates who might benefit most from IVIG therapy. Furthermore, several recent studies have been published since the last meta-analysis, making it necessary to update the evidence base with these new findings. There is also a need for a more detailed examination of the heterogeneity among studies, particularly regarding differences in study populations, sepsis definitions, and treatment protocols. Addressing these gaps is crucial to advancing our understanding of the potential role of IVIG in neonatal sepsis treatment.Given these uncertainties, this systematic review and meta-analysis aim to evaluate the efficacy and safety of IVIG as an adjunctive therapy to antibiotics in the treatment of neonatal sepsis. Specifically, we seek to assess whether the addition of IVIG to standard antibiotic therapy improves clinical outcomes in neonates diagnosed with sepsis.

METHODS

Participant or population A total of 303 studies were identified through the database search and reference screening. After removing duplicates and screening titles and abstracts, 15 studies underwent full-text review. Of these, 8 studies were excluded for the following reasons:repeated publication (n=2), conference abstract (n=2), outcome index does not match(n=4) . Seven studies involving 604 neonates were included in the meta-analysis [17-23] (Figure 1).

Intervention Not applicable.

Comparator Compared the use of IVIG plus antibiotics with antibiotics alone in neonates with sepsis.

Study designs to be included Conducted in accordance with PRISMA, we searched PubMed, Embase, and Cochrane Library for randomized controlled trials (RCTs) and case-control studies comparing IVIG plus antibiotics with antibiotics alone in neonates with sepsis. Outcomes included clinical efficacy, adverse events, total effective rate of treatment, and length of hospital stay. Pooled analyses used a random-effects model, with heterogeneity assessed by the I^2 statistic.

Eligibility criteria Studies were included in the meta-analysis if they met the following criteria: (1) randomized controlled trials (RCTs) or case-control studies; (2) compared the use of IVIG plus antibiotics with antibiotics alone in neonates with sepsis, defined as suspected or proven serious infection requiring antibiotic treatment and supported by one or more of the following: positive blood culture, cerebrospinal fluid analysis, or need for respiratory support through an endotracheal tube; (3) reported at least one of the following outcomes: clinical efficacy, adverse events, total effective rate of treatment, or length of hospital stay; (4) published in English or Chinese. Studies were excluded if they were: (1) non-comparative studies; (2) involved preterm infants exclusively; (3) did not report the outcomes of interest; (4) conference abstracts, letters, or editorials; (5) Evaluated non-IVIG interventions (e.g., exchange transfusion, oral immunoglobulins); (6) Included non-neonatal populations;(7) Utilized non-comparative or non-eligible study designs (e.g., retrospective cohorts).

Although RCTs are considered the gold standard for evaluating therapeutic interventions, we chose to include both RCTs and case-control studies to broaden the evidence base. This approach allows us to incorporate a wider range of studies, including those conducted in diverse clinical settings, thereby providing a more comprehensive assessment of the efficacy and safety of IVIG in neonatal sepsis. However, we acknowledge the potential methodological challenges associated with including case-control studies, such as selection bias and confounding factors. To mitigate these risks, we conducted a rigorous quality assessment using the Newcastle-Ottawa Scale (NOS) for case-control studies and performed sensitivity analyses to evaluate the robustness of our findings.

Information sources A comprehensive literature search was conducted in PubMed, Embase, and Cochrane Library databases from inception to March 2024. The search strategy included a combination of Medical Subject Headings (MeSH) terms and free-text words related to neonatal sepsis, intravenous immunoglobulin, and antibiotics. The reference lists of relevant systematic reviews and meta-analyses were also screened for additional studies. For PubMed, the search strategy combined Medical Subject Headings (MeSH) terms with free-text keywords: (((((((IVIG[Title/Abstract]) OR (Immunoglobulins, Intravenous[Title/Abstract])) OR (Antibodies,

Intravenous[Title/Abstract])) OR (Intravenous Antibodies[Title/Abstract])) OR (Intravenous Immunoglobulin*[Title/Abstract])) AND (((((Septic Shock[Title/Abstract]) OR (Septicemia[Title/Abstract])) OR (Sepsis[Title/Abstract])) AND (((((((randomized controlled trial[Publication Type]) OR (controlled clinical trial[Publication Type])) OR (randomized[Title/Abstract])) OR (controlled[Title/Abstract])) OR (trial[Title/Abstract])) OR (case-control[Title/Abstract]))))) OR (((((((IVIG[MeSH Terms]) OR (Immunoglobulins, Intravenous[MeSH Terms])) OR (Antibodies, Intravenous[MeSH Terms])) OR (Intravenous Antibodies[MeSH Terms])) OR (Intravenous Immunoglobulin*[MeSH Terms])) AND (((((Septic Shock[MeSH Terms]) OR (Septicemia[MeSH Terms])) OR (Sepsis[MeSH Terms])) AND (((((((randomized controlled trial[Publication Type]) OR (controlled clinical trial[Publication Type])) OR (randomized[Title/Abstract])) OR (controlled[Title/Abstract])) OR (trial[Title/Abstract])) OR (case-control[Title/Abstract]))))). For Embase, the strategy used was: ('Intravenous immunoglobulin'/exp OR 'intravenous immunoglobulin' OR 'IVIG' OR 'Intravenous Antibodies' OR 'Antibodies, Intravenous') AND ('sepsis'/exp OR 'septic shock' OR 'septicemia' OR 'sepsis') AND ('randomized controlled trial'/exp OR 'randomized controlled trial' OR 'controlled clinical trial' OR 'randomized' OR 'controlled' OR 'trial' OR 'case-control'). For the Cochrane Library, the search string was: (('Intravenous immunoglobulin' OR 'IVIG' OR 'Intravenous Antibodies' OR 'Antibodies, Intravenous') AND ('Sepsis' OR 'Septic Shock' OR 'Septicemia')) AND ('randomized controlled trial' OR 'controlled clinical trial' OR 'case-control study').

Main outcome(s)

Clinical efficacy

Two studies [17, 21] involving 170 neonates reported data on clinical efficacy. In these studies, clinical efficacy was defined as the resolution of clinical symptoms (e.g., fever, hypothermia, respiratory distress, and hemodynamic instability) and laboratory parameters (e.g., normalization of white blood cell count, CRP, and PCT levels) within 72 hours after the initiation of treatment. The pooled results showed no significant difference between the IVIG plus antibiotics group and the antibiotics alone group in terms of clinical efficacy (OR=1.11, 95% CI: 0.85-1.46, P=0.45; Figure 2). No significant heterogeneity was observed among the studies (I^2 = 0.0%, P = 0.788).

Total effective rate of treatment

Three studies [17,21,22] involving 250 neonates reported data on the total effective rate of treatment. The pooled results showed no significant difference between the IVIG plus antibiotics group and the antibiotics alone group in terms of the total effective rate of treatment (OR=1.05, 95% CI: 0.85-1.31, P=0.64; Figure 3). No significant heterogeneity was observed among the studies (I^2 = 0.0%, P = 0.758).

Quality assessment / Risk of bias analysis The risk of bias assessment for the included studies utilized the NOS for case-control studies and the Cochrane Risk of Bias Tool for RCTs. The single case-control study by Friedman et al. [19] received a score of 6, indicating moderate quality based on the NOS criteria. For RCTs, the methodological quality was assessed across several domains: random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting. Most RCTs were found to have a low risk of bias in the key domains of randomization and allocation concealment, though blinding of participants and personnel showed unclear risks in some studies. No studies were excluded due to poor quality, and the inter-judge reliability, assessed using Cohen's kappa coefficient, demonstrated substantial agreement between reviewers (κ = 0.82). Attrition bias: Most of the included studies had low dropout rates (<10%) and provided reasonable explanations for dropouts, indicating low risk of attrition bias. Performance bias: The majority of RCTs had low risk of bias in random sequence generation and allocation concealment, although some studies had unclear risks in blinding of participants and personnel. The single case-control study had moderate quality based on the NOS criteria. Reporting bias: All studies predefined their primary and secondary outcomes and reported all pre-specified outcomes. Funnel plots and Egger's test did not indicate significant publication bias, suggesting low risk of reporting bias.

Strategy of data synthesis The primary outcomes were clinical efficacy, adverse events, total effective rate of treatment, and length of hospital stay. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for dichotomous outcomes, and mean differences (MDs) with 95% CIs were calculated for continuous outcomes. Data were pooled using a random-effects model due to the expected clinical and methodological heterogeneity among the included studies. Heterogeneity was assessed using the I2 statistic, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively [15]. To ensure the accuracy and appropriateness of the meta-analysis, a statistician was intimately involved in every stage of the statistical analysis process, from the initial study

design to the final interpretation of results. Publication bias was evaluated using funnel plots and Egger's test [16]. Subgroup analyses were performed based on the type of sepsis (EOS vs. LOS) and the timing of IVIG administration (early vs. late). Sensitivity analyses were conducted by excluding studies with high risk of bias or low methodological quality. All analyses were performed using Review Manager 5.4 (The Cochrane Collaboration, Copenhagen, Denmark) and Stata 16.0 (StataCorp LLC, College Station, TX, USA).

Subgroup analysis Subgroup analyses based on the type of sepsis (EOS vs. LOS) and the timing of IVIG administration (early vs. late) were not performed due to the insufficient number of studies reporting these data.

Sensitivity analysis Sensitivity analyses excluding studies with high risk of bias or low methodological quality did not significantly alter the pooled results for any of the outcomes.

Country(ies) involved China.

Keywords neonatal sepsis, intravenous immunoglobulin, antibiotics, meta-analysis.

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