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Intravenous Immune Globulin (IVIG) as Adjunctive Therapy in Infectious Diseases—Indications, Evidence, Dosing, and Clinical Principles

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Abstract: Intravenous immune globulin (IVIG) is a pooled polyclonal IgG preparation derived from thousands of healthy plasma donors, which provides broad passive humoral immunity alongside significant immunomodulatory effects. In infectious diseases, IVIG occupies a defined role across three clinical contexts: (1) immunoglobulin replacement therapy for primary and secondary antibody deficiencies predisposing to recurrent infection; (2) neutralization of bacterial toxins and superantigens in severe toxin-mediated syndromes; and (3) attenuation of dysregulated host inflammation in conditions such as Kawasaki disease and multisystem inflammatory syndrome in children (MIS-C). Evidence strength varies widely, from robust randomized trial data for Kawasaki disease and primary immunodeficiency to largely observational support for toxic shock and sepsis. This review summarizes established and emerging IVIG indications in infectious diseases, key trial evidence, dosing reference tables, and settings in which IVIG is not indicated.

Keywords: intravenous immune globulin; immunodeficiency; immunomodulation

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Highlights

- Intravenous immune globulin (IVIG) provides broad passive humoral immunity and immunomodulation across 3 clinical contexts in infectious diseases: antibody replacement, toxin neutralization, and attenuation of dysregulated host inflammation.

- Matching the indication to the dominant mechanism, whether antimicrobial, anti-toxin, or anti-inflammatory, is the central principle guiding appropriate IVIG use.
- Evidence strength varies widely by indication, from robust randomized trial data in some conditions to case series and observational support in others.
- IVIG is adjunctive therapy, not a replacement for antimicrobials, source control, or vaccination, and large randomized trials have not confirmed benefit in several settings where its use was once considered promising.
- Disease-specific hyperimmune globulins and monoclonal antibodies are preferred over polyclonal IVIG when targeted products are available.
- Product selection, stewardship, and monitoring of adverse effects (thrombosis, renal injury, hemolysis, and anaphylaxis in IgA deficiency) are essential to safe use.

1. Introduction

Intravenous immune globulin is one of the most versatile biological agents in clinical medicine [1]. Prepared from the pooled plasma of thousands of donors, each lot contains millions of distinct antibody specificities reflecting the collective immunological experience of the donor population [1,2]. This breadth underlies both its therapeutic utility and the challenge of demonstrating efficacy in controlled trials, because the relevant antibody titers against any single pathogen vary between products and lots.

In infectious diseases, IVIG is not a replacement for antimicrobial therapy. Its role is adjunctive: reconstituting humoral immunity in patients incapable of generating their own antibody response, neutralizing preformed toxins that antibiotics cannot address, or dampening a pathological host inflammatory response driving organ injury [1,2]. Matching the right indication to the right mechanism is the central clinical challenge.

2. Mechanisms of Action

IVIG exerts effects through multiple concurrent mechanisms (Table 1) [2,3]. The balance of these mechanisms determines whether the dominant clinical effect is antimicrobial, anti-toxin, or anti-inflammatory, and informs appropriate indication selection.

Table 1: Mechanisms of Action of IVIG.

Mechanism	Details
Passive humoral immunity	Pooled polyclonal IgG from at least 1000 donors directly neutralizes bacterial and viral pathogens via specific antibody binding
Opsonization	IgG Fc regions enhance phagocyte recognition and killing of encapsulated organisms
Fc receptor blockade	Saturates Fc gamma receptors on macrophages, reducing antibody-mediated tissue destruction; key in autoimmune and inflammatory indications
Complement modulation	Fc regions scavenge activated complement fragments and reduce membrane attack complex–mediated lysis of host tissue
Anti-cytokine activity	Contains natural antibodies against interleukin 1, interleukin 6, and tumor necrosis factor alpha; relevant in sepsis and superantigen-mediated shock
Anti-idiotype regulation	Anti-idiotypic antibodies downregulate pathological B-cell clones and autoantibody production

3. Immunodeficiency and Recurrent Infection

3.1. Primary Antibody Deficiencies

Replacement immunoglobulin therapy is the standard of care for primary antibody deficiencies including common variable immunodeficiency (CVID), IgG subclass deficiencies, and specific antibody deficiency syndromes [4,5]. The goal is to maintain trough IgG levels above 500–800 mg/dL, with individualized targets based on infection history and breakthrough events [5,6].

3.2. Secondary Immunodeficiency

Patients with hypogammaglobulinemia following hematologic malignancy, allogeneic stem cell transplantation, chronic lymphocytic leukemia, or rituximab therapy may benefit from IVIG replacement when IgG levels fall below 400–500 mg/dL in the setting of recurrent or severe infections [4,6].

3.3. Pediatric HIV (Historical)

Before the highly active antiretroviral therapy era, IVIG reduced bacterial infections in HIV-infected children with hypogammaglobulinemia. This indication is largely supplanted by effective antiretroviral therapy and routine vaccination [4].

4. Toxin-Mediated Bacterial Infections

4.1. Streptococcal Toxic Shock Syndrome (STSS) and Necrotizing Fasciitis

Group A *Streptococcus pyogenes* superantigens (exotoxins A, B, and C) bypass normal antigen presentation to activate up to 20% of T cells simultaneously, driving a massive cytokine storm. Pooled IVIG contains anti-superantigen antibodies that can neutralize these toxins [7,8].

The European randomized, double-blind, placebo-controlled trial by Darenberg et al. demonstrated a non-significant trend toward reduced 28-day mortality with IVIG versus placebo (10% vs 36%; $P = 0.09$), limited by small sample size [7]. Observational data from Kaul et al support a mortality benefit [8]. IVIG is used adjunctively with surgical debridement, beta-lactam antibiotics, clindamycin, and linezolid (a protein synthesis inhibitor that halts toxin production) [9,10].

4.2. Staphylococcal Toxic Shock Syndrome

Toxic shock syndrome test 1 (TSST-1) and staphylococcal enterotoxins are similarly neutralized by pooled IVIG. Evidence is largely from case series; IVIG is considered when patients deteriorate despite appropriate antibiotics and source control [9].

4.3. Clostridial Infections

Adjunctive IVIG has been used in severe *Clostridium perfringens* gas gangrene with limited supporting data. For *Clostridium difficile* infection, IVIG is not recommended outside clinical trials; fecal microbiota transplantation and targeted antibiotics remain standard of care.

5. Kawasaki Disease

Kawasaki disease is a systemic vasculitis of presumed infectious etiology predominantly affecting children under 5 years of age. Coronary artery aneurysms occur in up to 25% of untreated patients [11,12]. The landmark 1986 randomized controlled trial by Newburger et al established IVIG 2 g/kg as a single infusion combined with high-dose aspirin as standard of care, reducing aneurysm incidence from approximately 25% to less than 5% [11,12].

IVIG-resistant Kawasaki disease (persistent or recrudescent fever more than 36 hours after infusion) affects approximately 10%–20% of patients and warrants repeat IVIG, addition of corticosteroids, or infliximab based on risk-stratification scoring [13].

6. Neonatal and Pediatric Infections

6.1. Neonatal Sepsis

Neonates, particularly premature infants, are relatively hypogammaglobulinemic due to incomplete transplacental IgG transfer. Despite a biologically plausible rationale, the large multicenter International Neonatal Immunotherapy Study (INIS) trial, enrolling 3493 neonates with proven or suspected serious infection, found no significant difference in death or major disability with IVIG versus placebo (relative risk 1.00; 95% CI 0.92–1.08) [14]. Accordingly, IVIG is not currently recommended for routine use in neonatal sepsis [14,15].

6.2. Enteroviral Encephalitis in Agammaglobulinemia

Patients with X-linked agammaglobulinemia or CVID lack the B-cell immunity required to clear enteroviral infections. High-dose IVIG, sometimes combined with intrathecal immunoglobulin, has produced viral clearance in case series [16]. This remains a rare but important indication.

7. Viral Infections

7.1. Parvovirus B19 (Immunocompromised Hosts)

Chronic parvovirus B19 infection causes pure red cell aplasia by infecting and destroying erythroid progenitors. In immunocompromised patients, including those with HIV, transplant recipients, and those on immunosuppressive therapy who cannot mount a neutralizing antibody response, IVIG is the treatment of choice [17,18]. Repeated courses are often required.

7.2. Cytomegalovirus in Transplant Recipients

Cytomegalovirus-specific hyperimmune globulin (CMV-IVIG) provides higher titers of anti-CMV antibodies than standard IVIG and has been used for prophylaxis and treatment in solid organ transplant recipients, particularly lung and kidney transplants [19]. Its use has declined with the availability of ganciclovir, valganciclovir, and letermovir for prophylaxis.

7.3. Measles Post-Exposure Prophylaxis

Immune globulin (0.5 mL/kg intramuscularly, maximum 15 mL) is recommended within 6 days of measles exposure for immunocompromised patients, unvaccinated infants under 12 months, and pregnant women without evidence of immunity [20].

7.4. Respiratory Syncytial Virus (Historical Note)

Polyclonal respiratory syncytial virus (RSV) IVIG has been replaced by palivizumab (a humanized monoclonal antibody against the RSV F protein) and nirsevimab for seasonal prophylaxis in high-risk premature infants and those with congenital heart disease or chronic lung disease [20].

7.5. MIS-C and COVID-19 Inflammatory Complications

MIS-C represents a post-infectious hyperinflammatory state following SARS-CoV-2 infection that parallels Kawasaki disease pathophysiology [21]. American College of Rheumatology (ACR) and American Academy of Pediatrics guidance recommends IVIG 2 g/kg combined with methylprednisolone as first-line therapy [22]. In adults with severe COVID-19, pooled convalescent-derived immunoglobulin was investigated but has not been adopted as standard of care.

8. Sepsis and Septic Shock

Multiple meta-analyses, including the Cochrane systematic review by Alejandria et al, have demonstrated a signal toward mortality benefit with polyclonal IVIG in sepsis [23]. IgM-enriched preparations have shown the most consistent benefit in observational and smaller randomized trial data [23].

However, the large randomized Score-Based Immunoglobulin Therapy of Sepsis (SBITS) trial found no reduction in 28-day mortality with IVIG in score-defined severe sepsis, and subgroup analyses from neonatal sepsis trials have likewise failed to confirm consistent benefit [14,24]. IVIG is not currently incorporated into the Surviving Sepsis Campaign Guidelines as standard of care. Heterogeneity of sepsis populations, variable dosing, and inconsistent product types complicate interpretation [23,25]. IVIG may be considered in refractory septic shock, particularly in patients with suspected or proven IgG deficiency [25].

9. Evidence Summary by Indication (Table 2)

Table 2: IVIG Indications in Infectious Diseases: Evidence Summary.

Indication	Agent/Dose	Primary Benefit	Evidence Level
Primary immunodeficiency (CVID, XLA)	Standard IgG replacement	Prevents recurrent bacterial infections	High; consensus guidelines [4]
Kawasaki disease	IVIG 2 g/kg single dose	Prevents coronary artery aneurysms	High; RCT, Newburger 1986 [11]
Streptococcal toxic shock syndrome (STSS)	IVIG 1–2 g/kg	Neutralizes superantigens; mortality trend	Moderate; RCT, Darenberg 2003 [7]
Staphylococcal toxic shock	IVIG 1–2 g/kg	Neutralizes TSST-1 and enterotoxins	Low to moderate; case series [9]
Neonatal sepsis	IVIG 500–750 mg/kg	Inconsistent; no confirmed benefit	Low; INIS trial negative [14]

Parvovirus B19 (immunocompromised)	IVIG 0.4 g/kg/day for 5 days	Resolves pure red cell aplasia	Moderate; case series, Crabol 2013 [18]
CMV post-transplant	CMV hyperimmune globulin	Prophylaxis and treatment in solid organ transplant	Moderate; transplant guidelines [19]
MIS-C (COVID-associated)	IVIG 2 g/kg plus steroids	Suppresses hyperinflammation; cardiac protection	High; ACR guidance [22]
Measles (post-exposure)	Immune globulin 0.5 mL/kg IM	Post-exposure prophylaxis in immunocompromised	Moderate; AAP Red Book [20]
Sepsis/septic shock	Polyclonal or IgM-enriched IVIG	Mortality signal in meta-analyses; not confirmed	Low to moderate; controversial [23,24]
Enteroviral encephalitis (agammaglobulinemia)	High-dose IVIG with or without intrathecal Ig	Viral clearance in B-cell deficiency	Low; case series [16]
Cerebral malaria (adjunctive)	Not applicable	NOT recommended; no proven benefit	Insufficient evidence

10. Dosing Quick Reference (Table 3)

Table 3: Recommended Dosing by Indication.

Indication	Product	Dose	Notes
CVID/primary immunodeficiency	IgG replacement	400–600 mg/kg IV every 3–4 weeks	Titrate to trough IgG above 500–800 mg/dL; may switch to subcutaneous Ig
Kawasaki disease	IVIG	2 g/kg IV single infusion	Give with aspirin; repeat if fever persists beyond 36 hours
Streptococcal/ staphylococcal TSS	IVIG	1 g/kg day 1; 0.5 g/kg days 2–3	Adjunct to surgery, beta-lactam, and clindamycin
Parvovirus B19 (immunocompromised)	IVIG	0.4 g/kg/day for 5 days	Repeat courses are often required; monitor reticulocyte response
MIS-C	IVIG	2 g/kg IV single infusion	Per ACR guidance; combine with methylprednisolone
Sepsis/septic shock (investigational)	Polyclonal or IgM-enriched IVIG	0.3–0.5 g/kg/day for 3 days	Not standard of care; consider in refractory cases
Neonatal sepsis	IVIG	500–750 mg/kg IV	Single dose; INIS trial showed no benefit in established infection

11. Situations Where IVIG Is Not Recommended (Table 4)

Table 4: Indications Where IVIG Should Not Be Used Routinely.

Scenario	Rationale
Routine bacterial sepsis (normal immune system)	No consistent mortality benefit in immunocompetent hosts; standard antibiotics and source control are the priority
HIV in adults on antiretroviral therapy	Effective antiretroviral therapy has supplanted the need for passive immunization
Uncomplicated viral infections	No clinically meaningful benefit in immunocompetent patients with self-limited viral illness
Clostridium difficile (standard cases)	Fecal microbiota transplantation and targeted antibiotics (vancomycin, fidaxomicin) are preferred; IVIG not recommended outside clinical trials
IgA deficiency (relative contraindication)	Risk of anaphylaxis due to anti-IgA antibodies in IgA-deficient recipients; use IgA-depleted preparations if IVIG is essential

12. Practical Considerations

Product selection matters. IgA content, osmolality, sucrose content, and half-life differ across formulations. The product should be matched to the patient risk profile; sucrose-containing products carry a higher risk of osmotic nephropathy [1].

Stewardship is essential. IVIG is plasma-derived and supply-constrained, and institutional stewardship programs govern its use. The clinical indication, expected benefit, and planned duration should be documented before initiating therapy.

Targeted products are preferred when available. For rabies (HRIG), varicella (VariZIG), hepatitis B (HBIG), and RSV (palivizumab, nirsevimab), disease-specific hyperimmune or monoclonal products are preferred over polyclonal IVIG [20].

12.1. Adverse Effects

Adverse effects range from mild to severe. Mild, common reactions include headache, flushing, fever, chills, and myalgia; these are rate-related and managed by slowing the infusion. Aseptic meningitis syndrome typically occurs within 24 h, is self-limited, and responds to nonsteroidal anti-inflammatory drugs. Hemolysis can occur from polyclonal anti-blood group antibodies, particularly in patients with blood group A, B, or AB; hemoglobin should be monitored. Thrombosis reflects hyperviscosity, particularly with high-dose regimens in older patients or those with cardiovascular risk factors. Renal failure from osmotic nephropathy is associated with sucrose-stabilized preparations, which should be avoided in patients with renal insufficiency. Anaphylaxis is rare, with the highest risk in patients with selective IgA deficiency due to anti-IgA antibodies [1,2].

12.2. Pre-Medication and Infusion Guidance

Acetaminophen and diphenhydramine given 30 minutes before infusion reduce infusion reactions. Infusions should begin at 0.5 mg/kg/minute and be titrated upward over 30 minutes if tolerated. Hydration before infusion reduces thrombosis risk with high-dose regimens [26].

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