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Use of Intravenous Immunoglobulin in Critically Ill Patients

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Abstract Intravenous immunoglobulin (IVIG) has been suggested for the treatment of many ailments due to its ability to modulate the immune system and to provide passive immunity to commonly circulating pathogens. Its use as primary and adjunctive therapy for the treatment of conditions affecting critically ill patients is an attractive option, especially when alternative therapy does not exist. The body of literature on the use of IVIG for the treatment of several serious conditions, including sepsis, toxic shock syndrome, acute myocarditis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and H1N1 influenza, were reviewed. Despite advances in treatment of these conditions since they were first described, there remains a paucity of well-designed studies on the use of IVIG for their treatment. Therefore, the use of IVIG for treatment of these conditions remains controversial.

Keywords IVIG · Immunoglobulin · Sepsis · Toxic shock syndrome · Toxic epidermal necrolysis · Stevens-Johnson syndrome · Myocarditis · Influenza

Introduction

Intravenous immunoglobulin consists of highly concentrated immunoglobulins that are derived from the pooled plasma of many healthy human donors. Intravenous immunoglobulin preparations contain not only mostly IgG but also traces of IgA and IgM. The Food and Drug Administration (FDA) requires that intravenous immunoglobulin (IVIG) contain at least a specified concentration of immunoglobulins to measles virus, *Corynebacterium diphtheriae*, poliovirus, and hepatitis B virus [1]. However, the concentration of immunoglobulins to other pathogens can be highly variable. Intravenous immunoglobulin has been used for many years for the treatment of humoral immunodeficiencies. Owing to its anti-inflammatory properties and immunomodulatory effects, IVIG has been used for various other conditions. Intravenous immunoglobulin derives its potent anti-inflammatory effects via several mechanisms. Intravenous immunoglobulin decreases proliferation of T cells and T cell subsets [2–5]. The production of pro-inflammatory cytokines TNF-alpha, IL-1, and IL-2 are reduced by IVIG [6–8]. Intravenous immunoglobulin is also thought to exert effects via competitive binding to Fc receptors on macrophages, thereby deactivating phagocytosis [9, 10]. The data supporting the use of IVIG in life-threatening conditions are varied with some supported by strong evidence, while others are merely anecdotal. This manuscript will review and summarize the supporting data for the use of IVIG in critically ill patients.

The mechanism of action of IVIG has not been clearly defined. Several proposed mechanisms have been suggested, with most evidence being limited to in vitro and animal studies. Anti-inflammatory effects of IVIG may arise from the presence of antibodies against pro-inflammatory cytokines (TNF-α, IL-1α, and IL-6) [11, 12]. Administration of IVIG also leads to increases in anti-inflammatory cytokines and potentially to downregulation of adhesion molecule, chemokine, and chemokine-receptor expression [13]. In individuals being treated for autoimmune and inflammatory conditions, excessive pro-inflammatory cytokines can lead to a state of decreased responsiveness to glucocorticoids [14]. Intravenous immunoglobulin has been shown to improve clinical responses and T cell affinity in glucocorticoid-resistant asthma,

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possibly via suppression of pro-inflammatory cytokine production [15, 16]. Immunomodulatory effects may be derived from interactions with IgG antigen-binding fragment (Fab) or Fc. The Fab portion of antibodies contained in IVIG binds to inflammatory proteins and receptors, such as cytokines, cytokine receptors, Fas, and CD5 [17, 18•]. An additional proposed mechanism of action is binding of IgG to complement fragments thereby blocking deposition on target tissues [19]. Neonatal Fc receptor (FcRn) prevents degradation of autoantibodies. Theoretically, IgG-saturated FcRn should result in increased autoantibody degradation. However, no studies have ever substantiated this theory. Intravenous immunoglobulin may upregulate expression of an inhibitory receptor, FcγRIIB, on macrophages and reduce pro-inflammatory response [20]. Additional evidence suggests that there may be a receptor on regulatory macrophages that recognizes sialylated Fc fragments of IgG contained in IVIG and promotes anti-inflammatory effects [18•].

Sepsis

Sepsis and septic shock are clinical syndromes characterized by a severe systemic inflammatory response to infection. The incidence of sepsis continues to increase. From 1997 to 2000, the incidence of sepsis increased from 82.7 to 240.4 per 100,000 population [21]. Fortunately, the mortality rate related to sepsis decreased during the same time period from 27.8 to 17.9 % [21]. The decreased sepsis mortality rate is likely related to advances in early recognition and attempts at early reversal of the condition. Despite decreasing mortality in sepsis, the disease burden and mortality rate remain unacceptably high. The backbone of sepsis therapy includes maintenance of appropriate hemodynamic status and prompt administration of antibiotics. Additional adjunctive therapies have been suggested for the treatment of sepsis, including IVIG. Intravenous immunoglobulin has been proposed for treatment of sepsis due to its ability to modulate inflammation and its ability to bind to endotoxin.

To date, trials have demonstrated conflicting results regarding the efficacy of IVIG in the treatment of sepsis. No conclusive evidence exists for the routine use of IVIG in the treatment of adult or pediatric sepsis. A randomized trial of 653 patients from 23 centers concluded that the use of IVIG for the treatment of sepsis did not decrease mortality rate or improve pulmonary function when compared to that of placebo. The 28-day mortality rate was 37.3 % in the placebo group versus 39.3 % in the IVIG group ($p=0.67$) [22]. Several meta-analyses, on the other hand, have demonstrated a reduction in 28-day mortality rate with the use of IVIG when compared to either placebo or no IVIG. However, all of these meta-analyses were limited by study heterogeneity. When the meta-analyses focused on only well-designed studies with low risk of bias, the mortality rate reduction disappeared [23–25]. One meta-analysis showed an overall reduction in mortality rate with the use of IVIG versus placebo (RR=0.79, 95 % CI 0.69, 0.9). This same study revealed a greater benefit of IgA- and IgM-enriched IVIG versus immunoglobulin preparation containing only IgG (RR=0.66, 95 % CI 0.51, 0.84) [26]. No large randomized controlled trials have compared IgA- and IgM-enriched IVIG versus placebo for the treatment of sepsis.

Likewise, data in children are conflicting. A randomized controlled trial of 100 children in Egypt with sepsis resulted in a decreased mortality rate and length of hospital stay in the group treated with IVIG [27]. In a meta-analysis, 640 neonates with suspected or proven sepsis reported a reduction in mortality rate with the use of IVIG versus no treatment or placebo. In this study, there was reduced mortality in both infants with suspected sepsis (RR=0.58, 95 % CI 0.38, 0.89) and in infants with proven sepsis (RR=0.55, 95 % CI 0.38, 0.98) [28]. This conclusion was encouraging for the potential utility of IVIG and provoked further investigation. Subsequently, a large and robust randomized controlled trial conducted by the International Neonatal Immunotherapy study (INIS) group of 3493 neonates being treated for suspected or proven sepsis found no benefit in the rates of mortality or major disability at 2 years of age with the use of IVIG versus placebo (RR=1.00, 95 % CI 0.92, 1.08) [29•].

Data on the use of IVIG for the treatment of adult and pediatric sepsis is not conclusive, yet most well-designed studies reveal no benefit. One adult meta-analysis demonstrated possible benefit with the use of IgA- and IgM-enriched IVIG. Large randomized controlled trials are needed to define the clinical utility of IVIG in sepsis treatment. Neonates are the only age group that have undergone a large randomized controlled trial; this demonstrated that there is no benefit for the use of IVIG in the treatment of sepsis in this age group. In this study, confounding was controlled for by randomizing neonates into treatment and placebo groups based on characteristics. In addition, the patients received a standard weight-based dose of IVIG. The main eligibility criterion for treatment was for infants to be receiving antibiotics for suspected or proven serious infection. The subjectivity of this inclusion criterion should be noted as a potential limitation of this study. Additionally, patients were not randomized according to the causative organism. Therefore, further studies analyzing the benefit of IVIG for the treatment of specific pathogens would be useful.

Toxic Shock Syndrome

Toxic shock syndrome, caused by *Staphylococcus aureus* or *Streptococcus pyogenes*, results from the release of bacterial exotoxins, such as toxic shock syndrome toxin-1 (TSST-1)

and streptococcal pyrogenic exotoxin A. These toxins, so-called superantigens, bypass the normal interaction of the antigen presenting cells and T-lymphocytes. The result is activation of large numbers of T cells and massive cytokine release [30]. Cytokine production accounts for the symptoms of toxic shock syndrome, including fever, hypotension, and skin manifestations. Normally, about 30 % of children demonstrate elevated titers of anti-TSST-1 antibody by the time they are 2 years old and greater than 90 % of people demonstrate elevated titers by the time they are 25 years old [31]. Conversely, patients presenting with toxic shock syndrome have a paucity of these antibodies [32]. Intravenous immunoglobulin has been shown in vitro to neutralize TSST-1 and streptococcal superantigens [33–35]. It has therefore been theorized that IVIG is helpful in the treatment of toxic shock syndrome due to its ability to neutralize superantigens, replace deficient antibodies, and via its general anti-inflammatory effects. In vitro neutralization of superantigens may depend on the specific IVIG preparation used [36].

Case reports suggest a potential role of IVIG for the treatment of streptococcal toxic shock syndrome [37, 38]. Furthermore, a retrospective observational study of 53 patients resulted in a reduction in 30-day mortality rate in the group treated with IVIG versus the group treated with placebo (67 versus 34 %, $p=0.02$) [39]. The only randomized controlled trial, consisting of 21 patients, was terminated early due to an inability to recruit an adequate number of patients. This study, however, did demonstrate a trend toward reduced 28-day mortality rate for patients with streptococcal toxic shock syndrome treated with IVIG (3.6-fold reduction). The trial did not achieve statistical significance ($p=0.3$) [40]. The effectiveness of IVIG for the treatment of streptococcal toxic shock syndrome in adults and children was challenged by a retrospective cohort of 192 pediatric patients. The use of IVIG versus placebo did not result in any difference in mortality rate (4.5 versus 4.5 %, $p=1.0$). Moreover, IVIG was associated with increased length of hospital stay (25 versus 12 days, $p=0.003$) [41]. The use of IVIG in the treatment of staphylococcal toxic shock syndrome is less well studied; however, an in vitro study suggests that *S. aureus* superantigen may be less effectively inhibited than that of *S. pyogenes* [42].

The treatment of streptococcal toxic shock syndrome is supported by several case reports and retrospective studies. At the same time, a pediatric retrospective cohort study demonstrated no benefit. Data on use of IVIG for the treatment of staphylococcal toxic shock syndrome is extremely lacking. While a large randomized controlled trial is needed to define the role of IVIG for the treatment of toxic shock syndromes, this would be challenging due to the rarity of the condition. With the given evidence, IVIG may be useful as adjunctive therapy for the treatment of streptococcal toxic shock syndrome.

Acute Myocarditis

Acute myocarditis is a clinical condition resulting from inflammation of cardiac muscle, which is often caused by viral illness. Both the antiviral and immunomodulatory effects of IVIG suggest that it may play a role in the treatment of acute myocarditis. In animal models using mice inoculated with coxsackievirus B3 or murine encephalomyocarditis virus, IVIG led to decreased myocardial damage, decreased production of the pro-inflammatory cytokines TNF-alpha, IFN-gamma, and IL-6, and better survival when compared to that of placebo (21/21 versus 10/21, $p<0.01$) [43, 44]. Multiple case reports and case series have documented the successful treatment of acute myocarditis with IVIG [45–48]. As none of these trials had a control arm, it is difficult to determine if patients improved as a result of the IVIG or as a result of the natural course of illness. The only randomized, controlled trial using 62 patients with acute dilated cardiomyopathy concluded no benefit of treatment with IVIG over placebo. Both groups demonstrated significant improvement in left ventricular ejection fraction over time; however, there was no significant difference between groups [49].

Viruses cause the majority of acute myocarditis in children. Intravenous immunoglobulin may be especially helpful in this group because the preparations contain pooled immunoglobulins against many viruses that circulate in the community. Still, the use of IVIG for the treatment of acute myocarditis remains controversial in children. No randomized controlled trials of IVIG for the treatment of myocarditis in children exist. A retrospective review compared 21 children treated with IVIG with a historical cohort of 25 children treated without IVIG. All had a diagnosis of acute myocarditis. Those treated with high-dose IVIG (2 g/kg) for presumed myocarditis had improved cardiac function at the time of treatment and up to 1 year after. There was also a trend toward improved survival 1 year later in the group treated with IVIG (84 versus 60 %, $p=0.069$) [50]. The results of this study may be confounded by the fact that the treatment group was observed from a later date, when other adjunctive therapy had improved, than that of the historical control group. The treatment group received cardiac medications (e.g., ACE inhibitors and inotropes) in addition to IVIG, whereas the historical control group did not. It is therefore difficult to differentiate whether the improvement in cardiac function was due to the IVIG versus other cardiac medications.

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are considered variants of the same pathologic process [51]. They are characterized by widespread blisters and purpuric lesions. Both are severe, life-

threatening reactions, most commonly in response to medications (or infection in children). Both conditions are caused by an overexpression of Fas ligand-induced keratinocyte apoptosis, which then leads to necrosis and sloughing of the epidermis. The most important component of therapy for SJS/TEN is supportive care with a focus on maintenance of fluid and electrolyte status and prevention of infection. Intravenous immunoglobulin is a suggested treatment adjunct as it blocks the Fas-Fas ligand-mediated keratinocyte apoptosis [52].

Several case reports and case series have reported the successful treatment of both SJS and TEN with IVIG [53–57]. A handful of retrospective cohort studies have failed to show a significant reduction in mortality rate, despite a trend toward reduced mortality rate [58–61]. All studies were small, owing to the rarity of SJS and TEN. One Chinese retrospective cohort of 82 patients did demonstrate a reduced hospital length of stay with the use of IVIG plus corticosteroids versus corticosteroids alone (26.4±9.5 versus 18.1± 5.3 days, $p<0.05$) [58]. Therefore, IVIG may have some utility in the treatment of SJS and TEN, but the evidence is not sufficient to say this with certainty.

H1N1 Influenza

Pandemic 2009 H1N1, sometimes called "swine flu," is a novel strain of influenza that was first described in April 2009. Compared to seasonal influenza in previous years, 2009 H1N1 disproportionately affects healthy people under the age of 65 [62]. A study by the CDC reported low levels of IgG against 2009 H1N1 in people younger than 65. Immunoglobulin G against pandemic influenza was found in the serum of no children, in 6–9 % of serum of 18- to 64-year olds, and in 33 % of serum of those greater than 65 years old [63]. Additional therapeutic options are needed for cases of severe influenza and for cases caused by oseltamivir-resistant strains.

Convalescent serum was historically used for treatment of many illnesses prior to the availability of antibiotics. A meta-analysis reported decreased crude mortality rate in patients infected with Spanish flu when treated with convalescent human serum from survivors [64]. More recently, case reports have demonstrated successful treatment of influenza-associated acute respiratory distress syndrome with either convalescent serum or IVIG [65, 66]. Intravenous immunoglobulin preparations from plasma obtained even prior to the 2009 pandemic influenza outbreak contain neutralizing antibody against 2009 H1N1 influenza [67, 68]. Treatment of 2009 H1N1 influenza virus-infected mice with IVIG resulted in improved survival when compared with that of placebo (88 versus 30 %) [69]. Hyperimmune IVIG (H-IVIG), prepared from convalescent plasma from patients who recovered from 2009 H1N1 influenza, may be a promising treatment for patients with severe influenza. A double-blind randomized controlled trial of 35 patients reported a significantly lower day 5 and day 7 post treatment influenza viral load (3.3 versus 4.67 $\log_{10}$ copies, $p=0.04$ and undetectable versus 4.53 $\log_{10}$

Table 1 Utility of IVIG therapy by condition and age group

Condition	Age group	Utility of IVIG therapy	Strength of evidence [ref no.]	Comments [ref no.]
Sepsis	Adult	None	None (meta-analyses of randomized controlled trials) [23–25]	IgA- and IgM-enriched immunoglobulin preparations may be of benefit, but require further study [26]
	Pediatric	Possible	Moderate (medium-sized randomized controlled trial) [27]	
	Neonates	None	Good (large randomized controlled trial) [29•]	
Toxic shock syndrome				
Streptococcal	Adult	Possible	Weak (case reports, retrospective observational study) [37–39]	Overall data to support the use of IVIG in Toxic Shock Syndrome is weak-moderate and should not be considered the standard of care
	Pediatric	Possible	Moderate (large retrospective cohort) [41]	
Staphylococcal	All	Unknown	Very weak (in vitro study) [42]	
Acute myocarditis	Adult	None	Moderate (medium-sized randomized controlled trial) [49]	May be of value in severe cases of myocarditis
	Pediatric	Possible	Weak (retrospective review) [50]	
SJS/TEN	All	Unlikely	Weak (case reports, retrospective cohorts) [53–61]	Overall data to support the use of IVIG in SJS/ TEN is weak and thus should be used with caution Although uncommon, SJS/TEN has been reported as an adverse event from IVIG
2009 H1N1	All	Possible	Weak (historical data, in vitro studies, small-sized randomized controlled trial) [65–70]	May be especially useful in subgroups of patients (IgG2 deficient/severe illness) [73]

copies, $p=0.02$, respectively) and reduced mortality (OR 0.14, 95 % CI 0.02, 0.92) when compared with that of the control group [70]. Patients with IgG2 subclass deficiency can have especially severe disease secondary to 2009 H1N1 influenza [71, 72]. A case series documenting treatment of this group of patients with H-IVIG resulted in clinical improvement [73]. Treatment with H-IVIG may be limited by practical aspects of convalescent plasma collection [74].

While no randomized controlled trials have assessed the utility of IVIG for the treatment of 2009 H1N1 influenza, prior success when using convalescent serum from influenza survivors suggest that immunoglobulins may serve as treatment adjuncts. Certain patient subgroups, including those with severe illness and those with IgG subclass deficiencies may derive greater benefit.

Adverse Events Associated with IVIG

A large percentage of patients receiving IVIG experience adverse effects [75]. These include mild reactions such as fever, chills, abdominal pain, myalgias, or headaches [76]. More serious reactions have been reported and include anaphylaxis, hypotension, thrombotic events, aseptic meningitis, Stevens-Johnson syndrome, and renal failure [76]. Potential risks and benefits must be fully considered when prescribing IVIG for critically ill patients.

Another consideration with the use of IVIG is the potential for transmission of infectious agents. Prior to 1985 and the advent of HIV antibody testing in blood products, an estimated 12,000 to 25,000 individuals were infected through receipt of red blood cells, platelets, or plasma [77]. Likewise, hepatitis C was once commonly spread through transfusion prior to 1992 when routine screening of blood products began in the USA [78]. Although the blood supply undergoes rigorous screening for known viruses and the risk of transmission is low, there is a very real risk of transmission of yet to be discovered infectious agents. This is evidenced through the history of HIV and hepatitis C transmission. Variant Creutzfeldt-Jakob disease (vCJD), which many people may have been exposed to during travels or residence in the UK and other European countries, can also be transmitted through the blood supply. Based on models, the risk of transmission through red blood cell transfusion is estimated to be between 1 in 480,000 to 1 in 134 million [79]. While prion filtration and donor deferral appear to be effective approaches to reduce the risk of transmission, they are not currently employed [80, 81].

Summary

Intravenous immunoglobulin exerts its effects through immunoglobulin replacement, anti-inflammatory effects, and immunomodulatory effects. Based on these properties, IVIG has been proposed as an adjunct therapy for critically ill patients. However, conclusive data to support the use of IVIG in sepsis, toxic shock syndrome, acute myocarditis, SJS/TEN and severe H1N1 is lacking (Table 1). The INIS trial provided definitive evidence of no utility of IVIG for treatment of sepsis in neonates. While most adult studies suggest no role of IVIG for the routine treatment of sepsis, there is some evidence to suggest that IgA- and IgM-enriched immunoglobulin preparations may play a role as treatment adjuncts. Additionally, sporadic, anecdotal case reports do show some benefit in individual patients. Despite this, to decide upon whether routine use of IVIG should be a standard of care in certain conditions, rigorous trials to support the use of IVIG in the treatment of pediatric and adult sepsis are still needed. Well-designed studies documenting the clinical utility of IVIG for treatment of streptococcal toxic shock syndrome are also lacking. However, in vitro and several smaller in vivo studies suggest that IVIG may play a beneficial role in streptococcal toxic shock syndrome. The evidence for use of IVIG for the treatment of staphylococcal toxic shock syndrome is virtually nonexistent. Data for the use of IVIG for the treatment of acute myocarditis is conflicting but may provide some benefit in the pediatric population where viral etiologies tend to predominate. Likewise, smaller studies resulted in inconsistent outcomes for the use of IVIG in the treatment of SJS and TEN. Influenza virus has been successfully treated in the past with convalescent serum of survivors, suggesting a current role of IVIG for the treatment of pandemic 2009 H1N1 influenza virus. A small randomized controlled trial reported improved survival. Intravenous immunoglobulin may be especially beneficial in patients with severe illness secondary to influenza virus and those with IgG2 deficiency. Larger, more rigorous studies are required for definitive evidence to support the use of IVIG in critically ill patients.

Compliance with Ethics Guidelines

Conflict of Interest Summer Donovan and Gonzalo Bearman have no disclosures relevant to this work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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