Immunoglobulin replacement has long been used in the prevention and treatment of infectious diseases. In the late 1800s, scientists first recognized the protective effect of sera obtained from rabbits immunized with tetanus toxin. This finding led to an initial interest in curative sera, which were primarily antitoxins obtained from animals. Complications from serum sickness, however, limited the use of these products and prompted investigation of human convalescent sera. During World War I, there was widespread use of curative sera for treatment of tetanus, diphtheria, and pneumococcal disease. Immunoglobulin replacement therapy was greatly improved in the 1930s and 1940s when fractionation techniques were developed that allowed separation of plasma proteins into stable fractions with different biologic functions, including targeted treatment of poliomyelitis, measles, mumps, pertussis, and hepatitis A.¹ Although largely replaced by vaccines, this foundation for the production of polyclonal immunoglobulins remains in use today and has lead to the development of multiple applications of immunoglobulin therapy for infectious and noninfectious diseases.

The authors have nothing to disclose.

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Intravenous immunoglobulin (IVIG) is a therapeutic preparation of pooled, normal, polyspecific immunoglobulin, which has activity against a broad spectrum of viral and bacterial pathogens. Immunoglobulin products are used extensively for the replacement of antibody deficiencies in primary and secondary immunodeficiency states. However, the mechanisms of action are far more complicated than restoration of normal humoral immune function through increased antibody levels (Box 1). Data showing immunomodulatory and antiinflammatory effects have heightened interest in the use of IVIG for prophylaxis against infection and treatment of severe infections, including sepsis, toxic shock syndrome, *Clostridium difficile* infection (CDI), and cytomegalovirus (CMV) disease, among others.3

Despite the application of IVIG therapy in more than 150 noninfectious and infectious disease states, there are limited conditions for which this therapy is approved by the US Food and Drug Administration (FDA). These conditions include idiopathic thrombocytopenia purpura, Kawasaki disease, primary immunodeficiency, secondary hypogammaglobulinemia caused by B-cell chronic lymphocytic leukemia, prophylaxis in stem cell transplant recipients, and prophylaxis in pediatric HIV/AIDS.4,5 The increased use of IVIG therapy in combination with its high cost, decreased reimbursement, and manufacturing limitations has placed new importance on determining the most efficacious and cost-effective applications of this treatment.4,6 The following review focuses on infectious disease states for which immunoglobulin therapy has been applied in adult populations and for which there are data regarding efficacy. Infections for which the data are more limited are outlined in Table 1.

**BACTERIAL INFECTIONS**

**Sepsis**

Because of the high mortality associated with bacterial sepsis, there has long been interest in understanding and developing treatments adjunctive to antibiotics, such as IVIG. Mechanisms for a possible benefit of IVIG in sepsis include enhanced bactericidal activity through opsonizing immunoglobulin (Ig)G and IgM antibodies, stimulation of phagocytosis, and neutralization of bacterial toxins.7,8 IVIG may also suppress the release of proinflammatory cytokines from endotoxin- or superantigen-activated blood cells.7,8 Although multiple individual observational studies and randomized controlled trials have supported the use of IVIG in sepsis and septic shock, more
recent meta-analyses have cast doubt on its benefit. In 2007, 3 systematic reviews were published showing a mortality benefit when IVIG was compared with placebo, with relative risk (RR) ratios of 0.74 and 0.79 in 2 of the reviews.9–11 Similarly, Laupland and colleagues11 reported a significant reduction in mortality associated with IVIG treatment with a pooled odds ratio of 0.66 (95% confidence interval [CI] 0.53–0.83, \( P < .0005 \)). However, these analyses were limited by considerable study heterogeneity and the result was not replicated when only high-quality trials were analyzed. Thus, the investigators emphasized the need for a well-designed, adequately powered, and transparently reported study.11 This recommendation was confirmed by the most recent Cochrane review, which included 42 studies comparing IVIG (polyclonal and monoclonal) to placebo or no intervention in patients with bacterial sepsis or septic shock. There was a significant mortality benefit when IVIG was compared with placebo (RR 0.81; 95% CI 0.70–0.93). However, analysis of trials with a low risk of bias yielded no reduction in mortality (RR 0.97; 95% CI 0.81–1.15).12

Patients with postoperative sepsis have also been examined separately from mixed populations with sepsis. Rodriguez and colleagues13 randomized patients with severe sepsis and septic shock of intra-abdominal origin to 2 treatment groups: antibiotics plus polyvalent IgM-enriched IVIG or antibiotics plus albumin (control). In this study, no specific benefit from the addition of IVIG was identified, and inappropriate antibiotic therapy was the only variable independently associated with death. Additionally, there has been interest in the use of IVIG in postcardiac surgery patients because of the high risk of postoperative sepsis in combination with postulated changes in immune function related to intraoperative extracorporeal membrane oxygenation.14 Pilz and colleagues15 showed a reduction in morbidity and severity of disease in patients treated with IVIG and IgM-enriched IVIG with an Acute Physiology and Chronic Health Evaluation II score greater than or equal to 24 on the first postoperative day following cardiac surgery with extracorporeal circulation. There are scant data, however, to draw any further conclusions regarding the benefit of IVIG in a general surgical population or specific subsets, such as cardiac surgery patients.

Overall, the small size of trials and heterogeneity, both in patient characteristics and treatment strategies, has limited the ability to draw conclusions regarding the use of IVIG in sepsis. Thus, IVIG is not routinely recommended for use in sepsis. High-quality randomized trials are needed to adequately answer this question.

Table 1

Infectious diseases with limited evidence for IVIG use

<table>
<thead>
<tr>
<th>Infection</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. jejuni</em></td>
<td>There was a single report of use in a patient with common variable immune deficiency with frequent recurrences; responded to treatment with oral Ig.85</td>
</tr>
<tr>
<td>Erythrovirus (Parvovirus B19)</td>
<td>Patients with congenital or acquired immunodeficiencies are at risk for chronic Erythrovirus infection, often manifested by pure red cell aplasia (PRCA). Case reports have shown success in treating erythrovirus-associated PRCA, and a single series showed success in treating dilated cardiomyopathy caused by Erythrovirus infection.87,88</td>
</tr>
<tr>
<td>Enteroviruses</td>
<td>Patients who are agammaglobulinemic are at risk for chronic enteroviral meningoencephalitis (CEM) with slowly progressive ataxia, loss of cognitive skills, and paresthesias. Twelve of 42 patients with CEM were treated with IVIG and intrathecal Ig and 6 were observed to have clinical improvement.89</td>
</tr>
</tbody>
</table>
**Toxic Shock Syndrome**

In 1992, IVIG was first reported as an adjunctive treatment in a previously healthy 32-year-old woman with refractory shock caused by toxin-producing *Streptococcus pyogenes*. Based on the rapid clinical improvement reported in this patient, interest in IVIG as an adjunctive treatment of toxic shock syndrome (TSS) grew. Early observational work showed IVIG administration was associated with survival because of the postulated mechanisms of enhanced bacterial neutralization and reduced T-cell production. IVIG also provides passive immunization against pyrogenic exotoxins.

In the first randomized, double-blind, placebo-controlled trial evaluating IVIG as an adjunctive therapy, a 3.6-fold higher mortality was identified in the placebo group, and a significant decrease in sepsis-related organ failure was seen in the IVIG group. However, statistical significance in the primary end point of decreased mortality was not reached because the trial was terminated early because of slow patient recruitment. Subsequent studies in mice have shown enhanced systemic clearance of bacteria and enhanced neutrophil infiltration into infected tissue, which would imply benefit. However, when penicillin and clindamycin were used concomitantly, IVIG did not confer additional benefit. Similar results were seen in a pediatric population in which IVIG increased cost, but did not show an association with improved outcome.

The use of IVIG in sepsis is biologically plausible and, therefore, clinicians continue to use it in life-threatening disease, most commonly in a single dose of 400 mg/kg. The current data, however, do not support a recommendation for use in streptococcal TSS.

As with streptococcal TSS, staphylococcal TSS is linked to the bacterial production of superantigens, such as TSS toxin (TSST-1). However, the mortality is lower than streptococcal TSS, averaging 5%. Evidence evaluating IVIG for staphylococcal TSS is limited to in vitro studies showing neutralization of superantigens and case reports. Thus, the level of evidence is weak, and IVIG is not recommended in staphylococcal TSS.

**Clostridium Difficile Infection**

Over the past decade, CDI has increased in incidence and severity, becoming the most common cause of health care–associated diarrhea in the United States, with an estimated cost of $1.1 billion per year. Additionally, there has been increasing concern for treatment failures with metronidazole, as well as failures among specific patient subsets, including elderly and immunocompromised patients. Because of the inadequacy of the current treatments, attention has turned to alternative means of therapy. Previous studies of passive immunization in animal models have shown positive results, and human data have shown that patients with low serum antibody levels to *C difficile* toxin A are at risk for development of CDI. Taken together, these observations provide a rationale for immunoglobulin therapy in CDI. Abougergi and Kwon summarized the available case reports and series reporting the use of IVIG treatment in CDI. In studies evaluating protracted or relapsed CDI, 40 of 46 patients (87%) experienced resolution of diarrhea. When severe CDI was examined separately, 32 of 51 patients (67%) survived their illness. Similarly, O’Horo and Safdar found an overall benefit in a small case series with the use of IVIG, but small sample sizes, publication bias, and lack of control groups did not allow for recommendation regarding the use of IVIG. Various dosages of IVIG, ranging from 1 dose of 150 mg/kg to 400 mg/kg weekly, have been used. Additionally, there is variation in the level of *C difficile*–specific antibodies among various IVIG preparations, and this may lead to mixed study results. This treatment strategy is biologically plausible and observational data are promising, but the level of evidence remains weak.
More recently, attention has turned to the treatment of CDI with human monoclonal antibodies directed against *C difficile* toxins A and B, which has the advantage of targeting therapy and avoiding the increased use of pooled IVIG. In a phase II trial, 200 patients receiving either metronidazole or vancomycin for CDI treatment were randomized to antibody and placebo. Among the antibody group, the rate of CDI recurrence was decreased compared with placebo (7% vs 25%; 95% CI 7–29; *P* < .001). No increase in adverse events was seen. This strategy is promising and further study is underway.

**Other Clostridial Infections**

The treatment of tetanus is a 2-part approach: antibiotics to decrease bacterial burden and immunoglobulins to neutralize unbound toxin or tetanospasmin. Although unbound toxin is identified in a minority of patients at presentation, substantial decreases in mortality have been seen with immunoglobulin therapy. Beginning in the late 1800s, equine antibodies, produced in response to vaccination with *Clostridium tetani*, were used for treatment of tetanus, resulting in a substantial decline in mortality rates in the United States. These rates further declined with the introduction of a tetanus vaccine in the 1940s and again, in 1960, with the introduction of human tetanus immunoglobulin (TIG). Currently, the Centers for Disease Control (CDC) recommend 1 dose of 250 IU TIG (HyperTET S/D) given intramuscularly in unimmunized or inadequately immunized patients who sustain high-risk wounds, including deep punctures or contaminated wounds, in addition to vaccination with a tetanus toxoid-containing vaccine for development of long-term immunity. Similar treatment is recommended for established tetanus infection; however, the recommended dose of TIG is 500 IU given in 1 dose.

Unlike tetanus, equine antitoxin remains the treatment of choice for *Clostridium botulinum* infection, or botulism, because there is no human hyperimmune globulin available. Heptavalent botulinum antitoxin is the only treatment available in the United States for the treatment of noninfant botulism, and it is available through a cosponsored CDC and FDA investigational new drug (IND) protocol.

**Diphtheria**

The primary sequelae of *Corynebacterium diphtheriae* infection are related to a potent toxin causing respiratory, cardiac, and neurologic disease. Because of vaccination, the burden of diphtheria in the United States is low, with no cases reported since 2003. However, travelers to endemic areas, such as sub-Saharan Africa, countries of the former Soviet Union, and much of Asia, are at risk. At present, no human diphtheria immunoglobulin product is available in the United States. Treatment of *C diphtheriae* infection relies on an equine antitoxin, in conjunction with antimicrobial agents. Because of the risk of allergic reaction, postexposure prophylaxis with antitoxin is not recommended, but rather vaccination and antimicrobial therapy should be implemented. Currently, diphtheria antitoxin can only be obtained through the CDC as an IND, and the recommended dose is based on the site, duration, and severity of infection (range 20,000 IU –120,000 IU). Skin sensitivity testing must be performed before use.

**VIRAL INFECTIONS**

**Cytomegalovirus Infection in Solid Organ Transplant**

Neutralizing antibodies are thought to play a role in the immune response that controls CMV infection and, therefore, interest has risen in the use of immunoglobulins as
a prophylaxis and adjunctive therapy for CMV in solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients. Both IVIG, containing a high titer of anti-CMV antibodies from healthy blood donors, and CMV hyperimmune globulin (CMV-Ig; CytoGam) have been used for the prevention of CMV disease, although supporting data are limited. IVIG and CMV-Ig use became widespread for SOT prophylaxis after the demonstration of benefit in reducing CMV disease in kidney and liver transplants.\textsuperscript{41,42} A subsequent systematic review of 37 trials (2185 participants) evaluating IVIG and CMV-Ig for prophylaxis in SOT recipients showed decreased risk of mortality from CMV disease (Fig. 1).\textsuperscript{43} However, there was no significant difference in the risk for CMV infection, CMV disease, or all-cause mortality when compared with placebo or antiviral therapy alone.\textsuperscript{43} These data do not support routine use of prophylactic IVIG or CMV-Ig in SOT recipients.

The risks associated with established CMV disease are extensive in SOT recipients, including directly attributable mortality, late-onset malignancy, acute and chronic allograft injury, and chronic allograft vasculopathy.\textsuperscript{44} Given these concerns, individual clinicians and transplant centers routinely elect to use immunoglobulin products in addition to first-line treatment with ganciclovir or valganciclovir. This practice is common in specific patient populations, such as lung transplants, in which as many as one-third of transplant centers use adjunctive immunoglobulins.\textsuperscript{45} Currently, it is unclear if the addition of IVIG or CMV-Ig is beneficial in specific SOT populations, but it may be considered for patients with CMV pneumonitis and possibly other severe or treatment-refractory forms of disease.\textsuperscript{44} Further research is needed to define appropriate use in SOT recipients with established CMV disease,

![Review: Immunoglobulins, vaccines or interferon for preventing cytomegalovirus disease in solid organ transplant recipients](image)

### Fig. 1. Comparison of IgG versus placebo/no treatment (all patients), all-cause mortality.

Eight studies comparing IVIG versus placebo for prevention of CMV among HSCT recipients examined all-cause mortality as a primary endpoint. No significant difference in mortality was identified when IVIG was used compared with placebo. (Reproduced From Hodson EM, Jones CA, Strippoli GF, et al. Immunoglobulins, vaccines or interferon for preventing cytomegalovirus disease in solid organ transplant recipients. Cochrane Database Syst Rev 2007;2:CD005129. Copyright Cochrane Collaboration; with permission.)
especially lung and intestine recipients and hypogammaglobulinemic heart transplant recipients.\textsuperscript{46,47}

**Cytomegalovirus Infection in Hematopoietic Stem Cell Transplant**

Similar to SOT recipients, hematopoietic stem cell transplant recipients are at a high risk from CMV infection and disease. Several trials published before 2000 prompted the National Institutes of Health to publish consensus guidelines endorsing the use of prophylactic IVIG after allogeneic bone marrow transplant (BMT).\textsuperscript{48–51} However, with the increased use of prophylaxis, an increased risk of venoocclusive disease was seen without an associated survival benefit.\textsuperscript{52} Thus, prophylaxis was examined further. In a recent meta-analysis, CMV infections were not significantly reduced with either polyvalent IVIG or CMG-Ig, and an increased risk of hepatic venoocclusive disease was seen with polyvalent IVIG.\textsuperscript{50} Similarly, analysis of the newer studies examining interstitial pneumonitis showed no benefit with IVIG.\textsuperscript{50} Based on these data, there seems to be no advantage for the use of IVIG or CMV-Ig in HSCT prophylaxis.

With the widespread use of ganciclovir and valganciclovir for CMV disease, the use of adjunctive IVIG or CMV-Ig has become less common in HSCT recipients. However, antiviral monotherapy failure rates often exceed 50\%, which has prompted some clinicians and transplant centers to use combined CMV-Ig and ganciclovir. The benefit of CMV-Ig among HSCT recipients has been examined in several small studies.\textsuperscript{47,53–55} In one study, 25 consecutive patients with CMV pneumonitis were treated with CMV-Ig and ganciclovir. Survival was enhanced in the combination therapy group (13/25, 52\%) compared with antiviral monotherapy (13/89, 15\%) (\(P<.001\)).\textsuperscript{54} Although this result was supported by other small studies, one trial found no benefit, with 4 out of 4 patients dying before hospital discharge.\textsuperscript{53,56} Recently, retrospective analysis of 35 patients at a single center showed a mortality rate of 49\% with combination therapy, comparable to other combination treatment studies but lower than in studies of antiviral monotherapy.\textsuperscript{55} In summary, the available data limit drawing firm conclusions regarding the use of adjunctive immunoglobulin products in HSCT recipients with CMV disease. Given the high mortality of this disease and the tolerability of immunoglobulin products, further research should be pursued.

**Hepatitis A**

IVIG has been used for the prevention of hepatitis A (HAV) infection since the mid-1940s when it was found to end outbreaks in communal living situations, including children’s camps, battlefields, and institutions for the mentally ill.\textsuperscript{57,58} IVIG is 80\% to 90\% protective against the development of clinical hepatitis when administered as a postexposure prophylaxis within 2 weeks, and despite waning antibody levels in pooled IVIG, antibody levels in pooled IVIG seem to be sufficient for replacement.\textsuperscript{58–61} The protection derived from IVIG results from the prevention of early clinical disease, whereas subclinical HAV viremia prompts the development of a longer-lived antibody response.\textsuperscript{36}

In 1995, highly effective HAV vaccines were first licensed in the United States for preexposure prophylaxis, thus, limiting the use of IVIG. Preexposure IVIG is only recommended for high-risk persons who could not be vaccinated, including infants aged younger than 12 months, individuals with an allergy to vaccine components, or travelers declining vaccination.\textsuperscript{60} More recently, HAV vaccination also became an acceptable option for postexposure prophylaxis based on data showing equivalent protection to IVIG when administered within 2 weeks of HAV exposure in persons aged 2 to 40 years.\textsuperscript{62} The current Centers for Disease Control (CDC) guidelines recommend a single dose of IVIG 0.02 mL/kg for groups requiring postexposure prophylaxis.
in whom the vaccine has not been evaluated, including children aged younger than 12 months; immunocompromised individuals; individuals with chronic liver disease; and individuals for whom the vaccine is contraindicated.\textsuperscript{59}

**Hepatitis B**

Hepatitis B immunoglobulin (HBIG; HepaGam B, HyperHEP B, Nabi-HB) is prepared from the plasma of donors with high concentrations of hepatitis B virus (HBV) surface antibody but no evidence of hepatitis B surface antigen (HBsAg). HBIG is most commonly used as part of passive-active immunization in postexposure settings, as well as in the prevention of maternal-child transmission. The combination of HBIG and vaccine are highly effective in preventing the transmission of HBV, with studies in health care workers and sexual contacts of HBV-infected persons showing 80\% to 90\% efficacy when treatment is completed within 7 days for needlesticks and 14 days for sexual contact.\textsuperscript{63–65} Use of HBIG alone provides temporary protection (3–6 months) and is also efficacious.\textsuperscript{66–68}

More recently, with an increase in liver transplantation for HBV infection, attention has turned to the use of HBIG for posttransplant treatment of HBV. Variation in antiviral regimens posttransplant, as well as dosing of HBIG, has limited conclusions regarding the efficacy of this therapy. A recent Cochrane review identified 4 randomized trials evaluating lamivudine or adefovir alone or combined with HBIG. The trials were underpowered and no statistically significant difference in all-cause mortality or recurrence of HBsAg was identified.\textsuperscript{69} Chen and colleagues\textsuperscript{70} completed a more recent systematic review on this subject. Examining 44 nonrandomized trials, they found that with long-term HBIG prophylaxis, hepatitis B recurrence ranged from 3.7\% to 65.0\% compared with lamivudine monotherapy, whereby recurrence ranged from 3.8\% to 40.4\%. The rate of recurrence was lowest with combination therapy, whereby recurrence decreased to less than 10\%. These data are encouraging; however, larger, randomized, controlled trials are needed to best assess optimal HBV prevention after liver transplantation.

**Varicella**

In 1969, zoster immune globulin (ZIG), prepared from patients recovering from herpes zoster, was shown to prevent clinical varicella among children when administered within 72 hours after exposure and to lower disease rates in immunocompromised persons when given within 96 hours after exposure.\textsuperscript{71,72} This effect was further demonstrated in patients receiving high-titer lots because they had a significantly lower rate of complications.\textsuperscript{73} In 1978, varicella zoster immune globulin (VZIG), prepared from healthy volunteer blood donors with high varicella zoster virus antibody titers, became available. Serologic and clinical comparison of ZIG and VZIG showed equal efficacy.\textsuperscript{74,75} As in other vaccine-preventable infections, use of immune globulin for varicella zoster infection has decreased since the varicella vaccine was implemented as part of a postexposure prophylaxis in healthy adults. VZIG as a prophylactic measure has not been evaluated in healthy or immunocompromised adults. However, VZIG can be considered in susceptible patients (no history of varicella disease or vaccination), if the exposure is likely to result in infection and the patient is at a greater risk for complications than the general population, including immunocompromised adults and pregnant women.\textsuperscript{74} Because of the lack of data in adult prophylaxis, the appropriate dose of VZIG is unknown.\textsuperscript{74} However, CDC guidelines state that 625 U should be sufficient to modify or prevent infection in healthy adults.\textsuperscript{74} The appropriate dose for immunocompromised adults is unknown. Finally, administration of VZIG
should take into account the high cost of this treatment ($400 for patients weighing more than 40 kg) in combination with the short-term nature of protection and limited production of VZIG.74

Rabies

Two human rabies immunoglobulin products (HRIG; HyperRab S/D, Imogam Rabies-HT) are derived from hyperimmunized donors and licensed for rabies postexposure prophylaxis in the United States. Two studies have demonstrated the role of HRIG administration in conjunction with vaccination as a postexposure prophylaxis, specifically in the development of a protective antibody response during the first 5 days after administration.76,77 Simultaneous vaccination provides longer-term protection. Therefore, the CDC recommends the administration of HRIG 20 IU/kg body weight once at the beginning of rabies prophylaxis. If not begun at the time of initial vaccination, HRIG can be administered up to and including day 7 of the postexposure prophylaxis series.78 If anatomically feasible, HRIG should be fully administered in and around the wound, and the first vaccine dose should be given at an anatomically distant location to prevent neutralization by HRIG.79 If the entire dose cannot be infiltrated around the wound, the remaining volume should be administered intramuscularly at an anatomic site distant from that used for the active vaccine.

Respiratory Syncytial Virus Infection

There are limited data for the use of IVIG or hyperimmune globulin to treat adults with respiratory syncytial virus (RSV) infection because it is typically a self-limited infection. BMT recipients, however, are at risk for severe upper respiratory tract infection followed by pneumonia with an associated mortality rate of 60%.80,81 Uncontrolled trials support the use of IVIG in combination with aerosolized ribavirin, especially in high-risk patients with an HSCT transplant in the pre-engraftment period.81,82 No controlled trials examining aerosolized ribavirin and IVIG together have been performed. This treatment approach remains controversial because of the cost and logistical issues with the use of aerosolized ribavirin.

ADVERSE EFFECTS

Immunoglobulin therapy is complex and the incidence of adverse reactions is high. One previous study showed 440 of 1000 patients with primary immunodeficiency reported adverse effects that were not related to the rate of infusion.5 These adverse effects are typically mild and nonanaphylactic, including back or abdominal pain, nausea, rhinitis, asthma, chills, fever, myalgia, or headache. Additionally, many of these reactions can be reversed by slowing the infusion or with the use of steroids and hydration. Up to 34% of reactions occur with the first infusion and the risk of adverse reaction declines with continued therapy.5 However, given the potential for severe and life-threatening reactions, including anaphylaxis, hypotension, adult respiratory distress syndrome, thrombosis, and Stevens-Johnson syndrome, vigilance must be maintained with each infusion. In addition to the potential for immediate complications, patients must be counseled on the risk of infection transmission, such as prion diseases, HIV, and viral hepatitides, as well as the risk of nephrotoxicity, which has primarily been reported with the use of sucrose-containing products.5,83 Lastly, complications related to venous access must also be considered when weighing the risks and benefits of Ig treatment.
Outside of the specific examination of oral Ig therapy in gastrointestinal infections with rotavirus, *Campylobacter jejuni*, and *C. difficile*, intravenous Ig has been the primary route of administration. More recently, subcutaneous infusion of Ig has been investigated as an alternative given the improved side-effect profile and enhanced

Table 2
Infectious Diseases Society of America: US public health service grading system for ranking recommendations in clinical guidelines

<table>
<thead>
<tr>
<th>Category, Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength of Recommendation</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Good evidence to support a recommendation for use</td>
</tr>
<tr>
<td>B</td>
<td>Moderate evidence to support a recommendation for use</td>
</tr>
<tr>
<td>C</td>
<td>Poor evidence to support a recommendation</td>
</tr>
<tr>
<td>D</td>
<td>Moderate evidence to support a recommendation against use</td>
</tr>
<tr>
<td>E</td>
<td>Good evidence to support a recommendation against use</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Evidence from ≥1 properly randomized controlled trial</td>
</tr>
<tr>
<td>II</td>
<td>Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from &gt;1 center); from multiple time series; or from dramatic results from uncontrolled experiments</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees</td>
</tr>
</tbody>
</table>


ROUTE OF ADMINISTRATION

Outside of the specific examination of oral Ig therapy in gastrointestinal infections with rotavirus, *Campylobacter jejuni*, and *C. difficile*, intravenous Ig has been the primary route of administration. More recently, subcutaneous infusion of Ig has been investigated as an alternative given the improved side-effect profile and enhanced

Table 3
Summary of evidence for use of IVIG in infectious diseases

<table>
<thead>
<tr>
<th>Indication</th>
<th>Level of Evidence</th>
<th>Plain Language</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>IIC</td>
<td>May be beneficial</td>
</tr>
<tr>
<td>Streptococcal TSS</td>
<td>IIC</td>
<td>May be beneficial</td>
</tr>
<tr>
<td>Staphylococcal TSS</td>
<td>IIIC</td>
<td>May be beneficial</td>
</tr>
<tr>
<td><em>C. difficile</em></td>
<td>IIC</td>
<td>May be beneficial</td>
</tr>
<tr>
<td><em>C. tetani</em></td>
<td>IIIB</td>
<td>Standard of care</td>
</tr>
<tr>
<td><em>C botulinum</em></td>
<td>IIIB</td>
<td>Standard of care</td>
</tr>
<tr>
<td><em>C diphtheriae</em></td>
<td>IIIB</td>
<td>Likely beneficial</td>
</tr>
<tr>
<td>CMV prophylaxis in SOT</td>
<td>IID</td>
<td>Likely not beneficial</td>
</tr>
<tr>
<td>CMV prophylaxis in HSCT</td>
<td>IIE</td>
<td>Not beneficial</td>
</tr>
<tr>
<td>CMV treatment in SOT</td>
<td>IIIC</td>
<td>May be beneficial</td>
</tr>
<tr>
<td>CMV treatment in HSCT</td>
<td>IIE</td>
<td>Not beneficial</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>IIB</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>IIB</td>
<td>Beneficial</td>
</tr>
<tr>
<td>Varicella</td>
<td>IIIC</td>
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</tr>
<tr>
<td>Rabies</td>
<td>IIIB</td>
<td>Beneficial</td>
</tr>
<tr>
<td>RSV</td>
<td>IIB</td>
<td>May be beneficial</td>
</tr>
</tbody>
</table>
levels of IgG in the blood. However, data exist for use in primary immunodeficiency only at this point. It is unclear if there is equivalent activity between intravenous and subcutaneous in conditions, such as infection, that may benefit primarily from immunomodulatory effects seen at high-peak IgG levels.

**SUMMARY**

The spectrum of IVIG use in the prevention and treatment of infectious disease is broad and particularly focuses on areas where disease is life threatening and effective treatment options are limited. The evidence for common uses of IVIG in infectious disease is summarized in Tables 2 and 3. In summary, limited data are available to guide therapy in the most infectious diseases. Although a great need for additional research exists, particularly focusing on randomized and controlled trials, these may be difficult to undertake in the United States for conditions that are becoming increasingly rare (eg, diphtheria) and for which the use of IVIG is firmly entrenched as the standard of care. For new or emerging pathogens that continue to pose a significant problem, such as *C difficile*, CMV, and sepsis, examination of the efficacy of IVIG is essential.

**REFERENCES**


