Role of Immunoglobulin Therapy to Prevent and Treat Infections

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Immunoglobulin Use in Therapeutics and Historical Overview

Immunoglobulin therapy has been used for the prevention and treatment of infectious disease before the introduction of antimicrobial agents into the clinical practice. In the early 1890s, Emil von Behring and Shibasaburo Kitasato set the basis of "serum therapy" showing that antibody preparations derived from the serum of immunized animals have the ability to protect against bacterial toxins [115]. Ehrlich's subsequent work contributed to the conception of passive immunity, demonstrating that increasing doses of bacterial toxins could provide immunity against lethal doses of toxin [68]. Cenci first used human serum in 1907 for the prevention of measles and thereafter for the prevention of pertussis and mumps [45]. Systemic administration of "serum therapy" was widely used in the 1930s for the treatment of bacterial and viral infections; however its use was often associated with adverse reactions due to administration of large amounts of animal proteins, ranging from fever and chills to "serum sickness," a form of immune complex disease, characterized by rash, proteinuria, and arthralgias [45]. After improvements in antibody purification methods, which reduced serum toxicity, the role of "serum therapy" was further expanded. In the pre-antibiotic era, serum therapy significantly reduced the mortality in some infectious outbreaks such as meningococcal and *Haemophilus influenzae* meningitis, pneumococcal pneumonia, and diphtheria. The efficacy of serum therapy varied with the type and severity of the infections and the timing of treatment administration in relation to symptom onset [27, 28, 43]. For some infections like whooping cough, anthrax, dysentery (*Shigella dysenteriae*), and gas gangrene, the efficacy of "serum therapy" was uncertain, while for other pathogens like *Staphylococcus*, *Mycobacterium*, and

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Salmonella species, no consistently effective sera were produced [28].

With the discovery of antibiotics in 1940s, the interest in "serum therapy" for the treatment of infectious disease waned. The initial interest in using combination therapies with antibiotics and serum was abandoned, as the potential benefits were marginal. Antimicrobial chemotherapy proved to be less toxic and more effective than serum therapy in the treatment of infections. However, Dr. Cohn's discovery of purified antibodies through cold ethanol fractionation of plasma during the Second World War revived the interest in antibody treatment especially for infections not able to be treated with antibiotics. The fractionation procedure stabilizes the product, denatures most viruses, and assures a more uniform antibody content. Cohn fraction (IgG from plasma after cold alcohol fractionation) was initially used for prophylaxis against prevalent and life-threatening infections, such as measles. It was not until 1952 that Bruton reported for the first time the use of immunoglobulin preparation injected subcutaneously for the treatment of a young boy with agammaglobulinemia [21]. Thereafter, the use of immunoglobulin injected intramuscularly became established as the standard therapy for primary immunodeficiencies, lasting until the development of purer and safer intravenous immunoglobulin preparation in the early 1980s [86].

The advent of hybridoma technology, which allows continuous generation of large quantities of monoclonal antibodies specific to antigens of interest and the generation of humanized antibodies, revolutionized antibody therapeutics [63]. Monoclonal antibody technology offers supply advantage, reduces the risks of adverse events, and decreases lot-to-lot variation. In the mid-1980s a monoclonal antibody (mAb) to CD3 was introduced into clinical practice to prevent organ rejection. Almost a decade later, the humanized mAb palivizumab (Synagis®, a humanized mouse monoclonal antibody to prevent RSV pulmonary infections in high-risk patients, especially infants) was licensed. Palivizumab was 50-fold more potent than the polyclonal product, resulting in reduced volume of administration and intramuscular use [45]. During the last three decades, 30 therapeutic mAbs have been licensed, mainly for treatment of malignancies and rheumatic or autoimmune diseases, but only two were licensed for infectious diseases (palivizumab and raxibacumab: human mAb to anthrax toxin). Although the use of mAbs to treat infectious diseases does not depend on discrimination between self-antigen as there are large antigenic differences between the microorganism and the host, the pace of discovery and development of new mAbs against infectious disease is limited. Currently, the areas of mAbs development have been focused on viral diseases without available vaccines [HIV, Ebola, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome, Marburg virus], viral disease with limited effective antiviral drugs (influenza, rabies), and bacterial toxin-mediated disease (anthrax, *Clostridium difficile* colitis). In the clinical setting, therapeutic mAbs can be used when there are nosocomial/iatrogenic outbreaks. For example, a new approach to the prevention of recurrent *C. difficile* infection is the administration of mAbs against *C. difficile* toxins (in addition to antibiotic therapy) as a form of passive immunity. Actoxumab and bezlotoxumab are fully human monoclonal antibodies that bind and neutralize *C. difficile* toxins A and B, respectively. A double-blind randomized placebo-controlled phase 3 trial showed that a single intravenous dose of bezlotoxumab when given with standard-of-care antibiotics provided protection against recurrent *C. difficile* infection for up to 12 weeks that was superior to that provided by treatment with standard-of-care antibiotics alone [114]. Other therapeutic mAbs can be applied in drug resistance (*Staphylococcus aureus*, *VRSA*), pandemic outbreaks (Ebola virus), bioterrorism attacks (*Bacillus anthracis*), emerging infectious diseases (Nipah or Hendra virus), and use in high-risk host groups or in severe diseases (respiratory syncytial virus, cytomegalovirus retinitis in HIV patients, hepatitis C virus, influenza virus). Another application of therapeutic mAbs concerns their use as adjunct therapies that have anti-inflammatory or immune

modulatory roles (mAbs against TNF-α and other immune mediators) [45, 55].

Immunoglobulins: Types and Characteristics

Immunoglobulins are glycoprotein molecules that are produced by plasma cells in response to antigens or immunogens and which function as antibodies. Serum contains a heterogeneous immunoglobulin pool that reflects the host response to endogenous microbiota and the immunological memory of the host for a variety of acquired microbial agents [26]. Different immunoglobulins can differ structurally; however, they are built from the same basic units.

There are five classes of immunoglobulin, classified according to the type of heavy chain they possess (Table 17.1) [70]. Each class of immunoglobulins has a specific function, and deficiency of each class leads to particular dysfunction of immune system. Serum IgM predominates in the acute immune response to most antigens and is the most efficient complement-fixing immunoglobulin. Immunoglobulin class switching subsequently occurs, leading to a predominance of IgG, which is responsible for protection during the first infectious attack and long-term protection via memory B cells. Secretory IgA, due to its abundance in mucosal secretions, provides primary defense mechanism against some mucosal infections. IgE primarily defends against parasitic invasion [2].

Immunoglobulins together with T cells are the key mediators of adaptive immunity, and deficiencies in either of these two arms of the adaptive immune system can result in higher host susceptibility to bacterial, fungal, or viral infections [76]. Immunoglobulins interact with the

Table 17.1 Properties of human serum immunoglobulin isotypes

	IgG							
	IgG1	IgG2	IgG3	IgG4	IgA	IgM	IgE	IgD
Molecular weight (x1000)	146	146	170	146	320	900	73	70
Heavy chain	γ1	γ2	γ3	γ4	α	μ	ε	δ
In vivo serum half-life (days)	21–23	20–23	7–8	21–23	6	5	2.5	3
Percent of total Ig	66%	23%	7%	4%	13%	6%	0.02%	0.2%
Activate classical complement pathway	+	+/−	++	−	−	+++	−	−
Crosses placenta	+	+/−	+	+	−	−	−	−
Present on membrane of mature B cells	−	−	−	−	−	+	−	+
Bind to Fc receptor of phagocytes	++	+/−	++	+	−	?	−	−
Mucosal transport	−	−	−	−	++	+	−	−
Distribution	Intravascular and extravascular				Intravascular and secretions	Mostly intravascular	Basophils, mast cells in saliva and nasal secretions	Lymphocyte surface
Structure	Monomeric				Dimeric	Pentameric	Monomeric	Monomeric

++, high; +, moderate; +/− minimal; ?, questionable

cellular immune compartment at multiple levels aiming different cells, including dendritic cells, the monocyte/macrophage system, granulocytes, natural killer cells, and various subsets of T cells and B cells [38, 102]. Understanding the mechanisms of interactions between immunoglobulins, immunomodulatory molecules, and cells of the immune system, both innate and adaptive, is the basis for understanding the future therapeutic perspectives of immunoglobulins [38].

Immunoglobulins, upon binding of a specific antigen, stimulate significant direct and indirect "effector functions." Classically, in bacterial disease, immunoglobulins neutralize toxins, facilitate opsonization, and, with complement, promote bacteriolysis. In viral diseases, immunoglobulins block viral entry into uninfected cells, promote antibody-directed cell-mediated cytotoxicity by natural killer cells, and neutralize virus alone or with the participation with the complement [62]. Furthermore, more recent studies have demonstrated the immunomodulatory functions of antibodies, including the potential for antibody therapy to reduce damage from the host inflammatory response to major infections [24, 25].

Notably, IgG can exert pro- and anti-inflammatory activities depending on its concentration. Low dose of IgG has pro-inflammatory activity and requires complement activation or binding of the Fc fragment from IgG to IgG-specific receptors (FcγR) on innate immune effector cells. This results in receptor clustering, recruitment of secondary effector functions, and subsequent activation of signaling pathways, leading to an increase in intracellular calcium levels and cell activation. By comparison, high concentrations of IgG have anti-inflammatory properties. The mechanisms proposed for this mode of action are modulation of the expression and function of FcγRs, interference with activation of the complement cascade and the cytokine network, neutralization of autoantibodies, and regulation of cell proliferation [38].

Immunoglobulin Preparations

The immunoglobulin preparations used in passive immunization are the standard human serum immunoglobulin, which is available in three forms: immune globulin (IG) for intramuscular use (IMIG), intravenous use (IVIG), and subcutaneous use (SCIG). IMIG is used primarily for the prevention of certain infections, such as hepatitis A, measles, and rubella, and less commonly for the treatment of antibody immunodeficiencies. IVIG is used in the treatment of primary and secondary antibody deficiencies, many immunoregulatory disorders (e.g., immune thrombocytopenic purpura, Kawasaki disease), and neurologic disorders (e.g., Guillain-Barré syndrome, peripheral neuritis). IGSC is used exclusively for the antibody deficiencies.

IVIG preparations comprise the pooled fraction of serum from ~3000 to 60,000 donors, which is generated by a cold ethanol precipitation, providing, thus, a broad spectrum of opsonic and neutralizing IgG antibodies. Opsonic and neutralizing IgG antibody content varies with each product batch, primarily due to differences in the local pathogen ecology of donor exposure. IgG and complement proteins are the principal classes of opsonins contributing to bacterial clearance. In addition to IgG, varying amounts of immunoglobulin isotypes, especially IgA, can be found in the IVIG preparation. Regarding the different human IgG subclasses (IgG1-IgG4), IVIG preparations reflect the hierarchy present in the serum, consisting mainly of IgG1 and IgG2 and containing much smaller amounts of the other IgG subclasses. Only the product Pentaglobin® (Biotest, Germany) is IgM-enriched [93]. The clinical use of IVIG can be distinguished by the infused amount [92]. The principal manufacturing process in all current IgG preparations is cold ethanol fractionation with product-specific additional processes for manufacturing. The commonest processes for virus reduction include solvents/detergent, low pH (pH 4), incubation, nanofiltration, and chromatography [93]. Other major quality control practices in the production process, besides viral reduction, include the depletion of blood coagulation factors and the

removal of IgG aggregates, since these aggregates could result in a cytokine release syndrome owing to the ubiquitous activation of innate immune effector cells via activating FcγRs. IgG aggregations are absent from the majority of IVIG preparation; however, depending on the provider and batch, up to 1–10% of IgG can be found in dimeric form in most IVIG preparations [92].

Immunoglobulins and Clinical Indications

The two major indications for which immunoglobulins are used are IgG replacement therapy and anti-inflammatory therapy in a variety of acute and chronic autoimmune diseases. Apart from immunoglobulin replacement therapy, currently licensed application of immunoglobulin (IVIG) administration includes Guillain-Barré syndrome, Kawasaki disease, and chronic inflammatory demyelinating polyneuropathy. Licensed indications, however, only account for approximately 40–50% of the worldwide immunoglobulin sales, as most immunoglobulin administrations are "off-label" [76]. The use of immunoglobulins for infectious disease can involve the passive transfer of antibodies for pre-/postexposure prophylaxis or for treatment. Passive immunization provides temporal immunity to unimmunized individuals either prophylactically or therapeutically. The different forms of passive immunotherapies are shown in Table 17.2 [96].

Table 17.2 Different forms of passive immunotherapy

Animal antisera and antitoxins (e.g., diphtheria antitoxin)
Human immune serum globulins for general use
Immunoglobulins for intramuscular use (normal and specific immunoglobulins)
Immunoglobulins for intravenous use (human and enriched immunoglobulins)
Special human immune serum globulins (e.g., hepatitis B immunoglobulin)
Humanized monoclonal antibodies

Modified from Annals of Internal Medicine 1987; 107: 367–382. Intravenous Immunoglobulins as Therapeutic Agents & Biologicals 2012; 40: 196. "Role of passive immunotherapies in managing infectious outbreaks"

The technology of ethanol fractionation of plasma resulted in products used for the treatment and prophylaxis of infectious diseases (Table 17.3). Human immune sera have fewer adverse effects, but there are concerns about availability, potency, and consistency.

Table 17.4 summarizes the adverse reactions of immunoglobulin used in the prevention and treatment of infectious diseases.

Immunoglobulins to Prevent Infections in Immunodeficiencies

Administration of immunoglobulins is indicated for the majority of patients with primary immune deficiencies and for patients with combined immune deficiencies and for those with secondary immune deficiency with significant antibody deficiency. The benefits of replacement immunoglobulin therapy for the prevention of infections in patients with antibody deficiencies are well established and pertain to the reduction of the incidence and the severity of infections and prevention long-term deterioration in organ function [12, 13].

Primary immune deficiencies (PIDD) are one of the US Food and Drug Administration (FDA)-approved indications for immunoglobulin therapy. Over 80% of all PIDD involve antibody-mediated immunity; however, each individual disorder has a different immunopathogenesis in terms of the number of B cells in the blood and B-cell function. Moreover, any persisting endogenous antibody production varies both between specific conditions and within individual disorders [10, 35, 97]. Table 17.5 describes the PIDD for which immunoglobulin replacement is or may be efficacious. The recommendations for immunoglobulin replacement treatment in primary and secondary immune deficiencies are shown in Table 17.6 [32, 84, 97]. The main indications are primary antibody deficiencies including agammaglobulinemia (autosomal recessive or X-linked) and common variable immunodeficiency disorders. Rarely, other

Table 17.3 Summary of the immunoglobulin uses for the prevention and treatment of the infectious diseases

Infection	Prophylaxis	Treatment	Recommendations	Immunoglobulin preparations used
Bacterial infections				
Respiratory infections (streptococcal, *Streptococcus pneumonia*, *Neisseria meningitidis*, *Haemophilus influenzae*)	Proven	Proven	For prophylaxis and treatment: recommended for immunodeficient patients	IVIG or IMIG
Diphtheria	Probable benefit	Proven	For prophylaxis: not recommended	Diphtheria antitoxin of equine origin
Pertussis	Unproven	Unproven	For prophylaxis and treatment: not recommended	No agent is available for passive immunity, high titer human IVIG was used
Tetanus	Proven	Proven		Hyperimmune human tetanus immunoglobulin (TIG), human IVIG can be used when TIG is not available, equine tetanus antitoxin is available for veterinary use
Other clostridial infections				
Clostridium botulinum	Proven	Proven		Botulinum antitoxins (heptavalent)
Newborn botulism	Unproven	Proven		Human botulinum intravenous immunoglobulin (BIG)
Clostridium difficile	Unproven	Possible benefit		IVIG, monoclonal antibodies for prevention of recurrence of diarrhea under development
Staphylococcal infections				
Toxic shock syndrome	Unproven	Probable benefit	For prophylaxis: not recommended for toxic shock syndrome	IVIG
Antibiotic resistance	Unproven	Possible benefit	For treatment: not recommended in cases of antibiotic resistance	IVIG
Staphylococcus epidermidis in newborns	Unproven	Possible benefit		IVIG
Toxic shock	Unproven	Probable benefit	For prophylaxis: not recommended	IVIG
Newborn sepsis	Possible benefit	Probable benefit	For prophylaxis: not recommended	IVIG
Shock, intensive care, and trauma	Unproven	Possible benefit	For treatment: not recommended	IVIG

Pseudomonas infections				
Cystic fibrosis	Unproven	No benefit	For prophylaxis and treatment: not recommended	IVIG
Burns	Unproven	No benefit	For prophylaxis and treatment: not recommended	IVIG or IMIG
Viral diseases				
Hepatitis A	Proven	No benefit		IMIG
Hepatitis B	Proven	No benefit		Hepatitis B immune globulin (HBIG) for subcutaneous or intramuscular use
Hepatitis C	Unproven	No benefit	For prophylaxis: not recommended	No passive immune product is available, monoclonal antibodies under development (for prevention for liver transplants)
HIV infection	Unproven	Unproven	For prophylaxis and treatment: not recommended	Monoclonal antibodies under development
RSV infection	Proven	Unproven	For treatment: not recommended	Palivizumab
Herpesvirus infections				
CMV	Proven	Possible benefit		CMV immune globulin
EBV	Unproven	Unproven	For prophylaxis and treatment: not recommended	Rituximab
HSV	Unproven	Unproven	For prophylaxis and treatment: not recommended	IVIG not recommended for the prevention or treatment of HSV
VZV	Proven	Unproven	For treatment: not recommended	Varicella-zoster immune globulin (VZIG) or IVIG
Parvovirus	Possible benefit	Proven	For treatment: not recommended	IVIG
Enterovirus infections				
In newborns	Unproven	Possible benefit		IVIG or IMIG
Encephalomyelitis	Possible benefit	Probable benefit	For treatment: not recommended	IVIG
Poliovirus	Proven	Unproven	For prophylaxis and treatment: not recommended	IMIG
Ebola	Unproven	Unproven		Hyperimmune serum, monoclonal antibodies under development
Rabies	Proven	No benefit		Rabies immune globulin, monoclonal antibodies under development
Measles	Proven	No benefit		IGIM or IVIG
Rubella	Unproven	No benefit	For prophylaxis: not recommended	IGIM

(continued)

Table 17.3 (continued)

Infection	Prophylaxis	Treatment	Recommendations	Immunoglobulin preparations used
Mumps	Unproven	No benefit	For prophylaxis: not recommended	Mumps immune globulin was ineffective, the product no longer manufactured
Tick-borne encephalitis	Possible benefit	No benefit		Hyperimmune human globulin
Vaccinia	Proven	Proven		Vaccinia immune globulin
Variola (smallpox)	Proven	Unproven		Vaccinia immune globulin

Modified from: Stiehm and Keller [120]
CMV cytomegalovirus, *EBV* Epstein-Barr virus, *HIV* human immunodeficiency virus, *HSV* herpes simplex virus, *RSV* respiratory syncytial virus, *VZV* varicella-zoster virus, *IVIG* standard human immune globulin intravenous, *IMIG* immune globulin intramuscular

Table 17.4 Adverse effects due to immunoglobulin therapy

Adverse reaction	Frequency[a]	Severity
Infusion site pain, swelling, erythema	Up to 75% in SCIG	Usually mild
Anxiety	20–40%	
Malaise, fatigue		
Myalgia, arthralgia, back pain		
Fever, chills, flushing		
Tachycardia		
Hypo-/hypertension		
Headache		Mild to moderate
Aseptic meningitis	<5%	Moderate
Hyponatremia		Moderate
Neutropenia		Mild/ transient
Hemolytic anemia		Moderate to severe
Interference with vaccine effectiveness and/or immunodiagnosis		N/A
Eczema		
Renal impairment		
Anaphylactoid reaction	<0.1%	
Severe thrombosis		
Blood-borne infectious diseases		

Modified from: Peter and Chapel [86]
SCIG subcutaneous immunoglobulin, *N/A* not applicable
[a]Frequencies are for patients using long-term therapy

antibody deficiencies, such as IgG subclass deficiency, may be managed by immunoglobulin replacement. In these immunodeficiencies, a trial of 12 months may be indicated if there is a substantial infection burden. On the contrary, for selective IgA deficiency, immunoglobulin replacement is not required or recommended, as anaphylactic reactions may occur during IVIG infusions. Combined immunodeficiencies with antibody deficiency also benefit from immunoglobulin therapy until the defects in cell-mediated immunity are corrected by hematopoietic stem cell transplantation. However, B-cell function is not restored universally after transplantation, and immunoglobulin therapy may be continued [86]. It is important that each patient receives a thorough evaluation before starting immunoglobulin therapy especially those with partial antibody defects.

The American Academy of Allergy, Asthma, and Immunology, based on a 2006 review of evidence, recommends for PIDD the dose of 400–600 mg/kg of IVIG every 4 weeks, titrating the dose and interval between infusions to achieve a trough IgG level at least greater than 500 mg/dl in agammaglobulinemic patients [84]. However, recent evidence suggests that the goal of IgG replacement therapy should be to reduce or prevent serious or recurrent infections instead of aiming to achieve a specific IgG level. The clinicians should identify for each patient with PIDD an individual "biological" IgG level with which the patient achieves the best clinical outcome instead of trying to reach a specific IgG level [16, 17].

The two modes of IgG replacement (IVIG and SCIG) have significant pharmacokinetic differences, which are important to know when choosing the mode of IgG delivery or switching from IVIG to SCIG. SCIG causes sustained release of IgG and thus attains higher IgG trough levels; this mode of delivery may benefit the 10–15% of patients who show increased risk of infection during the 3rd and 4th weeks after receiving IVIG or who experience extreme lethargy during the same period. IVIG achieves higher peak levels (160% higher than that obtained by SC infusion), and this mode of delivery is usually initially preferred for patients with PIDD who are very symptomatic (present with pneumonia or other serious infectious such as sepsis) and who present with pneumonia or for those with other medical problems such as sepsis [16].

IVIG has also been used in a number of diseases that cause secondary humoral immunodeficiency. While for the majority of secondary immunodeficiencies, the use of IVIG was supported only by anecdotal reports, and B-cell chronic lymphocytic leukemia (CLL) and pediatric HIV infection are FDA-approved indications. For both, CLL and HIV, infections are the most common complications. IVIG has been shown to be a useful prophylactic therapy against infections in such patients [29, 53, 54, 72, 95, 110].

Table 17.5 Primary immunodeficiencies and immunoglobulin replacement

Primary immunodeficiency	Immunologic findings	Immunoglobulin replacement	Immunoglobulin cessation
Antibody deficiency			
X-linked or autosomal agammaglobulinemia	<1% normal B cells, agammaglobulinemia, poor specific antibodies	Absolute indication, start immediately	Lifelong replacement
Common variable immunodeficiency disorders (CVID)	Hypogammaglobulinemia, poor specific antibodies, variable T-cell abnormalities	Absolute indication, start immediately	Lifelong replacement
IgG subclass deficiency with IgA deficiency	IgG subclass deficiency (usually IgG2), absent IgA, poor specific antibodies	Replacement only in symptomatic patients (clinically significant infections)	Reassessment for efficacy after 12-month treatment trial
Selective IgG subclass deficiency	Single IgG subclass deficiency, normal total IgG, poor specific antibodies	Replacement may not be necessary	
Specific antibody deficiency with recurrent infections	Normal IgG, IgA, IgM, abnormal IgG antibody responses to protein and/or unconjugated polysaccharide vaccines	Consider replacement if patient has vaccine unresponsiveness and clinically significant infections	Reassessment for efficacy after 12-month treatment trial, watch for development of more severe antibody failure
Transient hypogammaglobulinemia of infancy	Low serum IgG and IgA, poor specific antibodies	Preferable to use prophylactic antibiotics as deficiency is transient, some are given replacement for a period	Replacement stopped after some months to ascertain recovery
Combined immunodeficiencies			
Severe combined immunodeficiencies (SCIDs)	Absent or severely reduced lymphocytes and no antibody production	Replacement is required prior to HSCT	If B-cell reconstitution fails, replacement may still be required after HSCT
NEMO deficiency	Reduced IgG; IgA or IgM may be increased; B cells present	Replacement is required	Cessation inappropriate except after successful HSCT
X-linked lymphoproliferative syndromes	May have reduced B cells and low IgG and IgA levels post EBV infection	Consider replacement	Cessation inappropriate unless HSCT is successful
Hyper-IgE syndromes	IgE elevated, sometimes reduced class switching and low levels of IgA and IgG subclasses with poor antibody responses	Replacement in selected patients	Cessation inappropriate if antibody failure confirmed
Wiskott-Aldrich syndrome	Decreased lymphocytes, variable defects in T-, B-, and NK-cell function, variable IgM, normal or elevated IgA, elevated IgG and IgE, often abnormal IgG antibody response to unconjugated polysaccharide vaccines	Consider replacement	Cessation inappropriate if antibody failure confirmed until successful HSCT

(continued)

Table 17.5 (continued)

Primary immunodeficiency	Immunologic findings	Immunoglobulin replacement	Immunoglobulin cessation
Ataxia-telangiectasia	Partial antibody deficiency in some cases	Replacement in selected patients	Cessation inappropriate if antibody failure confirmed
Hyper-IgM syndromes	Normal or elevated IgM, low or absent IgG, IgA and IgE, poor specific antibodies, variable T-cell abnormalities	Start replacement at the time of diagnosis until successful HSCT	Cessation inappropriate

Modified from Peter and Chapel, Immunotherapy 2014; 6: 853–869, Albin and Cunningham-Rundles, Immunotherapy 2014; 6: 1113–1126
EBV Epstein-Barr virus, *HSCT* human stem cell transplantation, *NEMO* NF-κB essential modulator

Table 17.6 Recommendations for the use of immunoglobulins in immune deficiencies

Benefit	Disease
Definitely beneficial	Primary immune defects with absent B cells
	Primary immune defects with hypogammaglobulinemia and impaired specific antibody production
Probably beneficial	Chronic lymphocytic leukemia with reduced IgG and history of infections
	Prevention of bacterial infections in HIV-infected children
	Primary immune defects with normo-gammaglobulinemia and impaired specific antibody production
Unlikely to be beneficial	Isolated IgA deficiency
	Isolated IgG4 deficiency

The recommendations for immunoglobulin indications according to the Primary Immunodeficiencies Committee of the American Academy of Allergy, Asthma, and Immunology; 2006

Administration of IVIG in CLL patients with hypogammaglobulinemia has been shown to decrease the rate of bacterial infections; however, decision analysis modeling showed that this decrease might not improve the length or quality of treated patients' lives, and, furthermore, it is extraordinarily expensive [110]. The prophylactic administration of IVIG in CLL patients has not been studied extensively, and, thus, there are no guidelines to define the patient population that would benefit from this treatment; also the optimal dosing and timing of IVIG administration remained to be defined. Some experts support the use of IVIG in selected cases, depending on the history of the patient and especially in patients that IVIG has been shown to work in the past.

IVIG therapy together with antiviral therapy was beneficial in infants and children with AIDS and hypogammaglobulinemia or two or more bacterial infections in the previous year. Other indications for IVIG therapy in HIV-infected patients include those with severe parvovirus B19 or measles infection [72, 95, 119]. However, it is important to note that these studies occurred before the era of highly active antiretroviral treatment for HIV [84].

Transplantation

IVIG has been utilized in allogeneic bone marrow transplantation (BMT) in an attempt to decrease the incidence of cytomegalovirus (CMV) infection, infections due to other pathogens, and graft-versus-host disease (GVHD). Immunoglobulin use in the setting of BMT is FDA approved. The rationale for using IVIG in transplantation is that the administration of passive antibodies may prevent infections in these immunocompromised patients and especially infections caused by CMV [84]. Several randomized controlled trials provided the basis to recommend IVIG after allogeneic BMT [19, 31, 46, 87, 98, 116, 117]. Meta-analysis of these trials found significant reduction of fatal CMV infections, CMV pneumonia, non-CMV interstitial pneumonia, and transplant-related mortality

among patients receiving prophylactic IVIG [11]. While an improvement in survival was reported in some studies [46, 49, 118], a more recent meta-analysis showed that IVIG or hyperimmune CMV-IVIG had no effect on the reduction of all-cause mortality [90]. Collectively, the data regarding the benefit of prophylactic administration of IVIG after BMT remain controversial and contradictory. In addition, until currently, there is no consensus on the type, schedule, dose, and patients benefiting from IVIG. Subsequent studies suggested that double prophylaxis consisting of high-dose IVIG and ganciclovir was more successful than either treatment alone in reversing CMV pneumonia in patients after BMT [39, 69].

The American Society for Blood and Marrow Transplantation does not recommend the routine use of IVIG to hematopoietic cell transplant recipients for prophylaxis for CMV disease or for bacterial infections within the first 100 days after transplantation. For patients with severe hypogammaglobulinemia (IgG <400 mg/dl), IVIG prophylaxis of bacterial infections may be considered. IVIG dose and frequency for these patients should be individualized to maintain trough serum IgG concentrations >400 mg/dl [103]. Routine use of IVIG appears to offer little benefit to patients with malignancies undergoing HLA-identical sibling BMT [84]. Given that the landscape of patients receiving BMT is evolving, it is likely that the available data are outdated, and more updated randomized trials are warranted to inform clinical practice.

GVHD and infection are major complications of allogeneic BMT. In vitro and in vivo experimental models showed that the prevention of acute GVHD by IVIG is mediated by the induction of apoptosis of activated alloreactive CD4+ expressing CD134+ donor T cells and reducing the amount of IFN-γ produced by donor T cells [22]. IVIG was shown to decrease the severity of acute GVHD in recipients of allogeneic BMT [98, 116, 117]. On the contrary, administration of IVIG prophylaxis has no effect on the incidence or mortality of chronic GVHD on BMT [99]. While there is no consensus on the optimal dose of IVIG, it appears that the incidence of acute GVHD is less in patients receiving higher doses of IVIG. The benefits of IVIG appear to correlate with IgG trough levels where acute GVHD was less frequent among patients achieving maximum serum IgG levels ≥3000 mg/dl after the administration of IVIG. Trough serum IgG levels >1200 mg/dl were associated with less severe acute GVHD [1, 33, 40].

Over the last decade, IVIG usage in solid organ transplantation has increased significantly. There are encouraging data on the role of IVIG for the treatment of antibody-mediated rejection, desensitization to HLA and/or ABO antigens, as well as prevention and treatment of infectious complications for patients undergoing solid organ transplantation [74, 94]. There is also some evidence that IVIG may be useful for the treatment of autoimmune cytopenias after solid organ transplantation [91]. Dosing of IVIG is empiric although higher than those for replacement therapy. Especially for the treatment of antibody-mediated rejection, the dose is 1–2 gm/kg [23, 38, 58, 60, 61, 76]. The use of higher doses of IVIG is related to higher rates of adverse events. These include aseptic meningitis thrombotic events and bronchospasm [59].

Immunoglobulin Therapy for Sepsis and Septic Shock

Sepsis is the systemic inflammatory response of the host to an infectious insult. Severe sepsis is characterized by acute organ dysfunction, while septic shock is characterized by hypotension, which is refractory to fluid replacement, or by hyperlactatemia [9]. Severe sepsis and septic shock represent one of the oldest and most pressing problems in medicine. Care of patients with sepsis has improved over the last decades; however, the incidence of sepsis is increasing along with morbidity and mortality rates especially in critically ill adults. Worldwide, the annual incidence of severe sepsis lies between 100 and 300 cases per 100,000 population, and mortality for severe sepsis and septic shock reaches 30% and 50%, respectively [8, 56, 73, 109]. While our understanding of the underlying biologic features of sepsis has made significant

progress, the clinical assessment of several new strategies for implementation for sepsis treatment has led to disappointing results [3, 7, 15, 18, 108]. There have been more than 100 randomized clinical trials of strategies to modify the systemic inflammatory response during sepsis; however, no strategy showed to improve dramatically the survival of patients with sepsis [71].

The development of highly purified human plasma-derived polyclonal IVIGs presented a very compelling therapy for severe infections including sepsis and septic shock. IVIGs have broad and potent activity against microorganisms, their extracellular products, and potent immunomodulatory effects [78]. IVIG preparations, in particular IgM-enriched preparations, contain antibodies against lipopolysaccharides of *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella* spp. [104]. The effects of IVIGs on the sepsis-induced host response seem to be pleotropic, not yet completely clarified, and are likely to be secondary to both suppression of synthesis and direct scavenging of upstream and downstream mediators of the host response and complex immunomodulatory effects [93].

The cellular effects of immunoglobulins are mediated through the IgG constant fragment (Fc). Immunoglobulin acts as an adaptor between the innate and adaptive immune system by interacting with Fc, which mediate both pro- and anti-inflammatory signals. IVIGs have direct antibacterial effects through pathogen recognition and increased clearance. IVIGs also have anti-inflammatory properties mediated by the scavenging of bacterial toxins and pro-inflammatory cytokines, by immune cell depletion, by the blockade of activating receptors, and by modulating FcγR expression, dendritic cell activity, and T-cell expansion [77, 92, 93].

The challenging pathobiology of sepsis is associated with acquired hypogammaglobulinemia, which seems to prevent optimal pathogen clearance and pathogen toxin scavenging [100, 107, 113]. Furthermore, sepsis, by causing endothelial dysfunction and capillary leak together with the iatrogenic fluid resuscitation-related increase in extravascular volume, eventually causes an alteration in the distribution of immunoglobulins [93]. Consequently, it is logical to predict that the administration of IVIG during sepsis would be of benefit.

In the clinical setting, the role of IVIG as an adjunctive treatment in sepsis has been controversial for years. A number of randomized placebo-controlled clinical trials in adult critical care patients evaluating standard polyclonal IVIG- or IgM-enriched polyclonal adjunctive therapy in severe sepsis as well as the meta-analyses of these trials have been published [5, 65, 67, 75, 88, 105]. Positive findings of controlled trials and anecdotal reports have been criticized for methodological weakness including the small number of the patients and adequacy of blinding. The more recent studies, which were more meticulously designed, have shown much less effect of IVIG than older, smaller, and less well-designed studies [50]. Of note, the studies that used albumin as control showed less benefit of IVIG than those that did not [41]. The Score-Based Immunoglobulin G Treatment in Sepsis (SBITS) study, one carefully designed, large study representing almost half of all the adults studied to date, showed no reduction in mortality by IVIG in patients with score-defined sepsis and sepsis-induced multi-organ failure [113].

The first clinical trial, which evaluated the effect of IgMA-enriched immunoglobulin preparation (7.8 g IgM, 7.8 g IgA, and 49.4 g IgG), which have shown to contain superior antibody content against bacterial lipopolysaccharides, in an appreciable number of neutropenic patients with hematologic malignancies and sepsis or septic shock, showed that immunoglobulins had no beneficial effects [51]. However, as the editor comments, the study, with a high evidence level, demonstrates that neutropenic patients with malignancies and low-grade sepsis with no or only one organ failure will not benefit from adjunctive IVIG treatment [111].

The prophylaxis and treatment of neonatal sepsis has been a major global priority, and large international trials have been carried out testing IVIG ([57, 79–83]; Group et al. 2011). Mortality during hospital stay in infants with clinically suspected infection at trial entry was not significantly different after IVIG treatment [81]. The

results of the International Neonatal Immunotherapy Study (INIS) and recent meta-analyses showed that IVIG did not reduce mortality during hospital stay or major disability at 2 years of age in infants with sepsis [48, 83]. Based on the results of the INIS trial (3493 subjects), routine administration of IVIG to prevent mortality in infants with sepsis is not currently recommended [48].

When considering the administration of IVIG during sepsis, important aspects that should be taken into account are the dose, the type, the timing, and pharmacokinetics of IVIG [6, 50]. While dose-ranging studies have not been completed, studies that used high (>1 g/kg body weight) doses of IVIG demonstrated better effects. This seems plausible given the clinical observations in other inflammatory conditions, such as Kawasaki disease, where greater effect was noted with higher doses [52]. The type of IVIG may have an important effect, possibly in favor of a greater pooled effect of IgMA-enriched compared with standard preparations of IVIG. IgMA-enriched preparations are associated with greater complement inactivation and improvement in microvascular perfusion in experimental models [112]. However, collectively, the results from animal models and in vitro experiments show contradictory results and do not allow for a definite conclusion regarding the superiority of one specific immunoglobulin preparation in patients with sepsis. In an efficacy study, administration of polyvalent IgG versus IgMA in selected patients at high risk for sepsis was associated with a comparable improvement in disease severity [89].

Regarding the timing of IVIG administration during sepsis, there is probably a "window of opportunity" in the first days that follow clinical presentation of sepsis [14]. If this window is missed, probabilities of success could be greatly diminished [6]. Pharmacokinetic studies of IVIG in sepsis have not been performed yet. Data for dosage selection in current practice are primarily derived from studies in volunteers and in patients with primary immune deficiencies and other indications for immunomodulation. Existing pharmacokinetic studies also do not address immunoglobulin clearance or area under the curve parameters and target serum immunoglobulin concentrations [64]. In addition, it is still unknown whether the main goal of IVIG in sepsis is to refill low levels of endogenous immunoglobulins or alternatively whether IVIG could exert a beneficial effect regardless of these levels [6].

Most studies evaluating the use of IVIG for sepsis are small; some have methodological flaws and high-quality, large studies showed no effect [48, 113]. Given immunoglobulin high-cost, limited supply and the lack of strong evidence to support their beneficial effect, widely used guidelines either neglect or grade as a weak recommendation the use of polyclonal IVIG in sepsis [36]. While clinical judgment may guide immunoglobulin use in individual cases, particularly those due to Gram-negative etiologies or streptococcal toxic shock syndrome, these practices are based largely on theoretical rationale, anecdotal, and retrospective clinical observations [50, 66, 106].

The effect of monoclonal antibodies against tumor necrosis factor (TNF)-α has been evaluated in a series of trials on different anti-TNF-α-directed therapies [4, 30, 37, 42]. The long-anticipated sepsis trial (MONARCS [Monoclonal Anti-TNF, A Randomized Controlled Sepsis trial]) reported that afelimomab, which is made up of the Fab component of a monoclonal antibody against TNF-α, in patients with severe sepsis and elevated IL-6 levels decreased mortality and had a safety profile similar to placebo [85]. However, combining the results of these studies, a small improvement in mortality can be detected [34, 47]. As sepsis is increasingly being considered as an exaggerated, poorly regulated innate immune response to microbial products, by the time of diagnosis, an entire network of cytokines has already been activated. In this regard, the results of the previous studies would have been anticipated, as it seems unlikely that therapy aimed at only one cytokine would by itself have the highly significantly impact on sepsis mortality [34].

Future Directions

Immunoglobulins have been used widely in medicine for a variety of diseases including infectious diseases. While the two major indications for immunoglobulin use are as replacement and anti-inflammatory therapy in a variety of acute and chronic autoimmune diseases, their use in the prevention and treatment of infectious diseases is emerging as an attractive option especially in the era of multi-antibiotic resistance. Many aspects of immunoglobulin therapy remain controversial and contradictory. Consequently, immunoglobulin use is sometimes determined by clinical judgment or expert opinion, which is based largely on theoretical rationale, anecdotal, and retrospective clinical observations. Gaps of knowledge that need to be addressed are certain categories of patient populations that would benefit from immunoglobulin treatment or prophylaxis, the optimal immunoglobulin dosing, and duration, as well as timing of administration.

Monoclonal antibody technology has opened a new era in antibody therapy. On many occasions, human monoclonal antibodies have better therapeutic properties than immunoglobulins including low toxicity, longer protective immunity, higher than natural protection, and high specificity. Several antibodies for the treatment of bacterial and viral infections have been developed [101]. However, some challenges need to be overcome before they become preferred agents for the treatment and prophylaxis against infectious diseases.

Biofilms are now acknowledged to contribute to a plethora of chronic and recurrent infections. While treatment or eradication of biofilm-related infections is still challenging, there are sufficient in vitro and preclinical data to support the use of antibodies directed against extracellular DNA-binding proteins entrapped into the extracellular biofilm polymeric substance [20, 44]. While still an area of ongoing preclinical and clinical research, this use of antibodies constitutes a novel therapeutic approach for treatment of biofilm-related infections.

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