

Intravenous immunoglobulin for infectious diseases: back to the pre-antibiotic and passive prophylaxis era?

Jagadeesh Bayry, Sébastien Lacroix-Desmazes, Michel D. Kazatchkine and Srin V. Kaveri

INSERM U430 and Université Pierre et Marie Curie, Institut des Cordeliers, 15 rue de l'Ecole de Médecine, 75006, Paris, France

The dramatic increase in both the number of novel infectious agents and resistance to antimicrobial drugs has incited the need for adjunct therapies in the war against infectious diseases. Exciting recent studies have demonstrated the use of antibodies in the form of intravenous immunoglobulin (IVIg) against infections. By virtue of the diverse repertoire of immunoglobulins that possess a wide spectrum of antibacterial and antiviral specificities, IVIg provides antimicrobial efficacy independently of pathogen resistance and represents a promising alternative strategy for the treatment of diseases for which a specific therapy is not yet available.

Adaptive immune response against pathogens is an active cascade of events that involves antigen-presenting cells (APCs), T cells and B cells, and ultimately leads to protection through either humoral or cellular immunity. Humoral immunity is mediated by B cells, which produce antibodies that contribute towards neutralization of pathogens and their clearance. Vaccination is aimed at stimulating adaptive immune response in the long term in an antigen-specific manner, using modified or inactivated pathogens or components derived from pathogens. Instant and short-term protection against infection can be achieved through administration of specific antibodies in a passive manner [1]. Before antibiotics and antimicrobial drugs were available for clinical use, antibodies through passive serotherapy were used for the treatment of certain infections.

The 20th century witnessed remarkable discoveries, including antimicrobial agents, that changed the face of medical practice. The use of antibiotics and preventive vaccines led to a decline in major endemics in industrialized countries and, to a lesser extent, in developing countries. However, pathogens developed resistance to antimicrobial agents in both developing and developed countries (Figure 1). The emergence of an alarmingly significant resistance to antimicrobial agents in pathogens, together

with the recognition of an increasing range of novel infectious agents and the potential threat of biological warfare, have rekindled interest in antibody-based therapies as potential adjuncts in the battle against infectious diseases. The immunity conferred by vaccines depends on the condition of the host and demands a certain time-frame for a response whereas passive antibody, in principle, can deliver instant protection regardless of the immune status of the host. Several reports have recently re-emphasized the potential use of antibodies in the form of intravenous

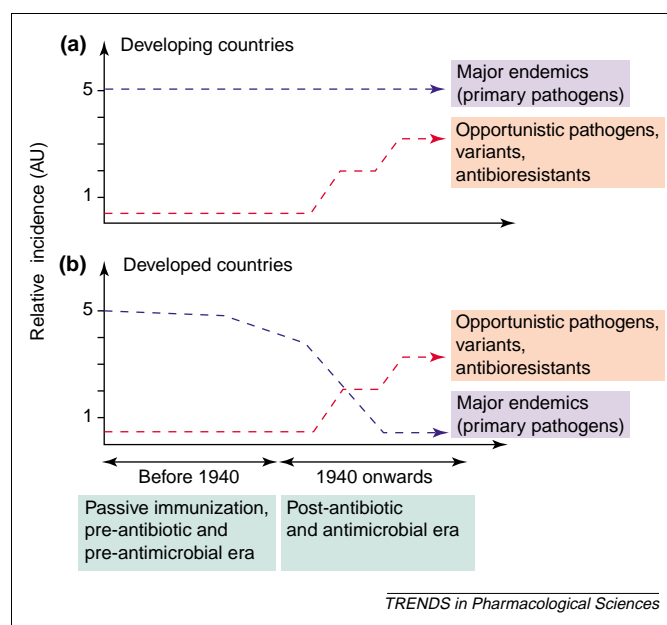


Figure 1. Evolution of infectious diseases and microbial resistance. The optimism generated by the dawn of the antimicrobial era in the mid-1940s was soon quenched by the emergence of penicillin-resistant *Staphylococcus aureus*. The evolution of increasingly antimicrobial-resistant pathogens in both developing (a) and developed countries (b) stems from a multitude of factors that include: the widespread and sometimes inappropriate use of antimicrobials, the extensive use of these agents as growth enhancers in animal feed, the relative ease with which antimicrobial-resistant bacteria cross geographic barriers and widespread industrial and agricultural use. Indiscriminate use of antimicrobials and failed treatments with 'old and simple' drugs because of economic reasons in developing countries has also led to more severe disease or to the spread of infection, along with its contingent selection pressure, leading to the emergence of variants. Figure courtesy of J.M. Alonso.

immunoglobulin (IVIg) as an anti-infectious agent in several viral and bacterial infections. IVIg is a therapeutic preparation of normal human IgG obtained from pools of plasma from thousands of healthy blood donors [2]. Exposure of such donors to their unique environment (e.g. geography, endemics of infections, vaccination and type of food antigens) gives rise to IVIg that consists of a diverse repertoire of immunoglobulin molecules that possess a wide spectrum of antibacterial and antiviral specificities. Although specific hyperimmune gammaglobulins are available, their application is limited to specific pathogens [3], whereas the advantage of IVIg for the treatment of infectious diseases lies in its polyclonality: that is, its ability to interact with a broad range of antigens and pathogens.

IVIg for the treatment of bacterial and viral diseases

Although the number of clinical trials using IVIg as a prophylactic or therapeutic agent for infectious diseases is limited (Table 1), results from various *in vivo* and *in vitro* studies suggest that IVIg represents a promising alternative strategy for the treatment of diseases for which a specific therapy does not currently exist or requires adjunctive treatment.

Patients with primary immunodeficiencies are susceptible to recurrent infections of the respiratory and intestinal tract caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Giardia lamblia* and *Campylobacter jejuni*. Since immunoglobulin therapy was introduced to treat immunodeficient patients [4] and subsequently after the standard dose of IVIg was doubled, the frequency and severity of infections have dramatically decreased [5].

A recent multi-centre, placebo-controlled trial provides support for IVIg as an efficacious adjunctive therapy for group A streptococcal toxic shock syndrome (STSS) [6]. The trial demonstrated a significant decrease in sepsis-related organ failure in IVIg-treated patients compared with patients treated with an equal volume of 1% albumin. In another study, prophylactic IVIg was shown to reduce the incidence of septic complications and to increase serum bactericidal activity in a small group of adult septic patients compared with patients receiving human albumin [7].

An IVIg preparation containing high antibody titres (1:1600) to West Nile virus (WNV) has been found to be beneficial in patients with WNV encephalitis [8,9]. Furthermore, experiments in mice suggest that IVIg might ameliorate or abort established WNV infection [10]. However, a patient's death was recently reported despite the successful clearance of the WNV from the nervous system using IVIg [11]. These anecdotal reports, although inconclusive, have stimulated interest in the off-label use of IVIg for treating severe WNV disease.

Parvovirus B19 (PV-B19) and cytomegalovirus infections have emerged as causes of glomerulopathy in both endogenous and transplanted kidneys. Treatment of patients with IVIg before kidney transplantation has been shown to successfully eradicate these viruses [12,13]. In addition, IVIg therapy led to the clearance of viremia, resolution of symptoms and reestablishment of cytokine balance in patients with chronic fatigue syndrome associated with acute PV-B19 infection [14].

The newly elucidated, human metapneumovirus (hMPV) is an important cause of respiratory disease in diverse subpopulations. No anti-viral agents or vaccines are currently approved for its treatment or prevention. IVIg and ribavirin were found to exert equivalent antiviral activity against hMPV in tissue culture-based assays [15]. These results point out that the clinical evaluation of IVIg alone or in combination with ribavirin should be undertaken for hMPV infection and might prove effective until agents that are more efficacious or vaccines are developed. Ribavirin has also been used during the recent outbreak of severe acute respiratory syndrome (SARS), for which no specific therapy is available. IVIg prepared from donors of geographical locations where SARS outbreak occurred might prove to be an effective adjunct therapy.

IVIg is undoubtedly not a 'magic bullet' of adjunctive treatment for all infectious conditions. Several studies have assessed the efficacy of IVIg in sepsis, with varying results. IVIg in immunocompromised patients, such as those undergoing cancer chemotherapy, bone marrow transplantation or transplantation of solid organs, has not significantly reduced the incidence of bacterial sepsis syndromes [16]. In addition, there are no conclusive data available to date to support the use of IVIg in all sepsis

Table 1. Human infectious diseases for which beneficial effects of intravenous immunoglobulin has been reported^a

Infectious conditions	Prophylaxis (P) or therapeutic (T)	Refs
Streptococcal toxic shock syndrome	P, T	[6,7]
Recurrent bacterial infections ^b in patients with hypogammaglobulinemia	P	[4,5]
Polyneuropathy associated with <i>Campylobacter jejuni</i>	T	[33]
<i>Clostridium difficile</i>	T	[34]
<i>Chlamydia pneumoniae</i>	T	[35]
<i>Salmonella typhimurium</i>	T	[36]
West Nile virus	T	[8,9]
Parvovirus B19	T	[12,14]
Cytomegalovirus	P	[13]
Childhood HIV	P, T	[37]
Enteroviruses ^c	P, T	[38]
Varicella zoster	P	[39]
Genital herpes simplex virus	T	[40]

^aOnly key references are provided because of space constraints.

^b*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Giardia lamblia*, *Campylobacter jejuni* and *Mycoplasma pneumoniae*.

^cEchovirus and coxsackievirus.

cases [17], with the exception of defined subgroups, such as STSS, surgical patients with severe, score-defined post-operative sepsis, and young patients with meningococcal septic shock.

Although IVIg prophylaxis treatment is recommended for infants whose mothers have hepatitis A, measles or poliomyelitis infections at or near the time of parturition, most other possible indications for infectious disease prophylaxis remain speculative [16]. IVIg failed to reduce the incidence of hospital-acquired infections in premature and low-birth-weight infants. Multiple studies conducted during the past 20 years suggest that IVIg treatment is only marginally useful in the prevention or treatment of serious neonatal infections [18]. Hence, the prophylactic use of IVIg for the prevention of neonatal nosocomial infections is discouraged.

Although substantial differences might be found among IVIg preparations and batches (e.g. neutralizing antibody levels for streptococci and WNV) [8,9,11,19], studies to evaluate the clinical efficacy of different IVIg preparations have yielded equivocal results. Protection in addition to sufficient amounts of antibodies to frequently isolated bacterial antigens were achieved in patients despite quantitative differences between the batches and preparations of IVIg [20]. However, significant differences between IVIg preparations in preventing sinopulmonary infections have been observed [21]. These studies imply that not all IVIg preparations and batches are equal and thus highlight the need for larger comparative studies to identify the standards for optimal treatment.

Mechanisms of actions of IVIg

The principal components of IVIg are natural antibodies (NABs) of IgG isotype. NABs, by virtue of their reactivity against pathogens and host receptors, have long been recognized to block or delay infection of cells by microbes. NABs can enhance the recruitment of virus into lymphoid organs where they are presented to T and B cells, thereby eliciting an active immune response [22]. In concert with complement, NABs act as endogenous adjuvants for the generation of a vaccine-induced protective CD8 T-cell response [23]. Indeed, antibodies within IVIg that are directed against CD4 and chemokine CCR5 receptors have been shown to block the infection of HIV *in vitro* [2,24]. Antibodies in IVIg enhance opsonization and thus promote phagocytosis and antibody-mediated cellular cytotoxicity [25] (Figure 2). Furthermore, IVIg has been shown to stimulate the production of PV-B19 virus-specific IgG with a concomitant increase in the levels of interleukin 2 (IL-2) and IL-4 [14], cytokines that are important in immunoglobulin class switch (the process by which a B cell produces a different class of antibody with the same specificity, indicating the progression of the immune response).

The protective effect of IVIg against infections has been attributed to the ability of specific antibodies to neutralize pathogens and bacterial toxins. IVIg preparations contain antibodies against a large variety of pathogens [26], which could be related to the exposure of donors who contributed to the IVIg preparations to infections and vaccination. For example, IVIg prepared from Israeli donors contains high

titres against WNV as a result of the endemic nature of WNV infection in this population. By contrast, North American IVIg preparations contain no detectable WNV antibodies [8–10].

Because of its ability to neutralize a wide variety of superantigens and to facilitate opsonization of streptococci, IVIg has been suggested as a potential adjunctive therapy for STSS and invasive group A streptococci (iGAS) [27]. A significant increase in plasma neutralizing activity against superantigens expressed by autologous streptococci has been observed in patients with iGAS following IVIg treatment [6]. A recent report suggesting that neutralizing anti-interferon gamma autoantibodies favour recurrent infections with intracellular pathogens might open novel prospects for IVIg therapy [28]. Owing to its high content of anti-idiotypes, IVIg can neutralize and downregulate the synthesis of such autoantibodies by B cells that express the relevant idotype [2].

Perspectives

Despite the use of IVIg in infectious diseases over 20 years, several fundamental questions remain unanswered, including what are the appropriate clinical indications, optimal dosage and frequency of administration?

Dose regimen

The first step towards therapeutic utilization of IVIg for infectious diseases would be the fine-tuning of the dose regimen in clinical trials. At high doses, as in the case of autoimmune conditions, IVIg inhibits the function of different arms of the immune system, including inhibition of the maturation and function of dendritic cells, and attenuation of T-cell proliferation and production of pro-inflammatory cytokines. Therefore, a high-dose regimen might not be appropriate for the treatment of infectious diseases.

Route of administration

The most common route of infusion for IVIg is the intravenous route. However, one might have to consider alternative routes of administration depending on the type of infection. For viral encephalitis, administration by an intraventricular or intrathecal route might prove more beneficial. During the first 48 h of intravenous infusion of IVIg, when the serum IgG level is high, the concentration of IgG in the cerebrospinal fluid (CSF) increases as much as twofold but returns to normal within one week [29]. Because the degree of penetration into CSF by the intravenous route is unpredictable, alternative routes of IVIg administration should be sought.

Topical immunotherapy is a promising approach for epithelial infections. Intranasal IVIg immunotherapy for *S. pneumoniae* was effective in mice against pneumonia but failed to prevent bacteremia [30] probably because of the short half-life of intranasally administered IVIg. Several barriers, including the geometry of the airways, and enhanced clearance by surfactants, enzymes and alveolar macrophages, might hinder the efficient delivery of IVIg in the respiratory tract. Attempts to enhance the half-life of IVIg by the intranasal route using a liposomal formulation have been unsuccessful [31].

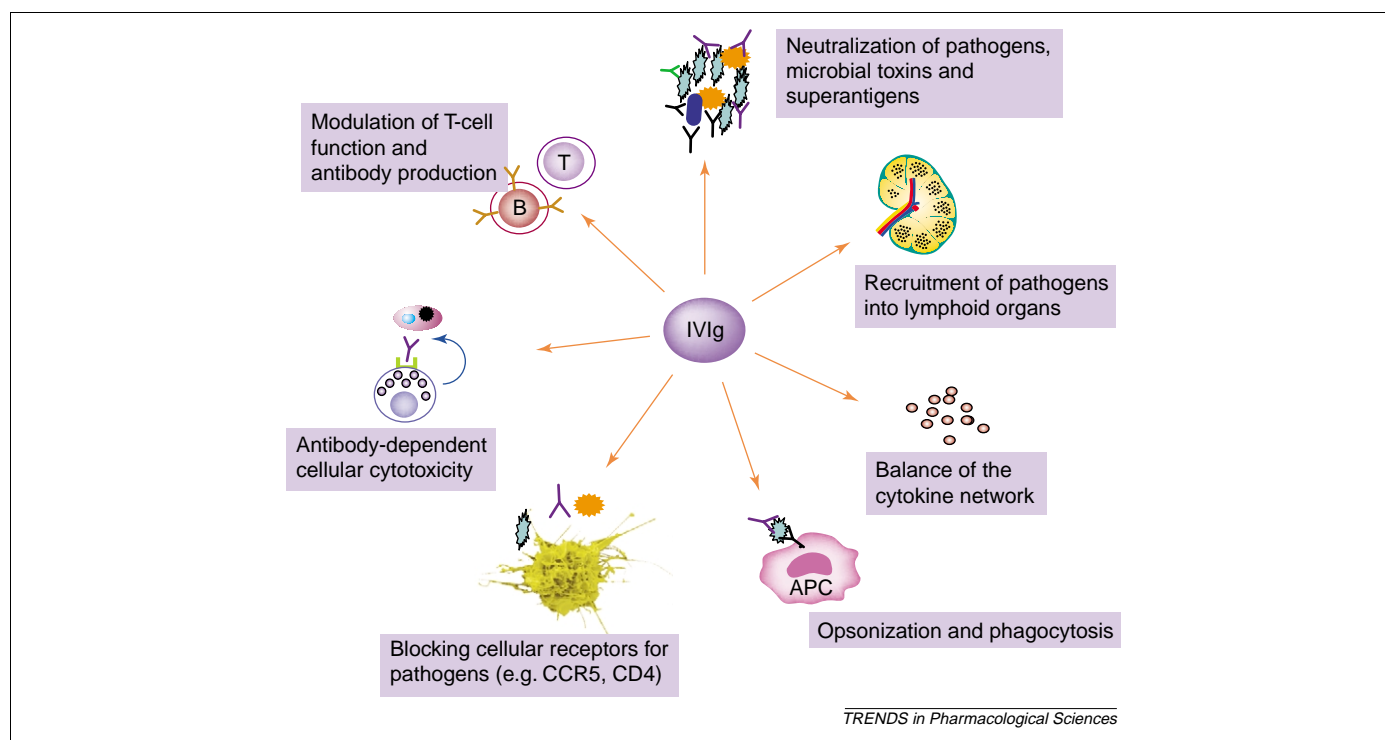


Figure 2. Proposed mechanisms of action of intravenous immunoglobulin (IVIg) in infectious diseases. The mode of action of IVIg in infectious diseases involves its direct interaction with pathogens and various cellular and soluble components of the immune system. Abbreviations: APC, antigen-presenting cell; B, B cell; T, T cell.

Combination therapy

A synergistic therapeutic efficacy of IVIg has been reported by combining with antibiotics and chemotherapy [30,32]. Combination therapy might achieve an effective anti-infection therapy for certain pathogenic strains, thereby reducing the risk of selection of more resistant variants.

Source of IVIg

Because each geographical region is endemic for specific diseases, selection of donors from the entire world rather than from a selective region for preparing IVIg might be advantageous, particularly for infectious diseases. An alternative approach would be the preparation of a tailor-made IVIg made from plasma pools of donors from endemic regions or by complementing with humanized mouse monoclonal antibodies or hyper-immune gamma-globulins [3].

Assessment for anti-pathogen activity

Identification of specific neutralizing anti-microbial activity in IVIg would be helpful in determining its therapeutic potential for some infectious diseases. Anti-pathogen ELISA (enzyme-linked immunosorbent assay) titres alone can sometimes mislead and should be complemented with other functional assays.

Concluding remarks

IVIg is safe and effective in treating several human diseases. Its use has been approved in patients with antibody deficiencies and a broad range of autoimmune and inflammatory disorders [2]. However, infectious diseases do not belong to the group of currently approved medical indications. The different schemes used in several studies have rendered the interpretation of the results

difficult. However, there are enough encouraging experimental and clinical data to maintain continuing interest in the IVIg field and demand further studies in infectious conditions for which IVIg has been found to be beneficial in uncontrolled studies (i.e. those that lack placebo-controlled clinical trials). Controlled trials, particularly with viral diseases and certain defined septic subgroups where IVIg represents a promising but unproven treatment, are imperative. It is evident, however, that IVIg preparations must contain the functionally active and optimal amounts of antigen-specific antibodies to be effective. IVIg preparations have not been compared thoroughly for efficiency and adverse events. According to regulatory guidelines, IVIg products are tested for sterility, purity, pyrogenicity and safety. However, no strict requirements exist concerning concentrations of specific antibodies. Further research is required to understand the mechanisms of action of IVIg in infectious diseases and the relative role of functional antibodies within IVIg.

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