

# Intravenous immune globulin use in children

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In the past decade concentrated immune globulin preparations suitable for intravenous use have become available with which normal or above normal IgG serum levels can be attained. The efficacy of intravenous immune globulin (IVIG) for the treatment of some conditions is well established; for others it is not yet proven.<sup>1,2</sup> Therapy with IVIG — particularly in high doses — is expensive, and adverse reactions may occur. This statement summarizes the available data on IVIG and provides guidelines for its use in children.

## Pharmacologic features

Three IVIG products are currently licensed in Canada; no clear advantage has been demonstrated for any one of them.<sup>2,3</sup> Pooled human plasma from large numbers of blood donors is the source of the immune globulin. Antibodies against a wide range of common pathogens are present in any IVIG preparation but not in controlled concentrations. Certain standards are met for the biologic activity and half-life (minimum 14 days) of the product, the proportions of IgG monomer, degradation products and aggregates, and the subclass distribution.<sup>3,4</sup> IVIG consists primarily of IgG with only trace amounts of IgA and IgM. On average the half-life in serum is 21 days, but it may be longer in agammaglobulinemic patients.<sup>1,5</sup>

## Mechanism of action

IVIG can be used for antibody replacement or immunomodulation therapy. Antibody replacement therapy may be required for global or partial immunodeficiencies in immunocompromised people or for selective antibody deficiencies in otherwise healthy people. IVIG has also been used to modulate the idiotypic antibody network and to block Fc-receptor-immunoglobulin interactions.<sup>6,7</sup>

## Established uses of IVIG

In some cases well-designed studies have demonstrated the efficacy of IVIG therapy (Table 1).

Table 1: Conditions in which the efficacy of intravenous immune globulin (IVIG) therapy has been established

|                                                                                                                             |
|-----------------------------------------------------------------------------------------------------------------------------|
| Congenital antibody deficiency <sup>4,5</sup>                                                                               |
| X-linked agammaglobulinemia                                                                                                 |
| Severe combined immunodeficiency                                                                                            |
| Wiskott-Aldrich syndrome                                                                                                    |
| Common variable hypogammaglobulinemia                                                                                       |
| X-linked immunodeficiency with hyperimmunoglobulin M                                                                        |
| Immune thrombocytopenic purpura (especially in selected patients at increased risk of intracranial hemorrhage) <sup>8</sup> |
| Kawasaki disease <sup>9,10</sup>                                                                                            |

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## Congenital antibody deficiency states

IVIG therapy is of proven benefit in patients with generalized antibody deficiency states (Table 1).<sup>4,5</sup> It increases serum antibody levels<sup>1</sup> and makes the painful, poorly tolerated intramuscular injections used since 1952 unnecessary. By providing specific antibody replacement, IVIG therapy has resulted in fewer and less severe infections from a wide variety of pathogens. In addition, survival rates have improved.<sup>4,5</sup> The replacement dose of IVIG is usually 400 mg/kg every 3 to 4 weeks; however, the dosage should be adjusted to maintain the preinfusion IgG serum level at 5 g/L.

## Immune thrombocytopenic purpura

In some centres IVIG therapy has become standard for immune thrombocytopenic purpura.<sup>8</sup> After IVIG infusion there is a rapid increase in the platelet count in children with this condition. The mechanism of action may involve Fc-receptor blockade<sup>6</sup> or interference with antiplatelet antibody binding and immune modulation of interactions involving T cells and B cells.<sup>11,12</sup>

IVIG has been used to treat acute and chronic immune thrombocytopenic purpura. Spontaneous remission occurs in many acute cases, and so IVIG may not be required in all instances. In a subset of children spontaneous remission does not occur; early use of IVIG may prevent progression to the chronic stage.<sup>13</sup> IVIG is often used in severe thrombocytopenia (platelet count of less than  $20 \times 10^9/L$ ) because of the increased risk of intracranial hemorrhage.

A dose of 400 mg/kg for 5 days is effective in the treatment of immune thrombocytopenic purpura. Others have used a single infusion of 1 g/kg in acute cases and additional doses in chronic cases.<sup>14</sup>

## Kawasaki disease

Treatment with IVIG early in the course of Kawasaki disease reduces the risk of lesions of the coronary arteries.<sup>9,10</sup> Several mechanisms of immunomodulation have been hypothesized, including diminution of the immune activation seen in the disease.<sup>7</sup> A dose of 400 mg/kg daily for 4 days or 2 g/kg as a single dose is currently recommended for all patients with Kawasaki disease seen in the first 10 days of their illness. Even if the diagnosis is not established until after 10 days IVIG should be used if the patient remains febrile.

## Unestablished uses of IVIG

IVIG has been used to treat other antibody deficiency states and autoimmune diseases (Table 2).

Published reports are often anecdotal, include few patients, are poorly controlled or await confirmation. For this reason IVIG use in these conditions has been listed under "Possible efficacy" (Table 2). These interventions should still be considered experimental and be undertaken as part of a clinical trial protocol. Recommendations for general use await controlled trials or confirmation of studies that have demonstrated benefit.

## Partial antibody deficiency

There are few data available concerning the efficacy of IVIG in the treatment of partial antibody deficiency. Recently there has been interest in replacement therapy in children with IgG subclass deficiency,<sup>15,16</sup> however, it is unknown which subgroups of such patients are at risk for recurrent infection. Moreover, there has been no standardization of assays used to determine IgG concentrations and to detect deficiencies. Groups with combined IgG<sub>2</sub> and IgA deficiency appear to be at increased risk of infection but, like all patients with IgA-selective deficiency, are also at increased risk of adverse reactions to IVIG infusions.

## Acquired immunodeficiencies

Patients with this group of disorders account for a large proportion of IVIG use, but such use is not of

Table 2: Conditions in which the efficacy of IVIG therapy is unknown

|                                                                                                |
|------------------------------------------------------------------------------------------------|
| Probable efficacy                                                                              |
| Partial antibody deficiency <sup>15,16</sup>                                                   |
| IgG subclass deficiency                                                                        |
| Antibody deficiency with normal immunoglobulin levels                                          |
| Acquired immunodeficiency <sup>17-19</sup>                                                     |
| Prevention of bacterial infection associated with human immunodeficiency virus (HIV) infection |
| Bone marrow or organ transplantation                                                           |
| Hematologic malignant disease                                                                  |
| Chemotherapy for malignant disease                                                             |
| Prophylaxis for neonatal sepsis <sup>20-22</sup>                                               |
| Possible efficacy                                                                              |
| Prophylaxis for cytomegalovirus infection after bone marrow or organ transplantation           |
| Hypogammaglobulinemia due to burns                                                             |
| Systemic onset juvenile rheumatoid arthritis                                                   |
| Guillain-Barré syndrome                                                                        |
| Myasthenia gravis                                                                              |
| Systemic lupus erythematosus                                                                   |
| Polymyositis                                                                                   |
| Dermatomyositis                                                                                |
| Immune thrombocytopenic purpura of pregnancy                                                   |
| Neonatal alloimmune thrombocytopenia                                                           |
| HIV-associated thrombocytopenia                                                                |
| HIV-associated polyneuropathy                                                                  |
| Steroid-dependent asthma                                                                       |
| Intractable seizures                                                                           |

proven efficacy. Children with acquired immunodeficiency syndrome have high gamma globulin levels but are deficient in functional antibodies and have recurrent bacterial infections. Several reports have documented a lower rate of invasive bacterial infection in patients receiving routine IVIG therapy.<sup>17,18</sup> IVIG has been used to treat transient hypogammaglobulinemia due to burns or severe trauma and has reduced the number of infectious episodes.<sup>23</sup> It has also been widely used to prevent infections associated with hypogammaglobulinemia due to bone marrow or organ transplantation and chemotherapy for malignant disease.<sup>19</sup> A number of controlled trials are under way to assess the efficacy of these interventions.

### *Neonatal infection*

Encouraging results have been reported for the treatment of late-onset neonatal sepsis in low-birth-weight infants.<sup>20,21</sup> There have also been mixed results described for this form of treatment,<sup>22</sup> possibly as a consequence of variation in antibody levels with different IVIG lots. In some experimental infections in animals adverse outcomes occurred with high doses of IVIG because of immune blockade.<sup>24</sup> Variable results have also been reported from pilot studies assessing the efficacy of IVIG prophylaxis of late-onset sepsis in very-low-birth-weight infants. Until further information is available no recommendation for the routine use of IVIG in the prophylaxis or treatment of neonatal infection can be made.

### *Other conditions*

The use of IVIG has been proposed for a number of other purposes, including the prophylaxis and treatment of specific infections, collagen vascular diseases, autoimmune diseases and miscellaneous conditions (Table 2), but further study is required.

### **Adverse reactions**

The incidence rate of side effects is less than 3%.<sup>3</sup> Anaphylactoid reactions are caused by aggregates of IgG, which activate the alternative pathway of complement. If there is a heavy antigenic load, such as in children with agammaglobulinemia or human immunodeficiency virus (HIV) infection who are receiving their first IVIG infusion, immune complex formation with a subsequent inflammatory response (including fever, chills and malaise) may occur. In children with selective IgA or combined IgG subclass and IgA deficiencies, anti-IgA antibodies may develop, causing hypersensitivity to the small quantity of IgA present in IVIG. A less well

understood reaction to IVIG consists of chills, flushing and abdominal pain or nausea. Although no objective signs may be present a sensation of nervousness or anxiety may be reported. Additional side effects include headache, back pain, chest pain, muscle ache and, rarely, aseptic meningitis. The cause of these reactions is unknown but may involve contaminated vasoactive and pyrogenic products.

During infusion with IVIG patients should be monitored for hypotension, hypertension and other adverse reactions. Mild reactions may respond to slowing the rate of infusion. More severe reactions may be prevented by pretreatment with hydrocortisone (50 to 100 mg intravenously) 30 minutes before the IVIG infusion.<sup>25</sup>

Because IVIG is a biologic material there is concern about the transmission of infectious agents. There has been no transmission of hepatitis B virus or HIV, because the IVIG manufacturing process inactivates or eliminates viral antigens at several stages.<sup>26</sup> However, there have been reports of the transmission of non-A, non-B hepatitis from a few IVIG preparations.<sup>27-29</sup> Although there has been no documented transmission of pathogens from the products licensed in Canada IVIG should be used only if there is a clear indication for it. Because of interference with the immune response live virus vaccines should not be given for 3 months after IVIG therapy.

### **Summary and recommendations**

IVIG has revolutionized the treatment of antibody deficiency states and has been an effective immunomodulator for the treatment of immune thrombocytopenic purpura and Kawasaki disease. Its use is therefore recommended for these conditions. IVIG may also be effective in a number of other antibody deficiency states and as prophylaxis against infection in high-risk groups; however, recommendations for routine use must await the results of controlled trials. A wide range of possible uses of IVIG have been suggested. These preliminary reports should stimulate the design of well-controlled studies to confirm any beneficial effect and justify the high cost of IVIG therapy.

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### ***Obiter dictum***

*Perfection of means and confusion of goals seem — in my opinion — to characterize our age.*

— *Albert Einstein (1879-1955)*  
*Out of My Later Years*, ch 15