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Intravenous immunoglobulin in critically ill adults: When and what is the evidence?

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ABSTRACT

Intravenous immunoglobulin (IVIg) use is growing dramatically internationally due to the increasing numbers of acute and chronic conditions that may benefit from IVIg. Patients with conditions that may benefit from IVIg might require intensive care unit (ICU) admission, supporting the need to review IVIg use in the critical care setting. The most common clinical indications for IVIg in adults that may require ICU admission and are commonly supported under clinical practice guidelines are Guillain-Barré syndrome, myasthenia gravis and Lambert-Eaton myasthenic syndrome, inflammatory myopathies, and primary or secondary immunodeficiency diseases complicated by severe bacterial sepsis. Other emerging indications include necrotizing fasciitis, toxic epidermal necrolysis/Stevens-Johnson syndrome, and toxic shock syndrome. The evidence for IVIg use in sepsis and septic shock remains controversial and insufficient to recommend its routine use.

Intravenous immunoglobulin is expensive and also carries risks of adverse effects, including common and benign infusion-related reactions, as well as relatively rare and more serious problems, such as thromboembolic events, renal failure, and aseptic meningitis.

In this article, we review the literature on conditions requiring ICU admission and IVIg, and we classify them as supported, emerging, or unsupported indications based on the available evidence and guidelines for clinical use of IVIg.

1. Introduction

Intravenous immunoglobulin (IVIg) was first used in the 1950s as replacement therapy in immune deficiencies but is now widely used for treatment of inflammatory and autoimmune diseases. In the past few decades, IVIg use has increased internationally [1,2]. Intravenous immunoglobulin use has doubled in the last decade in North America and Australia, leading to major increases in annual direct product costs [2,3]. Improving knowledge of the current use of IVIg, including the specific indications contributing to growth in demand, and the evidence underpinning their clinical use, is highly relevant for clinicians, blood services, and governments.

Although IVIg is mostly prescribed in immunology, neurology, and hematology, there is considerable overlap between diseases requiring IVIg and critical illnesses requiring intensive care unit (ICU) admission, explaining why IVIg use in ICUs has also risen. An international study reported that, based on expenditure per bed, IVIg ranked fourth for ICU therapeutic agent costs [4]. However, no recent report has reviewed IVIg use in critically ill patients [1].

This narrative review summarizes production and mechanisms of action of IVIg and describes the main indications for IVIg in critically ill adults and the evidence behind these indications.

2. Intravenous immunoglobulin

2.1. Production of IVIg and different preparations of IVIg

Production of polyclonal IVIg involves collection of whole blood or plasma from large numbers of healthy donors (either paid or volunteer), plasma processing, viral testing, separation, and purification, followed by viral inactivation and/or removal [2,5].

A wide range of IVIg products is available internationally. Most preparations consist predominantly of concentrated immunoglobulin G (IgG). Although many commercial preparations are available, the 2 main types of products are (i) polyclonal IVIg, composed primarily of IgG but often containing traces of immunoglobulin A (IgA) and immunoglobulin M (IgM), and (ii) IgM-enriched IVIg. Proportion of IgA in products varies between 5 μg/mL or less and more than 700 μg/mL [6]. Differences between manufactured products can be substantial, but there are few "head-to-head" studies comparing various preparations in terms of their efficacy or complications [7,8]. When characteristics of IVIg products are not specified in clinical research, it is often assumed that polyclonal IVIg has been used.

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2.2. Mechanisms of action of IVIg

Mechanisms by which IVIg acts are classically divided into 2 main categories: replacement for absolute or functional immunoglobulin deficits and immunomodulatory and anti-inflammatory actions [2,9]. Immunomodulatory and anti-inflammatory use may require high doses, but effects typically persist beyond the circulating IVIg half-life. Immunomodulatory and anti-inflammatory mechanisms by which IVIg acts remain unclear and may reflect the involvement of several biological pathways. Gelfand [10] has recently distinguished effects that are mediated by the antigen-binging fragment (Fab) of IgG from those mediated by the crystallizable fragment (Fc). The Fab-mediated activities include (i) decrease in the production or neutralization of proinflammatory cytokines (tumor necrosis factor α, interleukin 1α, and interleukin 6), (ii) suppression or neutralization of autoantibodies, (iii) down-regulation of adhesion molecules and chemokines, (iv) neutralization of superantigens, (v) neutralization of activated complement components, (vi) restoration of idiotypic–anti-idiotypic networks, and (vii) modulation of maturation and function of dendritic cells. Fc-dependent activities of immunoglobulin include blockade of Fc receptors and immunomodulation by sialylated IgG. In inflammatory diseases, IVIg may also play a role by improving glucocorticoid receptor binding [10].

3. Current use of IVIg

Over the past decade, neurologic and hematological disorders have become the main indications for IVIg consumption [11]. In terms of overall use, the 3 most common indications for IVIg are acquired hypogammaglobulinemia secondary to hematological malignancies, chronic inflammatory demyelinating polyneuropathy, and primary immunodeficiency diseases [2,12,13]. Focusing on critically ill patients, the most common indications for IVIg include Guillain-Barré syndrome (GBS), necrotizing fasciitis (NF), and toxic epidermal necrolysis (TEN) [1].

The following sections review the most common conditions where IVIg use has been reported in adults and where intensive care is usually required. These indications are divided into 3 categories based on the available literature and guidelines: well-established indications, emerging indications (or "off label," potentially indicated), and unsupported indications (IVIg is not indicated) are summarized in Tables 1 to 3. Randomized controlled trials (RCTs) are firstly mentioned when available; in absence of RCT, observational studies and then cases report are described. Recent relevant reviews or meta-analyses are also mentioned when possible.

4. Well-established indications for IVIg likely to require intensive care

4.1. Guillain-Barré syndrome

Guillain-Barré syndrome is an acute peripheral neuropathy leading to acute neuromuscular paralysis and, potentially, respiratory failure requiring invasive mechanical ventilation. Guillain-Barré syndrome is the main indication for IVIg in ICU [1] and ranked fourth in "on label" IVIg prescriptions in an international study [12]. Although there is no adequate comparison between IVIg and placebo in adults with GBS (as efficacy of plasma exchange [PE] in GBS had been established previously), there is strong evidence to support equivalence of efficacy of IVIg and PE in decreasing morbidity and mortality (Table 1) [14,16,18]. A first pivotal RCT including 150 patients found that improvement in strength was significantly more frequent and faster in patients treated by IVIg compared to PE [14]. In an adequately powered RCT of 383 GBS patients, IVIg had a similar effect to PE in decreasing disability grade but also time on invasive mechanical ventilation and disease relapses and sequelae [16]. A recent updated Cochrane review analyzing 5 RCTs (536 patients with severe GBS) with the same outcome of disability grade at 4 weeks postrandomization also concluded equivalent efficacy of PE and IVIg (dose of 2.0 g/kg, given as 0.4 g/kg for 5 days) [18]. Finally, the available literature suggests that administration of IVIg, which does not require the specialized equipment and staff needed for PE, is associated with fewer complications [76].

4.2. Myasthenia gravis and Lambert-Eaton myasthenic syndrome

Myasthenia gravis (MG) is an autoimmune neuromuscular disease leading to fluctuating muscle weakness and, sometimes, respiratory failure requiring intensive care. In a single small RCT, IVIg has been reported to be effective in MG crisis and severe exacerbation when compared to placebo, with an improvement in functional score at days 14 and 28 after IVIg administration [20]. A number of other trials suggested the equivalence of IVIg with steroids or plasma exchange in patients with an MG exacerbation [19,21,22].

Lambert-Eaton myasthenic syndrome is an autoimmune disease mediated by antibodies to the presynaptic voltage-gated calcium channels at motor nerve terminals, leading to neuromuscular weakness and, potentially, respiratory failure. It is paraneoplastic in more than half of cases. Only 1 small RCT compared IVIg to placebo in patients with Lambert-Eaton myasthenic syndrome; it demonstrated that IVIg (1 g/kg per day for 2 days) was associated with strength improvement [23]. Reviews including case reports on this topic also support the potential beneficial effect of IVIg in this disease [27,77].

4.3. Inflammatory myopathies (polymyositis, dermatomyositis, and inclusion body myositis)

The inflammatory myopathies include rare diseases of unknown etiology, featuring chronic muscle inflammation, resulting in muscle weakness and debilitation. Progression to respiratory failure can lead to ICU admission. Therapies have centered on immunosuppressants and anti-inflammatory medications including IVIg as a second-line or adjunctive therapy [28]. Intravenous immunoglobulin can benefit patients with steroid-resistant disease and/or esophageal or pulmonary involvement [78,79].

4.4. Immunodeficiency diseases

Acquired hypogammaglobulinemia from a range of causes, including secondary to hematologic malignancy, can result in ICU admission as a consequence of infections and sepsis. They are the second most frequent indication for IVIg prescription in this setting, as reported in the international literature [12,80].

Most of the 120 different diseases included in the group of primary immunodeficiency diseases (PIDs) lead to failure of antibody production or function [2]. The increased risk of infections makes patients with PID at risk for ICU admission. However, IVIg therapy in these patients is managed by immunologists due to the chronic nature of PID and will not be reviewed further here [2,81].

4.5. Idiopathic thrombocytopenic purpura

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disease leading to changes in production and half-life of platelets and is associated with an increased risk of bleeding [82]. Although ITP is an uncommon reason for ICU admission, it may be required when a low platelet count can have life-threatening consequences (1%-5% of cases) [83]. An urgent increase in platelet count is necessary in patients with severe thrombocytopenia ($<30 \times 10^9$/L) and a high bleeding risk, before surgery; in pregnant patients before delivery; and in patients with severe active bleeding including central nervous system, gastrointestinal, and genitourinary bleeding [84]. Efficacy of IVIg in acute ITP is supported by observational studies and RCTs [83]. Godeau et al [85] conducted a well-powered RCT including 122 adults with severe ITP (platelet count $<20 \times 10^9$/L) and found that patients receiving IVIg had better