SECTION 6

Immunoglobulin replacement therapy-related adverse events

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Although immunoglobulin (Ig) replacement therapy (IRT) is considered safe, side effects, usually mild and reversible, can develop during or after intravenous (IV) or subcutaneous (SC) administration of IRT. The overall incidence of IVIg side effects range from <1% to 83% and occur in 20%-40% of patients at one time or another. [1-11]

IVIg products are not identical and there is an increased risk of adverse events (AEs) when switching from one IVIg preparation to another.[12] SCIg IRT is associated with significantly fewer systemic AEs than IVIg IRT.[13] In one analysis of more than 40 000 SCIg infusions, the incidence of systemic AEs was 0.43%.[14]

However, up to 75% of patients receiving SCIg infusions will at some point experience reactions at the site of infusion. [14-18] Prospective studies have shown no significant difference in the overall rate of AEs between children and adults. [5,8]

Advanced age in adults who receive IVIg is a risk factor for some rare complications such as thromboembolic events and renal insufficiency. An initial high rate of AEs has been observed for both IVIg and SCIg, which decreases over time with continued infusions. [10,19]

Some of the AEs are related to the manufacturing process, others to the impurities in Ig preparations and some to patient factors. The current commercially available Ig products are much safer than first-generation products. The manufacturing procedure and/or constituents of Ig products are not uniform, variation in the safety profile of different licensed products remain a consideration. [21-24]

The onset of AEs varies widely. [19] There is currently limited evidence from randomised controlled trials to support the prevention, or treatment of IRT-related side effects. Management recommendations in this section are primarily based on observational studies or expert opinion and include adaptation of consensus recommendations. [19]

Immediate side effects

Immediate reactions occur within six hours of the infusion and usually within the first 30 minutes. [10,19]

Immediate systemic non-anaphylactic side effects: Systemic side effects are more frequent during or following IVIg administration and vary from mild to severe. This spectrum of events includes chills, flushing, fever, backache, tension headache, nausea, vomiting, diarrhoea, dizziness, arthralgia, myalgia, transient maculopapular eruptions or urticaria, fluctuation in blood pressure, tachycardia, shortness of breath and fatigue. [5,8,10,19,25,26]

Most of these reactions are common, mild, associated with rapid infusion of IVIg, start within the first hour of an infusion and resolve within 24 hours, and usually occur with the first or second infusion. [8,10,19] An infection at the time of an infusion may also be associated with systemic reactions. [8,25] Some events such as fatigue and migraine may occasionally commence more than 24 hours after an infusion. A minority of patients, particularly those with a preceding history of migraine, may experience severe headache accompanied by photophobia, nausea, and vomiting.[19]

Anaphylaxis: This is a rare systemic complication of IRT, occurring particularly in patients with common variable immunodeficiency and those with selective IgA-deficiency.[33] The diagnostic criteria for anaphylaxis are summarised and discussed in a recent review.[34]

Immediate infusion site reactions: AEs to IVIg at the drip insertion site are uncommon but may cause pain, bleeding, or bruising.[10] By contrast, site reactions are common with SCIg infusions and include discomfort, pruritis, swelling and/or redness at the insertion site. These reactions usually subside within 24-48 hours. Furthermore, the prevalence and severity of site reactions decrease with repeated infusions and by inserting the needle correctly prior to infusion. [14,26]

Delayed side effects

These side effects occur between six hours and one week post-IVIg infusion.[10,19] A wide range of uncommon or rare delayed AEs may occur after IRT including neurological effects such as severe headache, migraine, and aseptic meningitis, thromboembolic events such as myocardial infarction, transient ischaemic attacks, stroke, deep venous thrombosis or pulmonary embolism, acute renal failure, haemolysis and haemolytic anaemia, transient neutropaenia, hyponatraemia, dermatological reactions such as eczema, dyshidrosis, refractory epidermolysis bullosa and alopecia, and transfusion-related acute lung injury.[10,19,25,26,36-48] Management strategies for delayed reactions are summarised in Table 5.

Late side effects

These are reactions that occur one week to months post IVIg infusion.[10,19] Hepatitis C infection and rarely parvovirus B19 infection were reported following IVIg administration in the 1990s.[49,50] Donors of blood used for the production of Ig preparations are routinely screened and tested for human immunodeficiency virus (HIV) 1 and 2, as well as hepatitis B and C.

New procedures have been implemented during the manufacturing process to maximise viral safety. Consequently, there have been no further reports of hepatitis C since 1996. Furthermore, transmission of HIV and prion diseases by Ig products has never been reported.[10,19] An association between IRT and neurodegeneration has very rarely been reported. In one case series of 14 patients, neurological manifestations developed between 0.5 and 13.5 years after IRT was initiated.[51]

Table 1**: Strategies for managing delayed adverse reactions** (adapted from Cherin, Marie, Michallet, *et al* with permission from the authors)[19]

Adverse event	Management recommendations
Migraine	• Analgesia • For patients with a history of migraine, give prophylactic migraine medication before, during and after infusion
Aseptic meningitis	• Manage with analgesia and anti-emetics • To prevent, lower the infusion rate, pre-hydrate with 10-15mL/kg (maximum: 1 litre) normal saline 2-3 hours prior to the infusion and ensure adequate hydration during and after an infusion • To prevent recurrent episodes of aseptic meningitis switch from IVIg to SCIg

Renal dysfunction	• All patients should be screened for renal dysfunction (serum creatinine) before the first infusion
	• For patients with known renal impairment or at high-risk for renal disease:
	  • Commence hydration 6 hours prior to infusion and continue for several hours after infusion
	  • Use sucrose-free IVIg, if available
	  • Reduce dose, concentration, and rate of infusion; consider fractionating into smaller but more frequent doses
	  • Avoid diuretics and angiotensin-converting-enzyme inhibitors
	• For IVIg-related renal failure consider dialysis
	• For patients who experienced renal dysfunction following IVIg switch to SCIg

Thromboembolic events	• Assess risk of thrombosis (age, mobility, hypercoagulable states, indwelling central lines, oestrogen use and history of thrombosis). • For patients with risk factors prescribe SCIg instead of IVIg • For patients who have experienced thromboembolic events

	following IVIg switch to SCIg
Haemolysis	• Consider treatment with glucocorticosteroids • Blood transfusion should be considered on an individual basis • If haemolysis recurs consider switching to SCIg
Neutropaenia	• This event usually resolves without treatment • Recurrent neutropaenia may be prevented with pre-IVIG glucocorticosteroid administration
Hyponatraemia	• Usually resolves spontaneously • The risk of morbidity is increased in patients with comorbid conditions such as cardiac and renal disease
Transfusion-related acute lung injury	• Manage this rare adverse event with appropriate oxygen therapy and ventilator support • Premedication with glucocorticosteroid therapy may prevent recurrence or consider switching from IVIg to SCIg

Recommendations

1. Because most of the immediate side effects are related to rapid infusion of IVIg, these reactions can be prevented by commencing an infusion rate slowly for the first 15-30 minutes and then progressively increasing the rate according to the manufacturer recommendations (level of evidence: IV).[19,25, 26]
2. Slowing (or stopping) the infusion rate will reverse most immediate side effects.
3. Once the side effect has subsided, the infusion should can be re-started at a slower rate.[8,19,26]
4. Ibuprofen or glucocorticosteroids can be used for treating moderate or severe reactions.[19]
5. If moderate or severe reaction occurred with previous infusions, pre-treatment (one hour before the next infusion) should be considered with a dose of ibuprofen (5mg/kg PO, maximum: 400mg/dose). If reactions recur, consider pre-infusion ibuprofen plus an oral dose of an antihistamine (e.g., promethazine). If the reactions persist despite the combination of ibuprofen and antihistamine then IV hydrocortisone (6mg/kg/dose, maximum: 100mg) can be considered one hour before the next.[27,28,29]
6. If adverse reactions persist with IVIg despite pre-medication, switching to SCIg should be considered.[13]
7. If the immediate side effect is urticaria, stop the infusion temporarily and administer oral/IV promethazine or IV hydrocortisone. Re-commence the infusion once urticaria has resolved.[19,30,31,32]
8. If urticaria or eczema was experienced with previous infusions, premedication with an oral antihistamine or IV hydrocortisone should be considered.[19,32]
9. In patients who experience anaphylactic reactions, the infusion should be stopped, intramuscular adrenaline should be administered, and additional therapeutic and supportive measures should be implemented according to the local strategy for treating anaphylactic reactions. [19,35]
10. In patients who experience anaphylactic reactions, use SCIg for future IRT.[19]

11. In patients who experience anaphylactic reactions, future SCIg infusions should initially be done under observation of an experienced clinician in a facility capable of managing anaphylaxis.[1)]
12. Most infusion site reactions will resolve spontaneously and do not require treatment.[25]
13. Infusion site reactions can be managed with gentle massage and warm/cold compresses.[19]
14. If there is persistent pain as a result of an infusion site reactions, administer oral ibuprofen as required.[19]
15. For previous, severe local infusion site reactions, review the technique of administration and a topical steroid cream may be used to prevent recurrent reactions.[19]

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