SECTION 4

IRT products and administration procedures

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IRT products

Administration routes include IV immunoglobulin (IVIg), SC immunoglobulin (SCIg) and recombinant human hyaluronidase facilitated SCIg (fSCIg). IV and SC delivery IRT is equally effective in preventing infections in adults and children with PID as well as pregnant women with PID.[1-12]

The decision on the route should be individualised and taken with patient preferences in mind. Patients should have access to either route as needed.[4,6,7,13,14] The intramuscular administration of IRT is not recommended in PID.[15-17] The differences between the routes of IRT administration and the respective monitoring requirements are summarised in Table 3.

Table 1: Main differences between IRT routes and monitoring of Ig administration [4, 9,18-20]

Requirements	IVIg	SCIg	fSCIg	Manual push
Pump requirement	No	Yes	Yes	No
Patient and caregiver training	No	• Yes • Observed administration before self- administration at home	• Yes • Observed administration before self- administration at home	• Yes • Observed administration before self- administration at home

Venous access	Yes	No	No	No
Possibility of home treatment	• Yes, but always in the presence of a trained nurse • Initial dose always in medical facility that can manage acute adverse reactions	Yes, after 4-6 training sessions	Yes, after 4-6 training sessions	Yes, after 4 training sessions
Monitoring of systemic adverse events	Yes, according to a fixed protocol (Be aware of signs and symptoms of anaphylaxis)	Looser monitoring (Be aware of signs and symptoms of anaphylaxis)	Looser monitoring (Be aware of signs and symptoms of anaphylaxis)	Looser monitoring (Be aware of signs and symptoms of anaphylaxis)
Dose	• Starting dose of 400-600 mg/kg every 3-4 weeks • Higher doses may be needed to keep patients, infection free	Starting dose of 100-200mg/kg/week	Starting dose of 400-600mg/kg every 3-4 weeks	Starting dose of 100-200mg/kg/week
Pretreatment and hydration	Helpful	Not necessary. May use local anaesthetic creams	Not necessary. May use local anaesthetic creams	Not necessary. May use local anaesthetic creams
Peak/trough variation	Large	Minor (slightly more with fortnightly dosing)	Intermediate, dependent on treatment interval	Minor

Table 2: Contrasting IVIg and SCIg therapy [8,18,19,21-25]

	Intravenous IRT	**Subcutaneous IRT**
Route and timing	• Mostly administered in hospitals • Every 3-4 weeks • Faster increase of trough level at initiation • Trained and experience staff necessary • Need for venous access	• Home-based therapy • Weekly or biweekly • Given by self-administration • Advantageous when venous access is poor
Monitoring	Closer monitoring	Looser monitoring
Tolerance of drug	• Systemic reactions are possible, especially on first infusions • Usually no local reactions (e.g., redness and swelling)	• No systemic reactions • Local reactions include redness and itching, but these diminish over time • Possibly better in patients with renal or cardiac insufficiency
Time needed	Individualised, may be up to 12 hours or longer	• 60-90 minutes with conventional infusions • 5-20 minutes with push method
Infusion rate	• Maximum infusion rate with IVIg is much higher at 300mL/hour • Infusion time with IVIG is shorter • Allow for high dose indication (e.g., immunomodulation neurology, weight, higher trough needed X-linked agammaglobulinaemia, bronchiectasis) • Convenient when need to load quickly	Maximum desired infusion rate of 40mL/hour with the SC route.
Trough levels	• Peak and trough IgG levels may vary substantially • The low trough level of IgG has been linked to the increased susceptibility of PID patients to bacterial infections during the week before the monthly IVIg infusions	More stable IgG levels

Patient involvement and compliance	• The patient is not involved • Does not require patient training	• Greater Independence, increase patient's autonomy • Ability to self-infuse requires patient reliability and compliance • Portable for use during travel

Intravenous administration of IgG

All initial doses of IVIg should always be administered in a medical facility that can manage acute adverse reactions. Once a certain product is well tolerated, a decision can be made where to infuse the IVIg, in hospital or in an outpatient setting, doctor's office or home-based setting. These decisions should be made based on clinical considerations and on patient experience and circumstances.

Close monitoring for AEs is always indicated. When changing to another IVIg or SCIg product, this should be done under close supervision. Switching between IVIg products without a clear indication is not recommended nor advised due to risk of AEs. IVIg products are not interchangeable. The placement and use of indwelling venous catheters for IVIg administration is discouraged as these devices have the potential to cause severe adverse events including infections and thrombotic events. [16,26-40]

Subcutaneous administration of IgG

SCIg has been shown to be efficacious and safe and reach IgG trough levels that protect against infections. SCIg and IVIg is considered to be equivalent with regard to efficacy for reducing infection. Consequently, if there is cost equivalency, the patient should be able to make the decision as to the route of administration.

It also has reduced systemic adverse effects when compared with IVIg. Due to more regular administration, it provides consistent serum IgG trough concentrations as opposed to the initial high peak followed by low trough levels associated with IVIg therapy. [1-9,13,14,21,41,42] For at home administration, patients should have access to biological waste containers.[43]

Treatment AEs include infusion-site reactions, mild-to-moderate in severity and involve swelling, redness, and itching. Other AEs reported are headaches, and rarely nausea, rash, asthenia (weakness) and gastrointestinal complaints. These side effects tend to decrease in severity over time.

The rate of withdrawal due to AEs can be minimised by ensuring optimal patient education, so that the product is administered with the correct technique and the patient recognises that some local reaction is to be expected but will decrease and even disappear over time.

Serious systemic side effects, including anaphylaxis, have not been reported, in as much that European countries do not provide patients with a self-injectable epinephrine anymore. Prescription of an epinephrine autoinjector should be based on the provider's discretion but should be considered in patients who have had prior allergic reactions or anaphylaxis to IVIg. [1,4,9,11,18,44,45]

A SCIg dose equal to the standard IVIg dose (100-200mg/kg/week) is recommended. Frequent SC infusions of IgG will generate a local depot resulting in slow absorption and in a nearly constant serum levels of IgG of approximately 9.20g/L, that provides adequate protection to patients while not being associated with additional serious bacterial infections. [1,8,9,11,22,46]

SCIg significantly improves QoL in patients due to the increased independence and scheduling flexibility associated with home-based, self-administered therapy many patients prefer this route. Self-administration is easy to learn and has been demonstrated to be cost-effective. [6,10,20,22,47-51]

Many factors affect QoL. It is therefore important to have individualised discussions with patients and allow them to make the decision. Patient preference should be considered when deciding on the route of administration. Some patients still prefer IVIg and self-infusing IVIg at home under supervision of a qualified nurse.
SCIg can be offered to anyone who prefers this route who is compliant, independent, and self-motivated or who has a good support structure at home. In addition, patients who have time constraints during business hours of infusion centers, should also be offered SCIg. [1,10,13,14,41,42,50,52-54] SCIg should be the preferred route of administration in patients with difficult access to an IV transfusion centre.

Definitive indications for SCIg include patients who experience intolerable or unacceptable systemic with IVIg therapy AEs and patients with problematic venous access. Indwelling ports are not indicated in patients with a PID due to the increased risk of infection. SCIg is definitely indicated in patients with severe reactions to IVIg, including those who have IgA deficiency and systemic reactions when receiving IVIg. SCIg is also indicated where therapeutic levels to prevent infection cannot be achieved by IVIg.

Facilitated subcutaneous IRT with rHuPH20

Hyaluronidase administration allows increased movement of fluid through the extracellular matrix. It facilitates significant reductions in the infusion pressures required (compared to SCIg) and improves subcutaneous perfusion. The availability of recombinant human hyaluronidase (rHuPH20), added to Ig, makes it possible to facilitate the administration of SCIg. The pre-administration of rHuPH20 is associated with 10% Ig, which allows for the infusion of larger (up to 600Ml) amounts of Ig at a single infusion site and enables patients to receive the necessary treatment in a single dose every three to four weeks while still achieving adequate trough levels. [31,55-58]

Three weekly infusions at an equivalent dose of IVIg or SCIg (1:1 conversion) are recommended. Adjust the dose upwards to avoid wasted product (100-

111%).[59] The advantages of facilitated SCIg (fSCIg) include fewer needle punctures, longer infusion intervals and an improved AE profile relative to IVIg.

The sharp peak in serum IgG level immediately after IVIg infusion is avoided with fSCIg, which is reflected by an AE profile closer to conventional SCIg. It has been demonstrated to have a low rate of adverse reactions allowing home-based administration for adequately trained patients, also in the paediatric population (children >2-years).

The prospect of safe and effective administration in children is particularly important because of the special needs of this population where fSCIg may provide a more acceptable alternative.[59] Safety studies have not yet been done in pregnant women.[55,57-59]

IRT administration procedures

For administration of either IVIg or SCIg, refer to the new European Nursing Guidelines for Ig Administration. Go to https://ingid.org/nursing-guidelines-english/.

Summary statements

1. IVIg and SCIg are equally effective for reducing infections and can be equivalently dosed. Patients should have access to either route as needed.
2. All initial infusions of IVIg should be provided in a facility that is fully equipped to handle the most severe acute medical complications.
3. Definite indications for SCIg include systemic Aes to IVIg, patients with difficult access to an IV transfusion centre, problematic venous access necessitating consideration of an indwelling catheter, inability to achieve therapeutic infection free levels of serum IgG with IVIg.
4. Indwelling catheters for the sole purpose of applying IRT should not be considered.
5. Intramuscular Ig should not be given for PID.
6. Patients and practitioners must realise that IRT may be lifelong. Treatment is indicated as ongoing replacement therapy and should not be interrupted once a definitive diagnosis has been established in category 1 and 2 patients (Table 1).
7. Before initiation of IRT, HIV and TB testing should be a prerequisite in South Africa, regardless of socioeconomic circumstances.
8. Careful consideration should be made when considering changing between products. We do not recommend unnecessary switching of products for minor Aes or patient inconvenience as side effects may be increased.

9. In category 3 and 4 patients (Table 1), macrolide prophylactic antibiotics should be started before considering IRT.

59. Patient preference and resources should be considered when choosing the route of administration.

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UPDATED December 2021