Clinical Guideline

British Society for Immunology and United Kingdom Primary Immunodeficiency Network (UKPIN) consensus guideline for the management of immunoglobulin replacement therapy

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Summary
Currently, there is no guideline to support the use of immunoglobulin replacement therapy (IgRT) in primary and secondary immunodeficiency disorders in UK. The UK Primary Immunodeficiency Network (UK-PIN) and the British Society of Immunology (BSI) joined forces to address this need. Given the paucity of evidence, a modified Delphi approach was used to generate consensus from specialists with experience in managing immunodeficiency from across the UK. Statements regarding the decision to start and to stop IgRT were included as well as monitoring requirements and decisions relating to patients self-administering IgRT at home.

Keywords: human, immunodeficiency disorders, immunoglobulin, antibodies

Abbreviations: ARA: autosomal recessive agammaglobulinaemia; BPAIIG: British Paediatric Allergy: Immunity and Infection Group; BSI: British Society of Immunology; CDSR: Cochrane Database of Systematic Reviews; CVID: Common Variable Immune Deficiency; ESID: European Society for Immunodeficiencies; GILD: Granulomatous Lymphocytic Interstitial Lung Disease; HIES: hyper IgE syndrome; IgRT: immunoglobulin replacement therapy; IV: intravenous; MDT: multi-disciplinary team; NGC: National Guideline Centre; NTM: non-tuberculous mycobacteria; PID: primary immunodeficiency; PID-UK: primary immunodeficiency UK; QPIDS: quality in primary immunodeficiency services; RCP: Royal College of Physicians; SC: subcutaneous; SCID: severe combined immunodeficiency; SID: secondary immune deficiency; SPAD: specific antibody deficiency; SRIAPs: sub regional immunoglobulin advisory panels; UKPIN: UK Primary Immunodeficiency Network; UKPIPS: UK Primary Immune-deficiency Patient Support charity; XLA: X-linked agammaglobulinaemia

Introduction
Immunoglobulin replacement (IgRT) therapy is used in the management of patients with both primary and secondary antibody deficiencies. In the UK, the use of immunoglobulin follows NHS England commissioning criteria (updated for immunology, haematology, and neurology in 2019 [1]) and is overseen by sub regional immunoglobulin advisory panels (SRIAPs). It was identified by the UK Primary Immunodeficiency Network steering group (UKPIN) that there was a need for national guidelines regarding the use of replacement immunoglobulin in both primary and secondary immunodeficiencies to support the long-term management of patients with these conditions. As there was a lack of published evidence, a modified Delphi process was used to generate consensus from specialists with experience in managing immunodeficiency from across the UK. Statements regarding the decision to start and to stop immunoglobulin replacement were included as well as monitoring requirements and decisions relating to patients self-administering IgRT at home. The consensus statements provide more detail in these areas.
than the commissioning criteria in order to support decision making by clinicians and the SRIAPs in particular circumstances.

This survey was undertaken before the COVID-19 pandemic changed clinical practice regarding remote (telephone or video) patient reviews and no questions were asked regarding the location of the specialist review in this survey.

Methods

Delphi methods

A joint guideline writing group was established with input from UKPIN, the British Society for Immunology (BSI), and the National Guidelines Centre (NGC; within the Royal College of Physicians, RCP). A formal consensus survey was conducted on the use and management of immunoglobulin replacement therapy. The aim was to gather views from consultant immunologists, paediatric immunologists, haematologists, and immunology specialist nurses involved in the management of patients with primary and secondary immunodeficiencies. Experts were identified from the RCP 2016 census of immunology consultants and other contact lists including UK immunology specialist nurses network, British Paediatric Allergy, Immunity and Infection Group (BPAIIG), haematologists involved in SRIAPs, and the UKPIN membership.

A total of 68 people took part in the survey, of whom 62 also completed a follow-up second round survey. The survey questionnaire was conducted via SurveyGizmo online software. Data were collected on participant specialism, place of work, years involved with IgRT and number of PID or SID patients cared for; however, responses to statements remained anonymous. The guideline steering group did not participate in the survey. Invitations to take part were sent out via the RCP, and two email reminders were circulated for each round of the survey.

The survey used a modified Delphi process, which uses a multi-round, consensus-building technique. This type of survey has been used successfully for generating, analysing, and synthesising expert views to reach a group consensus position. In the first round, participants were asked to rate clinical statements according to a four-point Likert scale: “Strongly Agree, Agree, Disagree, and Strongly Disagree”. A fifth option of ‘I don’t have the expertise to answer’ was included, and these responses were excluded from the analysis of consensus for that statement. A threshold of 75% of agreement (strongly agree or agree) or disagreement (strongly disagree or disagree) was chosen to define consensus agreement [2].

Following the first round, the steering group analysed consensus results and free-text participant feedback to create a second-round survey. Second round statements were either re-drafted from first round statements according to participant feedback or introduced as new statements to address areas of the immunoglobulin replacement management that participants thought were omitted or unclear in the first round.

Literature review

In parallel with the Delphi survey, a systematic review of the literature was conducted by the NGC in clinical areas identified by the guideline steering group. The following databases were searched using medical subject headings and free-text terms to identify all published clinical evidence relevant to immunoglobulin replacement therapy: Embase, Medline, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR). Full search strategy and search terms used can be found in Supplementary Appendix 4. From the resulting library, the reviewer identified all relevant studies by reviewing titles and abstracts before ordering full papers for assessment. Questions that informed paper assessment were: who should receive IgRT; when should IgRT be started; how should IgRT be administered; how should IgRT be monitored; when/if IgRT should be stopped; and when/if IgRT should be restarted. Relevant studies were included if they had a comparative design (including randomised controlled trials or cohort studies) and were conducted in adults or children/young people with primary or secondary immunodeficiency. Papers were excluded according to the following criteria: single-arm or non-comparative studies; safety studies; IgRT vs placebo comparisons e.g. proof-of-concept or early efficacy studies; case studies; non-English language papers; conference abstracts. Systematic reviews and secondary analyses were not included but references were checked for relevant published and includable primary studies.

Thirty-eight studies were included. The following form the framework of this evidence review: (1) comparative studies of IgRT administration route (intravenous (IV) vs subcutaneous (SC)); (2) comparative studies of dosage and/or serum IgG levels required for protection against infection; and (3) comparative or survey studies of home therapy (SC). Included studies are summarized in Supplementary Appendix 1 and evidence statements below.

Definitions

While it is recognized that all patients are considered individually when clinical judgements are being made, in order to ensure consistency of responses the following definitions were provided to experts when the statements were circulated.

Increased burden of infection

- ≥4 infections* per annum requiring treatment with antibiotics (ideally microbiologically proven)
- radiologically proven pneumonia
- sepsis proven with cultures
- other infection requiring hospitalization and IV antibiotics

*Not all infections are relevant in the assessment of suitability for IgRT. Demonstration of infection with encapsulated organisms (e.g. Haemophilus influenzae, Streptococcus pneumoniae) is important in predicting efficacy of immunoglobulin. Other organisms (e.g. Pseudomonas aeruginosa, non-tuberculous mycobacteria (NTM), fungal or opportunistic infections) will not be prevented by IgRT, and other treatment or eradication strategies are required.

Response to immunization

This guideline does not intend to provide consensus on what constitutes adequate response to immunization but as part of the survey the following definition was used:
- At least a 3-fold increase in antibody level or titre and/or a rise to an accepted reference range of protection.
- For pneumococcal serotype testing at least 7/13 at baseline or following immunization with polysaccharide pneumococcal is considered an adequate response.
- If using Salmonella typhi immunization to reassess humoral immunity, it was proposed that an S. typhi level of >50 U/mL should be considered a good response.

Recommendation 1

Results

Sixty-eight participants from across the UK took part in the first round survey; a total of 46 consultant adult immunologists, 10 consultant paediatric immunologists, ten immunology specialist nurses and two haematologists. Of the approximately 324 people who received a link to take part, 21% completed the survey. Of this group, 65% had over 10 years’ experience of caring for immunodeficiency patients on IgRT; 18% had spent over 20 years supervising IgRT patients. The second round was sent only to people who completed the first round survey. Sixty-two people completed the second round (91% of the people who were invited). Two patient groups, UKPIPS and PID-UK, were asked to comment on the final draft of this guideline.

The guideline steering committee that developed the Delphi survey comprised six consultant immunologists, three immunology nurse specialists, and a facilitator from the NGC. The following consensus guideline consists of 73 consensus recommendations. They are divided into four sections of the IgRT pathway; starting IgRT, monitoring IgRT, home therapy, and stopping IgRT. Of the 67 first round statements, 59 achieved a consensus of over 75% agreement. In the second round, 27 out of 35 statements achieved consensus. Eleven first round statements that reached consensus were replaced by new statements in the second round according to participant feedback and steering group analysis. In two cases, separate statements were combined to create single statements; this was done where equivalent statements existed for both IV and SC IgRT or primary and secondary immunodeficiency.

Participant comments and feedback themes are incorporated into the discussions below. Statements that did not reach consensus in the first instance are listed in Supplementary Appendix 3. Statements that reached consensus but were replaced by modified second round consensus statements are listed in Supplementary Appendix 2. Evidence of comparative studies was included under each statement where available.

Consensus recommendations and discussion

Starting immunoglobulin replacement therapy

Recommendation 1:

Patients with the following confirmed diagnoses should be given immunoglobulin replacement therapy (IgRT):

- Common variable immune deficiency (CVID) according to current ESID* criteria, with recurrent infections.
- CVID according to current ESID criteria, without recurrent infections but with significant autoimmunity or inflammatory disease (e.g. GLILD†).
- XLA (X-linked agammaglobulinaemia)/autosomal recessive agammaglobulinaemia (ARA).
- Severe combined immunodeficiency (SCID).
- Hyper IgM syndromes.
- Good’s syndrome with low IgG level and recurrent infections. *European Society for Immunodeficiencies.

Recommendation 2

Patients with other immunodeficiencies should not be routinely started on IgRT unless IgG levels are low or there is evidence of impaired humoral response. These cases should be discussed in an Immunology multidisciplinary team meeting before a decision to start IgRT is made.

Although there is broad consensus on the above statements it is imperative to emphasize the importance of a multidisciplinary approach taking into account clinical information and alternative treatment options, regardless of diagnosis and absolute numerical results, in the decision to start IgRT. Improved access to genetic diagnosis should also facilitate decision making. Several comments from the respondents to the Delphi survey highlighted that some individuals with well-defined immunodeficiency, such as Good’s syndrome and CVID, may remain well without immunoglobulin replacement. It was also highlighted by respondents that in some other immunodeficiencies, not listed above, IgRT may be of benefit; however, no comparative evidence was identified in the literature searches. A retrospective analysis of 32 patients with hyper IgE syndrome (HIES) and recurrent pulmonary infections did however conclude that in patients with HIES suffering from recurrent pulmonary infections a combination of prophylaxis with oral antibiotics and IgRT reduced the incidence of bacterial pneumonia [3].

Recommendation 3

If IgG is ≥ 4 g/L with preserved vaccine responses and a low infection burden, IgRT is not routinely indicated.

Recommendation 4

If IgG is ≥ 4 g/L and vaccine responses are poor (this will include patients with normal total immunoglobulin levels diagnosed as SPAD*), IgRT should not be routinely started unless the patient has recurrent and/or significant infection (see definition above) despite prophylactic antibiotics for 6 months and optimised medical management (e.g. including chest clearance) and/or radiologically confirmed bronchiectasis.

*Specific Antibody Deficiency

Recommendation 5

If IgG is < 4 g/L with poor vaccine responses, IgRT should be considered unless the patient has a low frequency or severity of infection.

Recommendation 6

If IgG is < 4 g/L with preserved vaccine responses, IgRT should not be routinely started unless the patient has recurrent and/or significant infection despite prophylactic antibiotics for 6 months and optimised medical management and/or radiologically confirmed bronchiectasis.
Recommendation 7
In patients with primary immunodeficiency and increased burden of infection, if IgG is < 2 g/L, IgRT may be started without a trial of prophylactic antibiotics.

Note that this statement did not achieve consensus for secondary immunodeficiency.

Recommendation 8:
If IgG is < 2 g/L, vaccine response testing is unlikely to be helpful and IgRT should be considered unless the patient has low IgG due to protein loss (where vaccine responses may be preserved).

These consensus statements provide a framework on which to base clinical decisions. It is recognised that using IgG levels with defined cut-offs (eg 2 or 4 g/L) relies on arbitrarily chosen threshold values and is not evidence based. It should be emphasised (and was highlighted in the comments from respondents) that any treatment decision should be individualised taking into account the full clinical picture. Respondents to the Delphi survey commented that vaccine response assessment is not straightforward and a number of responses highlighted the importance of the clinical context. There was consensus that vaccine responses may not be useful if IgG levels were below 2g/L, but also agreement that if in this situation the vaccine responses had been checked and found to be reduced this would provide further support to the use of immunoglobulin in primary immunodeficiency.

Although reaching consensus, concerns were expressed about the statement regarding 6 months of prophylactic antibiotics, highlighting that there is no evidence to support the 6 month time interval and that in some cases a shorter period of treatment with prophylactic antibiotics may be sufficient to demonstrate the need for IgRT.

Respondents also highlighted that bronchiectasis has a number of causes that do not respond to immunoglobulin and can be managed with respiratory therapy, and therefore the alternative causes and management of bronchiectasis should be considered at the same time as immunoglobulin therapy. Ideally treatment should be initiated before end organ damage such as bronchiectasis occurs, but it is recognised that diagnostic delays in immunodeficiency mean that this is not always possible.

Recommendation 9
Where possible, reversible causes of secondary immunodeficiency should be treated prior to consideration of IgRT.

Although there was consensus for this statement, respondents commented that in some cases the use of IgRT may be necessary as a short-term bridging measure for the time needed to manage and reverse the cause of the secondary immunodeficiency.

Recommendation 10
All patients starting IgRT should be dosed according to ideal body weight, with a cumulative dose of 400-500 mg/kg every month (in divided doses according to delivery method).

Consensus was achieved on the proposed starting dose. Some respondents would consider a higher dose in the context of complications (eg bronchiectasis). Many respondents commented on the importance of adjusting the dose once treatment has been established according to response (see monitoring section below).

Evidence review: Dosage for primary immunodeficiency. Six comparative studies [4–9] were identified for IgRT dosing strategies in primary immunodeficiency patients. In identified comparative dosage studies of primary immunodeficiency patients, a target of 6 g/L trough IgG was reached with a range of doses. Two studies [5, 6] (PID, total n = 36) used a dose of between 350-600 mg/kg or 400 mg/kg body weight every three weeks for a mean trough IgG of 6 g/L. Elsewhere, a dosage of 300 mg/kg body weight per month was sufficient to produce a study group mean trough IgG level of 6.5 g/L, while a high dosage of 600 mg/kg body weight monthly produced a mean trough IgG of 9.4 g/L [4] (PID, n = 43). Two other small studies used the following dosages to raise mean trough serum IgG to around 6 g/L: 300-400 mg/kg every month [8] (for an IgG range 4.87-7.48 g/L; PID, n = 9); a 20 mL IV dose of 150 mg/mL 2-4 times weekly [9] (for a mean plasma IgG of 6.5 g/L; PID, n = 8).

In one study [7] (PID, n = 21) that considered protection against infection rather than target trough IgG levels, 400 mg/kg body weight per month was recommended as the dosage for best protection against infection and highest number of infection-free months, even when compared to a dose of 600 mg/kg per month which did not provide better protection.

Evidence review: Dosage for secondary immunodeficiency. Four studies were identified comparing dosage regimes in secondary immunodeficiency patients [10–13]. In a study of n = 332 allogenic bone marrow transplant recipients [10] a dosage of 250 mg/kg body weight weekly was found to have no significant difference to a dosage of 500 mg/kg per week in terms of infection frequency, but the higher dose was associated with reduced acute graft-versus-host disease. Two studies [11, 12] (total n = 70) similarly found that a lower dose of 250 mg/kg per month provided similar protection against serious infections as a higher dose of 500 mg/kg per month, in patients with chronic lymphocytic leukaemia and non-Hodgkin’s lymphoma. Elsewhere, one study [13] (n = 62) found that a 400 mg/kg 3-weekly dose was optimal for chronic lymphocytic leukaemia patients (reducing to 400 mg/kg 5-weekly after steady state is reached), but a higher initial dose of 800 mg/kg followed by 400 mg/kg every week was recommended for patients with multiple myeloma.

Evidence review: Dosing by ideal body weight. One study was identified [14] (PID, n = 18) in which a comparison of dosing by actual, adjusted or ideal body weight showed that in adults the correlation between IV dose and post-dose change in serum IgG was strongest when dosing by ideal body weight [14].

Recommendation 11
Prior to starting IgRT for the first time, patients should routinely undergo the following tests:

- Long-term archiving of serum
- PCR for hepatitis C
- Surface antigen for hepatitis B
- Full blood count
- Liver function test
- U&E test
Recommendation 12
Prior to commencing IgRT, anti-IgA levels are not routinely required.
Regardless of the current safety of immunoglobulin products, there was a consensus that viral assessment and serum storage is necessary prior to starting IgRT. Some respondents to the Delphi survey favoured serum storage over PCR testing.

Recommendation 13
Prior to starting IgRT, the patient (or parent/carer for children) should provide written informed consent supported by written information.

Recommendation 14
Provision of consent should include awareness of:
- thrombosis risk
- potential transmission of known and unknown infectious agents
- immediate systemic reactions
- delayed systemic reactions
- local reactions
- severe reactions (e.g. aseptic meningitis)
- forward plan for stopping IgRT if underlying diagnosis does not require continued treatment
- need to engage with the department providing treatment for monitoring and clinical review to ensure safe prescribing.

A number of respondents suggested in the comments that clear documentation of the discussion could be sufficient in place of written consent. However, feedback from patient representatives emphasized the importance of written information provided to patients and written consent.

Recommendation 15
In the majority of cases, intravenous (IV) and subcutaneous (SC) immunoglobulin delivery should be considered equivalent and patients should be given a choice between them.

Evidence review: Nine adult studies [14–22] (7 studies in PID patients, total n = 230; 2 studies in SID patients, total n = 75) demonstrated that subcutaneous therapy routinely produces higher mean serum IgG levels than the same doses given via the intravenous route. The majority of these studies showed that mean serum IgG increased following a switch from IV to SC therapy. Three comparative studies conducted in children and young people supported this [23–25] (PID patients, total n = 126), showing that subcutaneous administration tended to produce higher mean serum IgG.

In studies considering specific antibody levels against Streptococcus pneumoniae, results were comparable between intravenous and subcutaneous IgRT in one study [26] (PID patients, children/young people, n = 24) whilst subcutaneous therapy produced higher pneumococcal titres in another [27] (mixed paediatric and adult PID patients, n = 28).

There was mixed evidence regarding rates of infection under each administration route. Three adult studies [21, 22, 26] (1 study in PID patients, n = 30; 2 studies in SID patients, total n = 75) demonstrated that each route provides equivalent overall protection against infection, with one study [29] (PID, n = 11) showing more infections under SC than IV. Three studies in children and young people [23, 24, 26] (PID patients, n = 54) demonstrated better protection against infection with subcutaneous therapy when compared with intravenous administration, while one adolescent study [30] (PID patients, n = 12) showed evidence of equivalence between SC and IV in terms of IgG levels and infection rates.

Two other studies supported patient choice between IV and SC, with one study [31] (PID, n = 304) showing that patients had an equivalent quality of life under IV and SC, but another [17] (PID, n = 30) suggesting patients showed preference for the SC route.

Recommendation 16
Subcutaneous immunoglobulin should be favoured in patients with:
- past thrombosis
- renal failure
- risk of hyperviscosity syndromes
- conditions associated with IgM paraprotein (e.g. Waldenstrom’s macroglobulinaemia)
- past history of aseptic meningitis
- past complications with IV therapy
- poor venous access

Evidence review: One study [32] (PID, n = 13) supported switching to SC after severe adverse events under IV, with the majority of patients who withdrew from IV later tolerating SC therapy.

Recommendation 17
Intravenous immunoglobulin delivery should be favoured in patients:
- Who have a past history of adverse reactions to subcutaneous delivery
- Are physically unable to administer via the subcutaneous route and have no infusion partner to do so (and where no homecare nursing provision is available)

There was a broad consensus on giving patients the options between SC and IV therapy and this was supported by feedback from patient groups. Respondents commented that other side effects of Ig therapy have not been included in the statement. It was highlighted that in some cases a change in product rather than route might improve tolerance depending on the nature of the adverse effects. Overall comments favour an individualised, multifactorial approach to recommending the route of therapy to patients. One comment suggested SC should be considered in all children unless there are absolute contraindications. Many respondents mentioned that an infusion partner is not required for SC home therapy. It should also be noted that these guidelines were circulated before the COVID-19 pandemic; clinicians and patients should also consider the risks associated with attending hospital sites in the context of extraordinary circumstances such as a pandemic. However, patient choice should remain the overriding consideration.
Recommendation 18
First dose of immunoglobulin should not be routinely given to patients with evidence of severe active infection.

Recommendation 19
Rarely, it may be necessary to administer the first dose of immunoglobulin to patients with active infection on antibiotic treatment; this should be done with close inpatient monitoring (e.g. in High Dependency Unit) under consultant supervision.

This document relates to the use of IgRT in the management of primary and secondary immunodeficiency, it was highlighted in the comments that there may be circumstances when the use of immunoglobulin is indicated for treatment of other specific conditions (e.g. toxic shock and for immunomodulation) where guidelines specific to those conditions should be followed. In addition to reaching consensus, comments suggested that appropriate treatment settings and level of supervision required would vary between units according to local policies and staffing arrangements.

Recommendation 20
Patients should not routinely receive pre-medication before their first SC IgRT infusion.

Pre-medication typically includes antihistamines and corticosteroids, but this was not specified in the Delphi survey. Of note, there was no consensus for a statement proposing that the use of pre-medication before the first dose of IV immunoglobulin was NOT necessary.

Recommendation 21
Patients do not require an observation period after their first SC immunoglobulin infusion has completed assuming the infusion was tolerated.

A statement with the same wording did not achieve consensus for the first IV immunoglobulin infusion suggesting that some respondents did consider a period of observation necessary after the first IV immunoglobulin infusion. Patient groups emphasised that individual needs should also be taken into consideration for both statements.

Recommendation 22
When prescribing immunoglobulin dosage, available vial size should be taken into account to avoid waste.

Monitoring immunoglobulin replacement therapy

Dose monitoring and adjustments

Recommendation 23
Following initiation of IgRT, IgG levels should only be measured to assess appropriate dosing of IV or SC IgRT after a minimum of 3 months.

On starting IgRT, a number of initial dosing regimens are used. Some clinics employ loading doses over a short period, some start by the IV route and then switch to SC dosing, while others simply start the planned long-term treatment regimen without any initial priming.

Recommendation 24
For the majority of primary immunodeficiency patients, the optimal IgG target should be ≥ 8 g/L (trough for IV, random for SC) to avoid recurrent infection.

Recommendation 25
In some primary immunodeficiency cases (XLA, antibody deficiency with end organ damage/persistent infections) it may be necessary to maintain an IgG level of ≥ 10 g/L (trough for IV, random for SC) to minimise infection or progressive end organ damage.

Recommendation 26
In some secondary immunodeficiency cases, it may be necessary to maintain an IgG level of up to 10 g/L (trough for IV, random for SC) to avoid infection or progressive end organ damage.

Recommendation 27
In primary immunodeficiency patients, immunoglobulin doses should be adjusted according to infection burden and/or progression of organ disease.

Evidence review: One dose comparative study was identified [4] (PID, n = 43) in which the authors suggested that after starting patients on standard dose therapy, dose should be increased if patients developed two or more severe infections per year.

Recommendation 28
If a patient with primary or secondary immunodeficiency is stable and free of infection on IgRT, immunoglobulin dose reduction should be considered. (Children’s doses should continue to be weight adjusted.)

The Delphi included two separate recommendations for primary and secondary immunodeficiencies both of which reached consensus and have therefore been combined into a single statement.

Recommendation 29
Patients with primary immunodeficiency treated with IgRT who continue to have a high infection burden despite trough IgG level ≥ 8 g/l should have other treatments optimised (e.g. antibiotic prophylaxis, physical therapy) prior to immunoglobulin dose increase.

Recommendation 30
Patients with secondary immunodeficiency treated with IgRT who continue to have a high infection burden despite trough IgG level in the normal range should have other treatments optimised (e.g. antibiotic prophylaxis, physical therapy) prior to immunoglobulin dose increase.
Recommendation 31
Immunoglobulin dose increases should be undertaken on a trial basis for 6-12 months, with a reduction to the previous dose if there is no measurable improvement in clinical infection burden.

Recommendation 32
Immunoglobulin dose decreases should be undertaken on a trial basis for 6-12 months, with a return to the previous dose if there is a significant increase in infection frequency.

For primary immunodeficiency there was strong consensus from the first round that patients’ trough IgG levels should be maintained at over 8 g/L. Comments highlighted that infection monitoring was important, and that many patients were well controlled with much lower IgG levels. Despite these reservations regarding an 8 g/L threshold, there was an even stronger consensus that trough levels of over 10 g/L were necessary in some PID and SIDs.

Two rounds of questions regarding a minimal target trough IgG level for SIDs patients did not achieve consensus. In the first round a range of options (6, 7 and 8 g/L) were offered in a single question. While there was a majority in favour of the lower limit, there was no consensus. Many respondents appeared to agree with more than one suggested trough level. Therefore, in the second round target trough levels of 6 g/L and 8 g/L were offered in separate questions. Again, slightly more respondents favoured the lower figure, but without reaching consensus criteria. It seems that lower levels of IgRT are considered adequate in SIDs patients than in PIDs patients, although several comments acknowledged that there is little or no evidence to support many of optimum trough level.

Evidence review: Five studies were identified with comparative data on the trough serum IgG level required to significantly reduce infections in patients with primary immunodeficiency. Two studies suggested 5 g/L as a minimum IgG level, above which a strong protection was provided against acute infection [33] (PID, n=12) or all evaluated infections [6] (PID, n=29; particularly bacterial meningitis and pneumonias, bronchitis, ear-nose-throat and GI infections). Two other small studies recommended 6 g/L as a minimum IgG level to provide best protection against overall infection rate [5] (PID, n=7; particular effects on lower respiratory tract and severe infection numbers) and to reduce the number of days spent in bed at home or medication use, or with a fever [9] (PID, n=8). A larger study [4] (PID, n=43) showed that at a trough IgG serum concentration of 8 g/L or above (study mean 9.4 g/L) there was a significant reduction in number of infections compared to 6 g/L (study mean 6.5 g/L).

Half of the respondents agreed that it was not useful to routinely monitor IgG levels in patients with SPAD on IgRT, although several commented that immunoglobulins should be monitored to look for possible progression to hypogammaglobulinaemia. The role of monitoring infections as a tool in assessing the adequacy of IgRT received strong support as a single question in round one, as well as being the subject of many free-text comments. In the second round we therefore included more statements to explore the role of infection monitoring in adjusting immunoglobulin dosing. There was a high level of agreement with the statements that Ig dose reduction could be considered in stable infection-free PID and SIDs patients. Some comments raised concerns that dose reductions would be driven by cost-saving, but others also reflected that immunoglobulin therapy is not risk-free and all drug treatments should be optimized according to response.

There was strong support for statements regarding the need to optimize antibiotic and physical therapies in patients who continue to suffer from infections despite IgRT. This reflects the reality that there are a large number of factors that predispose to infection, and immunoglobulin therapy is by no means a panacea. Physical therapies including patient exertion and exercise, physiotherapy techniques and sputum clearance with saline nebulizers can all help to dramatically reduce infections. Knowledge of the organisms causing infections is also vital to optimize antibiotic choices for treatment and prophylaxis.

Where dose adjustments are implemented, there was consensus that this should be for a trial period with return to previous dosing levels if the goals of treatment are not met. A 6-month period was suggested in the statement, although comments highlighted the need to individualize this and the role of seasonal factors in interpreting the response to the intervention and this was supported by patient groups.

Dose adjustments should always take into account vial size to avoid waste (see Recommendation 22 in Starting).

Administration, clinical and blood test monitoring
Recommendation 33
The following should be tested at a minimum of every six months:
- IgG levels (trough for IV, any time for SC)
- full blood count
- liver function test
- U&E test

Recommendation 34
Patients with primary immunodeficiency who are established on IgRT and are stable with no complications should be monitored at an immunology specialist clinic at least every six months.

Recommendation 35
In all patients on IgRT, the following should be monitored:
- infection frequency and site of infections (patients should be encouraged to keep their own personal infection diaries)
- hospital admissions
- microbiological cultures
- antibiotic use

Recommendation 36
Patients receiving IgRT should start antibiotic treatment promptly if they have symptoms suggestive of bacterial infections.

Recommendation 37
IgRT should not be administered to patients with symptoms or signs associated with severe active infection until they have received at least 48 hours of appropriate antimicrobial therapy and are clinically improving.
Recommendation 38
Patients previously receiving prophylactic antibiotics should have their antibiotic prescription reviewed when IgG levels are in their target range.

Recommendation 39
Patients on IgRT should have antibiotic prophylaxis reviewed at each visit considering previous culture results and infection burden.

Recommendation 40
There must be a system in place to record batch numbers for each immunoglobulin infusion that patients receive (hospital and home-based therapy). Batch number records should be kept at the prescribing centre.

Recommendation 41
Patients receiving immunoglobulin in a hospital setting should follow local hospital policy in the event of adverse reactions. This should be pre-approved by the prescribing immunology specialist centre.

Once established on IgRT, there was consensus that the minimum frequency of blood testing for patients on IgRT, should be 6-monthly for IgG trough levels, FBC, liver function, urea and electrolytes although comments suggested this should be individualised according to patient needs. In the first round most respondents agreed that a clinical review should take place at least annually, several comments suggested the ideal should be 6-monthly, especially in children when dose adjustments may be necessary. On the second round there was agreement that stable patients should be reviewed every 6 months with several suggestions that this could be annual review in the specialist immunology clinic with input by local teams/GP for those patients who live away from the centre. Shared care protocols between primary care, treating centres and patients could facilitate this as suggested by patient groups. Flexibility therefore about frequency of clinical assessments and according to individual needs is recommended.

There was no consensus on the need to routinely save serum samples from patients on IgRT each year reflecting the lack of evidence in this area as well as challenges associated with laboratory storage. Record of batch numbers was recommended as a more efficient way of monitoring. There was very strong agreement from respondents to the Delphi survey regarding the need to monitor infection burden including cultures, antibiotic use and hospital admissions as well as the prompt use of antibiotics to treat symptoms of infection. There was consensus that IgRT should not be administered in patients with active infection unless treated for 48hr with antibiotics, although it was suggested that the presence of fever may be a better indicative marker. There were comments whether 24hr rather than 48hr as minimal treatment with antibiotics was appropriate.

Switching product
Recommendation 42
If immunoglobulin products are switched, blood should be taken for serum save.

Recommendation 43
Patients established on IgRT should not have their immunoglobulin products switched except for clinical or supply reasons. This decision should be made by the prescribing immunology specialist centre.

Recommendation 44
If a patient is switched from one IV immunoglobulin product to another, it should be done in a hospital setting.

There was a strong consensus that patients should not switch product except when there is a clinical need or supply problems and that a serum sample should be saved if a product switch occurs. There was agreement with the statement that immunoglobulin product switch should be done in the hospital setting when switching between IV products. However, there was no agreement whether this should be done in hospital or at home for SC products with advantages for hospital and home therapy switch mentioned in the comments (easiness of logistics in favour of hospital attendance, no evidence of adverse effects to preclude home switch which is considered safe) or dependent on whether there was a brand switch or not.

Home therapy
Recommendation 45
All patients should have the option to have treatment provided at home. Where this is not already available, referral pathways with established home therapy centres should be agreed.

Recommendation 46
Patient training for self-administered home IgRT should be undertaken by a centre where staff have been trained in competency assessment.

Recommendation 47
Before being approved for self-administered home IV therapy, patients should be stable on IV therapy in hospital, with number of infusions decided according to safety assessment by the immunology clinical nurse specialist who supervises their training.

Recommendation 48
Before being approved for home SC therapy, patients should have received hospital training infusions, with number of infusions decided according to safety assessment by the immunology clinical nurse specialist who supervises their training.

Whilst there was strong agreement that patients should not start self-administered home IV or SC immunoglobulin therapy without having infusions in hospital first for either treatment modality, there was no consensus as to the number of infusions required to be delivered in hospital before patients are transferred to community-based treatment.

Recommendation 49
Training competency for IV or SC home therapy must be assessed by an immunology specialist nurse and include a written questionnaire and contract signed by both the patient/carer and clinician/nurse.
Recommendation 50
For all patients on home therapy, competency training should include clear instructions on:

- ‘Know-that’ (disease understanding), ‘know why’ (behavioural factors), ‘know-how’ (skills for proper use) knowledge training
- What to do if they get an infection
- How to manage and record adverse events
- Who to contact for advice

Recommendation 51
Optimal home therapy training should include a single assessment visit at the patient’s home.

Recommendation 52
Home therapy training and competency testing should be done by an immunology specialist nurse or other appropriately trained and competency-tested health care professional, working as part of a team based in a specialist immunology centre.

Recommendation 53
Home therapy training centres should have the capacity to offer all patients annual practical competency assessments. (Actual frequency based on clinical assessment or patient request.)

Recommendation 54
If problems with home therapy administration are identified, a patient must have a practical home therapy competency assessment.

Recommendation 55
For home therapy patients, as a minimum, a practical re-assessment of competency should be done after one year by an immunology specialist nurse working in an immunology specialist centre or other QPIDS*-registered practice.

While there was a clear consensus that patients should generally be given the option of treatment at home, it was highlighted in the comments that the home environment needs to be suitable and that the patient should be engaged with the process. There was overall agreement that either an Immunology or other specialty nurse (as long as adequately trained) can deliver home therapy training with positive comments on working within a network with relevant specialities. There was consensus that the staff undertaking the training and competency assessment should be adequately trained and competency assessed.

There was a consensus that a patient’s competency to self-administer immunoglobulin at home should involve a written questionnaire. Standardized validated questionnaires for common use across the country were recommended by patient groups. It was suggested that the assessment could be undertaken by an appropriately trained member of the medical team as well as by an immunology specialist nurse. Respondents to the Delphi survey highlighted that a written questionnaire may make patients anxious and this should be taken into account when training and assessing patients. Questionnaires should be adopted to patients’ needs (i.e. dyslexia) as highlighted by patient groups. It was also emphasized that the “contract” should be designed to provide clarity regarding the need for patients to comply with the agreed conditions concerning self-administration of immunoglobulin at home (for example engaging with monitoring and follow up requirements).

The consensus was that optimal home therapy training should involve a visit to the patient’s home. However, comments suggested that this wasn’t always possible due to resource limitations. A number of responses described that alternative methods could be used to understand the patient’s home arrangements including thorough assessment of social circumstances in clinic, video calls and liaison with primary care providers (i.e. district nurses).

Although there was agreement that regular competency assessments should be available, the majority of comments recommended individual patient assessment rather than prescriptive time frames for competency assessments. It was also stressed that requiring regular competency assessments for all patients increased the burden of treatment for patients as well as being resource intensive for services. It was commented that if problems with infusions occur then in some cases the immunology team may be able to provide solutions without seeing the patient, but there was consensus that a review of home therapy technique should be available if needed.

Evidence review: Nine studies were identified that looked at quality of life or patient preference for home therapy versus hospital treatment [14, 17, 21, 34–39]. Six of these studies [17, 21, 34–36, 38] showed that home therapy improved patients’ quality of life (5 studies in PID patients, total n = 287; 1 study in SID patients, n = 61). Additionally, in five of these studies [14, 17, 35, 37, 39] patients expressed a preference for receiving home subcutaneous replacement therapy over therapy administered in hospital or in clinic. One study [37] (PID, n =91) suggested that for patients, loss of supervision was a concern when switching to home therapy, supporting the need for home visits, training and competency assessments.

Two studies in children and young people [40, 41] (PID patients, total n =56) similarly showed that switching to home subcutaneous therapy from hospital IV treatment can improve several aspects of the patient’s quality of life.

Stopping immunoglobulin replacement therapy

Recommendation 56
The need for ongoing IgRT should be reviewed with all patients on an annual basis, with the exception of the conditions listed in the first statement of this survey (CVID, XLA/ARA, SCID, hyper-IgM, Good’s syndrome).

Recommendation 57
Patients with a historic diagnosis of primary immunodeficiency in whom there is not sufficient historical evidence to fulfil diagnostic criteria for an identified PID and who are clinically stable should be considered for a trial of withdrawal of IgRT to confirm ongoing need for therapy and to reassess initial diagnosis if there is no evidence of increased frequency and severity of infection compared to general population (taking into account other comorbidities).
Recommendation 58
Patients with primary antibody deficiency (as in first statement; CVID, XLA/ARA, SCID, hyper-IgM, Good’s syndrome) with a definite diagnosis should not normally have their IgRT stopped.

Recommendation 59
Patients with secondary hypogammaglobulinaemia should have a trial of withdrawal of IgRT if the cause of the immunodeficiency has been reversed (e.g. withdrawal of immunosuppression or evidence of immune reconstitution) and immunological recovery demonstrated on assessment.

Recommendation 60
A trial of withdrawal of IgRT should be considered in patients with secondary hypogammaglobulinaemia if there is evidence that the humoral immune system has recovered (e.g. otherwise unexplained increase in IgA/IgM/trough IgG levels, improved B cells or S. Typhi vaccination response).

Recommendation 61
A trial of withdrawal of IgRT should be undertaken in all patients currently receiving IgRT who have not previously fulfilled criteria for treatment.

Recommendation 62
Patients undergoing a trial of IgRT withdrawal should:
- Be monitored closely
- Have a self-management plan
- Have an emergency strategy for the treatment of infections
- Have access to advice from the specialist immunology medical and nursing teams
- If appropriate, be offered rescue antibiotics at home

Recommendation 63
Patients undergoing a trial of IgRT withdrawal should be offered a follow-up appointment at the immunology clinic and/or other relevant specialty centre (if secondary hypogammaglobulinaemia).

Recommendation 64
Patients undergoing a trial of IgRT withdrawal should have IgG monitored at least every 12 weeks (until stable).

Recommendation 65
A record of infectious symptoms should be maintained and reviewed at least every 12 weeks for patients having a trial of IgRT withdrawal (including number and type of infections, microbiology results, hospital admissions and antibiotic usage).

Recommendation 66
Prophylactic antibiotics should be considered in all patients with bronchiectasis having a trial of IgRT withdrawal and their respiratory care should be optimised under the supervision of a respiratory physician.

Recommendation 67
Prophylactic antibiotics should be considered in all patients having a trial of IgRT withdrawal when IgG levels fall below the normal range.

Recommendation 68
IgRT should be re-started if the criteria in section 1 (‘Starting immunoglobulin replacement therapy’) are fulfilled after a trial of withdrawal of immunoglobulin therapy.

Recommendation 69
If a patient fails two trials of IgRT withdrawal (e.g. a two-yearly interval), no further trials off treatment should be undertaken unless there is clear evidence of immune reconstitution.
Recommendation 70
For patients nearing end of life, the decision to discontinue IgRT should be proactively discussed with the patient/carers, including a discussion of benefits versus burden of treatment.

Recommendation 71
Patients with SPAD commenced on IgRT should have a trial of withdrawal of immunoglobulin if there is no evidence of increased frequency and severity of infection compared to the general population (taking into account other comorbidities).

Recommendation 72
Patients with SPAD commenced on IgRT should have a trial of withdrawal of immunoglobulin if there is no measurable improvement in infection frequency on therapy.

The proposal to trial all patients with SPAD off IgRT after one year did not reach consensus and there were a large number of comments. Predominantly, respondents suggested an individualised approach taking into consideration prior history and current clinical assessment rather than recommending automatic discontinuation of therapy in all cases.

Recommendation 73
When patients fail to engage with monitoring and reviews, the centre should make all reasonable efforts to engage with patients and arrange alternative treatment strategies where possible. Where nonengagement involves children and young people, local safeguarding policies should be followed.

Recommendation 74
When, despite centres making all reasonable efforts to engage with patients, a prescribing centre is unable to monitor the safety and efficacy of IgRT, (e.g. due to poor attendance at monitoring appointments and/or lack of agreed haemovigilance documentation), immunoglobulin should no longer be prescribed.

This statement received a strong consensus, but comments highlighted that this should only apply to adults. Comments suggested that alternative strategies for replacing IgRT such as converting home therapy patients to hospital-based therapy should be explored.

Areas for research
The IgG level at which IgRT should be initiated in patients with hypogammaglobulinaemia outside the listed established diagnoses of PID remains a matter of controversy, especially for secondary antibody deficiencies; the levels chosen in this guideline in order to establish consensus are arbitrary. It would certainly be desirable if further research/evidence could be produced towards this goal. However, in the setting of a heterogeneous group of rare conditions, further evidence may be difficult to produce, especially for PID, and the MDT approach may remain the best tool for patient assessments. In certain conditions causing secondary antibody deficiency this may be more achievable (i.e. haematological malignancies).

Although there is some evidence of the optimal trough IgG level for IgRT in PID, there was no consensus for this in the setting of secondary antibody deficiency and this is an area where further studies are warranted in order to optimise patient care with relatively limited resources. Improved and consistent data collection on quality of life including infection rates with standardised questionnaires can also address further the issues of adequate dosing for both PID and SID.

Whilst the surveys for this guideline were conducted before the time of the COVID-19 pandemic, the challenges that all clinicians and patients faced and the ways services had to adapt during the pandemic highlight the potential for improvements in some aspects of care delivery. One such example is face to face versus remote telephone and/or video-based consultations when clinically appropriate to improve patient compliance and engagement with services, especially for those patients who live further away from the treating centre. Further studies investigating how to best deliver remote home therapy training and nursing support will align with this. Development and validation of patient questionnaires that can be used by all centres would certainly help this process. In addition, ways of standardising and streamlining competency training to provide optimal nursing support should also be explored.

A deeper understanding of patients experiences and the factors that impact on their quality of live (especially in the evolving group of SID patients) will provide further insight into ways of improving care delivery. Long term outcome data to better understand the impact of treatment and different management options, including stopping IgRT, on both patient quality of life and cost for the NHS will certainly be informative.

Future studies with patient input could provide more insight into improved ways of delivering care.

Conclusions
This is the first consensus guideline for the initiation, monitoring and discontinuation of IgRT for primary and secondary immunodeficiency disorders in the UK. Given the lack of evidence in most areas a Delphi approach was used. There was more consensus for the management of IgRT for patients with primary immunodeficiency compared to those with secondary immunodeficiency. As the cases of iatrogenic secondary immunodeficiencies are increasing and better recognised [42–44], further research into optimal management of IgRT in this heterogeneous group of patients is warranted.

We hope this guideline will help harmonise practises across the country and provide initiatives for service improvements.

Supplementary data
Supplementary data is available at Clinical and Experimental Immunology online.

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**Conflict of Interest**

The authors have no financial conflicts of interest.

**Author Contributions**

All authors contributed to the generation of the statements for the Delphi process and subsequent analysis. R.C. conducted the literature search which was reviewed by all authors. All authors contributed to the manuscript which was reviewed by S.G., R.C., and C.B.

**Data Availability**

The data underlying this article are available in the article and in its online supplementary material.

**References**

1. NHS England, Updated Commissioning Criteria for the use of therapeutic immunoglobulin (Ig) in immunology, haematology, neurology and infectious diseases in England, November 2019. [http://igd.mdsas.com/wp-content/uploads/NHSE_Commissioning_Criteria_for_the_use_of_Ig_V1.4_November_2019.pdf](http://igd.mdsas.com/wp-content/uploads/NHSE_Commissioning_Criteria_for_the_use_of_Ig_V1.4_November_2019.pdf) (May 2022, date last accessed)

2. Hsu, CC, Sandford, BA. The Delphi technique: making sense of consensus. *Pract Assess Res Eval* 2007; 12; Article 10. doi:10.7275/p9-th90.

3. Chandresri MO, Melki I, Natividad A, et al. Autosomal dominant STAT3 deficiency and hyper-IgE syndrome: molecular, cellular, and clinical features from a French national survey. *Medicine (Baltim)* 2012, 91, e1–e19. doi:10.1097/MD.0b013e31825f95b9.

4. Eijkhout HW, van Der Meer JW, Kallenberg CG, et al. The effect of two different dosages of intravenous immunoglobulin on the incidence of recurrent infections in patients with primary hypogammaglobulinemia. A randomized, double-blind, multicenter crossover trial. *Ann Intern Med* 2001, 135, 165–74. doi:10.7326/0003-4819-135-3-20010807-00008.

5. Favre O, Leimgruber A, Nicole A, et al. Intravenous immunoglobulin replacement prevents severe and lower respiratory tract infections, but not upper respiratory tract and non-respiratory infections in common variable immune deficiency. *Allergy* 2005, 60, 385–90. doi:10.1111/j.1398-9995.2005.00756.x.

6. Liese JG, Wintergerst U, Tympner KD, et al. High- vs low-dose immunoglobulin therapy in the long-term treatment of X-linked agammaglobulinemia. *Am J Dis Child* 1992, 146, 335–9. doi:10.1001/archpedi.1992.02160150075025.

7. Pruzański W, Sussman G, Dorian W, et al. Relationship of the dose of intravenous gammaglobulin to the prevention of infections in adults with common variable immunodeficiency. *Inflammation* 1996, 20, 353–9.

8. White WB, Desbonnet CR, Ballow M. Immunoregulatory effects of intravenous immune serum globulin therapy in common variable hypogammaglobulinemia. *Am J Med* 1987, 83, 431–6.

9. Remvig L, Andersen V, Hansen NE, et al. Prophylactic effect of self-administered pump-driven subcutaneous IgG infusion in patients with antibody deficiency: a triple-blind cross-over study comparing P-IgG levels of 3 g l-1 versus 6 g l-1. *J Intern Med* 1991, 229, 73–7.

10. Abdel-Mageed A, Graham-Pole J, Del Rosario ML, et al. Comparison of two doses of intravenous immunoglobulin after allogeneic bone marrow transplants. *Bone Marrow Transplant* 1999, 23, 929–32.

11. Chapel H, Dicato M, Gamm H, et al. Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: a comparison of two dose regimes. *Br J Haematol* 1994, 88, 209–12.

12. Gamm H, Huber C, Chapel H, et al. Intravenous immune globulin in chronic lymphocytic leukaemia. *Clin Exp Immunol* 1994, 97, 17–20.

13. Sklenar I, Schiffman G, Jonsson V, et al. Effect of various doses of intravenous polyclonal IgG on in vivo levels of 12 pneumococcal antibodies in patients with chronic lymphocytic leukaemia and multiple myeloma. *Oncology* 1993, 50, 466–77.

14. Anderson CR, Olson JA. Correlation of weight-based i.v. immune globulin doses with changes in serum immunoglobulin G levels. *Am J Health Syst Pharm* 2015, 72, 285–9.

15. Gardulf A, Nicolay U, Asensio O, et al. Rapid subcutableous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies—a prospective, multi-national study. *J Clin Immunol* 2006, 26, 177–85.

16. Gürcetinkaya P, Çağdaş-Ayvaz DN, Öksüz AB, et al. Advantage of the subcutaneous immunoglobulin replacement therapy in primary immunodeficient patients with or without secondary protein loss. *Turk J Pediatr* 2018, 60, 270–6.

17. Hoffmann F, Grimbacher B, Thiél J, et al. Home-based subcutaneous immunoglobulin G replacement therapy under real-life conditions in children and adults with antibody deficiency. *Eur J Med Res* 2010, 15, 238–45.

18. Ochs HD, Gupta S, Kessling P, et al. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. *J Clin Immunol* 2006, 26, 263–73.

19. Waniek JS, Gardulf A, Hammarstrom L. Bioavailability of gamma-globulin after subcutaneous infusions in patients with common variable immunodeficiency. *J Clin Immunol* 1994, 14, 90–7.

20. Wasserman RL, Irani A-M, Tracy J, et al. Pharmacokinetics and safety of subcutaneous immune globulin (human), 10% caprylate/chromatography purified in patients with primary immunodeficiency disease. *Clin Exp Immunol* 2010, 161, 518–26.

21. Compagno N, Cinetto F, Semenzato G, et al. Subcutaneous immunoglobulin in lymphoproliferative disorders and rituximab-related secondary hypogammaglobulinemia: a single-center experience in 61 patients. *Haematologica* 2014, 99, 1101–6.

22. Spadaro G, Pecoraro A, De Renzo A, et al. Intravenous versus subcutaneous immunoglobulin replacement in secondary hypogammaglobulinemia. *Clin Immunol* 2016, 166–167, 103–4.

23. Bezrodnič L, Raccio AG, Belardinelli G, et al. Comparative study of subcutaneous versus intravenous IgG replacement therapy in pediatric patients with primary immunodeficiency diseases: a multicenter study in Argentina. *J Clin Immunol* 2013, 33, 1216–22.

24. Pac M, Bernatowska E. Polish experience with immunoglobulin replacement treatment by subcutaneous infusion. *Cent Eur J Immunol* 2005, 30, 78–82.

25. Shapiro RS. Subcutaneous immunoglobulin: rapid push vs. infusion pump in pediatrics. *Pediatr Allergy Immunol* 2013, 24, 49–53.

26. Knutsen AP, Leiva LE, Caruthers C, et al. Streptococcus pneumoniae antibody titres in patients with primary antibody deficiency.
receiving intravenous immunoglobulin (IVIG) compared to subcutaneous immunoglobulin (SCIG). *Clin Exp Immunol* 2015, 182, 51–6.

27. Abghari PF, Poowuttikul P, Secord E. Pneumococcal antibody titers: a comparison of patients receiving intravenous immunoglobulin versus subcutaneous immunoglobulin. *Glob Pediatr Health* 2017, 4, 2333794X–16689639.

28. Chapel HM, Spickett GP, Ericson D, et al. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. *J Clin Immunol* 2000, 20, 94–100.

29. Desai SH, Chouksey A, Poll J, et al. A pilot study of equal doses of 10% IGIV given intravenously or subcutaneously. *J Allergy Clin Immunol* 2009, 124, 854–6.

30. Fasth A, Nystrom J. Safety and efficacy of subcutaneous human immunoglobulin in children with primary immunodeficiency. *Acta Paediatr* 2007, 96, 1474–8.

31. Pulvirenti F, Cinetto F, Pecoraro A, et al. Health-Related quality of life in patients with CVID under different schedules of immunoglobulin administration: prospective multicenter study. *J Clin Immunol* 2019, 39, 159–70.

32. Quinti I, Sioresina A, Agostini C, et al. Prospective study on CVID patients with adverse reactions to intravenous or subcutaneous IgG administration. *J Clin Immunol* 2008, 28, 263–7.

33. Roifman CM, Levison H, Gelfand EW. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinemia and chronic lung disease. *Lancet* 1987, 1, 1075–7.

34. Bienvenu B, Cozon G, Hoarau C, et al. Does the route of immunoglobulin replacement therapy impact quality of life and satisfaction in patients with primary immunodeficiency? Insights from the French cohort “Visages”. *Orphanet J Rare Dis* 2016, 11, 93.

35. Gardulf A, Nicolay U, Math D, et al. Children and adults with primary antibody deficiencies gain quality of life by subcutaneous IgG self-infusions at home. *J Allergy Clin Immunol* 2004, 114, 936–42.

36. Nicolay U, Kiessling P, Berger M, et al. Health-related quality of life and treatment satisfaction in North American patients with primary immunodeficiency diseases receiving subcutaneous IgG self-infusions at home. *J Clin Immunol* 2006, 26, 63–72.

37. Reid B, Pires L. Home gammaglobulin therapy: a patient survey of intravenous and subcutaneous options in Canada. *LymphoSign Journal*. 2014, 1, 27–37.

38. Vultaggio A, Azzari C, Milito C, et al. Subcutaneous immunoglobulin replacement therapy in patients with primary immunodeficiency in routine clinical practice: the VISPO prospective multicenter study. *Clin Drug Invest* 2015, 35, 179–85.

39. Zuizewind CA, van Kessel P, Kramer CM, et al. Home-Based Treatment with immunoglobulins: an evaluation from the perspective of patients and healthcare professionals. *J Clin Immunol* 2018, 38, 876–85.

40. Fasth A, Nystrom J. Quality of life and health-care resource utilization among children with primary immunodeficiency receiving home treatment with subcutaneous human immunoglobulin. *J Clin Immunol* 2008, 28, 370–8.

41. Pasquet M, Pellier I, Aladjidi N, et al. A cohort of French pediatric patients with primary immunodeficiencies: are patient preferences regarding replacement immunotherapy fulfilled in real-life conditions? *Patient Prefer Adherence* 2017, 11, 1171–80.

42. Casulo C, Maragulia J, Zelentz AD, et al. Incidence of hypogammaglobulinemia in patients receiving rituximab and the use of intravenous immunoglobulin for recurrent infections. *Clin Lymphoma Myeloma Leuk* 2013, 13, 106–11.

43. Roberts DM, Jones RB, Smith RM, et al. Rituximab-associated hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease. *J Autoimmun* 2015, 57, 60–5.

44. Patel SY, Carbone J, Jolles S, et al. The expanding field of secondary antibody deficiency: causes, diagnosis, and management. *Front Immunol* 2019, 10, 33.