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HIGHLIGHTS

Guideline

Treatment and management of primary antibody deficiency: German interdisciplinary evidence-based consensus guideline

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This evidence-based clinical guideline provides consensus-recommendations for the treatment and care of patients with primary antibody deficiencies (PADs). The guideline group comprised 20 clinical and scientific expert associations of the German, Swiss, and Austrian healthcare system and representatives of patients. Recommendations were based on results of a systematic literature search, data extraction, and evaluation of methodology and study quality in combination with the clinical expertise of the respective representatives. Consensus-based recommendations were determined via nominal group technique. PADs are the largest clinically relevant group of primary immunodeficiencies. Most patients with PADs present with increased susceptibility to infections, however immune dysregulation, autoimmunity, and cancer affect a significant number of patients and may precede infections. This guideline therefore covers interdisciplinary clinical and therapeutic aspects of infectious (e.g., antibiotic prophylaxis, management of bronchiectasis) and non-infectious manifestations (e.g., management of granulomatous disease, immune cytopenia). PADs are grouped into disease entities with definitive, probable, possible, or unlikely benefit of IgG-replacement therapy. Summary and consensus-recommendations are provided for treatment indication, dosing, routes of administration, and adverse events of IgG-replacement therapy. Special aspects of concomitant impaired T-cell function are highlighted as well as clinical data on selected monogenetic inborn errors of immunity formerly classified into PADs (APDS, CTLA-4-, and LRBA-deficiency).

Keywords: autoimmunity · CVID · hypogammaglobulinemia · immunoglobulins · primary antibody deficiency

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Introduction

The International Union of Immunological Societies (IUIS) lists ten groups and 416 monogenetic primary immunodeficiencies (PID)/inborn errors of immunity (IEI) [1] (Table 1). Predominantly antibody deficiencies confer the largest group (group 3) [2]. In addition, antibody deficiency is of clinical relevance in many other PIDs. The present guideline focuses on diseases of IUIS group 3, however there are overlaps with other PIDs, in particular with combined immunodeficiency and monogenetic disorders previously categorized as CVID (e.g., activated PI3KCD syndrome (APDS), CTLA-4-deficiency, and LRBA-deficiency). This guideline does not cover secondary antibody deficiencies. Patients with antibody deficiencies present with an increased susceptibility to infections, affecting predominantly the respiratory and gastrointestinal tract [3]. However, infections may neither be the first nor the leading clinical symptom [4, 5]. Immune dysregulation, autoimmunity, and cancer affect a significant proportion of patients, including for instance immune cytopenia, lymphoproliferation, or granulomatous diseases [6]. Therefore, this guideline covers aspects of IgG-replacement as well as monitoring and treatment of "non-infectious" manifestations.

Table 1. Human Inborn Errors of Immunity: 2019 Update of the IUIS Phenotypical Classification (adapted from (1))

I.	Immunodeficiencies affecting cellular and humoral immunity
II.	Combined immunodeficiences (CID) with associated or syndromic features
III.	Predominantly Antibody deficiencies
IV.	Diseases of immune dysregulation
V.	Congenital defec of phagocyte
VI.	Defects in intrinsic and innate immunity
VII.	Auto-inflammatory disorders
VIII.	Complement deficiencies
IX.	Bone marrow failure
X.	Phenocopies of PID

Methods

Literature search was conducted (date of search: 31.5.2018) in PUBMED (http://www.ncbi.nlm.nih.gov/pubmed/) using MeSH terms and keywords for the following terms:

1. Use of immunoglobulin replacement therapy in primary antibody deficiency
2. Immune cytopenia
3. Granulomatous disease including interstitial lung disease
4. APDS I / II, CTLA4 deficiency, LRBA deficiency
5. Bronchiectasis

More details of the search strategy are shown in the Supporting Information (M1). Number of records and included citations are presented in Supporting Information Table M2.

This interdisciplinary guideline was developed by mandated members of 20 medical societies from Austria, Germany, and Switzerland including a representative of the German patient organisation for patients with primary immunodeficiencies. Recommendations were developed at S3-level of methodology according to regulations issued by the Association of Scientific Medical Societies in Germany (AWMF). Evidence is rated according to Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (see Supporting Information Table S1). Methodology was evaluated according to SIGN (Scottish Intercollegiate Guidelines Network). Recommendations were graded following a formal consensus procedure (see Supporting Information Table S2). This included nominal group processes and structured consensus conferences moderated by AWMF-representatives during which recommendations were formally voted on by the mandated members. Strength of consensus for each recommendation was graded as shown in Supporting Information Table S3. Recommendations without sufficient level of evidence were classified as "expert consensus."

Additional studies and publications were identified when analyzing retrieved literature. Those studies did not impact on the recommendations of participants of the consensus conference. In an update, selected literature published after May 31, 2018 and not affecting recommendations of the consensus conference was included to the current manuscript. The present publication is a summary of the full-length version published in German (https://www.awmf.org/uploads/tx_szleitlinien/189-001l_S3_Therapie-primaerer-Antikoerpermangelerkrankungen-2019-05_01.pdf) and is the revised and extended second edition of the German evidence based and consensus guideline published in 2012 [7].

IgG-replacement therapy in primary antibody deficiencies

Published evidence allows to group antibody deficiencies into diseases with "definitive benefit," "probable benefit," or "possible benefit" of IgG-replacement and into ones in which IgG-replacement is not beneficial. The definition along clinical effectiveness may not completely overlap with immunological definitions or the molecular genetic basis of antibody deficiencies (e.g., "hypogammaglobulinemia" or "NFkB1-deficiency" may be a condition with proven or only with probable benefit, depending on absence or presence of specific antibody responses to vaccinations). The indication for IgG-replacement in hypogammaglobulinemia should be based—at least—on increased susceptibility to infections and the assessment of specific vaccine responses. Before the start of IgG-replacement in hypogammaglobulinemia, specific antibody responses upon vaccination should be evaluated. Individual vaccine responses should be assessed together with experienced clinical immunologists. This should be performed before Ig replacement therapy as vaccine responses cannot be assessed with certainty after IgG-replacement. Alternatively, in non-vaccinated individuals antibody titers against pathogens documented in the patient (e.g., Haemophilus influencae) is also useful. In patients with agammaglobulinemia and/or severely ill patients the evaluation of vaccine responses is dispensable and must not delay initiation of IgG-replacement.

Consensus-based recommendation 1:

"Before initiating IgG-replacement therapy we recommend assessment of specific antibody-responses to vaccination. In clinical emergencies we do not recommend to delay start of therapy for diagnostic vaccination. In agammaglobulinemia assessment of vaccine responses is dispensable."

Expert consensus: strong consensus

Antibody deficiencies with proven effectiveness/definitive benefit of IgG-replacement

Agammaglobulinemia

In agammaglobulinemia (IgG < 2 g/L) and absent B cells (<2% B cells in peripheral blood) effectiveness of IgG-replacement is proven [8–13].

Consensus-based recommendation 2:

"We recommend IgG-replacement therapy in agammaglobulinemia."

Level of evidence: 2; Level of recommendation: A

Hypogammaglobulinemia with impaired response to vaccinations

Hyper-IgM-Syndromes (Immunoglobulin class switch recombination deficiencies): Due to deficient class switch recombination, patients present with low levels of IgG and IgA, normal or elevated levels of IgM, normal numbers of B-cells and are characterized by severely impaired specific antibody responses upon vaccination. Effectiveness of IgG-replacement is proven [12,14–17]. Due to the accompanying T-cell-deficiency, in particular in CD40L-deficiency and in CD40-deficiency, there is still an increased risk for opportunistic infections [15,16]. Besides the initiation of IgG-replacement patients with HIGM should be evaluated for possible stem cell transplantation [18].

Common variable immunodeficiency disorders (CVID): The umbrella term, "CVID", comprises most of the clinically relevant antibody deficiencies. The current diagnostic criteria of the European Society for immunodeficiency (ESID) are listed in Supporting Information Table S4. There is proven effectiveness of IgG-replacement in CVID [11–14,19–23]. Patients may suffer from increased susceptibility to infections and from immune dysregulation (see section 5). Even in the absence of infectious susceptibility there is strong expert consensus that IgG-replacement should be considered in CVID patients on immunosuppressive therapy and/ or with immune cytopenia.

Consensus-based recommendation 3a:

"***We recommend IgG-replacement therapy in hypogammaglobulinemia with absent or strongly impaired, specific IgG-production and increased susceptibility to infections.***"

Level of evidence: 2; Level of recommendation: A

Consensus-based recommendation 3b:

"In patients with hypogammaglobulinemia and absent or strongly impaired specific IgG-production, IgG-replacement may be considered even in the absence of increased susceptibility to infections, when clinically relevant immune dysregulation is present (immune cytopenia or other non-infectious manifestations requiring immunosuppressive treatment).

Expert consensus: strong consensus

Antibody deficiencies with probable effectiveness/probable benefit of IgG-replacement

Hypogammaglobulinemia with normal response upon vaccination, yet increased susceptibility to infections

Unclassified antibody deficiency (uAD) or idiopathic hypogammaglobulinemia. This entity comprises conditions that do not fulfill defined criteria of agammaglobulinemia, CVID, or otherwise defined antibody deficiencies (e.g., selective IgA-deficiency; see Supporting Information Table S5 for ESID definition). Among this group, some patients may be classified as hypogammaglobulinemia with impaired antibody responses to vaccination (see above). There are no prospective studies on the effectiveness of IgG-replacement in these patients. The decision on IgG-replacement should be based on the level of IgG-deficiency and the severity of infections [24,25].

"Specific antibody deficiency" (SAD) is defined by impaired formation of specific antibodies (mostly against polysaccharides) despite normal total Ig levels and normal B cell counts [26,27]. In clinical practice, the response to non-conjugated pneumococcal vaccine is widely available as a surrogate to assess for SAD. Interpretation of antibody responses to polysaccharides and the indication for IgG-replacement should be discussed with an experienced center for primary immunodeficiencies [28,29]. The prophylactic use of antibiotics is recommended as first-line treatment in SAD [30]. IgG-replacement in SAD is recommended in patients:

- with very frequent and/ or very severe infections;
- with severely impaired response to vaccination with non-conjugated polysaccharide, pneumococcal vaccine ($\leq$2 pneumococcal serogroups with concentration >1.3 μg/mL)
- with severe side-effects due to antibiotic prophylaxis; or
- without clinical improvement on antibiotic prophylaxis.

SAD may be indicative for more severe primary immunodeficiencies and must initiate advanced immunological diagnostics.

Selection of monogenetic primary immunodeficiencies with impaired formation of antibodies

In addition to the conditions discussed above, there are other primary immunodeficiencies with probable effectiveness of IgG-replacement [31–37].

Consensus-based recommendation 4

"***We suggest IgG-replacement therapy in patients with increased susceptibility to infections with hypogammaglobulinemia and normal vaccine responses*.***"

Expert consensus: strong consensus *(*see section 3 for vaccine response)*

Antibody deficiencies with possible benefit of IgG-replacement

Isolated IgG1-3 subclass deficiency, combined IgA/IgG subclass deficiency

Data on IgG-replacement in IgG-subclass deficiencies, defined as isolated IgG-subclass deficiencies in patients with normal levels of global IgG and B cells, are insufficient for evidence-based recommendations [38–42].

Consensus-based recommendation 5:

"***In persistently increased susceptibility to infections despite antibiotic prophylaxis, IgG-replacement therapy may be considered in isolated or combined IgG1-3 subclass-deficiency."***

Level of evidence: 4; Level of recommendation: A

Transient hypogammaglobuliemia of infancy

Transient hypogammaglobuliemia of infancy (THI) is defined as prolonged IgG-levels below normal values, which resolve with age. Specific antibody responses upon vaccinations are normal. Data on IgG-replacement in THI are insufficient for evidence-based recommendations [43,44].

Antibody deficiencies unlikely to benefit from of IgG-replacement

Selective IgA-deficiency

There is no indication for IgG-replacement in selective IgA-deficiency.

Selective IgM-deficiency

There are only retrospective studies with few patients using inconsistent definitions of IgM-deficiency. Some patients may present with increased susceptibility to infections [45–47]. Data on IgG-replacement are insufficient for evidence-based recommendations. "Selective IgM-deficiency" must initiate advanced immunological diagnostics as it may be indicative for severe primary immunodeficiencies.

IgG4-subclass-deficiency

Data on IgG-replacement in "IgG4-subclass-deficiency" are insufficient for evidence-based recommendations. Available data argue strongly against IgG-replacement.

Consensus-based recommendation 6:

"***We do not recommend IgG-replacement therapy in selective IgA-deficiency, IgM-deficiency and IgG4-subclass-deficiency if vaccine responses are normal."***

Expert consensus: consensus

Antibody deficiencies in combined T/B cell deficiencies without defined genetic cause

In patients with hypogammaglobulinemia in combined T/B cell deficiencies with at least two of the following three criteria:

(a) Reduction of CD4+T-cells: <300/μl in 2–6 years, <250/μl in 6–12 years, <200/μl in >12 years;
(b) Reduced percentage of naïve CD4+T-cells: <25% in 2–6 years, <20% in 6–16 years, <10% in >16 years;
(c) Reduced T-cell response upon T-cell-receptor stimulation or stimulation with mitogens

an increased risk for (opportunistic) infections is likely [48]. Additional antibiotic prophylaxis with TMP/SMX is recommended [49] (see section 7). Genetic diagnostics are recommended. In severe impairment of T-cell immunity, assessment in a center with experience in allogenic stem cell transplantation is strongly recommended.

Consensus-based recommendation 7:

"***In patients with additional impairment of T-cells, IgG-replacement therapy alone may not be sufficient. We recommend referral of patients to a center for primary immunodeficiency, including expertise in stem cell transplantation if needed."***

Expert consensus: strong consensus

Practical management of IgG-replacement

Route of administration

Different routes of administration are feasible for IgG-replacement.

IVIg: Intravenous IgG-replacement (IVIg) must be given under medical supervision in a hospital, an outpatient clinic or a private praxis familiar with the application of IVIG (legal obligation in Germany). Other countries also offer the possibility of IVIg treatment at home.

SCIg: In subcutaneous IgG-replacement (SCIg) IgG is administered via catheter and pump (alternatively manually as "rapid push") into subcutaneous tissue (usually of abdomen, thighs, or arms).

fSCIg: "Facilitated IgG-replacement" (fSCIg) combines the subcutaneous application of immunoglobulines with previously applied hyaluronidase [50–52] .

Subcutaneous IgG-replacement, SCIg and fSCIg, are licensed for home therapy. In patients on SCIg "Health-related quality of life" improved stronger than in patients on IVIg [53–59]. Prior to home-therapy informed consent for the application of IgG must be given to the prescriber. The intramuscular application of IgG (IMIg) is not recommended any more.

Consensus-based recommendation 8:

"***Polyvalent immunglobuline products of different manufactures are equally effective."***

Expert consensus: consensus

Consensus-based recommendation 9:

"***We do not recommend intramuscular IgG-replacement therapy."***

Level of evidence: 2; Level of recommendation: A

Consensus-based recommendation 10:

"***Subcutaneous and intravenous IgG-replacement are equally effective."***

Level of evidence: 2; Level of recommendation: A

Dosing and management of therapy

General remarks: Success of IgG-replacement can be judged by trough levels that measures the concentration of IgG and the trough level needed for sustained clinical improvement ("biological trough level") [60,61]. "Trough level" is defined as the serum concentration of IgG before next IgG-replacement. There are minimal trough levels regarded as necessary for sufficient prophylaxis against infections. Due to the relatively stable levels of serum IgG in SCIg, which is applied more frequently than IVIG, the term steady state level is preferred.

IVIg: The effectiveness of IVIg for the reduction of infections has been proven [11,13,62]. However, there is a broad individual range in trough levels required [23]. There is sufficient evidence that the severity of infections is reciprocally proportional to the IgG trough level and that a trough level > 4.5 g/L reduces the rate of bacterial infections [63]. A meta-analysis on the incidence of pneumonia in correlation with trough levels on IVIg showed a fivefold higher incidence at a trough level of 5 g/L (0.113 pneumonia/patient/year) compared to a trough level of 10 g/L (0.023 pneumonia/patient/year) [64]. Individual dosing and trough levels may also depend substantially on comorbidity (e.g., presence of bronchiectasis) and underlying cause for IgG-replacement. The general recommendation of IgG-trough level >4.5 g/L does therefore not exclude that some individuals may require IgG-trough levels > 10 g/L

("Expert opinion"). Most clinicians start IgG-replacement with 400–600 mg/kg body weight [65]. The usual interval for IVIg is 21–28 days. However, interval and dose must be adjusted individually [66]. We recommend starting IVIg with a 10% solution at a flow rate of 0.5–1 mL/kg body weight/h, as most adverse events are related to flow rate. Flow rates may be increased stepwise according to manufactures instructions.

SCIg and fSCIG: In SCIg treatment, Igs enter the blood via lymphatic vessels resulting in different pharmacokinetics. Since injectable volumes per treatment session are lower on SCIg, this treatment must be applied more frequently than in IVIg. Depending on clinical status and body weight, SCIg is applied 1–2×/week, or even every second week. For adults, usual volumes per injection-site are 10–25 mL, lower for children (depending on weight). To reach targeted IgG-levels quickly, SCIG is initially conducted two to three (even 5) times per week. Alternatively, an IVIg-loading-dose can be used. Pharmacokinetics of facilitated SCIg (fSCIg) are similar to IVIg treatment. It is usually applied every 2–4 weeks. In fSCIg-therapy up to 600 mL (60 g Igs) can be administered per injection site.

Dosing of IgG in obese patients: In patients with greatly decreased or elevated Body Mass Index (BMI), frequent monitoring of IgG-levels is recommended at the beginning of treatment or when switching application of therapy (e.g., IVIg to SCIg). We recommend to calculate the initial IgG-dose according to the adjusted body weight (if the actual weight is >30% of the ideal BMI) and adjust the dose according to the trough/steady state level and clinical symptoms [67–70].

Consensus-based recommendation 11:

"***In obese patients we recommend dose calculation by using ideal/adjusted body weight."***

Expert consensus: strong consensus

Switch of application

Switching from one application to another is not uncommon [71]. When switching to SCIg, FDA recommends a conversion factor of 1:1.37 (IVIg:SCIg); however, most clinicians continue with the previous dose and adjust according to clinical and laboratory parameter [72–74].

Consensus-based recommendation 12a:

"***We recommend to initiate IgG-replacement therapy in a dose of ≥ 400 mg/kg/month (sc or iv)."***

Level of evidence: 2; Level of recommendation: A

Consensus-based recommendation 12b:

"***We suggest a dose of 0.4–0.6 g/kg/month of IgG for intravenous IgG-replacement therapy (IVIg). We recommend IgG-trough-levels ≥ 4.5 g/L. Maintenance therapy should by guided according to clinical response (biologic trough level)."***

Level of evidence: 2; Level of recommendation: A

Consensus-based recommendation 12c:

"***We suggest a dose of 0.4–0.6 g/kg/month of IgG for subcutaneous IgG-replacement therapy (SCIg). Maintenance therapy should by guided according to clinical response (biologic trough level)***.

Expert consensus: strong consensus

Monitoring and management of adverse events

We recommend monitoring of IgG levels every 3 months in the first year of treatment. In stable patients, we recommend monitoring IgG levels ≥2 times per year. Adverse events are rare [75].

Transfusion-related adverse events

Severe transfusion-related adverse events are very rare [75]. Most events are mild, reversible, and occur at fast infusion flow rates. In adverse events, during IVIg reduction of IVIg flow rate is recommended. Severe adverse events are treated according to recommendations for anaphylaxis. In patients with persistent adverse events or in patients with ongoing need for premedication on IVIg, switching to SCIg should be considered.

Hemolysis

Immunoglobuline products contain isohemagglutinins that may cause transfusion associated hemolysis. Hemolysis was almost exclusively reported in IVIg patients [76,77].

Anti-IgA antibodies

Serum IgG anti-IgA antibodies have been associated with the development of adverse reactions, to IVIg in patients with undetectable IgA levels [78–81]. Consequently, most manufactures consider the presence of anti-IgA antibodies as a contraindication to Ig replacement therapy. Due to the very low incidence of severe adverse events caused by anti-IgA antibodies, screening for these antibodies is not routinely performed. Monitoring of patients receiving their first IVIg infusion or IVIg infusions after a long treatment pause is mandatory. Patients with anaphylactic reaction upon IVIg should switch treatment to subcutaneous application (SCIg). The absence of IgA is no contraindication for Ig replacement therapy. Patients with known anti-IgA antibodies have a higher risk of anaphylaxis during IVIg treatment (in particular, with IgE-anti-IgA antibodies). SCIg application is considered safe in these patients.

Risk of pathogen transmission

Immunoglobulin products are produced from plasma of >10000 healthy donors. Due to the transmission of HCV in 1994, the processes for reducing pathogen contamination have improved significantly. Viral removal by depth filtration and nanofiltration as well as viral inactivation with low pH, pasteurization, caprylate, and detergent reduce the risk for viral transmission to almost zero. Nanofiltration can further remove non-lipid-coated viruses and prions [82].

Miscellaneous

Acute renal failure is usually mild and reversible [83]. Patients with renal disease and/or chronic heart failure might benefit from lower IVIg concentrations (5%). Thromboembolic events have been reported, however, a systematic review and meta-analysis of RCT found no evidence of an increased risk for thromboembolic among IVIg-treated patients [84]. Aseptic meningitis is rare [85] and usually observed in high dose IVIg treatment (1–2 g/kg BW) [86]. To avoid hyperviscosity patients with renal insufficiency require additional hydration. In patients with relevant proteinuria, SCIg seems more reasonable.

In IVIg products containing maltose, erroneously elevated blood sugar values can occur when using GDH-PQQ test strips [87]. Diagnostic assays using Beta-D-Glucan for fungal testing can be false positive [88]. Immunoglobulin treatment can transfer antibodies to blood groups, affecting serological test.

Consensus-based recommendation 13a:

"***We recommend clinical monitoring of IgG trough levels every three months in the first year of treatment. We recommend follow-up visits in clinically stable patients every six months.***"

Expert consensus: strong consensus

Consensus-based recommendation 13b:

"***Patients should be followed up regularly for whole blood count, liver enzymes and kidney function.***"

Expert consensus: consensus

Management and treatment of non-infectious manifestations

The risk for non-infectious manifestations affects 20–30% of patients with CVID, immune cytopenia being the most common one [2,89]. Immune dysregulation (in particular immune cytopenia and interstitial lung diseases) may be the presenting sign in patients with CVID [4,90–95].

Immune cytopenia

Management of immune cytopenia follows recommendations for non-PID patients [92]. Present data support first-line treatment with steroids. If manageable as outpatients, oral application is preferred [93]. In severe courses, adjunctive treatment with high dose immunoglobulins may be considered. Rituximab is recommended as second-line therapy in PID patients [94,95]. There are only case reports for the use of thrombopoietin receptor agonists [94,96]. Risk of recurrence is high. In selected cases, splenectomy may be considered, but must be weighed carefully against the potentially increased risk of infections [97]. We recommend interdisciplinary follow-up for patients with antibody deficiency and immune cytopenia.

Consensus-based recommendation 14a:

"***We suggest interdisciplinary follow-up with hematologist/oncologists in patients with primary antibody deficiencies and immune cytopenia.***"

Expert consensus: strong consensus

Consensus-based recommendation 14b:

"***We suggest treatment of ITP and AIHA with steroids and adjunctive high dose of immunoglobulines in severe courses.***"

Expert consensus: strong consensus

Pulmonary manifestations

The vast majority of patients with antibody deficiency suffers from chronic pulmonary manifestations [98–101]. Pulmonary manifestations affect survival in patients with CVID [102]. The two largest entities of pulmonary manifestations are bronchiectasis and granulomatous lymphocytic interstitial lung disease (GLILD).

Bronchiectasis

In the presence of clinical symptoms or suggestive history, detection of bronchiectasis is usually performed by CT scan. Chest X-ray fails to identify bronchiectasis in up to 60% [103]. Management of bronchiectasis aims at reducing/preventing acute exacerbations and infections, improving mucocilliary clearance, and stabilizing pulmonary function. We recommend microbiological sputum surveillance every 3–6 months for early identification of colonization with potential harmful germs (*Pseudomonas aeruginosa*, MRSA), and for guidance of initial decision on empiric antibiotic treatment in acute infections, before current microbiological data are available. According to ERS (European Respiratory Society) guideline, duration of antibiotic treatment is 14 days [104]. *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Moraxella catarrhalis*, *Staphylococcus aureus*, or *Enterobactericae* ia frequently colonizing the airways in patients with bronchiectasis. Colonization with *Pseudomonas aeruginosa* was shown to affect long-term pulmonary function [105]. In agreement with ERS guidelines, we recommend early eradication of *Pseudomonas aeruginosa*. For additional treatment options, including inhaled therapy and exercise training, see section 8.

RCT assessing the role of antibiotic prophylaxis in non-CF bronchiectasis are only available for non-PID patients. Using macrolides, a significant reduction of exacerbation rate and symptoms was detected [106–109]. Development of non-susceptibility to macrolides, cardiac arrhythmia, and gastrointestinal adverse events need to be considered [107]. ERS guidelines recommend antibiotic prophylaxis with 250—500 mg Azithromycin three times per week in patients with >3 exacerbations/year. It is mandatory to test for colonization with non-tuberculous mycobacteria and to check QT time prior to macrolide prophylaxis. Two prospective cohort studies showed that CVID patients with bronchiectasis required higher IgG-dosing for reaching

target IgG-levels [21,23]. Patients with or without bronchiectasis did not differ in rates of infection when treated at similar IgG trough levels [23]. In patients with bronchiectasis, IgG levels should be adapted individually.

Interstitial lung diseases

Granulomatous lymphocytic interstitial lung disease (GLILD) is found in 10–30% of CVID patients, either developing during disease course [110] or as first clinical presentation [5]. GLILD affects survival in patients with CVID [102]. For clinical diagnosis, radio-morphological findings as wells as lung function and histopathology must be taken into consideration [111]. We recommend annual pulmonary function testing including measuring DLCO (diffusion capacity) for surveillance of CVID patients. Routine chest imaging is not recommended. Its use should be reserved for deterioration of lung function or clinical symptoms. Lung MRI can avoid radiation [112]. GLILD should prompt a detailed (and genetic) immunological work-up [113]. There are no RCTs for the treatment of GLILD in CVID patients. Depending on the histopathology and/or BALF, it is reasonable to begin with steroids. Only limited data are available for second-line treatment of GLILD. Successful combination therapy targeting B-cells (using rituximab) and T-cells (using azathioprine or MMF) at the same time was reported by different groups [114–117] (see Supporting Information Table S6 for summary of treatment of GLILD in CVID). Treatment of GLILD should only be considered in cases with clinical symptoms, reduced pulmonary function, or radiomorphological progression, since many patients remain clinically stable [118]. There is some evidence that patients with CVID and GLILD might benefit from higher IgG trough levels [23,119]. We recommend interdisciplinary follow-up for patients with chronic pulmonary manifestations.

Consensus-based recommendation 15a:

"***At diagnosis and in yearly intervals we recommend body plethysmography and DLCO in patients with CVID. We suggest lung CT or MR-imaging in adult patients at diagnosis.***"

Expert consensus: strong consensus

Consensus-based recommendation 15b:

"***We suggest interdisciplinary follow up with a (pediatric) pulmonologist in patients with chronic pulmonary disease.***"

Expert consensus: strong consensus

Consensus-based recommendation 15c:

"***We suggest regular sputum analyses in patients with bronchiectasis.***"

Expert consensus: strong consensus

Granulomatous lesions can affect all organs

In CVID patients, extra-pulmonary manifestations include lesions in spleen, liver, lymph nodes, skin, kidney, or CNS [118]. In histopathology most lesions present as "sarcoid-like," non-caseating epithelioid granuloma, while lymphocytic infiltrates can be detected as well. Granulomatous/lymphocytic organ manifestations should prompt a detailed immunological and genetic work-up. There are no RCT for treatments, case reports are summarized in Supporting Information Table S7. Treatment options should be evaluated in cooperation with an immunodeficiency center.

Other manifestations

Neoplasia

Patients with CVID express an elevated risk for neoplasia, in particular for lymphoma and gastric cancer [120–122]. In a recent large Italian cohort, gastric cancer was the leading cause of death in CVID patients [123]. Patients should be educated to report unusual or persistent lymphadenopathy. Annual screening for lymphadenopathy or hepatosplenomegaly by abdominal sonography is recommended. During clinical visits, history and examination should also cover specific symptoms (lymphadenopathy, weight loss, sweating at night, etc.). Annual CT scans for surveillance of asymptomatic patients are not recommended.

Gastrointestinal manifestations

Gastrointestinal manifestations, such as autoimmune gastritis, celiac disease, chronic diarrhea, malabsorption, nodular lymphatic hyperplasia, etc., may affect patients with primary antibody deficiencies [124]. We recommend assessing specifically gastrointestinal symptoms in all patients with antibody deficiency. Abdominal ultrasound is recommended in all patients with CVID at diagnosis and for annual follow-up examinations. In adult patients with CVID, esophago-gastroduodenoscopy (EGD) is recommended at diagnosis. There are no clinical trials that assessed the efficacy of early detection of gastric cancer in different screening settings. Some reports suggest follow-up examinations to be guided by histopathology [125]. In a recent large Italian cohort of 455 CVID patients, gastric cancer appeared on average 15 years earlier than in non-CVID patients. Based on their results, Pulverenti et al. recommend follow-up EGD every 24 months in patients with normal histology and every 12 months (in patients with atrophic gastritis or intestinal metaplasia) or even every 6 months (in patients with dysplasia). Due to the higher prevalence of gastric cancer in Italy, it is uncertain if those recommendations are applicable to other populations [123]. As non-invasive follow-up, we recommend annual *Helicobacter pylori* testing (by HP-Ag in stool or urea breath test) and measuring vitamin B12 in blood or methylmalonic acid in urine, since HP and autoimmune gastritis are known risk factors for gastric cancer. Autoantibody diagnostic (e.g., for Transglutaminase-Ab) may be misleading. Microbiological stool analysis should also cover parasites and Norovirus infections. Endoscopy may be required in patients with unclear enteropathies or, e.g., for diagnosing infection with *Giardia*

lamblia. We recommend interdisciplinary follow-up for all chronic gastrointestinal manifestations.

Consensus-based recommendation 16a:

"***We suggest interdisciplinary follow up with a (pediatric) gastroenterologists in patients with liver and / or gastrointestinal manifestations.***"

Expert consensus: strong consensus

Consensus-based recommendation 16b:

"***We recommend ultrasound of the abdomen at diagnosis and yearly follow up in patients with CVID. We recommend esophago-gastroduodenoscopy and colonoscopy in symptomatic patients.***"

Expert consensus: strong consensus

Treatment of selected monogenetic PIDs

APDS I and II

APDS (activated phosphoinositide 3-kinase delta syndrome) is caused by autosomal-dominant "gain of function" mutations in *PI3KCD* (APDS I) [126,127] or *PI3KR1* (APDS II) [128]. Clinical symptoms include an increased infection rate, bronchiectasis, EBV viremia, lymphoproliferation, and autoimmunity. Approximately 50% of patients present with hypogammaglobulinemia or fulfill criteria for CVID. There are no RCTs on treatment in APDS. Current literature and data from ESID level 3 registry report improvement on rapamycin [129]. Targeted therapy using the selective PI3Kdelta-Inhibitor leniolisib was only tested in a small trial [130].

CTLA4 deficiency

Haploinsufficiency caused by autosomal-dominant "loss of function" mutations in *CTLA4* [131]. Overall 84% of patients present with hypogammaglobulinemia. Clinical symptoms are lymphoproliferation (73%), autoimmune cytopenia (62%), and lymphocytic infiltration of various organs (lung, gastrointestinal tract, CNS, skin, etc.). There are no RCTs on treatment. Current data report clinical improvement on CTLA4-IgG-fusionprotein (Abatacept) or rapamycin [132].

LRBA deficiency

LRBA (LPS-responsive beige-like anchor protein) deficiency: caused by autosomal-recessive mutation in LRBA [133]. There are no RCTs on treatment. Analysis of different treatments in an international multicenter cohort reported an overall survival after HSCT in 70% (mean follow-up 20 months). Immunosuppressive treatment with Abatacept or rapamycin was associated with significantly lower disease scores than was treatment with steroids [134].

Antimicrobial treatment

At the time of consensus meeting, no RCTs on the use of antimicrobial prophylaxis in primary antibody deficiency were available. A recent publication by Milito et al. is included to the present version of these guidelines due to its clinical importance. In a 3-year, double-blind, placebo-controlled, randomized clinical trial, it was shown that oral azithromycin (250 mg administered once daily 3 times a week for 2 years) reduced respiratory exacerbations in patients with primary antibody deficiency. The rate of additional antibiotic treatment per patient-year was 2.3 (95% CI, 2.1-3.4) in the intervention group and 3.6 (95% CI, 2.9-4.3) in the placebo group (p: 0.004). There was no difference in safety or in non-susceptibility rates to macrolides [135].

In patients with agammaglobulinemia or CVID with persistently increased susceptibility to bacterial infections despite adjustment of IgG trough level, antibiotic prophylaxis with TMP/SMX may be considered [49]. Persistently increased infection rates should prompt reevaluation of the immune status and identification of putative foci (bronchiectasis, chronic sinusitis, etc.).

Patients with antibody deficiency and additional impairment of T-cellular immunity (i.e. CID, HIGM due to mutation in CD40L) have an increased risk for opportunistic infections and require antimicrobial prophylaxis [15]. TMP/SMX is recommended trice a week for patients with CD4 cell counts $<200/\mu l$ or $<15\%$ of lymphocytes. An increased mortality and risk for opportunistic infections was shown for CVID patients with low naive CD4 cells ($<20/\mu L$) [48].

In acute infections, direct microbiological testing is recommended, since serological tests are difficult to interpret under immunoglobulin replacement treatment and classic early IgM-reponse to specific pathogens is not likely to occur in most patients with primary antibody deficiency.

Consensus-based recommendation 17a:

"***We recommend microbiological diagnostics and targeted anti-infectious therapy in patients with recurrent infections despite IgG-replacement therapy. We do not recommend serological infectious disease work-up due to impaired immune responses and diagnostic interference with IgG-replacement therapy.***"

Expert consensus: strong consensus

Consensus-based recommendation 17b:

"***In patients with symptomatic bronchiectasis, additional antibiotic prophylaxis may be considered.***"

Level of evidence: 3; Level of recommendation: O

Physiotherapy and airway treatment

According to current ERS (European Respiratory Society) guidelines [104], respiratory physiotherapy is recommended for patients with bronchiectasis. Regular pulmonary rehabilitation should be offered in patients with respiratory distress [136–138].

BTS (British Thoracic Society) guidelines for non-CF bronchiectasis recommend special breathing techniques, (oscillating) PEP therapy (positive expiratory pressure), positional drainage and forced exhalation techniques as well as autogenic drainage [139]. It is recommended to use bronchodilators and inhaled mucolytic drugs before physiotherapy, and before inhaling antibiotics . Long-acting bronchodilators should not be offered routinely for all patients with bronchiectasis.

Despite the undisputed high occurrence and clinical relevance of chronic or recurrent sinusitis, there are no controlled studies on the treatment of chronic sinusitis, which could lead to evidence-based recommendations. Symptomatic management (saline irrigation, analgesic treatment, etc.) is recommended. Patients require an allergic work up and ENT consultation.

Consensus-based recommendation 18a:

"***We suggest to initiate respiratory physiotherapy early in the course in symptomatic patients with bronchiectasis.***"

Expert consensus: strong consensus

Consensus-based recommendation 18b:

"***We recommend physical exercise and pulmonary exercise training for all patients with clinically symptomatic bronchiectasis.***"

Level of evidence: 1; Level of recommendation: A

Further measures

Possible burdens of treatment or side effects of a lifelong therapy should be addressed proactively by the attending physician [140, 141]. Contacting (local) patient organizations is encouraged. We suggest participation in structured, patient-centered educational workshops.

Consensus-based recommendation 19:

"We suggest to inform patients and family fully on all available therapeutic options and to enable patients decision making. "

Expert consensus: strong consensus

Consensus-based recommendation 20:

"We suggest participation in structured, patient-centered educational workshops."

Expert consensus: strong consensus

Participating medical societies

Arbeitsgemeinschaft Pädiatrische Immunologie (API) e.V.

Berufsverband der Kinder- und Jugendärzte e. V. (BVKJ)

Berufsverband der Niedergelassenen Hämatologen und Onkologen e. V. (BNHO)

Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie e.V. (DGHO)

Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Halschirurgie e. V.

Deutsche Gesellschaft für Immunologie e. V. (DGfI)

Deutsche Gesellschaft für Infektiologie e.V. (DGI)

Deutsche Gesellschaft für Innere Medizin e.V. (DGIM)

Deutsche Gesellschaft für Kinder- und Jugendmedizin e.V. (DGKJ)

Gesellschaft für Kinder- und Jugendrheumatologie e.V. (GKJR):

Deutsche Gesellschaft für Pädiatrische Infektiologie e. V. (DGPI)

Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e. V. (DGP)

Deutsche Gesellschaft für Rheumatologie e. V. (DGRh)

Deutsche Selbsthilfe Angeborene Immundefekte e. V. (dsai)

Deutscher Verband für Physiotherapie (ZVK) e. V.

Gesellschaft für Pädiatrische Onkologie und Hämatologie e. V. (GPOH)

Gesellschaft für Pädiatrische Pneumologie e. V. (GPP)

Österreichische Gesellschaft für Kinder- und Jugendheilkunde (ÖGKJ)

Schweizerische Gesellschaft für Pädiatrie/Swiss Society of Paediatrics (SGP)

Deutsche Gesellschaft für Transfusionsmedizin und Immunhämatologie e. V. (DGTI)

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References

1 **Bousfiha, A., Jeddane, L., Picard, C., Al-Herz, W., Ailal, F., Chatila, T. et al.**, Human inborn errors of immunity: 2019 update of the IUIS phenotypical classification. *J. Clin. Immunol.* 2020: https://doi.org/10.1007/s10875-020-00758-x.

2 **Gathmann, B., Mahlaoui, N., Ceredih, G. L., Oksenhendler, E., Warnatz, K. et al.**, Clinical picture and treatment of 2212 patients with common variable immunodeficiency. *J. Allergy Clin. Immunol.* 2014. **134**: 116–126.

3 **Oksenhendler, E., Gérard, L., Fieschi, C., Malphettes, M., Mouillot, G., Jaussaud, R. et al.**, Infections in 252 patients with common variable immunodeficiency. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 2008. **46**: 1547–1554.

4 **Wang, J. and Cunningham-Rundles, C.**, Treatment and outcome of autoimmune hematologic disease in common variable immunodeficiency (CVID). *J. Autoimmun.* 2005. **25**: 57–62.

5 **Hanitsch, L. G., Wittke, K., Stittrich, A. B., Volk, H. D. and Scheibenbogen, C.**, Interstitial Lung Disease Frequently Precedes CVID Diagnosis. *J. Clin. Immunol.* 2019. **39**: 849–851.

6 **Fischer, A., Provot, J., Jais, J-P., Alcais, A., Mahlaoui, N. and members of the CFPIDsg**. Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies. *J. Allergy Clin. Immunol.* 2017. **140**: 1388–1393.e8.

7 **Krudewig, J., Baumann, U., Bernuth von, H., Borte, M., Burkhard-Meier, U., Dueckers, G. et al.**, Interdisciplinary AWMF guideline for the treatment of primary antibody deficiencies. *Klin. Padiatr.* 2012. **224**: 404–415.

8 **Quartier, P., Debré, M., De Blic, J., de Sauverzac, R., Sayegh, N., Jabado, N. et al.**, Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. *J. Pediatr.* 1999. **134**: 589–596.

9 **Liese, J. G., Wintergerst, U., Tympner, K. D. and Belohradsky, B. H.**, High- vs low-dose immunoglobulin therapy in the long-term treatment of X-linked agammaglobulinemia. *Am. J. Dis. Child.* 1992. **146**: 335–339.

10 **Lederman, H. M. and Winkelstein, J. A.**, X-linked agammaglobulinemia: an analysis of 96 patients. *Medicine (Baltimore)* 1985. **64**: 145–156.

11 **Roifman, C. M., Levison, H. and Gelfand, E. W.**, High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinaemia and chronic lung disease. *Lancet* 1987. **1**: 1075–1077.

12 **Ammann, A. J., Ashman, R. F., Buckley, R. H., Hardie, W. R., Krantmann, H. J., Nelson, J. et al.**, Use of intravenous gamma-globulin in antibody immunodeficiency: results of a multicenter controlled trial. *Clin. Immunol. Immunopathol.* 1982. **22**: 60–67.

13 **Nolte, M. T., Pirofsky, B., Gerritz, G. A. and Golding, B.**, Intravenous immunoglobulin therapy for antibody deficiency. *Clin. Exp. Immunol.* 1979. **36**: 237–243.

14 **Skull, S. and Kemp, A.**, Treatment of hypogammaglobulinaemia with intravenous immunoglobulin, 1973–93. *Arch. Dis. Child.* 1996. **74**: 527–530.

15 **Levy, J., Espanol-Boren, T., Thomas, C., Fischer, A., Tovo, P., Bordigoni, P. et al.**, Clinical spectrum of X-linked hyper-IgM syndrome. *J. Pediatr.* 1997. **131**(1 Pt 1): 47–54.

16 **Winkelstein, J. A., Marino, M. C., Ochs, H., Fuleihan, R., Scholl, P. R., Geha, R. et al.**, The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. *Medicine (Baltimore)* 2003. **82**: 373–384.

17 **Quartier, P., Bustamante, J., Sanal, O., Plebani, A., Debré, M., Deville, A. et al.**, Clinical, immunologic and genetic analysis of 29 patients with autosomal recessive hyper-IgM syndrome due to Activation-Induced Cytidine Deaminase deficiency. *Clinical Immunology (Orlando, Fla.)* 2004. **110**: 22–29.

18 **de la Morena, M. T., Leonard, D., Torgerson, T. R., Cabral-Marques, O., Slatter, M., Aghamohammadi, A. et al.**, Long-term outcomes of 176 patients with X-linked hyper-IgM syndrome treated with or without hematopoietic cell transplantation. *J. Allergy Clin. Immunol.* 2017. **139**: 1282–1292.

19 **Cunningham-Rundles, C., Siegal, F. P., Smithwick, E. M., Lion-Boulé, A., Cunningham-Rundles, S., O'Malley, J. et al.**, Efficacy of intravenous immunoglobulin in primary humoral immunodeficiency disease. *Ann. Intern. Med.* 1984. **101**: 435–439.

20 **Busse, P. J., Razvi, S. and Cunningham-Rundles, C.**, Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. *J. Allergy Clin. Immunol.* 2002. **109**: 1001–1004.

21 **de Gracia, J., Vendrell, M., Alvarez, A., Pallisa, E., Rodrigo, M.-J., de la Rosa, D. et al.**, Immunoglobulin therapy to control lung damage in patients with common variable immunodeficiency. *Int. Immunopharmacol.* 2004. **4**: 745–753.

22 **Quinti, I., Soresina, A., Spadaro, G., Martino, S., Donnanno, S., Agostini, C. et al.**, Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. *J. Clin. Immunol.* 2007. **27**: 308–316.

23 **Lucas, M., Lee, M., Lortan, J., Lopez-Granados, E., Misbah, S. and Chapel, H.**, Infection outcomes in patients with common variable immunodeficiency disorders: relationship to immunoglobulin therapy over 22 years. *J. Allergy Clin. Immunol.* 2010. **125**: 1354–1360.e4.

24 **Driessen, G. J., Dalm, V. A., van Hagen, P. M., Grashoff, H. A., Hartwig, N. G., van Rossum, A. M. et al.**, Common variable immunodeficiency and idiopathic primary hypogammaglobulinemia: two different conditions within the same disease spectrum. *Haematologica*. 2013. **98**: 1617–1623.

25 **Janssen, L. M. A., Bassett, P., Macken, T., van Esch, J., Pruijt, H., Knoops, A. et al.**, Mild Hypogammaglobulinemia Can Be a Serious Condition. *Front. Immunol.* 2018. **9**: 2384.

26 **Ambrosino, D. M., Siber, G. R., Chilmonczyk, B. A., Jernberg, J. B. and Finberg, R. W.**, An immunodeficiency characterized by impaired antibody responses to polysaccharides. *N. Engl. J. Med.* 1987. **316**: 790–793.

27 **Orange, J. S., Ballow, M., Stiehm, E. R., Ballas, Z. K., Chinen, J., De La Morena, M. et al.**, Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. *J. Allergy Clin. Immunol.* 2012. **130**(3 Suppl): S1–S24.

28 **Ruuskanen, O., Nurkka, A., Helminen, M., Viljanen, M. K., Kayhty, H. and Kainulainen, L.**, Specific antibody deficiency in children with recurrent respiratory infections: a controlled study with follow-up. *Clin. Exp. Immunol.* 2013. **172**: 238–244.

29 **Yong, P. L., Boyle, J., Ballow, M., Boyle, M., Berger, M., Bleesing, J. et al.**, Use of intravenous immunoglobulin and adjunctive therapies in the treatment of primary immunodeficiencies: A working group report of and study by the Primary Immunodeficiency Committee of the American Academy of Allergy Asthma and Immunology. *Clin. Immunol.* 2010. **135**: 255–263.

30 **Bonilla, F. A., Khan, D. A., Ballas, Z. K., Chinen, J., Frank, M. M., Hsu, J. T. et al.**, Practice parameter for the diagnosis and management of primary immunodeficiency. *J. Allergy Clin. Immunol.* 2015. **136**: 1186–1205.e2078.

31 **Leung, D. Y., Ambrosino, D. M., Arbeit, R. D., Newton, J. L. and Geha, R. S.**, Impaired antibody responses in the hyperimmunoglobulin E syndrome. *J. Allergy Clin. Immunol.* 1988. **81**: 1082–1087.

32 **Sheerin, K. A. and Buckley, R. H.**, Antibody responses to protein, polysaccharide, and phi X174 antigens in the hyperimmunoglobulinemia E (hyper-IgE) syndrome. *J. Allergy Clin. Immunol.* 1991. **87**: 803–811.

33 **Sanal, O., Ersoy, F., Yel, L., Tezcan, I., Metin, A., Ozyürek, H. et al.**, Impaired IgG antibody production to pneumococcal polysaccharides in patients with ataxia-telangiectasia. *J. Clin. Immunol.* 1999. **19**: 326–334.

34 **Picard, C., Casanova, J.-L. and Puel, A.**, Infectious diseases in patients with IRAK-4, MyD88, NEMO, or IκBα deficiency. *Clin. Microbiol. Rev.* 2011. **24**: 490–497.

35 **McKelvie, B., Top, K., McCusker, C., Letenyi, D., Issekutz, T. B. and Issekutz, A. C.**, Fatal pneumococcal meningitis in a 7-year-old girl with interleukin-1 receptor activated kinase deficiency (IRAK-4) despite prophylactic antibiotic and IgG responses to Streptococcus pneumoniae vaccines. *J. Clin. Immunol.* 2014. **34**: 267–271.

36 **Gobin, K., Hintermeyer, M., Boisson, B., Chrabieh, M., Ghandil, P., Puel, A. et al.**, IRAK4 deficiency in a patient with recurrent pneumococcal infections: case report and review of the literature. *Front. Pediatr.* 2017. **5**: 83.

37 **Stentzel, S., Hagl, B., Abel, F., Kahl, B. C., Rack-Hoch, A., Bröker, B. M. et al.**, Reduced Immunoglobulin (Ig) G Response to Staphylococcus aureus in STAT3 Hyper-IgE Syndrome. *Clin. Infect. Dis.* 2017. **64**: 1279–1282.

38 **Bernatowska-Matuszkiewicz, E., Pac, M., Skopcynska, H., Pum, M. and Eibl, M. M.**, Clinical efficacy of intravenous immunoglobulin in patients with severe inflammatory chest disease and IgG3 subclass deficiency. *Clin. Exp. Immunol.* 1991. **85**: 193–197.

39 **Barlan, I. B., Geha, R. S. and Schneider, L. C.**, Therapy for patients with recurrent infections and low serum IgG3 levels. *J. Allergy Clin. Immunol.* 1993. **92**: 353–355.

40 **Olinder-Nielsen, A. M., Granert, C., Forsberg, P., Friman, V., Vietorisz, A. and Bjorkander, J.**, Immunoglobulin prophylaxis in 350 adults with IgG subclass deficiency and recurrent respiratory tract infections: a long-term follow-up. *Scand. J. Infect. Dis.* 2007. **39**: 44–50.

41 **Abdou, N. I., Greenwell, C. A., Mehta, R., Narra, M., Hester, J. D. and Halsey, J. F.**, Efficacy of intravenous gammaglobulin for immunoglobulin G subclass and/or antibody deficiency in adults. *Int. Arch. Allergy Immunol.* 2009. **149**: 267–274.

42 **Abrahamian, F., Agrawal, S. and Gupta, S.**, Immunological and clinical profile of adult patients with selective immunoglobulin subclass deficiency: response to intravenous immunoglobulin therapy. *Clin. Exp. Immunol.* 2010. **159**: 344–350.

43 **Duse, M., Iacobini, M., Leonardi, L., Smacchia, P., Antonetti, L. and Giancane, G.**, Transient hypogammaglobulinemia of infancy: intravenous immunoglobulin as first line therapy. *Int. J. Immunopathol. Pharmacol.* 2010. **23**: 349–353.

44 **Memmedova, L., Azarsiz, E., Edeer Karaca, N., Aksu, G. and Kutukculer, N.**, Does intravenous immunoglobulin therapy prolong immunodeficiency in transient hypogammaglobulinemia of infancy? *Pediatr. Rep.* 2013. **5**: e14.

45 **Goldstein, M. F., Goldstein, A. L., Dunsky, E. H., Dvorin, D. J., Belecanech, G. A. and Shamir, K.**, Selective IgM immunodeficiency: retrospective analysis of 36 adult patients with review of the literature. *Ann. Allergy Asthma Immunol.* 2006. **97**: 717–730.

46 **Yel, L., Ramanuja, S. and Gupta, S.**, Clinical and immunological features in IgM deficiency. *Int. Arch. Allergy Immunol.* 2009. **150**: 291–298.

47 **Chovancova, Z., Kralickova, P., Pejchalova, A., Bloomfield, M., Nechvatalova, J., Vlkova, M. et al.**, Selective IgM deficiency: clinical and laboratory features of 17 patients and a review of the literature. *J. Clin. Immunol.* 2017. **37**: 559–574.

48 **Bertinchamp, R., Gérard, L., Boutboul, D., Malphettes, M., Fieschi, C., Oksenhendler, E. et al.**, Exclusion of patients with a severe t-cell defect improves the definition of common variable immunodeficiency. *J. Allergy Clin. Immunol. Pract.* 2016. **4**: 1147–1157.

49 **Aguilar, C., Malphettes, M., Donadieu, J., Chandesris, O., Coignard-Biehler, H., Catherinot, E. et al.**, Prevention of infections during primary immunodeficiency. *Clin. Infect. Dis.* 2014. **59**: 1462–1470.

50 **Wasserman, R. L., Melamed, I., Stein, M. R., Gupta, S., Puck, J., Engl, W. et al.**, Recombinant human hyaluronidase-facilitated subcutaneous infusion of human immunoglobulins for primary immunodeficiency. *J. Allergy Clin. Immunol.* 2012. **130**: 951–957.e11.

51 **Wasserman, R. L., Melamed, I., Kobrynski, L., Puck, J., Gupta, S., Doralt, J. et al.**, Recombinant human hyaluronidase facilitated subcutaneous immunoglobulin treatment in pediatric patients with primary immunodeficiencies: long-term efficacy, safety and tolerability. *Immunotherapy*. 2016. **8**: 1175–1186.

52 **Wasserman, R. L., Melamed, I., Stein, M. R., Engl, W., Sharkhawy, M., Leibl, H. et al.**, Long-term tolerability, safety, and efficacy of recombinant human hyaluronidase-facilitated subcutaneous infusion of human immunoglobulin for primary immunodeficiency. *J. Clin. Immunol.* 2016. **36**: 571–582.

53 **Gardulf, A., Andersen, V., Björkander, J., Ericson, D., Frøland, S. S., Gustafson, R. et al.**, Subcutaneous immunoglobulin replacement in patients with primary antibody deficiencies: safety and costs. *Lancet*. 1995. **345**: 365–369.

54 **Abrahamsen, T. G., Sandersen, H. and Bustnes, A.**, Home therapy with subcutaneous immunoglobulin infusions in children with congenital immunodeficiencies. *Pediatrics*. 1996. **98**(6 Pt 1): 1127–1131.

55 **Gardulf, A., Nicolay, U., Math, D., Asensio, O., Bernatowska, E., Böck, A. 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**: 936–942.

56 **Gardulf, A., Nicolay, U., Asensio, O., Bernatowska, E., Böck, A., Carvalho, B. C. et al.**, Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies–a prospective, multi-national study. *J. Clin. Immunol.* 2006. **26**: 177–185.

57 **Nicolay, U., Kiessling, P., Berger, M., Gupta, S., Yel, L., Roifman, C. M. et al.**, Health-related quality of life and treatment satisfaction in North American patients with primary immunedeficiency diseases receiving subcutaneous IgG self-infusions at home. *J. Clin. Immunol.* 2006. **26**: 65–72.

58 **Fasth, A. and Nyström, 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**: 370–378.

59 **Gardulf, A., Borte, M., Ochs, H. D., Nicolay, U. and Vivaglobin Clinical Study, G.**, Prognostic factors for health-related quality of life in adults and children with primary antibody deficiencies receiving SCIG home therapy. *Clinical Immunology (Orlando, Fla.)* 2008. **126**: 81–88.

60 **Bonagura, V. R.**, Using intravenous immunoglobulin (IVIG) to treat patients with primary immune deficiency disease. *J. Clin. Immunol.* 2013. **33**(Suppl 2): S90–S94.

61 **Bonilla, F. A., Barlan, I., Chapel, H., Costa-Carvalho, B. T., Cunningham-Rundles, C., de la Morena, M. T. et al.**, International Consensus Document (ICON): Common Variable Immunodeficiency Disorders. *J. Allergy Clin. Immunol. Pract.* 2016. **4**: 38–59.

62 **Bernatowska, E., Madaliński, K., Janowicz, W., Weremowicz, R., Gutkowski, P., Wolf, H. M. et al.**, Results of a prospective controlled two-dose crossover study with intravenous immunoglobulin and comparison (retrospective) with plasma treatment. *Clin. Immunol. Immunopathol.* 1987. **43**: 153–162.

63 **Quinti, I., Soresina, A., Guerra, A., Rondelli, R., Spadaro, G., Agostini, C. et al.**, Effectiveness of immunoglobulin replacement therapy on clinical outcome in patients with primary antibody deficiencies: results from a multicenter prospective cohort study. *J. Clin. Immunol.* 2011. **31**: 315–322.

64 **Orange, J. S., Grossman, W. J., Navickis, R. J. and Wilkes, M. M.**, Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies. *Clinical Immunology (Orlando, Fla.)* 2010. **137**: 21–30.

65 **Hernandez-Trujillo, H. S., Chapel, H., Lo Re, V., 3rd, N. L. D., Gathmann, B., Grimbacher, B. et al.**, Comparison of American and European practices in the management of patients with primary immunodeficiencies. *Clin. Exp. Immunol.* 2012. **169**: 57–69.

66 **Rojavin, M. A., Hubsch, A. and Lawo, J.-P.**, Quantitative evidence of wear-off effect at the end of the intravenous IgG (IVIG) dosing cycle in primary immunodeficiency. *J. Clin. Immunol.* 2016. **36**: 210–219.

67 **Hodkinson, J. P., Lucas, M., Lee, M., Harrison, M., Lunn, M. P. and Chapel, H.**, Therapeutic immunoglobulin should be dosed by clinical outcome rather than by body weight in obese patients. *Clin. Exp. Immunol.* 2015. **181**: 179–187.

68 **Berger, M., Rojavin, M., Kiessling, P. and Zenker, O.**, Pharmacokinetics of subcutaneous immunoglobulin and their use in dosing of replacement therapy in patients with primary immunodeficiencies. *Clinical Immunology (Orlando, Fla.)* 2011. **139**: 133–141.

69 **Khan, S., Grimbacher, B., Boecking, C., Chee, R., Allgar, V., Holding, S. et al.**, Serum trough IgG level and annual intravenous immunoglobulin dose are not related to body size in patients on regular replacement therapy. *Drug Metab. Lett.* 2011. **5**: 132–136.

70 **Shapiro, R.**, Subcutaneous immunoglobulin (16 or 20%) therapy in obese patients with primary immunodeficiency: a retrospective analysis of administration by infusion pump or subcutaneous rapid push. *Clin. Exp. Immunol.* 2013. **173**: 365–371.

71 **Bienvenu, B., Cozon, G., Hoarau, C., Pasquet, M., Cherin, P., Clerson, P. et al.**, Does the route of immunoglobin 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**: 83.

72 **Ochs, H. D., Gupta, S., Kiessling, P., Nicolay, U., Berger, M. and Subcutaneous Ig, G. S. G.**, Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. *J. Clin. Immunol.* 2006. **26**: 265–273.

73 **Jolles, S., Bernatowska, E., de Gracia, J., Borte, M., Cristea, V., Peter, H. H. et al.**, Efficacy and safety of Hizentra(®) in patients with primary immunodeficiency after a dose-equivalent switch from intravenous or subcutaneous replacement therapy. *Clinical Immunology (Orlando, Fla.)* 2011. **141**: 90–102.

74 **Niebur, H. B., Duff, C. M., Shear, G. F., Nguyen, D., Alberdi, T. K., Dorsey, M. J. et al.**, Efficacy and tolerability of 16% subcutaneous immunoglobulin compared with 20% subcutaneous immunoglobulin in primary antibody deficiency. *Clin. Exp. Immunol.* 2015. **181**: 441–450.

75 **Cherin, P., Marie, I., Michallet, M., Pelus, E., Dantal, J., Crave, J.-C. et al.**, Management of adverse events in the treatment of patients with immunoglobulin therapy: A review of evidence. *Autoimmun. Rev.* 2016. **15**: 71–81.

76 **Desborough, M. J., Miller, J., Thorpe, S. J., Murphy, M. F. and Misbah, S. A.**, Intravenous immunoglobulin-induced haemolysis: a case report and review of the literature. *Transfus. Med.* 2014. **24**: 219–226.

77 **Quinti, I., Pulvirenti, F., Milito, C., Granata, G., Giovannetti, G., La Marra, F. et al.**, Hemolysis in patients with antibody deficiencies on immunoglobulin replacement treatment. *Transfusion* 2015. **55**: 1067–1074.

78 **Vyas, G. N. and Fudenberg, H. H.**, Isoimmune anti-IgA causing anaphylactoid transfusion reactions. *N. Engl. J. Med.* 1969. **280**: 1073–1074.

79 **Burks, A. W., Sampson, H. A. and Buckley, R. H.**, Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia. Detection of IgE antibodies to IgA. *N. Engl. J. Med.* 1986. **314**: 560–564.

80 **Björkander, J., Hammarström, L., Smith, C. I., Buckley, R. H., Cunningham-Rundles, C. and Hanson, L. A.**, Immunoglobulin prophylaxis in patients with antibody deficiency syndromes and anti-IgA antibodies. *J. Clin. Immunol.* 1987. **7**: 8–15.

81 **Eijkhout, H. W., van den Broek, P. J. and van der Meer, J. W. M.**, Substitution therapy in immunodeficient patients with anti-IgA antibodies or severe adverse reactions to previous immunoglobulin therapy. *Neth. J. Med.* 2003. **61**: 213–217.

82 **Perez, E. E., Orange, J. S., Bonilla, F., Chinen, J., Chinn, I. K., Dorsey, M. et al.**, Update on the use of immunoglobulin in human disease: A review of evidence. *J. Allergy Clin. Immunol.* 2017. **139**(3S): S1–S46.

83 **Daphnis, E., Stylianou, K., Alexandrakis, M., Xylouri, I., Vardaki, E., Stratigis, S. et al.**, Acute renal failure, translocational hyponatremia and hyperkalemia following intravenous immunoglobulin therapy. *Nephron Clin. Pract.* 2007. **106**: c143–c148.

84 **Ammann, E. M., Haskins, C. B., Fillman, K. M., Ritter, R. L., Gu, X., Winiecki, S. K. et al.**, Intravenous immune globulin and thromboembolic adverse events: A systematic review and meta-analysis of RCTs. *Am. J. Hematol.* 2016. **91**: 594–605.

85 **Hopkins, S. and Jolles, S.**, Drug-induced aseptic meningitis. *Expert Opin. Drug Saf.* 2005. **4**: 285–297.

86 **Brennan, V. M., Salome-Bentley, N. J. and Chapel, H. M.**, Prospective audit of adverse reactions occurring in 459 primary antibody-deficient patients receiving intravenous immunoglobulin. *Clin. Exp. Immunol.* 2003. **133**: 247–251.

87 **Frias, J. P., Lim, C. G., Ellison, J. M. and Montandon, C. M.**, Review of adverse events associated with false glucose readings measured by GDH-PQQ-based glucose test strips in the presence of interfering sugars. *Diabetes Care* 2010. **33**: 728–729.

88 **Lo Cascio, G., Koncan, R., Stringari, G., Russo, A., Azzini, A., Ugolini, A. et al.**, Interference of confounding factors on the use of (1,3)-beta-D-glucan in the diagnosis of invasive candidiasis in the intensive care unit. *Eur. J. Clin. Microbiol. Infect. Dis.* 2015. **34**: 357–365.

89 **Feuille, E. J., Anooshiravani, N., Sullivan, K. E., Fuleihan, R. L. and Cunningham-Rundles, C.**, Autoimmune Cytopenias and Associated Conditions in CVID: a Report From the USIDNET Registry. *J. Clin. Immunol.* 2018. **38**: 28–34.

90 **Michel, M., Chanet, V., Galicier, L., Ruivard, M., Levy, Y., Hermine, O. et al.**, Autoimmune thrombocytopenic purpura and common variable immunodeficiency: analysis of 21 cases and review of the literature. *Medicine (Baltimore)* 2004. **83**: 254–263.

91 **Sève, P., Bourdillon, L., Sarrot-Reynauld, F., Ruivard, M., Jaussaud, R., Bouhour, D. et al.**, Autoimmune hemolytic anemia and common variable immunodeficiency: a case-control study of 18 patients. *Medicine (Baltimore)* 2008. **87**: 177–184.

92 **Barcellini, W.**, Current treatment strategies in autoimmune hemolytic disorders. *Expert Rev. Hematol.* 2015. **8**: 681–691.

93 **Wei, Y., Ji, X.-B., Wang, Y.-W., Wang, J.-X., Yang, E.-Q., Wang, Z.-C. et al.**, High-dose dexamethasone vs prednisone for treatment of adult immune thrombocytopenia: a prospective multicenter randomized trial. *Blood* 2016. **127**: 296–370.

94 **Gobert, D., Bussel, J. B., Cunningham-Rundles, C., Galicier, L., Dechartres, A., Berezne, A. et al.**, Efficacy and safety of rituximab in common variable immunodeficiency-associated immune cytopenias: a retrospective multicentre study on 33 patients. *Br. J. Haematol.* 2011. **155**: 498–508.

95 **Kim, J. J., Thrasher, A. J., Jones, A. M., Davies, E. G. and Cale, C. M.**, Rituximab for the treatment of autoimmune cytopenias in children with immune deficiency. *Br. J. Haematol.* 2007. **138**: 94–96.

96 **Carrabba, M., Barcellini, W. and Fabio, G.**, Use of thrombopoietin-receptor agonist in CVID-associated immune thrombocytopenia. *J. Clin. Immunol.* 2016. **36**: 434–436.

97 **Wong, G. K., Goldacker, S., Winterhalter, C., Grimbacher, B., Chapel, H., Lucas, M. et al.**, Outcomes of splenectomy in patients with common variable immunodeficiency (CVID): a survey of 45 patients. *Clin. Exp. Immunol.* 2013. **172**: 63–72.

98 **Chapel, H., Lucas, M., Lee, M., Bjorkander, J., Webster, D., Grimbacher, B. et al.**, Common variable immunodeficiency disorders: division into distinct clinical phenotypes. *Blood* 2008. **112**: 277–286.

99 **Touw, C. M. L., van de Ven, A. A., de Jong, P. A., Terheggen-Lagro, S., Beek, E., Sanders, E. A. M. et al.**, Detection of pulmonary complications in common variable immunodeficiency. *Pediatr. Allergy Immunol.* 2010. **21**: 793–805.

100 **Resnick, E. S., Moshier, E. L., Godbold, J. H. and Cunningham-Rundles, C.**, Morbidity and mortality in common variable immune deficiency over 4 decades. *Blood* 2012. **119**: 1650–1657.

101 **Baumann, U., Routes, J. M., Soler-Palacín, P. and Jolles, S.**, The Lung in Primary Immunodeficiencies: New Concepts in Infection and Inflammation. *Front. Immunol.* 2018. **9**: 1837-.

102 **Bates, C. A., Ellison, M. C., Lynch, D. A., Cool, C. D., Brown, K. K. and Routes, J. M.**, Granulomatous-lymphocytic lung disease shortens

survival in common variable immunodeficiency. *J. Allergy Clin. Immunol.* 2004. **114**: 415–421.

103 **Thickett, K. M., Kumararatne, D. S., Banerjee, A. K., Dudley, R. and Stableforth, D. E.**, Common variable immune deficiency: respiratory manifestations, pulmonary function and high-resolution CT scan findings. *QJM* 2002. **95**: 655–662.

104 **Polverino, E., Goeminne, P. C., McDonnell, M. J., Aliberti, S., Marshall, S. E., Loebinger, M. R. et al.**, European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur. Respir. J.* 2017. **50**: 1700629.

105 **Loebinger, M. R., Wells, A. U., Hansell, D. M., Chinyanganya, N., Devaraj, A., Meister, M. et al.**, Mortality in bronchiectasis: a long-term study assessing the factors influencing survival. *Eur. Respir. J.* 2009. **34**: 843–849.

106 **Wong, C., Jayaram, L., Karalus, N., Eaton, T., Tong, C., Hockey, H. et al.**, Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. *Lancet* 2012. **380**: 660–667.

107 **Altenburg, J., de Graaff, C. S., Stienstra, Y., Sloos, J. H., van Haren, E. H. J., Koppers, R. J. H. et al.**, Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. *JAMA* 2013. **309**: 1251–1259.

108 **Serisier, D. J., Martin, M. L., McGuckin, M. A., Lourie, R., Chen, A. C., Brain, B. et al.**, Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. *JAMA* 2013. **309**: 1260–1267.

109 **Fan, L.-C., Lu, H.-W., Wei, P., Ji, X.-B., Liang, S. and Xu, J.-F.**, Effects of long-term use of macrolides in patients with non-cystic fibrosis bronchiectasis: a meta-analysis of randomized controlled trials. *BMC Infect. Dis.* 2015. **15**: 160-.

110 **Mannina, A., Chung, J. H., Swigris, J. J., Solomon, J. J., Huie, T. J., Yunt, Z. X. et al.**, Clinical predictors of a diagnosis of common variable immunodeficiency-related granulomatous-lymphocytic interstitial lung disease. *Ann. Am. Thorac. Soc.* 2016. **13**: 1042–1049.

111 **Hurst, J. R., Verma, N., Lowe, D., Baxendale, H. E., Jolles, S., Kelleher, P. et al.**, British Lung Foundation/United Kingdom Primary Immunodeficiency Network Consensus Statement on the Definition, Diagnosis, and Management of Granulomatous-Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency Disorders. *J. Allergy Clin. Immunol. Pract.* 2017. **5**: 938–945.

112 **Milito, C., Pulvirenti, F., Serra, G., Valente, M., Pesce, A. M., Granata, G. et al.**, Lung magnetic resonance imaging with diffusion weighted imaging provides regional structural as well as functional information without radiation exposure in primary antibody deficiencies. *J. Clin. Immunol.* 2015. **35**: 491–500.

113 **Steele, C. L., Doré, M., Ammann, S., Loughrey, M., Montero, A., Burns, S. O. et al.**, X-linked inhibitor of apoptosis complicated by granulomatous lymphocytic interstitial lung disease (GLILD) and granulomatous hepatitis. *J. Clin. Immunol.* 2016. **36**: 733–738.

114 **Chase, N. M., Verbsky, J. W., Hintermeyer, M. K., Waukau, J. K., Tomita-Mitchell, A., Casper, J. T. et al.**, Use of combination chemotherapy for treatment of granulomatous and lymphocytic interstitial lung disease (GLILD) in patients with common variable immunodeficiency (CVID). *J. Clin. Immunol.* 2013. **33**: 30–39.

115 **Pathria, M., Urbine, D., Zumberg, M. S. and Guarderas, J.**, Management of granulomatous lymphocytic interstitial lung disease in a patient with common variable immune deficiency. *BMJ Case Rep.* 2016. **2016**.

116 **Moctezuma, S. I., Panizo, C. M. and Landecho, M. F.**, Common variable immunodeficiency-associated granulomatous and lymphocytic interstitial lung disease successfully treated with a combination regimen of rituximab and azathioprine. *Med. Clin. (Barc.)* 2017. **149**: 312-313.

117 **Jolles, S., Carne, E., Brouns, M., El-Shanawany, T., Williams, P., Marshall, C. et al.**, FDG PET-CT imaging of therapeutic response in granulomatous lymphocytic interstitial lung disease (GLILD) in common variable immunodeficiency (CVID). *Clin. Exp. Immunol.* 2017. **187**: 138–145.

118 **Boursiquot, J.-N., Gérard, L., Malphettes, M., Fieschi, C., Galicier, L., Boutboul, D. et al.**, Granulomatous disease in CVID: retrospective analysis of clinical characteristics and treatment efficacy in a cohort of 59 patients. *J. Clin. Immunol.* 2013. **33**: 84–95.

119 **Maglione, P. J., Overbey, J. R. and Cunningham-Rundles, C.**, Progression of common variable immunodeficiency interstitial lung disease accompanies distinct pulmonary and laboratory findings. *J. Allergy Clin. Immunol. Pract.* 2015. **3**: 941–950.

120 **Cunningham-Rundles, C., Siegal, F. P., Cunningham-Rundles, S. and Lieberman, P.**, Incidence of cancer in 98 patients with common varied immunodeficiency. *J. Clin. Immunol.* 1987. **7**: 294–299.

121 **Mellemkjaer, L., Hammarstrom, L., Andersen, V., Yuen, J., Heilmann, C., Barington, T. et al.**, Cancer risk among patients with IgA deficiency or common variable immunodeficiency and their relatives: a combined Danish and Swedish study. *Clin. Exp. Immunol.* 2002. **130**: 495–500.

122 **Vajdic, C. M., Mao, L., van Leeuwen, M. T., Kirkpatrick, P., Grulich, A. E. and Riminton, S.**, Are antibody deficiency disorders associated with a narrower range of cancers than other forms of immunodeficiency? *Blood* 2010. **116**: 1228–1234.

123 **Pulvirenti, F., Pecoraro, A., Cinetto, F., Milito, C., Valente, M., Santangeli, E. et al.**, Gastric cancer is the leading cause of death in italian adult patients with common variable immunodeficiency. *Front. Immunol.* 2018. **9**: 2546.

124 **Pikkarainen, S., Martelius, T., Ristimaki, A., Siitonen, S., Seppanen, M. R. J. and Farkkila, M.**, A High Prevalence of Gastrointestinal Manifestations in Common Variable Immunodeficiency. *Am. J. Gastroenterol.* 2019. **114**: 648–655.

125 **Dhalla, F., da Silva, S. P., Lucas, M., Travis, S. and Chapel, H.**, Review of gastric cancer risk factors in patients with common variable immunodeficiency disorders, resulting in a proposal for a surveillance programme. *Clin. Exp. Immunol.* 2011. **165**: 1–7.

126 **Lucas, C. L., Kuehn, H. S., Zhao, F., Niemela, J. E., Deenick, E. K., Palendira, U. et al.**, Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110delta result in T cell senescence and human immunodeficiency. *Nat. Immunol.* 2014. **15**: 88–97.

127 **Angulo, I., Vadas, O., Garcon, F., Banham-Hall, E., Plagnol, V., Leahy, T. R. et al.**, Phosphoinositide 3-kinase delta gene mutation predisposes to respiratory infection and airway damage. *Science* 2013. **342**: 866–871.

128 **Deau, M. C., Heurtier, L., Frange, P., Suarez, F., Bole-Feysot, C., Nitschke, P. et al.**, A human immunodeficiency caused by mutations in the PIK3R1 gene. *J. Clin. Invest.* 2014. **124**: 3923–3928.

129 **Maccari, M. E., Abolhassani, H., Aghamohammadi, A., Aiuti, A., Aleinikova, O., Bangs, C. et al.**, Disease evolution and response to rapamycin in activated phosphoinositide 3-kinase delta syndrome: the european society for immunodeficiencies-activated phosphoinositide 3-kinase delta syndrome registry. *Front. Immunol.* 2018. **9**: 543.

130 **Rao, V. K., Webster, S., Dalm, V., Šedivá, A., van Hagen, P. M., Holland, S. et al.**, Effective "activated PI3Kδ syndrome"-targeted therapy with the PI3Kδ inhibitor leniolisib. *Blood* 2017. **130**: 2307–2316.

131 **Schubert, D., Bode, C., Kenefeck, R., Hou, T. Z., Wing, J. B., Kennedy, A. et al.**, Autosomal dominant immune dysregulation syndrome in humans with CTLA4 mutations. *Nat. Med.* 2014. **20**: 1410–1416.

132 **Schwab, C., Gabrysch, A., Olbrich, P., Patino, V., Warnatz, K., Wolff, D. et al.**, Phenotype, penetrance, and treatment of 133 cytotoxic T-lymphocyte antigen 4-insufficient subjects. *J. Allergy Clin. Immunol.* 2018. **142**: 1932–1946.

133 **Lopez-Herrera, G., Tampella, G., Pan-Hammarstrom, Q., Herholz, P., Trujillo-Vargas, C. M., Phadwal, K. et al.**, Deleterious mutations in LRBA are associated with a syndrome of immune deficiency and autoimmunity. *Am. J. Hum. Genet.* 2012. **90**: 986–1001.

134 **Tesch, V. K., Abolhassani, H., Shadur, B., Zobel, J., Mareika, Y., Sharapova, S. et al.**, Long-term outcome of LRBA deficiency in 76 patients after various treatment modalities as evaluated by the immune deficiency and dysregulation activity (IDDA) score. *J. Allergy Clin. Immunol.* 2019.

135 **Milito, C., Pulvirenti, F., Cinetto, F., Lougaris, V., Soresina, A., Pecoraro, A. et al.**, Double-blind, placebo-controlled, randomized trial on low-dose azithromycin prophylaxis in patients with primary antibody deficiencies. *J. Allergy Clin. Immunol.* 2019. **144**: 584–593.e7.

136 **Lee, A. L., Hill, C. J., Cecins, N., Jenkins, S., McDonald, C. F., Burge, A. T. et al.**, The short and long term effects of exercise training in non-cystic fibrosis bronchiectasis–a randomised controlled trial. *Respir. Res.* 2014. **15**: 44.

137 **Zanini, A., Aiello, M., Adamo, D., Cherubino, F., Zampogna, E., Sotgiu, G. et al.**, Effects of pulmonary rehabilitation in patients with non-cystic fibrosis bronchiectasis: a retrospective analysis of clinical and functional predictors of Efficacy. *Respiration* 2015. **89**: 525–533.

138 **Lee, A. L., Hill, C. J., McDonald, C. F. and Holland, A. E.**, Pulmonary rehabilitation in individuals with non-cystic fibrosis bronchiectasis: a systematic review. *Arch. Phys. Med. Rehabil.* 2017. **98**: 774–782.e1.

139 **Pasteur, M. C., Bilton, D. and Hill, A. T.**, British Thoracic Society Bronchiectasis non CFGG. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010. **65**(Suppl 1): i1–i58.

140 **Jones, G. L., Vogt, K. S., Chambers, D., Clowes, M. and Shrimpton, A.**, What Is the Burden of Immunoglobulin Replacement Therapy in Adult Patients With Primary Immunodeficiencies? A Systematic Review. *Front. Immunol.* 2018. **9**: 1308.

141 **Pasquet, M., Pellier, I., Aladjidi, N., Auvrignon, A., Cherin, P., Clerson, P. 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**: 1171–1180.

Abbreviations: **AIHA**: autoimmune hemolytic anemia · **APDS**: activated PI3KCD syndrome · **BALF**: bronchoalveolar lavage fluid · **CF**: cystic fibrosis · **CID**: combined immunodeficiency · **CT**: computer tomography · **CTLA4**: cytotoxic T-lymphocyte-associated protein 4 (CD152) · **CVID**: common variable immunodeficiency disorder · **DLCO**: diffusing capacity of the lungs for carbon monoxide · **EGD**: esophago-gastroduodenoscopy · **EMA**: European Medicines Agency · **ERS**: European Respiratory Society · **ESID**: European Society for Immunodeficiencies · **FDA**: Food and Drug Administration (US) · **fSCIg**: facilitated SCIg · **GLILD**: granulomatous lymphocytic interstitial lung disease · **GMP**: good manufacturing practice · **HCV, hepatitis C virus; HIgM**: hyper-IgM Syndrome · **HIV**: human immunodeficiency virus · **HP**: Helicobacter pylori · **ITP**: immune thrombocytopenia · **IMIg**: intramuscular immunoglobulines · **IVIg**: intravenous immunoglobulines · **IUIS**: International Union of Immunological Societies · **LRBA**: LPS-responsive beige-like anchor protein · **MMF**: mycophenolate mofetil · **PID**: primary immunodeficiency · **RCT**: randomized controlled trial · **SAD**: selective antibody deficiency · **SCID**: severe combined immunodeficiency · **SCIg**: subcutaneous immunoglobuline · **SIGN**: Scottish Intercollegiate Guidelines Network · **TCR**: T cell receptor · **THI**: transitional hypogammaglobulinemia of infancy · **TMP/SMX**: trimethoprim/sulfamethoxazole · **uAD**: unclassified antibody deficiency · **XLA**: X-linked agammaglobulinemia

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