

REVIEW ARTICLE

Modern management of primary B-cell immunodeficiencies

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Abstract

B-cell defects constitute the majority of primary immunodeficiencies. Although a heterogeneous group of diseases, all are characterized by the reduction in or absence of immunoglobulins and/or specific antimicrobial antibodies. Substitution of immunoglobulin G (IgG) is therefore the mainstay of treatment. While from the late 1970s, the intravenous route of administration was the most common, in the past decades, subcutaneous immunoglobulin replacement therapy has become more popular among patients and physicians. Independently of the optimal route of administration, dosage and IgG trough level remain subjects of debate. Higher IgG trough levels seem to improve the protection against recurrent infections and thus better prevent complications such as bronchiectasis. Some patients, however, achieve protection with IgG trough levels on the lower IgG limit of healthy persons. Therefore, an individual protective IgG trough level needs to be defined for each patient. Use of additional prophylactic antibiotics and immunosuppressive drugs differs amongst specialized immunodeficiency centres and clearly requires future investigation in multi-centre trials. Haematopoietic stem cell transplantation (HSCT) is to date indicated as curative treatment in certain patients with B-cell defects associated with cell deficiencies, for example in two class-switch recombination defects and in selected severe forms of common variable immunodeficiency.

B-cell defects are a heterogeneous group of disorders with variable reduction in B-cell numbers and function, sharing the reduction in or absence of serum immunoglobulins (Ig) and/or specific antimicrobial antibodies. Antibody deficiency is frequent among primary immunodeficiency diseases (PID), accounting for more than half of the known PIDs (7482 of 13,444 patients; i.e., 55.65%), according to the PID registry of the European Society for Immunodeficiencies (May 2011, <http://www.esid.org>, Fig. 1). Affected patients present first in early childhood up to young adulthood, mainly with increased susceptibility to bacterial infections (1). Most infections are caused by encapsulated bacteria, particularly *Streptococcus pneumoniae* and *Haemophilus influenzae* (2). Both recurrent or chronic bronchitis and pneumonia, resulting in chronic lung disease such as bronchiectasis and interstitial lung disease following inflammatory and fibrotic infiltration of the respiratory

interstitium, are the most frequent manifestations. Small children may additionally suffer from recurrent otitis media, and adults from chronic sinusitis (3). Also common are gastrointestinal infections with *Giardia lamblia* and *Cryptosporidium* spp. (the latter mainly in patients with certain class-switch recombination defects), or CNS infection with enteroviruses. In contrast to T-cell defects, most B-cell defects are associated with an otherwise normal response to viral infection.

Numerical or functional B-cell defects can be divided into three major categories: (i) defects in early B-cell development (agammaglobulinaemias), (ii) class-switch recombination defects (hyper-IgM syndromes) and (iii) common variable immunodeficiency (CVID) (2). Residual amount of immunoglobulin production as well as B-cell function depend on the stage at which B-cell development is blocked (Fig. 2). In this review, we will not discuss antibody deficiencies such as selective IgA

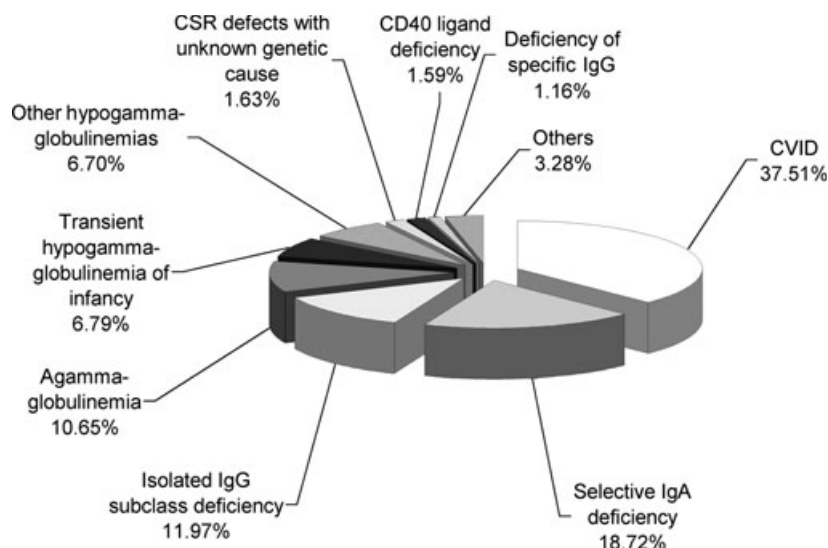
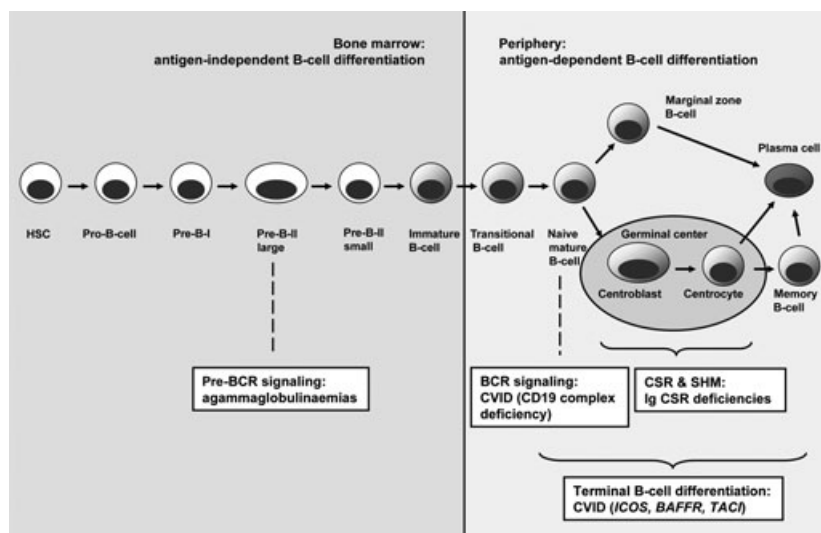


Figure 1 Distribution of antibody deficiencies in Europe. Based on the registry of the European Society for Immunodeficiencies (ESID), May 2011 (<http://www.esid.org>) (CVID, common variable immunodeficiency; IgA, immunoglobulin A; IgG, immunoglobulin G; CSR defects, Class-switch recombination defects; CD40, Cluster of differentiation 40).

Figure 2 Complete or incomplete blocks in B-cell development in patients with agammaglobulinemia, CD19-complex deficiency, Ig class-switch recombination (CSR) deficiencies and common variable immunodeficiency (CVID). HSC, haematopoietic stem cell; BCR, B-cell antigen receptor; SHM, somatic hypermutation; ICOS, inducible costimulator; BAFFR, B-cell activating factor receptor; TACI, transmembrane activator and calcium-modulating cyclophilin ligand interactor.



deficiency, isolated IgG subclass deficiency, specific antibody deficiency or transient hypogammaglobulinaemia of infancy, which are all characterized by normal B-cell counts.

Defects in early B-cell development (agammaglobulinaemias)

Due to a block in early B-cell development, affected patients have markedly reduced or absent B cells, resulting in absent IgG, IgA and IgM (agammaglobulinaemia). Onset of bacterial infections is usually in the first 5 yr of life. Infants typically present first bacterial infections once maternal IgG have disappeared, that is between 3 and 18 months of age (2, 4). There may be a history of common respiratory viral infections, but as soon as T-cell immunity has developed, severe viral infections are no longer a problem (2). Exceptions are infections with enteroviruses, such as *Polio*, *Coxsackie* and

Echo viruses, which may cause serious disease in certain but not in all patients (5–7). In addition to typical infections with *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Giardia lamblia*, which may occur in all patients with antibody deficiency, there is a higher incidence of infections with *Mycoplasma* spp., *Ureaplasma* spp. (8, 9) and *Helicobacter* spp. (10) in patients with agammaglobulinaemia.

The most common genetic defect (85%) is a mutation in the BTK gene encoding *Bruton's tyrosine kinase* (*Btk*), causing X-linked agammaglobulinaemia (XLA; see Table 1). All of the known mutations cause leaky defects in B-cell development, leading to differences in the amount of residual circulating B-cells and immunoglobulins (10, 11): Mild mutations with residual Btk expression result in higher amount of B-cells and serum IgM, accounting for first disease manifestations and diagnosis at a later age (12). About half of the remaining 15% of patients have different

Table 1 Classification of primary B-cell defects. Abbreviated IUIS-classification of PIDs 2011 ('primary immunodeficiency diseases: an update on the Classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency' Al-Herz et al. *Frontiers in Primary Immunodeficiencies*. doi: 10.3389/fimmu.2011.00054.)

Disease (cellular phenotype)	Associated features	Inheritance
Agammaglobulinaemias (severe reduction in all serum immunoglobulin isotypes with profoundly decreased or absent B cells)		
BTK deficiency	Severe bacterial infections; normal numbers of pro-B cells	XL
μ heavy chain deficiency	Severe bacterial infections; normal numbers of pro-B cells	AR
$\lambda 5$ deficiency*	Severe bacterial infections; normal numbers of pro-B cells	AR
Ig α deficiency*	Severe bacterial infections; normal numbers of pro-B cells	AR
Ig β deficiency*	Severe bacterial infections; normal numbers of pro-B cells	AR
BLNK deficiency*	Severe bacterial infections; normal numbers of pro-B cells	AR
Class switch recombination defects (severe reduction in serum IgG and IgA with normal/elevated IgM and normal numbers of B cells)		
CD40L deficiency	Opportunistic infections, neutropenia, autoimmune disease	XL
CD40 deficiency*	Opportunistic infections, neutropenia, autoimmune disease	AR
AID deficiency	Enlarged lymph nodes and germinal centers	AR
UNG deficiency	Enlarged lymph nodes and germinal centers	AR
CVID (Severe reduction in at least two serum immunoglobulin isotypes with normal or low number of B cells)		
Common variable immunodeficiency disorders	Clinical phenotypes vary: most have recurrent infections, some have lymphadenopathy, splenomegaly, autoimmune cytopenias and/or granulomatous disease	Variable
ICOS deficiency*		AR
CD19 deficiency*	May have glomerulonephritis	AR
CD81 deficiency*	May have glomerulonephritis	AR
CD20 deficiency*		AR
TACI deficiency	Variable clinical expression	AD or AR or complex
BAFF receptor deficiency*	Variable clinical expression	AR

XL, X-linked inheritance; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; BTK, Bruton tyrosine kinase; BLNK, B cell linker protein; AID, activation-induced cytidine deaminase; UNG, uracil-DNA glycosylase; ICOS, inducible costimulator.

*Ten or fewer unrelated cases reported in the literature.

forms of autosomal-recessive agammaglobulinaemia (see Table 1). All patients with autosomal-recessive agammaglobulinaemia show similar clinical findings as XLA patients, but have more severe infections within the first year of life because of complete absence of CD19 + B cells (13).

All patients with agammaglobulinaemia require IgG replacement. Additional antibiotic prophylaxis is utilized by

some centres (in 80–90% of agammaglobulinaemia patients in the USA (14) and in 14% in Europe (<http://www.esid.org>)). In the absence of curative therapy, IgG substitution has to be lifelong. Preliminary preclinical results on the development of gene therapy, aiming to reconstitute Btk expression in B-cells without overexpression of the kinase, might offer a promising curative approach in the more distant future (15).

Class-switch recombination defects (Hyper-IgM syndromes)

The common feature of hyper-IgM syndromes (HIGM) is a defect in class-switch recombination (16) resulting in normal or elevated IgM, low IgG, IgA and IgE, which leads to recurrent bacterial respiratory or gastrointestinal infections mainly by encapsulated bacteria (*Streptococcus pneumoniae* and *Haemophilus influenzae*), or opportunistic infections (CMV, *Pneumocystis jirovecii* and *Cryptosporidium* spp.) (see Table 1).

Lifelong IgG replacement is the mainstay of treatment in all HIGM patients. Patients presenting severe chronic neutropenia should be treated with recombinant granulocyte colony-stimulating factor (G-CSF). In CD40L and CD40 deficiencies, patients must drink only bottled water for prophylaxis against infections with *Cryptosporidium* spp. (tap water is prohibited). All patients should receive Trimethoprim/sulfamethoxazole as prophylaxis against pneumocystis (75–80% of HIGM patients in USA (14) and 31% in Europe (<http://www.esid.org>) received this prophylaxis), and some centres use additional antibiotic prophylaxis to prevent cryptosporidium infection, for example paromomycin. Because of the risk of sclerosing cholangitis (19.6% in Europe (17), 6% in North America (18), respectively) in CD40L and CD40 deficiency, eventually leading to biliary cirrhosis, a more aggressive therapeutic approach is proposed to these patients, including haematopoietic stem cell transplantation (HSCT) (19).

Common variable immunodeficiency

Common variable immunodeficiency accounts for the majority of antibody deficiencies and for ~30% of all PIDs. This heterogeneous group of disorders (20–22) should always be a diagnosis of exclusion. Diagnostic criteria are recurrent infections, reduction in IgG and at least one other immunoglobulin isotype, as well as failure to mount a protective specific antibody response after challenge with vaccines or natural infection (23, 24). Symptoms may start at any age, a few patients presenting in mid-childhood but most in early to mid-adulthood (21). About 10–20% of patients have a family history of immunodeficiency and/or autoimmunity. Secondary hypogammaglobulinaemia by protein loss should be excluded in all patients before diagnosis of CVID. In children <10 yr of age constitutive delay in immunoglobulin production, as well as single gene defects of the immune system (e.g. hypomorphic SCID variants) should be excluded. In adults malignancies such as chronic lymphoid leukaemia, B-cell lymphoma or non-Hodgkin's lymphoma are important differential diagnoses. However, lymphoid malignancy can also develop on the basis of CVID. Underlying genetic defects have been identified only in a minority of CVID patients (see Table 1).

All patients with CVID suffer from infections, predominantly sinopulmonary infections with *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Mycoplasma* spp., as well

as gastrointestinal infections with *Giardia lamblia* (20, 25). There have been several attempts to subdivide CVID patients into different groups according to clinical and immunological phenotypes (26, 27): Depending on non-infectious complications, five distinct clinical phenotypes have been described (27) – no complications, autoimmunity, enteropathy, polyclonal lymphocytic infiltration and lymphoid malignancy.

Bronchiectasis caused by recurrent pneumonias and non-infectious complications are challenges for attending immunologists and need a more intense treatment besides IgG replacement, including prophylactic antibiotics, immunosuppressive agents or even HSCT (28).

Current treatment options of primary B-cell defects

Immunoglobulin (IgG) replacement

IgG replacement is the mainstay of treatment of antibody deficiencies (29). The first IgG replacement was performed in 1952 by subcutaneous route in a patient with agammaglobulinaemia (30). In the following decades, intramuscular injection became the preferred route of administration, replaced in the late 1970s by intravenous infusion. In 1980, the advent of a portable syringe for subcutaneous therapy was reported (31). A decade later subcutaneous IgG administration by an infusion pump for home therapy has been widely established (32).

To date, 4462 of 10,039 patients with PID listed in the ESID registry (<http://www.esid.org>) receive IgG replacement (74% intravenous, IVIg; 26% subcutaneous, SCIG; and <0.5% intramuscular, IMIG). The frequency of subcutaneous IgG replacement differs widely amongst individual countries in Europe. In Sweden, which started first to administer IgG via the SC route, more than 80% of all patients with antibody deficiencies receive SCIG (33). The current indications for IgG replacement therapy for children >6 yr and adults are (34):

IgG < 2 g/l: all patients

IgG 2–5 g/l: patients with antibody deficiency and frequent bacterial infections

IgG > 5 g/l: patients with antibody deficiency and severe bacterial infections

For children <6 yr, the indication for IgG replacement therapy depends on their IgG levels, clinical symptoms and the kind of B-cell defect. The overall aim should be to protect them from future organ damage. For example, infants or children diagnosed with XLA should immediately be started on IgG replacement therapy.

Intravenous IgG replacement (IVIg)

Indications

Intravenous IgG replacement has been thoroughly reviewed, proving its efficacy in antibody deficiencies (35, 36). Intravenous IgG replacement can improve frequency and severity of recurrent bacterial infections, pneumonia and lung damage in

patients with CVID (37, 38), agammaglobulinaemia (39), or class-switch recombination defects (18, 40).

Safety

Following adverse reactions can occur: Milder reactions are more frequent and include headache, nausea, malaise, myalgia, arthralgia, abdominal cramps, chills, low-grade fever, rash and flushing. These phlogistic reactions can often be prevented by slower infusion rate. Caution is mandatory, however, as some of these symptoms can herald more severe adverse reactions, such as anaphylaxis (41), stroke (42), myocardial infarction (43), deep venous thrombosis (44) or pulmonary embolization (45), aseptic meningitis (46) and in insufficiently hydrated patients or in those using sucrose-stabilized products acute renal failure (47). The prevalence of anaphylaxis may be increased in patients with the presence of high-titre IgG anti-IgA antibodies (48), but the role of anti-IgA antibodies in causing anaphylaxis in IgA-deficient patients receiving IgG replacement therapy remains controversial (49). For these patients and for patients with other serious adverse reactions, a change of administration route is recommended, as in SCIG only local side effects have been reported so far.

Subcutaneous IgG replacement (SCIG)

Indications

The rapid administration of SCIG was first described in Sweden in 1991 (32); since then an increasing number of patients from all over Europe and the USA (50) changed their IgG replacement from IVIg to SCIG. Current indications for SCIG are severe side effects on IVIg, difficult venous access, long distance from hospital, or a full diary. The convenience of home SCIG therapy has been demonstrated in adult patients and in children (50, 51). The efficacy of SCIG is comparable to IVIg (52).

Cost

While a theoretical model in an economic evaluation from a French PID study group showed little difference between home-based SCIG and hospital-based IVIg costs, the authors concluded from field data that SCIG appeared to be 25% less expensive if one accounts that lower doses were necessary to achieve the same IgG trough levels (53). In a Swedish analysis, savings of \$10'000 per patient per year have been observed on change from IVIg to SCIG (54); similar results have been reported from other countries (55, 56).

Advantages of SCIG over IVIg

An advantage of SCIG vs. IVIg is the more physiological, constantly high IgG level, when smaller doses are given more frequently (33, 57, 58) (see Fig. 3). The higher peak of total serum IgG by IVIg vs. SCIG has been hypothesized to result in increased catabolism of IgG and subsequent rapid decline of IgG serum levels after infusion (59). In CVID patients with enteropathy, a high peak of IgG serum level may cause higher protein loss (personal communication H. Chapel, University of Oxford, United Kingdom). In some CVID patients with enteropathy, improvement of IgG trough levels resulted

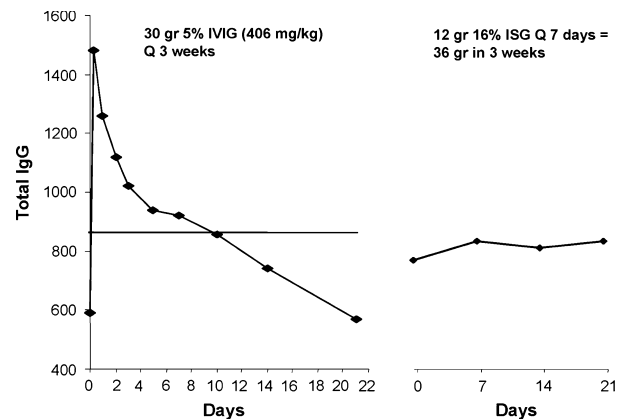


Figure 3 Pharmacokinetics of Iv vs. Sc administration of IgG. Serum IgG concentrations in a 34-year-old men with X-linked agammaglobulinaemia receiving a single IV infusion of 30 g (406 mg/kg) of 5% IVIg Left: Solid horizontal line shows average of daily concentrations over a 21-day period, calculated by interpolation from the graph shown, which equals 850.6 ± 43 mg/dl (mean $\pm$ s.e.m.). Right: Serum IgG concentrations in the same patient receiving 12 g of 16% IgG subcutaneously every 7 days. Average equals 816 ± 16 mg/dl. With permission: Berger M. (59).

after change from IVIg to SCIG; an ongoing multi-centre study analyses this issue further (K. Warnatz, personal communication, University of Freiburg, Germany).

Safety

Safety with regard to serious side effects is superior in all SCIG preparations compared to IVIg (60–62). Only a few moderate and no severe adverse reactions have been reported (32, 52, 54, 55, 57, 60, 63, 64). Mild local side effects are infusion-site reactions involving swelling, redness and itching, reported in up to 91% of the patients at initial treatment; incidence of these side effects, however, decreases over time to <20% (60).

Recent advances

More concentrated SCIG products [e.g. 20% stabilized by L-proline (65)] have been developed, which are stable at room-temperature; other advances are addition of hyaluronidase to increase infusion-volume per injection-site by dissolution of the subcutaneous tissue (66, 67), or the rapid-push technique with an infusion time of only 5–20 minutes per infusion, because of smaller volumes applied, however, necessitating a higher infusion frequency (daily or every second day) (68, 69).

Dosing and IgG trough levels

Dosing/administration

A total IgG dose of at least 400 mg IgG/kg bodyweight/month is recommended for patients with B-cell defects (70). SCIG is usually administered at 100 mg IgG/kg/wk (33) or at 200 mg IgG/kg/2 wk (59, 71). For a 16% SCIG preparation,

the necessary infusion volume can be calculated as follows: bodyweight (kg) $\times$ 0.6 = x ml/wk. Different groups have demonstrated that mean trough levels increased after changing from IVIg to SCIG using 100% of the previous monthly IVIg dose (53, 57, 69). In an efficacy and safety multi-centre study, North American patients received weekly subcutaneous doses of 126% of the previous weekly equivalent IVIg doses because the FDA required an IgG systemic exposure similar to the previous IVIg dose. European and Brazilian patients received a weekly SCIG dose that equalled their previous weekly equivalent IVIg dose, also leading to higher median serum IgG trough levels as compared with previous intravenous therapy (72).

To switch from IVIg to SCIG, a starting dose of 100 mg SCIG/kg/wk 2 wk after the last IVIg dose administered is recommended, as at this time point IgG trough levels should still be >700 mg/dl (see Fig. 3), which should offer sufficient anti-infectious protection over the following 2 wk. Provided initial substitution is to be started with SCIG, and the IgG serum level of the patient is very low, rapid IgG increase can only be achieved by administering 100 mg SCIG/kg/day over 5–10 consecutive days (58, 73).

The first dose of IVIg and/or SCIG should always be given in a safe setting, such as a day care clinic of a hospital equipped with an ICU. Afterwards the patient and/or his parents can be trained by a nurse to carry out SCIG infusions at home. On average, 3–5 training visits are necessary. The majority of patients improve under home SCIG with regard to health-related quality of life and treatment satisfaction. However, elderly people (50) or adolescents (74) should be trained more intensively to achieve the same results as other patient groups with regard to safety, efficacy and compliance.

IgG trough levels

Mean IgG trough levels have increased in most studies over the past three decades (75). Even with an IgG trough level of >400 mg/dl, however, some patients suffer recurrent infections of the upper and lower respiratory tract, including severe bacterial infections that require intravenous antibiotic therapy. Discussion about the ideal protective IgG trough level is therefore ongoing.

In the UK, a large single-centre study including 90 CVID patients over a study period of 22 yr (with a total of 741 patient-years) investigated infection outcome with regard to IgG replacement (76): All 90 patients received individualized IgG substitutions, adapted to the occurrence of infection under IVIg, doses ranging from 200 to 1200 mg IgG/kg/month, resulting in IgG trough levels of 500–1700 mg/dl. Necessary trough IgG levels to prevent infections were higher in CVID patients with complications such as bronchiectasis, as were the trough levels of a smaller comparison group of XLA patients. This study concludes that substitution therapy should be oriented at the clinical outcome and that IgG trough levels to prevent bacterial infections are individual.

An Italian 5-year multi-centre prospective study on 201 CVID and 101 XLA patients (with altogether 1.365 patient years) (77) showed a higher risk for pneumonia in patients with IgG trough levels <400 mg/dl, but no correlation with

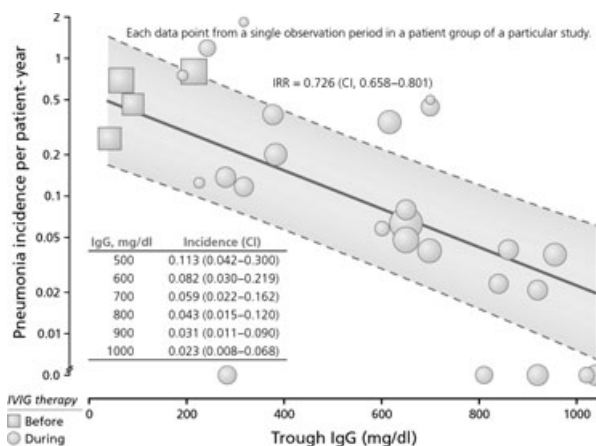


Figure 4 Effect of trough IgG level (mg/dl) on pneumonia incidence per patient-year. Each data point corresponds to a single observation period in a patient group of a particular study. Data points labelled by preference citation and scaled in proportion to log-transformed patient-years of observation. Observations before start of IVIg replacement shown as squares and after start as circles. Solid line shows multilevel model predictions, and dashed lines indicate CI of metaregression. CI, 95% confidence interval; IRR, incidence rate ratio per 100 mg/dl increase in trough IgG level. With permission: Orange JS et al. (78).

pneumonia incidence for patients with higher IgG trough levels. Risk factors for pneumonia in CVID patients in this study were bronchiectasis and IgA <7 mg/dl, or IgG <400 mg/dl and IgA <7 mg/dl at diagnosis. The only risk factor for pneumonia in XLA patients was bronchiectasis. Therefore, higher IgG trough levels are mandatory in patients with bronchiectasis and in patients with XLA.

A recent meta-analysis of 17 studies, comprising 676 patients with antibody deficiencies (2.127 patient-years), investigated the impact of IgG trough levels on pneumonia incidence (78) and demonstrated lower incidence of pneumonia with increasing IgG trough levels (see Fig. 4): pneumonia incidence declined by 27% with each 100 mg/dl increment in trough IgG level; pneumonia incidence under a maintenance IgG trough level of 500 mg/dl was 5-fold that with a level of 1000 mg/dl.

In conclusion, there is convincing evidence that *IgG trough levels should approach or exceed the lower limit of IgG concentration for healthy adults*, that is 700 mg/dl, as already suggested in evidence-based practice guidelines from Canada (70). An *individualized IgG trough* or 'biological IgG' level should then be defined for each patient with the aim of *prevention of bacterial infections and infectious complications* (see Fig. 5), which might in some cases be as high as >1000 mg/dl. The necessary trough levels in children are still a matter of debate.

Treatment of bronchiectasis

The best prevention of recurrent pneumonia and bronchiectasis is an early diagnosis of B-cell defects and early start of

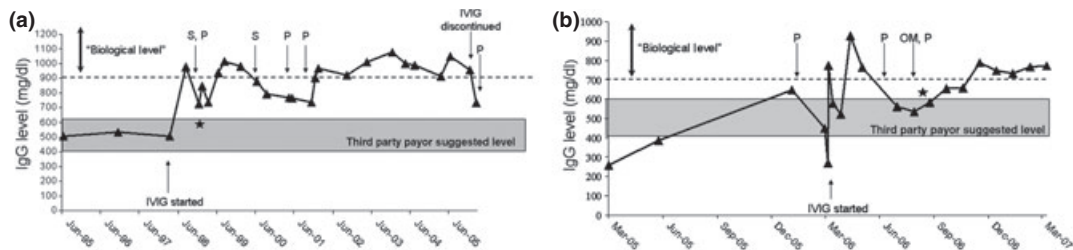


Figure 5 Determination of biological IgG trough levels. IgG trough levels in patients A and B before, during and after initiating IVIg therapy and associated infection history. *Time at which the practice of the authors assumed the care of this patient. S, acute sinusitis; P, pneumonia; OM, otitis media. With permission, adapted from: Bonagura VR et al. (116).

adequate IgG replacement therapy (37, 79). Although early IVIg and IgG trough levels of >500 mg/dl decrease the incidence of bacterial infections and bronchiectasis, they cannot fully prevent this complication in patients with XLA (39, 79, 80) and CVID (80).

Patients with existing bronchiectasis may need up to twice the IgG dose than patients without bronchiectasis to achieve the same trough levels (76, 81).

IgG trough levels >600 mg/dl improved HR-CT images and pulmonary lung function in all nine adult patients with CVID and bronchiectasis followed in a 2-year prospective study (38). IgG trough levels between 800 and 1100 mg/dl resulted in a slower decline of lung function tests in adults with primary B-cell defects (82). In a cohort of 18 children with primary B-cell defects and bronchiectasis, eight children showed a stable or improved HR-CT score but 10 deteriorated despite 2 yr of intensive IVIg treatment, antibiotic prophylaxis with amoxicillin and clavulanic acid or azithromycin, and chest-physiotherapy (83).

Antibiotic treatment

Antibiotic treatment of infections

The choice and dosage of antibiotics for specific infections are identical to those used in patients without PID, for example infections of the upper and lower respiratory tract should be treated first line with amoxicillin and clavulanic acid due to likely infection with *Haemophilus influenzae* or *Streptococcus pneumoniae*. If *Mycoplasma ssp.* are suspected, macrolides or, in children >12 yr, tetracyclines should be used. Antibiotic treatment must start early after vigorous search of the causative organism by bacterial culture or PCR. Diagnosis of infectious agents by the determination of specific antibodies is useless in patients with B-cell defects.

Antibiotic prophylaxis

IgG replacement is not sufficient to completely prevent recurrent infections of the upper and lower respiratory tract (84) or bronchiectasis (39) in all patients with B-cell defects. In patients with recurrent infections despite high IgG trough levels antibiotic prophylaxis has been used in addition to IVIg, (85). The most frequently used antibiotics for prophylaxis are amoxicillin and clavulanic acid or ciprofloxacin. Long-term prophylaxis with ciprofloxacin has been claimed

to offer enhanced protection from chronic pulmonary *Haemophilus influenzae* infection, as it is a bacterial DNA gyrase inhibitor with additional immunomodulatory properties (86).

There are no published data yet to compare the outcome of patients with B-cell defects under IgG replacement with or without prophylactic antibiotics. In view of the development of bronchiectasis despite IgG trough levels >500 mg/dl (39), some centres are regularly administering prophylactic antibiotics (M. E. Conley, personal communication, University of Tennessee, USA). Additional prophylactic antibiotics should always be administered around each dental or surgical procedure: Amoxicillin and gentamycin should be given IV 1 h before, 8 and 18 h after major surgery, or 3 days of oral broad-spectrum antibiotics can be used for less serious manipulation (e.g., dental procedures) (87).

Vaccinations

Patients with B-cell defects show variable responses to vaccinations (88–91). Killed vaccinations are safe in patients with B-cell defects and are able to induce some specific memory T cells in XLA patients (88), as well as a protective antibody responses in a small percentage of CVID patients with class-switched memory B cells $>0.4\%$ of peripheral blood mononuclear cells (89–91). Especially the pandemic influenza vaccination should be given to all patients with B-cell defects, as there is no protection in IgG preparations against the rapidly changing viral antigens. An influenza-specific $CD4^+$ Th1-cell response has recently been demonstrated in one patient with XLA and three patients with CVID after vaccination (92). In addition, as in all patients with PID, close contact persons should be vaccinated against seasonal and pandemic influenza to protect the patient indirectly. Full prevention of other vaccine preventable infections in the patient should be achieved by using IgG preparations from at least 10'000 donors from the same geographical region as the patient.

Treatment of immunologic complications

Especially patients with CVID often develop autoimmune, granulomatous or lymphoproliferative complications (27). Under IgG replacement, a lower incidence (93), but not complete prevention (93, 94) of *autoimmune cytopenias* has

been reported. Treatment of autoimmune cytopenias in CVID is based on corticosteroids (95). Rituximab, a chimeric monoclonal antibody against CD20, has also been reported to improve autoimmune thrombocytopenia (96–99) and autoimmune haemolytic anaemia (100) in CVID patients. To date, there are no treatment recommendations for *lymphoproliferative complications* involving splenomegaly, hepatomegaly and/or abdominal lymphadenopathy, or lymphoid interstitial pneumonitis. There is currently also no evidence of efficacy of splenectomy in the treatment of cytopenias in CVID (101). The indication for any immunosuppressive therapy in PID patients has to be considered very carefully, as opportunistic infections like *Pneumocystis jirovecii* pneumonia may result (20).

There are no conclusive data showing an influence of IgG replacement on *granulomatous complications* in CVID (20, 102). Corticosteroids are effective (21), but their long-term use is limited because of infectious risk. Steroid sparing agents, such as cyclosporine A, methotrexate, 6-mercaptopurine, azathioprine or mycophenolate mofetil, have been used successfully in anecdotal reports, but controlled or open trials are lacking (95). Alternative or additional immunosuppressive agents such as hydroxychloroquine have demonstrated a certain benefit (103). New treatment options like the monoclonal antibodies Infliximab directed against soluble and membrane-bound TNF- α (104, 105), and Etanercept, a TNF- α (106), can be effective in some cases, and cyclosporin A has been demonstrated to be effective in CVID patients with lymphoid interstitial pneumonitis (106) and Etanercept in CVID patients with inflammatory enteropathy (107). Patients with enteropathy may also benefit from treatment with enteric-coated oral budesonide or low-dose immunomodulators such as 6-mercaptopurine or azathioprine (95, 108).

In conclusion, the use of immunosuppressive therapy in patients with B-cell defects is severely limited by the lack of scientific studies with sufficiently large patient cohorts. An ongoing multi-centre study will help to improve the situation and elucidate the question of increased risk of opportunistic infections (oral communication H.H. Peter, Freiburg/Germany). Full resolution of autoimmune complications ultimately depends on complete immune reconstitution which is potentially only provided by HSCT (101).

Haematopoietic stem cell transplantation (HSCT)

The indication for HSCT should be evaluated in two groups of patients:

1 Patients with severe CVID presenting with malignancy or therapy-resistant inflammatory complications: Only four cases of HSCT for severe CVID have been documented so far (28): two patients suffered from malignancy (T-cell lymphoma and large granular lymphocyte syndrome, respectively) and two from intractable complications (deterioration of respiratory function with high-dose steroid dependence and massive splenomegaly with cytopenia). Two patients achieved cure of their malignancy and one reduction in steroid dependence. The fourth patient died on day 100 after

HSCT because of multi-organ failure following reactivated infections. Only one of the four patients was cured of CVID and could discontinue IgG replacement. These results underline that HSCT in CVID is experimental and should only be proposed for therapy-refractory life-threatening complications. Careful donor selection is vital, especially if sibling donors are available, in whom silent CVID has to be carefully excluded (e.g. slight reduction in serum Ig together with low memory B cells).

2 Patients with CD40L and CD40 deficiency (because of combined humoral and cellular immunodeficiency with life-long increased susceptibility for opportunistic infections) (19, 109): Even on conventional immunoglobulin substitution, cotrimoxazole prophylaxis and avoidance of cryptosporidium exposure long-term survival rate of patients with CD40L deficiency remains poor (17, 18). The main complications are opportunistic infections, for example with pneumocystis leading to severe pneumonia and with *Cryptosporidium* ssp. leading to sclerosing cholangitis and biliary cirrhosis. The largest reported HSCT series (19) included 38 patients with CD40L deficiency. A cure was achieved in 58%, the cure rate being better in patients without liver disease (72%). All 12 fatal cases (32%) were associated with infection, in six cases with severe cryptosporidial infection. While fully Human leucocyte antigen (HLA)-matched unrelated donors did as well as matched siblings (preferable because of identity of other minor HLA groups), mismatched unrelated donors correlated with poorer survival.

Early HSCT after myeloablative conditioning is therefore recommended in CD40L/CD40 deficiencies, if an HLA identical donor is available. If a fully matched donor cannot be found, watchful waiting and monitoring on supportive treatment is adopted with transplantation at the first sign of hepatic disease or lung damage, possibly using a reduced-intensity conditioning regimen (110).

Outlook

Newborn screening

The kappa-deleting recombination circles (KRECs) are co-products during B-cell formation. Their detection by PCR allows the estimation of the average number of B-cell divisions (111); they are possible targets for neonatal screening for defects of B-cell formation in Guthrie cards (112). While KREC concentration in CVID patients has been found to be lower than in controls (111), specificity and sensitivity of KREC screening in neonates still has to be further evaluated in CVID and other B-cell defects. This would enable an earlier diagnosis and earlier IgG substitution, providing better clinical outcome, especially improved prevention of chronic lung disease.

Gene therapy

For two B-cell defects, namely for CD40L deficiency (113) and X-linked agammaglobulinemia (15), gene therapies are

currently being developed. These are two diseases for which the gene of interest has to be tightly regulated. CD40 ligand is only expressed by activated CD4 T cells. The constitutive expression of CD40 ligand, for example in mice induces lymphoma (114). Kinases involved in cell activation are also potentially toxic, as shown for overexpression of Btk, leading to myeloproliferation (115). These important obstacles have to be overcome, before embark-

ing on clinical gene therapy studies in the more distant future.

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