

Immunodeficiency in adults a practical guide for the allergist

OLIVER HAUSMANN^{1,2}, KLAUS WARNATZ³

¹Allergological-Immunological Polyclinic, University Clinic for Rheumatology, Clinical Immunology and Allergology, Bern University Hospital, Switzerland; ²Löwenpraxis, Lucerne, Switzerland; ³Center for Chronic Immunodeficiency (CCI), Freiburg University Clinic, Germany

Abstract

Knowing the clinical warning signs of immunodeficiency (ID) in adulthood is crucial for early detection of the over 200 forms of primary ID known to date. Many of these congenital diseases with a genetic background already manifest in childhood. Antibody deficiency diseases represent an important exception, with common variable immunodeficiency (CVID) being the most common form of ID. The median age of onset of CVID is 24 years. Unfortunately, the delay in diagnosis is still in excess of 4 years. General practitioners as well as allergists play a particularly important role in early detection. ID patients who present primarily with signs of immune dysregulation pose an even greater diagnostic challenge. Thus, autoimmune cytopenia, inflammatory bowel diseases, or sarcoid-like granulomatous inflammation can be the first manifestation in up to 20 % of ID patients. Secondary forms of ID [e.g., due to long-term corticosteroid treatment, HIV-infection, leukemia, lymphoma, nephrotic syndrome, malabsorption syndrome] need to be differentiated from primary antibody deficiency.

Considering the overlap with allergic symptoms [ID accompanied by a susceptibility to eczema, elevated total IgE, blood eosinophilia], the present article discusses, the clinical warning signs of ID, the first diagnostic steps required and the option of further diagnostic work up at specialist centers for complex cases, as well as the treatment options for such cases.

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Abbreviations

ANA	Antinuclear antibodies
AWMF	German Association of the Scientific Medical Societies (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V)
CMV	Cytomegalovirus
CVID	Common variable immunodeficiency, variable immunodeficiency syndrome
EBV	Epstein-Barr viruses
ESID	European Society for Immunodeficiencies
G-CSF	Granulocyte colony-stimulating factor
HIES	Hyper-IgE syndrome
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
ID	Immunodeficiency
Ig	Immunoglobulin
IL	Interleukin
IUIS	International Union of Immunological Societies
OS	Omenn syndrome
PCR	Polymerase chain reaction
SCID	Severe combined immunodeficiency
SD	Standard deviation
Th	T-helper cells
WAS	Wiskott-Aldrich syndrome
WASP	WAS protein

Key words

immune defects – immunodeficiency – warning signs – early detection – therapy – immunoglobulin – autoimmunity

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IUIS classification and division into disease groups [2]	
1. Combined T- and B-cell immunodeficiency	Table 1
2. Combined immunodeficiencies with associated or syndromic features	
3. Predominantly antibody deficiencies	
4. Diseases of immune dysregulation	
5. Congenital defects in phagocyte number and/or function	
6. Defects in natural immunity (innate immunity)	
7. Autoinflammatory disorders	
8. Complement deficiencies	

IUIS, International Union of Immunological Societies.

Predisposition to infection with no underlying immunodeficiency	
Location	Cause
Skin	Barrier disorder in atopic eczema, burns, etc.
Respiratory tract	Smoking, dry mucosae, allergy Bronchiectasis, cystic fibrosis Impaired ventilation of the paranasal sinuses and middle ear, dysphagia, fistulae
Intestinal tract	Proton pump inhibitors (reduced gastric acid) Impaired intestinal flora under antibiotic therapy
Urinary tract	Reflux, stenosis, residual urine, sexual intercourse, dry mucosae between urinary tract and bowel
Foreign bodies	Catheter, prostheses

Table 2

Introduction

In an era where food supplements, vitamin preparations, and a wide range of complementary medical therapy forms are being promoted with the argument that they strengthen and stimulate the immune system – and given that the response to this promotion suggests that there are large numbers of people who apparently believe their immune systems to be weak or who feel unsure or generally fragile – it is essential for the experienced specialist physician with an interest in immunology to establish clarity in individual cases and respond to patients need for advice and reassurance with targeted and cost-effective diagnostics.

The present overview article highlights the clinically relevant warning signs of immunodeficiency (ID) and discusses which steps are helpful in its diagnosis and when these steps should be taken. The article deliberately restricts its scope to adult-onset forms of ID. An overview of the more than 200 primary immune defects now described in children and adults of largely genetic background can be found elsewhere [1, 2]. The IUIS (International Union of Immunological Societies) classification of primary immune defects [2] has provided

a current overview of this group of diseases (Tab. 1). Most congenital primary immune defects manifest in childhood. Antibody deficiency diseases are a notable exception here (group 3 according to the IUIS classification), in particular common variable immunodeficiency (CVID), which manifests on average at the age of 24 years [3, 4]. As the most common form of ID, CVID will be discussed in greater detail below. Overlap with allergic diseases is also discussed, as is the opportunity for further diagnostic work up of complex cases at specialist centers.

Clinical presentation of immunodeficiencies

The body’s immune defense begins at the anatomical barriers, i. e., the skin and mucosae. Even in immune competent individuals, most infections occur here. Concerns are raised when infections with typical pathogens such as pneumococci, staphylococci, or salmonellae follow a complicated and protracted course or when these anatomical barriers are repeatedly breached. Infections at unusual sites, as well as infections with essentially harmless pathogens that the immune system is normally able to cope with, so-called opportunistic pathogens such as mycobacteria, candida, or Pneumocystis jirovecii, should prompt concern. In such cases, pathogen detection alone, regardless of the clinical course, should suggest ID. In all of the above-mentioned cases, further investigations to establish the patient’s immune status should be initiated.

Taking a careful patient history of past infections is crucial to any assessment of immunocompetence.

Directed questions are used to record the type, localization, frequency, and severity of infections. In some cases, this step already allows ID to be distinguished from a secondary susceptibility to infections due to local barrier disorders of the skin and mucosae. Thus, particularly in the case of focal infections, such as recurrent urinary tract infections or chronic rhinosinusitis or bronchitis, local non-immunological disorders of the body’s defense mechanisms or anatomical abnormalities need to be considered. Examples of common secondary susceptibility to infections that are not the result of ID are listed in Tab. 2. Particularly noteworthy in this context is an atopic diathesis which, due to allergen-mediated mucosal lesions, is sometimes associated with an increased susceptibility to respiratory tract infections and gastrointestinal symptoms. This cause needs to be excluded prior to an immunological evaluation.

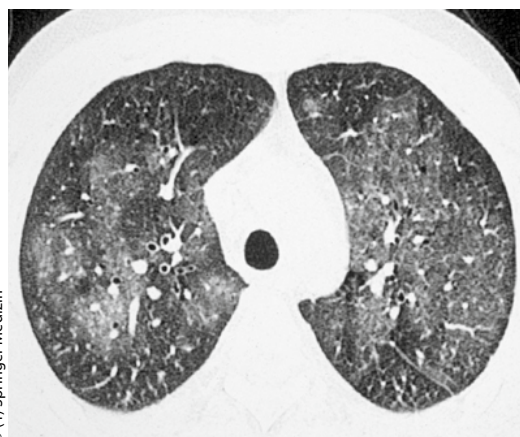
If an ID is present, the type of infection may guide in terms of the type of immune defect. Recurrent bacterial infections of the respiratory and gastrointestinal tract are particularly suggestive of a humoral immune defect (antibody deficiency, complement de-

fect). Unusual (opportunistic) infection, on the other hand, point in particular to cellular immune defect, as seen for example in HIV infections. Persistent abscess formation, particularly when internal organs are involved, systemic fungal infections, or osteomyelitis may be the result of neutrophil/macrophage dysfunction (impaired phagocytosis, neutropenia). On the other hand, mucocutaneous candidiasis restricted to the skin and mucosae is suggestive of a particular defect of the interleukin (IL)-17-producing T cells (Th-17 deficiency) [5].

For this reason, the classic warning signs of ID have been formulated and summarized for patients with increased susceptibility to infection in a german mnemonic, ELVIS, on behalf of the German Association of the Scientific Medical Societies (AWMF, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V., www.awmf.org) [4]. Although neither exhaustive nor specific, these warning may guide provide the practicing physician:

- Pathogen (Erreger): Infections due to opportunistic pathogens such as *Pneumocystis jirovecii* (Fig. 1) should prompt suspicion of ID.
- Localization (Lokalisation): Atypical localization of the infection, e. g., brain abscess due to *Aspergillus* (Fig. 2), cerebral toxoplasmosis, or pneumococcal arthritis, are suggestive of ID.
- Course (Verlauf): An unusual course in terms of chronicity/recurrence and an unsatisfactory response to antibiotic therapy represent signs (although difficult to differentiate) of ID.
- Intensity (Intensität): The same applies to infections that follow an unusually severe course.
- Number of infections (Summe der Infektionen): This parameter is distinctly age-dependent: ≥ 8 minor infections/year, ≥ 2 cases of pneumonia or severe sinusitis/year are considered abnormal in young children, while the rule of thumb in adults is that ≥ 3 bacterial infections per year each lasting over 4 weeks should prompt further investigation (Tab. 3) [6–8].

Family history (evidence of a genetic defect? mode of inheritance?) and ideally also a history provided by third parties, e. g., parents regarding childhood infections and umbilical cord healing, or the general practitioner regarding the treatment course of infections, are helpful in the diagnosis of ID. In the case of antibody deficiency (hypogammaglobulinemia), secondary causes need to be sought in a targeted manner prior to the diagnosis of primary ID. These include medication (e. g., corticosteroids, immunosuppressive agents, chemotherapy, some antiepileptic drugs), infectious diseases [human immunodeficiency virus (HIV) infection, Epstein-Barr virus (EBV), congenital rubella/cytomegalovirus (CMV)/toxoplasma infections], tumors (in particu-



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Fig. 1: Bilateral interstitial pneumonia with *Pneumocystis jirovecii*, seen predominantly in combined immunodeficiency

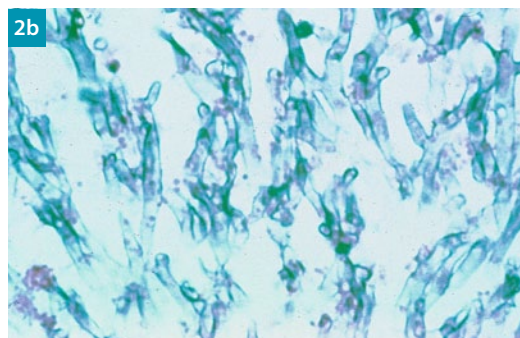
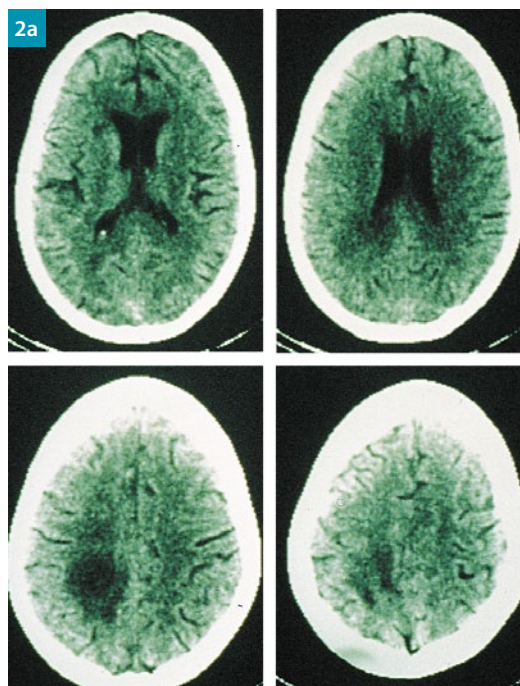


Fig. 2a: Invasive aspergillosis with brain abscess in the right parieto-occipital lobe. **2b:** Histology with direct pathogen detection, predominantly in combined immune defects and WAS

lar chronic lymphatic leukemia, non-Hodgkin's lymphoma, thymoma), and syndromes associated with excessive protein loss (nephrotic syndrome, malabsorption syndrome, lymphangiectasia). Systemic corticosteroid therapy in excess of 20 mg/day can result in a sustained reduction in serum IgG levels [9].

Other manifestations of immunodeficiency

In addition to a susceptibility to infection, it is important to know that other signs of immune system impairment can be due to ID. These include chronic inflammation, autoimmunity, and lymphoproliferative disorders, which are summarized in the AWMF guidelines by the German mnemonic GARFIELD [4]:

- Granulomas (Granulome): in particular in the lungs, lymph nodes, skin, as well as in other organs
- Autoimmunity (Autoimmunität): in particular autoimmune cytopenia, as well as organ autoimmunity
- Recurrent fever (Rezidivierendes Fieber): periodic fever, hemophagocytosis, among others
- Eczema (Ekzeme): often early-onset, atypical, refractory to therapy
- Lymphoproliferative disorders (Lymphoproliferation): chronic benign lymphadenopathy, splenomegaly (Figs. 3 and 4)
- Inflammatory bowel disease (Darmentzündung): often early-onset, atypical, refractory to therapy (Fig. 5)

It is not uncommon for this type of immune dysregulation to manifest before a susceptibility to infection is apparent, so that the differential diagnosis of ID needs to be considered in some patients with autoimmune cytopenia, celiac disease-like but gluten-independent enteropathy, Crohn's disease-like intestinal disease, or sarcoid-like granulomatous inflammation. Although an immune defect is suspected earlier in the case of increased susceptibility to infections, a diagnostic work up for ID is often postponed in patients with immune dysregulation. Antibody deficiency can be either secondary as in the setting of lymphomas, or due to the underlying disease with subsequent (secondary) lymphoma development. In this context, it can be challenging, both clinically and even histologically, to distinguish between chronic benign lymphadenopathy associated with ID and malignant lymphoma.

Primary immunodeficiency with elevated IgE or allergic manifestations

Specific, rare IDs exhibiting early manifestation of chronic eczema, high total IgE (hyper-IgE syndrome, Wiskott-Aldrich syndrome, Omenn syndrome), or cold urticaria (PLCG2 mutation) are of particular interest to allergists.

Age (years)	Respiratory infections/year	SD	Maximum
<1	6.1	±2.6	11.3
1–2	5.7	±3.0	11.7
3–4	4.7	±2.9	10.5
5–9	5.5	±2.6	8.7
10–14	2.7	±2.2	7.2

SD, Standard deviation

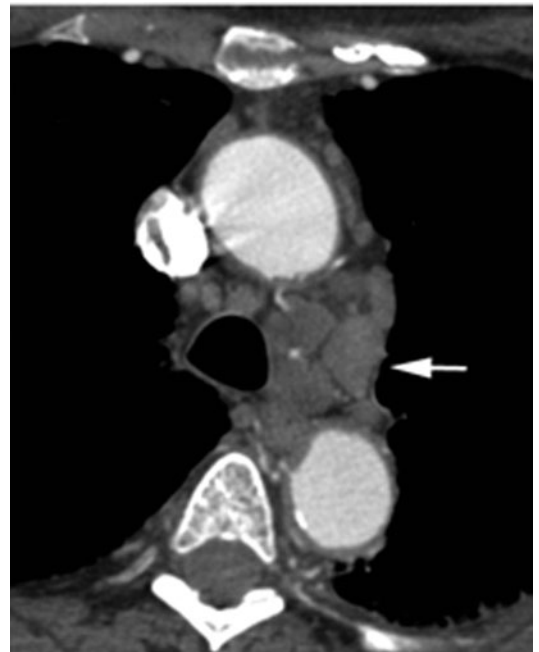


Fig. 3: Mediastinal lymphadenopathy in common variable immunodeficiency (CVID). Computed tomography (CT) of the chest

The clinical distinction between true atopic eczema and *hyper-IgE syndrome* (HIES) resulting from autosomal dominant mutations in the STAT3 gene can sometimes be challenging. Serum IgE levels alone do not permit a distinction here [10]. Moreover, a positive family history, usually extensive eczema, and blood eosinophilia are observed in both cases. In contrast, pneumonia, abscesses, and candida infections (particularly in combination) are typical of HIES, whereas these occur for the most part only as isolated phenomena in atopic eczema. Empyemas, “internal” abscesses (e. g., liver, lymph nodes, perirenal), and severe complications of infections, such as bacterial meningitis or osteomyelitis in eczema patients, are seen almost exclusively in HIES. Characteristic facial features (broad nose, high palate), articular hyperlaxity, and problems with change of dentition are important clinical



Fig. 4: Impressive splenomegaly in common variable immunodeficiency (CVID) reaching almost to the lower pole of the kidneys. Computed tomography (CT) of the chest/abdomen, coronal section



Fig. 5: Crohn's disease-like chronic inflammatory bowel disease in common variable immunodeficiency (CVID). Coloscopy

signs of STAT3 deficiency, whereas true atopic diathesis is extremely rare in STAT3 deficiency [11]. Thus, increased or unusual susceptibility to infections in eczema patients should prompt consideration of HIES. A diagnostic score has been developed to differentiate STAT3 from other diseases with high total IgE [12].

As a second ID group exhibiting elevated total IgE, combined immune defects that cause impaired T-cell regulation warrant mention here. Particularly

noteworthy in this context is autosomal recessive DOCK8 deficiency, which typically causes increased susceptibility to human papilloma virus (HPV) infections, herpes viruses, molluscum contagiosum, candida, and bacterial respiratory infections [13]. In contrast to STAT3 deficiency, the clinical picture here often includes true atopy with severe eczema, asthma, and predominant sensitization to food allergens [10].

In addition to the combination of recurrent infections and early-onset chronic eczema, *Wiskott-Aldrich syndrome* (WAS) is predominantly characterized by severe thrombocytopenia. Since WAS protein (WASP) defects are inherited in an X-linked recessive manner, almost only boys are affected. All effector cells of the immune system are involved in WAS, thus making it a combined immune defect, as with *Omenn syndrome* (OS) [14]. OS is a clinically distinct variant of severe combined ID (SCID), involving hypomorphic mutations in the RAG genes. OS becomes apparent as early as in the first months of life through opportunistic infections and generalized eczema with associated blood eosinophilia and elevated total IgE. Impaired T-cell maturation with an oligoclonally restricted T-cell repertoire and significantly impaired development of central tolerance in the thymus results in extensive autoimmune phenomena (alopecia, lymphadenopathy, hepatosplenomegaly, etc.). OS also has a dismal prognosis given that underlying problems with tolerance impede immune reconstitution following allogeneic stem cell transplantation.

Patients exhibiting persistent cold urticaria, antibody deficiency (IgA/IgM) with frequent respiratory infections, and autoimmune phenomena (autoimmune thyroiditis, elevated antinuclear antibody [ANA] titers) may be affected by an extremely rare defect in the *phospholipase-Cy2* (PLCCG2) gene first described in 2012 [15], which, as a signal transduction molecule in B cells, natural killer cells, and mast cells, plays an important role in immunoregulation.

Common variable immunodeficiency

CVID syndrome is an antibody deficiency syndrome that represents the commonest form of symptomatic ID in adulthood, with a point prevalence of between 1 : 25,000 and 1 : 75,000, depending on the population group investigated [3, 16]. Prevalence is approximately equal in men and women. Although isolated IgA deficiency with a point prevalence of 1 : 225–1 : 3,000 is more common [17], it is usually an incidental diagnosis and generally remains asymptomatic throughout life. In contrast to many other primary ID, CVID is often diagnosed in adulthood, predominantly between the ages of 20 and 40 years, and typically with a latency of approximately

ESID diagnostic criteria for CVID [19]	
CVID is diagnosed when at least one of the following criteria is met:	
	<ul style="list-style-type: none"> — Increased susceptibility to infections — Autoimmune manifestations — Granulomatous disease — Unexplained polyclonal lymphoproliferation — Other family members with antibody deficiency
and	IgG and IgA deficiency of at least two standard deviations below the mean-age appropriate level (not the lower norm!), with or without reduced IgM, detected in at least two measurements
and	At least one of the following criteria:
	<ul style="list-style-type: none"> — Inability to detect a significant rise in specific IgG following vaccination (and/or absence of iso-hemagglutinins), i.e., failure to achieve a protective level of IgG, where this is defined — Low class-switched memory B-cell count (< 70% age-adjusted standard value)
and	Exclusion of secondary causes of hypogammaglobulinemia (see text)
and	Disease diagnosis after the age of 4 years (previous symptoms possible)
and	No indication of marked T-cell deficiency, defined as two of the following criteria:
	<ul style="list-style-type: none"> — CD4 helper cell count: 2–6 years, < 300/μl; 6–12 years < 250/μl; > 12 years, < 200/μl — % Naive CD4 helper cells: 2–6 years, < 25%; 6–16 years, < 20%; > 16 years < 10% — Absent T-cell proliferation in vitro
CVID, common variable immunodeficiency; ESID, European Society for Immunodeficiencies; Ig, immunoglobulin	

Table 4

4 years between initial manifestation and first diagnosis.

The exact cause of CVID remains unclear in most cases, although individual gene defects have meanwhile been described. These mutations affect, e.g., co-stimulatory molecules of the B-cell line (CD19, CD21, CD81, TACI, and BAFF-R) [16]. The process by which B cells mature to antibody-producing plasma cells is impaired in most patients [18, 19]. **Tab. 4** summarizes the new criteria issued by the European Society for Immunodeficiencies (ESID) for the diagnosis of CVID [20].

Diagnostic approach in suspected immunodeficiency

A stepwise approach to diagnosing immune defects would be:

1. Screening
2. Confirmation
3. Considering differential diagnoses
4. Classification of the immune defect

As part of this process, there should be a low threshold for cost-effective screening methods, i.e., even in the case of low clinical suspicion. More detailed analysis of the immune system (including IgG subclass determination), which is often technically complex and expensive, should be carried out in specialized practices or centers.

For the first step, the clinical picture determines the choice of screening: a differential blood count (neutropenia? monocytopenia?) in the case of a suspected congenital immune defect; in the case of a suspected cellular defect, an absolute CD4 helper

cell count, the CD4 : CD8 ratio, and an HIV screening test are required in addition to a complete blood count. Any indication in the patient history of a humoral immune defect should be investigated by quantitatively measuring the serum antibodies IgG, IgA, and IgM. These investigations are cost-effective (immunoglobulin determination excluding subclasses: 4 EUR in Germany, 18 sFr in Switzerland) and can significantly shorten the often protracted suffering of patients prior to diagnosis and effective therapy. Repeating these tests within 1–6 months is necessary in order to avoid classifying post-infectious or transient hypogammaglobulinemia (e.g., in infancy) as ID. It is important to consider the age-dependence of normal values, including immunoglobulins, when analyzing results.

A joint decision-making process between treating physician and specialized center on further diagnostic steps on a case-by-case basis helps to avoid unnecessary investigations and costs on the one hand, while ensuring that the sometimes technically complex functional immunological tests are performed to a qualitatively high standard. Many of the more specialized laboratory investigations can be carried out on blood samples dispatched via express mail.

If a monogenetic defect is suspected and given the associated therapeutic relevance, confirmation via genetic analysis is recommended. On the other hand in the case of CVID with negative family history, genetic diagnosis is currently not advised, since treatment is (as yet) not affected by results.

Treatment

In addition to general measures including optimal (hand) hygiene and dental care, preventing transmission by improving barrier protection (skin moisturizers/emollients, local treatment for upper airway infections including vasoconstrictive nose drops, saline rinses, possible avoidance of large crowds of people), as well as prompt and targeted use of antibiotics in the event of bacterial infections, immunodeficient patients (particularly in the case of complement defects and asplenia) should consistently undergo all recommended vaccinations. It should be noted here that live vaccinations are contraindicated in ID. Immunoglobulin substitution therapy provides good passive protection against classic pathogens in national vaccine plans (tetanus, diphtheria etc.), which do not need to be additionally vaccinated against. On the other hand, annual anti-influenza vaccines in cases where there is a residual capacity for an immune response certainly make sense, since it can be assumed that immunoglobulin preparations lack protective antibodies. Local and national vaccine recommendations, including those for risk groups

such as ID, can be obtained from the following country-specific sites:

- Germany: www.rki.de
- Switzerland: www.bag.admin.ch/impfungen
- Austria: www.bmg.gv.at/impfen

Specific treatment measures are determined by the type of immune defect; therefore, we can provide only an overview of the general treatment principles.

In the case of humoral ID, IgG substitution is the most important form of treatment. It can be administered either intravenously at an initial dose of 0.4 g/kg bodyweight (BW) (ca. 20–25 g/3–4 weeks) in the physician's office, or subcutaneously at weekly intervals by the patients themselves (initial dose, 0.1 g/kg BW per week). Prior to initial administration, the patient needs to be informed about the fact that they are receiving a blood product and about the associated side effects. Immunoglobulin preparations available meet pharmaceutical requirements and no cases of pathogen transmission via immunoglobulin preparations have been seen in Europe and the US since 1994 [21].

In the case of subcutaneous substitution, patients are instructed on self-administration using a micro-pump and a set of sterile needles prior to administering the preparation themselves at home. Home therapy is complemented by follow-up checks every 3–6 months by the prescribing physician. The dose is adjusted according to the individual patient requirements over the course of therapy with the aim of achieving an infection-free status. An important clinical exception here is chronic rhinosinusitis, which can persist despite treatment. The target IgG serum level of 7 g/l, the commonly used laboratory surrogate marker for adequate substitution, cannot be applied universally to all patients. Dose increases with resultant serum trough IgG levels in the 10–12 g/l range are necessary in order to achieve infection-free status in some cases.

In other forms of ID or in the case of humoral ID refractory to therapy, long-term antibiotic prophylaxis as a sole treatment or in combination with immunoglobulin substitution is required.

- Cotrimoxazole 960 mg (3 × weekly) in combined ID (CD4 cell count <200/μl)
- Penicillin (2 × 1 million IE/day), in patients with splenectomy
- Ciprofloxacin in severe neutropenia (additionally, granulocyte colony-stimulating factor [G-CSF])
- Tobramycin or colistin inhalations in cystic fibrosis and complicated bronchiectasis
- Itraconazole (2 × 100 mg) and cotrimoxazole 960 mg/day in septic granulomatosis

Infections can occur even under immunoglobulin substitution. Symptoms of acute infection require prompt identification with a low threshold for initiating antibiotic therapy. It is important that all

treating colleagues are aware that the serological diagnosis of infections in CVID patients is invalid due to impaired antibody formation. In this setting, direct pathogen detection using histology, culture, or polymerase chain reaction (PCR) are the only reliable diagnostic options. Antibiotic prophylaxis should be considered prior to surgical and dental interventions.

In the case of some immune defects, in particular cellular ID, only immune system „replacement“ by means of stem cell transplantation is an effective and causal treatment. Gene therapy is an option in specific cases of clearly defined immune defects, particularly in the absence of a suitable donor. Although stem cell transplantation is standard in children with SCID, it is considered an experimental treatment approach in adults with congenital immune defects and is restricted to isolated cases that prove complicated and refractory to therapy. It is essential that specialized centers are involved in indication for this treatment as well as its administration.

The systematic recording of patients with primary immune defects by the treating physician in registers such as the European ESID register (www.esid.org) helps build a scientific basis to improve our understanding of these complex and rare diseases, in particular their clinical course and the clinical significance of the warning signs discussed above.

In addition to their medical care, some patients benefit from the networking opportunities offered by patient and stakeholder organizations, which promote communication, organize public lectures, and offer many practical tips on how to cope with ID in everyday life. These can be found under:

- Germany: www.dsai.de
- Switzerland: www.immunschwaecher-schweiz.ch, www.svai.ch, www.aha.ch
- Austria: www.oespid.org

German centers of expertise in ID have set up the FIND-ID (www.find-id.net) network in order to achieve a continuous exchange of information between established centers, clinics, and physicians' practices, thereby promoting the early detection and treatment of patients with congenital ID – a goal wholeheartedly supported by the present article.

Dr. Oliver Hausmann

Allergological-Immunological Polyclinic
University Clinic for Rheumatology, Clinical
Immunology and Allergology
Bern University Hospital
3010 Bern, Switzerland
E-Mail: hausmann.allergie@hin.ch

Conflict of interest

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