

Prevention of Infections During Primary Immunodeficiency

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Because infectious diseases are a major source of morbidity and mortality in the majority of patients with primary immunodeficiencies (PIDs), the application of a prophylactic regimen is often necessary. However, because of the variety of PIDs and pathogens involved, and because evidence is scarce, practices are heterogeneous. To homogenize practices among centers, the French National Reference Center for PIDs aimed at elaborating recommendations for anti-infectious prophylaxis for the most common PIDs. We performed a literature review of infectious complications and prophylactic regimens associated with the most frequent PIDs. Then, a working group including different specialists systematically debated about chemoprophylaxis, immunotherapy, immunization, and recommendations for patients. Grading of prophylaxis was done using strength of recommendations (decreasing from A to D) and evidence level (decreasing from I to III). These might help infectious diseases specialists in the management of PIDs and improving the outcome of patients with PIDs.

Keywords. prophylaxis; primary immunodeficiency; immunizations; immunoglobulins.

Primary immunodeficiencies (PIDs) expose carriers to infectious risks (Table 1) that vary in their severity and presentation as a function of the underlying pathology [1]. The French National Reference Center for Primary Immune Deficiencies (CEREDIH) has issued recommendations about prevention of infections based on published data and the opinions of different French

PID experts coming from multiple disciplines. We used a validated grading system ([2] and Table 2). For each PID, a summary of recommendations is provided in [Supplementary Data](#), as well as [Supplementary Bibliography](#).

CHRONIC GRANULOMATOUS DISEASE

Chronic granulomatous disease (CGD) is a PID affecting the microbicidal ability of phagocytic cells, resulting from mutation(s) in the genes coding for the subunits of the nicotinamide adenine dinucleotide phosphate [3]. CGD is usually revealed in early life by repeated invasive bacterial and/or fungal infections.

Infections

Bacterial abscesses are the most frequent infections. Fungal infections affect one-third of patients with

Received 29 April 2014; accepted 4 August 2014; electronically published 14 August 2014.

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Clinical Infectious Diseases® 2014;59(10):1462–70

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DOI: 10.1093/cid/ciu646

Table 1. Most Frequent Infections According to Primary Immunodeficiencies

Immunodeficiency	Bacteria	Viruses	Parasites	Fungi
Chronic granulomatous disease	<i>Staphylococcus aureus</i> (abscesses of various sites) <i>Burkholderia</i> spp Enterobacteria (septicemia, urinary infections) <i>Nocardia</i> spp (adenitis, skin infections, abscesses) <i>Actinomyces</i> spp (adenitis, skin infections) <i>Mycobacteria</i> spp			<i>Aspergillus</i> spp (pulmonary, bone lesions) Rare filamentous fungi
Congenital neutropenia	<i>Staphylococcus</i> spp (all sites) Enterobacteria (septicemia, abscesses, cellulitis) <i>Streptococcus pneumoniae</i> (pneumonitis)			<i>Aspergillus</i> spp (pulmonary infections) <i>Candida</i> spp (disseminated infections)
Complement factor deficiencies: classical, C3, factor H, factor I	<i>S. pneumoniae</i> (pulmonary, ENT infections) Hib (pulmonary, ENT infections)			
Complement factor deficiencies: properdin, late components	<i>Neisseria meningitidis</i> (meningitides)			
Asplenia	<i>S. pneumoniae</i> (OPSI) Hib (OSPI) <i>N. meningitidis</i> (OSPI) <i>Ehrlichia</i> spp (infections after bite) <i>Capnocytophaga</i> spp (infections after bite)		<i>Plasmodium falciparum</i> <i>Babesia</i> spp	
Agammaglobulinemia	<i>S. pneumoniae</i> (ENT, pulmonary infections, meningitides) Hib (ENT, pulmonary infections, meningitides) <i>N. meningitidis</i> (meningitides) <i>Pseudomonas aeruginosa</i> (superinfection of bronchiectasis) <i>Campylobacter jejuni</i> (gastrointestinal infections)	Enterovirus (central nervous system infections)	<i>Giardia intestinalis</i> (gastrointestinal infections)	
Hyper-IgM syndrome with cellular defect (mutations in CD40, CD40L)	<i>S. pneumoniae</i> (ENT, pulmonary infections meningitides) Hib (ENT, pulmonary infections meningitides) <i>N. meningitidis</i> (meningitides) <i>P. aeruginosa</i> (superinfection of bronchiectasis) <i>C. jejuni</i> (gastrointestinal infections)		<i>Giardia intestinalis</i> <i>Cryptosporidium parvum</i> (gastrointestinal and biliary infections)	<i>Pneumocystis jiroveci</i> (pulmonary infections)
Hyper-IgM syndrome without cellular defect (mutations in AID, UNG, PMS2)	<i>S. pneumoniae</i> (ENT, pulmonary infections, meningitides) Hib (ENT, pulmonary infections, meningitides) <i>N. meningitidis</i> (meningitides) <i>P. aeruginosa</i> (superinfection of bronchiectasis) <i>C. jejuni</i> (gastrointestinal infections)			
CVID	<i>S. pneumoniae</i> (ENT, pulmonary infections, meningitides) Hib (ENT, pulmonary infections meningitides) <i>N. meningitidis</i> (meningitides) <i>P. aeruginosa</i> (superinfection of bronchiectasis) <i>C. jejuni</i> (gastrointestinal infections)		<i>Giardia intestinalis</i> (gastrointestinal infections)	

Table 1 continued.

Immunodeficiency	Bacteria	Viruses	Parasites	Fungi
SCID/CID	<i>S. pneumoniae</i> (ENT, pulmonary infections, meningitides) Hib (ENT, pulmonary infections, meningitides) <i>N. meningitidis</i> (meningitides) <i>P. aeruginosa</i> (superinfection of bronchiectasis) <i>C. jejuni</i> (gastrointestinal infections) Intracellular pathogens <i>Mycobacteria</i> spp	Herpes virus Adenovirus Respiratory viruses Gastrointestinal viruses	<i>G. intestinalis</i> (gastrointestinal infections) <i>Toxoplasma gondii</i>	<i>P. jiroveci</i> (pulmonary infections) <i>Aspergillus</i> spp (pulmonary infections) <i>Candida</i> spp (mucocutaneous, invasive infections)
STAT 3 deficiency	<i>S. aureus</i> (cutaneous and pulmonary abscesses) Enterobacteria (abscesses) <i>P. aeruginosa</i> (superinfection of bronchiectasis and pneumatoceles)			<i>Aspergillus</i> spp <i>Candida</i> spp (mucocutaneous)

Abbreviations: CID, combined immunodeficiency; CVID, common variable immunodeficiency; ENT, ear, nose, and throat; Hib, *Haemophilus influenzae* type b; IgM, immunoglobulin M; OPSI, overwhelming post-splenectomy infection; SCID, severe combined immunodeficiency; STAT 3, signal transducer and activator of transcription 3.

Table 2. Grid Used for the Establishment of Recommendations, for Each Primary Immunodeficiency

Criteria	Recommendation										
	Chemoprophylaxis Anti-			Immunotherapy			Immunization				
	<i>Pneumocystis</i>	Bacterial	Fungal (Not <i>Pneumocystis jiroveci</i>)	Viral	Immunoglobulin Replacement	G-CSF	IFN- γ	Versus Encapsulated Bacteria	Influenza	Live Attenuated Vaccines	Other Usual Vaccines
Modalities											
Strength ^a											
Level of proof ^b											
Comments/alternatives											

Recommendation strength and level of proof are sometimes indicated globally for a given item. For detailed modalities and their level of proof, see the corresponding manuscript section.

Abbreviations: G-CSF, granulocyte colony-stimulating factor; IFN- γ , interferon gamma.

^a Strength of the recommendation: strong (A), moderate (B), or weak (C) French National Reference Center for Primary Immune Deficiencies (CEREDIH) support, or not recommended by CEREDIH (D).

^b Level of proof: I, data from at least 1 well-designed and -conducted randomized controlled trial; II, data from at least 1 well-designed and -conducted clinical trial, without randomization, cohorts or case-control analyses (preferably multicenter), multiple retrospective series, or major findings of noncontrolled studies; III, expert opinions based on clinical experience, descriptive case series, or expert committee reports.

CGD, frequently due to *Aspergillus fumigatus* or *Aspergillus nidulans* [4].

Prophylaxis

All patients should receive cotrimoxazole prophylaxis, at a daily dose of 25 mg/kg/day of sulfamethoxazole (5 mg/kg/day of trimethoprim; maximum dose: 800 mg/day of sulfamethoxazole) [5–7] (AII).

Itraconazole prophylaxis is systematically recommended at a starting dose of 10 mg/kg/day for children and at least 200 mg/day for adults [8] (AI). Serum levels must be measured because of inter- and intraindividual absorption variabilities.

Primary prophylaxis with posaconazole was reported, but its efficacy was not evaluated for this indication (CIII). Voriconazole is not recommended as primary prophylaxis because of photosensitivity in long-term use, which can be complicated by squamous skin carcinoma (DIII).

Interferon gamma (IFN- γ) has been used because of its role in increasing macrophage phagocytosis, but side effects are frequent [9]. IFN- γ is not used routinely in Europe, and CEREDIH does not recommend its use as first-line prophylaxis [10, 11] (CII). In contrast, IFN- γ could have a place in treating infections not controlled by anti-infectious agents.

Immunizations against pneumococci, *Haemophilus influenzae*, and influenza are recommended (AIII), as well as usual inactivated vaccines (AIII). Live attenuated vaccine (measles, mumps, and rubella [MMR]) is authorized (BIII). BCG vaccine is contraindicated (DII). Yellow fever immunization seems theoretically possible, but justifies referral to an expert (CIII) [12].

SEVERE CONGENITAL NEUTROPENIAS

Chronic neutropenias is defined as having a level of <500 neutrophils/ μ L for several months or years. Severe congenital neutropenia has varied hereditary transmission. The most common genetic anomaly is a mutation in the neutrophil elastase-encoding (*ELANE*) gene. Cyclic neutropenias are transmitted via autosomal-dominant heredity by mutation in the *ELANE* gene. Idiopathic and autoimmune neutropenias can occur in adults and in children [13].

Infections

The risk of bacterial infections is very high for patients with permanent congenital neutropenia, but less for patients with cyclic neutropenia and low for patients with autoimmune neutropenia. Mucosal infections are very frequent. Invasive fungal infections occur in <10% of patients.

Prophylaxis

In the absence of severe infection or severe mucosal manifestations, antibacterial prophylaxis is indicated as first-line treatment.

Cotrimoxazole is the treatment of choice (AIII). Long-term fluoroquinolone administration is not recommended (DIII).

Granulocyte colony-stimulating factor (G-CSF) efficacy was demonstrated in a randomized controlled crossover trial [14]. Data on the long-term efficacy of G-CSF are scarce. Prolonged use increases the risk of myelodysplasia and/or acute leukemia, especially during prolonged exposure and at high doses.

G-CSF should be prescribed first for severe infection (AI) or extensive mucosal manifestations. It should also be prescribed as second-line treatment if moderate relapsing infections or severe infection occur under antibiotic prophylaxis. The systematic prescription of antifungal prophylaxis is not justified (DIII). For persistent profound neutropenia despite G-CSF administration, prophylaxis by itraconazole can be envisaged (BIII).

Usual inactivated vaccines should be administered (AIII). Annual influenza and pneumococcal vaccination are recommended (AIII). BCG vaccination is contraindicated by analogy with CGD, even though disseminated “BCGitis” has never been described in this population (AIII). Other live attenuated vaccines (MMR) are not contraindicated by isolated neutropenia (BIII).

COMPLEMENT FACTOR DEFICIENCIES

Infections

Deficiencies of factors intervening early in the classical pathway (C1, C2, C4) predispose the individual to invasive infections with *Streptococcus pneumoniae* and *H. influenzae* type b. C3 deficiency is the complement defect conferring the most marked susceptibility to invasive pneumococcal infections. Deficiencies of factors H and I share the same infectious phenotype. Properdin deficiency, with a X-linked inheritance, exposes the individual to an increased risk of fulminating infections with *Neisseria meningitidis*. Deficiencies of the terminal complement pathway factors expose the carrier to infections with *N. meningitidis*, characterized by their occurrence during adolescence, a low mortality rate, and frequent recurrences [15, 16].

Prophylaxis

Vaccinations against encapsulated bacteria are recommended for patients with complement factor deficiencies (AII). Immunization against pneumococcus should use the 13-valent pneumococcal conjugate vaccine (PCV13) [17]. A “prime-boost” strategy, with PCV13 vaccine first followed by the 23-valent pneumococcal polysaccharide vaccine (PPSV23) given 2 months later, combines the advantages of both vaccines. The efficacy of this strategy remains to be evaluated in patients with PID. Booster shots for PPSV23 are classically given, but no information is available about their efficacy. Antibody response should be monitored. Anti-*H. influenzae* type b vaccination is necessary.

The tetravalent meningococcal conjugate vaccine (A, C, W135, Y) can be given to children >1 year old with risk factors

and to adults. For children aged <1 year, the conjugate C vaccine can be given. The new vaccine against meningococcus B is also recommended [18]. Influenza vaccination is recommended annually (AIII). No contraindications for live attenuated vaccines have been raised (AIII). Inactivated vaccines should be given (AIII).

Given the severity of infections, antibiotic prophylaxis with penicillin at a dose of 50 000 IU/kg/day in 2 intakes per day (1 million units twice daily for adults) is recommended for all patients with complement factor deficiencies (AIII), except those with terminal complement factor deficits because infections are of moderate severity.

An obvious problem is compliance with long-term antibiotic prophylaxis. An alternative could be to inject penicillin intramuscularly (2.4 million units every 2–3 weeks).

ASPLENIA

Congenital asplenia is rare. Asplenia can also be secondary to splenectomy performed for various reasons, sometimes in patients also affected by PID.

Infections

Asplenic patients have marked susceptibility to encapsulated bacteria, with frequent fulminating progression [15]. Asplenic patients are also sensitive to *Ehrlichia* species or *Capnocytophaga canimorsus* (transmitted by dog bites) and the intracellular parasites *Plasmodium* species and *Babesia* species.

Prophylaxis

Vaccines against encapsulated bacteria represent a major arm for the management of these patients (AII). Annual influenza vaccination is recommended [19] (AII), as well as usual inactivated vaccines (AIII). Asplenia itself does not contraindicate the use of live attenuated vaccines (AIII). However, should the splenectomy be performed in the setting of a more complex immunodeficiency, the cellular immunity defect must be taken into consideration.

The possible occurrence of severe bacterial infections associated with potential weak vaccine responses raises the question of antibiotic prophylaxis. Penicillin V is the most frequently used molecule. Only 1 study conducted on children with sickle-cell disease (which causes functional asplenia) showed that antibiotic prophylaxis lowered the mortality rate [20].

The optimal duration of this antibiotic prophylaxis after splenectomy is still being debated, with a mean of 2 years for adults and 5 years for children. In the context of a patient with underlying PID, the cumulative increased risk of severe infections leads to the recommendation of lifelong antibiotic prophylaxis (AIII). In the case of poor adherence, regular intramuscular injections of penicillin G could be prescribed. In the case of allergy to penicillin, cotrimoxazole could be a valid alternative (BIII).

AGAMMAGLOBULINEMIA

X-linked agammaglobulinemia, or Bruton disease, is due to mutation in the gene *Btk* coding for Bruton tyrosine kinase, a protein involved in intramedullary differentiation of B-lymphocyte precursors. B cells are absent, and the antibody production is null. The disease generally becomes manifest after the first months of life, after the waning of the protection provided by maternal immunoglobulin [21].

Infections

The most frequent clinical manifestations are upper and/or lower respiratory tract infections due to encapsulated bacteria. Gastrointestinal infections are frequent. One of the particularities of agammaglobulinemia is the very marked susceptibility to enteroviral acute or chronic meningoencephalitis, responsible for high mortality and major morbidity [22].

Prophylaxis

Immunoglobulin replacement therapy is always indicated (AII), intravenously or subcutaneously [23]. Several studies have tried to define the ideal dose of immunoglobulins. In a recent prospective trial, the risk of pneumopathies was higher for patients whose residual immunoglobulin G (IgG) levels were <5 g/L [24]. A very high IgG level (>10 g/L) obtained even better protection. A meta-analysis also found that the pneumopathy frequencies decreased with increasing residual IgG concentrations [25]. Substitution should be started as soon as agammaglobulinemia is diagnosed (AII), starting at a dose of 400 mg/kg every 3 weeks, with the aim of achieving a residual IgG level of at least 8 g/L (BIII).

Although immunoglobulin replacement decreases the frequency of invasive bacterial infections, it does not seem to completely prevent the occurrence of chronic sinusitis and bronchiectasis.

Antibiotic prophylaxis can be proposed when infections persist despite well-conducted replacement therapy (with residual IgG >10 g/L) (BIII). Cotrimoxazole can be used. Indeed, in a study on human immunodeficiency virus-infected patients taking cotrimoxazole prophylaxis (to prevent *Pneumocystis jirovecii* pneumonia), daily cotrimoxazole was able to lower the frequencies of ear, nose, and throat (ENT) infections and pneumopathies [26]. An alternative option could be to prescribe long-term macrolides in case of bronchiectasis. It was shown that macrolides have an antiinflammatory effect, independent of their direct antibacterial activity. The most used is azithromycin [27].

Finally, once bronchiectasis has been established, it could be informative to document colonizations. Indeed, for cystic fibrosis patients colonized by *Pseudomonas aeruginosa*, long-term inhaled antibiotics led to a lower frequency of exacerbations and improved pulmonary function. Such a strategy, although not validated in the PID setting, might be proposed.

The efficacy of inactivated vaccines is probably very low to null, but they are not contraindicated (CIII). In practice,

immunoglobulin replacement therapy contains protective levels against these pathogens.

Immunization with the oral poliomyelitis vaccine is strictly contraindicated (DII) because of the risk of vaccinal enterovirus infection. Yellow fever immunization is contraindicated because of the risk of vaccinal disease and probably very weak efficacy (DIII). Influenza vaccine could be contributive by producing a cellular response; it is recommended annually (AIII).

COMMON VARIABLE IMMUNODEFICIENCY

Common variable immunodeficiency (CVID) is defined by hypogammaglobulinemia associated with a <5 g/L IgG deficit and immunoglobulin A (IgA) deficit, whereas the immunoglobulin M (IgM) concentration can be normal or low, and a diminished vaccinal response. CVID generally appears during adolescence or early adulthood. A deficit of memory B cells is frequent. In only a small percentage of cases, genetic mutations have been identified [28].

In addition, within the French national study on adults with PID and hypogammaglobulinemia, 8% of the patients diagnosed with CVID had clinical pictures of late-onset combined immunodeficiency (LOCID), defined by the occurrence of an opportunistic infection and/or the existence of profound CD4 T lymphopenia [29].

Infections

As in agammaglobulinemia, infections most frequently concerned the ENT area, the bronchi, and the lungs, with a large majority of the infections caused by encapsulated bacteria [21].

Prophylaxis

Immunoglobulin replacement therapy should be started immediately for all patients with previous severe infection or repeated infections (>3 per year) (AII). Symptoms are not necessarily indicative of hypogammaglobulinemia intensity. Hence, when hypogammaglobulinemia is discovered in an asymptomatic patient, no data exist to determine the threshold of IgG plasma level under which replacement therapy is necessary. However, it seems reasonable to propose immunoglobulin replacement if the IgG titer is <3.5 g/L (BIII). Immunoglobulin replacement therapy can be administrated intravenously or subcutaneously.

A recent study highlighted the variability of the immunoglobulin doses administered and the residual IgG levels necessary to prevent infections. In another study, although no "ideal" threshold existed, the risk of pneumopathy seemed clearly higher for a concentration <4 g/L [30].

In practice, replacement is started with 400 mg/kg/month; patients with bronchiectases or gastrointestinal diseases need higher immunoglobulin doses.

Replacement therapy must achieve a minimal residual IgG concentration of 5 g/L (BII). Then, the dose must be adapted to clinical findings, being increased when severe infections or relapsing moderate infections (>2 per year) persist.

However, development and/or worsening of bronchiectases can occur in patients receiving adequate immunoglobulin replacement. Antibiotic chemoprophylaxis could thus play a major complementary role in patients with persistent infections despite "optimal" immunoglobulin replacement (in practice, with a residual IgG concentration >8 g/L), with same modalities as in agammaglobulinemia.

Certain vaccinations are given during the course of the initial workup for hypogammaglobulinemia, and the poor vaccinal response is one of the diagnostic criteria for CVID. However, the results of several studies seem to show that vaccinal responses are not always abolished for all types of antigens [31]. These observations could encourage reconsideration of the dogma concerning the inefficacy of vaccinations in this patient population. In particular, immunizations against capsulated bacteria and influenza are recommended (AIII). For LOCID patients, live attenuated vaccines are contraindicated.

HYPER-IgM SYNDROMES

Hyper-IgM (HIGM) syndromes cover several groups of hereditary immune system pathologies, during which profoundly decreased plasma levels of IgG and IgA coexist with a normal-to-increased IgM plasma level. HIGM syndromes with a combined immunodeficiency are linked to mutations in the genes encoding for CD40L or CD40 [32], the interaction of which plays a major role in the phenomenon of isotype switching. CD40L also interacts with CD40 expressed on dendritic cells and monocytes/macrophages; thus, a cellular immunity deficit is associated. HIGM syndromes with a pure humoral defect linked to intrinsic B-lymphocyte anomalies are attributed to mutations in genes coding for enzymes involved in isotype switching (AID, UNG, PMS2) [33].

Infections

Patients with HIGM syndromes develop bacterial infections as in agammaglobulinemia.

During the course of HIGM linked to mutations in CD40L or CD40, other infectious agents are often involved, revealing the cellular immunity deficit. Pneumocystosis is particularly frequent, as well as *Cryptosporidium* species infection that can cause diarrhea and sclerosing cholangitis.

Prophylaxis

As in other humoral deficiencies, immunoglobulin replacement is associated with fewer bacterial infections. Severe decrease in IgG argues for a therapeutic approach similar to that used for agammaglobulinemia.

The high prevalence of pneumocystosis justifies systematic prophylaxis by cotrimoxazole to patients with HIGM associated with cellular immunodeficiency, but not when linked to an intrinsic B-lymphocyte anomaly.

Vaccinations should be administered as in agammaglobulinemic patients, with the notable difference that in HIGM with cellular deficiency, live attenuated vaccines are contraindicated.

SEVERE COMBINED IMMUNODEFICIENCIES AND COMBINED IMMUNE DEFICIENCIES

Severe combined immunodeficiencies (SCIDs) are characterized by a very profound deficit of T-cell immunity, always associated with a humoral immunity deficiency. SCID can be associated with different genetic anomalies [34]. Other cellular immune deficiencies, less severe, variably associated with a humoral immunodeficiency, called combined immune deficiencies (CIDs), can become evident later in life [35].

Infections

Unusual and repeated infections reveal SCIDs very early, during the first weeks of life. In the absence of curative treatment, survival does not exceed several months [36, 37]. The most frequent opportunistic infection is pneumocystosis, which often reveals the disease, but a wide spectrum of bacterial, viral, and fungal infections is possible.

Immunoglobulin deficiency exposes the patient to the constant risk of infections with encapsulated bacteria.

Prophylaxis

SCID represents major pediatric diagnostic and therapeutic emergencies. Patients must imperatively be isolated in sterile rooms and urgently transferred to a referral center for curative therapy (allogeneic hematopoietic stem cell transplant [HSCT], gene therapy, enzyme replacement therapy). Prophylaxis has its role during the waiting period before HSCT/gene therapy and during the ensuing immune reconstitution. As soon as a cellular immunodeficiency is identified, cotrimoxazole prophylaxis against pneumocystosis must be initiated (AII).

No antifungal prophylaxis against other fungal infections has been specifically evaluated for SCID patients. Fluconazole is prescribed before 1 month of age, at which time itraconazole can be used. Polyvalent immunoglobulin replacement should be initiated immediately (AII), and maintained until the humoral immune deficit is corrected.

For SCID, vaccinations are useless because no immune response can be mounted (CIII). For CID, the cellular immunity deficiency contraindicates the use of live attenuated vaccines. Inactivated vaccines and immunizations against encapsulated pathogens are recommended, but need an evaluation of the humoral response when possible. Influenza vaccine should be given annually (BIII).

STAT3 Deficiency

This disease, historically called Job-Buckley syndrome, is caused by a signal transducer and activator of transcription 3 (STAT3) deficiency [38]. It is a multisystemic disease with specific cutaneous

involvement (neonatal rash, eczematiform dermatitis) and developmental anomalies, including dental, osteoligamentous connective tissue, facial dysmorphism, and vascular abnormalities [39].

Hyper-immunoglobulin E is constant and hypereosinophilia is frequent. A B-memory-lymphocyte deficiency is associated with a defective T helper 17 response, an important pathway in the immune response in the skin and lungs.

Infections

Infections are notable by their extreme lack of associated local or general inflammatory signs. The most characteristic is recurrent subcutaneous cold abscesses due to *Staphylococcus aureus*. ENT and pulmonary infections are very frequent. Healing as sequelae with the appearance of pneumatoceles is highly suggestive of the diagnosis of STAT3 deficiency. Pulmonary aspergillosis affects about one-quarter of patients. Pulmonary sequelae of infections constitute a prerequisite for *Aspergillus* colonization and prepare the way for secondary invasive infections. Chronic cutaneous and/or mucosal candidiasis are very frequent [40].

Prophylaxis

Cotrimoxazole is recommended as first-line therapy for all patients (AII). Long-term oral cloxacillin (at 2–4 g/day) can be an alternative for documented, relapsing methicillin-sensitive *S. aureus* infections (AIII).

For chronic symptomatic bronchial colonization, management comprises oral azithromycin 3 times per week for bronchiectases and inhaled tobramycin/colimycin to treat chronic *P. aeruginosa* colonization with frequent exacerbations.

The presence of pulmonary lesions justifies effective anti-*Aspergillus* prophylaxis with antifungal azole to prevent invasive infections (AIII). As primary prophylaxis, itraconazole is the most frequently prescribed molecule for patients with STAT3 deficiency.

Anti-*Haemophilus* and antipneumococcal (with PCV13) vaccinations are justified (AIII); however, the quality of the vaccinal response and its clinical efficacy remain to be evaluated. Annual influenza immunization is recommended (AIII). MMR vaccination is authorized (BIII); yellow fever immunization should be discussed with an expert. Inactivated vaccinations should be administered (AIII).

Because of the deficiency of the memory B cells, immunoglobulin replacement therapy should be prescribed for recurrent bacterial infections despite well-conducted antibiotic prophylaxis (AII).

CONCLUSIONS

The prophylactic measures to be applied during the course of PID rely schematically on the following: antibiotic and antifungal prophylaxis for innate immune deficiencies; cotrimoxazole for cellular immune deficiencies; polyvalent immunoglobulin replacement therapy for humoral immune deficiencies; and vaccinations and antibiotic prophylaxis for patients with asplenia or

complement factor deficiencies. General recommendations for patients and families are provided in the “Appendix” section.

Little is known about acquisition of resistant bacteria or fungi following the use of such prolonged antimicrobial prophylaxis, a topic inviting further investigation.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. The authors thank Janet Jacobson for excellent editing of the manuscript.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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APPENDIX

General Recommendations for Patients and Families

- As soon as primary immunodeficiency (PID) is diagnosed, prophylactic measures must begin.

- Observance to prophylactic treatments is essential but can be difficult because of lifelong treatment.
- Some treatments need specific times for administration (ie, itraconazole capsules during meals or itraconazole liquid suspension at distance of meal intake).
 - Patients and their family must be aware of their diagnosis of PID, their susceptibility to infections, and the signs that indicate a consultation is needed.
 - Patients with PID should consult an infectious disease expert before traveling.
 - Patients with innate immune defects should avoid exposure to molds (eg, construction/renovation areas and gardening).
 - Patients with combined deficiencies should drink bottled water in countries where cryptosporidiosis is particularly present.
 - All healthcare professionals consulted must be informed of the diagnosis (eg, to avoid intramuscular injections in patients with PID).
 - Almost all patients with PID should be vaccinated against influenza, but immunogenicity of the vaccine remains uncertain in the context of PID. Vaccination of the entourage is recommended.
 - Live vaccines are contraindicated in persons with PID with cellular immune deficiencies.