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PEDIATRIC FUNGAL INFECTIONS (T LEHRNBECHER, SECTION EDITOR)

Invasive Fungal Infection in Primary Immunodeficiencies Other Than Chronic Granulomatous Disease

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Abstract
Purpose of review We aimed to review invasive fungal infections complicating primary immunodeficiencies (PID).
Recent findings Several PID predisposing to fungal infections were recently deciphered. CARD9 deficiency selectively predisposes to fungal infections including candidiasis, aspergillosis, deep dermatophytosis, and phaeohyphomycosis, with frequent central nervous system location, especially after *Candida* infection. Patients with heterozygous *STAT1* gain-of-function mutations are mostly predisposed to chronic mucocutaneous candidiasis but may also display, even though less frequently, invasive fungal infections. Aspergillosis complicating STAT3 deficiency is also a major concern in patients with lung cavities. Antifungal prophylaxis is recommended in this first group of patients. Previously well-reported PID are known to predispose to fungal infections, such as genetic defects impairing the IL-12/IFN-γ axis can predispose to cryptococcosis, and dimorphic fungal infections.
Summary Patients developing invasive fungal infections including candidiasis, aspergillosis, cryptococcosis, phaeohyphomycosis, pneumocystosis, or disseminated infections caused by dimorphic fungi, without known underlying risk factors, should be explored immunogenetically in order to diagnose primary immunodeficiencies, even in the absence of previous other infectious episodes.

Keywords Primary immunodeficiencies (PIDs) · Invasive fungal diseases · Pediatric fungal infections · Chronic mucocutaneous candidiasis · Dimorphic fungi · CARD9 · STAT1 · STAT3 · Opportunistic infections

Introduction

Early diagnosis of a primary immunodeficiency (PID) is crucial in order to reduce morbidity and premature mortality from infectious diseases. PID are usually diagnosed early in life, 80% before the age of 20 years [1, 2, 3•]. Consequently, pediatricians are in first line to identify signs of PID. A PID

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should be suspected in front of a history of an unusually severe, persistent, recurrent, difficult to treat, or opportunistic infections, including invasive fungal infections [4, 5]. Among incriminated infections, invasive fungal infections, especially occurring in children, are highly suggestive of a PID and therefore, warrant to actively seek an inborn error of immunity. The coordinated contribution of innate and adaptive host immunity is necessary to protect against fungi [6, 7]. Invasive fungal infections complicating chronic granulomatous disease (CGD) are well described with *Aspergillus* spp. and other mold infections [8, 9]. Over the last decades, development of high-throughput sequencing approaches led to new PID identification. Apart from CGD, we will review the spectrum and the clinical presentation of the PID predisposing to invasive fungal infections (Table 1).

Primary Immunodeficiencies Mainly Predisposing to Fungal Infection

Autosomal Recessive CARD9 Deficiency

CARD9 is a major component of antifungal innate immune response, involved in the signaling downstream of C-type lectin receptors (CLRs), such as Dectin-1, Dectin-2, Mincle [10••], or complement receptor 3 (CR3), leading to the production of pro-inflammatory cytokines after fungal recognition [11]. CARD9 has a role in phagocyte killing of unopsonized yeasts and neutrophil trafficking into the CNS [12••] and tissues [13]. That could explain the high frequency of CNS location of fungal infections in CARD9-deficient patients, mainly for *Candida* spp. CARD9-deficient patients have an elective susceptibility to fungal infections, as no other type of infection was reported in those patients.

Most frequent presentation of autosomic recessive CARD9 deficiency is deep dermatophytosis as it is so far responsible for all reported deep dermatophytosis cases [14–17]. Deep dermatophytosis is a severe form of dermatophytosis, invading dermis. In CARD9-deficient patients, infection is resistant to local and systemic antifungal treatments and can disseminate to lymph nodes, bones, digestive tract, or central nervous system (CNS) [16]. Overall, 21 patients have now been reported with deep dermatophytosis and AR CARD9 deficiency [11, 12••, 14, 15]. Based on published studies, median age at first symptoms was 8 years. The first symptoms were severe or recurrent *tinea capitis* for 84.2% patients, severe or recurrent *tinea corporis* for 63.1%, and onychomycosis for 42.1%. Patients developed skin invasive dermatophytic infection as well as lymph node (52.6%) or organ (15.7%) extension in young adulthood [14–16].

Fourteen patients with CARD9 deficiency were reported with *Candida* CNS infection (cerebral abscesses or/and meningoencephalitis). Median age at diagnosis was 22.5 years. Isolated *Candida* spp. was *Candida albicans* for most patients. It is noticeable that no candidemia was evidenced at the time of *Candida* CNS infection diagnosis. Other locations of invasive *Candida* infection were also reported in CARD9-deficient patients, including colitis, endophtalmitis, and osteomyelitis [13, 18, 19].

Phaeohyphomycosis were also reported in CARD9-deficient patients with *Phialophora verrucosa* subcutaneous infections in four patients [20] and *Exophiala* spp. disseminated infections in two patients [21]. The first patient was 5 years old and presented an *Exophiala dermatitidis*-related cholangitis and cerebral abscesses, the second an *Exophiala spinifera* subcutaneous, bone and lung disease. Recently, two patients were reported with invasive aspergillosis with digestive location (associated with CNS infection in one). It is noticeable that none had lung aspergillosis which is classically aspergillosis clinical presentation [13]. Despite the absence of specific recommendations and based on our experience, secondary antifungal prophylaxis is recommended for all CARD9-deficient patients, in particular for patients with deep dermatophytosis.

STAT1 Gain-of-Function Mutations

Heterozygous *STAT1* gain-of-function (GOF) mutations were recently identified by genome-wide sequencing strategies [22••, 23••]. STAT1 is activated by various Janus kinases (JAKs) in response to cytokines, hormones, and growth factors. STAT1 is a major downstream transducer for the type I and type II IFNs. Monoallelic *STAT1* loss-of-function (LOF) mutations were shown to be associated with Mendelian susceptibility to mycobacterial diseases (MSMD), and biallelic *STAT1* LOF mutations are associated to susceptibility to both intracellular bacterial and viral infections [24–26]. By contrast, monoallelic *STAT1* mutations leading to increased STAT1 phosphorylation (by impairing nuclear dephosphorylation) were found in about half of patients with inherited chronic mucocutaneous candidiasis (CMC). Low IL-17 producing T cell proportions and IL-17 production are observed in patients with *STAT1* GOF mutations, explaining at least in part the occurrence of CMC in these patients [27, 28••]. It is most probably responsible for CMC, and could result from the inhibition of the development of IL-17-producing T cells by IFNs and IL-27 [29], and/or impaired STAT3-dependent gene transcription [30].

Until today, more than 350 patients with heterozygous *STAT1* GOF mutations have been described worldwide [28••, 31–33]. In a large international survey of more 274 patients, approximately 60% of the cases were sporadic. Most had CMC (98%), with a median age at onset of 1 year. They can develop other infectious diseases such as recurrent bacterial infections (mainly of the respiratory tract and the skin), recurrent viral skin infections, mostly due to *Herpes*

Table 1 Primary immunodeficiencies associated with invasive fungal infections

Disease	Fungal infection	Immunological defect	Gene	Transmission
PID mainly predisposing to fungal infections				
CARD9 deficiency	Deep dermatophytosis CMC Phaeohyphomycosis Aspergillosis Central nervous system candidiasis	Neutrophil trafficking dysfunction Impaired production of pro-inflammatory cytokines	*CARD9*	AR
STAT1 gain-of-function	CMC Dimorphic fungal infections - Cryptococcosis Aspergillosis Mucormycosis Pneumocystosis (rare)	IL-17 producing T cell defect Impaired response to INF-γ stimulation	*STAT1*	AD
AD-HIES (STAT3 deficiency)	CMC Aspergillosis Histoplasmosis Cryptococcosis	IL-17 producing T cell defect Epithelial lung dysfunction	*STAT3*	AD
Combined immunodeficiencies				
SCID	Pneumocystosis Candidiasis Aspergillosis	T cell deficiency +/− associated B and NK cell lymphopenia	>30 genes (*IL2RG*, *JAK3*, *RAG 1 or 2*, *ADA*, *ARTEMIS*…)	Depend on mutation
Hype IgM syndrome (HIGM)	Pneumocystosis Candidiasis	Impaired T cell activation Impaired immunoglobulin class switch recombination	*CD40L*	X-linked
Idiopathic CD4 lymphopenia	Cryptococcosis Pneumocystosis Histoplasmosis	CD4 T cells <300/mm^3	*UNC119* *MAGT1* *RAG1*	AD X-linked AR
Wiskott-Aldrich syndrome	Pneumocystosis Candidiasis Aspergillosis	Impaired immunological synapse formation	*WAS*	X-linked
AR-HIES (DOCK8 mutations)	Aspergillosis Candidiasis Pneumocytosis	Reduced number T cells, B cells and NK Impaired CD8 T cell proliferation and activation	*DOCK8*	AR
MHC class II deficiency	Pneumocystosis	Impaired CD4 T cell development and function	*CIITA*, *RFX5*, *RFXAP*, and *RFXANK*	AR
Neutropenia and leukocyte dysfunction				
Congenital neutropenia	Candidiasis Aspergillosis Mucormycosis	Neutrophils cells <500/mm^3	*ELA2*	AD
LAD	Candidiasis Aspergillosis	Impaired neutrophil adhesion	*CD18* (LAD1)	AR
Deficiency of the IL-12/interferon γ axis				
Interferon gamma/IL12 defect	Dimorphic fungal infection: - Histoplasmosis - Coccidioidomycosis - Paraccocidioidomycosis Cryptoccocosis	Impaired INF-Y production by T cells and NK cells Impaired INF-Y production by T cells and NK cells	*HAX1* *IFNGR1*	AR AD

CMC chronic cutaneous candidiasis, *CNS* cerebral nervous system, *AD* autosomic dominant, *AR* autosomic recessive

viridae, but also autoimmune manifestations, cerebral aneurysms, and cancers, which are associated with disease severity and/or poor outcome [28••].

CMC is the most common infectious manifestation reported in patients carrying *STAT1* GOF mutations, mainly presented as recurrent thrush, skin (pustules, annular plaques, intertrigo), esophageal, genital, and/or nail (onyxis, perionyxis) infections. These superficial infections are mainly due to *C. albicans* and frequently resistant to long-term antifungal treatment [28••]. They also can develop aphtous stomatitis or recurrent superficial dermatophytic infections. As most of the cases were tested for *STAT1* GOF mutation because of CMC manifestations, other clinical manifestations might be underestimated. Since 2011, 39 *STAT1* GOF patients with invasive fungal infections have been reported, 16 during childhood. All but 3 out of the 39 had co-existing CMC [28••, 34, 35•, 36, 37]. Half suffered from systemic candidiasis including candidemia, renal, liver or splenic abscess, or retinitis. Less frequently, fungal pneumonia can be observed in these patients, with *Pneumocystis jirovecii*, *Aspergillus* spp., *Cryptococcus* spp., and *Histoplasma* spp. Some patients can develop disseminated fungal infections (mainly affecting lung, lymph nodes, bones, or joints), often depending on the country of living of the patients, i.e., *Coccidioides* spp. and *Histoplasma capsulatum* in USA, or *Penicillium marneffei* in China. One case of disseminated mucormycosis was reported [28••, 38•]. S*TAT1* GOF patients with invasive fungal diseases have a higher rate of associated bacterial (85%), mycobacterial (14%), or systemic viral infections (25%), autoimmunity (50%), and less likely cancer or aneurysm. They also have a higher mortality rate (25, vs. 11% without invasive fungal diseases). Long-term antifungal therapy remains recommended for CMC treatment and antifungal prophylaxis after invasive fungal infection.

Autosomal Dominant STAT3 Deficiency

The autosomal dominant hyper-immunoglobulin E syndrome (AD-HIES) results from heterozygous dominant negative loss-of-function mutations in *STAT3* [39••]. Patients present hypereosinophilia, high serum IgE levels, low proportions of IL-17-producing T cells, and low memory B lymphocyte counts. Between 2007 (first report on genetic identification) and 2012, more than 300 patients with AD STAT3 deficiency have been reported [40••, 41••, 42–45]. In a recent French study, including 60 patients from 47 kindreds, the mean age at clinical diagnosis was 6.8 years (range 0–30), whereas the mean age at the first infection was 10.5 months [40••].

Bacterial and fungal infections are a major clinical features of the disease [40••]. Patients with AD-HIES present recurrent *Staphylococcus aureus* skin or tissue abscesses, recurrent pneumonia that cause lung damages, mucocutaneous candidiasis, chronic dermatitis, and developmental disorders such as facial dysmorphism and dental, vascular, or skeletal abnormalities [41••, 46]. Due to abnormalities in lung repair, bacterial pneumonias are often complicated with lung cavities. Apart from *S. aureus* skin infections, fungal mucocutaneous infections are described in more than 80% of the patients [40••, 42]. *C. albicans* is the most frequently isolated infectious agent (88%). The affected sites are the oral cavity (thrush, glossitis, and/or cheilitis), nails (chronic onychomycosis), genital, cutaneous, and esophageal mucosa in respectively 63, 57, 18, 16, and 8% of patients [40••].

A. fumigatus is the most common fungus involved in lung infections in AD-HIES patients. Previous publications report that almost 20% of these patients develop pulmonary aspergillosis, always secondary to pre-existing lung abnormalities due to bacterial infections: 22% in the French cohort study of Chandesris et al., with a mean age at onset of 11 years (range, 3–16 years); and 25% of 64 STAT3 patients in another study [40••, 47••]. More occasionally, disseminated *Aspergillus* infection, with central nervous system invasion and mycotic aneurysms, has been reported [40••, 47••, 48, 49]. Thanks to the national French cohort of STAT3-deficient patients ($n = 74$), we reported 18 episodes of filamentous fungal infections in 10 (13.5%) patients. Median age at first episode was 12 years (IQR 10.2–25). Ninety percent of patients who developed mold infection had an underlying pulmonary disease, bronchiectasis, and cavitation, usually multiple. Mold infections were aspergilloma, chronic pulmonary aspergillosis, allergic broncho-pulmonary aspergillosis-like episodes, or mixed forms. We did not observe any case of invasive aspergillosis according to EORTC/MSG definitions. One patient died from respiratory failure at 11 years old [50]. Few cases of *Scedosporium* spp.-related lung and brain infections were also described [47••, 51]. *Cryptococcus neoformans* and *Histoplasma* spp. also may cause disseminated fungal infections in AD-HIES patients. Like for aspergillosis, *Histoplasma* tends to be responsible for pulmonary infections following lungs defects, whereas cryptococcosis are mainly neuromeningeal [47••, 52]. According to these elements, antifungal prophylaxis by an azole therapy with mold activity is justified in patients with structural airway abnormalities or after an invasive fungal infection [53, 54••].

Combined Immunodeficiencies

Severe Combined Immunodeficiency

Severe combined immunodeficiency (SCID) is a heterogeneous group of inherited disorders characterized both cellular and humoral immunity impairment [55]. Hypomorphic SCID can be diagnoses in adulthood. SCID arises from mutations of critical genes involved in the development of the adaptive immune system and is defined by a profound depletion of T

lymphocytes resulting in markedly increased susceptibility to severe infections from early infancy [56••]. In a recent US study on newborn screening for SCID performed in more than 3 millions of infants, the overall incidence of SCID was of 1 out of 58,000 births [57]. SCID is usually fatal without restoration of immune function by hematopoietic stem cell transplant (HSCT) [58, 59].

SCID patients are usually affected by severe bacterial, viral, or fungal infections early in life and often present with interstitial lung disease, chronic diarrhea, and failure to thrive. Patients are susceptible to develop fungal infections; *Pneumocystis*, *Candida*, and *Aspergillus* being the most commonly implicated [60–64]. *P. jirovecii* is responsible for interstitial pneumonia; antifungal prophylaxis with trimethoprim/sulfamethoxazole is therefore recommended in SCID patients [65, 66]. Candidiasis presents as oral thrush or meningitis [61, 63, 67–69] and aspergillosis with lung location [62, 64]. Rare pathogens such as *Acremonium falciforme* were also reported as a cause of invasive fungal infections in SCID infants [70].

Combined Immune Deficiency

CD40L Deficiency

Hyper IgM (HIGM) syndromes are a group of rare genetic disorders leading to loss of T cell-driven immunoglobulin class switch recombination (CSR) and/or defective somatic hypermutation as well as impaired T cell activation [71, 72••]. The most common causes are mutations in *CD40 ligand* (*CD40L*) leading to X-linked HIGM in males [73]. *CD40L* encodes for CD40L transmembrane glycoprotein expressed on activated $CD4^+$ T lymphocytes. USIDNET registry included 132 patients with HIGM and reported infections in 91% of patients; pulmonary infections were the most commonly reported (75%). *P. jirovecii* occurred in 32% of patients. Other common infectious organisms were *Candida* spp. (12%) and *Cryptosporidium* (6%). Increased susceptibility to *Cryptococcus* and *Histoplasma* spp. was reported. Cryptococcosis may present as central nervous system, lymph node, bloodstream, or disseminated disease. Histoplasmosis may manifest as pneumonia, hepatitis, or disseminated disease [8, 74].

Combined Immunodeficiency with Isolated CD4 Lymphopenia

In the absence of HIV infection, CD4+ T cells lymphopenia was called "idiopathic $CD4^+$ T cell lymphocytopenia" (ICL). The Centers for Disease Control and Prevention (CDC) definition includes $CD4^+$ T cells/mL below 300 or 20% of the total T cell counts, no evidence of HIV infection and absence of any defined immunodeficiency, or therapy associated with depressed levels of $CD4^+$ T cells. It is a heterogeneous group of disorders with a few genetic causes identified, such as MCH class II deficiency, RAG1, MST1, or ITK deficiency [75, 76].

The majority of ICL cases were diagnosed in adults (usually in middle age), but several cases of ICL have been described in children [77, 78]. Beyond the significant infectious risks, patients with ICL are exposed to more complications, particularly autoimmune manifestations (35% of patients in a recent French cohort study) and tumoral complications (malignant lymphoma or solid tumor) [79]. Majority of the patients (87.6%) developed at least one opportunistic infection, and the mean age at diagnosis of the first opportunistic infection was 40.7 +/− 19.2 years. Cryptococcosis is the most frequent fungal infection, in 26.6% of patients. The commonest clinical presentation was meningoencephalitis, followed by pneumonia and osteomyelitis [80–84]. *Candida* sp. (16.2%), *P. jirovecii* (7.7%), and dimorphic fungi such as *Histoplasma* or *Penicillium* were also responsible for severe infections [80, 84–88].

Other Combined Immunodeficiencies

Wiskott-Aldrich syndrome (WAS) is a complex X-linked PID caused by loss-of-function mutations in *WAS*. Even if occasional, patients with WAS were reported to develop invasive candidiasis, invasive aspergillosis, or *P. jirovecii* pneumonia [89].

Mutations in *DOCK8* underlie most cases of AR hyper-IgE syndrome and are associated with reduced numbers of T cells, B cells, and natural killer cells, with impaired CD8 T cell proliferation and activation. In a review of 136 patients with DOCK8 mutations, life-threatening infections were reported in 58% of them. The most frequent reported fungal infections are invasive aspergillosis, invasive candidiasis, and pneumocystosis [90••].

MHC class II plays a pivotal role in CD4 T cell development and function [91]. *P. jirovecii*-related pneumonia were reported in patients with MHC class II deficiency [92].

Due to high risk of pneumocystosis in patients with cellular immunodeficiency, antifungal prophylaxis with trimethoprim-sulfamethoxazole should be recommended.

Neutropenia and Leukocyte Dysfunction

Congenital Neutropenia

Congenital neutropenia is defined by permanent or periodic circulating neutrophil cell count $<500/mm^3$. Neutropenia can be isolated or part of syndromes with extra-hematopoietic manifestations (as seen in the Shwachman-Diamond syndrome with pancreatic insufficiency) [93]. Severe congenital neutropenia (SCN) is characterized by permanent severe neutropenia (usually $<200/mm^3$) driven by various genetic defects, including mutations in the neutrophil elastase gene

(*ELANE*) with AD transmission or the AR *HAX1* gene deficiency. The SCN International Registry estimated a prevalence of 0.7 per million inhabitants [94]. In 2014, the French congenital neutropenia registry had collected 605 patients with SCN [95]. Less common, cyclic neutropenia is an AD disorder, also due to a mutation in the *ELANE* gene, responsible for regular episodes of severe neutropenia [96–98].

In both defects, neutropenia exposes to opportunistic bacterial and fungal infections. Patients suffer from severe bacterial infections that classically begin in the first months of life, such as omphalitis, cellulitis, perirectal abscess, pneumonia, peritonitis, stomatitis, or meningitis [98–100]. This risk is inversely proportional to the rate of circulating neutrophils. Fungal infections, mainly due to aspergillosis, remain rare (especially in cyclic neutropenia), but reported observations are generally severe: a 8-year-old girl with SCN developed filamentous fungal lung infection and a 3-year-old girl, an extensive ear, nose, and mastoid mucormycosis [101, 102]. Beyond antimicrobial prophylaxis, with trimethoprim-sulfamethoxazole, recombinant human granulocyte colony-stimulating factor (G-CSF) helps to increase the numbers of circulating neutrophils [94, 103].

Leukocyte adhesion deficiency

Leukocyte adhesion deficiency (LAD) is a group of rare inherited disorders characterized by defects in proteins involved in leukocyte rolling, adhesion, and cytosqueletal regulation. Four types are described: AR disorders for LAD1 (mutation in the β2 integrin subunit, CD18) [2, 104, 105]; LAD2 (a defect in binding of the leukocyte to P and E-selectins on endothelial cells) [106]; or LAD3 (lead to an activation defect of all beta-integrins); and an AR disorder for Rac2LAD (a defect in regulation of the actin cytoskeleton and the NADPH oxidase) [2, 7, 105].

Clinical presentation results from phagocyte dysfunction. Deficiency may be suspected from the first days of life, in case of delayed umbilical cord separation [104], poor wound healing, skin ulcers, severe gingivitis/periodontitis, or recurrent bacterial and fungal infections, resulting from leukocyte inability to migrate to the sites of infections [107]. Majority of the infectious complications reported in LAD are bacterial. However, increased susceptibility to fungal pathogens, like *Candida* or *Aspergillus*, has also been reported in older reviews. *Candida* spp. are the primary fungi isolated from patients with LAD1, in whom cutaneous candidiasis were seen in approximately 16% of patients. Persistent prepubertal severe periodontitis related to *Candida* are also described [107, 108]. In a series of nine children suffering from LAD1, three patients developed fungal infection: a *Fusarium oxysporum* fungemia with metastatic skin lesions, a 6-month-old boy with proven pulmonary aspergillosis, and a patient with lymph node and superficial fungal infections, healed with antifungals [109, 110].

Deficiency of the IL-12/Interferon-γ Axis

IL-12, the main stimulus of IFN-γ production by T and NK cells, is a key cytokine in the interaction between innate and adaptive immune responses. Several genes are known to be responsible for the deficiency in IL-12/IFN-γ axis, transmitted by a AD, AR, or X-linked mode of inheritance (IFNGR1, IFNGR2, IL12B, IL12RB1) [111–114]. Patients with inherited defects in the INF-γ/IL-12 axis have an increased susceptibility to *Salmonella* and mycobacterial infections. INF-γ production following recognition of these pathogens is important in macrophage activation and phagocytosis and results in inhibition of growth and death of the mycobacteria [115].

Recurrent or persistent *Candida* mucocutaneous infections are found in about 25% of patients with AR IL-12Rβ1 deficiency, mainly as oropharyngeal manifestations (78%) [116•]. Disseminated fungal infections seem less frequent. Nevertheless, some cases of cryptococcal infections, with osteomyelitis or meningitis, were described in children with IL-12/interferon-γ axis deficiency, especially with IL12RB1 mutation [117]. There are also a significant proportion of disseminated dimorphic fungal infections reported, especially in children or young adults: coccidioidomycosis (three cases, mean age of 13 years), histoplasmosis (one boy aged 3 years and 8 months), and paracoccidioidomycosis (one man, 24 years old) [118, 119]. Consequently, patients with disseminated dimorphic infections should be explored for IFN-γ/IL-12 axis defects.

Conclusion

High-throughput sequencing led to discovery of a large panel of new PID-causing genes predisposing to various infections including those caused by fungal pathogens. One PID, CARD9 deficiency, selectively predisposes to fungal infections. STAT1 GOF patients are susceptible to CMC and some invasive fungal diseases. STAT3-deficient patients develop severe and difficult to treat forms of pulmonary aspergillosis. Antifungal prophylaxis is recommended in these PIDs predominantly predisposing to fungal infections. Patients with combined immunodeficiency are at risk to *P. jirovecii* pneumonia, therefore trimethoprim-sulfamethoxazole prophylaxis is recommended. Presentation, diagnostic efficiency, evolution, and treatment vary according to the fungal pathogen and the PID. Specific knowledge of presentation and treatment of fungal infections in these PID is necessary to optimize patients' care. Diagnosis of an invasive fungal disease in a patient without any known underlying risk factor, even in the absence of previous infection, should lead to immunologic and genetic exploration in order to diagnose a PID.

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Compliance with Ethical Standards

Conflict of Interest Olivier Lortholary reports personal fees from Pfizer, MSD, Gilead, and Astellas.

Fanny Lanternier reports personal fees from Basilea, MSD, and Gilead.

Aurelie Garraffo, Benoît Pilmis, Julie Toubiana, A. Puel, Nizar Mahlaoui, and S. Blanche declare that they have no conflict of interest.

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- • Of importance
- •• Of major importance

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