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REVIEW

Fungal infections in primary immunodeficiencies

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Abstract Patients with phagocytic, cellular, combined and other primary immunodeficiencies exhibit immune deficits that confer increased susceptibility to fungal infections. A number of yeasts and moulds, most commonly *Candida* and *Aspergillus* but also *Cryptococcus*, *Histoplasma*, *Paecilomyces*, *Scedosporium*, *Trichosporon*, *Penicillium* and other, rarely isolated, fungal organisms, have been variably implicated in causing disease in patients with chronic granulomatous disease, severe combined immunodeficiency, chronic mucocutaneous candidiasis, hyper-IgE syndrome, myeloperoxidase deficiency, leukocyte adhesion deficiency, defects in the interferon-γ/interleukin-12 axis, DiGeorge syndrome, X-linked hyper-IgM syndrome, Wiskott-Aldrich syndrome and common variable immunodeficiency. Differences in the spectrum of fungal pathogens as well as in the incidence and clinical presentation of the infections may be observed among patients, depending upon different immune disorders. Fungal infections in these individuals may occasionally be the presenting clinical manifestation of a primary immunodeficiency and can cause significant morbidity and potentially fatal outcome if misdiagnosed or mistreated. A high degree of suspicion is needed and establishment of diagnosis should actively be pursued using appropriate imaging, mycological and histological studies. A number of antifungal agents introduced over the last fifteen years, such as the lipid formulations of amphotericin B, the second-generation triazoles, and the echinocandins, increase the options for medical management of these infections. Surgery may also be needed in some cases, while the role of adjunctive immunotherapy has not been systematically evaluated. The low incidence of primary immunodeficiencies in the general population complicates single-center prospective or retrospective clinical studies aiming to address diagnostic or therapeutic issues pertaining to fungal infections in these patients.

Keywords Primary immunodeficiencies · Fungal infections · Antifungal agents · *Candida* · *Aspergillus*

Abbreviations

AIRE	Autoimmune regulator
APECED	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy
CGD	Chronic granulomatous disease
CMC	Chronic mucocutaneous candidiasis
CT	Computed tomography
CVID	Common variable immunodeficiency
G-CSF	Granulocyte colony-stimulating factor
HIV	Human immunodeficiency virus
IFN	Interferon
IL	Interleukin
LAD	Leukocyte adhesion deficiencies
MRI	Magnetic resonance imaging
NADPH	Nicotinamide adenine dinucleotide phosphate
NK	Natural killer
SCID	Severe combined immunodeficiency
STAT	Signal transducer and activator of transcription
Th	T-helper
WASP	Wiskott-Aldrich syndrome protein

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Introduction

Primary immunodeficiencies are hereditary disorders involving one or multiple components of the immune system, which result in increased susceptibility to infections and significant morbidity and mortality if untreated. They are predominantly single-gene abnormalities and although approximately 100 different entities have already been described, less than about 20 account for more than 90% of the cases. These disorders should be distinguished from acquired immunodeficiencies due to immunosuppressive regimens, malignancies, the human immunodeficiency virus (HIV), and other causes. Primary immunodeficiencies are usually diagnosed during early life, with more than 80% of cases diagnosed before the age of 20 years [93]. Thus, pediatricians bear the responsibility for initial diagnosis and management of these immune disorders in the majority of cases, which usually present as recurrent, protracted or severe infections caused by common organisms or as infections caused by opportunistic pathogens [81].

Depending on the component of the immune system which is affected most, primary immunodeficiencies are divided into broad categories, including humoral, cellular, combined humoral and cellular, phagocytic, complement, and other, well characterized immunodeficiency syndromes [20, 81, 87] (Table 1). For each of these disorders, the pattern of infectious organisms (bacteria, viruses, fungi, protozoa) to which increased susceptibility is observed and, often, the clinical presentation of the infection, largely depend on the underlying immune deficit. The present review discusses the spectrum, clinical presentation and management of fungal infections associated with primary immunodeficiencies. For better understanding of the association between particular immune deficits and fungal diseases, a concise overview of the mechanisms of host immune response to fungal pathogens is initially presented. Although *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) is now known to be a fungus [44], the distinct epidemiology, clinical course and management of infection caused by this organism is not discussed in this review.

Immune response to fungal infections

Innate immune response

In humans, the coordinated contribution of both innate and adaptive immunity is required in order to mount an effective host response against fungi [138, 150]. The innate response is mediated through a variety of cells, which exhibit phagocytic and antigen-presenting activity. These include neutrophils, mononuclear leukocytes (macrophages

Table 1 Summary of primary immunodeficiencies and associated fungal infections

Immune deficit	Most common clinical entities	Fungal infections
Humoral	X-linked or autosomal recessive agammaglobulinemias Common variable immunodeficiency Selective IgA deficiency	Unlikely*
Cellular and combined	Severe combined immunodeficiency (various defects) Deficiencies of major histocompatibility complex molecules (I, II) DNA repair defects DiGeorge syndrome Hyper-IgM syndrome (X-linked) Wiskott-Aldrich syndrome	Variable, depending on immune deficit (*Candida*, *Aspergillus*, *Cryptococcus*, dimorphic fungi)
Phagocytic	Chronic granulomatous disease Myeloperoxidase deficiency Leukocyte adhesion deficiency Chediak-Higashi syndrome Congenital neutropenia Defects in the interferon-γ/IL-12 axis	Variable, depending on immune deficit (*Aspergillus* and other filamentous fungi (mostly in chronic granulomatous disease), *Candida*, dimorphic fungi)
Complement	Classic, late or alternative complement defects Mannose-binding lectin pathway defects	Unlikely
Other	Hyper-IgE syndrome	*Candida*, *Cryptococcus*, dimorphic fungi, *Aspergillus*
	Chronic mucocutaneous candidiasis	*Candida*, rarely *Cryptococcus*, dimorphic fungi

*With the exception of common variable immunodeficiency (when associated with T-cell abnormalities)

and monocytes) and dendritic cells, while natural killer (NK), γδT cells, epithelial and endothelial cells may also be involved to a variable extent [64, 138]. Innate immunity host cells recognize fungal pathogens through Toll-like receptors (TLR, mainly TLR-2 and TLR-4) and other components of the fungal cell wall [117]. Additional phagocytic cells are recruited to sites of infection by the action of inflammatory mediators, such as cytokines, chemokines and complement components. Intracellular killing or extracellular damage of fungal elements is achieved through oxidative and non-oxidative mechanisms and may be augmented by opsonins and T-cell derived cytokines. In the oxidative pathway, enzymes such as the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and nitric oxide (NO) synthase produce reactive oxygen intermediates mediating toxic effects on the fungal cells. Non-oxidative fungal killing is achieved through degranulation and release of defensins, neutrophil cationic peptides and other fungicidal molecules [101, 150].

Adaptive immune response

The development of adaptive immune response against fungi is mediated through differentiation of $CD4^+$ T cells along a T-helper (Th) cell type 1 (Th1) or type 2 (Th2) pathway. Th1 response involves the production of cytokines such as interferon (IFN)-γ, interleukin (IL)-2, IL-12, and IL-18, which stimulate phagocytic activity, generation of cytotoxic $CD4^+$ T cells, and production of opsonizing antibodies. The development of Th2 response is associated with the production of cytokines such as IL-4 and IL-10, which elicit production of non-opsonizing antibodies and allergic reactions and down-regulate the extensive inflammatory reaction caused by Th1 cytokines. Effective protection against invasive mycoses correlates with predominance of Th1 over Th2 adaptive responses [64, 109, 138].

While the importance of phagocytes and T-cells is well established, the role of humoral immunity in the immune response against fungal infections has long been a matter of controversy. Cell walls of fungi possess various carbohydrate and other antigens that elicit antibody responses. However, there is little evidence that these antibodies modulate the pathogenesis of fungal infections [24, 36]. For example, although antibodies to *Candida albicans* and *Cryptococcus neoformans* are acquired early in life, they do not seem to protect from infection [55]. In addition, patients with hypo- or agammaglobulinemia are not particularly vulnerable to fungal infections. It is now well understood that the numerous antibodies generated during colonization or infection by a particular fungal species target different epitopes and demonstrate various and sometimes opposing activities that can be protective, non-protective or indifferent. Sometimes, antibodies formed against irrelevant fungal constituents may even obscure protective epitopes [26]. Consequently, the fact that this polyclonal antibody response may not confer protection does not exclude the possibility that protective antibodies are generated. However, identification of these antibodies requires search at the monoclonal level, and has attracted great scientific interest lately as it may lead to novel therapeutic interventions or vaccine development [36, 122].

In this article, we comprehensively discuss the fungal infections affecting patients with primary immunodeficiencies, starting from the disorders where these infections are most likely to occur, i.e. the phagocytic disorders followed by cellular and combined immune deficits (Table 1). We only present those immune disorders for which there is at least some evidence for occurrence of fungal infections in the literature.

Phagocytic disorders

Chronic granulomatous disease

Chronic granulomatous disease (CGD) is caused by the absence or very low level of superoxide-generating NADPH oxidase activity in phagocytes and is characterized by increased susceptibility to infections caused by catalase positive bacteria and fungi (i.e. *Staphylococcus aureus*, *Aspergillus fumigatus*, etc.) [9, 62]. The role of superoxide and its derivatives (hydrogen peroxide, hydroxyl radical and hypohalous acid) in the microbicidal activity of phagocytes has been recently shown to be mediated through release and activation of granule proteases, including elastase and cathepsin G, into the phagocytic vacuoles. Briefly, superoxide and its derivatives have been shown to cause an influx of K^+ into the phagocytic vacuoles with an attendant rise in ionic strength to the optimal level for release and activation of these proteases from the anionic proteoglycan matrix where they are bound. Activation of elastase and cathepsin G is likely the principal mechanism for NAPDH oxidase-mediated phagocytic activity; knockout mice that are normal in superoxide production but deficient in granular proteases are highly susceptible to bacterial and fungal infections [132, 145, 163]. The frequency of CGD has been estimated to range between 1/200,000 and 1/250,000 live births. Of all CGD cases, almost two-thirds are X-linked recessive, resulting from defects in the *CYBB* gene encoding the gp91-*phox* subunit of the NADPH oxidase complex; the remaining one-third are autosomal recessive, resulting from defects in *CYBA*, *NCF-1* and *NCF-2* genes, which encode subunits p22-*phox*, p47-*phox* and p67-*phox*, respectively [9, 62, 148].

CGD is the primary immunodeficiency with the highest incidence of fungal infections. Patients suffering from CGD

are at increased risk for fungal infections mainly due to *Aspergillus* spp.; however, *Candida* and other fungal genera may also occur. The introduction of routine antibacterial prophylaxis for CGD patients has changed the relative frequency of fungal versus bacterial infections in this population. While the frequency of bacterial infections has been significantly reduced, the frequency of fungal infections has remained unchanged (0.2–1.7 fungal infections/100 patient-months) [104] or even increased from 0.2 to 1.9 serious infections/100 patient-months, according to data from 39 CGD patients followed-up for a period of 22 years [90].

Aspergillus infections in CGD patients

In older series of CGD patients the prevalence of *Aspergillus* infections was as low as 7% [72], while the mortality associated with this filamentous fungus was slightly more than 10% of the total infectious mortality [84]. However, in a subsequent study at the end of the 1980s, 40% of 48 patients with CGD had at least one infection caused by *Aspergillus* species [112]. In 2000, among 322 hospitalized children with CGD in the United States, 21 were diagnosed with invasive aspergillosis, reflecting an incidence of 6.5% [192]. In a report from the United States registry of 368 patients with CGD, *Aspergillus* species were the most commonly isolated organism from CGD patients with pneumonia (41% of 290 cases) and the second most commonly isolated from those with osteomyelitis (22% of 90 cases) [181]. In this and other series, invasive aspergillosis was the most common cause of death, accounting for over one-third of all deaths [90, 112, 181].

The most common *Aspergillus* species affecting CGD patients is *A. fumigatus*, followed by *A. nidulans* [4, 99, 147]; infection with *A. flavus* also has been reported [99]. Of note, while *A. nidulans* is a relatively unusual pathogen in other immunocompromised patients, it is isolated with increased frequency from CGD patients. In a review of 23 cases of invasive aspergillosis among 145 CGD patients, *A. fumigatus* was isolated from 17 of the cases and *A. nidulans* from the remaining six [147]. Several case reports also denote the relatively increased frequency of *A. nidulans* infections among CGD patients [42, 76, 179]. *Aspergillus nidulans* is distinctive in that it tends to be highly resistant to most antifungal agents, such that surgery may be the only therapeutic recourse for eradication of infection caused by this organism.

Invasive aspergillosis usually affects CGD patients during their first two decades of life and may even be the first manifestation of this disease. The infection most commonly affects the lungs and can present as a pulmonary infiltrate in routine imaging studies of otherwise asymptomatic CGD patients. Indeed, at diagnosis, up to one third of the patients may be asymptomatic and only around 20% may be febrile. Other signs and symptoms are not specific. Leukocytosis and moderate elevation of the erythrocyte sedimentation rate may occur; however, normal values also have been observed in a significant proportion of cases [4, 99, 147].

Extrapulmonary primary sites of infection may occasionally be observed for *A. fumigatus*, and consist of bone, brain, liver or lymph node lesions. Rarely, an anterior mediastinal mass, manifested as anterior cell wall protrusion, or endocarditis may be observed [4, 25, 98, 99]. In contrast to *A. fumigatus*, infections caused by *A. nidulans* in CGD patients almost always originate from the lungs. However, in this patient population, *A. nidulans* infections tend to be more aggressive than those caused by *A. fumigatus*, with a high propensity for local extension or dissemination. Common sites for local extension of *A. nidulans* infections are the adjacent pleura, chest wall and vertebrae [4, 5, 25, 98, 99, 147]. In a recent review of osteomyelitis cases caused by *Aspergillus* species in CGD patients, the site of infection in 12 out of 14 cases of *A. nidulans* osteomyelitis was in the ribs or vertebrae and represented contiguous spread from the primary pulmonary lesion. By comparison, in only 4 out of 10 cases of *A. fumigatus* osteomyelitis the infection was contiguously spread from the lungs to the ribs, sternum or vertebrae; in the remaining six cases there was no pulmonary lesion and the site of infection primarily involved the cranium, humerus, femur and tibia [43]. Dissemination of primary pulmonary aspergillosis may occur in several sites, including the central nervous system, orbit, internal organs, bones and the skin [4, 43, 52, 147].

In contrast to neutropenic hosts, where invasive aspergillosis is characterized by hyphal angioinvasion, coagulative necrosis and rare inflammatory cells, pathological studies in CGD patients or mice with *Aspergillus* infection usually reveal extensive pyogranulomatous lesions composed mostly of neutrophils, with giant cell formation and occasional foci of necrosis with microabscesses. Despite accumulation of neutrophils, however, fungal hyphae remain intact due to the attenuation of microbicidal activity of host phagocytes [4, 39, 79, 157]. Recently, the aberrant and persistent inflammatory response of CGD patients to a variety of infectious stimuli was found to be associated with delayed apoptosis of neutrophils and deficient production of the anti-inflammatory mediators prostaglandin D_2 and transforming growth factor-β [9, 18].

Timely diagnosis of invasive aspergillosis in CGD patients requires a high degree of suspicion. For pulmonary infection, even in the presence of mild or non-specific symptoms, radiological evaluation of the lungs should be performed using high-resolution computed tomography (CT). In these patients, the differential diagnosis of the cause of pulmonary lesions should include *S. aureus*, *Nocardia* spp., *Burkholderia cepacia* as well as non-*Aspergillus* fungal

pathogens, while mixed infections are not uncommon [181]. The radiological findings of pulmonary aspergillosis may be varying and non-specific, including segmental and lobar consolidation, perihilar infiltrates, multiple small nodules, peripheral nodular masses and pleural effusions. Because of the above described differences in the inflammatory response in invasive aspergillosis between CGD and neutropenic patients, "classic" radiological signs of this infection in the lungs, such as halo, air crescent and other signs of cavitation within areas of consolidation, are not typically seen in CGD patients [136, 161]. When the infection involves sites other than the lung, imaging studies may also include magnetic resonance imaging (MRI) or even radioisotope bone scans. Brain involvement often presents as rim enhancing lesions in the MRI, consistent with brain abscesses [5, 161].

Besides imaging studies, every effort to establish the diagnosis through isolation and identification of the organism or through visualization of hyphae in appropriately stained tissue specimens should be pursued. Bronchoalveolar lavage fluid and specimens obtained by percutaneous or even open lung biopsy may be useful for this purpose. Among other recently introduced non-invasive diagnostic modalities for invasive aspergillosis, the detection of aspergillus galactomannan antigen in serum through currently available enzyme-linked immunosorbent assays is encouraging. However, some reports indicate high false positive results in young infants [61, 136, 151]. Additionally, in CGD hosts, both in humans and mice, the galactomannan assay may have low sensitivity as compared to other immunocompromised populations, possibly because of the lack of significant angioinvasion in the former [39, 169, 176]. For these reasons, galactomannan testing may have limitations in pediatric CGD patients. Other diagnostic modalities, including the (1,3)-β-D glucan assay and the detection of *Aspergillus* nucleic acid by polymerase chain reaction, either have not yet been standardized or their sensitivity and specificity in pediatric CGD patients has not been studied [136].

The introduction of newer triazoles and echinocandins during recent years has increased the options for medical treatment of invasive aspergillosis. Voriconazole was superior to amphotericin B deoxycholate as primary therapy of invasive aspergillosis in an open, randomized trial [60] and is currently the antifungal treatment of choice for this infection. This newer triazole has also demonstrated efficacy against infections due to the more virulent *A. nidulans* in CGD patients, according to case reports [139, 165]; however, wide clinical experience regarding its use against this species is still limited. Particular consideration should be given to appropriate dosing of voriconazole in the pediatric population. Previous studies have shown that voriconazole clearance in children is greater than that of adults and drug exposure in pediatric patients following the initially recommended maintenance dosage of 4 mg/kg IV every 12 hours is significantly lower compared to adults [173]. Recent data suggest that, in order to achieve drug exposure comparable to that of adults treated with 4 mg/kg IV every 12 hours, children should be dosed at 8 mg/kg every 12 hours [172]. Among other agents, the lipid formulations of amphotericin B have at least comparable efficacy with amphotericin B deoxycholate, with the advantage of less nephrotoxicity and infusion-related reactions [121]. Both posaconazole and caspofungin have shown efficacy as salvage therapy for invasive aspergillosis in patients refractory to or intolerant of conventional therapy [96, 175]. In a series of eight CGD patients with *Aspergillus* or other filamentous fungal infections that failed or were intolerant of primary antifungal therapy, salvage treatment with posaconazole was safe and effective [146]. Dosage of posaconazole in pediatric patients is not well understood and requires further study for its safety and plasma pharmacokinetics. Other recent studies have shown that dosing of caspofungin at 1 mg/kg/day in pediatric patients results in plasma levels that are lower than those of adults treated with 50 mg/day and that drug exposure comparable to adults is achieved by dosing at 50 mg/m^2/day (maximum 70 mg/day) in the pediatric population [171].

In addition to antifungal chemotherapy, surgical debridement, sometimes extensive, may be needed, particularly in cases of osteomyelitis or aggressive pulmonary infection caused by *A. nidulans* [43, 147]. However, this need for early surgical intervention may be altered with the availability of newer antifungal triazoles and accumulation of further evidence of their clinical efficacy in this setting.

In the case of refractory or life-threatening infections, other interventions may be considered as adjunctive therapy. Transfusion of granulocytes from healthy donors may partially restore the patient's impaired phagocytic activity and potentially improve outcome. These healthy granulocytes have been shown to cooperate with those of CGD patients for synergistic damage of *Aspergillus* hyphae. This synergistic effect may be mediated through diffusion of hydrogen peroxide from the normal granulocytes [135]. The use of granulocyte colony-stimulating factor (G-CSF) has markedly enhanced the yield of leucocytes from healthy donors and helped to optimize granulocyte dose per patient body weight. Preliminary clinical data appear encouraging, although well-designed clinical trials are still lacking [13, 17, 66, 67]. If administered, granulocyte transfusions should be given several hours apart from amphotericin B, in order to avoid the risk of pulmonary leukostasis [185].

IFN-γ is a key cytokine in the innate and adaptive host response against fungi. It stimulates migration, adherence and phagocytic activity of neutrophils and macrophages, and has an important regulatory role in the development of protective Th1 responses against the invading organism [6]. Earlier studies demonstrated some augmentation or partial

restoration of superoxide production of phagocytes from CGD patients after addition of IFN-γ [46, 47, 144]. Indeed, Rex et al. demonstrated that IFN-γ therapy augments the ex vivo ability of CGD neutrophils to damage *Aspergillus* hyphae [134]. However, subsequent reports did not confirm that enhancement of superoxide production is the principal mechanism of IFN-γ action in CGD individuals [114, 160, 184]. Consequently, the beneficial prophylactic effect of IFN-γ in CGD patients (see next paragraphs) is currently thought to occur through mechanisms other than augmentation of NADPH oxidase complex function [4, 102]. IFN-γ has also been used as adjunctive therapy of invasive aspergillosis in CGD patients in a number of case reports [11, 100, 143]. Its clinical efficacy in this setting, however, has not been systematically evaluated.

Due to the increased risk for development of devastating fungal infections in CGD patients, the possibility of antifungal prophylaxis has been investigated. Itraconazole has demonstrated efficacy in reducing the frequency of severe invasive fungal infections when administered prophylactically in CGD patients [53, 113]. In the large, double-blind, placebo-controlled trial conducted by the National Institutes of Health, itraconazole was administered prophylactically as capsule formulation, together with food or carbonated beverage to maximize absorption, at a single daily dose of 100 mg for patients younger than 13 years and weighing less than 50 kg (the youngest patient in the study was 5 years old) or 200 mg for all other patients. During a total patient follow-up of 113 patient-years, few adverse events were noted, including rash, moderate liver enzyme elevation and headache in three patients (one side-effect per patient), which resolved after discontinuation of the drug [53]. In the series published by Liese et al., eight patients received itraconazole prophylaxis for a mean period of 23 months with an average dose of 5.1 mg/kg of body weight, and no adverse effects were observed [90]. Long-term itraconazole prophylaxis in three CGD patients has been associated with infection from *A. fumigatus* resistant to itraconazole and other azoles [168]. Additional information on the emergence of resistance and possibly a comparison between continuous and intermittent prophylaxis is warranted. However, the efficacy of itraconazole in preventing invasive fungal infections in CGD patients and its high safety profile, demonstrated by the previous studies, strongly support its use as prophylaxis in this patient population. An oral suspension of itraconazole, more recently developed, has better bioavailability than the capsules when taken without food.

A randomized, placebo-controlled trial demonstrated that prophylactic administration of IFN-γ in CGD patients was associated with a significant reduction in the frequency of serious infections [160]. Long-term prophylaxis of CGD patients with IFN-γ was safe and well tolerated, with fever being the main adverse event. In this patient series (in which, however, 27 of the 76 patients were co-enrolled in a double-blind study of itraconazole prophylaxis for prevention of fungal infections [53]), the incidence of serious fungal infections was 0.12 cases per patient-year [102]. In these studies, IFN-γ was administered subcutaneously three times per week at a dose of 50 $\mu g/m^2$ in patients with a body surface area ≥ 0.5 m^2 and 1.5 μg/kg in those with body surface area <0.5 m^2 [102, 160].

Candida infections in CGD patients

Infections caused by *Candida* species in CGD patients are less common than invasive aspergillosis. In the United States registry of 368 patients with CGD, *Candida* species ranked as the most common cause of meningitis (20% of 15 cases), the third most common cause of bacteremia/fungemia (11% of 65 cases) and suppurative adenitis (7% of 194 cases), and the fourth most common cause of death (4% of 65 cases). In the same series, *Candida* species were isolated only from 2% of 290 cases of pneumonia, 4% of 156 cases of subcutaneous abscesses and 2% of 98 cases of liver abscesses [181]. When interpreting these data, however, one should consider that some of the above cases may not be related to the primary host defense impairment associated with CGD but to other predisposing factors such as use of intravascular catheters, prolonged antimicrobial drug administration or possible steroid treatment. Indeed, mucosal candidiasis is very uncommon among CGD patients. There are no data on the relative frequency of different *Candida* species isolated from CGD patients. *Candida albicans*, *Candida glabrata*, *Candida lusitaniae* and *Candida dubliniensis* have been associated with invasive disease according to individual case reports [32, 41, 45, 49, 89, 97, 106, 110, 120].

The clinical presentation of *Candida* infection in CGD patients, in addition to those already mentioned above (meningitis, blood stream infection, lymphadenitis, pneumonia, subcutaneous or liver abscesses), may include esophagitis, ocular involvement (keratitis) and occasionally disseminated infection [14, 41, 89]. Lymphadenitis has been reported to involve the cervical but also intra-abdominal (retroperitoneal) lymph nodes [45]. Young infants seem to be at risk for disseminated infection [89].

The diagnosis of invasive candidiasis is established, or supported, in many cases by the isolation of *Candida* species from normally sterile (blood, cerebrospinal fluid) or clinically relevant biological specimens; not infrequently, tissue biopsy and histological examination is also necessary. A typical finding in this case is the presence of a necrotizing granulomatous lesion with possible microabscess formation and yeast forms or pseudohyphae [45, 89].

A number of antifungal agents, including the azoles, echinocandins and amphotericin B may be used in the treatment of *Candida* infections in CGD patients. *Candida glabrata* and *C. krusei* are frequently resistant to fluconazole and a significant proportion of isolates from these species may also have reduced susceptibility to amphotericin B. In addition, *C. lusitaniae* may be resistant to amphotericin B [123]. The choice of an appropriate agent should take into account a number of factors, including previous exposure to antifungal agents, the species identified (or, prior to identification, the incidence of fluconazole-resistant non-*C. albicans* species), patient's condition (i.e. hemodynamic instability, pre-existing organ dysfunction), concomitant nephrotoxic or hepatotoxic medications as well as the possibility of drug interactions, and has been extensively reviewed elsewhere [123, 156]. The administration of granulocyte transfusions or IFN-γ as adjunctive treatment as well as the use of itraconazole and IFN-γ as antifungal prophylaxis in CGD patients has already been discussed in the previous section of *Aspergillus* infections in these patients.

Other fungal infections in CGD patients

A number of other fungi have also been implicated in causing infection in CGD patients. Among these organisms, *Paecilomyces* species have been reported most commonly [33, 152, 153, 177, 180] and ranked as the third most common cause of osteomyelitis in CGD patients in the United States registry, after *Serratia* and *Aspergillus* (8% of 90 cases) [181]. A number of case reports also have implicated *Scedosporium* and *Trichosporon* species [12, 56, 70, 75, 88, 127, 128, 186], while *Acremonium*, *Exophiala*, *Penicillium*, *Rhizopus*, *Fusarium*, *Microascus*, *Inonotus* and *Chrysosporium* species have been rarely reported [15, 74, 105, 137, 142, 158, 181].

Most of the *Paecilomyces* infections in CGD patients were caused by *Paecilomyces variotii* [33, 177, 180]; *Paecilomyces lilacinus* was implicated in only one case [153]. In most cases the infection was manifested as osteomyelitis (occasionally multifocal), pneumonia, soft tissue infection, or abscess involving the lung, abdominal wall or spleen [33, 152, 153, 177, 180, 181]. As with other infections in CGD patients, histological examination of infected tissues may reveal granuloma formation with presence of giant cells [152]. Although the majority of cases of *Paecilomyces* infection were treated medically, in a number of patients surgery was required for pus drainage and debridement. Most of the reported cases were treated initially with amphotericin B (duration of treatment from 4 weeks to 2 months) followed by itraconazole for one year; in one case a 14-month course of fluconazole and flucytosine was administered [177]. Two patients also received adjunctive treatment with IFN-γ [33, 152]. In vitro susceptibility data suggest that *P. variotii* is generally susceptible to amphotericin B, most of the azoles (with the exception of fluconazole), caspofungin and flucytosine [1, 38]. In vitro and clinical resistance, however, has been occasionally observed for voriconazole, associated sometimes with prior exposure to this newer triazole [29]. In contrast to *P. variotii*, *P. lilacinus* is usually resistant to conventional antifungal agents, including itraconazole and amphotericin B. The newer triazoles, voriconazole, ravuconazole and posaconazole demonstrate good in vitro activity against *P. lilacinus*; favorable clinical outcomes have been reported after administration of voriconazole [125].

The majority of reported infections by the genus *Scedosporium* in CGD patients have been caused by *S. apiospermum*, which is the anamorph of *Pseudallescheria boydii* [56, 70, 127, 128]. The sites most commonly involved are the lungs and soft tissues, with occasional extension to the bone. Pulmonary disease may include infiltrates or abscess formation, and may resemble invasive aspergillosis in clinical presentation, as fever, hemoptysis, cough and tachypnea can be observed. Dissemination from the lung to distant foci (such as the scalp) has been reported [127]. *Scedosporium apiospermum* is almost invariably resistant to amphotericin B but generally susceptible to the newer triazoles voriconazole, posaconazole and ravuconazole [23, 56, 70, 107]. IFN-γ has been used as adjunctive therapy in three cases [56, 70, 127]. Recently a case of brain abscess caused by *Scedosporium prolificans* in a CGD patient has been reported [12]. This species is usually resistant to most antifungal agents, including the newer triazoles [107]. The patient's abscess resolved following combination therapy with voriconazole and terbinafine, based on previous in vitro studies showing synergism between these agents against *S. prolificans* [108]; adjunctive treatment with granulocyte transfusions, IFN-γ and G-CSF was also administered.

In most of the infections caused by yeasts of *Trichosporon* spp. in CGD patients, *Trichosporon inkin* was isolated [75, 115, 129, 186]; *Trichosporon pullulans* has also been isolated from one patient following immunosuppressive therapy (including steroids and infliximab) for colitis [88]. *Trichosporon inkin* infections were manifested as pneumonia and in one case as a lung abscess penetrating the chest wall. In two out of four reported cases, however, the diagnosis of pneumonia was made on routine CT scan, while the patients were asymptomatic. *Trichosporon pullulans* infection also presented as pneumonia with subsequent hematogenous dissemination of the organism to multiple sites. Despite in vitro susceptibility of *T. inkin* to a number of conventional and newer (i.e. second generation triazoles) antifungal agents, treatment of these infections in CGD patients with antifungal therapy alone was ineffective and surgery was required [75, 129, 186]. Similarly, *T. pullulans* pneumonia

did not respond to a combination of voriconazole, amphotericin B and subsequently caspofungin, and progressed to respiratory failure and septic shock [88]. *Trichosporon* spp. are usually resistant to the fungicidal effects of amphotericin B [174].

The clinical presentation, treatment and outcome of infections caused by fungal organisms other than *Aspergillus* and *Candida* in CGD patients are summarized in Table 2.

Myeloperoxidase deficiency

Deficiency of myeloperoxidase is the most common inherited phagocytic disorder with an estimated prevalence of 1 in 2,000–4,000 in Europe and the United States [35, 124]. Myeloperoxidase is a component of the primary azurophilic granules of neutrophils and lysosomes of monocytes, which catalyzes the transformation of hydrogen peroxide generated during the oxidative burst to highly microbicidal hypochlorous acid in the presence of chloride anion. Of those affected, approximately half have a complete deficiency of myeloperoxidase, while the rest have structural or functional defects of the enzyme [87].

Phagocytes deficient in myeloperoxidase expressed only a mild defect in killing of *S. aureus*, but a marked defect in killing of *C. albicans* [124]. In addition, myeloperoxidase-deficient neutrophils failed to damage *A. fumigatus* hyphae, but did damage *Rhizopus oryzae* hyphae, suggesting species-dependent differences in impairment of fungicidal activity [40]. In agreement with these in vitro observations, myeloperoxidase-deficient mice had a significantly increased

Table 2 Infections caused by fungal organisms other than *Aspergillus* and *Candida* in CGD patients

Fungus	Clinical presentation	Treatment administered	Number of cases with favorable outcome among those for which it was reported [references]
Paecilomyces variotii	Osteomyelitis, pneumonia, soft tissue infection, abscess (lung, spleen)	Amphotericin B followed by itraconazole; fluconazole plus flucytosine plus surgery; adjunctive IFN-γ in 2 cases	4 of 4 [33, 177, 180]
Paecilomyces lilacinus	Abdominal wall abscess	Amphotericin B[a]	1 of 1 [153]
Scedosporium apiospermum	Pneumonia, lung abscess, soft tissue infection, osteomyelitis, mycetoma	Azoles (miconazole, itraconazole, lately voriconazole); amphotericin B (followed by azoles); surgery (3 cases); adjunctive IFN-γ (3 cases)[b]	4 of 5 [56, 70, 127, 128]
Scedosporium prolificans	Brain abscess	Voriconazole plus terbinafine; adjunctive granulocyte transfusions, IFN-γ, G-CSF	1 of 1 [12]
Trichosporon inkin	Pneumonia, lung abscess	Azoles (miconazole, ketoconazole, itraconazole, voriconazole, posaconazole); amphotericin B; caspofungin; surgery (4 cases); granulocyte transfusions (3 cases)[c]	4 of 5 [75, 115, 129, 186]
Trichosporon pullulans	Pneumonia	Voriconazole, amphotericin B, caspofungin	0 of 1 [88]
Acremonium strictum	Pneumonia	Amphotericin B, ketoconazole	1 of 1 [15]
Exophiala dermatitidis	Pulmonary and central nervous system infection	Amphotericin B, flucytosine, ketoconazole, fluconazole; surgery; granulocyte transfusion	1 of 1 [74]
Penicillium piceum	Pulmonary nodule, osteomyelitis	Voriconazole; surgery	1 of 1 [142]
Rhizopus species	Pneumonia	Not reported	Not reported [181]
Fusarium species	Pneumonia	Not reported	Not reported [181]
Microascus cinereus	Skin lesions	Amphotericin B	1 of 1 [105]
Inonotus (Phellinus) tropicalis	Soft tissue infection/ abscess, osteomyelitis	Not reported	Not reported [158]
Chrysosporium zonatum	Pneumonia, pleuritis, pericarditis, osteomyelitis	Amphotericin B, itraconazole	1 of 1 [137]

[a] However, *P. lilacinus* is not usually susceptible to amphotericin B (see text)
[b] In contrast to amphotericin B, voriconazole, posaconazole and ravuconazole display good in vitro activity against *S. apiospermum*
[c] Antifungal therapy alone was ineffective in *T. inkin* infections and surgery was required

susceptibility to pulmonary infections caused by *C. albicans*, *C. tropicalis* and *Trichosporon asahii*, and a slight but significantly delayed clearance of *A. fumigatus* from the lungs compared to healthy controls; however, clearance of *C. glabrata* was comparable between myeloperoxidase-deficient and control mice [7, 8].

The great majority of individuals with myeloperoxidase deficiency are asymptomatic. However, increased susceptibility to *Candida* infections may be observed, especially if other predisposing conditions such as diabetes are present. These infections occur in less than 5% of reported myeloperoxidase-deficient subjects [82, 87]. In most of the reported cases the species implicated was *C. albicans*; in two patients *C. parapsilosis* was isolated. The infection presented as pneumonia, osteomyelitis, meningitis, liver abscess, pustular dermatitis, deep mucocutaneous or disseminated candidiasis, and generally responded to antifungal treatment [27, 31, 86, 94, 118, 119, 124, 178]. Antifungal prophylaxis is not advocated for myeloperoxidase-deficient individuals.

Leukocyte adhesion deficiency

Leukocyte adhesion deficiency (LAD) includes a group of rare inherited conditions, characterized by defects in proteins involved in leukocyte rolling, adhesion and cytoskeletal regulation [81, 87]. Four types are currently recognized: LAD1 is caused by a mutation of the gene encoding the common β_2 subunit, CD18, of integrin heterodimers, and thus resulting in lack of integrin β_2 adhesion molecules in the neutrophils; LAD2 is a defect of carbohydrate fucosylation, resulting in lack of fucosylated sialyl-Lewis-X on the leukocytes and subsequent impaired binding of the leukocytes to selectin molecules of endothelial cells; LAD3 is possibly due to abnormality of Rap1, a regulatory GTPase involved in integrin activation; and the fourth type is LAD with Rac2 deficiency. Rac2 is a GTPase involved in the regulation of NADPH oxidase and the actin cytoskeleton [81, 87].

Patients with LAD generally present with delayed separation of the umbilical cord, poor wound healing, leukocytosis and increased susceptibility to infections, as a result of inability of the leukocytes to migrate to the sites of infection in sufficient numbers [81]. Increased susceptibility to fungal infections has been reported in older reviews, including localized or disseminated infections caused by *Candida* and *Aspergillus* species [48, 87]. However, most cases of LAD reported in the literature were complicated by bacterial infections and there is a notable paucity of reports of invasive mycoses among these patients. In a recently published series of nine patients suffering from the LAD1/variant syndrome (a distinct clinical entity consisting of a moderate LAD1-like syndrome and a severe Glanzman-like bleeding tendency), two of the patients developed mould infections. One of these patients, a 6-month-old infant, developed chronic bilateral pulmonary infiltrates, not responding to multiple antimicrobial agents, with *A. fumigatus* cultured from bronchoalveolar lavage fluid; the infiltrates resolved after treatment with amphotericin B. The other developed painful subcutaneous nodules at 2 years of age with *Fusarium oxysporum* isolated from the blood; the patient responded to amphotericin B for 12 weeks, combined with flucytosine for the first 4 weeks and removal of the intravascular catheter [80].

Congenital neutropenias

This group of immunodeficiencies comprises isolated neutropenias, such as the so-called severe congenital neutropenia (Kostmann syndrome) and cyclic neutropenia, and neutropenias associated with metabolic or immunological disorders or with a particular syndrome (such as Shwachman-Diamond syndrome) [87, 193].

Patients with severe congenital neutropenia are at increased risk of life-threatening infections caused mainly by bacterial pathogens. Treatment with recombinant human G-CSF increases neutrophil count and decreases the incidence of severe infections; in the absence of response to G-CSF, hematopoietic stem cell transplantation is indicated [22, 193]. Fungal infections reportedly have been observed in these patients [193], but their frequency seems to be relatively low, and relevant information in the literature is scarce. In a small series of eight patients who showed no or partial response to treatment with recombinant human G-CSF, one developed fungal infection prior to bone marrow transplantation [194]. In another patient, documented pulmonary infection caused by a filamentous fungal organism occurred while on G-CSF therapy [37]. Finally, fungal infections are rare in patients with cyclic (probably due to the limited duration of the neutropenic phase) or other forms of congenital neutropenia [87, 193].

Defects in the IFN-γ/IL-12 axis

This group of immune disorders is caused by defects in components of IL-12, the IL-12 receptor, the IFN-γ receptor or the signal transducer and activator of transcription (STAT) 1, which is a molecule that allows signaling via the IFN-γ receptor. IL-12 is the main stimulus for production of IFN-γ by Th1 T-cells and NK cells; IFN-γ, as already mentioned, is a key cytokine in the development of innate and adaptive immune responses to a variety of infectious stimuli [81, 87].

Patients with defects in the IFN-γ/IL-12 axis are particularly susceptible to infections caused by intracellular pathogens such as mycobacteria and *Salmonella* spp. [81, 87]. Recently, disseminated infections caused by the dimor-

phic yeasts *Histoplasma capsulatum* and *Paracoccidioides brasiliensis* were reported in patients with deficiency of IFN-γ receptor 1 and the β1 subunit of the IL-12/IL-23 receptor, respectively [111, 195]. The occurrence of these fungal infections in this patient group is consistent with in vitro and in vivo studies suggesting the important role of IFN-γ and IL-12 in host immune responses against these organisms [111, 155, 196]. Control of relapses of histoplasmosis in the first patient was achieved through prophylactic administration of itraconazole and IFN-γ [195].

Cellular and combined immunodeficiencies

Severe combined immunodeficiency

The term "severe combined immunodeficiency" (SCID) refers to an expanding and genetically diverse group of inherited immune disorders, characterized by profound deficiency of T- and B- cell (and sometimes NK-cell) function. X-linked SCID with deficiency of common γ chain accounts for approximately 44% of SCID cases in the United States. A number of other molecular defects identified in autosomal chromosomes are responsible for other forms of this combined immunodeficiency [19, 20, 81]. Affected infants are lymphopenic and particularly vulnerable to serious infections caused by viruses, bacteria, mycobacteria and *P. jiroveci*. Fungal pathogens also have been implicated, including mainly *Candida* but also *Aspergillus* and other rare pathogens, such as *Acremonium* and *Pichia* species [10, 19, 78, 81, 83, 154, 190, 191].

Candida infections among SCID patients are caused mostly by *C. albicans* and may manifest as oral thrush, pneumonia or meningitis [19, 50, 154, 170, 190]. Persistent oral candidiasis in a neonate or young infant may in fact be a presenting symptom of SCID [50, 170]. Pulmonary aspergillosis was diagnosed in two infants with X-linked SCID and responded to antifungal treatment followed by hematopoietic stem cell transplantation [78, 191]. In one of these two cases, diagnosis was facilitated by increased levels of (1,3)-β-D glucan in serum and aspergillus galactomannan antigen in bronchoalveolar lavage fluid [191]. The infection caused by *Acremonium falciforme* in a 1-year-old girl was localized in the gastrointestinal tract and responded to treatment with amphotericin B, itraconazole and G-CSF [83]. The yeast *Pichia anomala* was associated with blood stream infection in an 11-month-old boy with SCID, which resolved after treatment with amphotericin B [10].

DiGeorge syndrome

DiGeorge syndrome is usually due to deletions in chromosome 22q11.2, resulting in abnormal development of the third and fourth pharyngeal pouches during early embryogenesis, and leading to hypoplasia or aplasia of the thymus and parathyroid glands. Other structures may also be affected resulting in abnormalities of the heart, great vessels, face and esophagus. Patients have variably decreased number of T-cells, and those with significant thymic hypoplasia or aplasia ("complete" DiGeorge syndrome) exhibit a SCID-like immunodeficiency pattern [19, 81, 190]. Invasive aspergillosis has been reported for patients with DiGeorge syndrome, presenting as pneumonia or fatal disseminated infection [103, 149]. In the latter case, the infection involved a newborn boy with atrioventricular septal defect and was manifested with clinical and laboratory signs of sepsis as well as large hyperdense periventricular areas shown by brain echogram, which were interpreted as intraparenchymal bleeding. On autopsy, these areas were hemorrhagic necroses caused by occlusion of vessels by *Aspergillus* hyphae and fibrin thrombi, while fungal dissemination was also evident in the adrenal gland, epicardium and pleura [103].

X-linked hyper-IgM syndrome

The X-linked hyper-IgM syndrome is caused by mutations in the gene encoding the CD40 ligand, a T-lymphocyte cell surface molecule that is necessary for T-lymphocytes to induce B-lymphocyte switching from IgM to IgG, IgA and IgE production. Thus, affected individuals have reduced levels of IgG, IgA and IgE, with normal or elevated IgM. They also have a variable defect in antigen-induced proliferative responses of T-lymphocytes as well as in T-lymphocyte and macrophage effector function. This X-linked hyper-IgM syndrome, which combines cellular and humoral immune deficits, should be distinguished from the autosomal hyper-IgM syndrome, which is a pure humoral defect caused by mutations in different genes [20, 81, 182].

Patients with the X-linked hyper-IgM syndrome have increased susceptibility to bacterial, viral, parasitic and fungal infections. In a recent review of 79 patients, the most common fungal pathogens implicated were *Candida*, *Cryptococcus* and *Histoplasma*. *Candida* infection manifested as oral candidiasis, esophagitis or sepsis; cryptococcal infection involved the central nervous system and the blood stream; and histoplasmosis presented as pneumonia or hepatitis [182]. Case reports also suggest that cryptococcosis may cause lymphonodular or disseminated disease [69, 85, 159]. *Histoplasma capsulatum* infection in these patients may also present as cutaneous or disseminated disease, invading the lungs, bone marrow and blood stream [63, 189].

Wiskott-Aldrich syndrome

The Wiskott-Aldrich syndrome is an X-linked recessive disorder characterized by thrombocytopenia and small

platelets, eczema, recurrent infections and increased risk for autoimmune manifestations and malignancy. It is due to various mutations or even deletions in the gene encoding the Wiskott-Aldrich syndrome protein (WASP), which is expressed selectively in lymphocytes and megakaryocytes and is involved in cell signaling and cytoskeleton reorganization [19, 81]. In a recent study from Japan, the clinical course of patients with Wiskott-Aldrich syndrome correlated with the presence or absence of WASP. In other words, those patients with no detectable or truncated WASP (WASP-negative) clearly had a more severe course and worse prognosis than those with normal or reduced amounts of full-length mutated WASP (WASP-positive), including greater susceptibility to infections. Fungal infections were observed exclusively in WASP-negative patients, with three episodes of invasive aspergillosis and nine of candidiasis among 23 WASP-negative patients [68]. In 2000, among 267 hospitalized children with Wiskott-Aldrich syndrome in the United States, 81 were diagnosed with invasive aspergillosis, reflecting an incidence of 30%. This surprisingly high incidence, however, may have been confounded by the fact that the majority of patients with Wiskott-Aldrich syndrome undergo bone marrow transplantation [192].

Humoral immunodeficiencies

Common variable immunodeficiency (CVID)

Humoral immunodeficiencies typically are associated with increased susceptibility to bacterial, enteroviral but not fungal infections. CVID includes a heterogeneous group of disorders with variable presentation, for which the genetic and molecular basis is largely unknown. CVID is characterized by poor antibody responses to exogenous antigens, with low IgG, usually low IgA and sometimes low IgM levels, resulting from defective B-cell differentiation into plasma cells. It has been recognized, however, that a significant proportion of CVID patients shows abnormalities in T-cell phenotype and function, including secretion of cytokines IL-2, IL-4, IL-6, IL-7, IL-10 and IFN-γ, as well as defects in early T-cell receptor (TCR) signaling events. In addition, deficiency of co-stimulatory molecules such as ICOS, a T-cell surface protein involved in T-cell-dependent B-cell differentiation, has been demonstrated in some cases [81, 140, 190].

Perhaps the variability of immune deficits in CVID together with the T-cell abnormalities in a number of cases may explain the occasional occurrence of fungal infections in this patient population. Oropharyngeal candidiasis has been reported among CVID patients and an increased susceptibility to ex vivo nail infection with *C. albicans* and *Trichophyton mentagrophytes* has been demonstrated [95, 130]. *Histoplasma capsulatum* has been implicated in disseminated infection (with manifestations from the gastrointestinal, lower respiratory and central nervous system) [73, 131] and isolated meningitis [34]. Invasive aspergillosis has been reported in two cases, manifesting as pulmonary infection or hepatic abscess [162, 164]. Finally, *Penicillium marneffei* was associated with systemic infection in a child with CVID. This mycosis manifested with a juvenile rheumatoid arthritis-like picture, including oligoarthritis, low grade fever and hepatosplenomegaly, while the fungus was isolated from the blood, bone marrow, synovial fluid and lymph nodes [92]. In most of the above cases, fungal infections responded to appropriate antifungal treatment; immunoglobulin replacement was administered in two patients [92, 162].

Other primary immunodeficiencies

Hyper-IgE syndrome

Hyper-IgE syndrome (also known as Job's syndrome) is characterized by extremely elevated serum IgE levels, eosinophilia, recurrent staphylococcal infections of the skin, lungs and other organs resulting in abscess or pneumatocele formation, chronic eczematous dermatitis, skeletal abnormalities and coarse facial features. The precise molecular defects associated with this syndrome have not yet been defined. Despite normal fractions of $CD4^+$ and $CD8^+$ T-cell populations, there is decreased humoral and cellular immune response to new antigens [57, 81, 190]. Recent studies in patients with hyper-IgE syndrome have demonstrated a distorted Th1/Th2 cytokine production pattern towards a non-protective Th2 response. This cytokine deregulation was manifested by decreased production of IFN-γ in response to infectious stimuli (*S. aureus*, *C. albicans*) or a combination of IL-12 and IL-18 [16, 30, 116]. The mode of inheritance of hyper-IgE syndrome appears to be autosomal dominant with variable penetrance [57, 81, 190]. Recently, an autosomal recessive form has been described, which has a distinctive immunologic and infectious phenotype and lacks the skeletal involvement seen in the autosomal dominant form [133].

Susceptibility to fungal infections has long been reported for patients with hyper-IgE syndrome and may at least in part be related to the dysregulation of Th1/Th2 cytokine production mentioned above. Among yeast infections, chronic candidiasis of mucosal sites and nail beds is a common finding, described in 83% of 30 patients with the autosomal dominant and in 77% of 13 patients with the autosomal recessive form of the syndrome [2, 57, 133]. *Candida* infection (commonly due to *C. albicans*) also has presented as endocarditis, endophthalmitis, visceral candi-

diasis, and disseminated disease with multiple pulmonary nodules, hepatic lesions and blood stream infection [57, 59, 187, 188]. *Cryptococcus neoformans* infection in patients with hyper-IgE syndrome has been reported to affect the gastrointestinal tract, particularly the esophagus and colon. Esophageal cryptococcosis presented unusually with massive hematemesis, while colonic cryptococcosis presented as Crohn's disease [65, 71]. Cryptococcal meningitis has also occurred [54]. Another yeast affecting the gastrointestinal tract in patients with hyper-IgE syndrome is *H. capsulatum*; ileocecal histoplasmosis, again mimicking Crohn's disease, as well as recurrent colonic infection have been reported [3, 21]. Finally, generalized lymphadenopathy (nontender, firm, 1.5–3.0 cm lymph nodes in the cervical, axillary, inguinal, perihilar and retroperitoneal areas) with no constitutional symptoms, caused by infection with the yeast *Trichosporon asahii*, led to the diagnosis of hyper-IgE syndrome in an otherwise asymptomatic 10-year-old boy [28].

In addition to yeast infections, *Aspergillus* species (most commonly *A. fumigatus*) have been reported to affect patients with hyper-IgE syndrome. The usual pathogenetic mechanism is colonization of preexisting pneumatoceles, which are a consequence of previous suppurative pulmonary infections, with *Aspergillus* conidia, leading eventually to the formation of a fungus ball or aspergilloma. Commonly, one cavitary lesion is infected; however, multiple pulmonary aspergillomas may occur in a patient. Local invasion of the lung parenchyma can be observed; in addition, dissemination to the central nervous system and formation of mycotic aneurysms is possible. The usual presentation includes non-productive cough or hemoptysis. Most cases in the literature have been managed with a combination of antifungal therapy and surgical resection [4, 51, 57, 58, 141, 166, 183]. Another filamentous fungus, *S. prolificans*, was isolated from lung and brain lesions of a patient with hyper-IgE syndrome in a recent autopsy series [51].

Chronic mucocutaneous candidiasis

Chronic mucocutaneous candidiasis (CMC) comprises a heterogeneous group of primary or secondary (i.e. due to HIV infection, inhaled corticosteroid use) immunological disorders associated with persistent or recurrent *Candida* infections of the skin, nails and mucous membranes. *C. albicans* is the species implicated in nearly every case. The precise molecular defect is not known for most forms of primary CMC, with the exception of the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome [81, 167]. Impaired cellular immunity to *Candida* species, including negative delayed-type hypersensitivity skin tests and absent or low T-cell proliferation in vitro, as well as impaired production of macrophage inhibitory factor have been reported for patients with primary CMC. Recent human studies have demonstrated inadequate production of Th1 cytokines (IFN-γ, IL-2) in response to *Candida* species [91].

Several clinical syndromes of CMC have been described and comprehensively reviewed by Kirkpatrick [77] including:

- Familial CMC. Most patients present with chronic/recurrent oral candidiasis by the age of 2 years; cutaneous and ungula candidiasis are less common.
- APECED, also known as autoimmune polyendocrine syndrome type 1. This rare autosomal recessive disease may occur worldwide but is relatively more common in Iranian Jews, Sardinians and Finns. It is due to mutations in the autoimmune regulator (AIRE) gene (21q22.3). The diagnosis is classically made in the presence of at least two of the following features: mucocutaneous candidiasis, hypoparathyroidism and adrenocortical failure. A number of additional autoimmune endocrinopathies, ectodermal defects and other manifestations may variably be observed [126].
- Chronic localized candidiasis (*Candida* granuloma). Skin lesions exhibit marked hyperkeratosis and acanthosis, resulting in the formation of thick, tightly adherent crusts or, rarely, cutaneous horns.
- CMC with thymoma. This entity appears to occur exclusively in adults.
- CMC with keratitis. The keratitis may affect children as young as 2 years of age and precede the presentation of mucocutaneous candidiasis.

Patients with CMC rarely develop invasive disease or disseminated *Candida* infection. However, *Candida* meningitis has occurred following a dental procedure in a patient with oral candidiasis. Occasionally these patients may develop other bacterial, viral or fungal infections. The latter may include dermatophyte infections of the skin and nails, which could be misinterpreted as candidiasis refractory to antifungal treatment. Invasive or disseminated infections caused by *H. capsulatum* and *C. neoformans* also have been reported [77]. Azole antifungal agents are effective in the treatment of CMC and prevention of relapses. However, emergence of resistance to azoles by *Candida* spp. may preclude long-term prophylaxis in CMC. Several immunomodulatory approaches also have been evaluated, with inconsistent results and moderate success [91, 167].

Conclusions

1. Fungal infections are less frequent compared to bacterial or viral infections among patients with primary immunodeficiencies. However, fungal infec-

tions can result in significant morbidity and potentially fatal outcome if misdiagnosed or not treated correctly. In this context, the knowledge of fungal pathogens likely to cause disease as well as of the expected clinical presentation of the infection is important.

2. A high index of suspicion is certainly needed and establishment of the diagnosis should actively be pursued using appropriate imaging, mycological, immunological and histological studies. Fortunately, most of the primary immunodeficiencies are not complicated by thrombocytopenia (as is the case for patients with hematological malignancies); consequently, invasive procedures for obtaining appropriate tissue specimens are not usually contraindicated in these patients.
3. Uncommon fungal species isolated from these individuals should not readily be discarded as contaminants, as they may possibly be associated with an infectious process.
4. Fungal infections may occasionally be a presenting symptom of a primary immunodeficiency provided that acquired causes of immunodeficiency (i.e. HIV infection) are excluded; for example, persistent/recurrent oral thrush in a young infant may be associated with CMC or SCID. As another example, a child presenting with unexplained invasive pulmonary aspergillosis who is not neutropenic or hypercortisolemic should be evaluated for CGD. In these cases an evaluation of the patient's immune function should be considered. Furthermore, the possibility of other potentially associated abnormalities should be investigated (i.e., autoimmune endocrinopathies in patients with mucocutaneous candidiasis as part of APECED).
5. The occurrence of particular fungal infections in populations with certain immunodeficiencies, coupled with recent and ongoing defining of molecular defects of these patients, may contribute to our further understanding of the pathogenesis of fungal infections. Still there are questions that need to be answered, i.e. the occurrence of *A. nidulans* infection in CGD patients or the absence of histoplasmosis and cryptococcosis cases among those with certain cellular immunodeficiencies, such as SCID and DiGeorge syndrome. On the other hand, similarities in the spectrum of fungal pathogens affecting patients with different primary immunodeficiencies may reflect common immune deficits among these entities (Table 3).
6. As many pediatricians may not be familiar with the treatment of invasive fungal infections, the choice and dosing of antifungal medications as well as decisions about surgical debridement and possibly adjunctive immunotherapy should be carefully considered. Consultation of experts in the field regarding these issues could be beneficial.

Table 3 Fungal pathogens isolated from patients with primary immunodeficiencies

Organism (genus)	Primary immunodeficiency
Candida	CMC, SCID, hyper-IgE syndrome, CGD, X-linked hyper-IgM syndrome, Wiskott-Aldrich syndrome, CVID, myeloperoxidase deficiency, LAD
Aspergillus	CGD, hyper-IgE syndrome, Wiskott-Aldrich syndrome, DiGeorge syndrome, SCID, CVID, LAD,
Histoplasma	CVID, hyper-IgE syndrome, X-linked hyper-IgM syndrome, IFN-γ/IL-12 axis defects, CMC
Cryptococcus	Hyper-IgE syndrome, X-linked hyper-IgM syndrome, CMC
Trichosporon	CGD, hyper-IgE syndrome
Acremonium	CGD, SCID
Penicillium	CGD, CVID
Fusarium	CGD, LAD
Scedosporium	CGD, hyper-IgE syndrome
Paracoccidioides	IFN-γ/IL-12 axis defects
Pichia	SCID
Others (*Chrysosporium*, *Exophiala*, *Inonotus*, *Microascus*, *Rhizopus*, *Paecilomyces*)	CGD

CGD chronic granulomatous disease, *LAD* leukocyte adhesion deficiency, *SCID* severe combined immunodeficiency, *CVID* common variable immunodeficiency, *CMC* chronic mucocutaneous candidiasis

7. The low frequency of primary immunodeficiencies in the general population complicates the conduction of single-center prospective or retrospective clinical studies aiming to address diagnostic or therapeutic issues pertaining to fungal infections in affected individuals. The construction of national or even international registries of patients with particular immunodeficiencies would probably help to overcome this problem and should be pursued. In the meantime, given the paucity of data from large patient series, case reports remain a useful source of information, provided that the fungal isolate was accurately identified, the constellation of signs and symptoms suggest its association to an infectious process, and, finally, the diagnosis of primary immunodeficiency was established based on contemporary diagnostic criteria. The optimal use of available clinical evidence and scientific information will contribute to the timely diagnosis and effective management of fungal infections in patients with primary immunodeficiencies.

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