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PEDIATRIC FUNGAL INFECTIONS (D CORZO-LEON, SECTION EDITOR)

Non-*Aspergillus* Fungal Infections in Chronic Granulomatous Disease

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Abstract

Purpose of Review Management of *Aspergillus* infection in chronic granulomatous disease (CGD) patients remains a challenge even in new azoles era. However, epidemiology, diagnosis, and management of non-*Aspergillus* fungal infection (NAFI) in CGD setting are poorly described.

Recent Findings NAFI appears to be rare in CGD patients and receiving antifungal prophylaxis. Clinical presentation is not specific of fungal species and patients often suffer from mild disease with prolonged course. While candidiasis and mucormycosis are also common in other immunocompromised population, infections caused by *Phellinus tropicalis*, *Trichosporon inkin*, and *Rasamsonia argillacea* have a unique predilection for CGD patients. Improved fungal identification with molecular methods allows description of new fungal species.

Summary The available data for NAFI during CGD are limited and based on case reports and small series. Invasive tissue biopsies and advanced molecular methods are often required for diagnosis and guiding antifungal strategy in addition to a close collaboration between clinician, pathologist, and mycologist.

Keywords Invasive fungal disease · Chronic granulomatous diseases · *Trichosporon inkin* · *Phellinus tropicalis* · *Rasamsonia argillacea* · Breakthrough infections · Pediatric patients

Introduction

Chronic granulomatous disease (CGD) is a primary immunodeficiency (PID) affecting approximately 1/200,000 to 1/250,000 births, caused by mutations in one of the five subunits of the nicotinamide dinucleotide phosphate (NADPH) oxidase, leading to a reduction in microbicidal activity of phagocytic cells [1–4]. Except CARD9 deficiency, CGD patients have the highest incidence of fungal infection among primary immunodeficiencies that confer susceptibility to fungal infections (e.g., severe combined immunodeficiency, STAT1 gain-of-function, STAT3 deficiency, myeloperoxidase deficiency, leukocyte adhesion deficiency, inborn errors of IFN-γ immunity). Median life expectancy reaches 30 years while CGD patients are continuously exposed to molds from their

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environment. Antifungal and antibiotic prophylaxes have changed the prognosis of the disease [5••, 6]. However, fungal infections of the lung remain the most common cause of infectious death [7]. Generalization of itraconazole prophylaxis since 1990 in CGD patients may have changed invasive fungal diseases epidemiology as in patients with hematological malignancy exposed to azoles prophylaxis, with breakthrough infections caused by rare *Aspergillus* species and non-*Aspergillus* opportunistic fungi [8, 9]. Indeed, all cases of non-*Aspergillus* fungal infection occurred in patients receiving itraconazole prophylaxis in a recent French retrospective study [5••]. This could be due to observance issue and/or emergence of azole resistant fungi.

Finally, molecular typing (PCRs with various targets ITS1-5.8S-ITS2 regions, 28S region, subunit (26S) D1/D2 region, IGS1 region, EF1alpha, RPB2, calmodulin, beta-tubuline, actin) and matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) have led to the identification of new non-*Aspergillus* fungi and could also explain the recent reported emergence of non-*Aspergillus* fungi in CGD patients while these infections were classified as probable or proven invasive fungal infections relying on histopathology before 2000. New detection system combining PCR, nanoparticles, and T2 nuclear magnetic resonance with greater ability to detect pathogens recently emerged like T2Candida. It showed promising results for earlier diagnosis of candidemia (< 5 h) but to date need to be combined with blood cultures [10].

We review here recent advances in epidemiology, diagnosis, and management of non-*Aspergillus* fungal infections in CGD patients. We chose to focus on new findings from the five past years and some specific clinical presentation pattern according to the fungal species.

Epidemiology

With an estimated incidence of 2.6 cases per 100 patient-years, *Aspergillus* remains the most common pathogen in CGD cohorts [7]. Data from national or multinational registries indicate that non-*Aspergillus* infection in CGD patients is a rare event. In the European cohort (1954 to 2002), identified fungi were *Aspergillus* spp. (26%), *Candida* spp. (6%), and others species (< 5%) [11]. Data from national American registry (before 1997) showed that 7% of pneumonia occurring in CGD patients were caused by non-*Aspergillus* fungi [1]. In a French study conducted by Blumental et al. (1984 through 2009) reporting 29 proven IFD, 6 (21%) were caused by non-*Aspergillus* species [5••]. The incidence of non-*Aspergillus* IFD remains low in a recent French retrospective study involving 80 adults CGD patients who reached adulthood (before 2013). We observed 15 non-*Aspergillus* IFD (14%) among 109 IFD [12, 13]. Table 1 shows the characteristics of each episode (unpublished data).

Dotis et al. performed a systematic review of non-*Aspergillus* fungal infections occurring in CGD in the English literature [14••]. They reported 68 cases in 65 CGD patients between 1984 and 2011. No more than 10 cases were published before 1999; however, increasing incidence could be attributed to publication bias. Overall mortality is unknown as most of the published researches on this topic are case reports.

Table 1 Fungal identification of 15 non-*Aspergillus* IFD occurring in a French cohort of 80 CGD patients reaching adulthood (personal data)

Age of onset of IFI (years)	NADPH complex defect	Fungal pathogen	Site of infection
< 1	$p47^{phox}$	*Pneumocystis jirovecii*	Pneumonia
< 1	$gp91^{phox}$	*Pneumocystis jirovecii*	Pneumonia
1	$p22^{phox}$	*Malassezia* spp.	Cutaneous abscess
14	$gp91^{phox}$	*Candida albicans*	Adenitis
2	$gp91^{phox}$	*Candida* spp.	Bloodstream infection
5	$gp91^{phox}$	*Candida albicans*	Hepatic abscess
8	$gp91^{phox}$	*Candida glabrata*	Hepatic abscess
14	$p67^{phox}$	*Acremonium* spp.	Pneumonia, thoracic involvement
16	$gp91^{phox}$	*Scedosporium apiospermum*	Disseminated (lung, skin, bones, thoracic)
10	$gp91^{phox}$	*Scedosporium apiospermum*	Pneumonia
14	$gp91^{phox}$	*Scedosporium apiospermum*	Disseminated
23	$gp91^{phox}$	*Arthrographis kalrae*	Pneumonia
30	unknown	*Phialophora richardsiae*	Pneumonia
20	$gp91^{phox}$	*Paecilomyces* spp.	Pneumonia
25	$gp91^{phox}$	*Rasamsonia argillacea*	Pneumonia, thoracic involvement

Another systematic review on proven and probable fungal infection in CGD was conducted by Henriet et al. between 1970 and 2010 [15••]. Among 127 fungal isolates out of 116 cases of invasive fungal disease, incidence of *Aspergillus* spp., *Candida* spp., and *non-Candida*/non-*Aspergillus* infections were 57%, 6%, and 37%, respectively. Epidemiological burden is also biased by the abundance of case reports concerning rare non-*Aspergillus* infection more frequently reported than *Aspergillus* infections.

Yeast Infection

Candida spp. and *Trichosporon* spp. are the most common yeast isolated in CGD patients. In contrast, cryptococcosis and infections caused by dimorphic fungus are rarely seen in CGD patients.

Candida

The most common yeast among invasive fungal infections in CGD setting is *Candida* spp. Invasive candidiasis incidence should be interpreted with caution as confounding cofactors such as corticosteroids, prolonged antibiotics, or presence of central venous catheter may influence the observed incidence. *Candida* is encountered in 6 to 14% of all isolated microorganisms in CGD cohorts [11, 16]. There was no invasive candidiasis specific clinical presentation except cases of hepatic abscesses, adenitis, or primary meningitis [14••]. We observed in the French cohort (Table 1) two cases of *Candida* hepatic abscesses, one adenitis and one bloodstream infection. It is important to ensure the absence of central nervous system, cardiac, hepatic, or ophtalmological involvement with appropriate imaging in CGD patients with *Candida* spp. bloodstream infection. Adenitis and invasive infection caused by *C. lusitaniae* were reported in CGD patients [17].

Trichosporon

Besides *Candida* spp., *Trichosporon* spp. infection predominated among yeast infections in CGD patients with some concerns about misidentification in old case reports. *Trichosporon* species are rare cause of invasive infections in humans especially in immunocompromised hosts. Currently, six cases of invasive fungal infections related to *Trichosporon* species have been reported in patients with chronic granulomatous disease (all were related to *Trichosporon inkin*) [18–22]. By contrast, most non-CGD patients *Trichosporon* invasive infections were related to *Trichosporon asahii* [23]. Most CGD patients with *Trichosporon inkin* invasive infections had minor or no symptoms, and infection was often discovered at an advanced stage. There is very scarce information published about treatment. Previous published data emphasized the importance of surgery and azoles especially voriconazole for these patients [24].

Mold Infections

Many non-*Aspergillus* mold infections have been described in CGD patients. Among them, mucormycosis is relatively rare in CGD patients and sometimes associated with various risk factors including diabetes mellitus, immunosuppressive therapy, hematological malignancies, and transplant [25–28]. Cutaneous, intestinal, and pulmonary involvement have been reported [29]. In old studies, *Paecilomyces* spp. and *Scedosporium* infections appear to be the most common of non-*Aspergillus* mold infections while there are increasing reports of invasive infections by emerging fungi like *Phellinus tropicalis* or *Rasamsonia argilacea* in recent years. We chose to focus on these new entities.

Inonotus (*Phellinnus*)

Phellinus spp. are saprophytic filamentous basidiomycetes not considered as human pathogen before 2005 when the first case of infection in a CGD patient was reported [30]. *Phellinus tropicalis* was the most frequent reported species but infections with *Phellinus igniarius*, *Phellinus mori*, or *Phellinnus undulates* were also reported.

Currently, 14 cases of *Phellinus* spp. infections have been reported in CGD patients [30–37]. Among these patients, only one had a possible environmental exposure with frequent mountain biking near tree-borne mushrooms. Interestingly, all but two cases of reported *Phellinus* spp. infections have been reported in patients with CGD [38, 39]. Therefore, invasive *Phellinus* spp. infection diagnosis should lead to investigation of a possible CGD. In addition, it is notable that six out of seven *Phellinus* infections were breakthrough while receiving itraconazole prophylaxis ($n = 5$) or posaconazole ($n = 1$). Involvement of soft-tissue and bones (e.g., chest wall, osteomyelitis) were mostly reported, and dissemination may occur in other organs like CNS. *Phellinus* spp. infections often have an indolent course. Diagnosis is difficult due to the low frequency of sporulating forms often leading to the erroneous diagnosis of contamination when fungal cultures grew sterile mycelia. *Phellinus* spp. colonies appear as golden or yellowish-brown colonies on Sabouraud media after 4 to 20 days of incubation [35, 36•]. Definitive diagnosis may be made by molecular identification.

There are limited data to guide treatment. Voriconazole and liposomal amphotericin B have lowest MICs and are associated with response in some patients in combination with surgical resection [35]. Isavuconazole had very low MICs and was successfully used in one patient in combination with liposomal amphotericin B [36•]. Echinocandins have higher MICs as *Phelinnus* spp. is a basidiomycete.

Rasamsonia argillacea

Geosmithia spp. genus has recently been changed to *Rasamsonia* [40]. Reports of *Rasamsonia* invasive infections are currently limited to patients with cystic fibrosis, chronic granulomatous disease, and allogenic hematopoietic stem cell transplantation (HSCT) recipients with graft-versus-host disease (GvHD) [41–43].

Ten cases of *Rasamsonia*-related infections have been reported so far in patients with CGD [42•, 44, 45]. Infection location is mostly pulmonary, but dissemination often occurs through invasion of contiguous structures and/or in CNS. If the number of *Rasamsonia* spp.-related infections in CGD patients is limited, it is important to consider that the recent description may be associated with an increase of observed cases. In addition, it is probable that some infections reported in the past 30 years in CGD patients as being related to *Paecilomyces* spp. were actually related to *Rasamsonia* infections as *R. argillacea* can be misidentified by phenotypic features with *P. variotti*.

R. argillacea infections require aggressive management sometimes with the use of surgery. Thermotolerance and broad azoles resistance is a serious challenge with 40% fatality rate in CGD patients [46]. Echinocandins, especially micafungin, have the lowest MICs among antifungals against *R. argillacea*, but additional studies are needed to draw any correlations between in vitro susceptibility and clinical outcomes.

Scedosporium sp.

Scedosporium sp. is found ubiquitously in the environment including in soil and polluted water [47]. Many cases of *Scedosporium* sp.-related infections have been reported in CGD patients [48–51]. All but one cases (caused by *Lomentospora prolificans*) were related to *Pseudallescheria boydii* (anamorph *Scedosporium apiospermum*). Pulmonary involvement was reported in most cases with possible chest wall extension. Disseminated cases with CNS involvement have also been reported [49]. Breakthrough infections have been described in CGD patients receiving long-term treatment with azoles or amphotericin B. Voriconazole is reference treatment for *Scedosporium* sp., while voriconazole combined with terbinafine is the standard for *Lomentospora prolificans* which is resistant to most antifungal agents [52]. This combination has been successfully used in cases of complicated *L. prolificans*-related infections [49, 53].

Non-*Aspergillus* Infection Related to Anti-Inflammatory Treatments

While anti-*Aspergillus* immunity is defective in CGD patients, very low incidences of some fungal species as mucormycosis indicate that NADPH oxidase-independent mechanisms are responsible for the clearance of these fungi. However, anti-inflammatory treatment like corticosteroids, anti-TNF agents sometimes increased susceptibility to non-*Aspergillus* infection. In 2009, a study from Vinh et al. showed that seven cases of mucormycosis in CGD patients were all preceded by a steroid-based immunosuppressive regimen for three or more weeks [54]. In addition, one study have suggested an increased risk of fungal (aspergillosis and invasive candidiasis) and bacterial infections in CGD patients receiving infliximab for inflammatory colitis [55].

Pitfalls in Identification

The cornerstone of diagnosis is fungus identification by culture of a sterile specimen. Two polar views exist when a rare fungi is identified in CGD settings: one could consider it as "contaminants" while the others will consider the possibility of an emerging fungus even if not previously described as human pathogen [56]. In addition, species misidentification could occur as it has been reported with *Paecilomyces variotii* and *Rasamsonia argillaccea*. This is an interesting finding regarding previous cases of *Paecilomyces* or *Penicillium* pulmonary infections that could retrospectively be *Rasamsonia* infections in CGD patients. Diagnosis may be made by prolonged fungal culture on specific media and identification should use molecular identification with various target genes according morphological features [57, 58].

Histopathologic data are important but unfortunately do not allow the identification of species. In this context, tissue molecular typing in presence of hyphae may be of major interest even in paraffin-embedded biopsy specimens.

Poor performances of galactomannan antigen in CGD settings during *Aspergillus* infection limit its use for the diagnosis of non-*Aspergillus* infection by cross-reaction (e.g., *Penicillium* spp.) [59]. Some rare fungi can cross-react with cryptococcal antigen that could be a valuable tool in some rare cases (e.g., *Trichosporon* spp.). Furthermore, basidiomycetes lack galactomannan and β-D-glucan in their cell walls limiting value of these tests for the non-invasive diagnosis of *Phellinus* and other basidiomycetous infections [33].

Therefore, for the diagnosis of IFD among CGD patients, clinicians should make every effort to obtain tissue specimen from infection site for diagnosis. Virtually all recent cases reported in literature have underwent multiple tissue biopsies. During thoracic fungal infection in adults with CGD, a two-step process could be performed incorporating BAL and fine needle biopsy. In adult patients, BAL and biopsy are positive up to 52% and 60% of CGD patients with pulmonary IFD, respectively [12]. Therefore, for adult CGD patients, we recommend performing less-invasive procedures first, i.e., BAL and to proceed to more aggressive tissue biopsy in case of inconclusive results [12]. Management is different in pediatric setting as BAL requires sedation or anesthesia.

Treatment

As non-*Aspergillus* fungal infections in CGD patients are highly heterogeneous, no global recommendations could be done on their management. Antifungal minimal inhibitory concentrations (MICs) should be handled with caution and treatment decided according to fungus identification. Long-term antifungal therapy is often the rule as CGD patients with IFD had delayed radiological improvement [60].

In any case, antifungal treatment especially azole drugs should be optimized with therapeutic drug monitoring and surveillance of long-term toxicities as patients often received prolonged treatment [61, 62]. Ensuring posaconazole, itraconazole, and voriconazole therapeutic drug monitoring is needed to assess adequate exposure, observance, and toxicities. Patients receiving voriconazole should have regular dermatological surveillance regarding the increased risk of photosensitivity/photoaging reactions and skin cancer with chronic use of voriconazole [63–65]. High daily doses of voriconazole are sometimes associated with periostitis with elevated plasma fluoride concentrations [66]. In 2015, isavuconazole has been approved by the FDA and the European Medicines Agency (EMA) for aspergillosis and mucormycosis [67, 68]. Isavuconazole showed improved safety and tolerability compared to voriconazole especially in patients with prolonged treatment. It has a broad spectrum including yeast and mold infections. Clinical breakpoints have been proposed by EUCAST for some *Aspergillus* species: *Aspergillus fumigatus* (1 μg/mL), *A. nidulans* (0.25 μg/mL), and *A. terreus* (1 μg/mL). In vitro activity against *Mucorales* depends on the species involved [69•]. Besides *Aspergillus* and *Mucorales* infections, isavuconazole demonstrates activity against rare molds that not include *Lomentospora prolificans*, *Pseudallescheria* spp., and *R. argillacea* complex which exhibit high MIC [69•].

Use of adjunctive therapy with granulocyte transfusions could be used as salvage therapy, though it has been poorly described as an effective therapy with robust evidence in literature [70]. Granulocyte transfusion should be limited to exceptional situations in non-responders to antifungal therapy. In addition, granulocyte transfusion was associated with the risk of HLA allo-sensitization in patients eligible for allogenic HSCT [71]. However, in a recent retrospective report, granulocyte transfusion procedure was safe and associated with good outcomes in the NIH experience: up to 80% of success (complete or partial response) in fungal infections in CGD patients [72••]. Rescue bone marrow transplantation or ex vivo gene therapy for patient lacking suitable donor are usually last resort treatments only reserved for refractory patients with life-threatening fungal infections [73–77]. A recent international study showed promising results of reduced intensity conditioning and HLA-matched HCST in 56 CGD patients including 75% with intractable infections or autoinflammation with a 2-year probability of overall survival of 96% and a low incidence of acute grade III/IV and chronic GvHDs (4 and 7%, respectively) [78]. Concerning gene therapy, we are waiting the results of ongoing clinical trials in the USA and Europe using a new codon-optimized self-inactivating lentiviral vector with gp91-phox cDNA and low-dose busulfan in patients with CGD including those with intractable infections [79].

Conclusion

The occurrence of invasive fungal infection related to non-*Aspergillus* species seems to be an increasingly common event in CGD patients. This phenomenon is probably multifactorial. First, generalization of lifelong azole prophylaxis in these patients may have decreased the occurrence of *Aspergillus* infections and promote the emergence of new azoles-resistant fungal species. Secondly, diagnostic tool improvement and radiological-guided invasive procedures allow a correct identification of non-*Aspergillus* species and a targeted therapy. Implementation of national and international databases of children and adults with CGD will probably improve the management of these rare fungal infections and prophylaxis strategies.

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Compliance with Ethical Standards

Conflict of Interest Romain Guery reports participating in CME with support from Gilead outside the submitted work. Benoît Pilmis reports personal fees from MSD outside the submitted work. Fanny Lanternier reports personal fees from Gilead outside the submitted work. Bertrand Dunogue, Stéphane Blanche, and Olivier Lortholary declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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