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Microbiological profile in chronic granulomatous disease patients in a single Brazilian primary immunodeficiency center

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Abstract

Background: Chronic granulomatous disease (CGD) is a rare primary immunodeficiency. Infections of lung, skin, lymph nodes, and liver are the hallmark of CGD and frequently the initial manifestation of the disease. The aim of the present paper is to describe the sites of infections and their causative agents in 38 pediatric patients with CGD.

Methods: This retrospective, single-center cohort study included CGD patients followed at the allergy and immunology unit of a tertiary hospital in São Paulo, Brazil over the last 40 years. Sites of infections and their causative agents were described.

Results: Thirty-eight patients were included (36 males). The median age of onset of symptoms was 45 days (ranging from 7 days–7 years), and the median age at diagnosis was 23 months (ranging from 1 month–12 years). In all, 31.6% of the patients reported a family history of child deaths and 21% (eight cases) had another male family member with CGD. The most common infections were pneumonia (81.6%), skin infections (50.0%), adenitis (42.1%), and liver abscess (23.7%); 188 cultures were positive (85.6% bacteria; 14.4% fungi). The most prevalent bacterial agents were *Staphylococcus sp.* (12.4%), *Staphylococcus aureus* (11.2%), and *Klebsiella pneumoniae* (9.3%). *Aspergillus sp.* and *Candida sp. were* 56% and 22.2% of the isolated fungi, respectively. *Mycobacterium tuberculosis* was isolated in 5.6% and *Mycobacterium bovis* in one patient (0.9%).

Conclusion: *Staphylococcus sp., Staphylococcus aureus, and Aspergillus sp.* were the most frequent agents found in this cohort. *M. tuberculosis* should be considered in endemic area. Detection of infectious agents drives to the adequate treatment and benefits the evolution of patients with CGD.

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Introduction

Chronic granulomatous disease (CGD) is a rare primary immunodeficiency (PID), with an estimated prevalence of around 1:200,000 to 1:250,000 live births. CGD is caused by mutations in genes related to one of the five components of the NADPH oxidase enzymatic complex, with about 70% of the cases having X-linked inheritance.[1-3]

The most frequent clinical manifestations of the disease are recurrent infections. However, inflammatory complications, especially of the gastrointestinal tract, have been described increasingly.[2-5]

Patients with CGD are at high risk of recurrent and severe infections, such as pneumonia, adenitis, osteomyelitis, and abscesses most commonly affecting the liver and lungs. Catalase-positive bacteria such as *Staphylococcus aureus*, gram negative bacteria such as *Serratia marcescens*, and *Aspergillus sp.* are the most frequently isolated agents. The implementation of lifelong antimicrobial prophylaxis with sulfamethoxazole–trimethoprim and azole antifungals considerably reduced the morbidity and mortality of these patients.[2,3,6]

Early diagnosis of infections and identification of the microbial agent are crucial to guide appropriate treatment and prevent serious complications. Patients' general clinical conditions may impact the outcome of hematopoietic stem cell transplantation (HSCT).[3,7]

The aim of the present study is to describe the infectious agents isolated and the most frequently involved sites of infections in a group of pediatric patients with CGD followed at a single reference center for primary immunodeficiencies in Brazil.

Method

Cross-sectional descriptive study of 38 patients followed at the Allergy and Immunology Unit of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP), Brazil, for the last 40 years (from January 1979 to January 2019). Epidemiologic, clinical, and laboratory characteristics, especially concerning infectious agents and their sites of infections, were obtained from patient´s electronic medical records. The Laboratory of Microbiology of HC-FMUSP analyzed samples sent for culture. A single patient may have presented different sites of infections or more than one microorganism isolated during the same hospitalization.

Microorganisms isolated from the lungs were obtained from bronchoalveolar lavage, sputum, or abscess drainage, and material from the liver was obtained by direct puncture or during abscess drainage.

This study was approved by the Ethics Committee of the HC-FMUSP (No. 2.269.479/set 2017). Owing to the characteristics of the study, Ethics Committee waived the requirement of written informed consent.

Results

Thirty-eight patients were analyzed (36 male and 2 females). The median age of onset of symptoms was 45 days (ranging from 7 days to 7 years) and the median age at diagnosis was 23 months (ranging from 1 month to 12 years). In all, 31.6% of the patients reported family history of child deaths and 21% had another male member in the family diagnosed with CGD. Twelve patients belonged to three family groups.

Diagnosis of CGD was based on nitroblue tetrazolium (NBT) dye reduction test performed in 18 patients (13 patients had negative test, and five had below 10% result), or by flow cytometry-based dihydrorhodamine (DHR) oxidation assay in 20 patients (median oxidation index = 1, ranging from 0 to 16).

Having infections was the reason for immunologic investigation in 76.3% of the patients and a family history of child death or CGD in 15.8% of cases (Figure 1). Only three patients were investigated for other findings: fever without infectious outbreak in one patient, recurrent thrush in another, and blood in stool in the last one. Pulmonary, skin, or lymph node infections were the most frequent occurrences before diagnosis. Less frequently, patients presented liver abscess, adverse reaction to BCG vaccine, hepatosplenomegaly, osteomyelitis, and cerebral abscess.

All the patients presented infections during follow-up, and pneumonia was the most frequent occurrence (81.6% of patients), followed by skin infections (50.0%), adenitis (42.1%), liver abscess (28.9%), acute otitis media (23.7%), urinary tract infection (21.1%), pulmonary abscess (15.8%), and osteomyelitis (10.5%) (Figure 2).

Microorganisms were isolated from 188 cultures from different sites. Bacteria were identified in 85.6% of the cultures (24 different species) and fungi in 14.4% (7 species).The most prevalent bacteria were *Staphylococcus sp.* (12.4%), *Staphylococcus aureus* (11.2%), *Klebsiella pneumoniae* (9.3%), *Streptococcus sp.* (8.7%), *Escherichia coli* (7.5%), *Pseudomonas sp.* (6.8%), *Mycobacterium tuberculosis* (5.6%), and *Enterobacter cloacae* (5.6%) (Table 1). Among the fungi, *Aspergillus sp.* was the most frequently isolated (56.0%) microorganism, followed by *Candida sp.* (22.2%) and *Trichosporon sp.* (7.4%). Other fungi such as *Rhodotorula sp., Cladosporium sp., Chrysosporium sp., and Acremonium kiliense* were isolated from one culture each (Table 2).

Regarding the site of infection, bacteria were identified in all cultures obtained from liver abscesses, *staphylococci* being the only isolated agent from that site. Bacteria were also the predominant infectious agent isolated in 93.2% of urinary tract cultures, 87.9% of blood cultures, 86.7% of skin abscesses, 83.3% of lymph node puncture cultures, and 76.4% from lower respiratory tract cultures. The bone marrow, ear, paravertebral, and parotid gland were rarely affected.

Fungi were isolated in 14.4% of positive cultures, *Aspergillus* being the most frequent microorganism (56%). The lungs and tracheal secretion were the most frequent sites of fungi isolation (48.2%), and *Aspergillus* corresponded to 46.2% at this site (Tables 2 and 3).

All patients received sulfamethoxazole–trimethoprim prophylaxis after diagnosis, and from 2006 onwards, antifungal prophylaxis with itraconazole or voriconazole was indicated. None of the patients received interferon-gamma, since the drug is not approved in Brazil for treating CGD patients.

During follow-up, 10 of the 38 patients (26.3%) experienced chronic inflammatory manifestations, especially of the gastrointestinal tract (n = 6). Most patients used corticosteroids and none of them received tumor necrosis factor (TNF) antagonists.

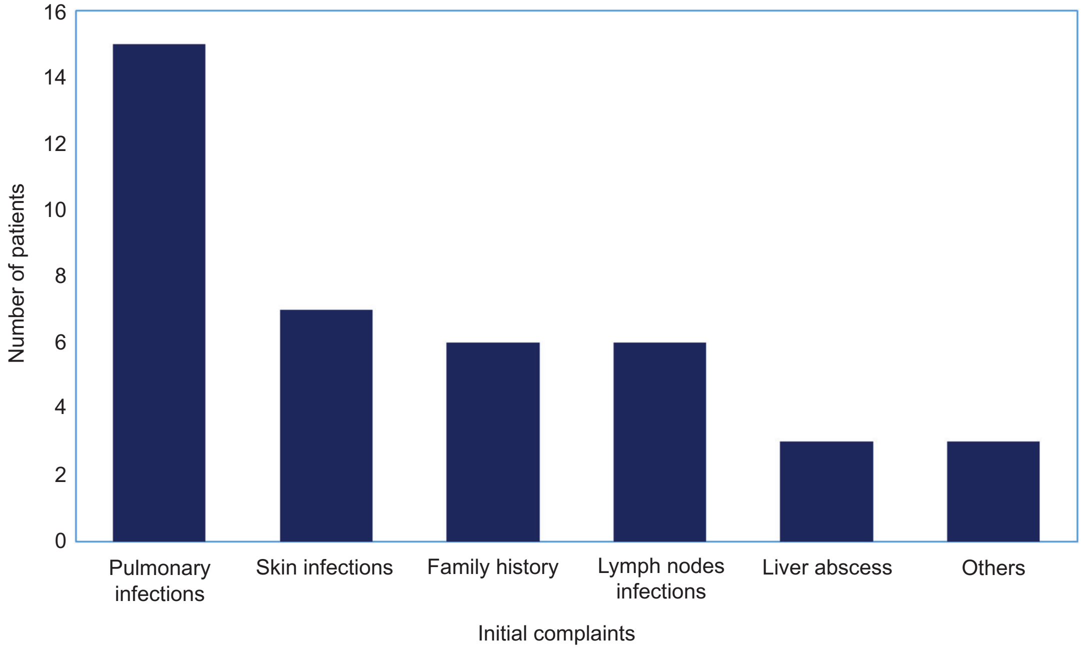

Figure 1 Initial referral complaints of 38 patients with CGD.

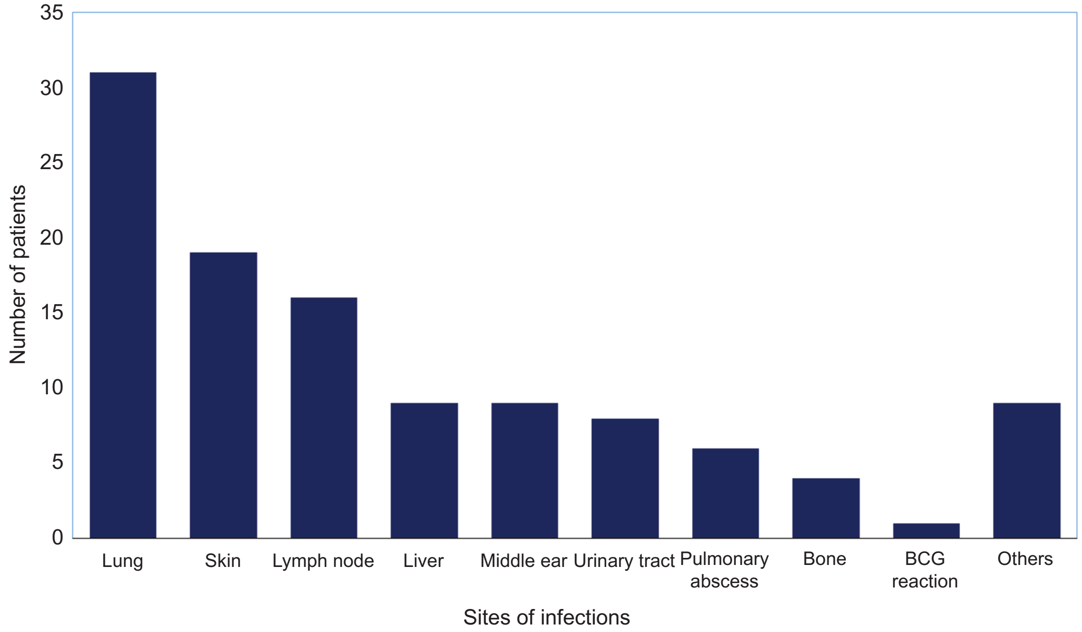

Figure 2 Sites of infection in the evolution of 38 patients with CGD.

Ten patients died (five due to HSCT complications), and nine patients were lost in the follow-up or were referred to other centers. Nineteen patients are being followed and six of them are reported well after receiving HSCT.

Discussion

The current study represents a summary of 40-year history of infections in children and adolescents with CGD from a tertiary immunodeficiency center in Brazil. Infections of the lungs, skin, lymph nodes, and liver are the hallmark of CGD and frequently the initial manifestation of the disease.[1] Infections caused by *Staphylococcus aureus* and *Aspergillus*, especially in complications, could be a warning sign for the diagnosis of CGD.[1]

Although CGD is considered a rare PID, we expect 12 new cases annually in Brazil where 2.9 million births occur each year.[8] Even considering the existence of other reference centers in the country, this finding may indicate that CGD is still underdiagnosed. According to the Latin American Society for Immunodeficiencies (LASID),

Table 1 Bacterial infectious agents and isolation sites in 188 positive cultures from 38 CGD patients.

Agent group	Infectious agent	N (%)	Isolation site	N (%)
Bacteria 161 isolations (85.6%)	*Staphylococcus sp.*	20 (12.4)	Blood	11 (55.0)
			Lung	2 (10.0)
			Liver abscess	1 (5.0)
			Lymph node	1 (5.0)
			Bone marrow	1 (5.0)
			others	4 (20.0)
	Staphylococcus aureus	18 (11.2)	Liver abscess	8 (44,4)
			Blood	4 (22.20
			Lung	1 (5.6)
			Lymph node	1 (5.6)
			Ear	1 (5.6)
			Urinary tract	1 (5.6)
			Others	2 (11.1)
	Klebsiella pneumoniae	15 (9.3)	Urinary tract	9 (60.0)
			Blood	5 (33.3)
			Lung	1 (6.7)
	Streptococcus sp.	14 (8.7)	Lung	10 (71.4)
			Lymph node	1 (7.1)
			Urinary tract	1 (7.1)
			Bone	1 (7.1)
			Other	1 (7.1)
	Escherichia coli	12 (7.5)	Urinary tract	8 (66.6)
			Skin	2 (16.7)
			Blood	1 (8.3)
			Bone marrow	1 (8.3)
	Pseudomonas sp.	11 (6.8)	Lung	6 (54.5)
			Lymph node	1 (9.1)
			Blood	1 (9.1)
			Urinary tract	1 (9.1)
			Tracheal secretion	2 (8.2)
	Mycobacterium tuberculosis	9 (5.6)	Lung	6 (66.7)
			Lymph node	2 (22.2)
			Bone	1 (11.1)
	Enterobacter cloacae	9 (5.6)	Urinary tract	5 (55.6)
			Blood	2 (22.2)
			Skin	2 (22.2)
	Enterococcus faecium	7 (4.3)	Urinary tract	3 (42.9)
			Skin	3 (42.9)
			Blood	1 (14.3)
	Burkholderia cepacia complex	6 (3.7)	Lung	2 (33.3)
			Tracheal secretion	2 (33.3)
			Lymph Node	1 (16.7)
			Skin	1 (16.7)
	Serratia marcescens	6 (3.7)	Skin	3 (50.0)
			Lymph node	2 (33.3)
			Urinary tract	1 (16.7)
	Enterococcus faecalis	5 (3.1)	Urinary tract	4 (80.0)
			Skin	1 (20.0)
	Corynebacterium sp.	5 (3.1)	Lung	4 (80.0)
			Ear	1 (20.0)
	Stenotrophomonas maltophilia	4 (2.5)	Blood	2 (50.0)
			Tracheal secretion	2 (50.0)
	Morganella morganii	4 (2.5)	Urinary tract	4 (100.0)
	Proteus mirabilis	4 (2.5)	Urinary tract	4 (100.0)
	Haemophilus influenzae	3 (1.9)	Lung	2 (66.7)
			Oropharyngeal	1 (33.3)
	Acinetobacter baumannii complex	2 (1.2)	Blood	2 (100.0)

(continues)

Table 1 Continued

Agent group	Infectious agent	N (%)	Isolation site	N (%)
	Raoultella planticola	2 (1.2)	Tracheal secretion	2 (100.0)
	Mycobacterium bovis	1 (0.6)	Lymph node	1 (100.0)
	Others (Micrococcus luteus, Chryseobacterium sp. Elizabethkingia meningoseptica, Rothia mucilaginosa	4 (2.5)	Ear	2 (50.0)
			Cerebrospinal fluid	1 (25.0)
			Skin	1 (25.0)

Table 2 Fungal agents and isolation sites in 188 positive cultures from 38 CGD patients.

Agent group	Infectious agent	N (%)	Isolation site	N (%)
Fungus **27 isolations (14.4%)**	*Aspergillus sp.*	15 (56.0)	Lung	6 (40.0)
			Lymph node	2 (13.3)
			Blood	2 (13.3)
			Skin	2 (13.3)
			Bone	1 (6.7)
			Others	2 (13.3)
	Candida sp.	6 (22.2)	Urinary tract	3 (50.0)
			Blood	2 (33.3
			Lung	1 (16.7)
	Trichosporon sp.	2 (7.4)	Lung	1 (50.0)
			Tracheal secretion	1 (50.0)
	Cladosporium sp.	1 (3.7)	Lung	1 (100.0)
	Chrysosporium sp.	1 (3.7)	Lung	1 (100.0)
	Rhodotorula sp.	1 (3.7)	Lung	1 (100.0)
	Acremonium kiliense	1 (3.7)	Lung	1 (100.0)

among the 7521 registered patients with PID, less than 5% (326 patients) have CGD.[9]

To our knowledge, this study represents the largest CGD cohort ever described by a single Brazilian center and contributes to understanding the infection profile of this group of patients in Brazil.

This cohort was represented almost entirely by males. These findings agree with other previous reports, since the most common genetic defect in CGD is located on the X chromosome.[2,3] Autosomal recessive inheritance is more common in countries with high frequency of consanguinity.[10-12] In a Turkish study,[11] consanguinity was reported by 13 of the 24 patients (54%), and 10 out of 13 patients had an autosomal recessive form of the disease. In this cohort, history of consanguinity in the family was reported by only three patients.

In this study, a high number of relatives with CGD were observed, highlighting the importance of accurate investigation of family history. This information certainly contributes to earlier diagnosis and implementation of preventive measures, including avoiding BCG vaccination. In a study conducted in China,[13] which included 159 children diagnosed with CGD, 21% of the patients reported a positive family history of the disease. In another study from a reference center in the United States,[14] 40.7% had other affected family members. In this study, affected families also had a high mortality rate of children without PID diagnosis, indicating that more efforts to improve diagnosis are necessary.

Having infections is the most common clinical manifestation in CGD and strongly related to mortality.[1] Initial symptoms can occur in very early life and the most commonly affected sites are the lungs and skin. In this cohort, the median age of onset of symptoms was 45 days and the earliest infection was impetigo diagnosed at the age of 7 days. Early onset of symptoms is frequent in CGD, as also observed in a Chinese study, which reported the earliest clinical manifestation at the age of 5 days.[13]

Among the study's patients, the most frequent initial manifestation was pulmonary infection, which was generally difficult to treat, requiring multiple antibiotic regimens, sometimes evolving to abscesses. The skin and lymph node infections, including abscesses, were also an early manifestation of the disease. These findings are similar to those established in large studies conducted in the United States,[14,15] Europe,[12,16] and other countries.[11-13,17] During follow-up, the lungs, skin, and lymph nodes remained the most frequent sites of infections in this cohort, which is in agreement with the data from our previous study and from a retrospective study conducted in Latin America.[8,18] In fact, the lungs are consistently described as the most frequent site for detection of agents in CGD.[13,16,18-20]

Table 3 Infectious agents according to the isolation site in 188 positive cultures.

Isolation site	Infectious agents	N (%)
Lung and tracheal secretion (N = 55)	*Streptococcus sp.*	10 (18.2)
	Pseudomonas sp.	8 (14.5)
	Mycobacterium tuberculosis	6 (10.9)
	Corynebacterium sp	4 (7.3)
	Burkholderia cepacia complex	4 (7.3)
	Staphylococcus sp.	2 (3.6)
	Stenotrophomonas maltophilia	2 (3.6)
	Haemophilus influenzae	2 (3.6)
	Raoultella planticola	2 (3.6)
	Staphylococcus aureus	1 (1.8)
	Klebsiella pneumoniae	1 (1.8)
	Aspergillus sp.	6 (10.9)
	Trichosporon sp.	2 (3.6)
	Candida sp.	1 (1.8)
	Cladosporium sp.	1 (1.8)
	Chrysosporium sp.	1 (1.8)
	Rhodotorula sp.	1 (1.8)
	Acremonium kiliense	1 (1.8)
Urinary tract (N = 44)	*Klebsiella pneumoniae*	9 (20.5)
	Escherichia coli	8 (18.2)
	Enterobacter cloacae	5 (11.4)
	Morganella morganii	4 (9.1)
	Proteus mirabilis	4 (9.1)
	Enterococcus faecalis	4 (9.1)
	Enterococcus faecium	3 (6.8)
	Staphylococcus aureus	1 (1.3)
	Pseudomonas sp.	1 (1.3)
	Serratia marcescens	1 (1.3)
	Streptococcus sp.	1 (1.3)
	Candida sp.	3 (6.8)
Blood (N = 33)	*Staphylococcus sp.*	11 (33.3)
	Klebsiella pneumoniae	5 (15.2)
	Staphylococcus aureus	4 (12.1)
	Stenotrophomonas maltophilia	2 (6.1)
	Enterobacter cloacae	2 (6.1)
	Acinetobacter baumannii complex	2 (6.1)
	Pseudomonas sp.	1 (3.0)
	Escherichia coli	1 (3.0)
	Enterococcus faecalis	1 (3.0)
	Aspergillus sp.	2 (6.1)
	Candida sp.	2 (6.1)
Skin (N = 15)	*Enterococcus faecium*	3 (20.0)
	Serratia marcescens	3 (20.0)
	Enterobacter cloacae	2 (8.3)
	Escherichia coli	2 (8.3)
	Enterococcus faecalis	1 (8.3)
	Rothia mucilaginosa	1 (8.3)
	Burkholderia cepacia complex	1 (8.3)
	Aspergillus sp.	2 (16.7)
Lymph node (N = 12)	*Mycobacterium tuberculosis*	2 (16.7)
	Serratia marcescens	2 (16.7)
	Staphylococcus aureus	1 (8.3)
	Staphylococcus sp.	1 (8.3)
	Streptococcus sp.	1 (8.3)
	Pseudomonas sp.	1 (8.3)
	Burkholderia cepacia	1 (8.3)
	complex	1 (8.3)
	Mycobacterium bovis	
	Aspergillus sp.	2 (16.7)
Liver abscess (N = 9)	*Staphylococcus aureus*	8 (88.9)
	Staphylococcus sp.	1 (11.1)
Others (N = 20)	*Staphylococcus sp.*	5 (25.0)
	Staphylococcus aureus	3 (15.0)
	Streptococcus sp.	2 (10.0)
	Corynebacterium sp.	1 (5.0)
	Escherichia coli	1 (5.0)
	Elizabethkingia	1 (5.0)
	meningoseptica	1 (5.0)
	Mycobacterium tuberculosis	1 (5.0)
	Haemophilus influenzae	1 (5.0)
	Micrococcus luteus	1 (5.0)
	Chryseobacterium sp.	
	Aspergillus sp.	3 (15.0)

Microorganisms were identified in 188 cultures from different sites. One-third of those specimens were obtained from the lower respiratory tract by bronchoalveolar lavage (BAL), pulmonary abscesses drainage, or sputum test. The urinary tract was the second most frequent site of microorganism's isolation, often obtained during the screening for fever without localizing signs in a patient with PID. Aerobic and anaerobic blood cultures were part of the investigation of patients with PID with clinical findings of severity or who need hospitalization and treatment with parenteral antibiotics. The identification of causative agents and their susceptibility profile are of great importance to guide treatment, and in this context, invasive procedures may be necessary.

In agreement with previous studies, *Staphylococcus* and *Aspergillus* were the most frequently isolated infectious agents.[14,16,18,21,22] In fact, susceptibility to *Staphylococcus aureus* infection is a hallmark of CGD and is due to defect in generating reactive oxygen species (ROS) during phagocytes, essential to eliminate pathogens.[23] Species of *Staphylococcus*, previously considered as simple commensal bacteria (today grouped under the name of coagulase-negative *staphylococcus*—CoNS), are now recognized for containing numerous virulence factors and are especially important in nosocomial infections.[24]

Aspergillus is a common cause of invasive infections in CGD, and even after the implementation of fungal prophylaxis, it remains an important cause of complications, and high morbidity and mortality rates.[25,26] In fact, CGD is the most common PID associated with invasive aspergillosis.[27]

In this cohort, we could not differentiate between the *Aspergillus* species responsible for invasive infections, but in literature *Aspergillus fumigatus* and *Aspergillus nidulans* are most frequently related with invasive infections.[25,26]

Mycobacterium tuberculosis was isolated exclusively from the lung and lymph node specimens in the study's cases. This finding is not surprising, since tuberculosis is endemic in Brazil.[28] On the other hand, *Mycobacterium bovis* was isolated only in one culture. In fact, in spite of the administration of BCG vaccine to many of the patients, adverse events were uncommon. This finding differs from a multicenter study conducted in Latin America,[18] where adverse reaction to BCG vaccine was the first clinical manifestation in many patients. A study including CGD patients that presented reaction to BCG vaccine found that 28% of them presented disseminated disease, emphasizing the risks related to administration of BCG vaccine.[20]

Although *Pseudomonas sp.*, *Serratia marcescens*, and *Burkholderia cepacia* were less frequently isolated, together with *Staphylococcus* and *Aspergillus*, these infectious agents are among the most commonly reported microorganisms in CGD.[4] Different from other studies, *Nocardia spp.* or *Salmonella sp.* were not isolated in this cohort.[13,14,16,18,21]

Unusual and opportunistic bacteria and fungi were also isolated in this cohort. Unusual fungi were identified mainly in the lungs. These fungi have already been described in other cases of CGD and are responsible for invasive infections. In fact, the prevalence of invasive fungal infection is high among patients with CGD, ranging from 20–40%.[29] Unexpectedly, *Candida sp.* was the second most prevalent and isolated fungus in the present study. This finding is probably related to long-term hospitalization with the use of broad spectrum antibiotics and invasive devices, and not directly related to the immunologic defects of CGD.[29]

Considering the sites where the microorganisms were isolated, some important remarks were observed. Not only the lungs were the most frequent site where the pathogens were detected, but it was also the site where the greatest variability of microorganisms was found, including opportunistic fungi. Blood culture represents an important tool to detect microorganisms, especially if there is sepsis. As we could see in the present study, in the bloodstream we could detect potentially pathogenic bacteria such as *Staphylococcus sp.*

Liver abscesses are frequent in patients with CGD. In a large US cohort, liver abscesses occurred in one-third of the patients and *Staphylococcus aureus* was the predominant organism isolated.[21,30] In the present cohort, the only microorganism isolated from liver abscesses drainage was *Staphylococcus*, and mainly *Staphylococcus aureus*. In fact, in this study liver abscesses were the source of almost a quarter of all isolated *Staphylococcus*.

This study contributes to the understanding of infectious profile of patients with CGD in a Latin American country. The number of patients included seems representative considering that this is a single center study, but it also has limitations. As a long-term retrospective study, changes in patient approach, awareness of the disease, new comorbidities, and availability and accuracy of diagnostic methods certainly occurred. In the past, initial treatment was empiric, based on the most common agents reported in literature, so cultures were only obtained from patients with severe or complicated infections. CGD is a rare PID and infections are the most frequent clinical manifestations. The knowledge of local microbiological profile is essential for the adequate treatment and favorable outcome of patients with CGD.

Impact statement

This study contributed to the understanding of the infectious profile of patients with CGD in a Latin American country. This single-center study included a representative number of Brazilian patients with CGD. The initial treatment was based on the most common agents reported in literature, but the active search for infectious agents contributed to guide treatment in this rare PID.

Conflict of interest

There was no conflict of interest on the part of authors.

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Author contributions

Aimée Filippini Bifulco Oliveira –Data collection and review.

Antonio Carlos Pastorino - Preparation, creation and/or presentation of the published work, specifically critical review, commentary or revision – including pre- or post-publication stages.

Mayra de Barros Dorna, Ana Paula Beltran Moschione Castro - Preparation, specifically writing the initial draft (including substantive translation).

José Roberto Mendes Pegler, Beni Morgenstern - Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data.

Magda Maria Sales Carneiro-Sampaio – final review of article and comments

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